UNIVERSITY OF ALBERTA
FACULTY OF MEDICINE & DENTISTRY
Department of Medicine

CCNA
Canadian Consortium on Neurodegeneration in Aging

CCNV
Consortium canadien en neurodégénérescence associée au vieillissement

Lewy Body Disease in Aging and Dementia

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NEUROSCIENCE AND
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CIHR IRSC
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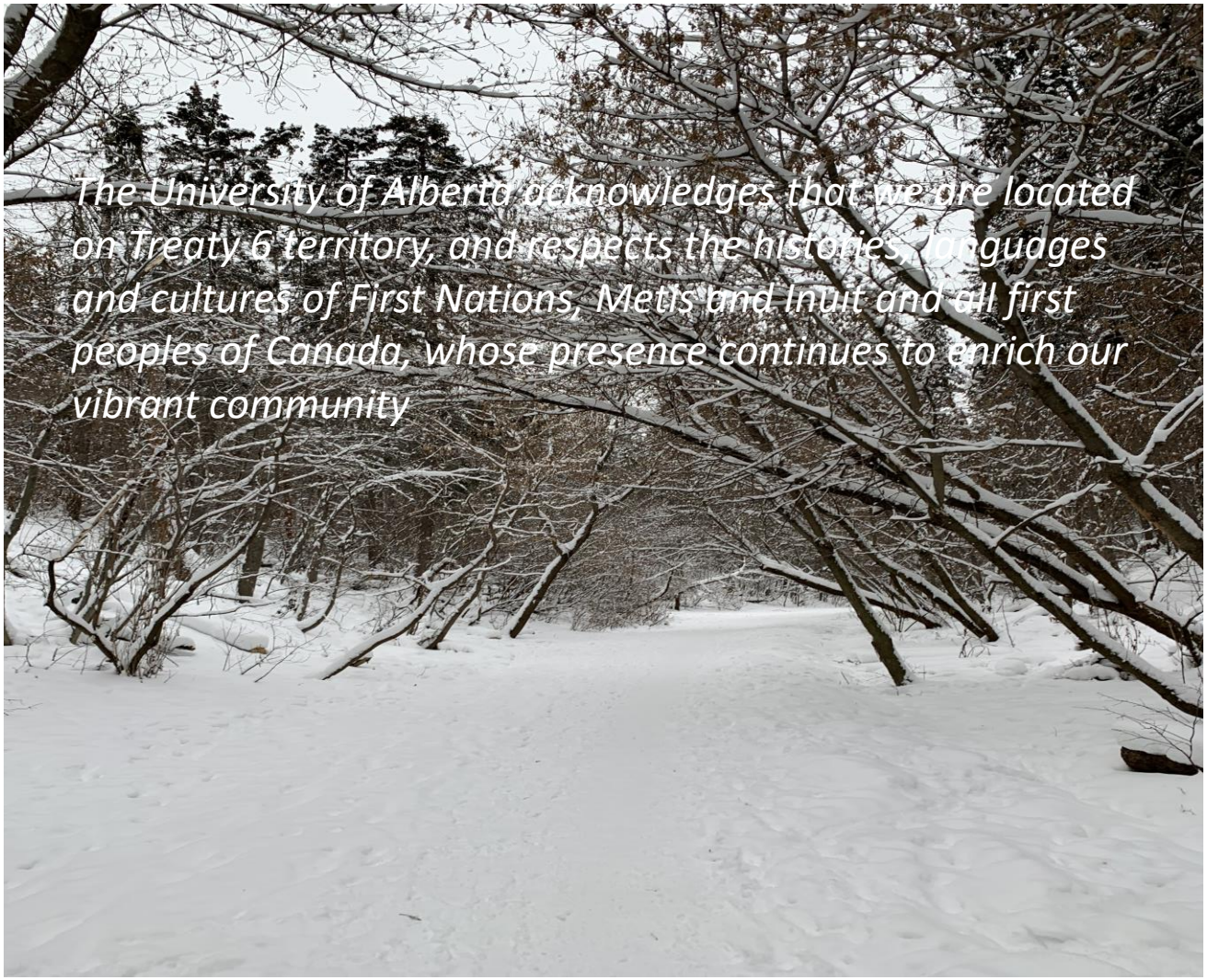
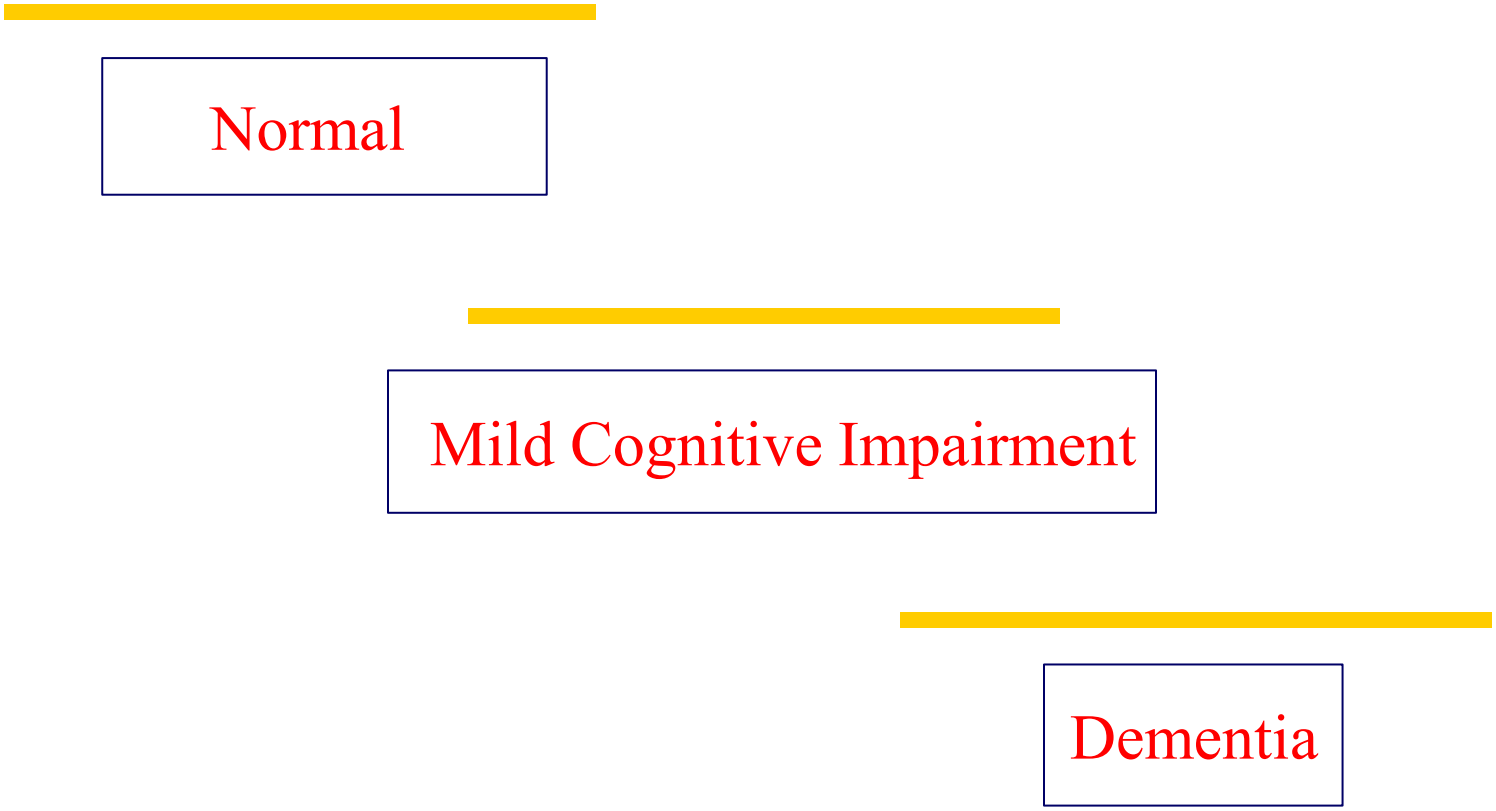
Land Acknowledgement



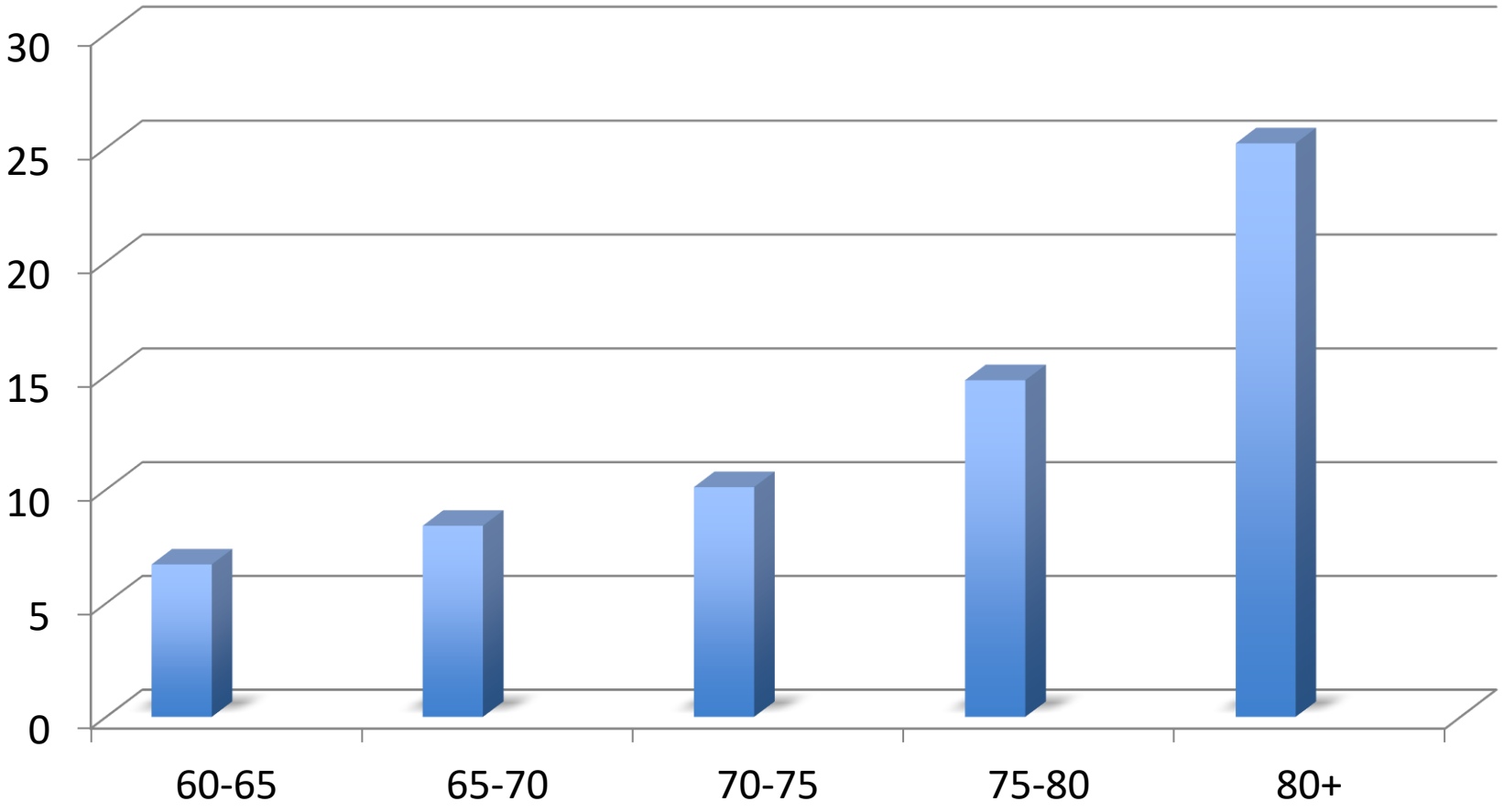
Objectives

- Review the concept of cognitive impairment in aging and Lewy body diseases
- Discuss the cognitive spectrum of Lewy body disorders
- Introduce interventions for motor and non-motor impairment in Lewy body diseases

Aging to Dementia: A Continuum?



Prevalence of MCI



Amnestic/Non-amnestic: Single domain; Multi-domain+/-memory

AAN Guidelines

New LBD Criteria

Table 1 **Revised[1,2] criteria for the clinical diagnosis of probable and possible dementia with Lewy bodies (DLB)**

Essential for a diagnosis of DLB is dementia, defined as a progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational functions, or with usual daily activities. Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression. Deficits on tests of attention, executive function, and visuoperceptual ability may be especially prominent and occur early.

Core clinical features (*The first 3 typically occur early and may persist throughout the course.*)

Fluctuating cognition with pronounced variations in attention and alertness.
Recurrent visual hallucinations that are typically well formed and detailed.
REM sleep behavior disorder, *which may precede cognitive decline.*
One or more spontaneous cardinal features of parkinsonism: these are bradykinesia (defined as slowness of movement and decrement in amplitude or speed), rest tremor, or rigidity.

Supportive clinical features

Severe sensitivity to antipsychotic agents; postural instability; repeated falls; syncope or other transient episodes of unresponsiveness; severe autonomic dysfunction, e.g., constipation, orthostatic hypotension, urinary incontinence; hypersomnia; hyposmia; hallucinations in other modalities; systematized delusions; apathy, anxiety, and depression.

Indicative biomarkers

Reduced dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET.
Abnormal (low uptake) ^{123}iodine-MIBG myocardial scintigraphy.
Polysomnographic confirmation of REM sleep without atonia.

Supportive biomarkers

Relative preservation of medial temporal lobe structures on CT/MRI scan.
Generalized low uptake on SPECT/PET perfusion/metabolism scan with reduced occipital activity ± the cingulate island sign on FDG-PET imaging.
Prominent posterior slow-wave activity on EEG with periodic fluctuations in the pre-alpha/theta range.

Probable DLB can be diagnosed if:

a. Two or more core clinical features of DLB are present, with or without the presence of indicative biomarkers, or

b. Only one core clinical feature is present, but with one or more indicative biomarkers.

McKeith I
Neurology 2017

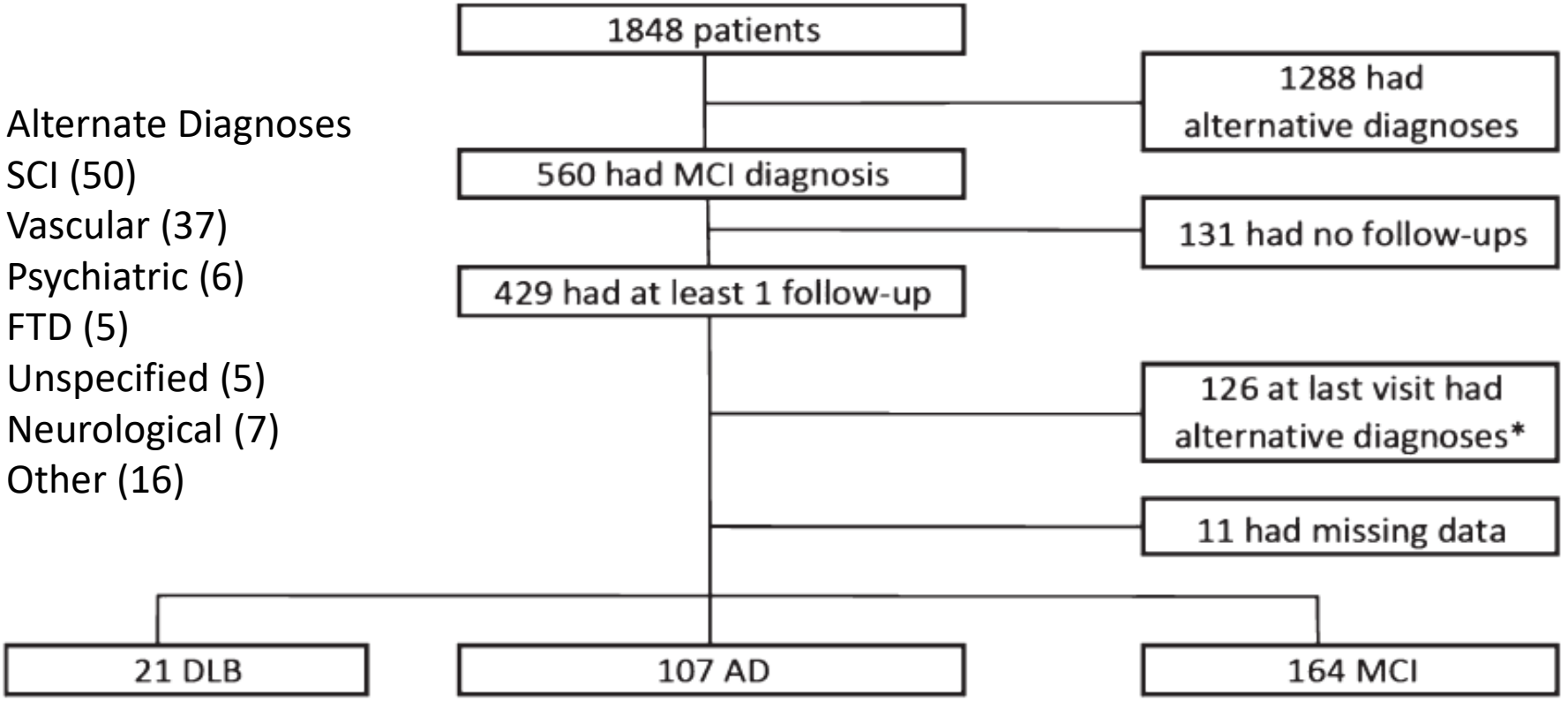
LBCRS Components

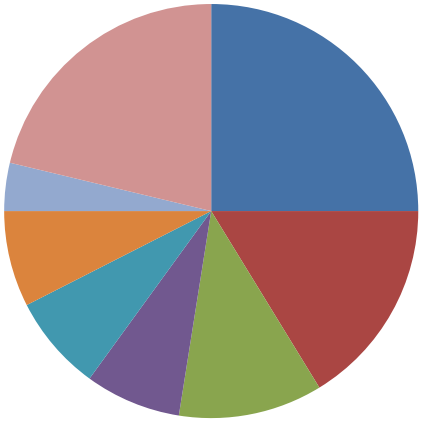
Please rate the following physical findings being present or absent for the past 6 months and symptoms as being present or absent for at least 3 times over the past 6 months.

Does the patient have…	**Yes**	**No**
Slowness in initiating and maintaining movement or frequent hesitations or pauses		
Rigidity (with or without cogwheeling) on passive range of motion in extremities?		
Loss of postural stability (balance) with or without frequent falls?		
Tremor at rest in any of the 4 extremities or head?		
Excessive daytime sleepiness and/or seem drowsy and lethargic when awake?		
Episodes of illogical thinking or incoherent, random thoughts?		
Frequent staring spells or periods of blank looks?		
Visual hallucinations (see things not really there)?		
Acting out of his/her dreams (kick, punch, thrash, shout or scream)?		
Orthostatic hypotension or other signs of autonomic insufficiency?		
Total		

Galvin JE Alzheimer‘s Dementia. 2015;1:316-324.

Alternate Diagnoses
SCI (50)
Vascular (37)
Psychiatric (6)
FTD (5)
Unspecified (5)
Neurological (7)
Other (16)





<UofA Clinic

DLB Predicted by:

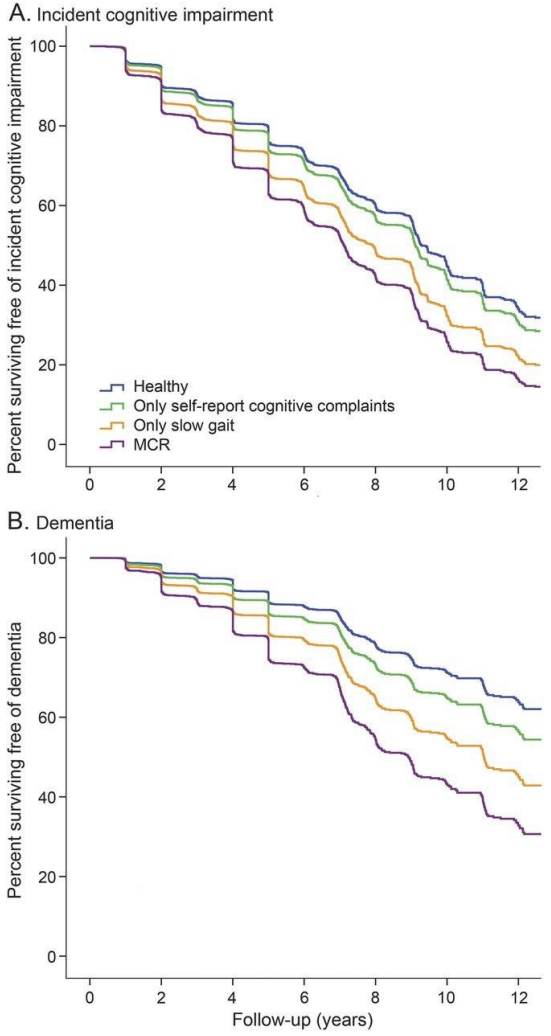
Fluctuations
RBD
Parkinsonism
Impaired: Visuospatial, Letter fluency
Spared: Episodic memory

D Safiq JAD 2017

S Payne JAD 2022

Prodromal Features

- Subjective cognitive impairment
  - Fluctuating cognition
- Mild motor impairment
  - Gait changes
    - Parkinsonism
- Mild behavioral impairment
  - Apathy, anxiety, depression
  - Hallucinations
- Sleep changes
  - REM sleep behavior disorder
- Autonomic changes
  - Urinary and gastrointestinal symptoms
  - Orthostatic blood pressure
- Anosmnia



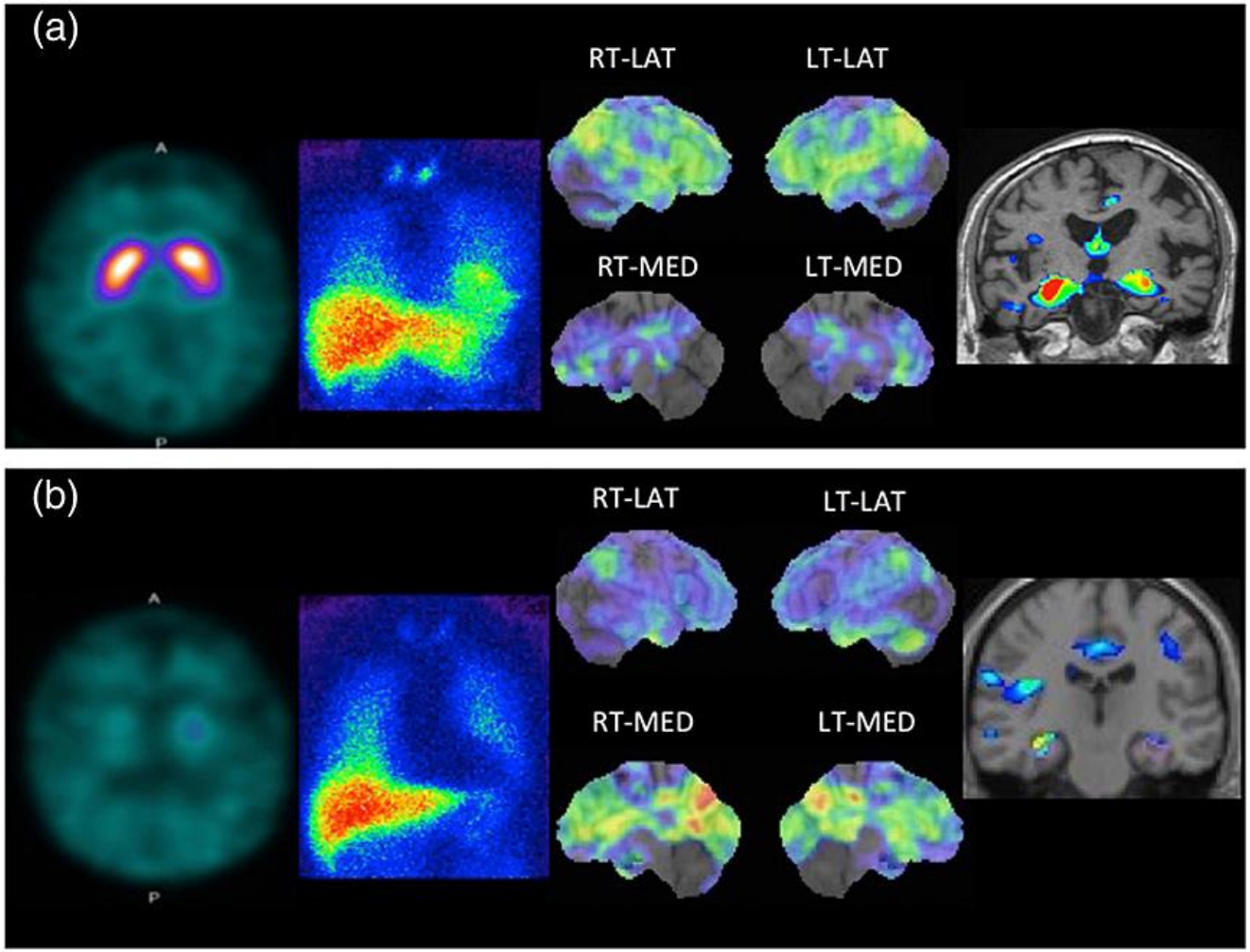
Montero-Odasso M 2020
Verghese J 2014

Prodromal Features

- Subjective cognitive impairment
  - **Fluctuating cognition**
- Mild motor impairment
  - Gait changes
    - **Parkinsonism**
- Mild behavioral impairment
  - **Apathy, anxiety, depression**
  - **Hallucinations**
- Sleep changes
  - **REM sleep behavior disorder**
- Autonomic changes
  - Urinary and gastrointestinal symptoms
  - **Orthostatic blood pressure**
- **Anosmia**

Montero-Odasso M 2020

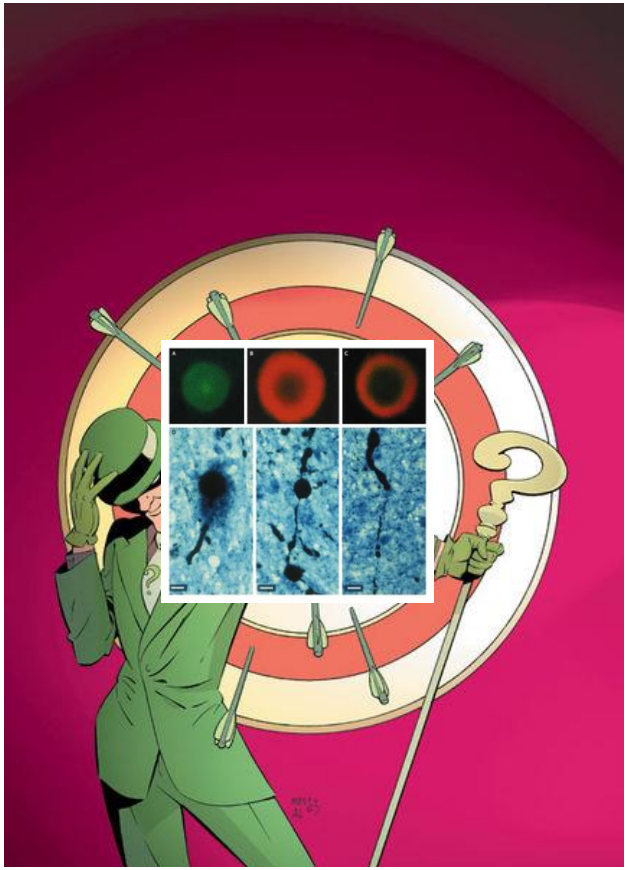
Neuroimaging for diagnosing dementia with Lewy bodies: What is the best neuroimaging technique in discriminating dementia with Lewy bodies from Alzheimer's disease?



Neuroimaging for diagnosing dementia with Lewy bodies: What is the best neuroimaging technique in discriminating dementia with Lewy bodies from Alzheimer's disease?, Volume: 17, Issue: 5, Pages: 819-824, First published: 03 May 2016, DOI: (10.1111/ggi.12794)

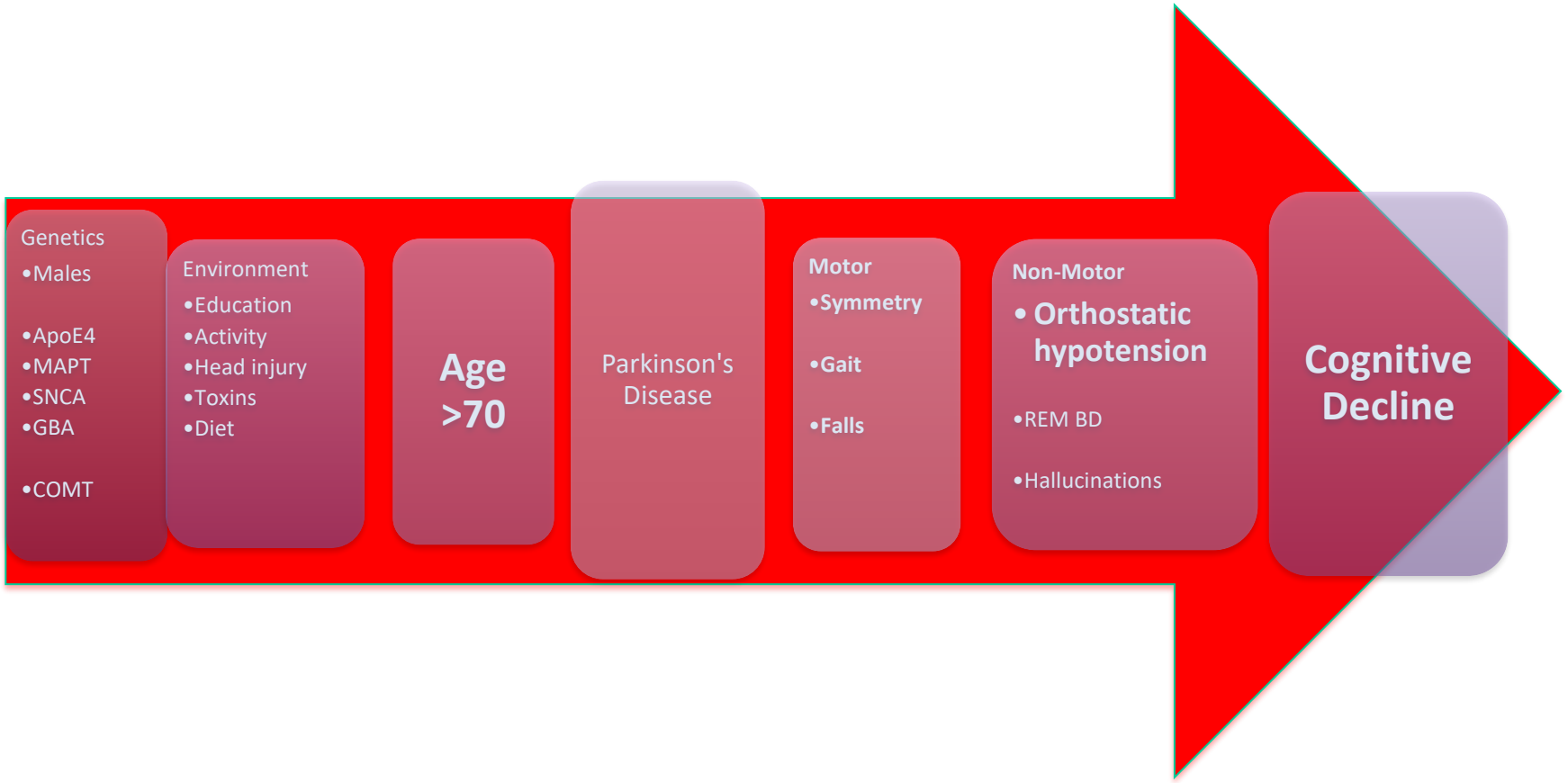
Clinical Features of PD: RIDDLER-NM

- *R*est tremor
- *I*nsidious, asymmetric onset (bradykinesia & rigidity)
- *D*evelopment of *D*yskinesias
- *L*ack of *E*arly atypical f*e*atures
  - *Dementia*
  - *Hypotension*
  - *Eye Movement Problems*
  - *Falls*
  - *Pyramidal signs*
- *R*esponse to levodopa
- *Non-motor*
  - *MCI, Olfaction, Neuropsychiatric (Apathy, Depression, Hallucinations), REM Sleep Behavior Disorder, Autonomic*



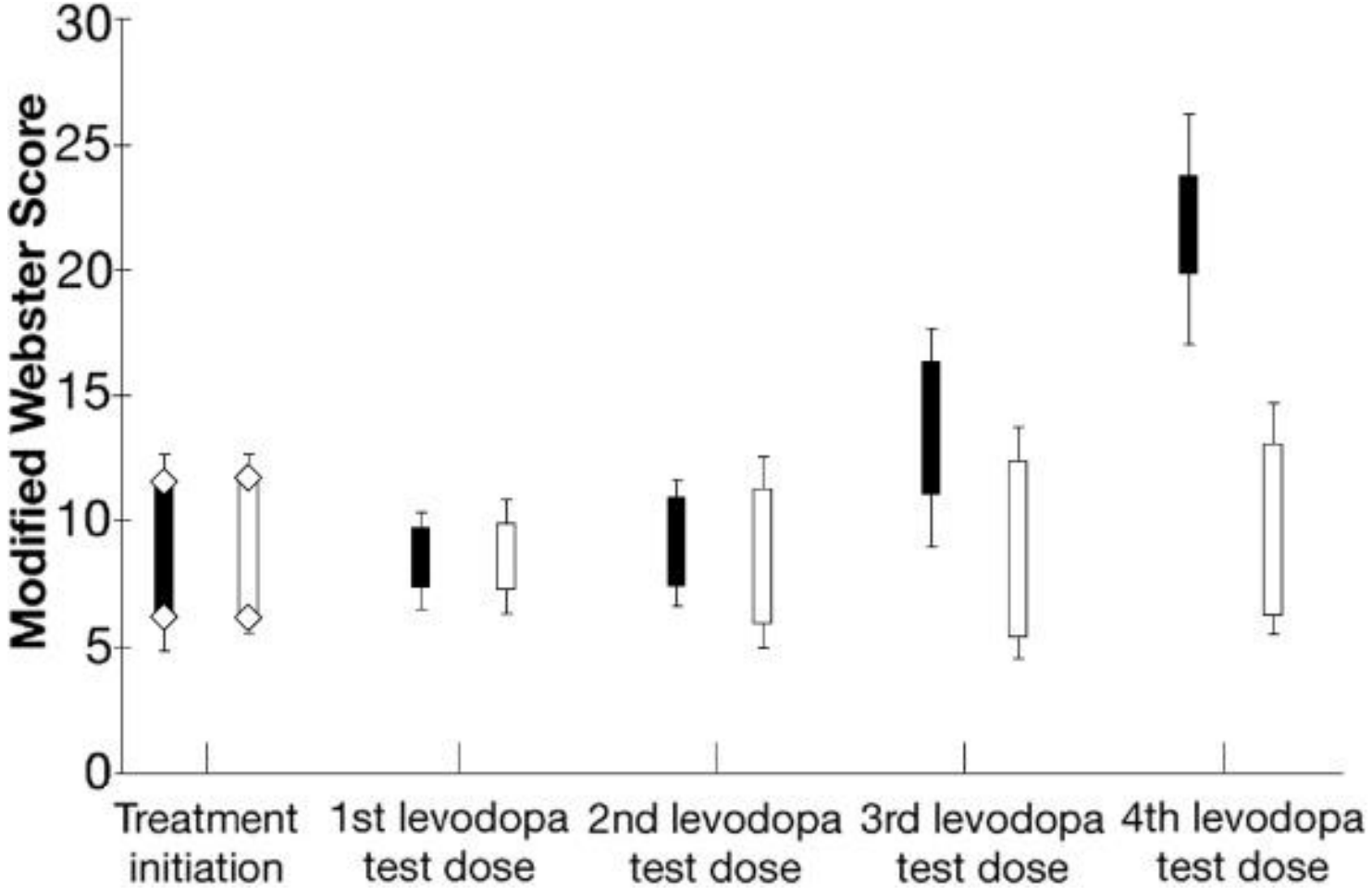
Based on Hughes AJ et al.

Dementia Risk in Parkinson's Disease



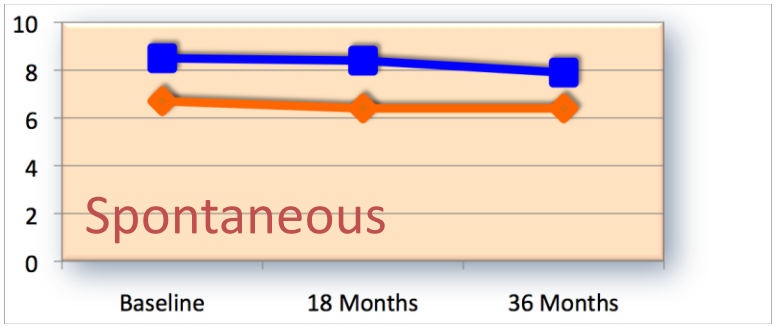
Dawson JAMANeurol 2018
Fagan ES Eur J Neurol 2017
Bohm L Can J Geriatr 2023

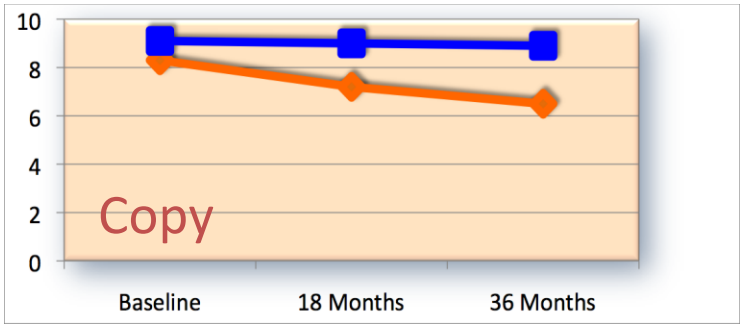
Levodopa Response and in PD and PDD

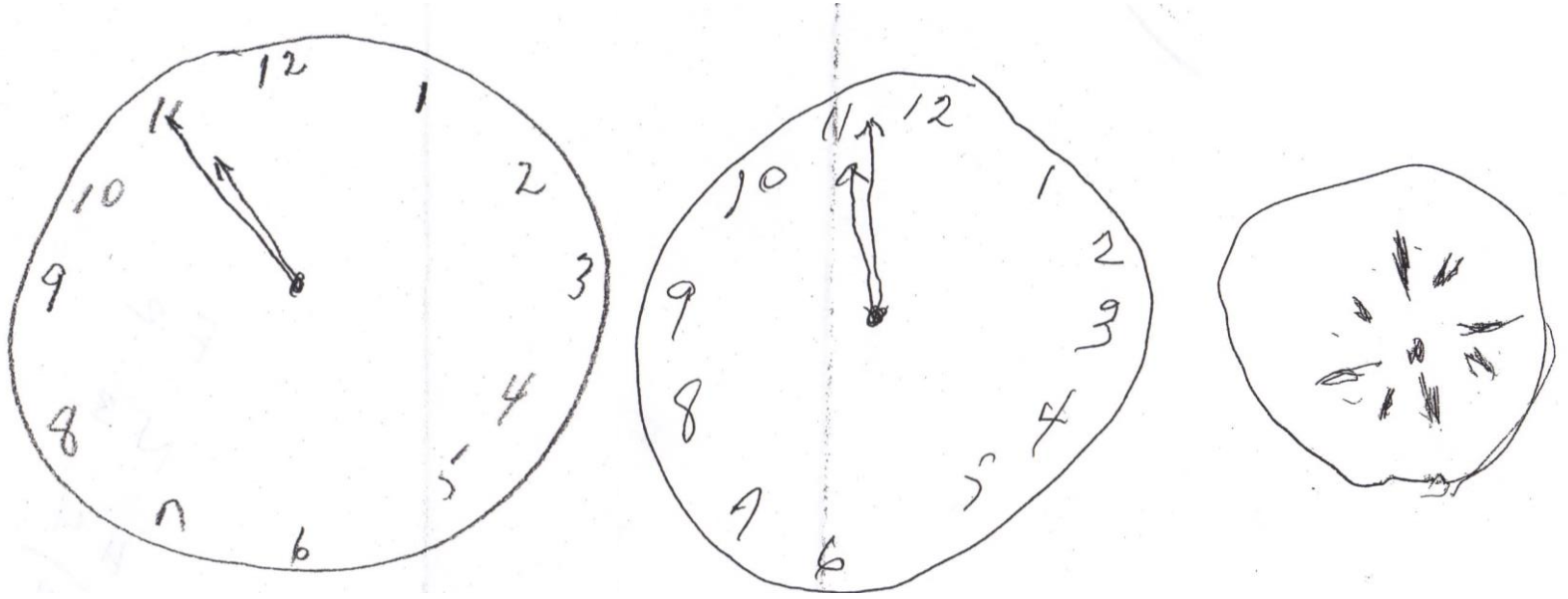


Kempster P 2007

Anterior to Posterior Progression







Muayqil T AAN 2011

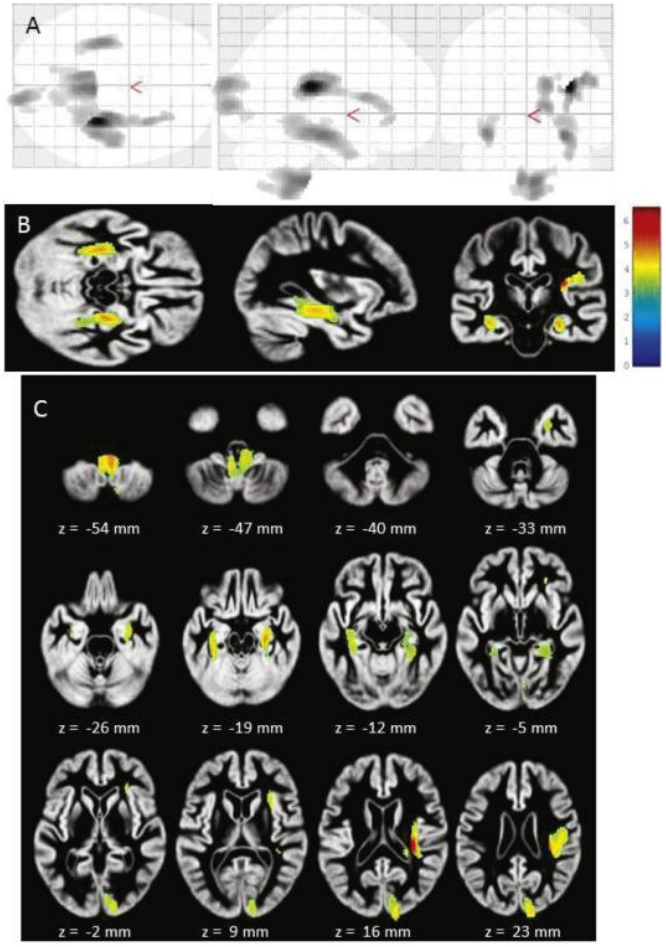
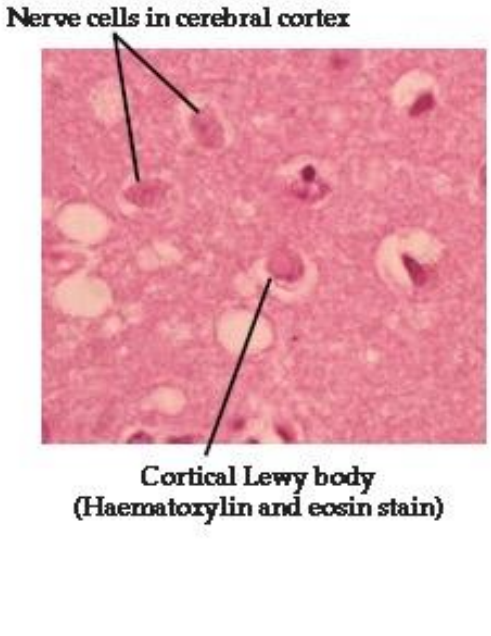
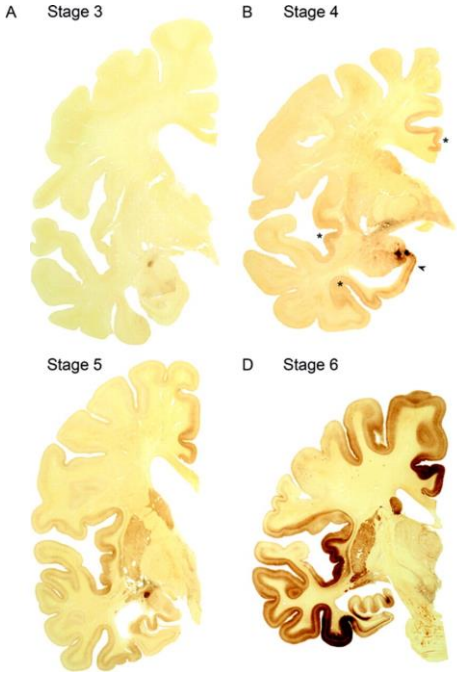


Fig. 4. Significant clusters of accelerated atrophy (cluster threshold at FWE p-corrected < 0.05) in PDD compared to PDND. The glass brain depiction is shown in (a). The clusters are overlaid on the mean GM volume in (b), with orthogonal views.





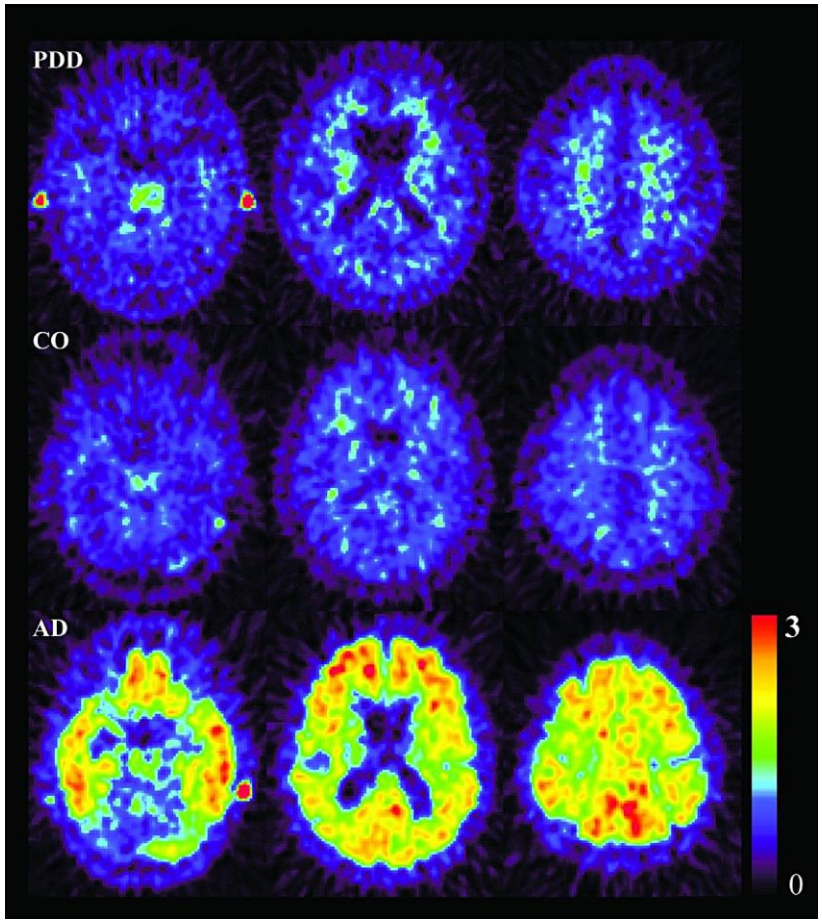
Myrlene Gee, Juergen Dukart, Bogdan Draganski, WR Wayne Martin, Derek Emery, Richard Camicioli

Regional volumetric change in Parkinson's disease with cognitive decline

Journal of the Neurological Sciences, Volume 373, 2017, 88–94

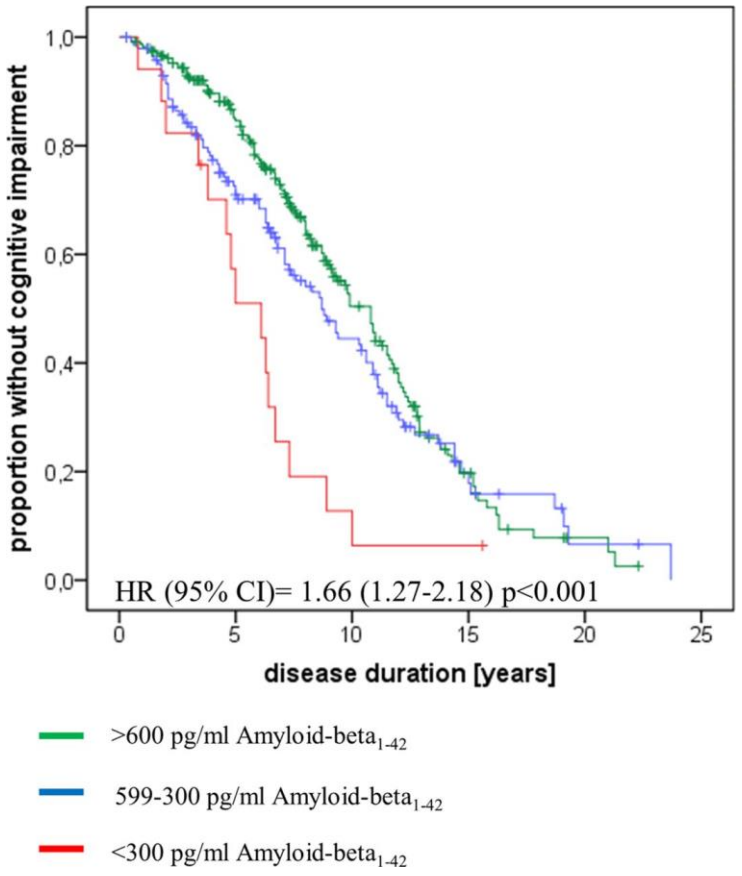
http://dx.doi.org/10.1016/j.jns.2016.12.030

Braak H Neurology 2008



Maetzler W 2008

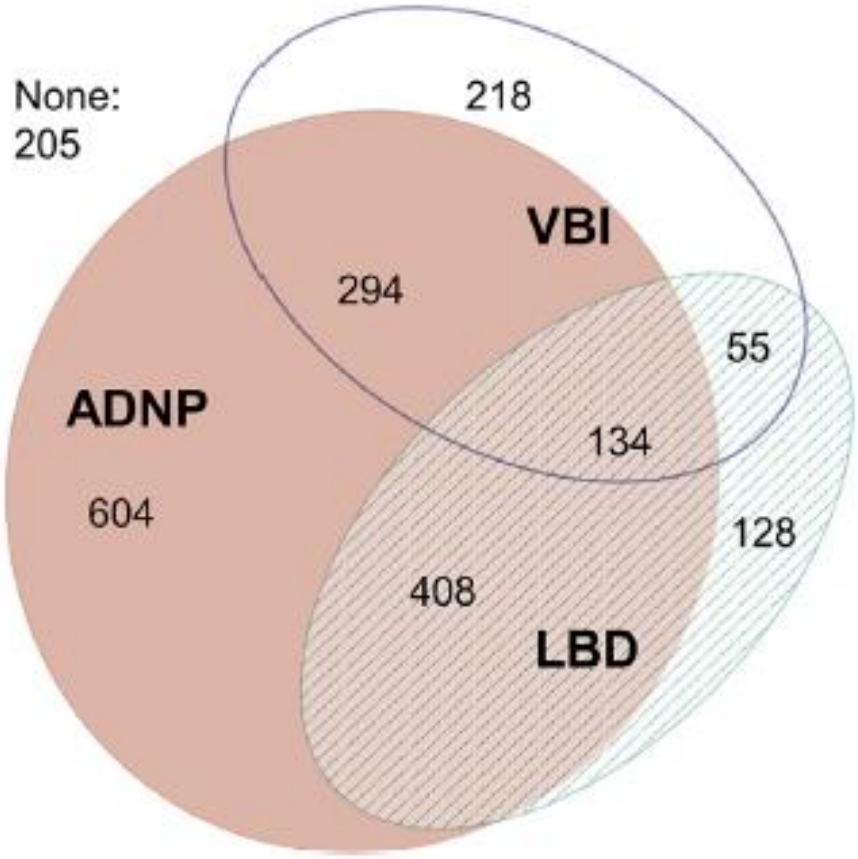
Association between baseline cerebrospinal fluid (CSF) Aβ subgroups (low vs intermediate vs high) and the risk of developing cognitive impairment.

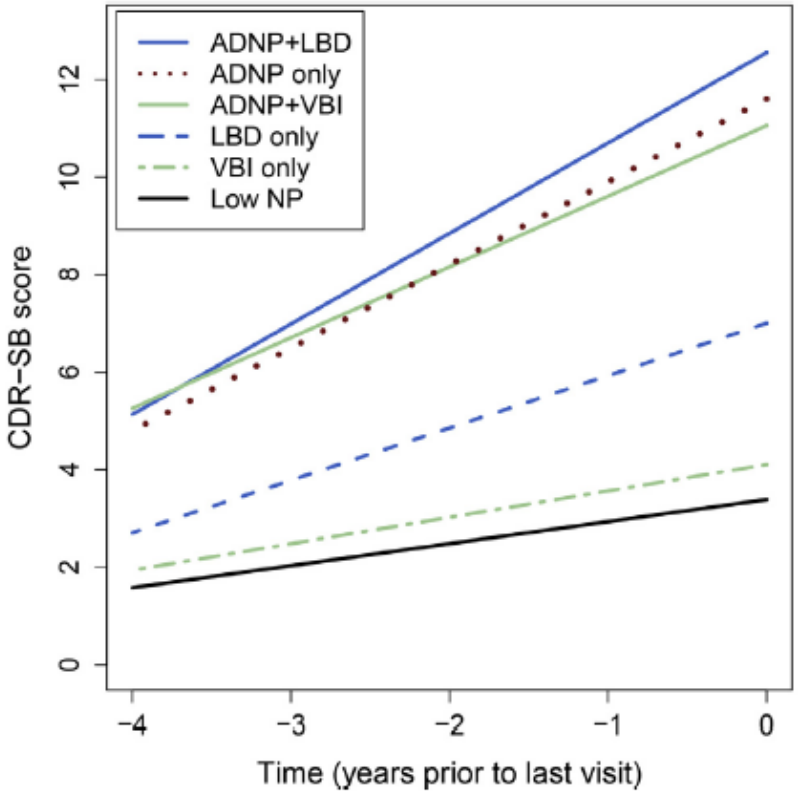


Stefanie Lerche et al. J Neurol Neurosurg Psychiatry 2019;90:165-170

JNNP

Mixed Pathology Contributes to Clinical Course

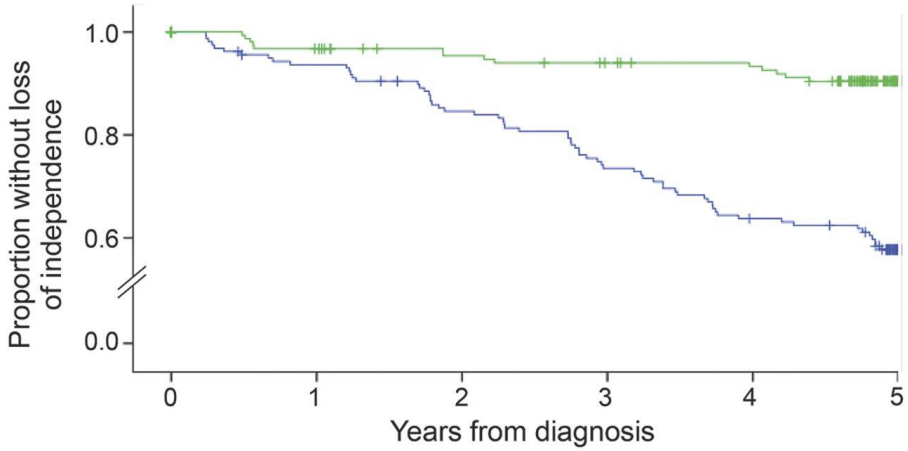




Brenowitz WD 2017
Cf. James BD 2020

Why Identify Cognitive Impairment

- Prognosis
  - Risk for future functional decline, falls and mortality
- Management
  - Co-morbid diseases
    - Medication monitoring
      - Medication selection
  - Health and wellness
  - Behavioral problems
  - Safety
- Planning
  - Personal directives and advance directives
- Treatment
  - Emphasize cognitive and social engagement, nutrition and exercise

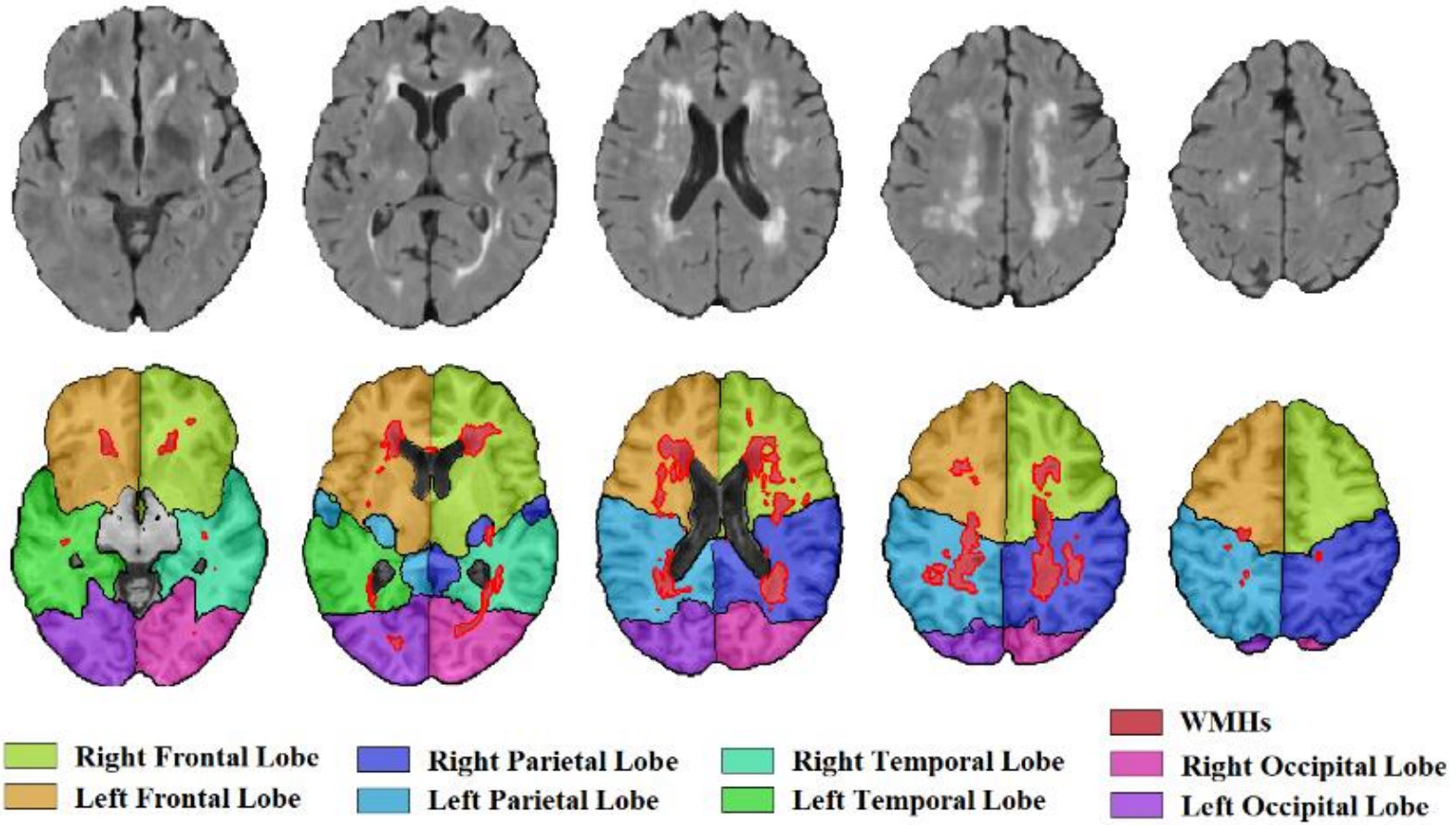


Bjornestad A 2016

Investigations in Dementia: Test in MCI

- Brain Imaging
- Blood Tests: Systemic/Metabolic
  - CBC (ESR optional)
  - Electrolytes, Glucose, LFTs, Renal Fcn
  - TSH
  - B12/Folate
- Other Tests: Infectious/Neoplastic
  - CXR
  - UA
  - CSF (A-beta, tau, RTQuIC)
  - HIV, FTA-ABS in selected patients

White Matter Changes in Aging and Dementia

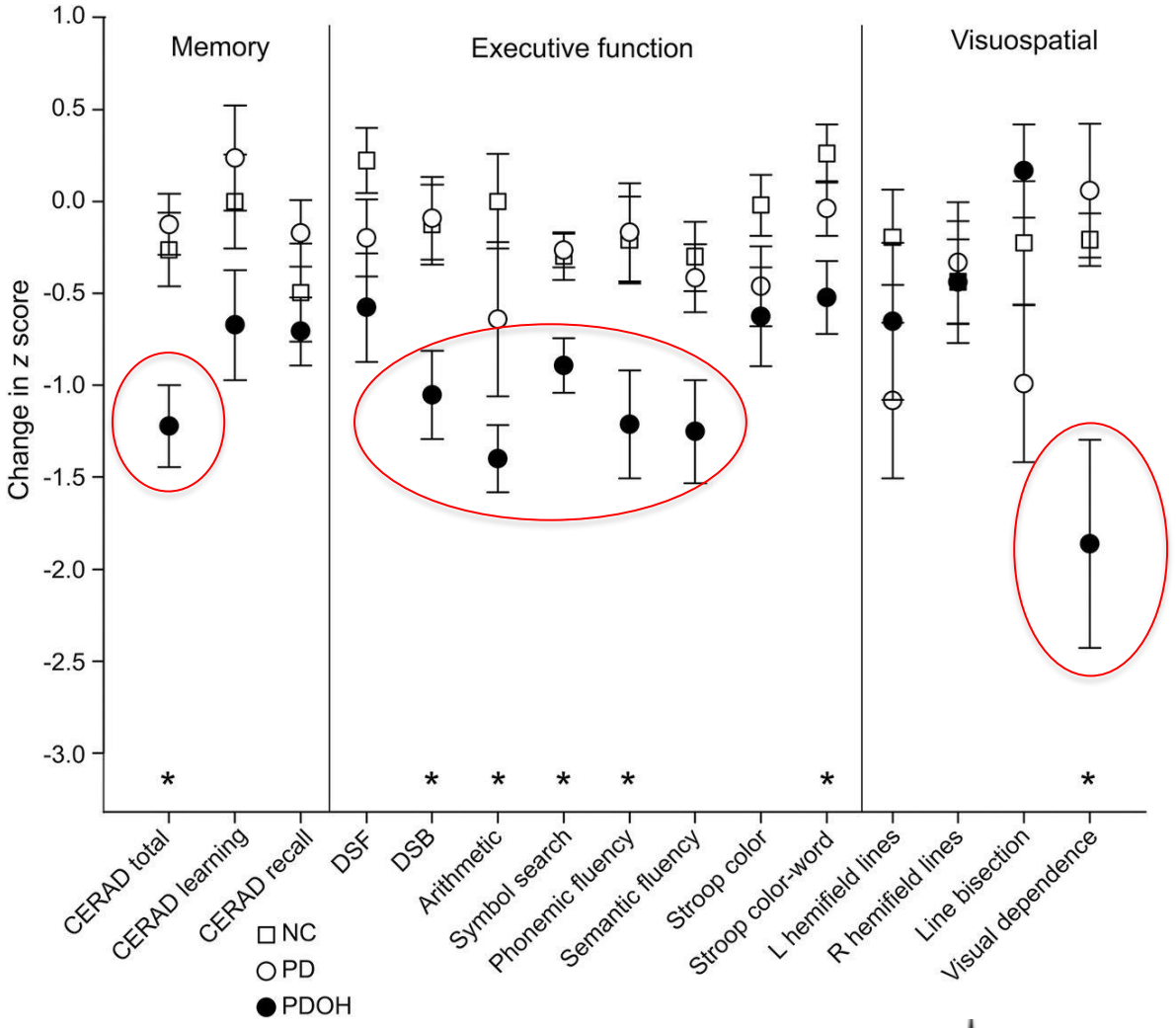


Dadar M 2020

Vascular Contribution to Dementia

- Not all progression is related to degeneration
- Vascular risk may be important
- Increased changes in Lewy body patients (PD, PDD, and DLB) associated with both cognitive neuropsychiatric and motor aspects
- Potentially preventable or treatable….carefully

Figure Cognitive performance reflected as group-specific (normal control [NC], Parkinson disease [PD], Parkinson disease with orthostatic hypotension [PDOH]) change from baseline following tilt



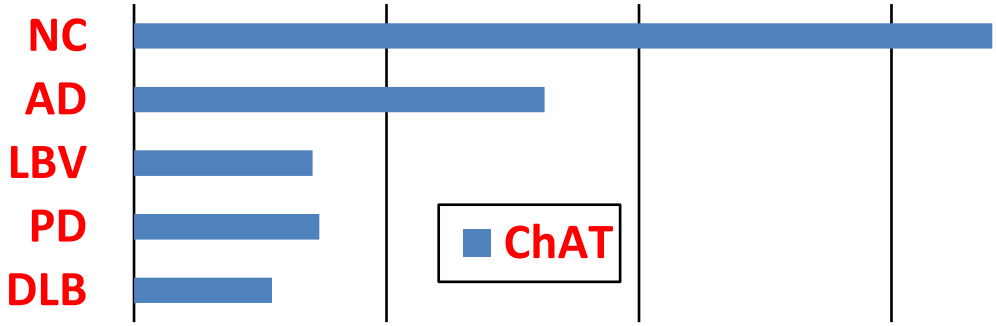
Justin Centi et al. Neurology 2017;88:17-24

Management of Cognitive Impairment

- Care for the caregiver
  - Supportive services
  - Resbite
- Safety
  - Driving/Weapons/Tools
- Treat depression, even with coexistent cognitive impairment
- Increase monitoring for medical illnesses
- Behavior problems are common
  - Varies with disease progression or stage
  - Possible effect of treatment or coexistent medications

Medications in LBD

- Simplify medications
  - Levodopa for parkinsonism
- Cholinesterase inhibitors
  - Donepezil
  - Rivastigmine
- Memantine
- REM Sleep behavior
  - Melatonin
    - Clonazepam
- Pimavanserine for hallucinations
  - Seroquel and clozapine don't worsen parkinsonism
- Options for agitation and behaviour problems (borrowed from AD)
  - Trazodone, antidepressants



Taylor JB Lancet Neurology 2019
Tiraboschi P 2002

Decision Making

Parkinsonism and Related Disorders 39 (2017) 77–79

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Editor's Comment: The desired nature and intensity of life-sustaining medical care is ideally determined by a patient at a time when intact cognitive capability allows the most fully informed decisions. As Parkinson's disease (PD) is commonly associated with various forms and degrees of cognitive dysfunction, the question arises as to which PD patients have that decisional capacity. In this article, Drs Snineh, Camicioli, and Miyasaki show that PD patients without overt dementia, may still have measureable impairment of decisional capacity, but nevertheless express choices in regard to these complex health care decisions. Based on these findings, the authors advocate discussion of these delicate and important end-of-life issues with PD patients early in the course of their illness while analytic capacity is less likely to be impaired and decisions regarding goals of care may more accurately reflect their true personal preferences.

Robert L. Rodnitzky, Associate Editor, Department of Neurology University of Iowa Hospital, 200 Hawkins Drive, Iowa City, IA, USA.

Short communication

Decisional capacity for advanced care directives in Parkinson's disease with cognitive concerns☆

Muneer Abu Snineh, MD, Richard Camicioli, MSc, MDCM,
Janis M. Miyasaki, MD, MEd, FAAN *

Division of Neurology, Department of Medicine, University of Alberta, Kaye Edmonton Clinic, Canada

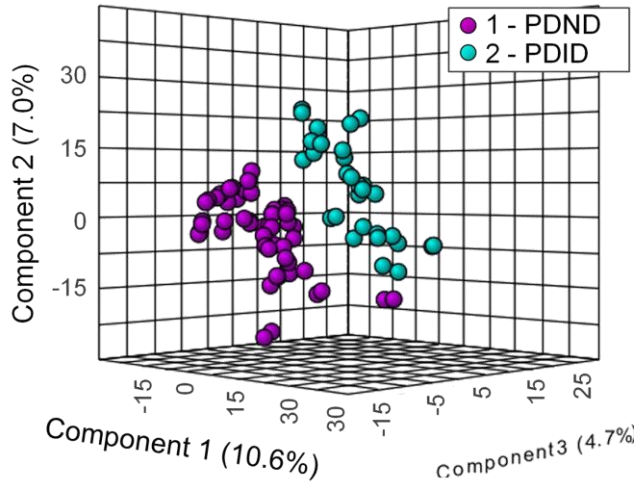
50 PD patients with SCI or MCI: Scenarios: ICU, Rx, Comfort Care

Total MoCa correlated with competency (MaCAT) r=0.55, p=0.001

Expressing a choice was not correlated!

Dietary Factors

- Malnutrition (15% prevalence; 24% at-risk) and weight loss common
  - Dysphagia is common (Hoehn and Yahr III or more)
    - Risk factor for pneumonia and mortality
  - GI problems, especially nausea and constipation
    - Disease related
    - Drug related
  - Energy expenditure
    - Related to levodopa/body weight ratio
  - Cognitive and neuropsychiatric problems
- Vitamins generally inconclusive, except
  - Vitamin D
  - B-vitamins (Vitamin B12/Folic acid)
    - Homocysteine/methylmalonic acid
- MIND diet – Mediterranean-DASH Intervention for Neurodegenerative may delay cognitive decline and may show benefit in non-PD



Lipidomics predictive
Buzatto AZ, Li L, 2021

ESPEN Guidelines 2018
Goldman JG 2018

Physical Activity

- Various types
  - Resistance, aerobic, walking, dance, Tai Chi
    - Duration, intensity, maintenance, combination
      - Control is an issue in studies
- Cognitive benefits shown with
  - Tango, cycling, treadmill training, multimodal therapy, combined resistance and aerobic training, resistance, aerobic
    - Few studies target PD-MCI/PDD/DLB
    - Combination with cognitive training?

Amara AW 2018; Ahlskog EH 2018

Conclusions

- Lewy body related disorders (LBRD) are common
- Cognitive impairment is common and has implications for prognosis and managment
- Pharmacological approaches need further study but some treatments are available
- Non-pharmacologic approaches need further study, but may be implemented

Acknowledgements and Disclosures

- Funding: CIHR, NIH, Brain Canada, Parkinson Alberta, University Hospital Foundation, Alberta Innovates Solutions
- Advisory: MJFF; Weston Foundation; Parkinson Disease Foundation
- Thanks to the Movement Disorders and the Geriatric and Cognitive Neurology clinic staff and people with lived experience
- Thanks to my research team and collaborators