PIA FONDAZIONE DI CULTO E RELIGIONE CARD. G. PANICO
Azienda Ospedaliera

Center for Neurodegenerative Diseases and the Aging Brain

University of Bari "Aldo Moro"
"Card. G. Panico" Fondation
Tricase – LECCE
Director: Prof. Giancarlo Logroscino

L'approccio diagnostico nelle fasi prodromiche del declino cognitivo nella malattia a corpi di Lewy

Daniele Urso, MD

Riunione Annuale Sin Appulo Lucana - 4 Novembre 2022

Caso clinico

- 77 anni. Maschio
- Sogni vividi *dream-enecting behaviour*
- *Apatia*
- *Storia di distacco di retina occhio destro (2018)*
- *Non ulteriori patologie degne di nota*

Inizio 2019

Allucinazioni visive ricorrenti:

- serpenti che strisciano sul condizionatore
- bambini che si rincorrono
- bambini in bicicletta
- uomini che approcciano sua moglie
- mezzi busti che si muovono,…

Non lamenta decadimento cognitivo o parkinsonismo (quindi nessuna interferenza sulle ADL).

Fine 2019

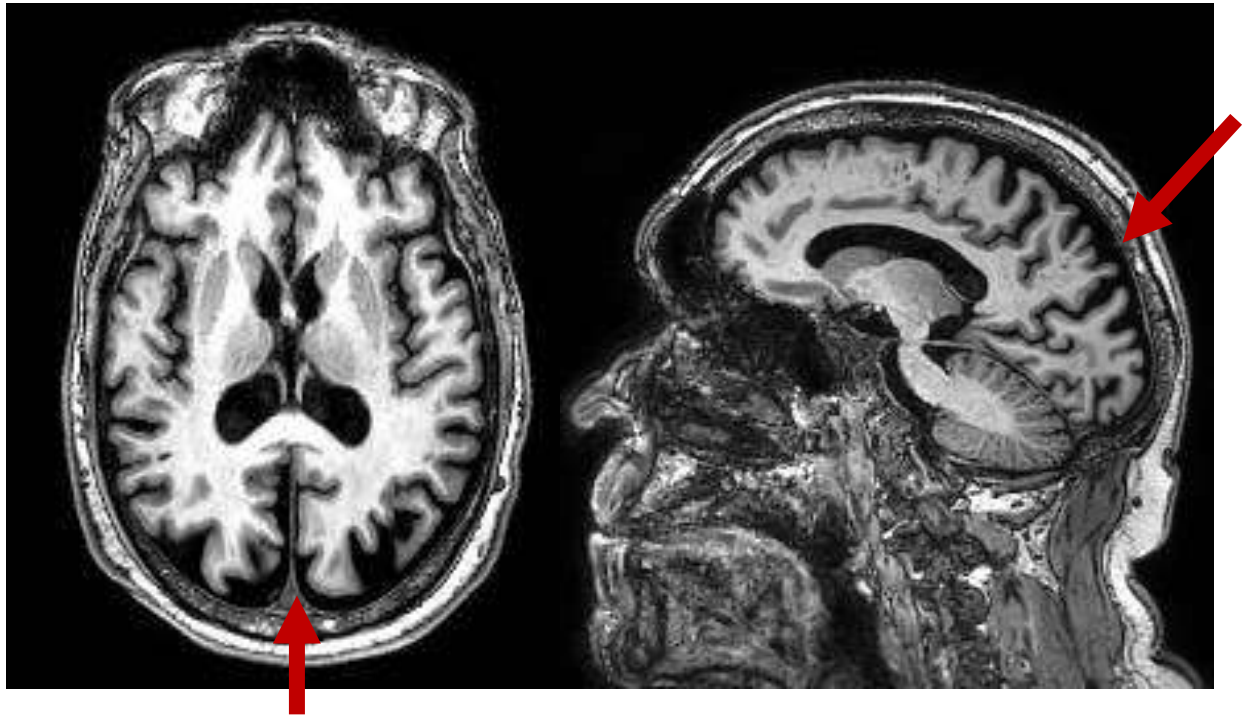
- Comincia Olanzapina 5 mg
- Lieve miglioramento quadro allucinatorio
- Sviluppa marcato parkinsonismo

Caso clinico

2020

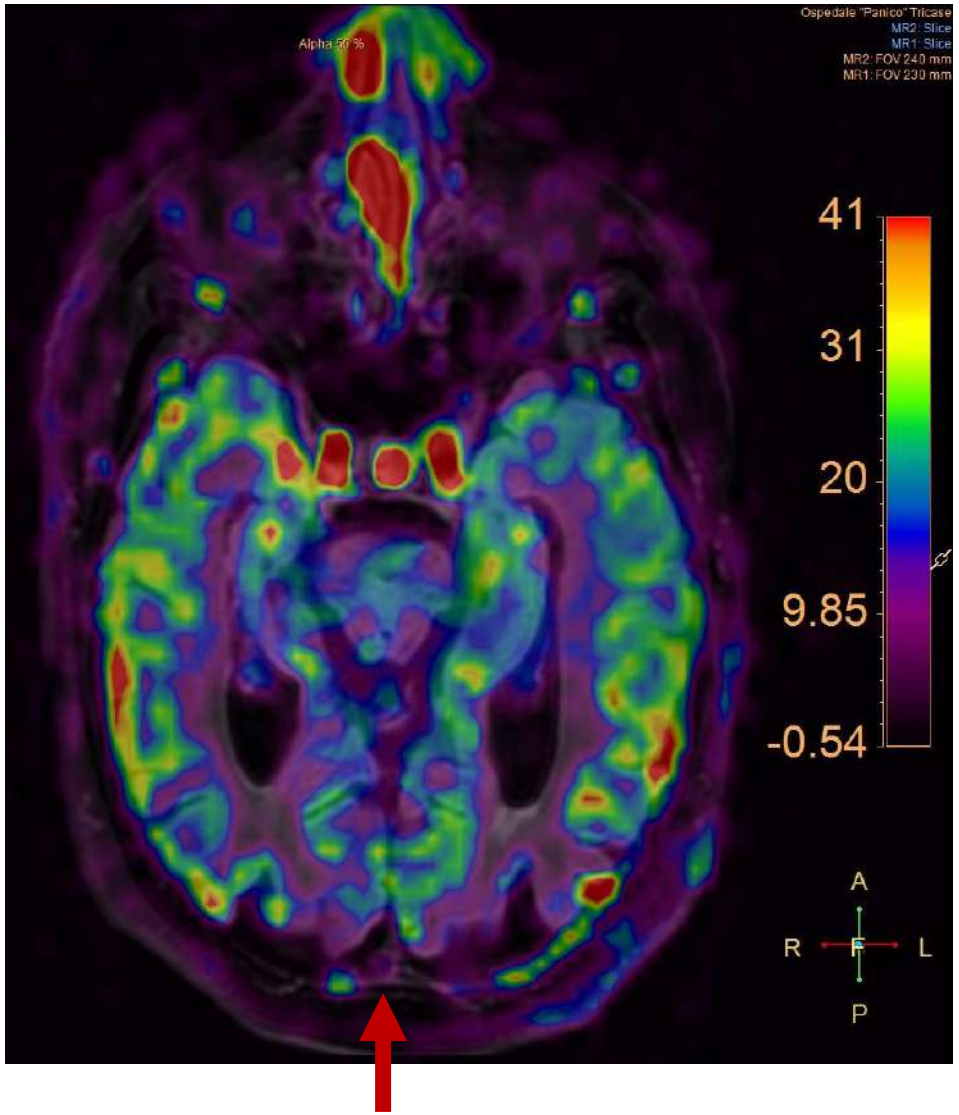
- Esame obiettivo neurologico: camptocormia, rigidità, bradicinesia (maggiore a sinistra)
- Batteria test neuropsicologici: profilo cognitivo normale
- Non decadimento cognitivo soggettivo (riportata da paziente e care-givers)
- DAT SCAN: denervazione dopaminergica striatale, predominante a sinistra
- MRI
  T1:atrofia parieto-occipitale
  pcASL: ipoperfusione parieto-occipitale
  rs-fMRI: ipoattivazione posteriore Default Mode Network

MRI T1

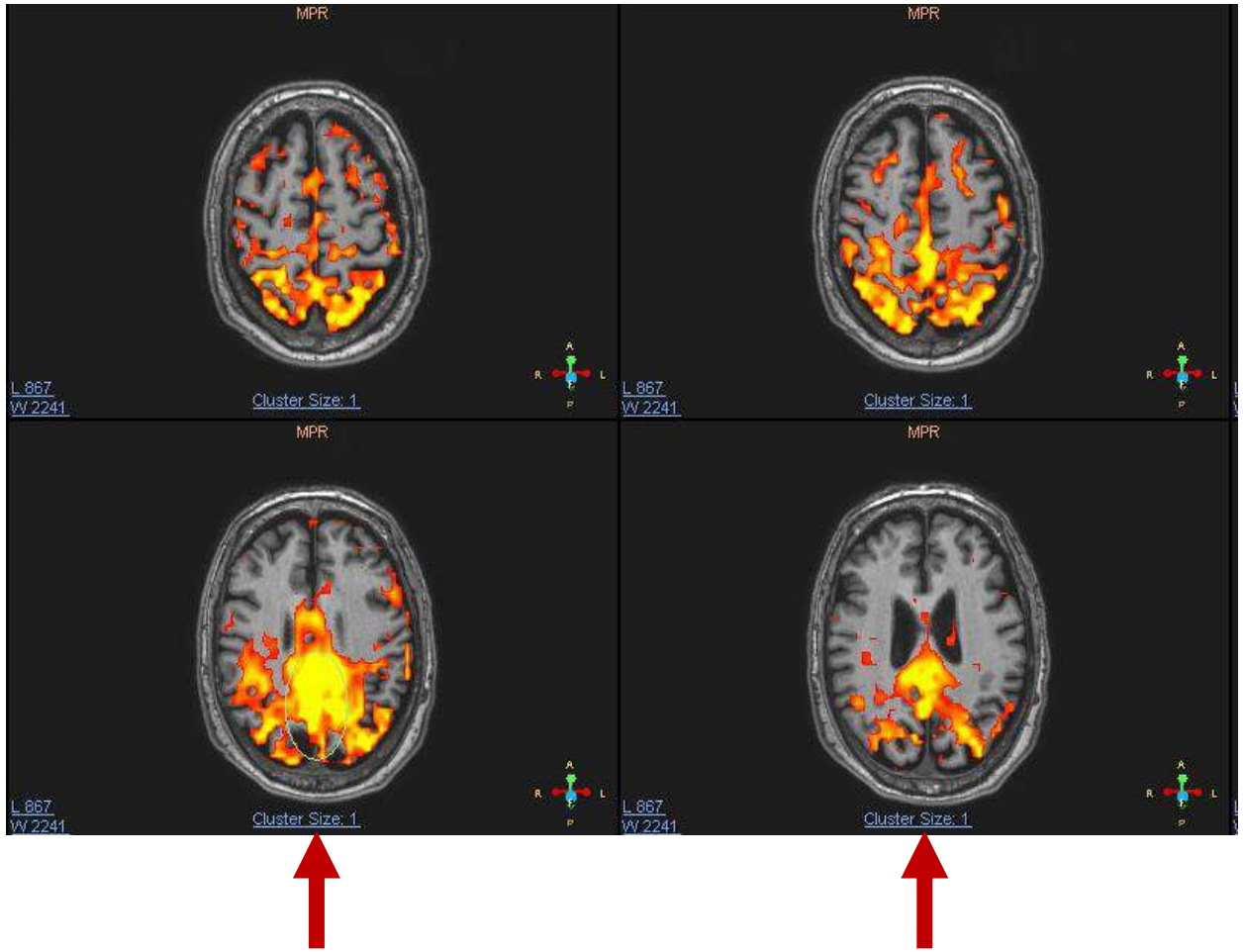


Caso clinico

pcASL

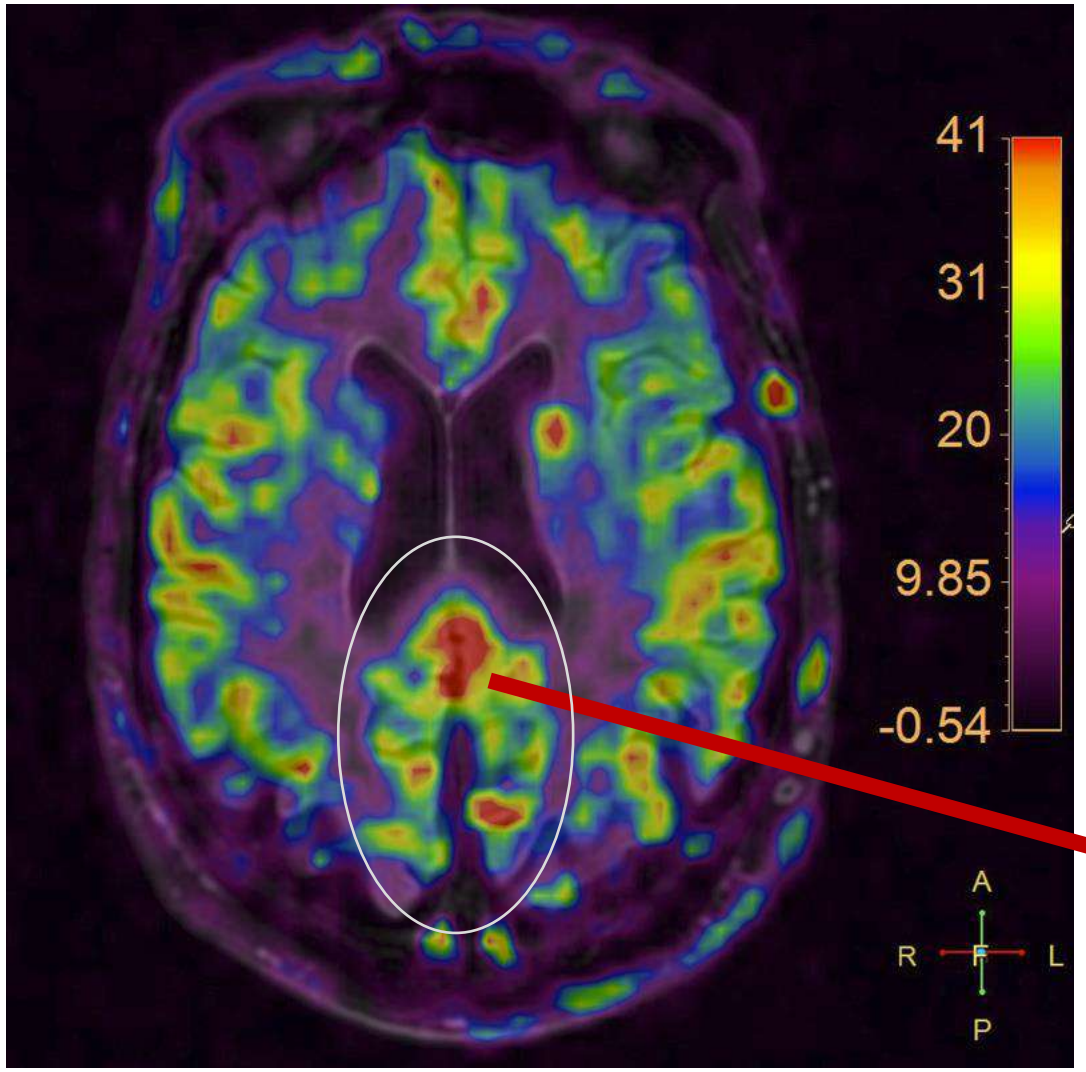


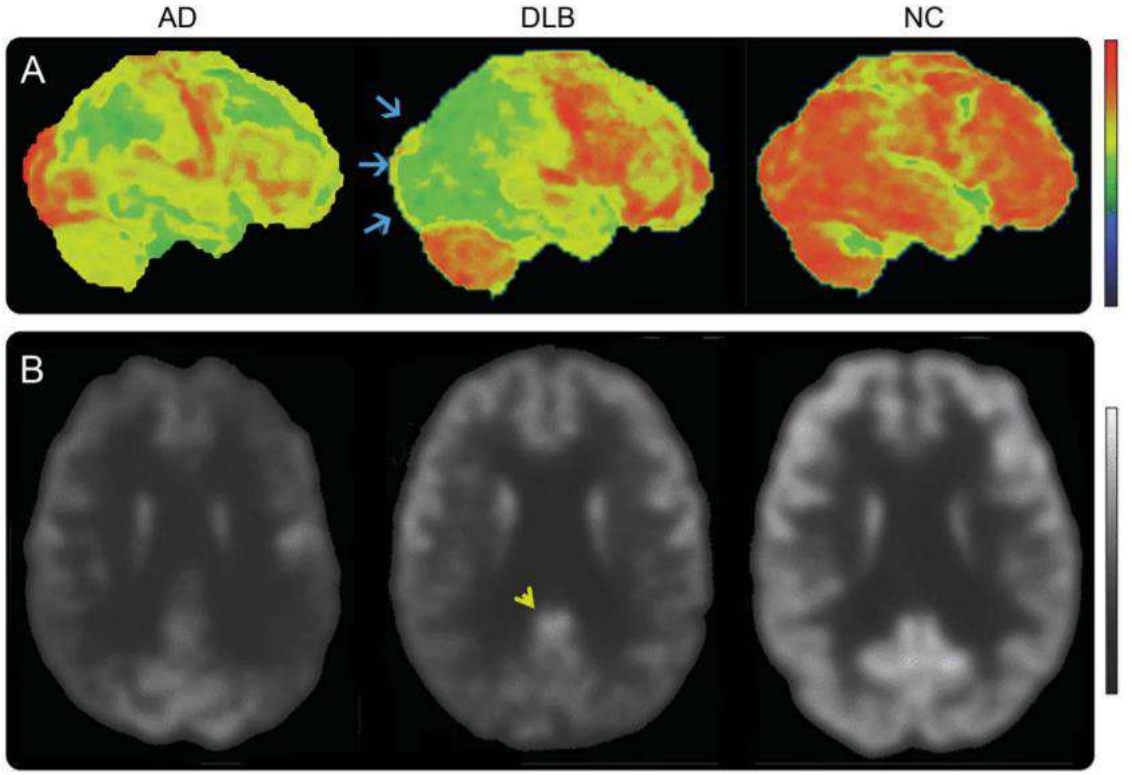
rs-fMRI



Caso clinico

pcASL





McKeith et al. 2017

"cingulate island sign"

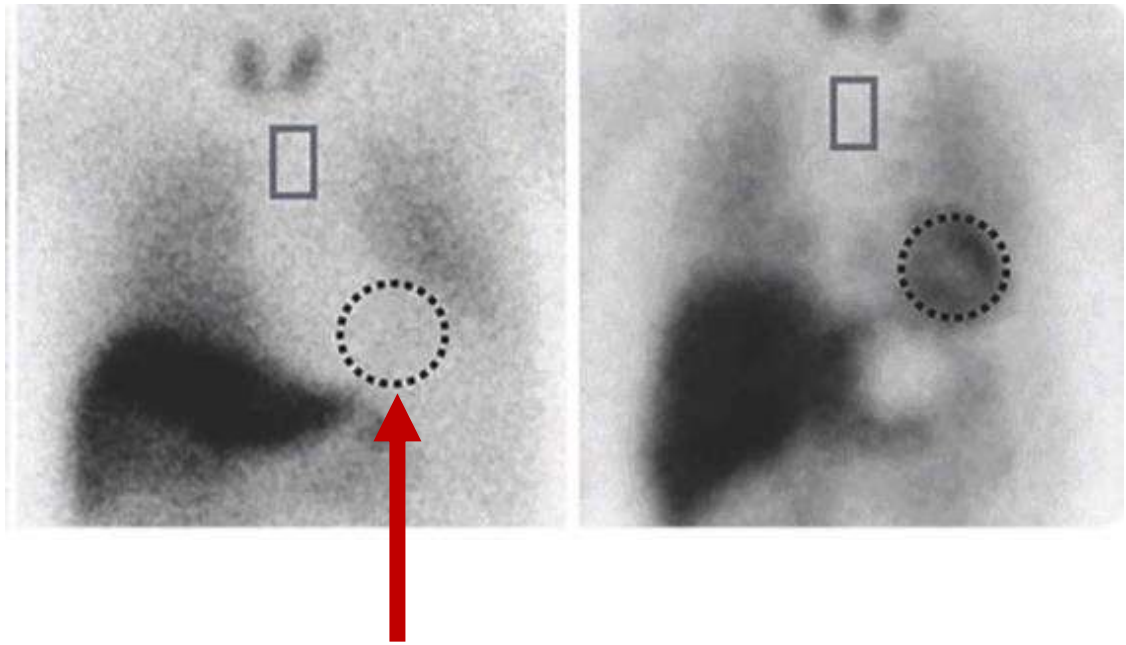
Caso clinico

2021

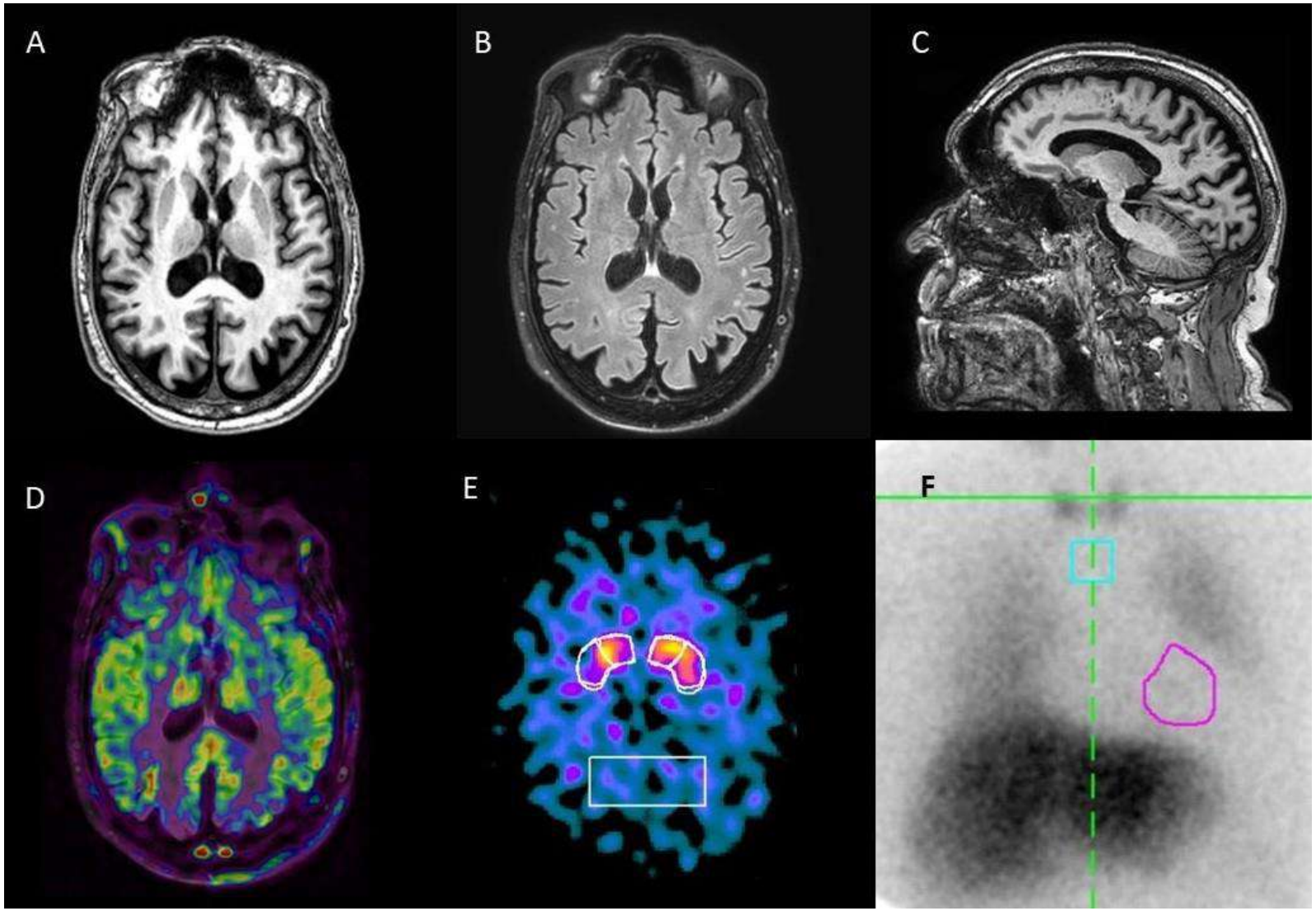
- Persistono allucinazioni (2,3/die). Associate sopratutto al sonno. Assume quetiapina.
- Esame obiettivo neurologico: camptocormia, rigiditá, bradicinesia (maggiore a sinistra)
- Batteria test neuropsicologici: profilo cognitivo normale
- Non decadimento cognitivo soggettivo (riportato da paciente e care-givers)
- MIBG: denervazione cardiaca simpatica severa
- EEG: sequenze delta sulle regioni fronto-temporo-centrali ad alterna prevalenza di lato

MIBG

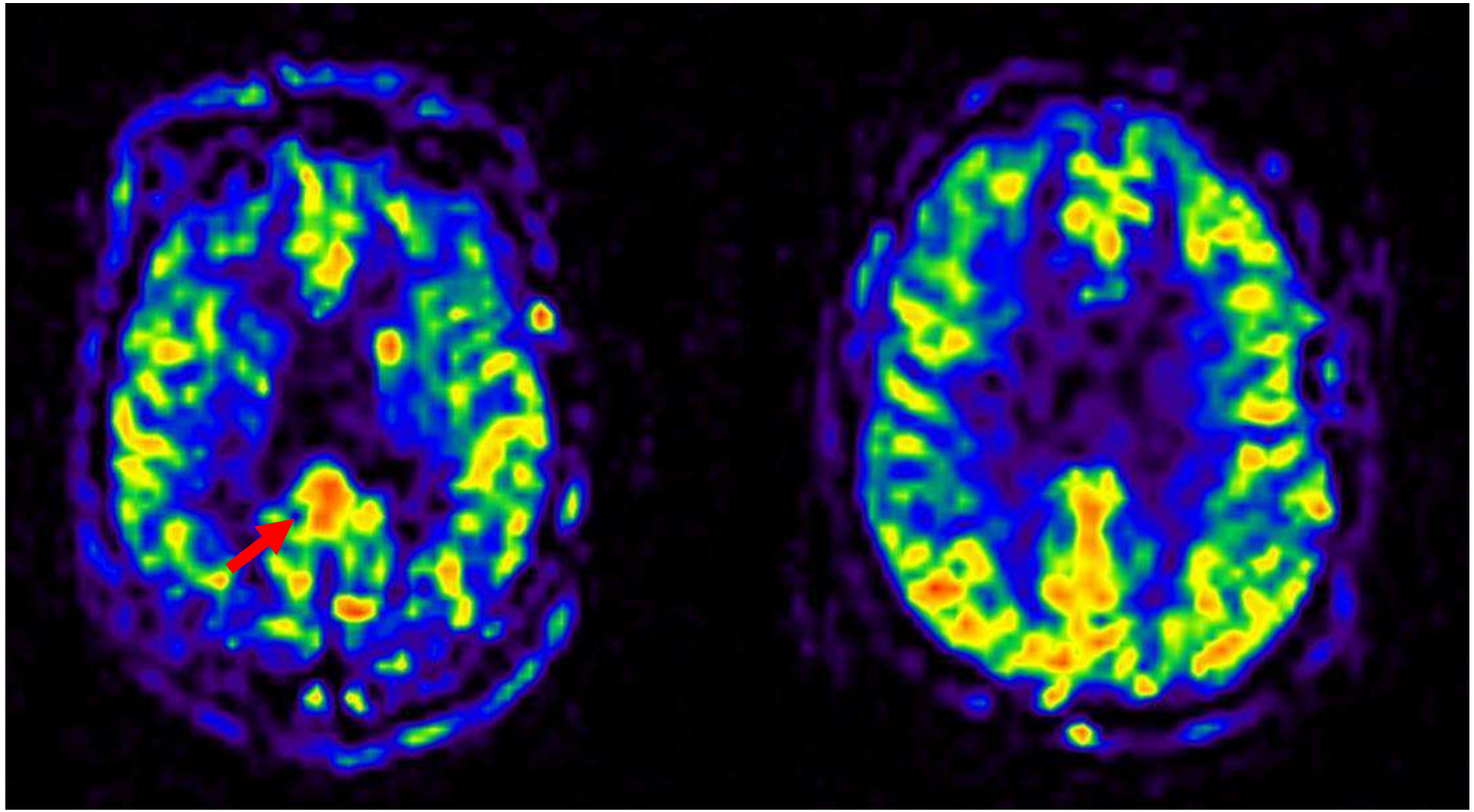
paziente *controllo sano*



Caso clinico



Cingulate Island Sign



Paziente

Controllo sano

Urso,…,Logroscino Neurology 2022

Caso Clinico

Diagnosis

DLB

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.

Parkinson's disease

Absolute exclusion criteria[1]

- Cerebellar signs
- Supranuclear gaze palsy
- Established diagnosis of BVFTD
- Parkinsonism restricted to the lower limbs only for >3 years
- Treatment with an antidopaminergic, or with dopamine-depletion agents
- Absence of response to levodopa
- Sensory–cortical loss
- No evidence for dopaminergic deficiency on functional imaging
- Other parkinsonism-inducing condition

Postuma et al. 2015

Il concetto di Prodromal DLB

VIEWS & REVIEWS | OPEN ACCESS

Research criteria for the diagnosis of prodromal dementia with Lewy bodies

Ian G. McKeith, F Med Sci, MD, Tanis J. Ferman, PhD, Alan J. Thomas, PhD, Frédéric Blanc, MD, Bradley F. Boeve, MD, Hiroshige Fujishiro, MD, Kejal Kantarci, MD, MS, Cristina Muscio, PhD, John T. O'Brien, F Med Sci, DM, Ronald B. Postuma, MD, MSc, Dag Aarsland, PhD, Clive Ballard, MD, Laura Bonanni, MD, PhD, Paul Donaghy, PhD, Murat Emre, MD, James E. Galvin, MD, MPH, Douglas Galasko, MD, Jennifer G. Goldman, MD, MS, Stephen N. Gomperts, MD, PhD, Lawrence S. Honig, MD, PhD, Manabu Ikeda, MD, PhD, James B. Leverenz, MD, Simon J.G. Lewis, MD, Karen S. Marder, MD, MPH, Mario Masellis, MD, PhD, David P. Salmon, PhD, John Paul Taylor, MB, BS, PhD, Debby W. Tsuang, MD, Zuzana Walker, MD, and Pietro Tiraboschi, MD, for the prodromal DLB Diagnostic Study Group

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McKeith et al. 2020

Il concetto di Prodromal DLB: MCI-DLB

Table 1 Research criteria for the clinical diagnosis of probable and possible MCI-LB

Essential for a diagnosis of MCI-LB is MCI defined by the presence of each of the following:
Concern by the patient, informant, or clinician regarding cognitive decline.
Objective evidence of impairment in 1 or more cognitive domains. The cognitive impairment may include any domain, but is more likely to be associated with attention-executive and/or visual processing deficits.
Preserved or minimally affected performance of previously attained independence in functional abilities, which do not meet the criteria for dementia.
Core clinical features
Fluctuating cognition with variations in attention and alertness.
Recurrent visual hallucinations.
RBD.
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.

McKeith et al. 2020

Il concetto di Prodromal DLB: Delirium-onset DLB

Table 2 Summary of key features of delirium-onset DLB

Patients with DLB are more susceptible to delirium than people with Alzheimer disease, and this delirium may occur as their presenting complaint before dementia develops.
Such episodes may be provoked by multiple factors including surgery, infections/sepsis, fever, or other systemic illness, or secondary to use, or sudden withdrawal of, alcohol or psychoactive drugs.
Prodromal DLB should be particularly suspected in patients
• in whom adequate provoking factors for the delirium are not found.
• with prolonged or recurrent delirium
• who later develop progressive cognitive decline or subsequent dementia
Core clinical features of DLB are likely to be of more limited diagnostic weight in a patient with delirium because
• cognitive fluctuation and clouding of consciousness can also occur in non-DLB delirium, i.e., are not diagnostically specific for DLB in this situation
• visual hallucinations may occur in non-DLB delirium, particularly drug-induced or provoked by alcohol abstinence
• motor parkinsonism present may be due to antipsychotic medications used to treat delirium
• the diagnostic significance of a history of RBD in a person with delirium is not yet established
Identification of delirium-onset DLB
• may be assisted by use of MCI-LB biomarkers, but further research evidence of this is required
• is important to inform the management plan including the avoidance or minimization of antipsychotic and anticholinergic agents

Abbreviations: DLB = dementia with Lewy bodies; MCI = mild cognitive impairment; MCI-LB = MCI with Lewy bodies; RBD = REM sleep behavior disorder.

McKeith et al. 2020

Il concetto di Prodromal DLB: Psychiatric-onset DLB

Table 3 Summary of key features of psychiatric-onset DLB

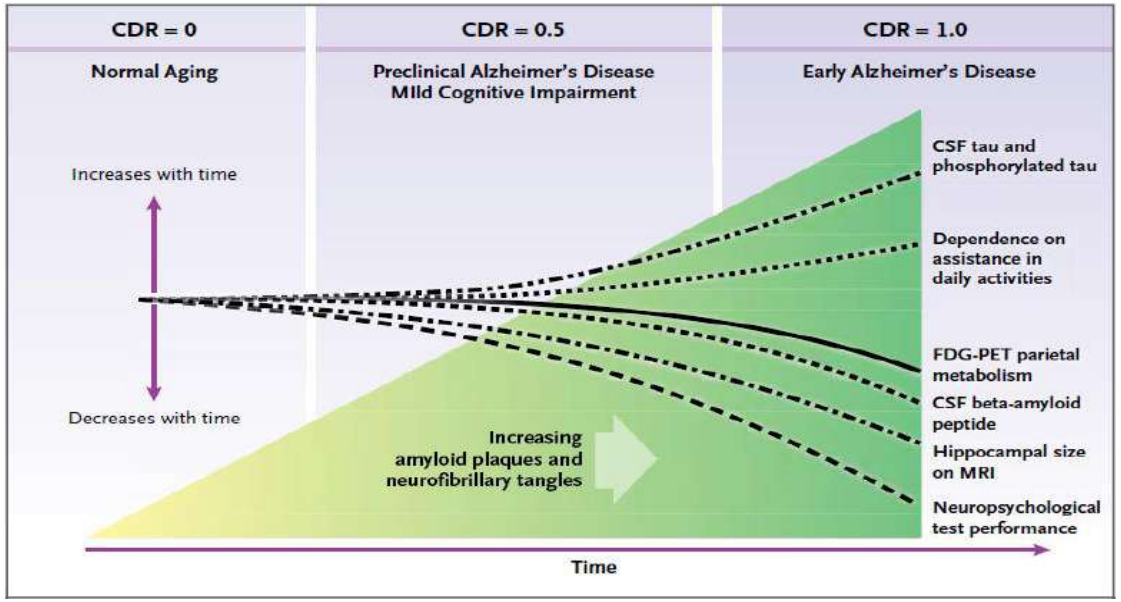
Is characterized by predominant psychiatric symptoms that typically correspond to late-onset major depressive disorder or late-onset psychosis, which may feature hallucinations in visual and in other modalities, and systematized delusions including Capgras syndrome
• may also present with apathy, anxiety, and depression
• may be sufficiently severe to require hospitalization
• the frequency of LB disease as a cause of late-onset psychiatric disorder is not known
When assessing for core clinical features of DLB in a patient with a primary psychiatric presentation:
• bradykinesia may be mimicked by psychomotor retardation, which is commonly seen in depressive disorders
• parkinsonism may be induced by antipsychotic medications used to treat psychiatric disorder
• RBD (and REM sleep without atonia) may be induced by antidepressant medications
• mild cognitive disturbance may be present but is not predominant and may fluctuate
• formal neuropsychological testing may be confounded by the psychiatric mental state
• the frequency and character of cognitive fluctuations is unknown
Identification of psychiatric-onset DLB
• may be assisted by use of MCI-LB biomarkers, but further research evidence of this is required
• is important to inform the management plan including the avoidance or minimization of antipsychotic and anticholinergic agents

Abbreviations: DLB = dementia with Lewy bodies; MCI = mild cognitive impairment.

McKeith et al. 2020

Storia Naturale della DLB

AD



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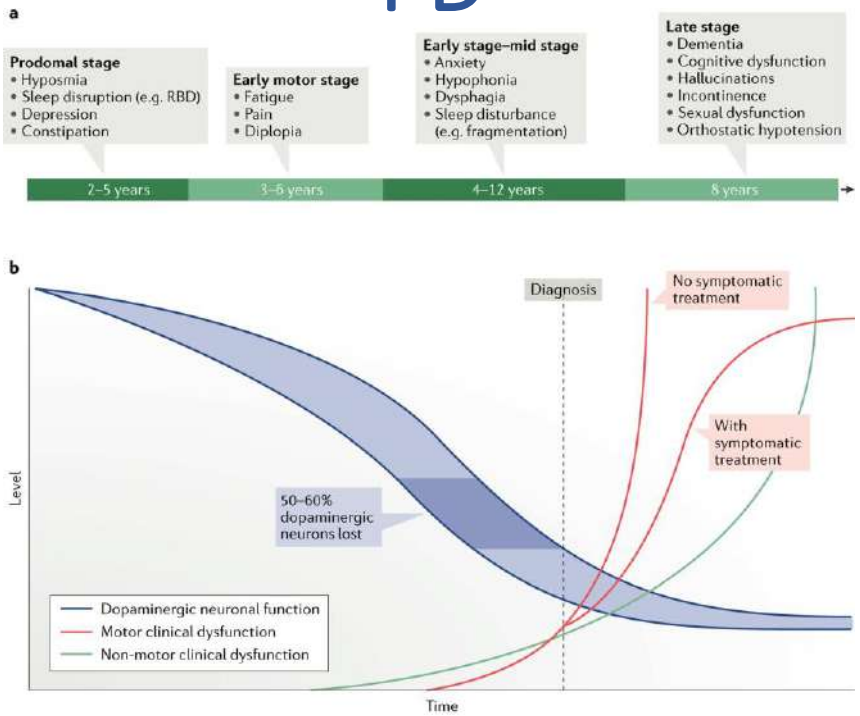


DLB?

Mayeux et al 2010; Shapira et al. 2017;

Storia Naturale della DLB

Prevalence of Symptoms on Neuropsychiatric Inventory Questionnaire

	5 Years Prior (N=14)	4 Years Prior (N=21)	3 Years Prior (N=39)	2 Years Prior (N=60)	1 Year Prior (N=95)	Time of DLB Diagnosis (N=116)
DLB Group						
Depression/Dysphoria	42.9%	57.1%	35.9%	45.0%	34.7%	46.6%
Irritability	35.7%	23.8%	41.0%	30.0%	34.7%	38.8%
Anxiety	35.7%	33.3%	23.1%	38.3%	43.2%	44.8%
Nighttime behaviors	14.3%	42.9%	33.3%	46.7%	57.9%	58.6%
Apathy/Indifference	28.6%	33.3%	33.3%	30.0%	49.5%	51.7%
Agitation/Aggression	28.6%	28.6%	23.1%	18.3%	22.1%	34.5%
Appetite/Eating Problems	21.4%	33.3%	35.9%	21.7%	33.7%	26.7%
Hallucinations	14.3%	19.0%	12.8%	15.0%	22.1%	35.3%
Delusions	0.0%	14.3%	2.6%	1.7%	10.5%	23.3%
Disinhibition	21.4%	4.8%	17.9%	1.7%	15.8%	18.1%
Motor Disturbances	0.0%	0.0%	7.7%	13.3%	9.5%	26.7%
Elation/Euphoria	7.1%	9.5%	2.6%	3.3%	3.2%	4.3%

Wyman-Chick et al., 2022

Storia Naturale della DLB

	5 Years Prior (N=14)	4 Years Prior (N=21)	3 Years Prior (N=39)	2 Years Prior (N=60)	1 Year Prior (N=95)	Time of DLB Diagnosis (N=116)
DLB Group						
Parkinsonism/Motor Symptoms	57.1%	85.7%	76.9%	83.3%	82.1%	93.1%
Motor Slowing	50.0%	81.0%	74.4%	71.7%	73.7%	90.5%
Parkinsonian Gait	28.6%	52.4%	59.0%	55.0%	64.2%	79.3%
Rigidity	28.6%	33.3%	46.2%	51.7%	55.8%	69.8%
Postural Instability	28.6%	28.6%	23.1%	15.0%	31.6%	34.5%
Tremors	14.3%	23.8%	30.8%	36.7%	33.7%	48.3%
Falls	0.0%	4.8%	7.7%	15.0%	26.3%	39.7%
RBD	21.4%	28.6%	38.5%	53.3%	56.8%	66.4%
Visual Hallucinations	0.0%	14.3%	12.8%	21.7%	25.3%	44.8%
Cognitive Fluctuations	0.0%	9.5%	23.1%	38.3%	30.5%	58.6%

Wyman-Chick et al., 2022

Storia Naturale della DLB

Kanemoto *et al.*
Alzheimer's Research & Therapy (2022) 14:137
https://doi.org/10.1186/s13195-022-01080-x

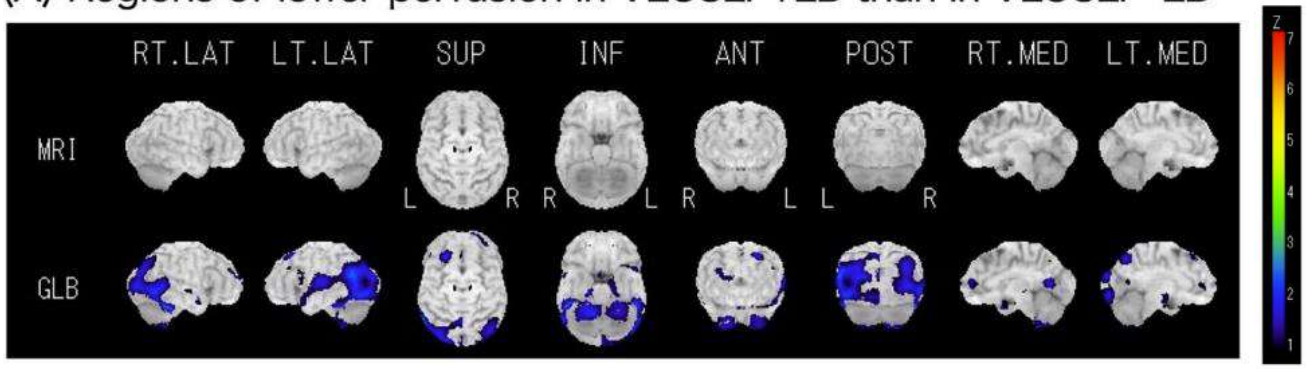
Alzheimer's
Research & Therapy

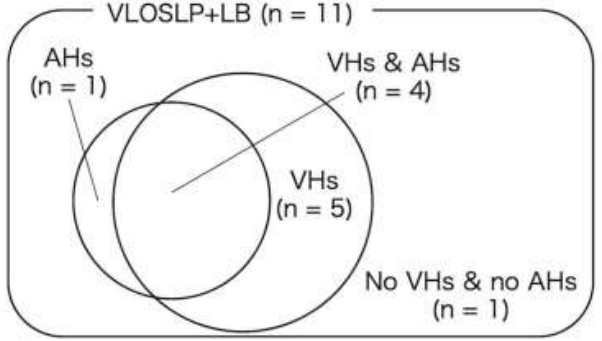
RESEARCH Open Access

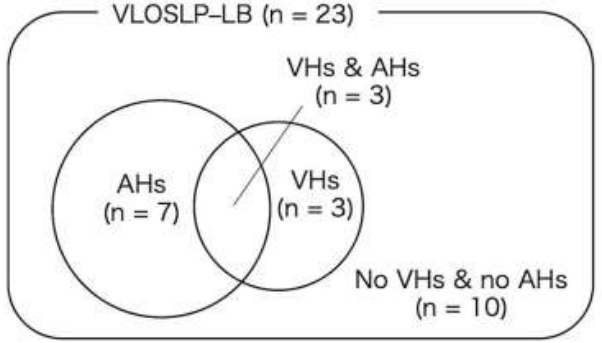
Characteristics of very late-onset schizophrenia-like psychosis as prodromal dementia with Lewy bodies: a cross-sectional study

Hideki Kanemoto[1*], Yuto Satake[1], Takashi Suehiro[1], Daiki Taomoto[1], Fuyuki Koizumi[1], Shunsuke Sato[1], Tamiki Wada[1], Keiko Matsunaga[2], Eku Shimosegawa[2], Mamoru Hashimoto[1,3], Kenji Yoshiyama[1] and Manabu Ikeda[1]

(A) Regions of lower perfusion in VLOSLP+LB than in VLOSLP–LB







Kanemoto et al., 2022

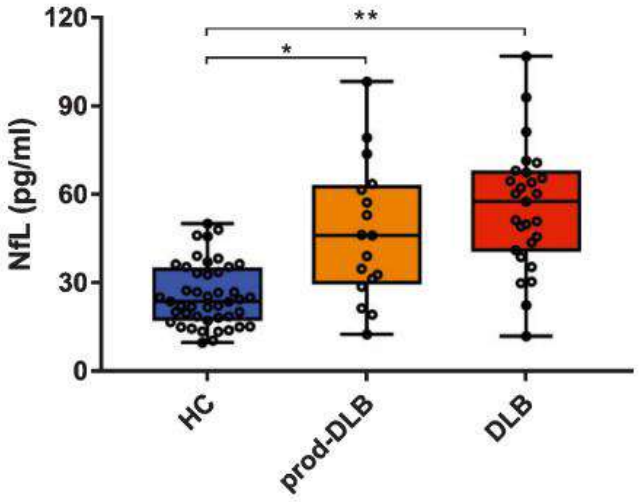
Storia Naturale della DLB

Journal of Alzheimer's Disease 82 (2021) 913–919
DOI 10.3233/JAD-210342
IOS Press

Short Communication

Plasma Neurofilament Light Chain Predicts Cognitive Progression in Prodromal and Clinical Dementia with Lewy Bodies

Andrea Pilotto[a,b,1,*], Alberto Imarisio[a,1], Claudia Carrarini[c], Mirella Russo[c], Stefano Masciocchi[a], Stefano Gipponi[a], Elisabetta Cottini[a], Dag Aarsland[d,j], Henrik Zetterberg[e,f,g,h], Nicholas J. Ashton[e,i,j,k], Abdul Hye[j,k], Laura Bonanni[c] and Alessandro Padovani[a]



Multivariable linear regression model for cognitive progression in total DLB cohort defined by changes in MMSE score including demographic, clinical baseline variables and plasma NfL levels

Independent variables	B	Standard error	Beta	t	*p*
Constant	–18.484	8.163		–2.264	0.030
Age	0.204	0.099	0.348	2.065	0.047
Gender	1.444	0.947	0.236	1.524	0.137
Disease duration	–0.284	0.171	–0.294	–1.657	0.107
$MMSE_{baseline}$	–0.026	0.109	–0.038	–0.239	0.813
$MDS\text{-}UPDRS\text{-}III_{baseline}$	0.043	0.037	0.193	1.152	0.258
NfL	–0.050	0.022	**–0.361**	–2.218	**0.034**

MDS-UPDRS-III, Movement Disorder Society Unified Parkinson's Disease Rating Scale, part III; MMSE, Mini-Mental State Examination; NfL, neurofilament light chain.

Kanemoto et al., 2022

Perche fare diagnosi precoce?

1-Appropriato management clinico

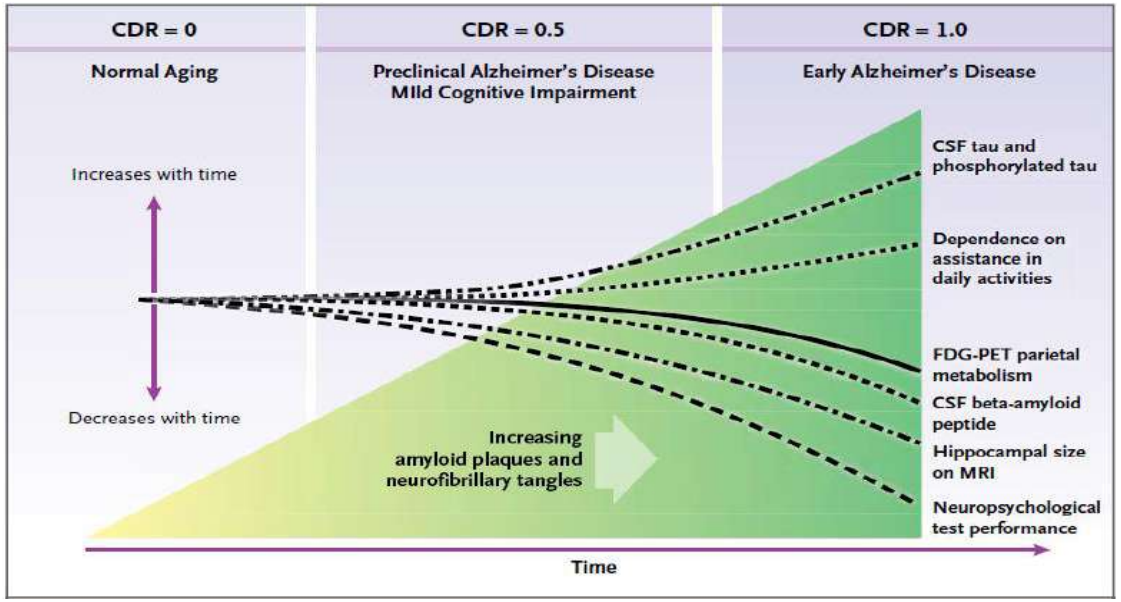
Supportive clinical features
Severe sensitivity to antipsychotic agents; postural instability; repeated falls; syncope or other transient episodes of unresponsiveness; prolonged or recurrent delirium; autonomic dysfunction, e.g., constipation, orthostatic hypotension, urinary incontinence; hypersomnia; hyposmia; hallucinations in other modalities including passage, and sense of presence phenomena; systematized delusions; apathy, anxiety, and depression.

Symptom	Pharmacological options
Cognitive impairment	Cholinesterase inhibitors (best evidence for donepezil, rivastigmine) Memantine (evidence mixed)
Neuropsychiatric symptoms	Psychosis: Quetiapine, pimavanserin, clozapine Other neuropsychiatric symptoms: SSRIs, SNRIs, memantine
Parkinsonism	Levodopa preparations (e.g. carbidopa/levodopa) Zonisamide (adjunctive)
Autonomic dysfunction	Orthostatic hypotension: midodrine, fludrocortisone, droxidopa Constipation: Stool softeners, laxatives Sialorrhea: Botulinum toxin injections, glycopyrrolate Urinary dysfunction: Mirabegron
REM sleep behavior disorder	Melatonin, clonazepam; potentially memantine

McKeith et al., 2020

2- Definizione della Storia Naturale

AD



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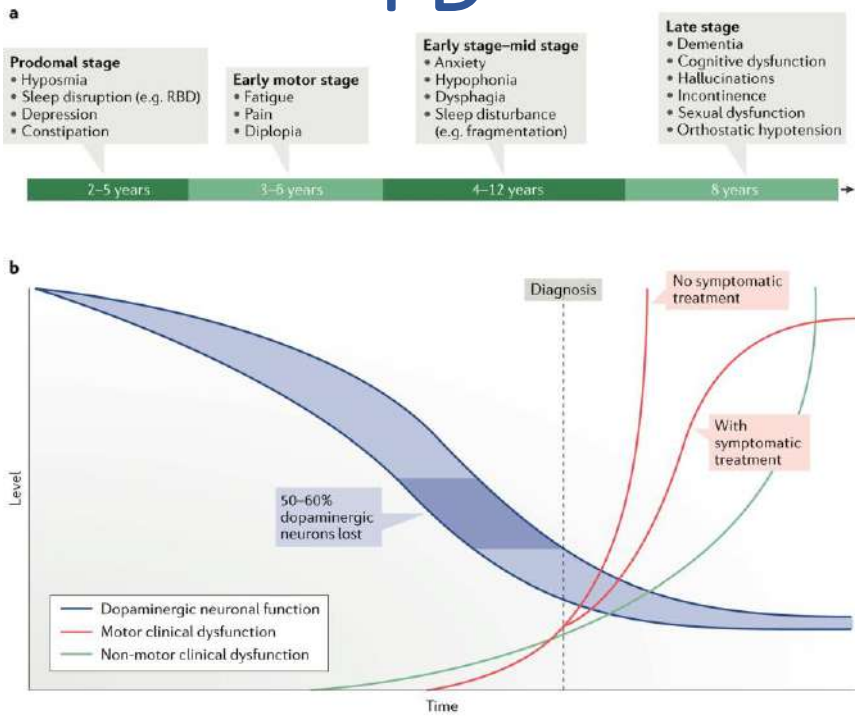
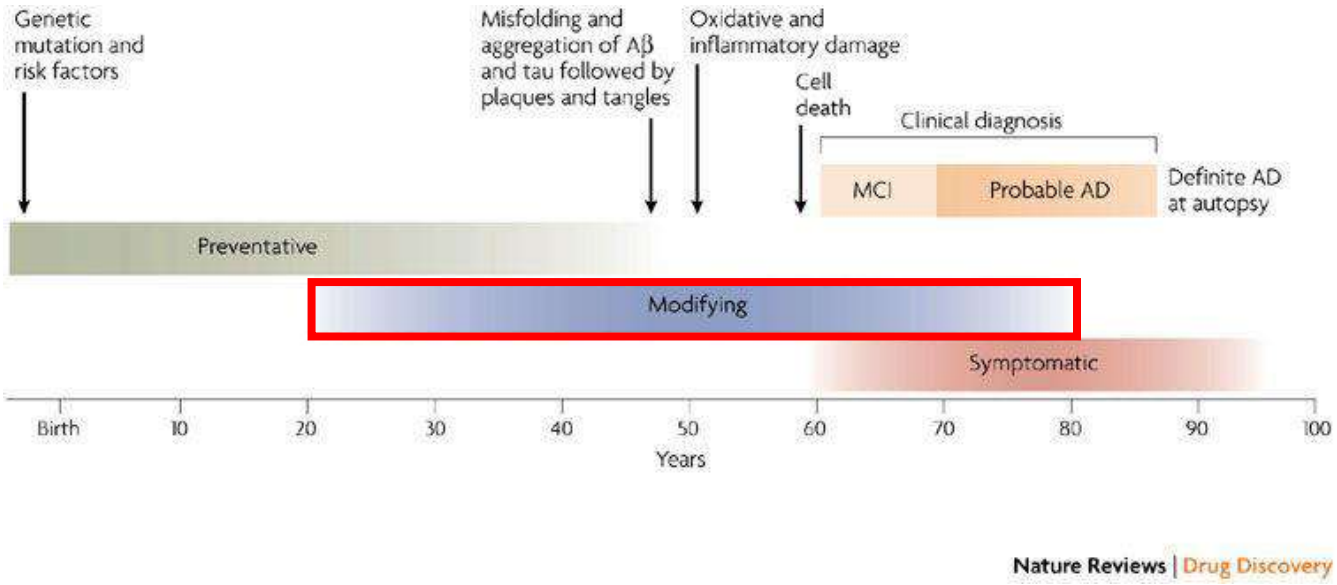
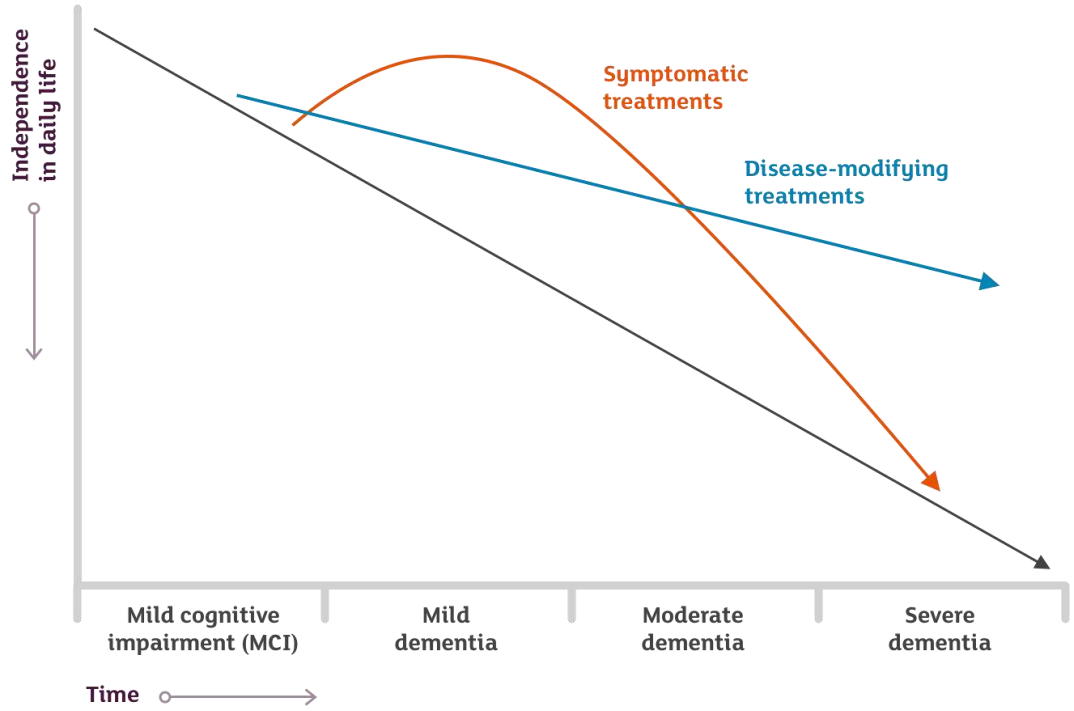


DLB?

Mayeux et al 2010; Shapira et al. 2017;

3- Intervento con terapie Disease-Modifying





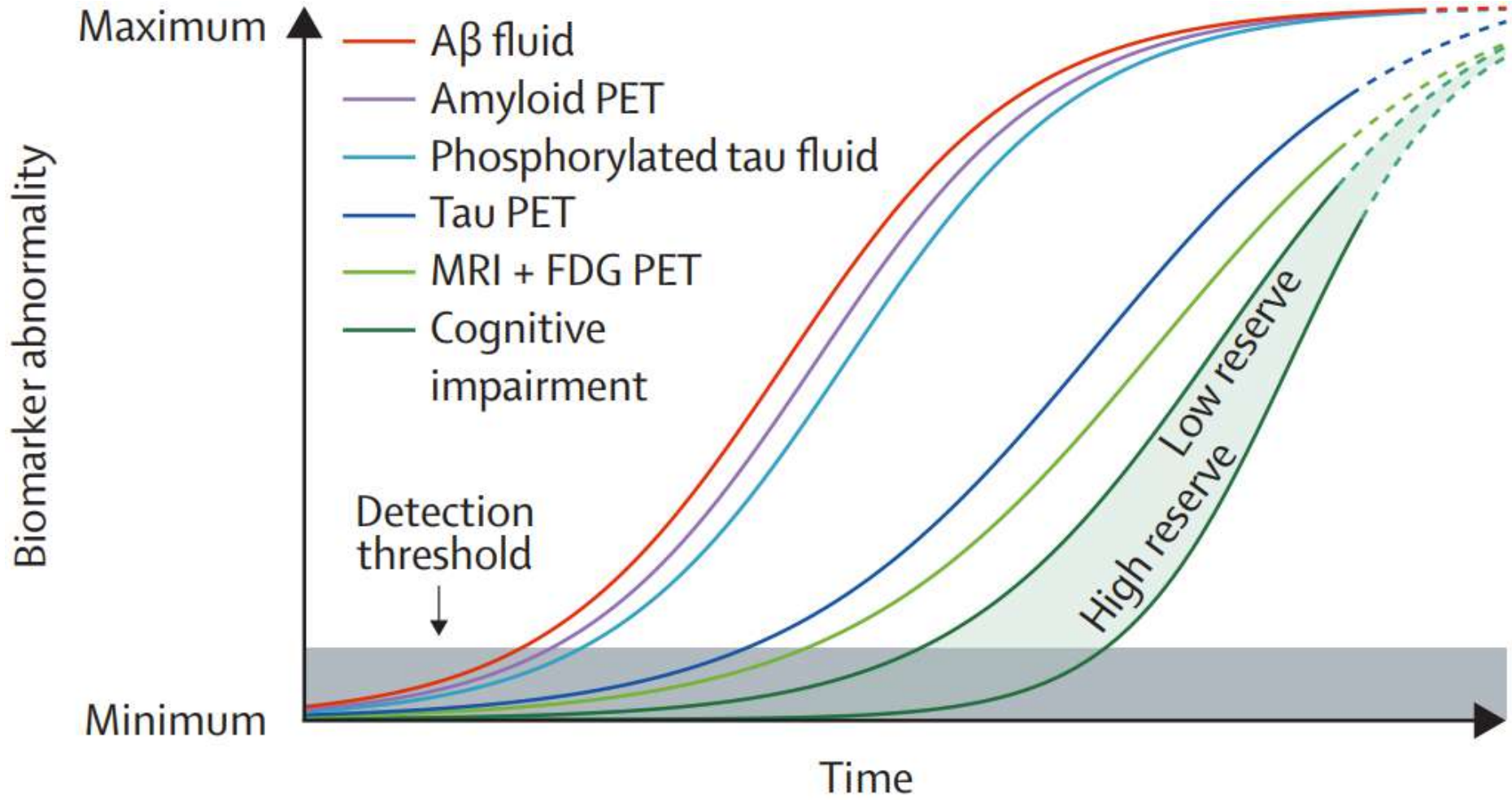
www.alzheimersresearchuk.org

Unmeet needs in DLB

Milestones in research over the past two decades	AD	DLB
Development of specific biomarkers	✓	✗
Improved understanding of the natural history	✓	✗
Development of diagnostic criteria and recommendations	✓	✓
Genetics discoveries	✓	✗
Development of large multimodality data resources that are publicly available	✓	✗
Advent of disease modifying clinical trials	✓	✗

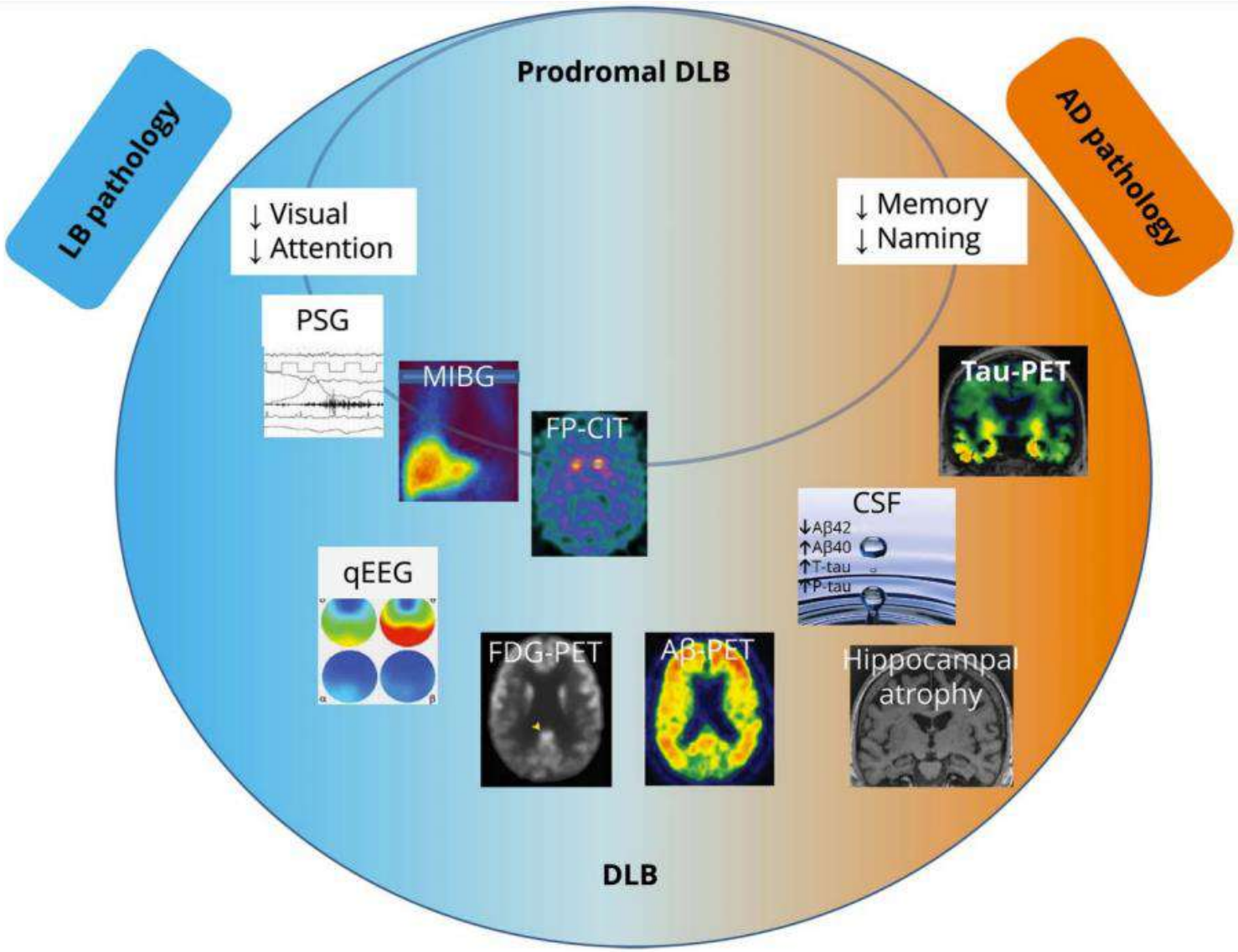
Clifford et al., 2022

Definizione biologica di malattia in AD



Clifford et al., 2022

Biomarkers della DLB



McKeith et al., 2020

Emerging DLB biomakers

CLINICAL/SCIENTIFIC NOTE

Neuroimaging Biomarkers in a Patient With Probable Psychiatric-Onset Prodromal Dementia With Lewy Bodies

Daniele Urso, MD, Valentina Gnoni, MD, Roberto De Blasi, MD, Antonio Anastasia, MD, Dag Aarsland, MD, PhD, Kallo Chaudhuri Ray, MD, PhD, and Giancarlo Logroscino, MD, PhD, FAAN

Neurology® 2022;99:654-657. doi:10.1212/WNL.0000000000201166

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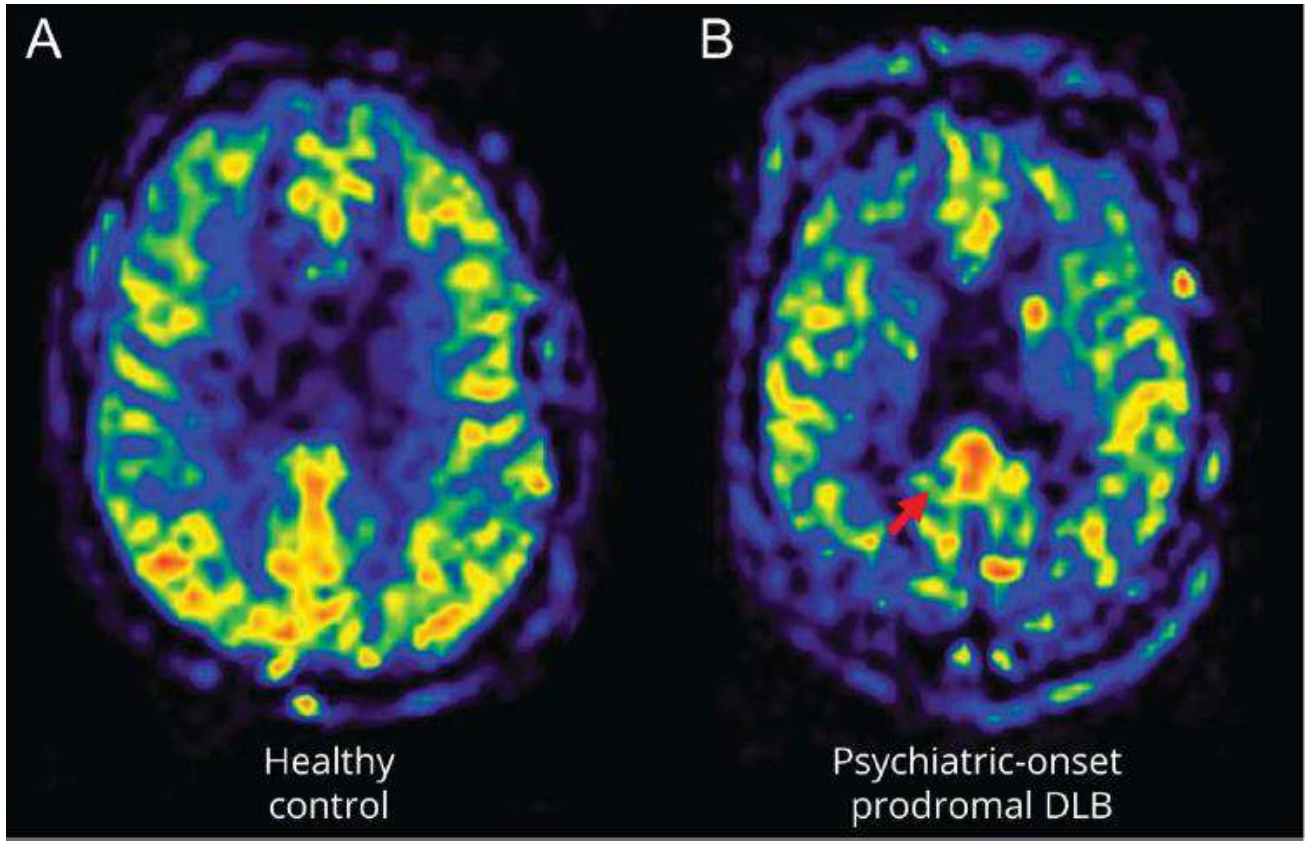

Verso una definizione biologica della DLB

RESEARCH ARTICLE

Diagnostic Value of the CSF α-Synuclein Real-Time Quaking-Induced Conversion Assay at the Prodromal MCI Stage of Dementia With Lewy Bodies

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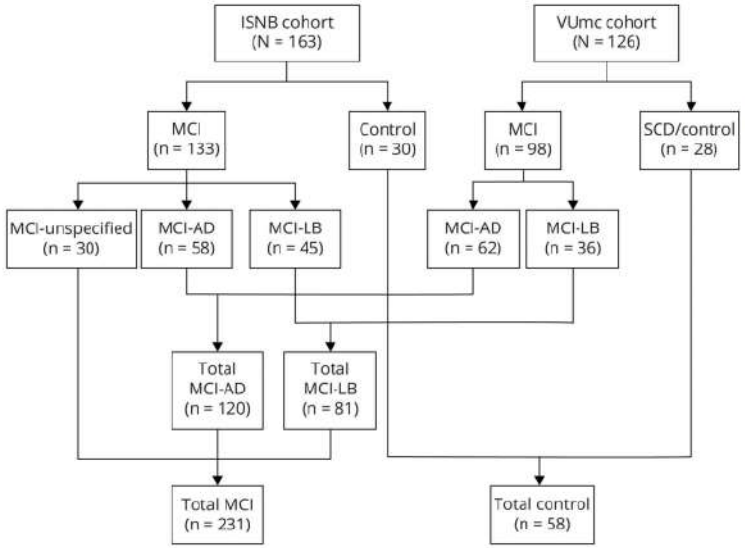
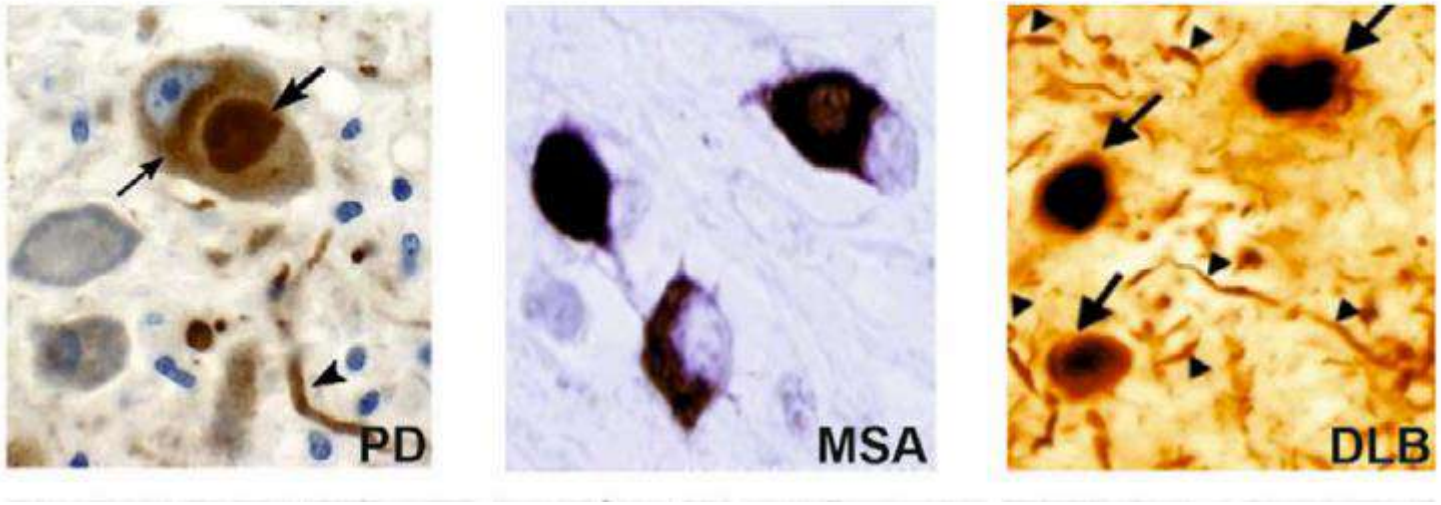


Table 3 Sensitivity and Specificity of the α-syn RT-QuIC Assay for MCI-LB Identification

	ISNB Cohort				VUmc Cohort				All			
	No.	±	Sens, %	Spec, %	No.	±	Sens, %	Spec, %	No.	±	Sens, %	Spec, %
MCI-LB	45	44/1	97.8		36	33/3	91.7		81	77/4	95.1	
MCI-AD	58	7/51		87.9	62	9/53		85.4	120	16/104		86.7
unsp-MCI	30	2/28		93.3					30	2/28		93.3
Ctrl	30	1/29		96.7	28	1/27		96.4	58	2/56		96.6
NP Ctrl	121	2/119		98.3					121	2/119		98.3

Abbreviations: α-syn =α-synuclein; AD = Alzheimer disease; Ctrl = clinical controls; ISNB = Institute of Neurological Sciences of Bologna; LB = Lewy body; MCI = mild cognitive impairment; NP Ctrl = neuropathologic controls; RT-QuIC = real-time quaking-induced conversion; Sens = sensitivity; Spec = specificity; unsp = not specified; VUmc = VU Medical Center.

α-synuclein Imaging

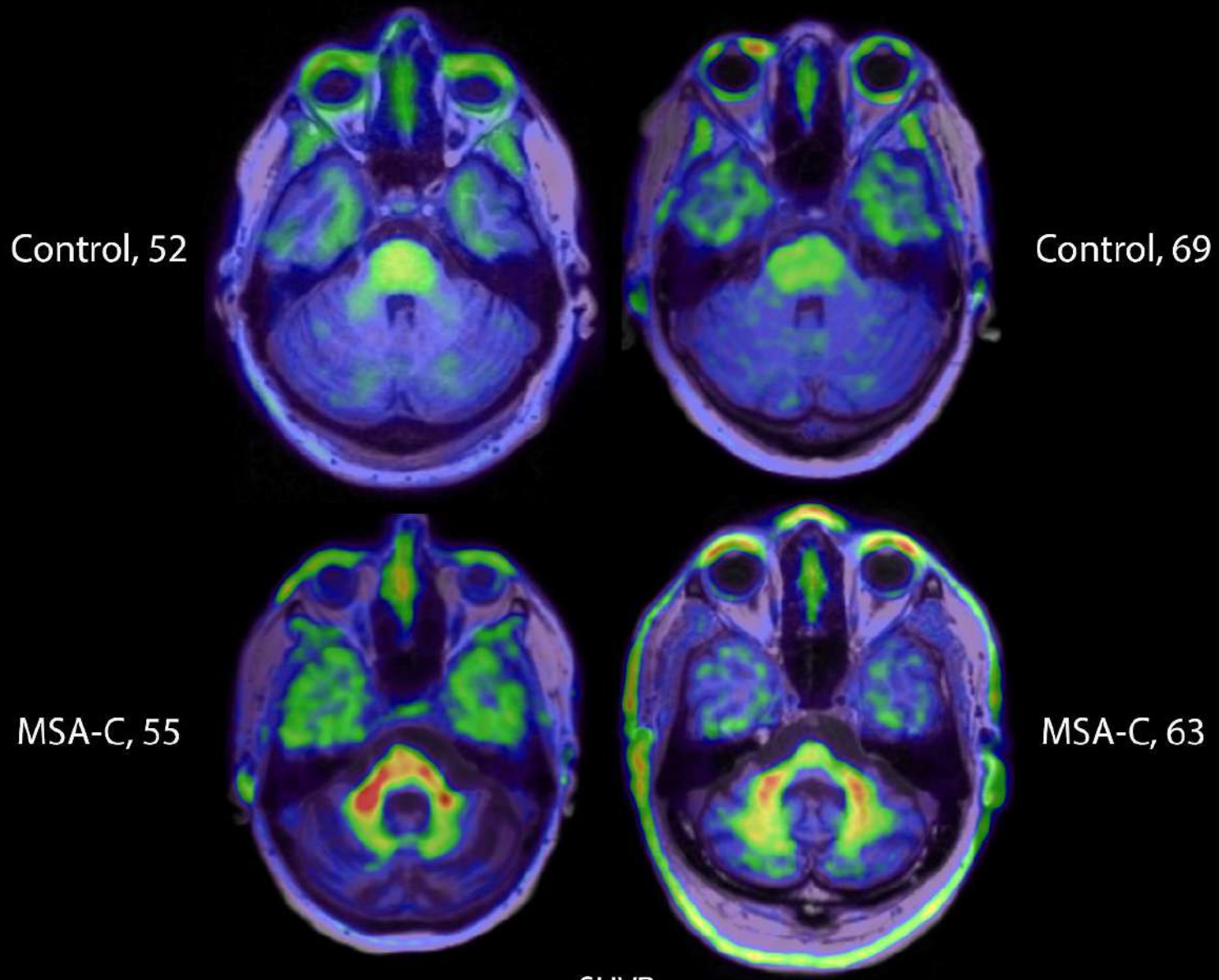


Currently, there **is no validate imaging biomarker** suitable for a definitive early diagnosis of α-synucleinopathies

Aggregated αSyn and Lewy pathology inclusion bodies **cannot be assessed ante-mortem** with SPECT or PET imaging because of the:
1) suboptimal binding characteristics (high binding affinity to **Aβ plaques and tau**)
2) physicochemical properties of current radiotracers (**BBB penetration**).

In 2022 two promising *proof-of-concept* studies have been presented
(1 published in *Mov Disord* and 1 presented at *AD/PD 2022 conference in Barcelona*)

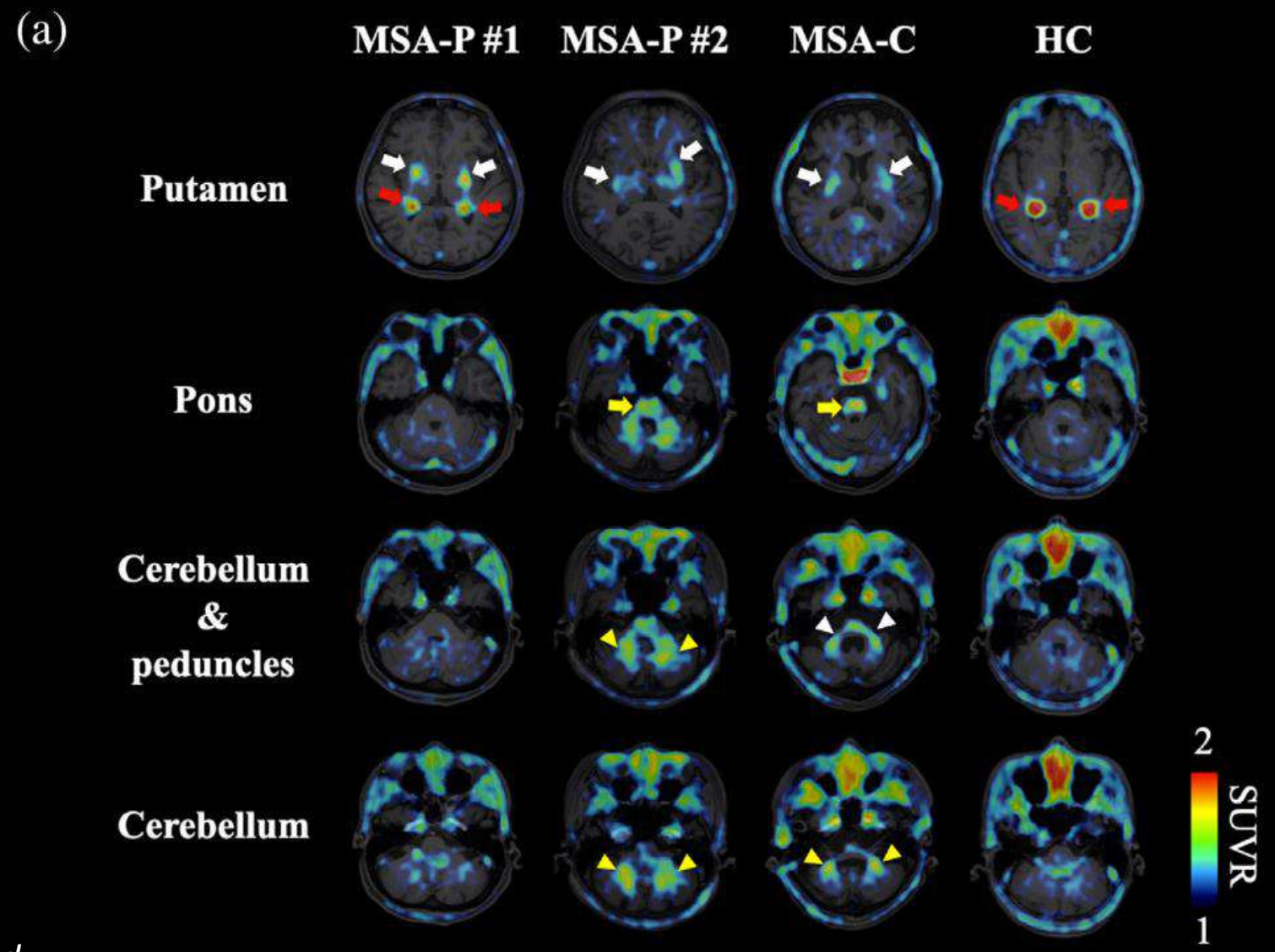
ACI-12589 PET Images



not yet published

AC Immune Reports at AD/PD 2022 Conference

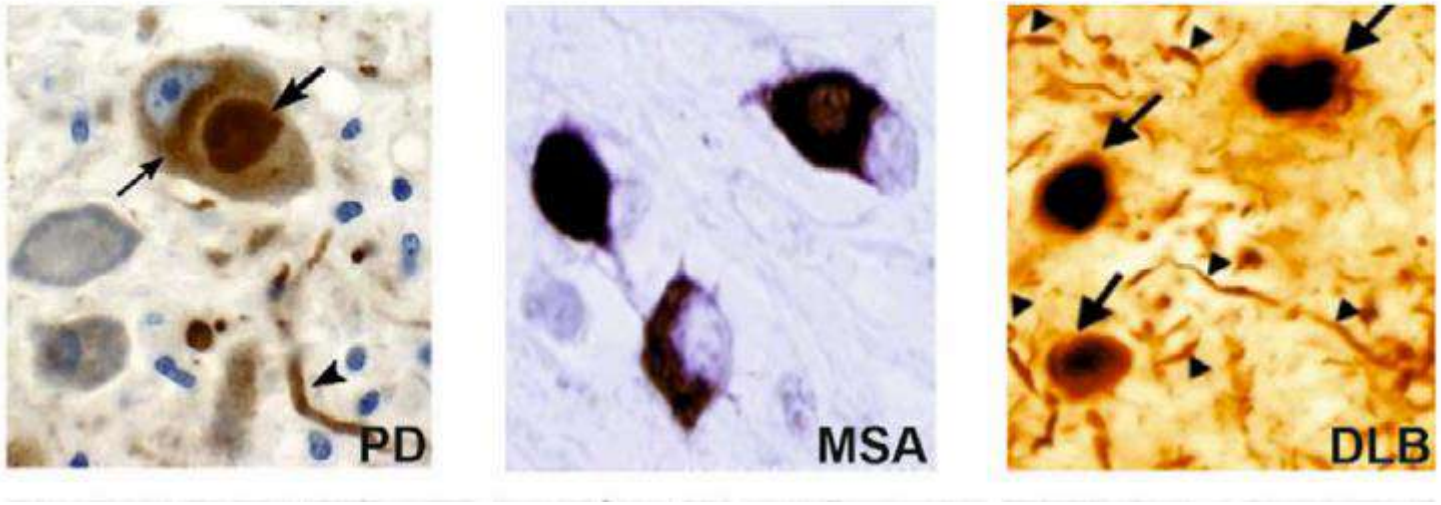
^{18}F-SPAL-T-06 PET imaging



first-in-human PET study

Matsuoka K, et al. Mov Disord. 2022

α-synuclein Imaging



These studies provides **the first *in vivo* demonstration** of **PET imaging of α-synuclein** pathologies in MSA-P and MSA-C patients with high contrast, **allowing visual read of images in each individual** for a diagnostic purpose.

PET assays of the ^{18}F-SPAL-T-06 and ACI-12589 binding in other α-synucleinopathies (idiopathic Parkinson's disease and **dementia with Lewy bodies**) are underway.

Ongoing Clinical trials

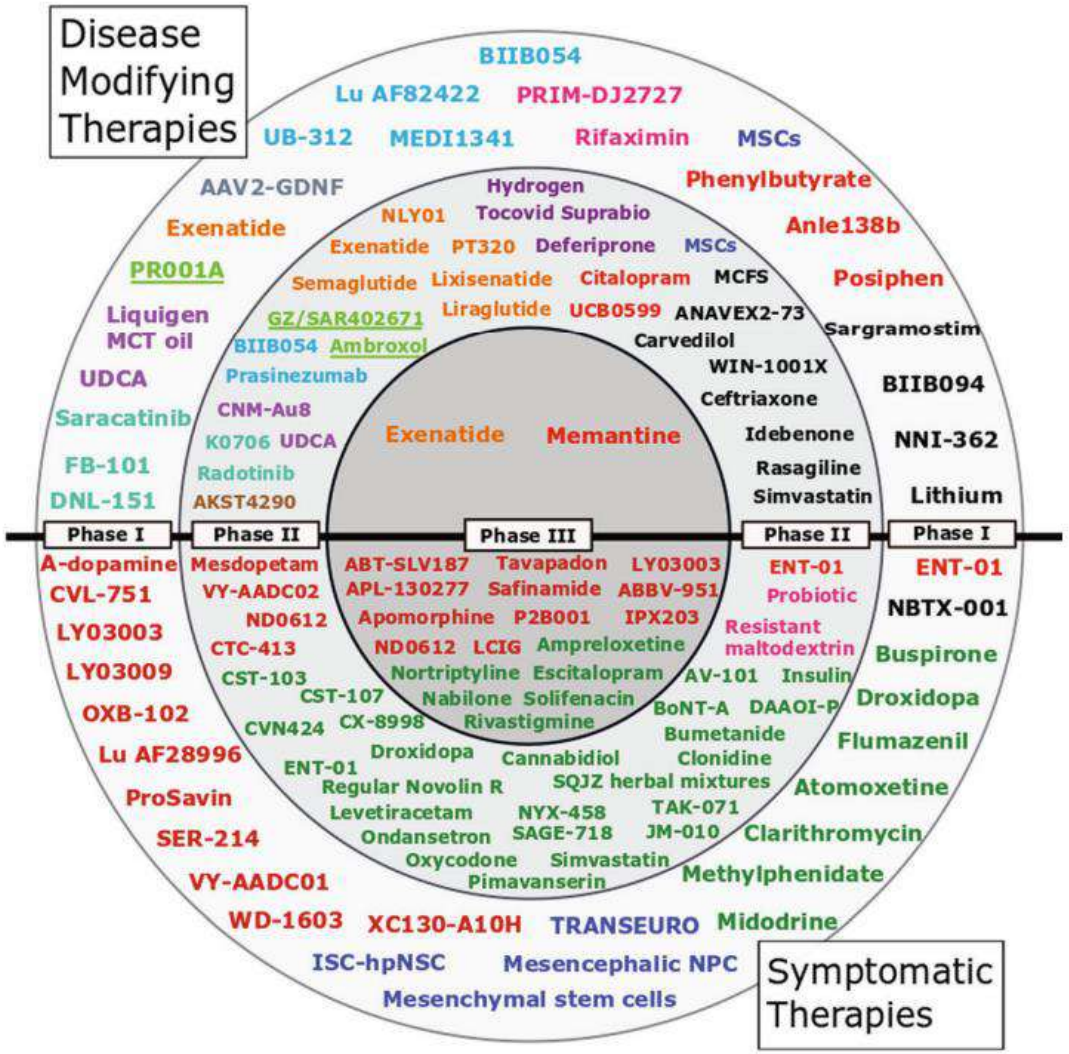


Table 4. Phase II clinical trials for dementia with Lewy bodies since 2016.

Goal[a]	Drug (mechanism of action)	ClinicalTrials.gov Identifier	Phase	Status[a]
Disease modification	Terazosin (α-1-selective adrenergic blocker)	NCT04760860	Phase I/II	Not yet recruiting
	K0706 (tyrosine kinase inhibitor)	NCT03996460	Phase II	Recruiting
	Nilotinib (tyrosine kinase inhibitor)	NCT04002674	Phase II	Recruiting
	Bosutinib (tyrosine kinase inhibitor)	NCT03888222	Phase II	Active, not recruiting
	Ambroxol (molecular chaperone for the lysosomal enzyme glucocerebrosidase (GCase))	NCT04405596	Phase I/II	Not yet recruiting
	Ambroxol (molecular chaperone for the lysosomal enzyme glucocerebrosidase (GCase))	NCT04588285	Phase II	Recruiting
	CST-103/clenbuterol + CST-107/nadolol (clenbuterol is a β2 adrenergic agonist; combined with nadolol to reduce side effects)	NCT04739423	Phase II	Recruiting
Symptomatic (parkinsonism, gait, cognition, psychosis)	RVT-101/intepirdine (5-HT-6 receptor antagonist)	NCT02669433 NCT02928445 NCT02910102	Phase II	Completed[67]
Symptomatic (cognition)	E2027 (selective inhibitor of phosphodiesterase 9; goal to increase cyclic GMP levels)	NCT03467152 NCT04764669	Phase II	Completed (NCT03467152); recruiting (NCT04764669)
Symptomatic (cognition)	LY3154207/mevidalen (D1 receptor positive allosteric modulator)	NCT03305809	Phase II	Completed
Symptomatic (cognition)	Neflamapimod (p38 MAP kinase alpha (p38α) inhibitor)	NCT04001517	Phase II	Active, not recruiting
Symptomatic (cognition)	NYX-458 (NMDA receptor modulator)	NCT04148391	Phase II	Recruiting
Symptomatic (psychosis, REM sleep behavior disorder)	Nelotanserin (selective antagonist at 5-HT2A serotonin receptor)	NCT02640729 NCT02708186 NCT02871427	Phase II	Completed (NCT02871427 terminated due to changes in development program)

Armstrong et al., 2021

Take-home messages

- I criteri della fase prodromica (MCI) della DLB sono stati recentemente definiti (*McKeith 2020*)
- I criteri della fase prodromica non-MCI (*psychiatric- and delirium- onset*) sono in corso di definizione
- Alcuni biomarkers (*fluidi, neuroimaging*) sono considerati di supporto per la diagnosi, sebbene vi sia necessita' di individuare e validare nuovi biomarkers
- La definizone biologica della DLB rimane un *unmeet need*, forse non piu' cosi lontana
- Questa definizione migliorera' il menagement dei pazienti ed il loro arruolamento nei futuri *disease-modifying trials*

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