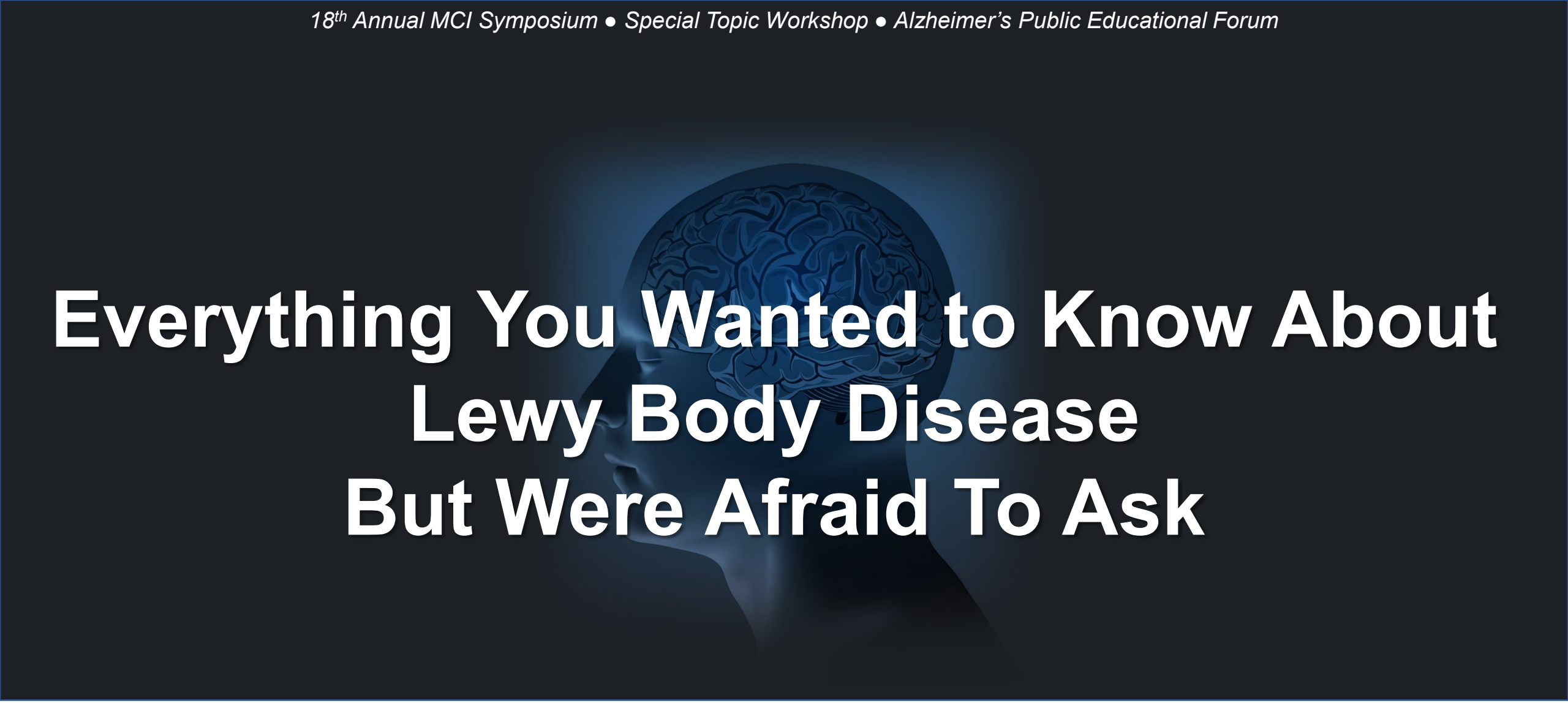

Everything You Wanted to Know About Lewy Body Disease But Were Afraid To Ask

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DISCLOSURES

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What is Lewy Body Dementia

- 2nd most common cause of dementia after AD
  - Causes 10-12% of irreversible dementia
  - Lewy bodies (LBs) found in up to 40% of autopsied brains
- Includes Dementia with Lewy Bodies (DLB) and Parkinson's Disease Dementia (PDD)
  - PDD: Movement Disorder begins 1st, at least 2 years before cognitive
  - DLB: Any other pattern
- More common in men
- May have faster decline than AD
- The combined sum of patients Lewy body dementia is estimated at 1.4 million
- Often significant delay to diagnosis and treatment
  - Commonly misdiagnosed as late-onset psychiatric disorder

Lewy Body Dementia Association (LBDA.org); Galvin JE *Practical Neurology 2019*

LBD Epidemiology (PDD)

- Point prevalence of dementia in PD is close to 30%
- Incidence rate is increased at 4-6 times relative to controls
- At least 75% of PD patients who survive more than 10 years likely to develop dementia
- Mean time from onset of PD to dementia is approximately 10 years
- Old age, more severe motor symptoms (in particular, gait and postural disturbances), mild cognitive impairment at baseline, and visual hallucinations

Lewy Body Dementia Association (LBDA.org); Galvin JE *Practical Neurology 2019*

LBD Epidemiology (DLB)

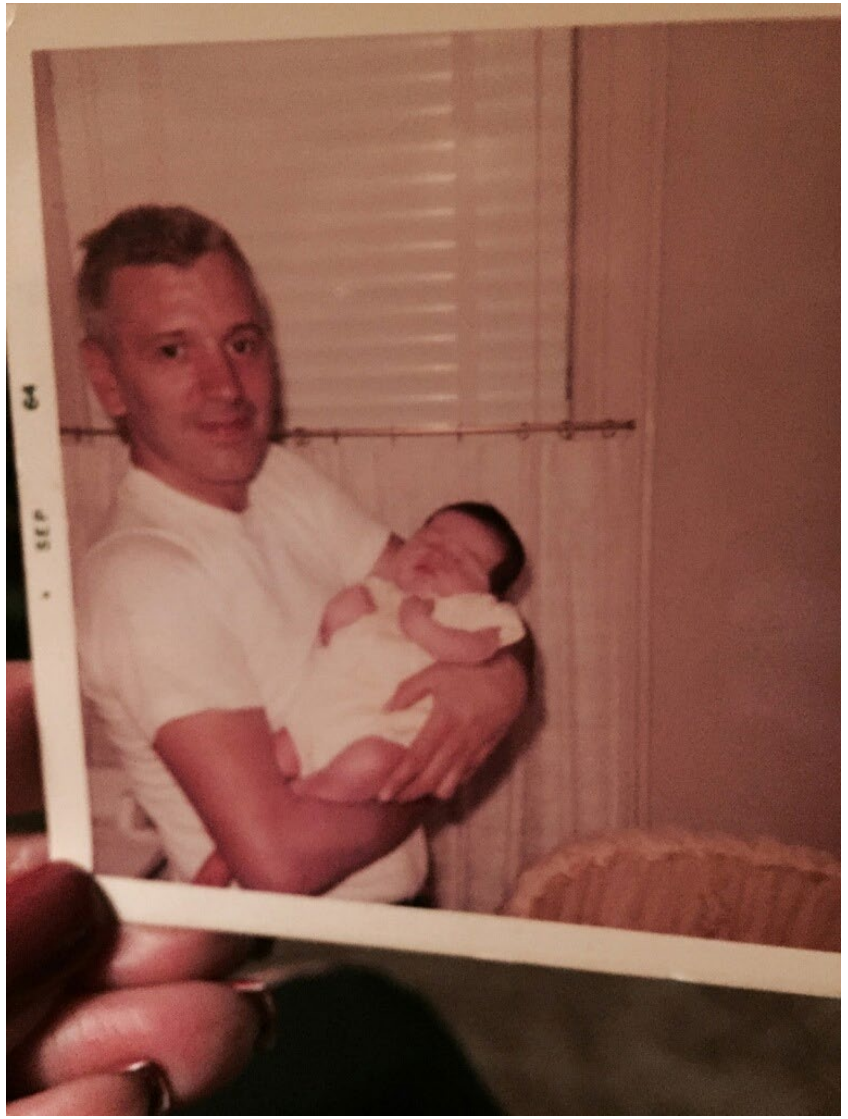
- Prevalence estimates of DLB range from 0% to 5% in the general population and from 0% to 30.5% of all dementia cases
- Incidence rates of 0.1% in the general population, and 3% for all new dementia cases
- A recent review examined 22 studies and reported incidence rates between 0.5 to 1.6 per 1000 person-years, accounting for 3-7% of dementia cases.
- Prevalence estimates ranged from 0.02-63.5 per 1000, higher with increasing age.

Lewy Body Dementia Association (LBDA.org); Galvin JE *Practical Neurology 2019*

Historical Perspective

- "the senses and intellect being unaffected"
  - James Parkinson, 1817
- Described changes in cognition and personality
  - Jean-Marie Charcot 1888
- "Parkinsonism is not necessarily accompanied by any mental change, and the sufferer's intellectually capacity…may continue unimpaired behind the mask in which his disorder fixes his features"
  - Lord Brain, 1933

MY Historical Perspective



Quickie Review of Things Associated With LBD

Movement Problems

- Bradykinesia
- Rigidity
- Postural instability with repeated falls
- Slow, shuffling gait
- Myoclonus
- Rare rest tremor but may have postural or action tremor

Cognitive Problems

- Visual tracking and attention
- Visual-spatial and perceptual
- Verbal and motor initiation
- Clock drawing and block design (construction)
- Timed attention tasks
- Executive tasks

Galvin JE, Practical Neurology (2019)

Quickie Review of Things Associated With LBD

Psychiatric/Behavioral Problems

- Visual Hallucinations
- Hallucination in other modalities
- Delusions
- Depression
- Anxiety
- Apathy
- REM Sleep behavior disorder
- Cognitive fluctuations

Autonomic/Constitutional Problems

- Loss of Smell
- Constipation
- Urinary incontinence
- Drooling
- Runny nose
- Dizziness and lightheaded
- Abnormal sweating
- Sexual dysfunction
- Oily flaky skin

Galvin JE, Practical Neurology (2019)

Simple Hallucinations

- Sense of presence
  - Sensation that someone is looking over your shoulder
  - Deceased relative, animal
- Passage
  - Seeing something pass sideways in the peripheral of vision
  - People, previously owned pet
  - Shadows
- Illusions
  - Misperception based on actual objects
  - Seeing a person when there is a coat on a hanger
  - Images emerging from wall paper

Galvin JE, Practical Neurology (2019)

Complex Hallucinations

- Predominantly visual in nature
  - Occur early in the course of the disease
  - May not be frightening to patients
  - Typically of little people, children, or furry animals
  - May or may not have an auditory component
  - Complex in nature
- Auditory (hear)
- Olfactory (smell)
- Gustatory (taste)
- Tactile (feel)

Galvin JE, Practical Neurology (2019)

Delusions

- Capgras
  - Familiar people are thought to be identical or near-identical imposters
- Fregoli
  - Familiar people are thought to be disguised as strangers
- Othello
  - Jealousy – usually spousal infidelity
- Cotard
  - Belief that one does not actually exist or is dead
- Reduplicative paramnesia
  - A place simultaneously exist in two or more physical locations
- Mirrored self-identification
  - Not recognizing self in mirror
- Ekbom
  - Infestation by insects or parasites
- Diogenes
  - Self-neglect, domestic squalor

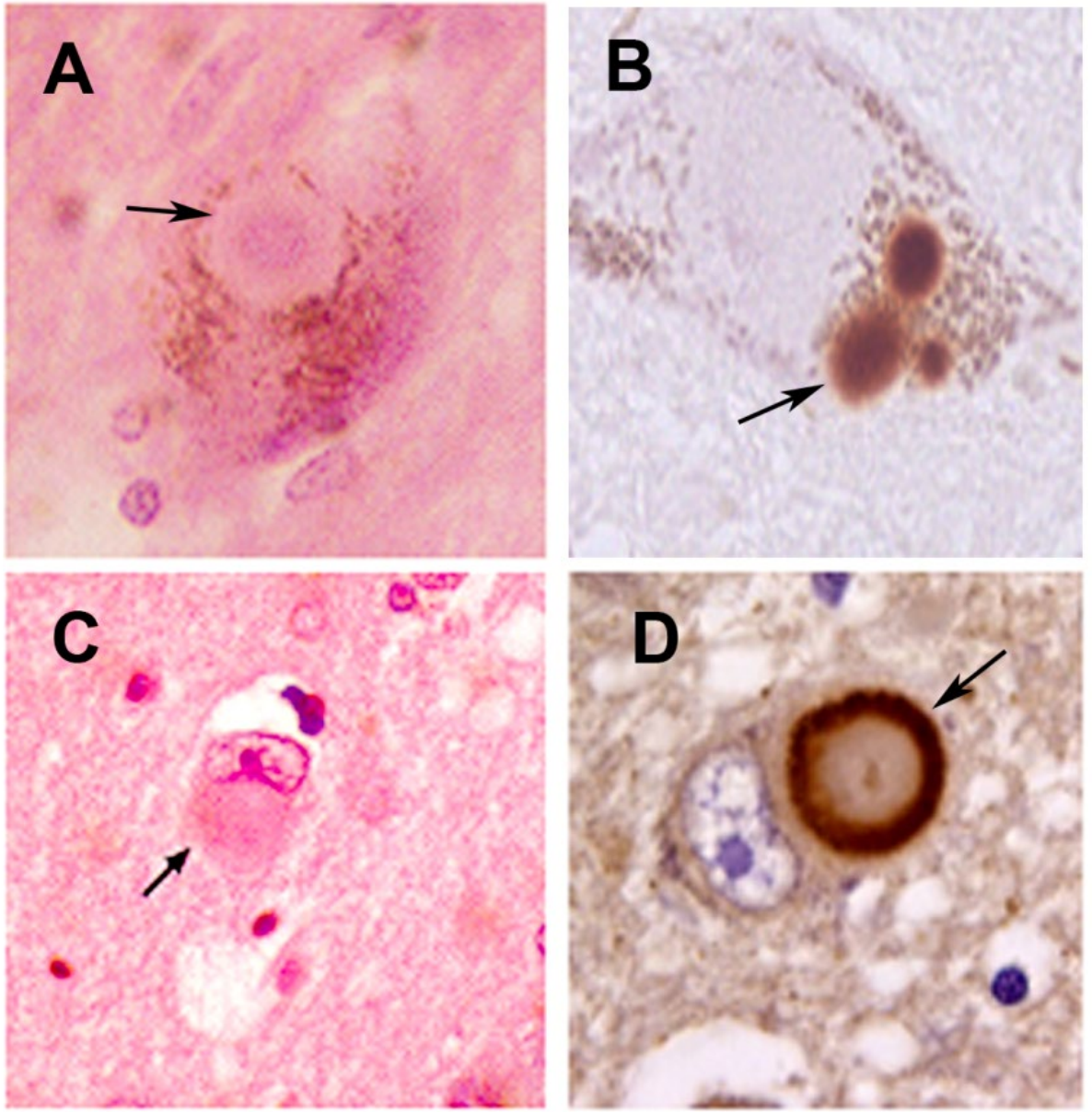
Galvin JE, Practical Neurology (2019)

Frequency of LBD Features

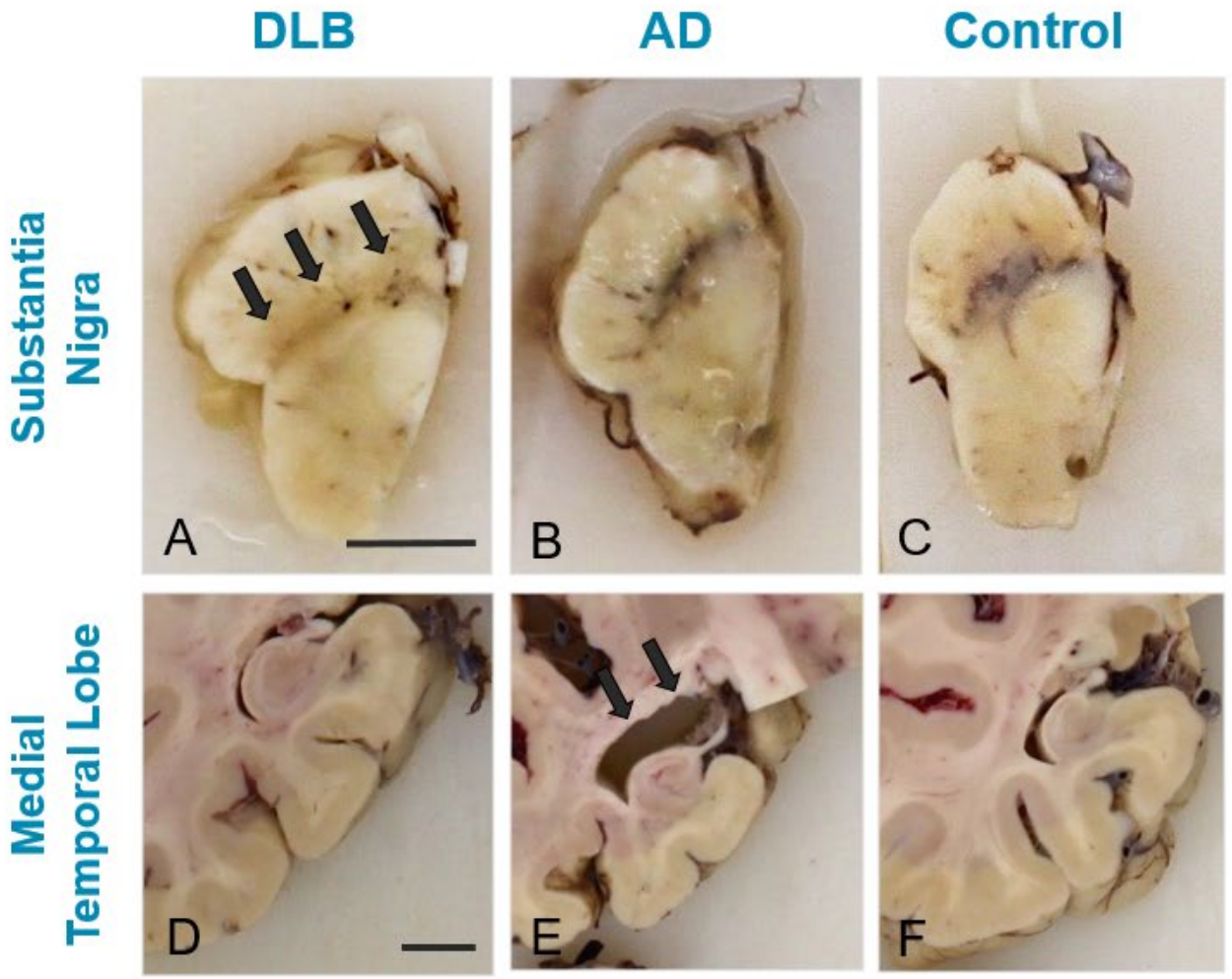
Characteristic (%)	Likelihood of LBD		
	Low	Possible	Probable
Parkinsonism	8.3	53.8	100
Bradykinesia	12.5	61.5	100
Rigidity	0	7.7	100
Tremor	0	7.7	33.3
Postural Instability	4.2	38.5	88.9
Hallucinations (any)	4.2	7.7	66.7
Fluctuations	33.3	59.5	93.5
RBD	4.3	22.2	36.7
Falls	23.3	47.6	83.3
Depression	23.5	28.6	52.0
Anxiety	22.1	25.7	32.0

Lewy Body Pathology

- Macroscopic
  - Mild atrophy, predominantly affecting limbic system
  - Depigmentation of the substantia nigra
- Microscopic
  - Essential – Lewy bodies
  - Associated (but not essential)
    - Lewy neurites
    - Regional neuronal loss including brainstem and nucleus basalis
    - Microvacuolation
    - Pale bodies
  - May also be present
    - Senile plaques
    - Neurofibrillary tangles



Neurodegeneration in LBD vs AD

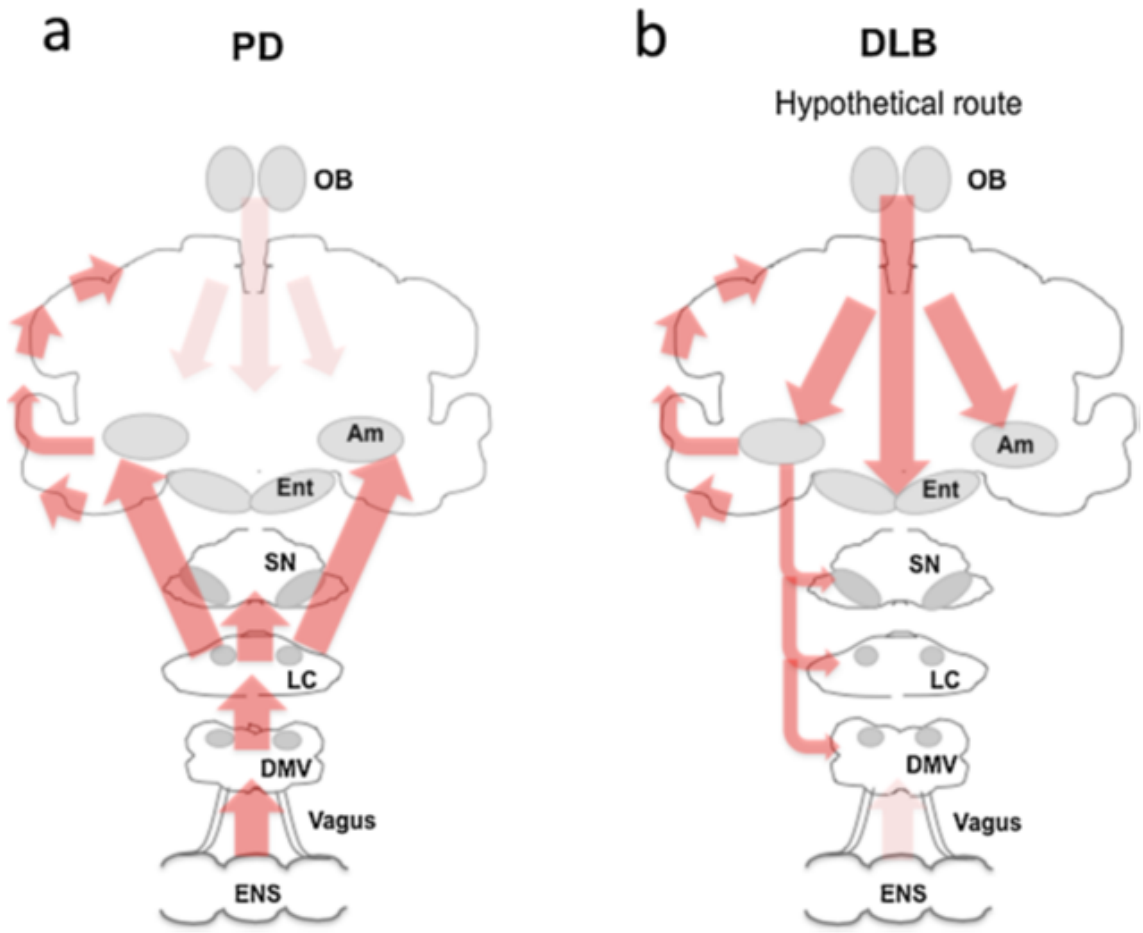


Dopaminergic cell loss is observed in the substantia nigra of a DLB patient (black arrows, A) compared with AD (B) and control (C).

In the same patients, atrophy of the medial temporal lobe is evident in AD (black arrows, E), whilst it is relatively spared in DLB (D) and control (F). Both scale bars represent 1 cm.

Outeiro et al. *Mol Neurodegener.* 2019;14:5.

Propagation of Lewy Body Pathology



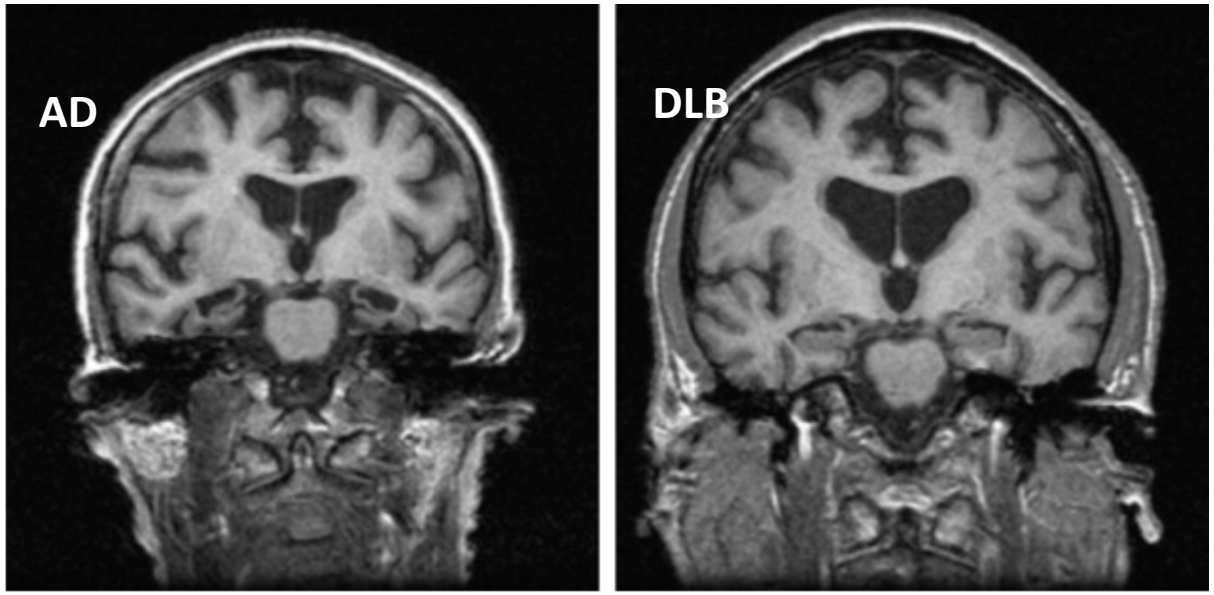
Schematic representation of α-synuclein pathology spreading routes in Lewy body disorders. **a.** Caudorostral route in PD **b.** Hypothetical olfactory route in DLB

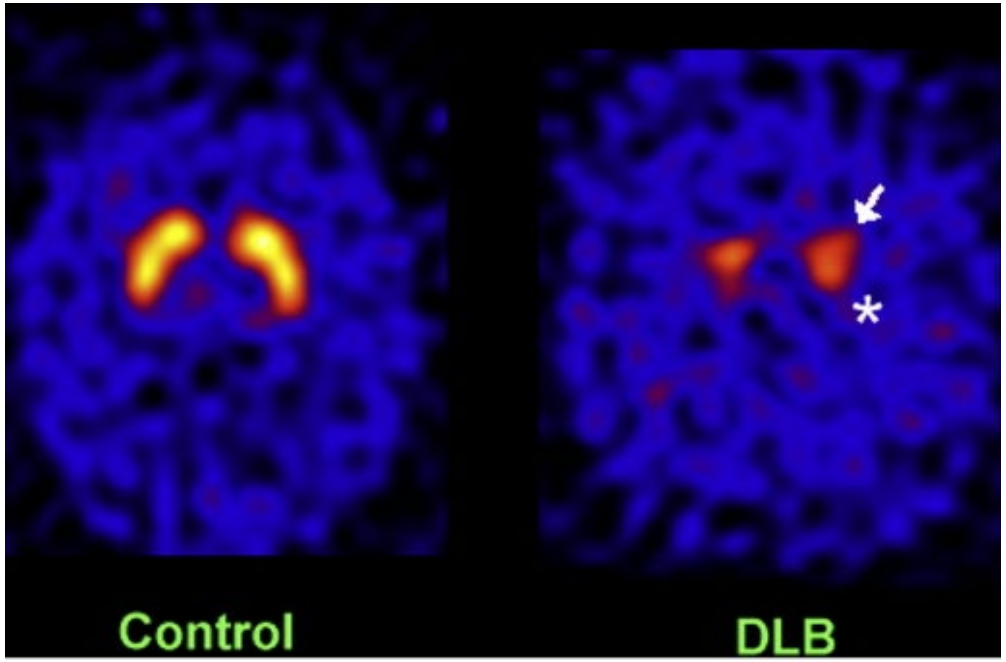
Light red arrows = weak incursions of α-synuclein pathology; dark red arrows = aggressive incursions of α-synuclein pathology

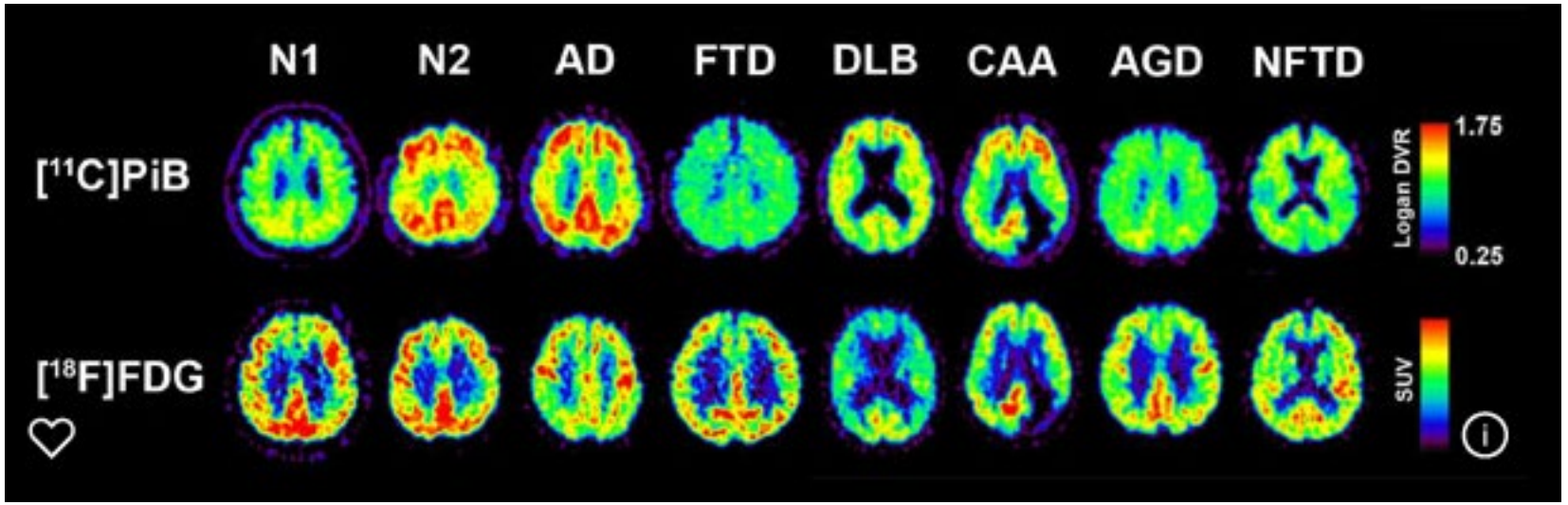
Am = amygdala; DMV = dorsal motor nucleus of the vagus; ENS = enteric nervous system; Ent = anterior entorhinal cortex; LC = locus coeruleus; OB = olfactory bulb; SN = substantia nigra.

Cersosimo et al. *Cell Tissue Res.* 2018;373:233.

Neuroimaging in LBD







Cognitive Profiles

	AD	LBD	bvFTD	VaD	Depression
Episodic Memory					
Free recall	+++	++	+/-	+	+
Recognition	+++	-	-	-	-
Prompting	x	√	√	√	√
Intrusions	+++	+++	+++	+	+
Semantic memory	++	+	+	+	+/-
Procedural memory	-	+	-	+	+
Working memory	++	+++	+++	++	+/-
Insight	+++	+	+++	-	-
Attention	++	+++	++	++	+++
Executive functions	++ typical AD +++ frontal variant	+++	+++	+++	++
Visuospatial skills	++ typical AD +++ PCA	+++	-	+	+

+++ Early and severe impairment; ++ moderate impairment; + mild impairment; +/- impairment in some studies but not others; - no significant impairment; x not helpful; √ helpful.

Karantzoulis and Galvin, Neurotherapeutics 2014; Galvin JE Practical Neurology 2019

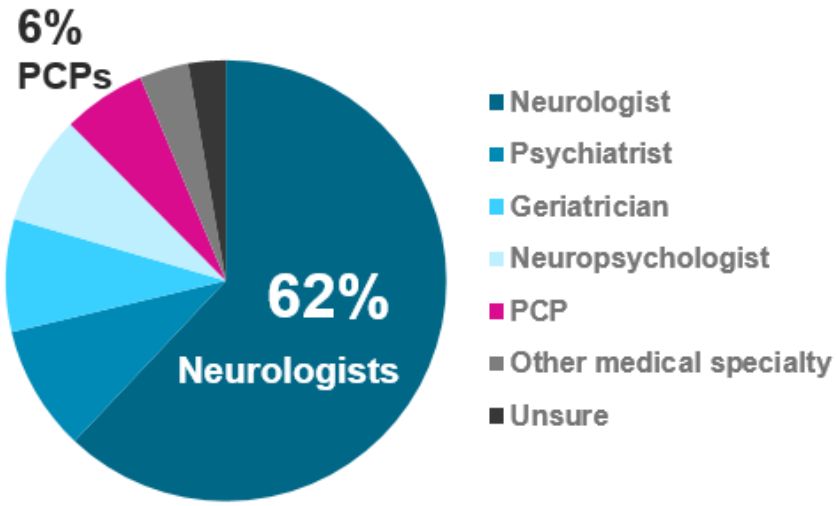
Caregiver Experience With Diagnosis

78% of patients had been diagnosed with something else first
- **53%** AD or other dementia
- **39%** PD or other movement disorder
- **24%** Primary psychiatric disorder

2/3 of patients saw at least 3 physicians before LBD diagnosis

Median time to diagnosis was 12-18 months

62% of diagnosing physicians were neurologists, and only **6%** were PCPs



PD = Parkinson's disease.

Galvin et al. *Parkinsonism Relat Disord.* 2010;16:388.

Caregiver Perception of Physician Knowledge

70%

had difficulty finding a physician knowledgeable about diagnosing LBD

After diagnosis,

53%

of patients returned to primary care for management

77%

had difficulty finding a physician knowledgeable about treating LBD

Galvin et al. *Parkinsonism Relat Disord.* 2010;16:388.

How useful it is to get a diagnosis?

DLB causes **significantly greater** functional disability than **AD**[1]

Care costs of **DLB** are **twice** those for **AD**[2]

Quality of life for people with **DLB** is significantly worse than for those with AD, with **1 in 4 caregivers** rating DLB as worse than death![3]

A correct **DLB diagnosis** increases the chances of correct management[4]

1. McKeith et al. *Am J Geriatr Psychiatry*. 2006;14:582; 2. Boström et al. *Int J Geriatr Psychiatry*. 2007;22:713; 3. Boström et al. *Alzheimer Dis Assoc Disord*. 2007;21:150; 4. National Institute for Health and Care Excellence website. https://www.nice.org.uk/guidance/ng97/chapter/Recommendations#pharmacological-interventions-for-dementia. Accessed February 4, 2019.

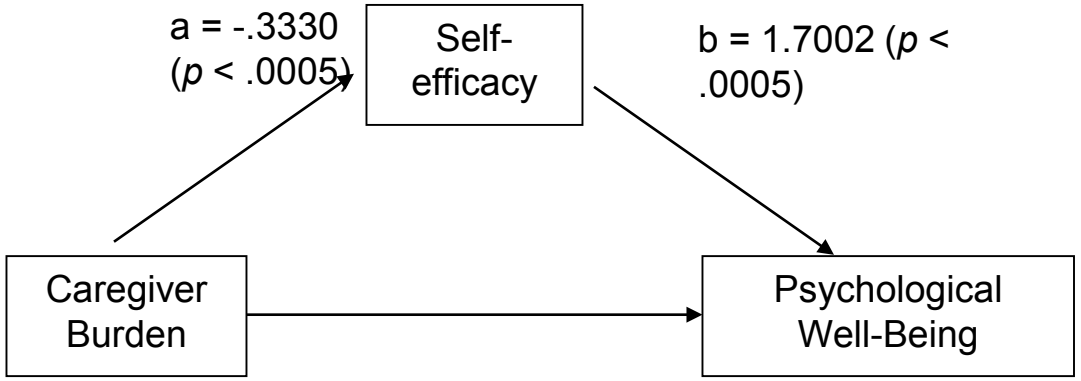
Experiences in LBD Caregiving

Adult child and spouse caregivers experience LBD differently

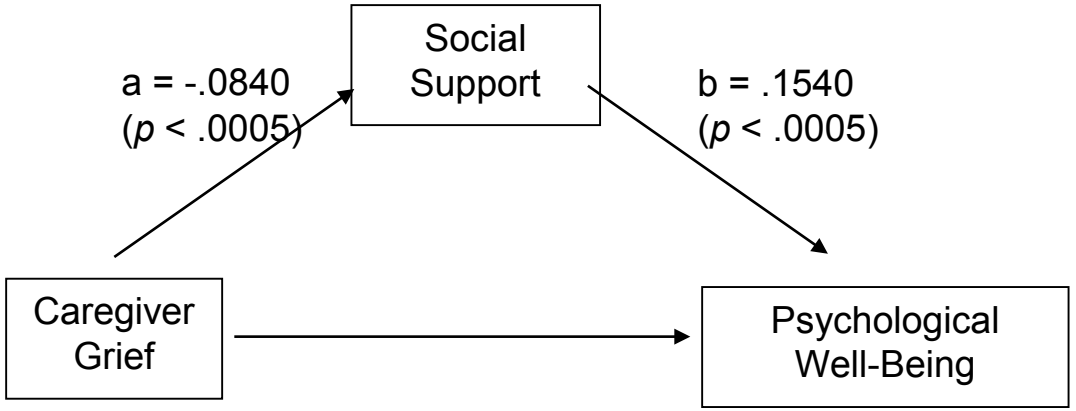
- Adult children vs Spouse
  - Less likely to live with patient
  - More likely to be caring for their mothers
  - Patients are more impaired
  - Report lower quality of life, more caregiver burden
  - Report greater social support
  - Report less grief

Variable	Spouse	Adult Child	p-value
Caregiver Quality of life	39.0 (7.1)	33.5 (7.6)	**<.001†**
Social Support	57.4 (17.8)	66.8 (20.9)	**<.001†**
Emotional	25.6 (8.3)	28.1 (9.0)	**.006†**
Tangible	10.7 (4.7)	13.3 (5.1)	**<.001†**
Affective	8.9 (3.3)	10.9 (3.6)	**<.001†**
Positive Social Interaction	11.4 (4.6)	14.3 (4.8)	**<.001†**
Social Networks	17.3 (4.5)	18.2 (4.5)	.077
Depression	1.9 (1.6)	2.2 (1.8)	.069
Psychological well being	83.5 (12.6)	81.7 (13.0)	.169
Caregiver grief	62.4 (12.9)	60.8 (12.7)	.229
Caregiver burden	24.6 (8.3)	26.9 (8.4)	**.009**
Role strain	11.7 (3.9)	12.6 (4.5)	.045
Personal strain	4.4 (2.7)	4.9 (2.7)	.072
Worry about performance	8.6 (3.3)	9.5 (3.2)	**.009**

Self-Efficacy and Social Support Mediate Psychological Well-Being in LBD Caregivers



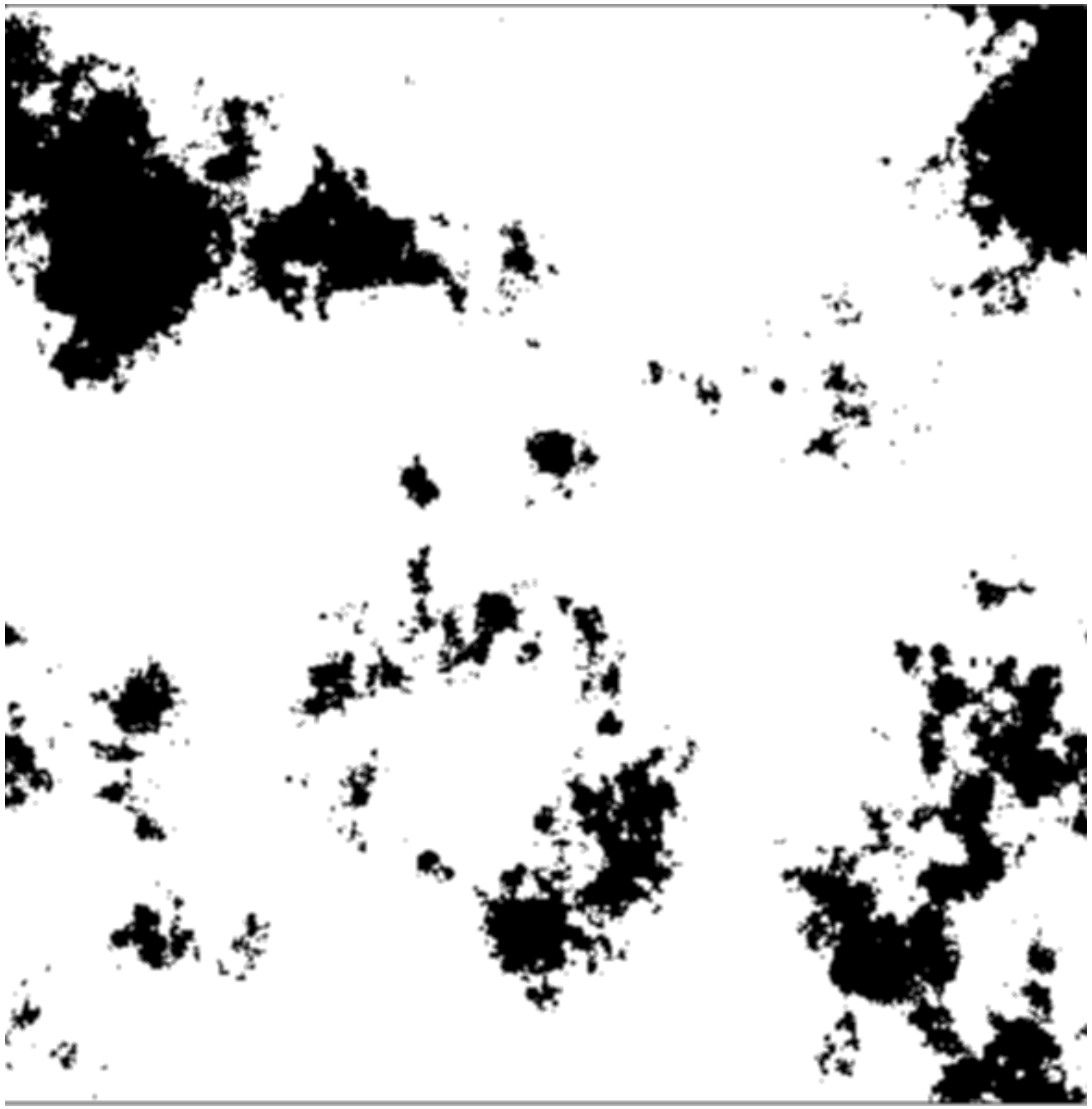
Direct (c') = -.3893 (p < .0005); indirect (ab) = -.722 (95%CI = -.834 to -.610)

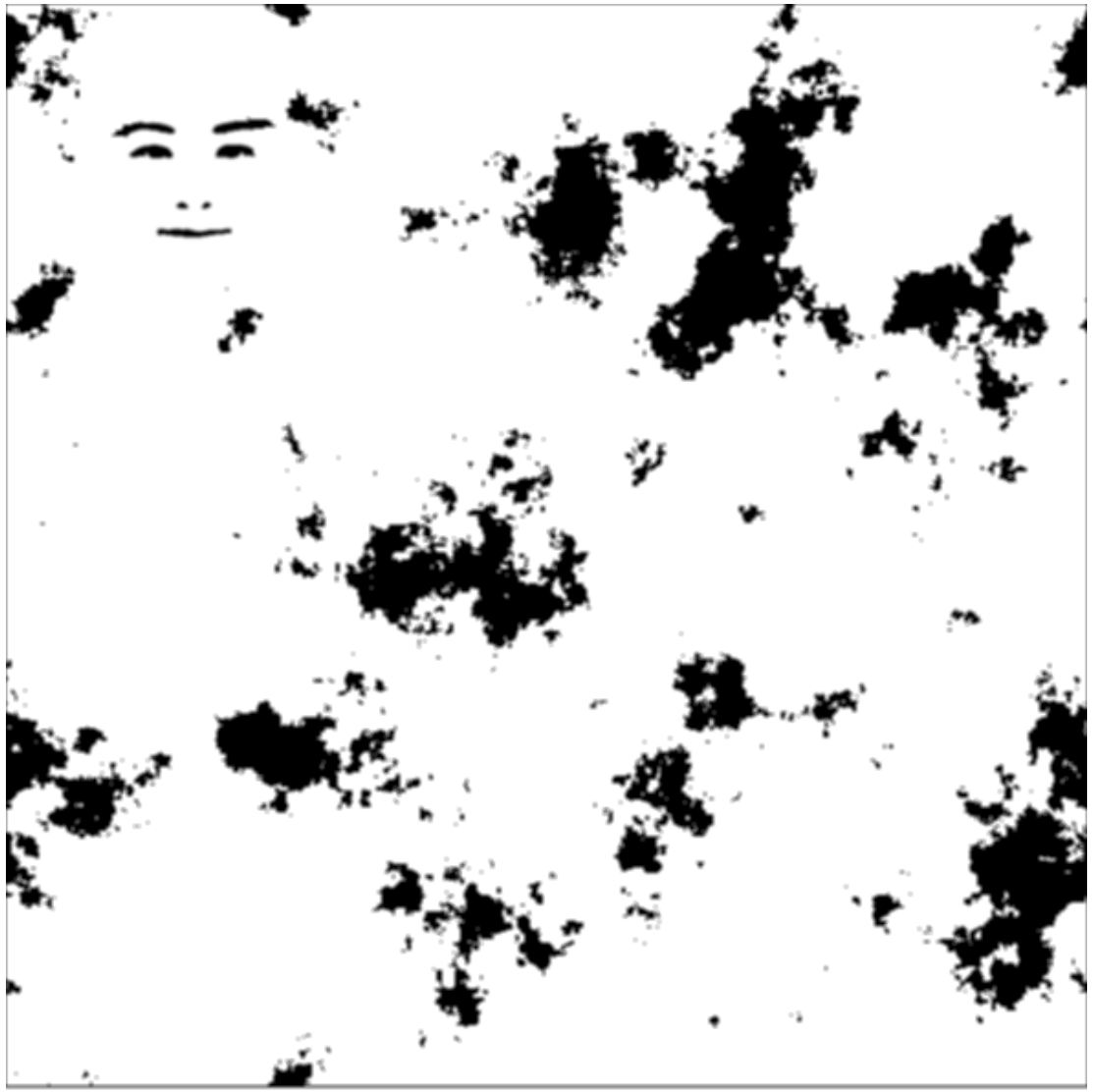


Direct (c') = -.3879 (p < .0005); indirect (ab) = -.472 (95% CI = -.541 to -.403)

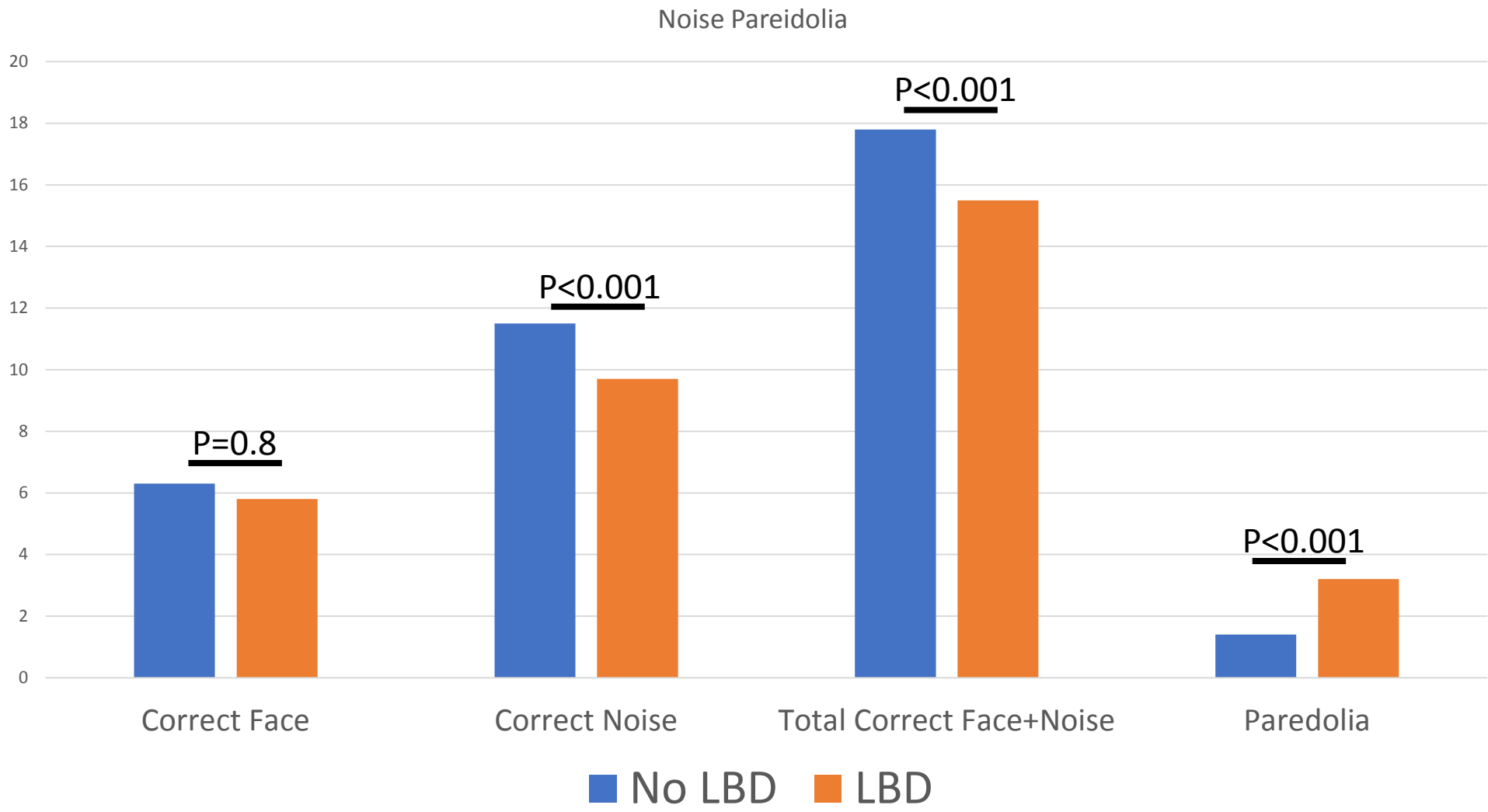
Park et al, Social Work in Mental Health, 2018

Noise Pareidolia





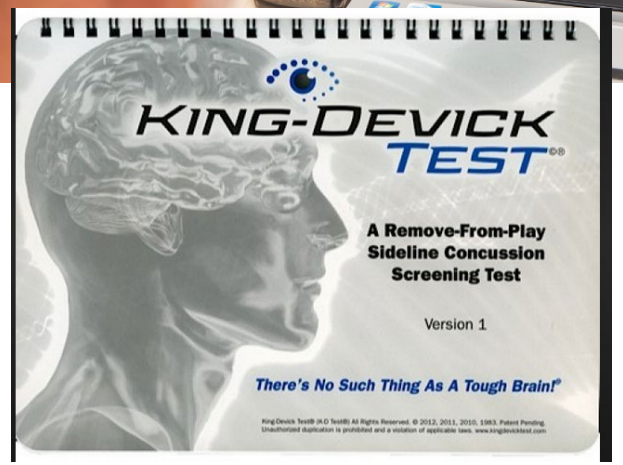
Noise Pareidolia Test Discriminates LBD



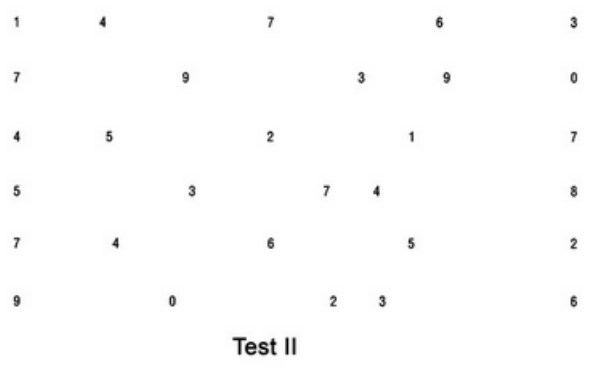
Galvin et al, In Preparation

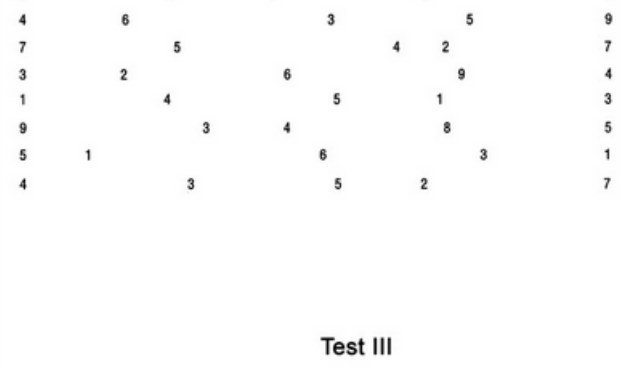
Proxy Markers of Basal Ganglia Dysfunction

18th Annual MCI Symposium
Special Topic Workshop
Alzheimer's Public Educational Forum



	Pursuits (2 Hz Gain%)	Saccades (Peak Velocity)	Saccades (Latency)
UPDRS	**-0.36 (<.001)**	**-0.41 (<.001)**	0.19 (.05)
LBCRS	-0.17 (.09)	**-0.31 (.001)**	0.22 (.01)
King-Devick	-0.37 (.16)	-0.51 (.03)	**-0.71 (.001)**
Noise Pareidolia	**0.32 (.003)**	**0.33 (.002)**	**-0.50 (<.001)**





Computerized Gait Analyses

- Develop a new metric of nu
- FI captures patients' normal
- Reproducible objective mar
- The FI increased significantl dementia (1.9±0.5).
- ROC analyses: AUC 0.703 (p<.001).
- A cut-off of 1.65 provides a sensitivity of 72.4% to detect individuals with cognitive impairment

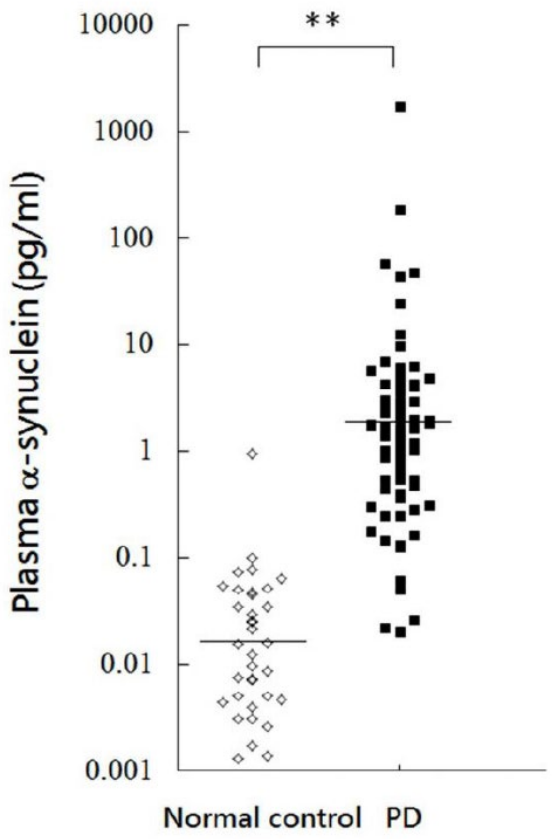
Frequency

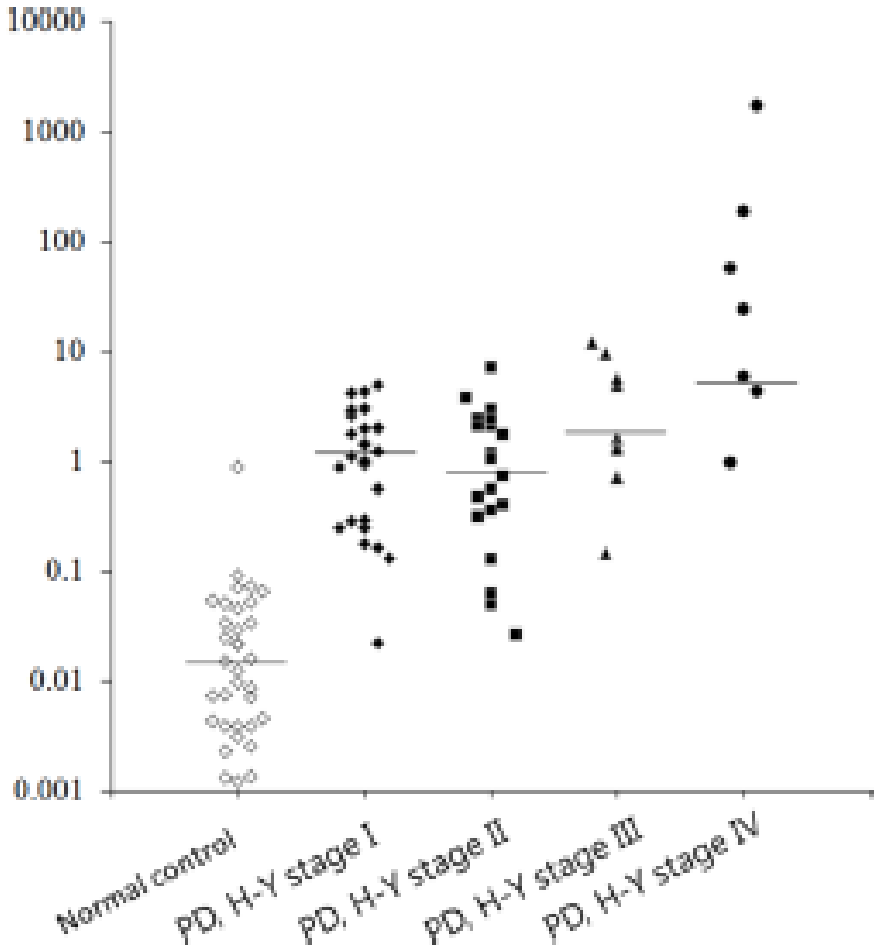
Table 3: Cognitive Performance by Festination Index Cut-off of 1.65

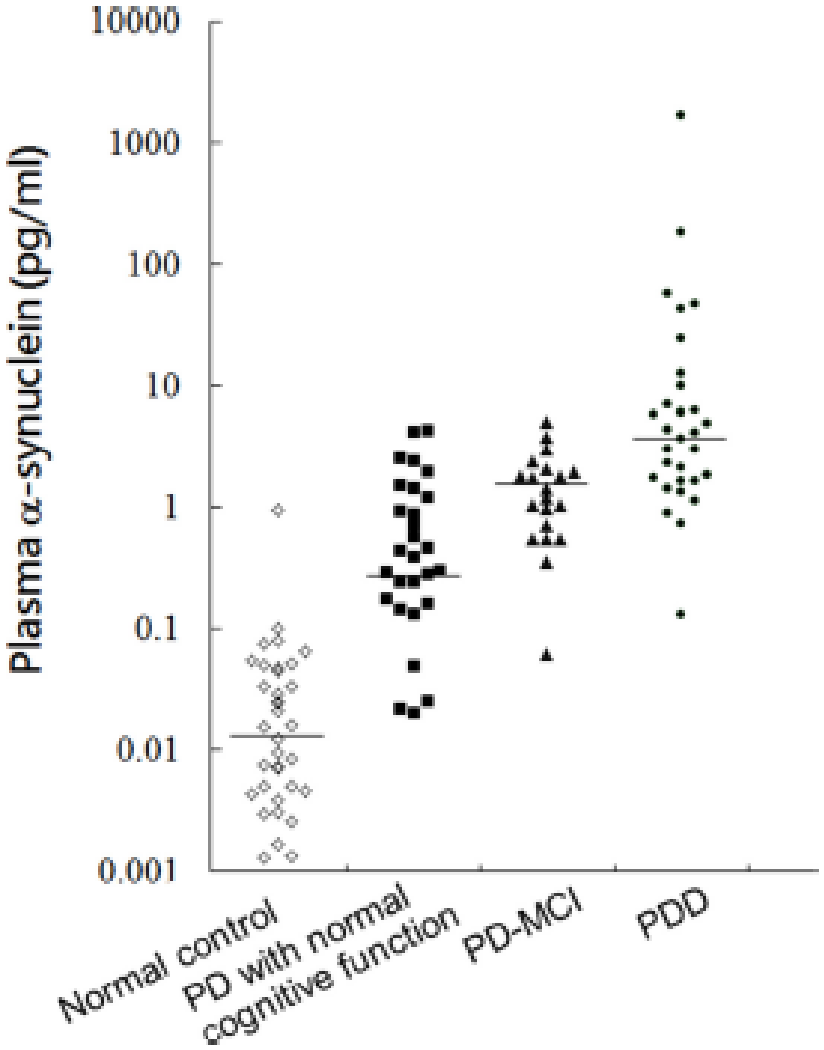
	<1.65	**>1.65**	***P-value**
MoCA	20.5 (5.3)	16.3 (6.4)	**<.001**
Numbers Forward	6.8 (1.8)	6.6 (1.3)	**.03**
Numbers Backward	4.8 (1.7)	3.9 (1.7)	**.02**
Animal Naming	16.2 (6.2)	10.4 (5.2)	**<.001**
15-item MINT	13.9 (2.6)	12.6 (3.8)	**<.001**
HVLT – Delay	4.2 (3.5)	2.6 (3.2)	**.003**
HVLT – Recognition	9.4 (2.6)	8.0 (3.2)	**.003**
Trails A, sec	53.6 (37.8)	77.7 (52.7)	.08
Trails B, sec	109.9 (51.8)	130.4 (46.2)	**.006**
Number-Symbol	31.6 (12.9)	26.9 (11.2)	**.01**
Noise Pareidolia, errors	1.4 (2.3)	2.2 (3.2)	.1
King-Devick	61.0 (19.6)	61.8 (22.3)	.9
Z-score	.233 (0.4)	-.310 (0.4)	**<.001**
CDR-SB	2.5 (2.4)	5.5 (4.5)	**<.001**

Adjusted for Age and Education

Plasma Alpha-Synuclein

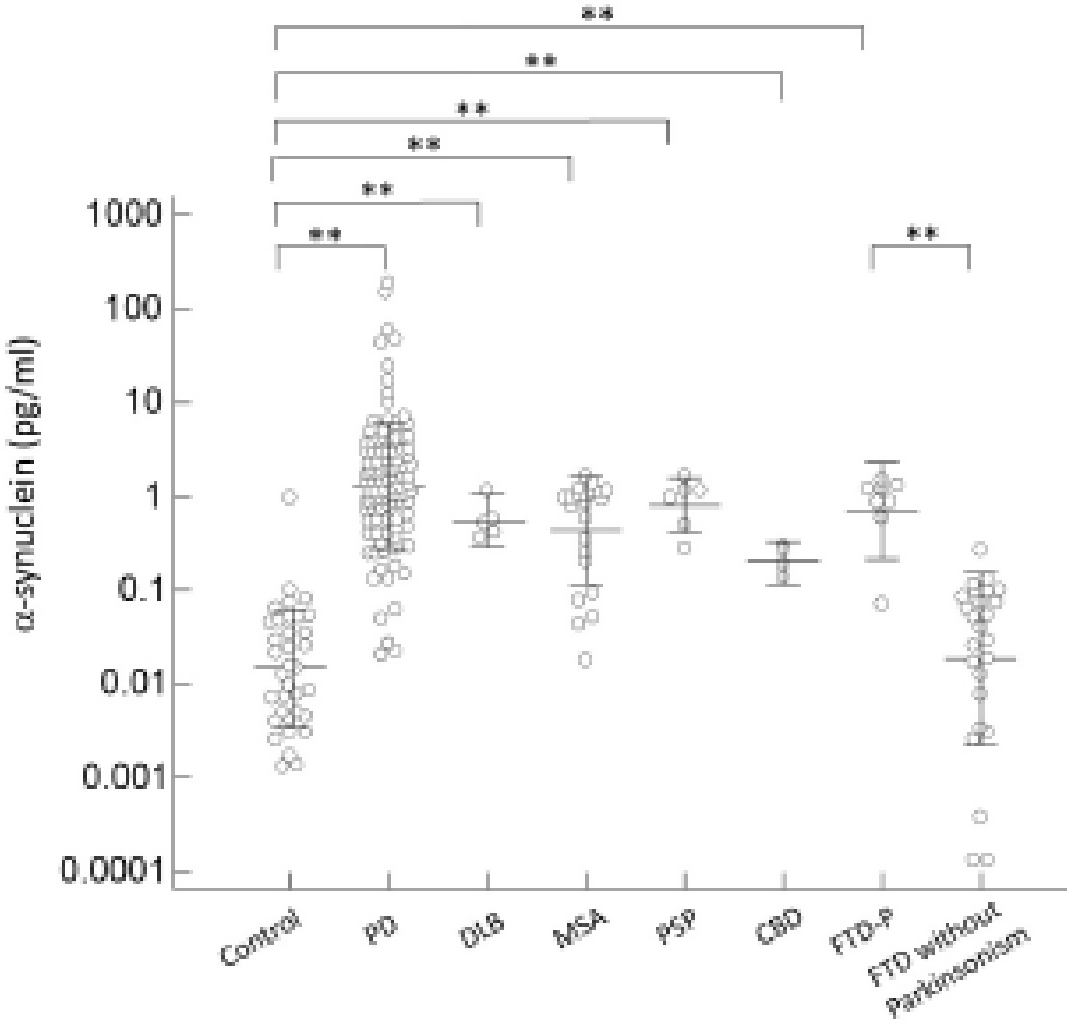


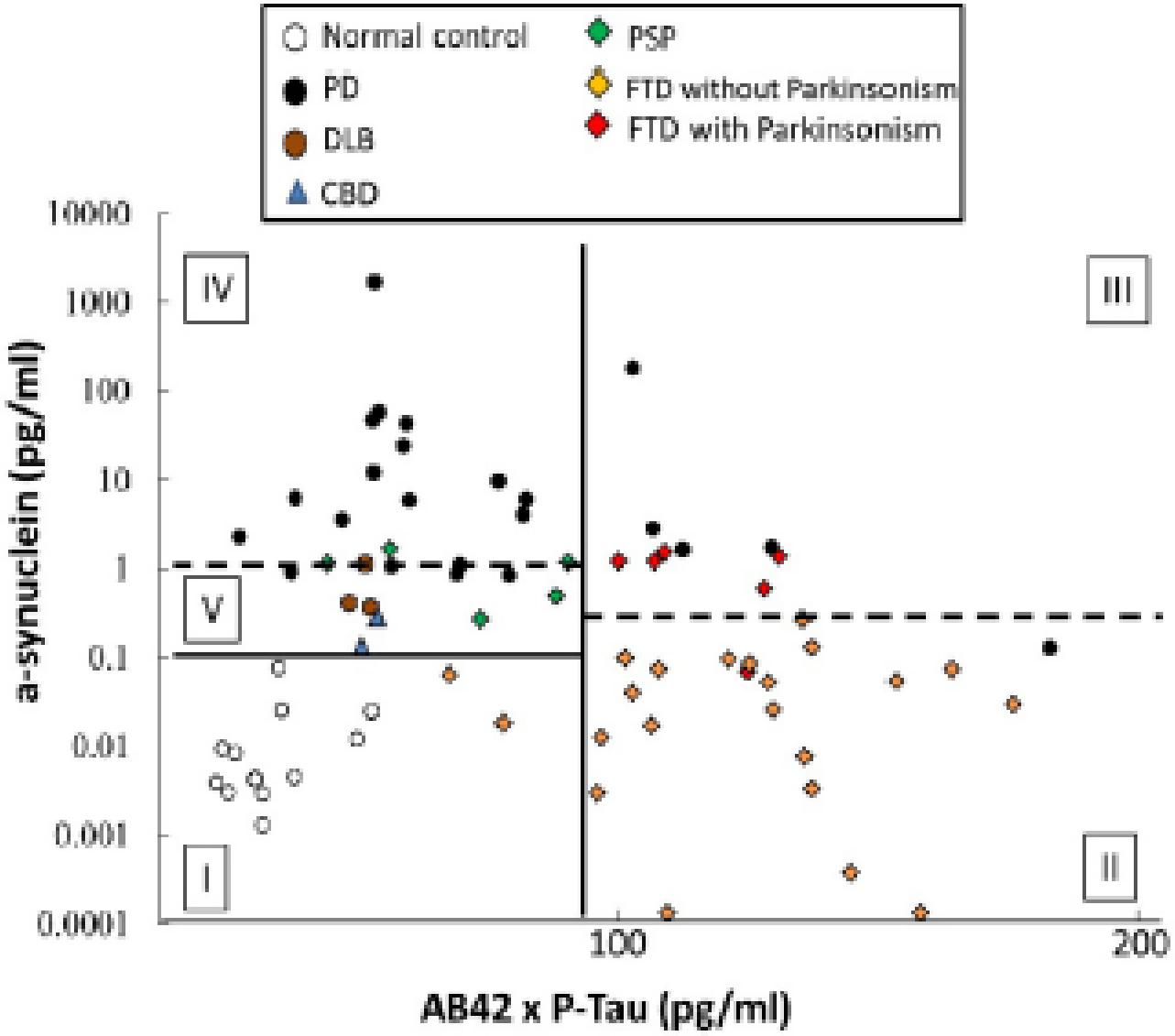




Data from MagQu Inc, Taiwan

Plasma Biomarkers





Lin et al Front Aging Neurosci 2018

Clinical Predictors of LB Pathology

Clinical Predictor	Present at any time		Present at 1st visit	
	OR	95% CI	Log Rank	p-value
Male gender	1.50	1.01-2.38	2.40	.08
Any EPS	2.50	1.64-3.82	24.50	<.001
Cognitive Fluctuation	4.98	1.63-15.15	4.66	.031
Visual Hallucinations	8.93	2.31-34.50	22.88	<.001
Auditory Hallucination	11.76	1.66-83.30	11.46	.001
Neuroleptic Sensitivity	3.75	1.05-13.30	8.02	.005
Myoclonus	3.90	1.27-12.05	14.75	<.001
Depression	1.81	1.16-2.82	7.51	.007
Sleep Disturbances	1.98	1.33-2.94	8.66	.003

Clinical features associated with AD such as aphasia, apraxia, agnosia not associated

Galvin et al, Neurology (2006) 67:1605-1611

Lewy Body Composite Risk Score

Please rate the following symptoms as being present or absent for at least 3 times over the past 6 months. Does the patient…	**Yes**	**No**
Have slowness in initiating and maintaining movement or have frequent hesitations or pauses during movement?		
Have rigidity (with or without cogwheeling) on passive range of motion in any of the 4 extremities?		
Have a loss of postural stability (balance) with or without frequent falls?		
Have a tremor at rest in any of the 4 extremities or head?		
Have excessive daytime sleepiness and/or seem drowsy and lethargic when awake?		
Have episodes of illogical thinking or incoherent, random thoughts?		
Have frequent staring spells or periods of blank looks?		
Have visual hallucinations (see things not really there)?		
Appear to act out his/her dreams (kick, punch, thrash, shout or scream)?		
Have orthostatic hypotension or other signs of autonomic insufficiency?		
TOTAL SCORE		

LBCRS

Demographics and Global Ratings	Dementia		
	AD (n=91)	LBD (n=48)	p-value
Age, y	79.9 (7.9)	78.5 (7.8)	.30
Gender, %M	37.4	60.4	**.009**
Education, y	15.2 (3.9)	14.6 (3.5)	.45
CDR-SB	5.9 (3.4)	8.8 (5.1)	**<.001**
CDR	0.9 (0.5)	1.5 (0.9)	**<.001**
Charlson Comorbidity Index	2.3 (1.3)	2.3 (1.4)	.98
Systolic BP, sitting, mm Hg	133.4 (18.9)	124.9 (23.6)	**.03**
Mean Arterial Pressure, sitting	94.5 (11.2)	89.4 (15.2)	**.03**
Systolic BP, standing, mm Hg	133.2 (18.7)	122.7 (23.9)	**.01**
Mean Arterial Pressure, standing	94.3 (11.1)	89.5 (16.8)	.08
Body Mass Index	25.0 (4.8)	25.4 (4.6)	.67
Mini-PPT	9.8 (2.5)	8.4 (3.2)	**.03**
UPDRS III	7.5 (9.1)	35.6 (23.3)	**<.001**
Hoehn and Yahr Stage	0.5 (1.2)	2.8 (1.5)	**<.001**
FAQ	10.3 (8.7)	17.4 (9.9)	**<.001**
NPI-Q	7.7 (5.7)	11.3 (5.7)	**.001**
Mayo Fluctuation Questionnaire	1.6 (1.1)	2.9 (0.9)	**<.001**
Epworth Sleepiness Scale	6.8 (4.8)	9.8 (5.3)	**.001**
Alertness Rating	7.2 (2.0)	5.6 (1.8)	**<.001**
LBCRS	**2.4 (1.3)**	**6.2 (2.1)**	**<.001**
Cohen's d (Effect Size correlation)	**2.17 (r=0.736)**		

Galvin JE, Alz Dementia 2015

DIAMOND LEWY Toolkit

18th Annual MCI Symposium
Special Topic Workshop
Alzheimer's Public Educational Forum

Assessment Toolkit for Dementia with Lewy Bodies

Name:	Date of testing:
Date of birth:	Tester's name:
NHS No:	Informant:

Please use this Assessment toolkit in all people with cognitive decline. Below are the diagnostic features of dementia with Lewy bodies (DLB) at two levels of confidence (probable DLB and possible DLB) and on the following pages are specific questions to assist in the identification of the core and suggestive features of DLB.

DLB Diagnostic Criteria

		Tick
1	Clinician diagnosis of dementia (cognitive decline sufficient to interfere with social/occupational function).	☐
2	Use screening questions below to cover the four domains of: cognitive fluctuation, visual hallucinations, RBD and parkinsonism.	
	Using your experience identify how many core and biomarker features of DLB are present (see below):	
3	**Core clinical features** • Fluctuation in cognition • Recurrent visual hallucinations • REM sleep behaviour disorder • One or more features of spontaneous parkinsonism	☐ ☐ ☐ ☐
4	**Indicative Biomarkers** • Dopaminergic abnormalities in basal ganglia on SPECT/PET • Low uptake on MIBG myocardial scintigraphy • Polysomnography (PSG) confirmation of REM sleep without atonia	☐ ☐ ☐

Diagnose **Probable DLB** if either 2 core features are identified or 1 core and 1 indicative biomarker feature. ☐

Diagnose **Possible DLB** if any one feature is present. In such circumstances consider whether to refer subject for a dopaminergic SPECT scan (DaTSCAN), or MIBG or PSG, depending on local availability. ☐

Other Diagnoses

Parkinson's Disease Dementia (PDD) (PD >1 yr before cognitive symptoms)	☐
Alzheimer's Disease	☐
Other Dementia	☐
MCI	☐
Patient informed of diagnosis.	Yes ☐ No ☐

Questions to Identify Symptoms of DLB

Please respond to each of the questions below, asking carer or patient as appropriate.

Cognitive Fluctuation (to carer)

If two or more of these are answered 'Yes' the subject is highly likely to have cognitive fluctuation

1	Does the patient show moderate changes in their level of functioning during the day?	Yes ☐	No ☐
2	Between getting up in the morning and going to bed at night, does the patient spend more than one hour sleeping?	Yes ☐	No ☐
3	Is the patient drowsy and lethargic for more than one hour during the day, despite getting their usual amount of sleep the night before?	Yes ☐	No ☐
4	Is it moderately difficult to arouse the patient so they maintain attention through the day?	Yes ☐	No ☐

REM Sleep Disorder
(to carer = bed partner)

Have you ever seen the patient appear to "act out his/her dreams" while sleeping (punched or flailed arms in the air, shouted or screamed)?	Yes ☐	No ☐

If answered affirmatively, then RBD is highly likely to be present.

REM Sleep Disorder
(to patient only if no bed partner and they have sufficient cognitive ability to be confident their answer is reliable)

Have you ever been told that you seem to "act out your dreams" while sleeping (punched or flailed arms in the air, shouted or screamed)?	Yes ☐	No ☐

Visual Hallucinations

For the participant: Some people see things that other people cannot see.

1	Do you feel like your eyes ever play tricks on you?	Yes ☐	No ☐
2	Have you ever seen something (or things) that other people could not see?	Yes ☐	No ☐

For the carer:

1	Does the patient have hallucinations such as seeing false visions?	Yes ☐	No ☐
2	Does he / she seem to see things that are not present?	Yes ☐	No ☐

If, according to clinical judgement, visual hallucinations are present, determine as far as possible their frequency and recurrence. As a guide, visual hallucinations associated with DLB should not only occur during delirium, and are often recurrent over a period of months.

Assessment of Parkinsonism (5-item UPDRS)

Parkinsonism in DLB requires the presence of at least one of bradykinesia, rest tremor or rigidity. The 5-item UPDRS is a brief and validated scale for identifying parkinsonism in DLB (See below for further details)

POSTURAL TREMOR OF THE HANDS			
Normal	No tremor.	0	☐
Slight	Tremor is present but less than 1 cm in amplitude.	1	☐
Mild	Tremor is at least 1 but less than 3 cm in amplitude.	2	☐
Moderate	Tremor is at least 3 but less than 10 cm in amplitude.	3	☐
Severe	Tremor is at least 10 cm in amplitude.	4	☐
KINETIC TREMOR OF THE HANDS			
Normal	No tremor.	0	☐
Slight	Tremor is present but less than 1 cm in amplitude.	1	☐
Mild	Tremor is at least 1 but less than 3 cm in amplitude.	2	☐
Moderate	Tremor is at least 3 but less than 10 cm in amplitude.	3	☐
Severe	Tremor is at least 10 cm in amplitude.	4	☐
FACIAL EXPRESSION			
Normal	Normal facial expression.	0	☐
Slight	Minimal masked facies manifested only by decreased frequency of blinking.	1	☐
Mild	In addition to decreased eye-blink frequency, masked facies present in the lower face as well, namely fewer movements around the mouth, such as less spontaneous smiling, but lips not parted.	2	☐
Moderate	Masked facies with lips parted some of the time when the mouth is at rest.	3	☐
Severe	Masked facies with lips parted most of the time when the mouth is at rest.	4	☐
GLOBAL SPONTANEITY OF MOVEMENT (BODY BRADYKINESIA)			
Normal	No problems.	0	☐
Slight	Slight global slowness and poverty of spontaneous movements.	1	☐
Mild	Mild global slowness and poverty of spontaneous movements.	2	☐
Moderate	Moderate global slowness and poverty of spontaneous movements.	3	☐
Severe	Severe global slowness and poverty of spontaneous movements.	4	☐
RIGIDITY			
Normal	No rigidity.	0	☐
Slight	Rigidity only detected with activation manoeuvre.	1	☐
Mild	Rigidity detected without the activation manoeuvre, but full range of motion is easily achieved.	2	☐
Moderate	Rigidity detected without the activation manoeuvre; full range of motion is achieved with effort.	3	☐
Severe	Rigidity detected without the activation manoeuvre and full range of motion not achieved.	4	☐

Total 5-item UPDRS Score =	☐
Is Parkinsonism present? (Use clinical judgement but for guidance a score >7 suggests significant parkinsonism is present, though a high score (>2) in a single domain may be sufficient to meet criteria)	Yes ☐ No ☐

Thomas AJ, et al. Int J Geriatr Psychiatry. 2018

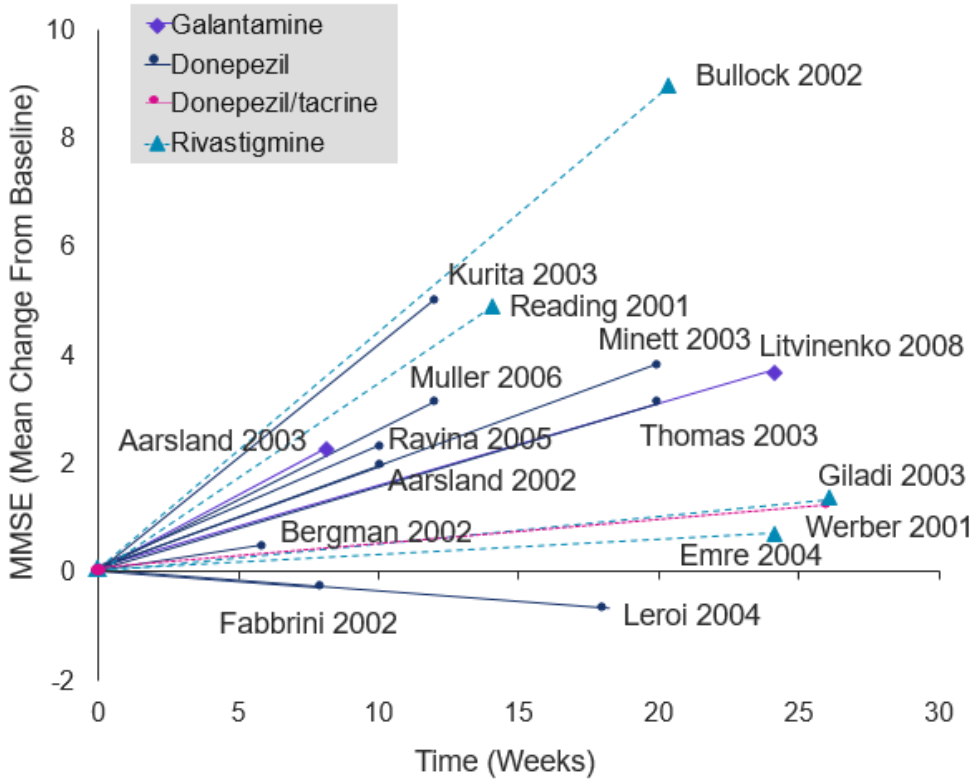
Treatment Options

Pharmacology[1-4]

(nearly all options are off-label use of medication for DLB)

Cognitive Symptoms	Donepezil (approved for DLB in Japan/Philippines)[5] Other cholinesterase inhibitors Memantine (?)
Behavior	Antidepressants Atypical antipsychotics Prazosin (?) Antiepileptics (?)
Motor Symptoms	Carbidopa Levodopa
Sleep	Melatonin Clonazepam
Fluctuation Attention	Modafinil Armodafinil
Autonomic	Fludrocortisone Midodrine Droxidopa Trospium

Overview of Change in MMSE Scores From Studies of Cholinesterase Inhibitors in PDD[6]



1. Walker et al. *Lancet*. 2015;386:1683; 2. Boot et al. *Curr Treat Options Neurol*. 2013:15:738; 3. Palermo et al. *Expert Opin Pharmacother*. 2018;19:1643; 4. Wang et al. *Am J Geriatr Psychiatry*. 2009;17:744; 5. Eisai, Inc. Press Release. 14 April 2016. https://www.eisai.com/news/news201624.html. Accessed 9 February 2019; 6. van Laar et al. *CNS Neurosci Ther*. 2011;17:428.

Ongoing Clinical Trials in LBD

Compound	Mechanism of Action	Phase/Location	Status/Timing	Clinical Trial
DLB/PDD				
Nelotanserin	5-HT_{2A} receptor inverse agonist[3]	Phase 2, US	**Completed – primary endpoint for RBD not met[4]**	NCT02708186
DLB				
Intepirdine	5-HT_6 receptor antagonist[3]	Phase 2/3, Global	**Extension terminated due to lack of efficacy in lead-in study**	NCT02928445
HTL0018318	M_1 receptor agonist[5]	Phase 2, Japan	**Suspended due to unexpected animal toxicology finding**	NCT03592862
E2027	PDE9 inhibitor[3]	Phase 2, Global	Recruiting – estimated completion 2020	NCT03467152
PDD				
SYN120	5-HT_6/5-HT_{2A} receptors antagonist	Phase 2, US	**Completed – primary endpoint for cognition not met[6]**	NCT02258152
IRL752	5-HT_7/cortical alpha receptors antagonist[7]	Phase 2, Sweden/Finland	**Completed – met primary endpoint for safety and tolerability**	2017-001673-17
Ambroxol	Increase β-glucocerebrosidase, reduce α-synuclein	Phase 2, Canada	Recruiting – estimated completion 2018	NCT02914366
LY3154207	D_1 receptor positive allosteric modulator[8]	Phase 2, Global	Recruiting – estimated completion 2019	NCT03305809
ANAVEX2-73	σ1 and M receptors agonist[9]	Phase 2, Spain	Recruiting – estimated completion 2019	NCT03774459
Nilotinib	Tyrosine kinase inhibitor[10]	Phase 2, US	Active, not yet recruiting	NCT02954978
Ceftriaxone	Antibiotic	Phase 2, Taiwan	Active, not yet recruiting	NCT03413384

DLB Consortium

- U01 from NINDS (part of the PDBP)
- Cleveland Clinic is primary site
- Miami, Rush, UNC, UPenn, UPitt, UCSD, Thomas Jefferson, UWashington
- 5-Year Longitudinal Study
- Clinical-cognitive-behavioral evaluations
- MRI
- DAT
- LP
- Autopsy

LBD Research Centers of Excellence

- 24 research centers across the country
  - 17 States and District of Columbia
- Excellence in Clinical Care and Research
- Form Clinical Trials Network
- Mayo Clinic – Rochester is the Coordinating Center
- ***U-Miami,*** Cleveland Clinic, Columbia, Emory,, Georgetown, Mass General, Johns Hopkins, Mayo Clinic-Jacksonville, Ohio State, Oregon, Rush, Stanford, Thomas Jefferson, UC-San Diego, U-Colorado, U-Florida, U-Michigan, UNC-Chapel Hill, U-Penn, U-Rochester, U-Virginia, U-Washington

SUMMARY

- The Lewy body dementias
  - PDD and DLB differ only by timing of movement disorder
  - While clinical criteria lack sensitivity, they are highly specific and correlated strongly with pathology
- For the present time, treatments are largely symptomatic
- We are spearheading novel research
  - Improving clinical practice
  - Improving diagnosis
  - Improving lives of patients and their caregivers
  - Developing new medications