

Diagnostic process in Lewy body disease: *the role of assessment tools and biomarkers*

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Stanford
MEDICINE



400,000 men and women across the US were involved in the Apollo programme.



support of over **20,000** industrial firms and universities.

We are working to END dementia



Outline

A

Lewy body disease **definition**

B

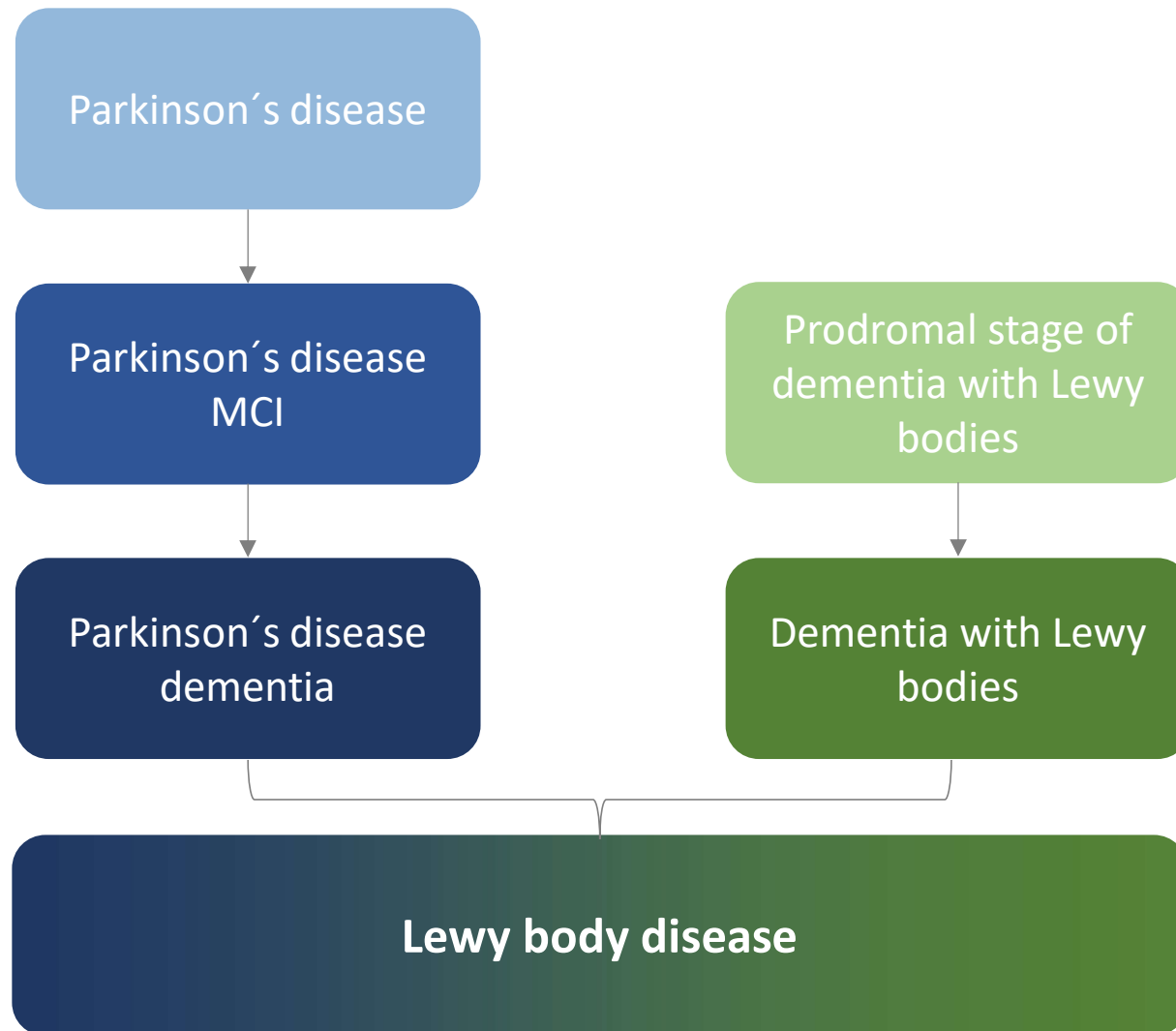
Current diagnostic tools
and biomarkers

C

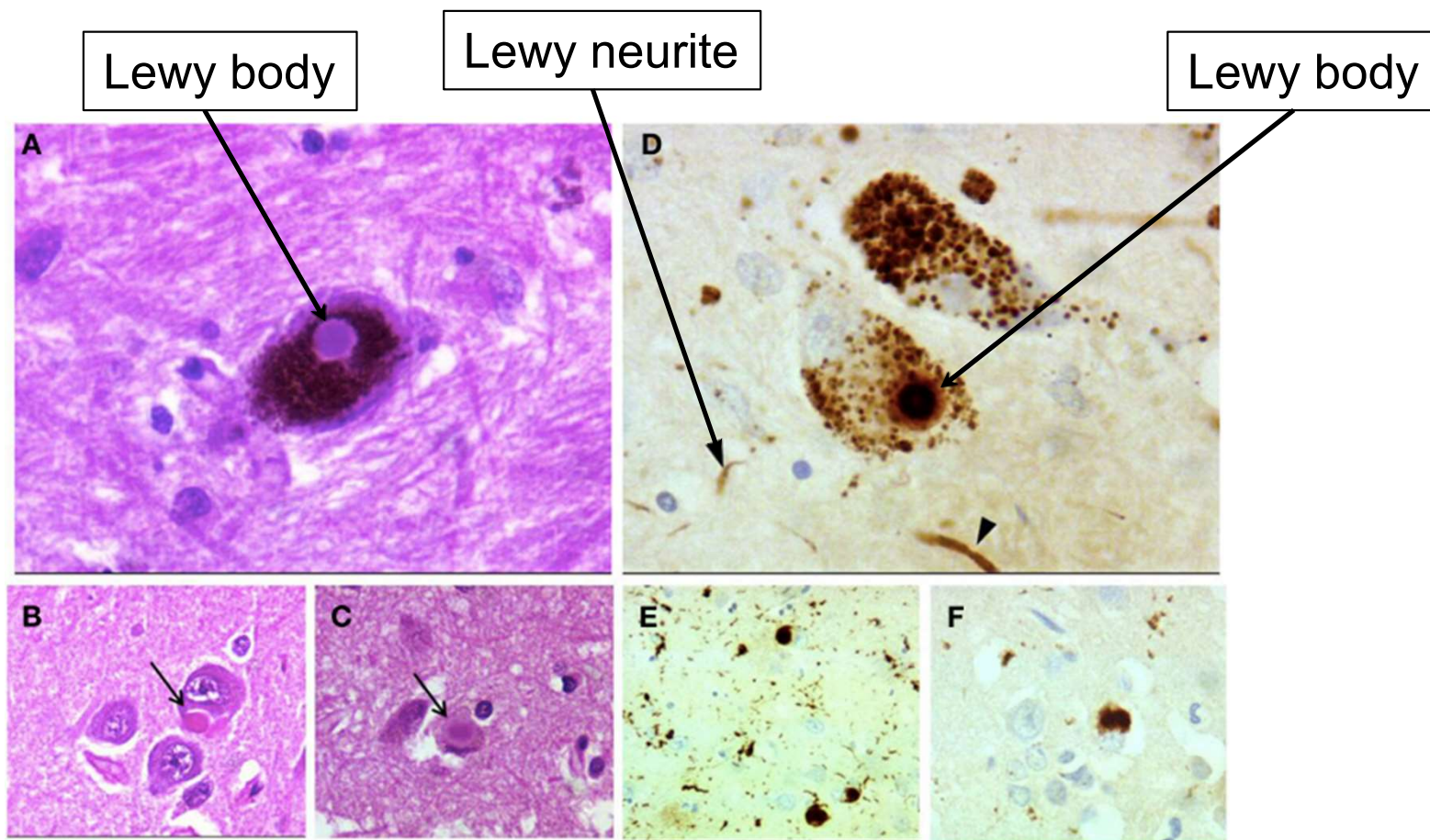
Future diagnostic tools
in LBD

Lewy body disease definition

Continuum



Deposits of α -synuclein



A) Lewy body in a neuron of the substantia nigra, B) in a pyramidal cell of CA1 area of the hippocampus, and C) in cingulate cortex (C) (arrows). Lewy body (arrow) and Lewy neurites (arrowheads) in the substantia nigra (D). Cortical Lewy bodies (E,F). (A-C) hematoxylin-eosin; (D-F) anti- α -synuclein immunostaining.

Taipa R et al. *Front Neurol.* 2019

Dementia with Lewy bodies

Parkinson's disease dementia

| Fourth consensus criteria for probable and possible dementia with Lewy bodies | | |
|---|--|---|
| Essential | Dementia | |
| | Clinical features | Biomarkers |
| Core | Recurrent visual hallucinations Fluctuating cognition REM sleep behavior disorder One or more spontaneous cardinal features of parkinsonism: bradykinesia, rest tremor or rigidity | Decreased dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET Decreased uptake ¹²³ Iodine-MIBG myocardial scintigraphy Polysomnography confirmation of REM sleep behavior disorder |
| Supportive | Severe sensitivity to antipsychotic agents Postural instability Syncope or other transient episodes of unresponsiveness Systematized delusions Hallucinations in other modalities Repeated falls Severe autonomic dysfunction Hypersomnia Apathy, anxiety and depression Hyposmia | Relative preservation of medial temporal lobe structures on CT/MRI Generalized low uptake on SPECT/PET perfusion/metabolism scan with reduced occipital activity +/- the cingulate island sign on FDG-PET Prominent posterior slow-wave activity on EEG with periodic fluctuations in the pre-alpha/theta range |

McKeith I et al. *Neurology*. 2017

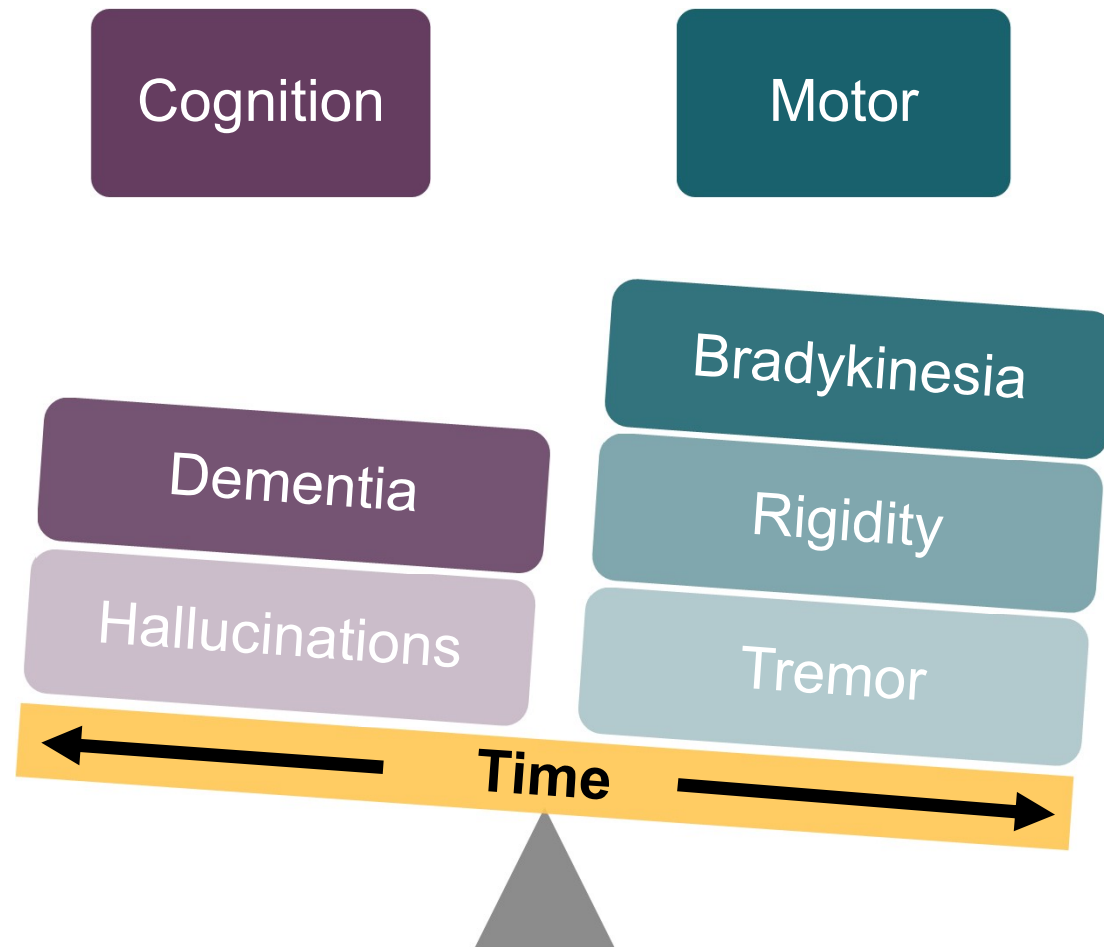
| Criteria for diagnosis of probable and possible PD-D | |
|--|--|
| Probable PD-D | |
| I. | Core features: both must be present <ul style="list-style-type: none"> • Diagnosis of Parkinson's disease according to Queen Square Brain Bank criteria. • A dementia syndrome with insidious onset and slow progression, developing within the context of established Parkinson's disease and diagnosed by history, clinical, and mental examination. |
| II. | Associated clinical features: <ul style="list-style-type: none"> • Typical profile of cognitive deficits including impairment in at least two of the four core cognitive domains (impaired attention which may fluctuate, impaired executive functions, impairment in visuo-spatial functions, and impaired free recall memory which usually improves with cueing) • The presence of at least one behavioral symptom (apathy, depressed or anxious mood, hallucinations, delusions, excessive daytime sleepiness) supports the diagnosis of Probable PD-D, lack of behavioral symptoms, however, does not exclude the diagnosis. |
| III. | Features which do not exclude PD-D, but make the diagnosis uncertain: <ul style="list-style-type: none"> • Co-existence of any other abnormality which may by itself cause cognitive impairment, but judged not to be the cause of dementia, e.g. presence of relevant vascular disease in imaging. • Time interval between the development of motor and cognitive symptoms not known. |
| IV. | Features suggesting other conditions or diseases as cause of mental impairment, which, when present make it impossible to reliably diagnose PD-D. |
| Possible PD-D | |
| I. | Core features: both must be present |
| II. | Associated clinical features: <ul style="list-style-type: none"> • Atypical profile of cognitive impairment in one or more domains, such as prominent or receptive-type (fluent) aphasia, or pure storage-failure type amnesia (memory does not improve with cueing or in recognition tasks) with preserved attention. • Behavioral symptoms may or may not be present. |
| OR | |
| I. | One or more of the group III features present. |
| II. | None of the group IV features present. |

Emre M et al. *Mov Disord*. 2007

Dementia occurs before or concurrently with parkinsonism

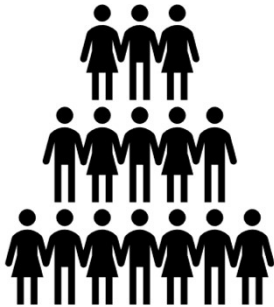
Dementia occurs in the context of well-established Parkinson's disease

What is the difference between Parkinson's disease dementia and Dementia with Lewy bodies?



Current diagnostic tools and biomarkers in LBD

Why is important to diagnose LBD?



Second most common cause of neurodegenerative dementia after Alzheimer 's disease.

Heidenbrink JL et al. *J Geriatr Psychiatry Neurol.* 2002
Aarsland D et al. *Dement Geriatr Cogn Disord.* 2008



Underdiagnosed disease

Prevalence:
4.2-4.6% community
7.5% secondary care
20% neuropathological diagnosis

Vann Jones S et al. *Psychol Med.* 2014
Outeiro TF et al. *Mol Neurodegener.* 2019

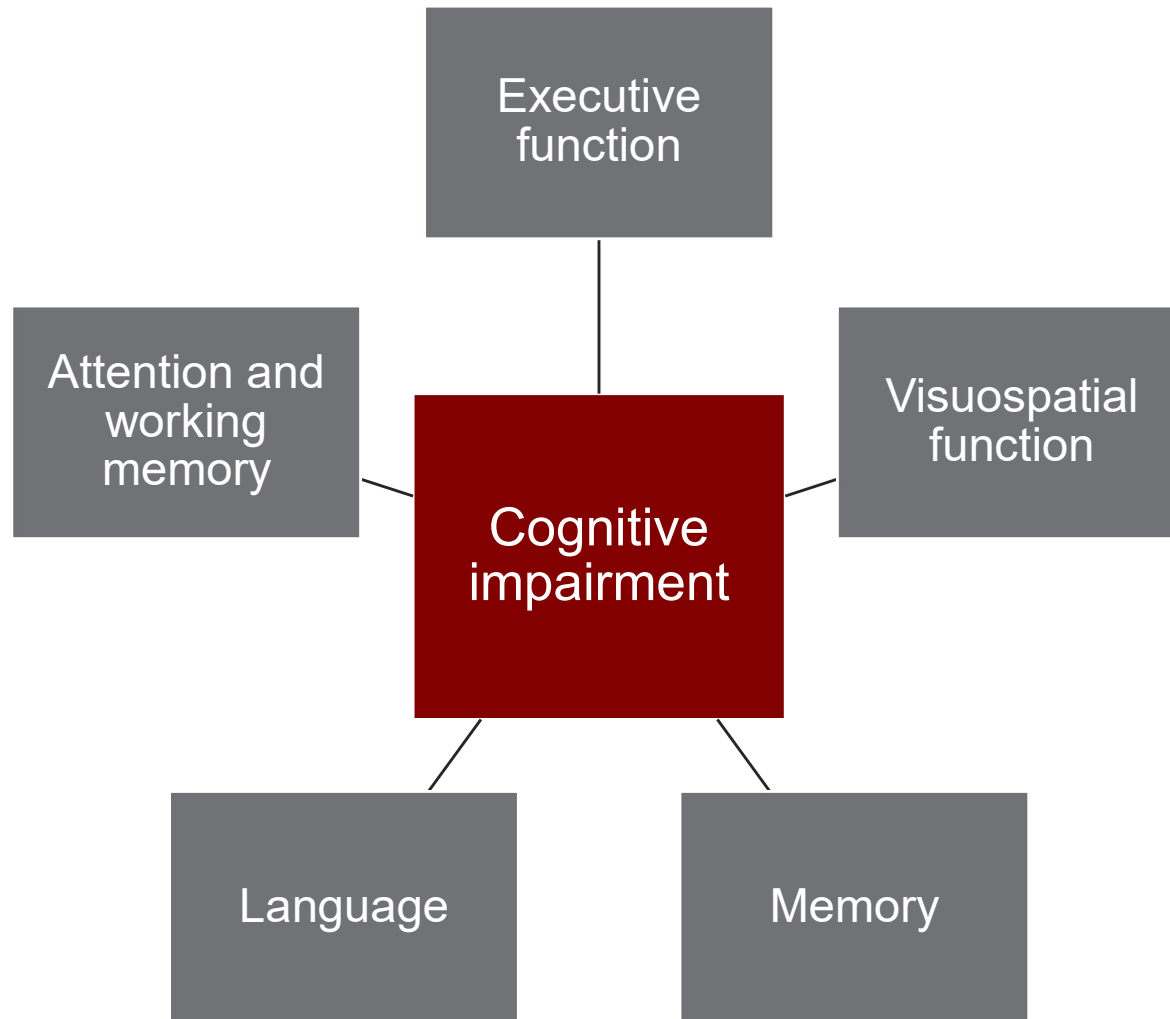


Worse health indicators

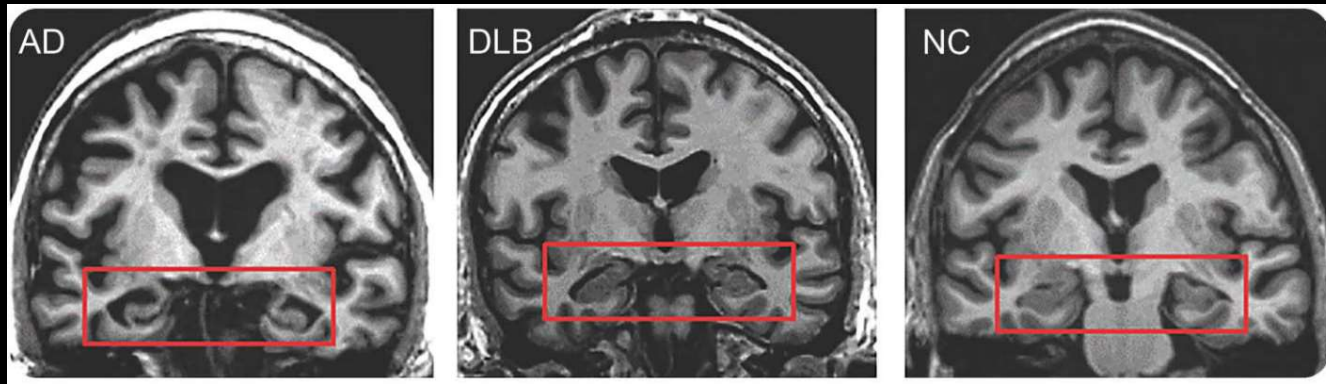
↑ Mortality
↑ Functional impairment
↑ Impact in quality of life
↑ Healthcare costs
Earlier nursing home admission
↑ Rates of hospitalization

García-Ptacek S et al. *J Alzheimers Dis.* 2014
Mueller C et al. *Lancet Neurol.* 2017
Rongve A et al. *Int J Geriatric Psychiatry.* 2014

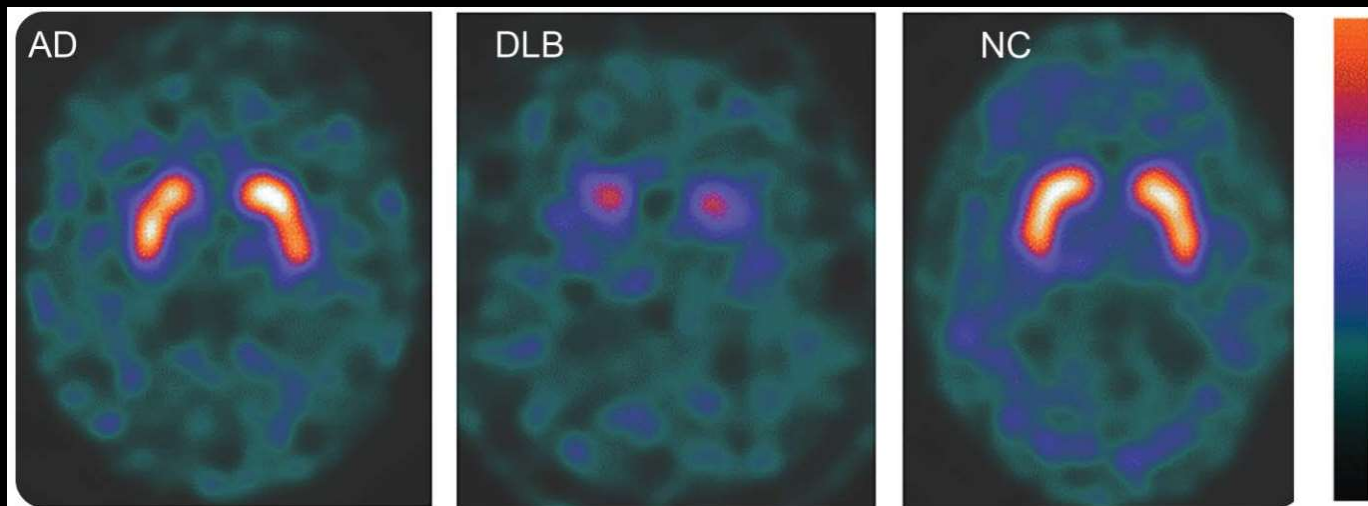
Profile of cognitive impairment in Lewy body disease



Current biomarkers in Lewy body disease

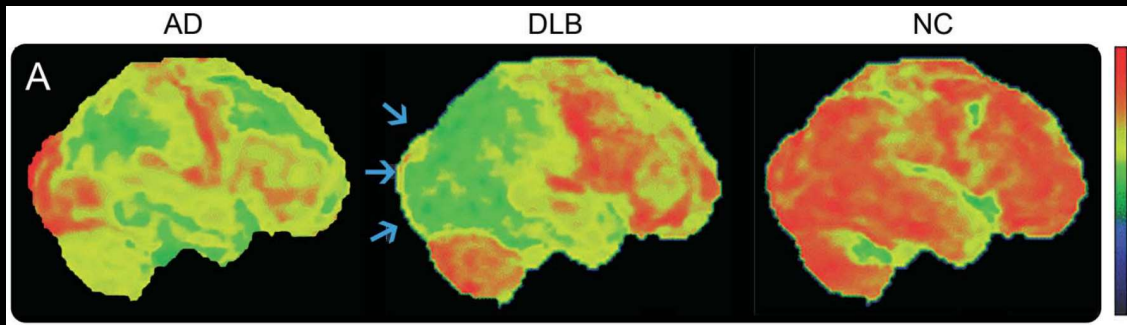


Relative preservation of medial temporal lobe on **CT/MRI**

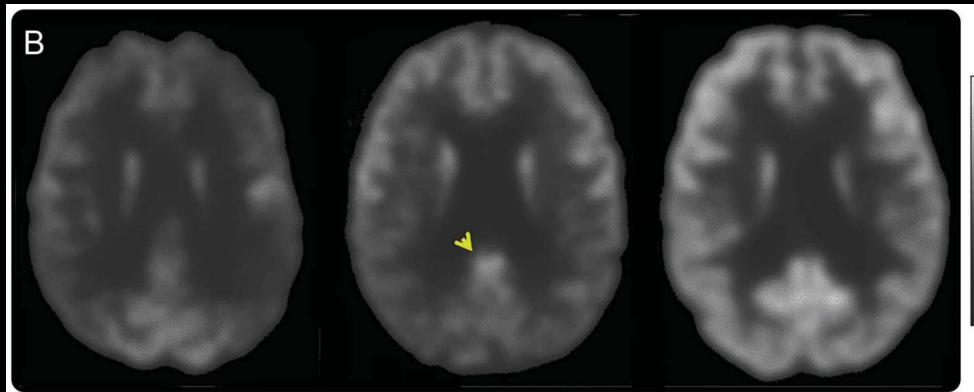


Reduced dopamine transporter uptake in basal ganglia demonstrated by **SPECT** or **PET**

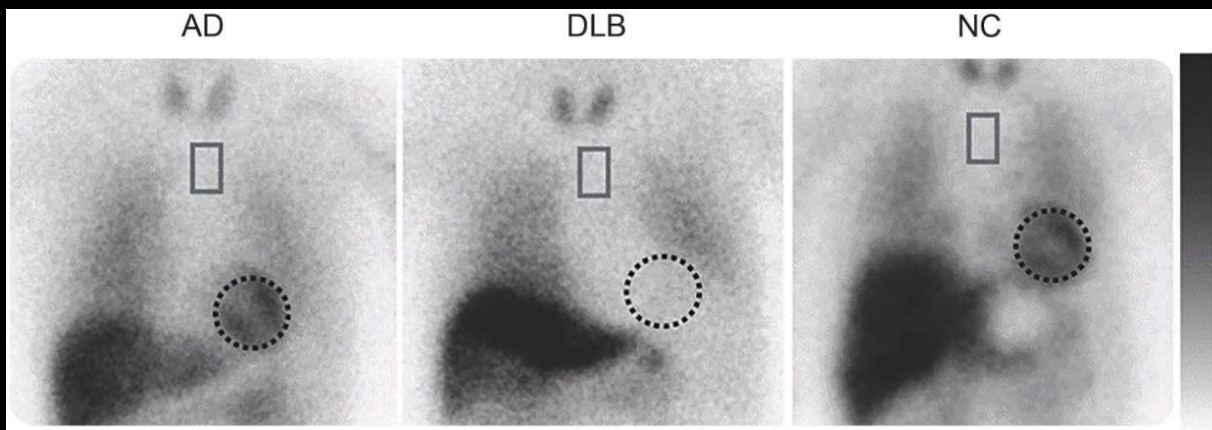
Current biomarkers in Lewy body disease



Generalized low uptake on SPECT/PET perfusion/metabolism scan, reduced occipital activity



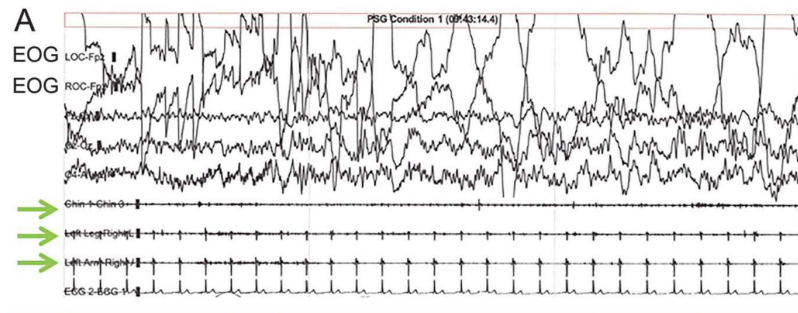
The posterior **cingulate island sign** on **FDG-PET** imaging



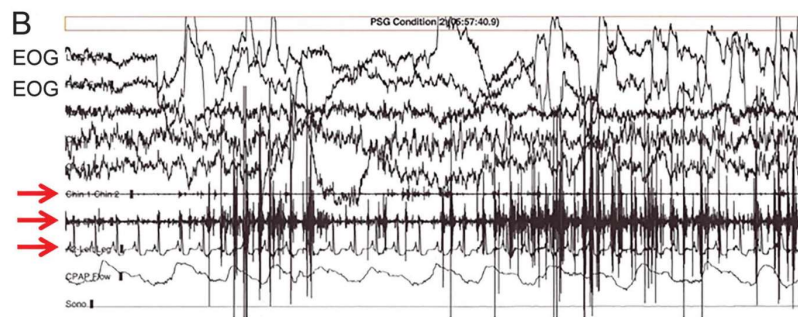
Abnormal (low-uptake) in ^{123}I iodine-metaiodobenzylguanidine myocardial imaging (**MIBG**)

Current biomarkers in Lewy body disease

Polysomnography confirmation of **REM** sleep without **atonia**.



PSG recordings of normal REM sleep



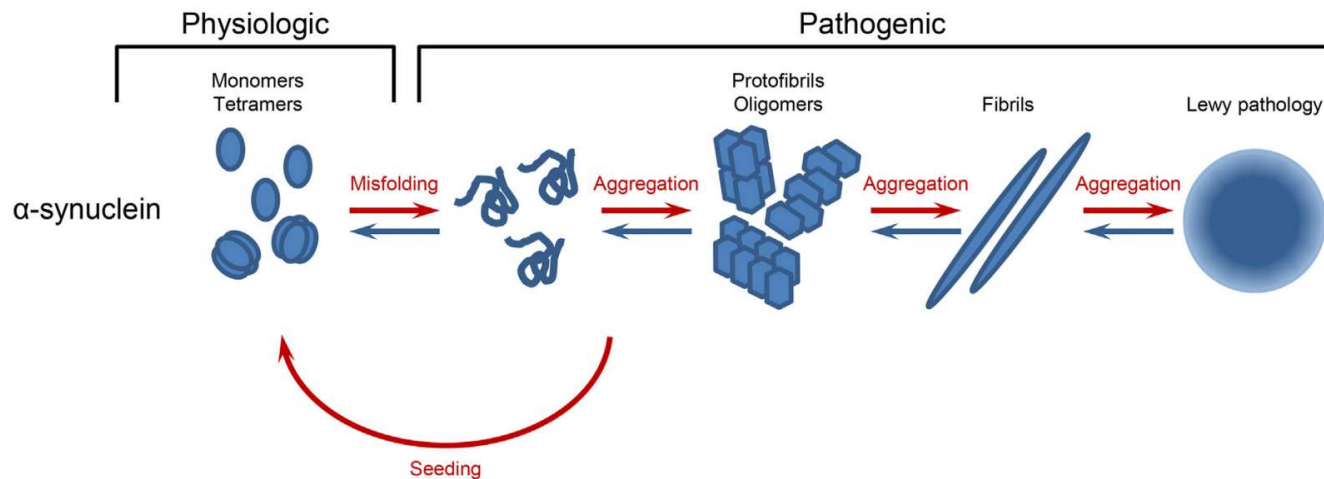
REM sleep without atonia, typical of REM sleep behavior disorder



Prominent **posterior slow-wave EEG** activity with periodic fluctuations in the pre-alpha/theta range

Future diagnostic tools in LBD

Biomarkers for Lewy body disease

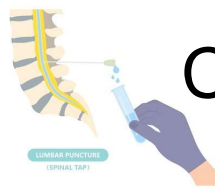


Kalia L. *Parkinsonism and Related Disorders*. 2020

Where?



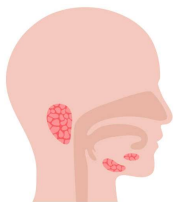
Blood



Cerebrospinal fluid



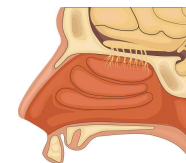
Skin



Submandibular gland

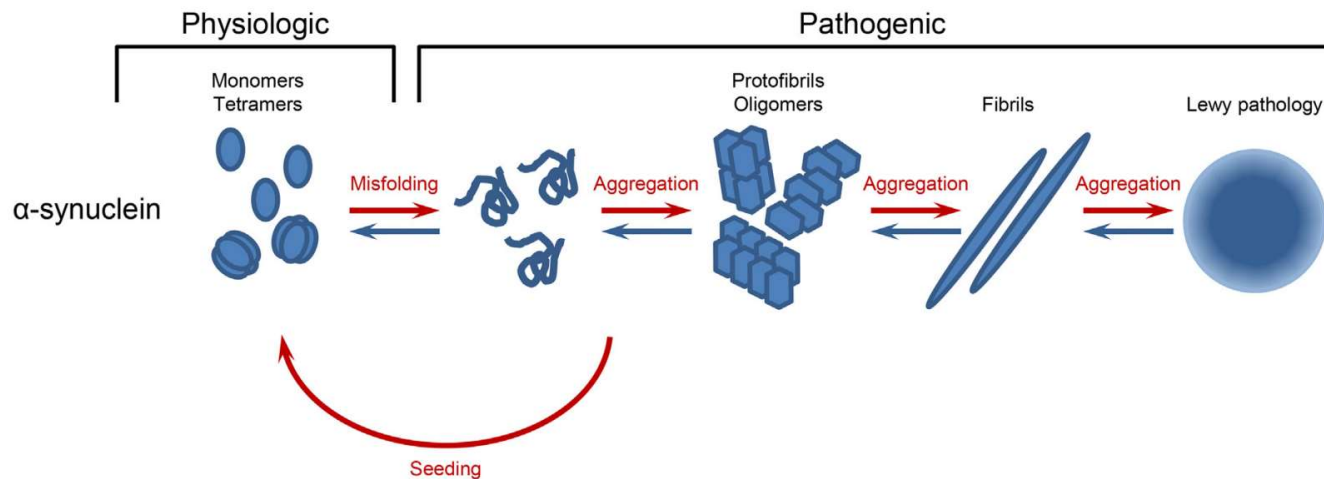


Saliva



Olfactory mucosa

Biomarkers for Lewy body disease

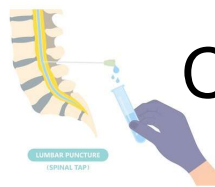


Kalia L. Parkinsonism and Related Disorders. 2020

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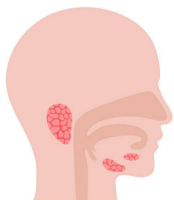
Blood



Cerebrospinal fluid



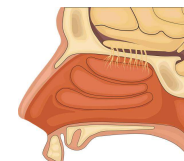
Skin



Submandibular gland



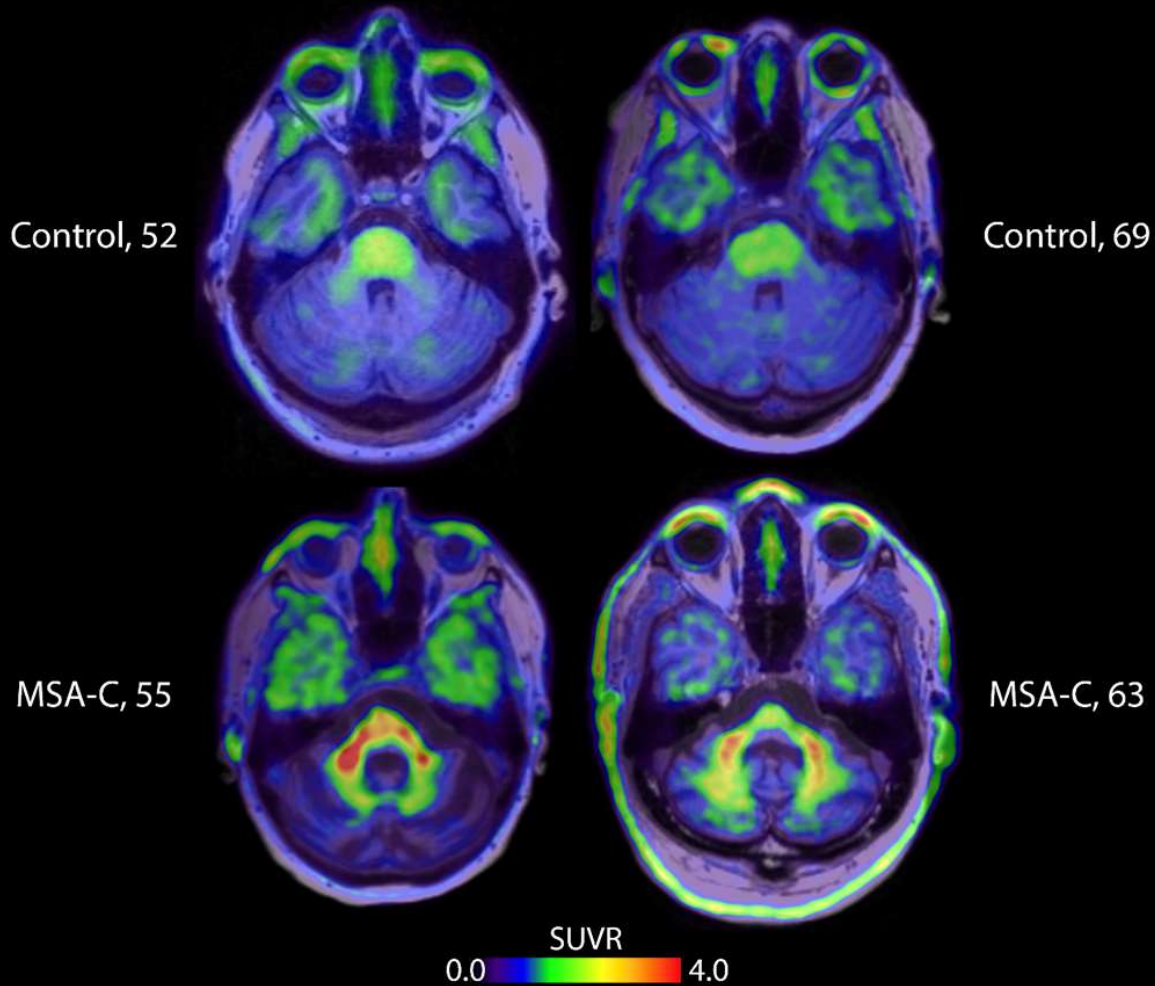
Saliva



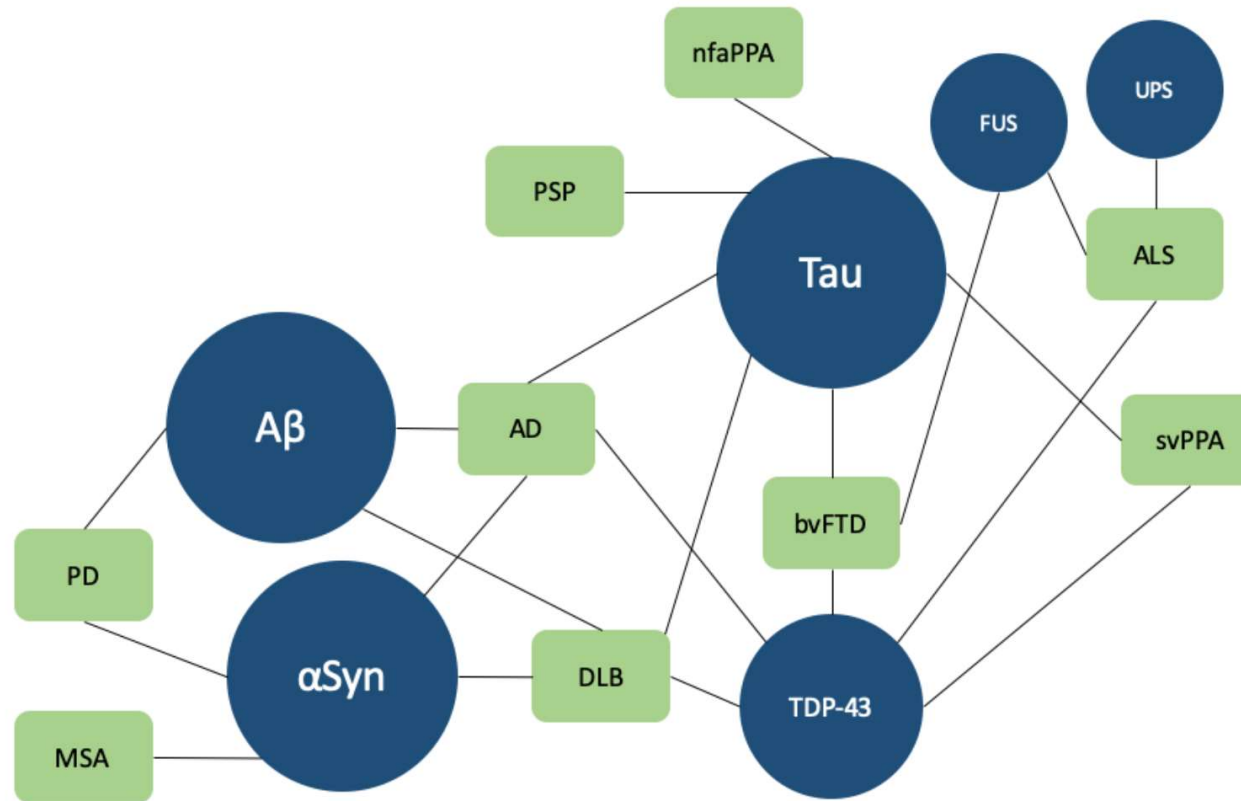
Olfactory mucosa

Biomarkers for Lewy body disease

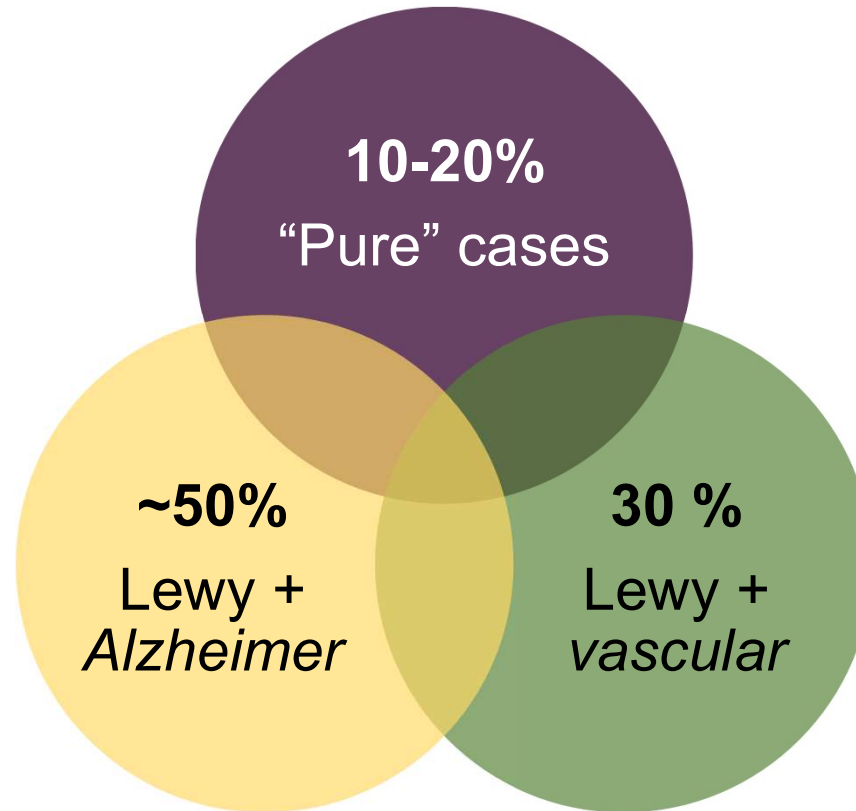
Alpha-synuclein Positron Emission Tomography



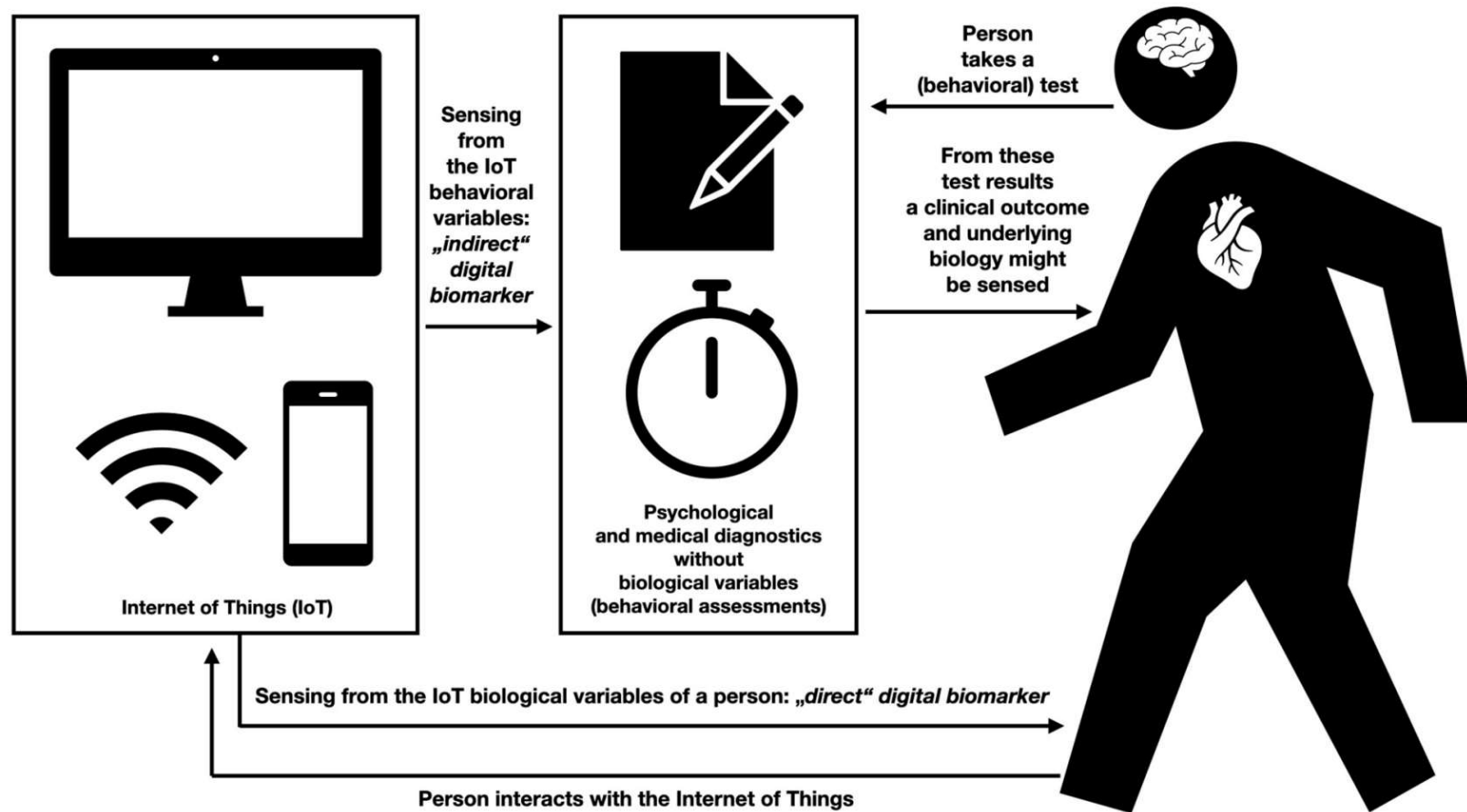
Identifying co-pathologies



Co-pathologies in Lewy body disease



Digital biomarkers



Montag et al. *Front. Psychiatry*. 2021

Summary

1. Lewy body disease = dementia with Lewy bodies and Parkinson's disease dementia.
 - Etiology: deposits of alpha-synuclein (*Lewy bodies* and *Lewy neurites*).
 - The difference between these two diseases relies on what symptom presented first: cognitive or motor?
 - Dementia with Lewy bodies: dementia occurs before or concurrently with parkinsonism.
 - Parkinson disease dementia: dementia occurs in the context of well-established Parkinson's disease.
2. Current diagnostic tools include: comprehensive neuropsychological examination, MRI, dopamine transporter SPECT or PET, MIBG, PSG, FDG-PET, and EEG.
3. Future diagnostic tools: biofluid biomarkers, alpha-synuclein tracers, digital biomarkers.

We choose to END dementia!



“We choose to go to the Moon!

We choose to go to the Moon...

We choose to go to the Moon in this decade and do the other things, **not because they are easy, but because they are hard**; because that goal will serve to organize and measure the best of our energies and skills, **because that challenge is one that we are willing to accept**, one we are unwilling to postpone, and **one we intend to win**, and the others, too.”

John F. Kennedy