SL&EP GRG
Sleep and Epilepsy
Genoa Research Group

OSPEDALE POLICLINICO SAN MARTINO
Sistema Sanitario Regione Liguria
Istituto di Ricovero e Cura a Carattere Scientifico

IL DISTURBO COMPORTAMENTALE IN SONNO REM ED IL DEFICIT COGNITIVO LIEVE

Dario Arnaldi, MD, PhD; DINOGMI; Genova

DINOGMI 2018-2022 | DIPARTIMENTO DI ECCELLENZA MIUR

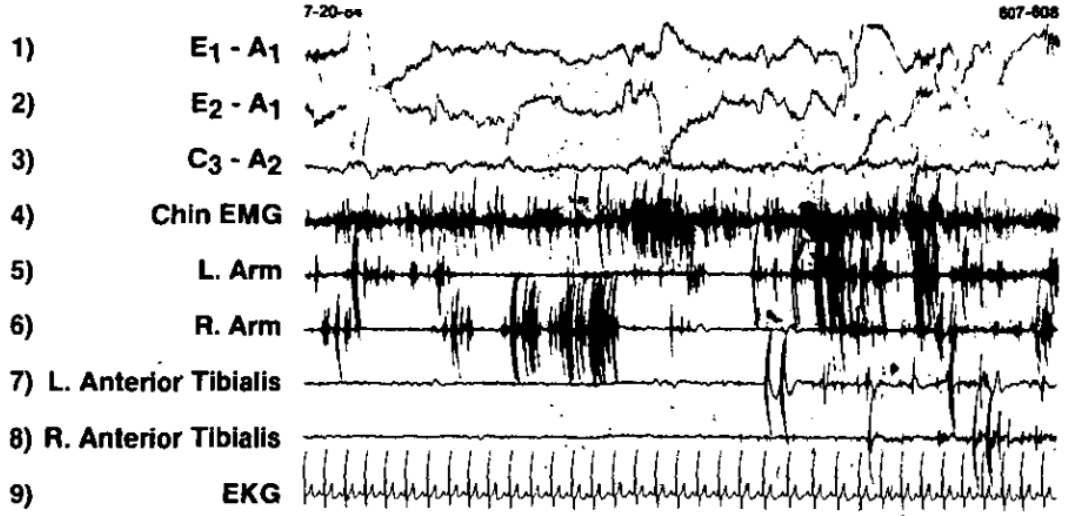
REM sleep Behavior Disorder (RBD)

- ✓ Complex and often violent behaviors occurring during REM sleep.
- ✓ Patients 'acting out their dreams' because of the loss of REM atonia.
- ✓ 1% in general population older than 50 yo.
- ✓ 'Idiopathic' = no evident neurological or psychiatric signs

Chronic Behavioral Disorders of Human REM Sleep: A New Category of Parasomnia

Carlos H. Schenck, Scott R. Bundlie, Milton G. Ettinger, and Mark W. Mahowald

Sleep, Vol. 9, No. 2, 1986



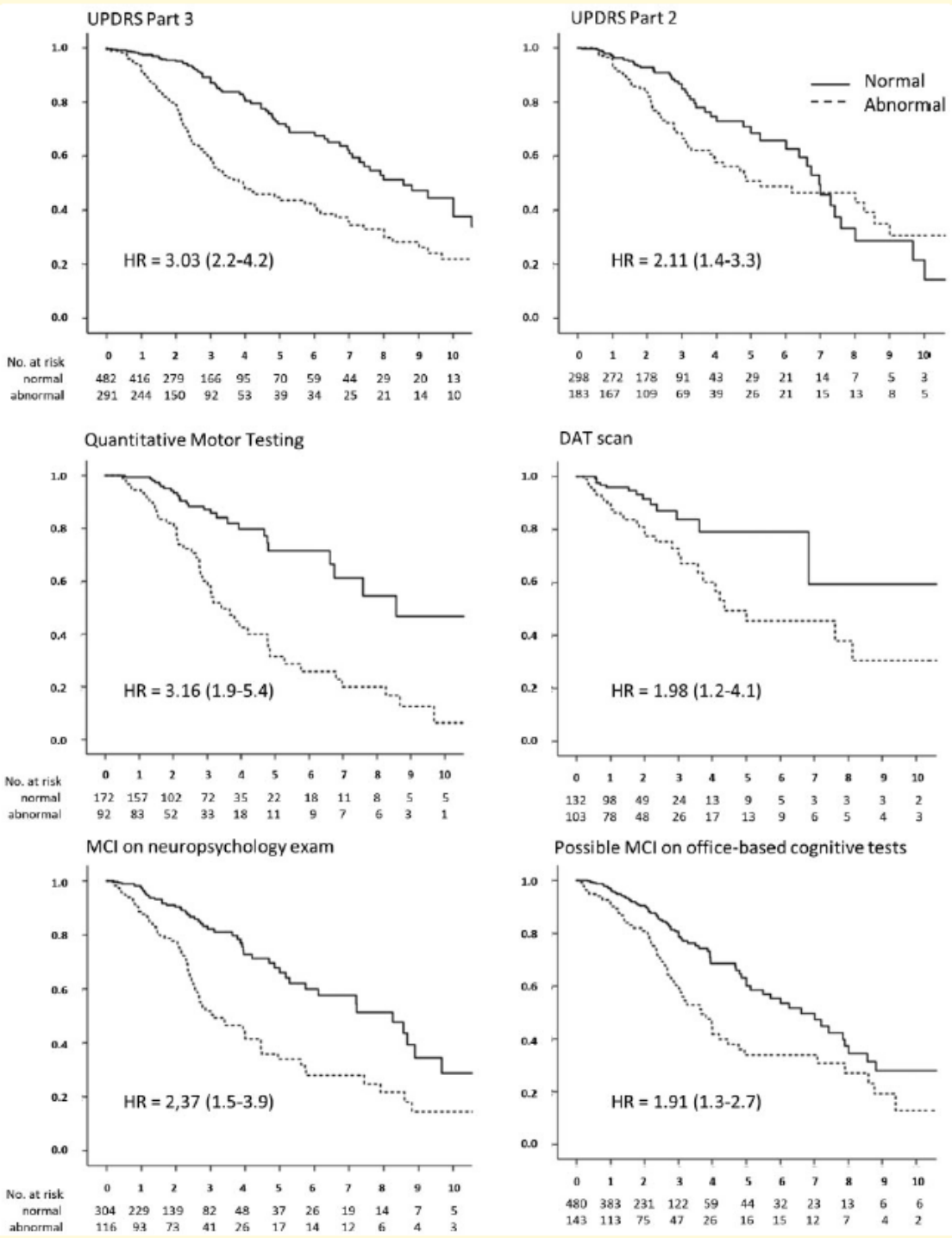
Johann Heinrich Füssli, The nightmare, 1781

’Typical’ RBD

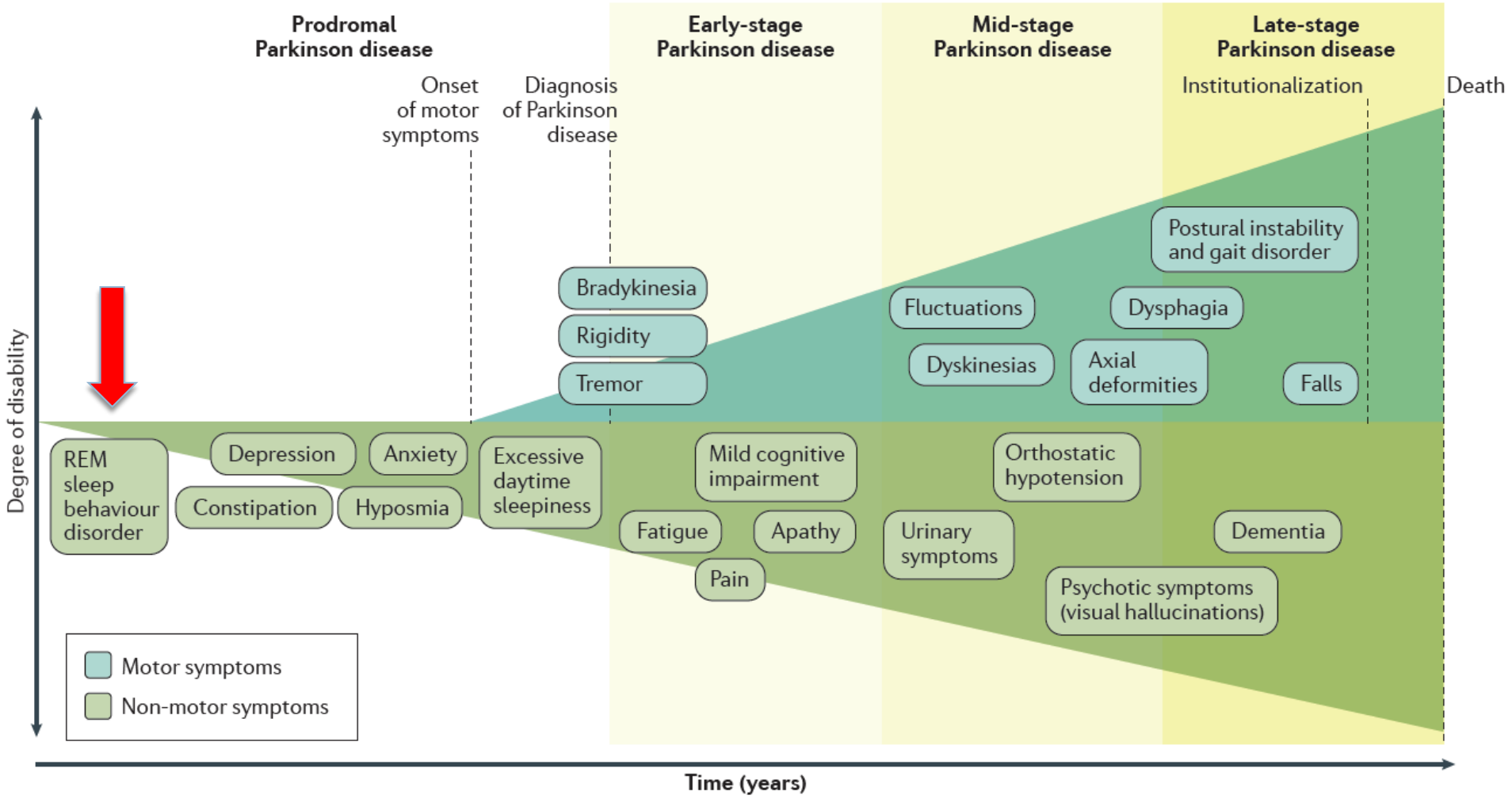
Risk and predictors of dementia and parkinsonism in idiopathic REM sleep behaviour disorder: a multicentre study

BRAIN 2019: 142; 744–759

- 24 centers worldwide
- 1280 patients
- Risk of phenoconversion:
  - 2 y → 10.6 %
  - 3 y → 17.9 %
  - 5 y → 31.3 %
  - 8 y → 51.4 %
  - 10 y → 60.2 %
  - 12 y → 73.5 %
- Disease manifestation
  - 56.5 % Parkinsonism first (4.5 % MSA)
  - 43.5 % Dementia first

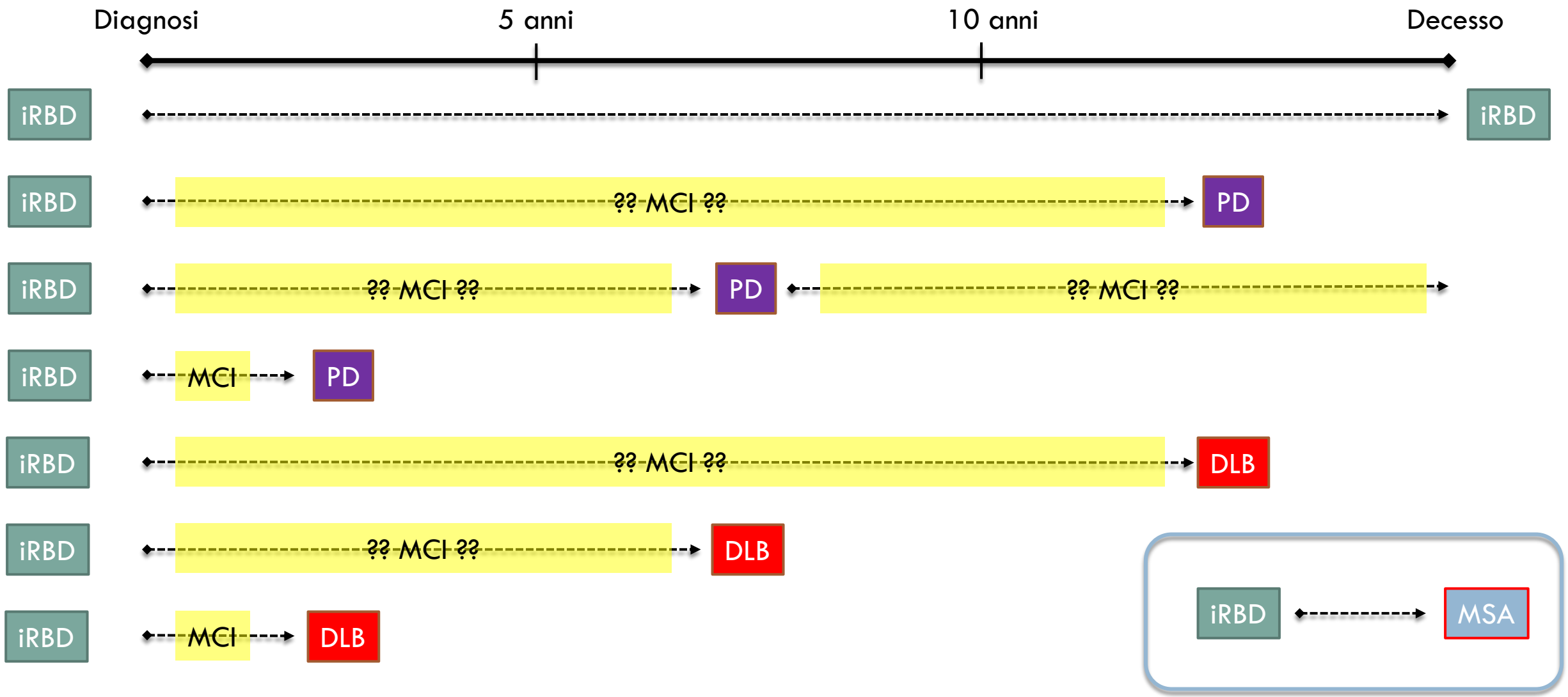


Clinical symptoms and time course of LBD progression



Nat Rev Dis Primers. 2017 Mar 23;3:17013.

Diverse traiettorie del paziente con iRBD

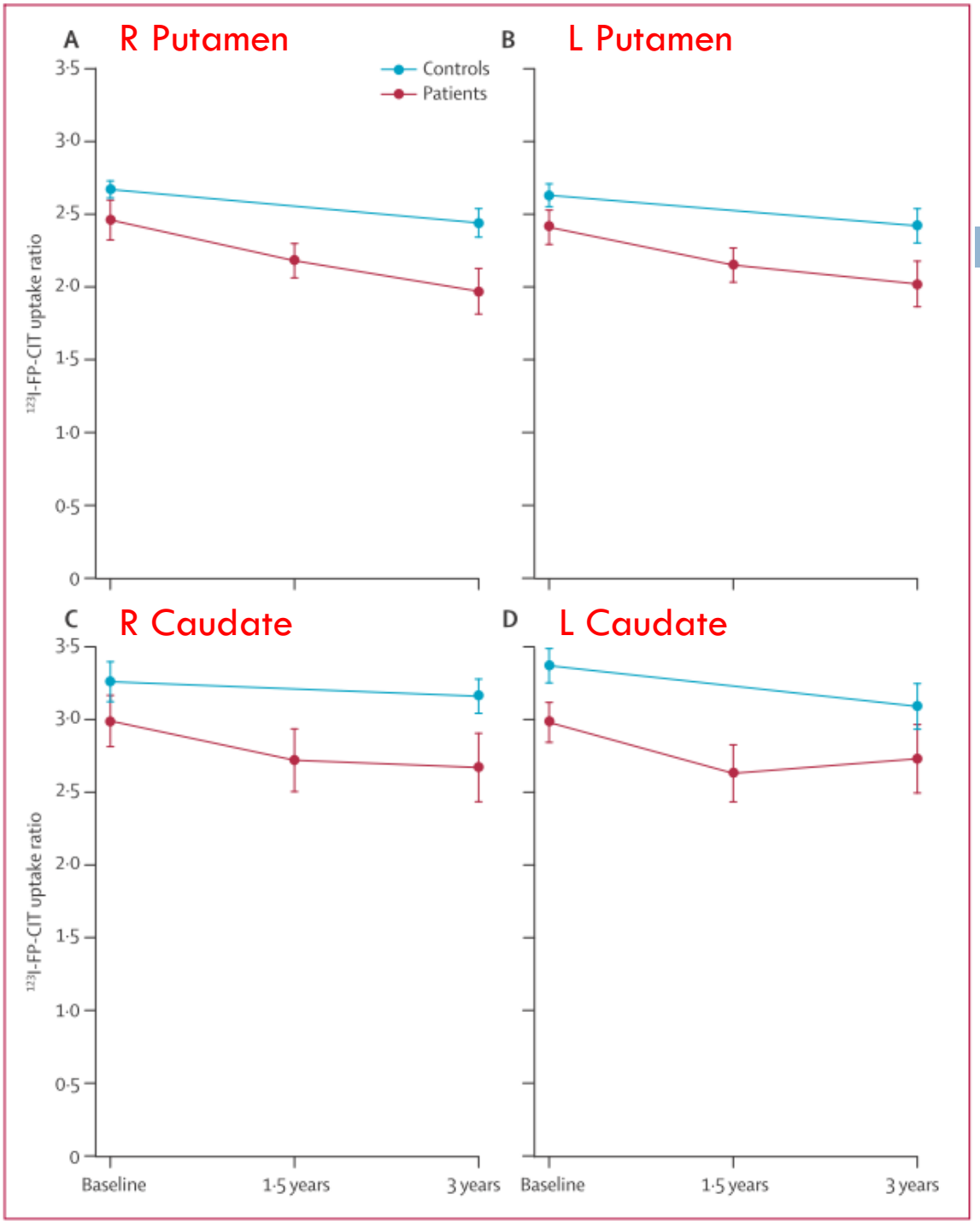


Biomarkers of conversion to α-synucleinopathy in isolated rapid-eye-movement sleep behaviour disorder

Lancet Neurol 2021; 20: 671–84

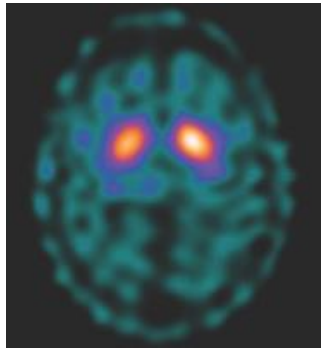
Mitchell G Miglis, Charles H Adler, Elena Antelmi, Dario Arnaldi, Luca Baldelli, Bradley F Boeve, Matteo Cesari, Irene Dall'Antonia, Nico J Diederich, Kathrin Doppler, Petr Dušek, Raffaele Ferri, Jean-François Gagnon, Ziv Gan-Or, Wiebke Hermann, Birgit Högl, Michele T Hu, Alex Iranzo, Annette Janzen, Anastasia Kuzkina, Jee-Young Lee, Klaus L Leenders, Simon J G Lewis, Claudio Liguori, Jun Liu, Christine Lo, Kaylena A Ehgoetz Martens, Jiri Nepozitek, Giuseppe Plazzi, Federica Provini, Monica Puligheddu, Michal Rolinski, Jan Rusz, Ambra Stefani, Rebekah L S Summers, Dallah Yoo, Jennifer Zitser, Wolfgang H Oertel

- Neurophysiology
- Motor function
- Cognition
- Olfaction
- Ophthalmic function
- Autonomic function
- Biofluids
- Neuroimaging
- Tissue biopsy
- Genetic testing

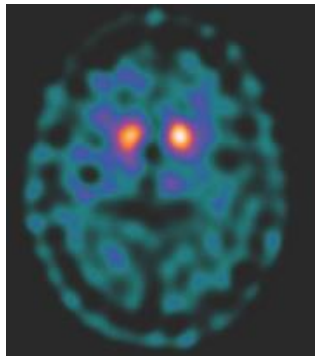


Serial dopamine transporter imaging of nigrostriatal function in patients with idiopathic rapid-eye-movement sleep behaviour disorder: a prospective study

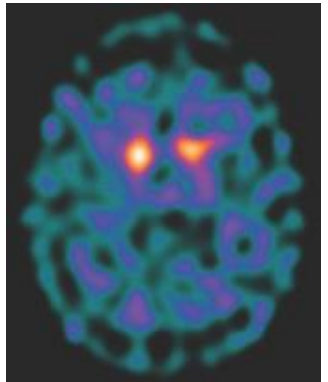
Lancet Neurol 2011; 10: 797–805



Baseline



1.5 y

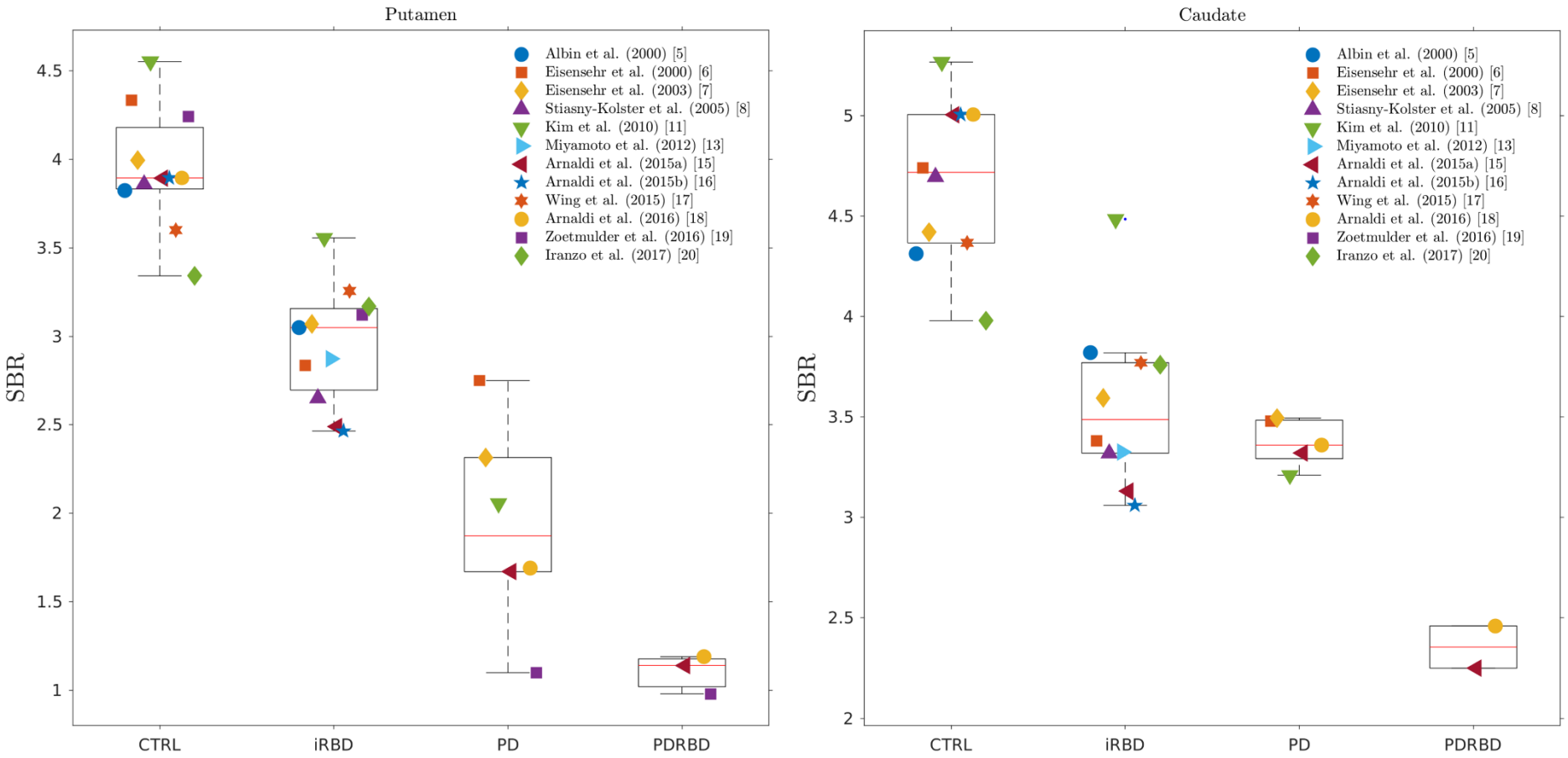


3 y

CLINICAL REVIEW

Presynaptic dopaminergic neuroimaging in REM sleep behavior disorder: A systematic review and meta-analysis

Matteo Bauckneht [a], Andrea Chincarini [b], Fabrizio De Carli [c], Michele Terzaghi [d], Silvia Morbelli [a], Flavio Nobili [e], Dario Arnaldi [e, *]



Sleep Med Rev. 2018 Apr 22

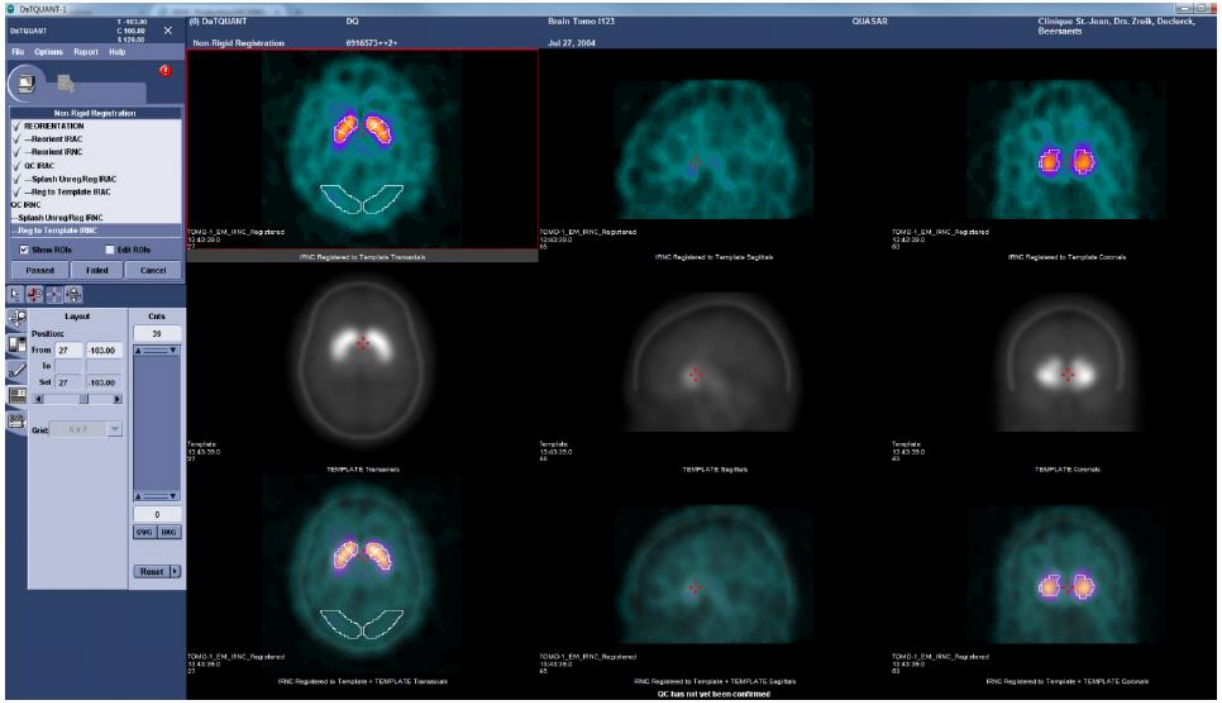
doi:10.1093/brain/awaa365

BRAIN
A JOURNAL OF NEUROLOGY

Dopaminergic imaging and clinical predictors for phenoconversion of REM sleep behaviour disorder

Dario Arnaldi,[1,2] Andrea Chincarini,[3] Michele T. Hu,[4] Karel Sonka,[5] Bradley Boeve,[6] Tomoyuki Miyamoto,[7] Monica Puligheddu,[8] Valérie Cochen De Cock,[9] Michele Terzaghi,[10,11] Giuseppe Plazzi,[12,13] Naoko Tachibana,[14] Silvia Morbelli,[15,16] Michal Rolinski,[4,17] Petr Dusek,[5] Val Lowe,[18] Masayuki Miyamoto,[19] Michela Figorilli,[8] Delphine de Verbizier,[20] Irene Bossert,[21] Elena Antelmi,[12,22] Riccardo Meli,[1,2] Thomas R. Barber,[4] Jiří Trnka,[23] Toji Miyagawa,[6] Alessandra Serra,[24] Fabio Pizza,[12,13] Matteo Bauckneht,[15,16] Kevin M. Bradley,[25] David Zogala,[23] Daniel R. McGowan,[26] Lennon Jordan,[18] Raffaele Manni[10] and Flavio Nobili[1,2]

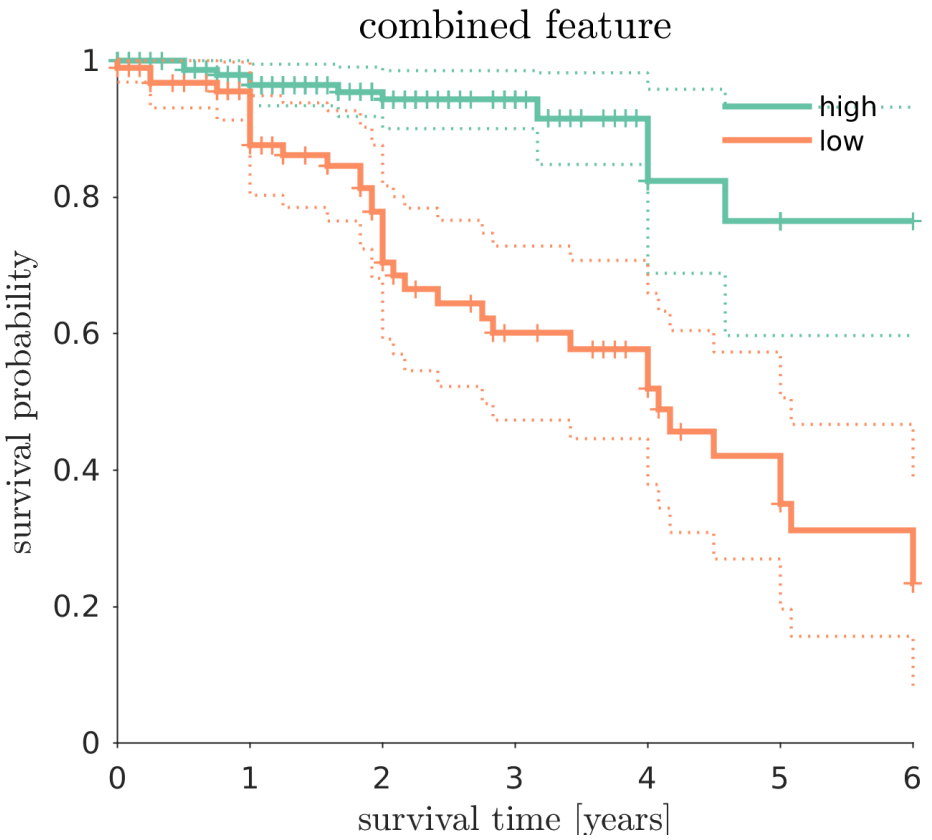
- Nine centers worldwide
- 263 iRBD patients
  - 67.6 ± 7.3 y, 229 males
- 243 Healthy controls
  - 67.2 ± 10.1 y, 110 males
- Baseline variables
  - ^{123}I-FP-CIT-SPECT (DAT-SPECT)
  - MDS-UPDRS-III
  - MMSE
  - Constipation
  - Hyposmia



Combination of clincal and imaging features

- Age over 70 years
- Most affected hemisphere (MAH) putamen uptake below 1.31 (1.5 SD)
- Presence of constipation

HR (95% C.I.) 5.71 (2.85-11.43)



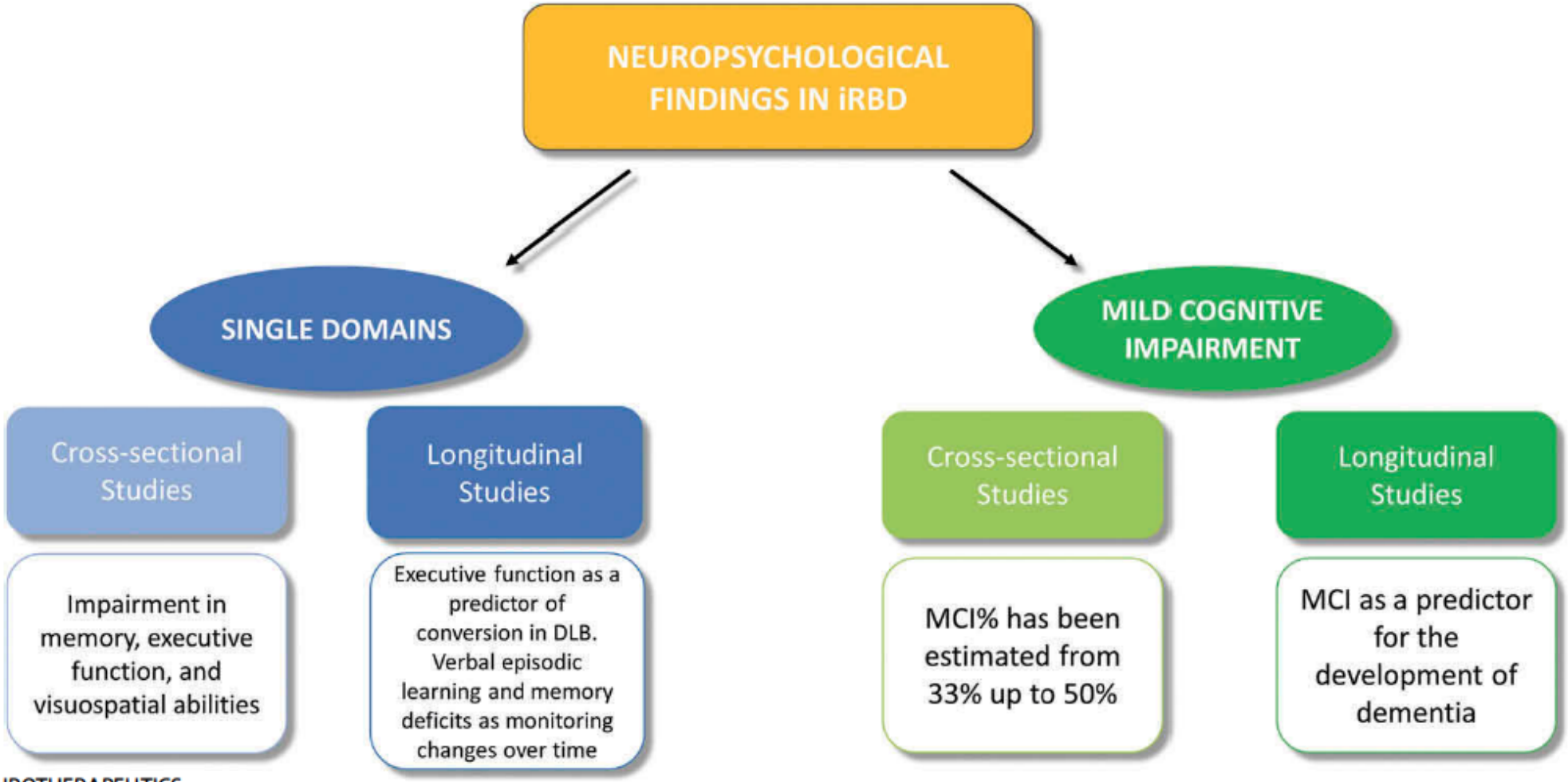
PD vs DLB

- Clinicamente non è facile distinguere le diverse traiettorie

	Parkinsonism-first $n = 184$	Dementia-first $n = 146$	*P*-value
Age	67.4 ± 6.6	68.3 ± 7.1	0.23
Sex, % male	81.0	88.4	0.068
UPDRS Part III			
Combined: abnormal	60.4%	63.7%	0.64
1987 UPDRS	5.40 ± 4.38 ($n = 60$)	6.17 ± 4.96 ($n = 77$)	0.34
MDS-UPDRS	5.56 ± 5.08 ($n = 41$)	6.36 ± 3.69 ($n = 14$)	0.53
Quantitative Motor Abnormal	47.2% ($n = 36$)	82.4% ($n = 34$)	0.002
UPDRS Part II			
Combined, above mean	50.0%	61.7%	0.22
1987 UPDRS	1.44 ± 1.84 ($n = 35$)	1.10 ± 1.46 ($n = 34$)	0.51
MDS-UPDRS	2.38 ± 2.75 ($n = 34$)	5.60 ± 6.12 ($n = 15$)	0.27
Olfaction abnormal	75.7% ($n = 70$)	86.5% ($n = 52$)	0.13
Colour vision abnormal	30.3% ($n = 33$)	73.5% ($n = 34$)	<0.001
Insomnia	26.1% ($n = 46$)	32.1% ($n = 28$)	0.58
Daytime somnolence	28.6% ($n = 133$)	40.4% ($n = 114$)	0.051
Restless legs syndrome	21.1% ($n = 95$)	11.3% ($n = 62$)	0.11
Apnoea (AHI ⩾ 15)	26.8% ($n = 158$)	31.9% ($n = 94$)	0.98
REM %: above mean	57.4%	64.3%	0.47
Tonic REM % (MTL)	50.2 ± 28.1 ($n = 60$)	56.3 ± 31.6 ($n = 39$)	0.33
Phasic REM % (MTL)	29.8 ± 19.9 ($n = 42$)	35.8 ± 16.6 ($n = 34$)	0.16
% Any (SINBAR)	66.4 ± 19.9 ($n = 13$)	61.2 ± 26.0 ($n = 5$)	0.70
Constipation	56.8% ($n = 111$)	57.5% ($n = 80$)	0.92
Urinary dysfunction	29.4% ($n = 85$)	39.6% ($n = 53$)	0.22
Erectile dysfunction	52.8% ($n = 36$)	75.0% ($n = 28$)	0.069
Orthostatic symptoms	28.4% ($n = 67$)	39.1% ($n = 46$)	0.23
Systolic blood pressure drop	12.7 ± 15.7 ($n = 44$)	17.0 ± 21.9 ($n = 37$)	0.32
Abnormal office: cognitive test (regardless of complaint)	43.2%	65.2%	0.003
MoCA	25.8 ± 2.6 ($n = 49$)	22.6 ± 3.5 ($n = 30$)	<0.001
MMSE	27.8 ± 1.7 ($n = 57$)	26.4 ± 3.3 ($n = 70$)	0.002
Neuropsychological abnormal (regardless of complaint)	29.8% ($n = 57$)	86.8% ($n = 76$)	<0.001
Mild cognitive impairment			
Neuropsychological testing	25.9% ($n = 54$)	84.1% ($n = 63$)	<0.001
MoCA/MMSE	30.1% ($n = 73$)	56.9% ($n = 72$)	0.001
Depression	28.6% ($n = 119$)	32.6% ($n = 92$)	0.53
Anxiety	22.5% ($n = 71$)	28.2% ($n = 39$)	0.52
Substantia nigra ultrasound	60.0% ($n = 10$)	66.7% ($n = 3$)	0.84
DAT scan (putamen) abnormal	70.3% ($n = 37$)	71.4% ($n = 14$)	0.94

BRAIN 2019: 142; 744–759

Mild Cognitive Impairment (MCI) e iRBD

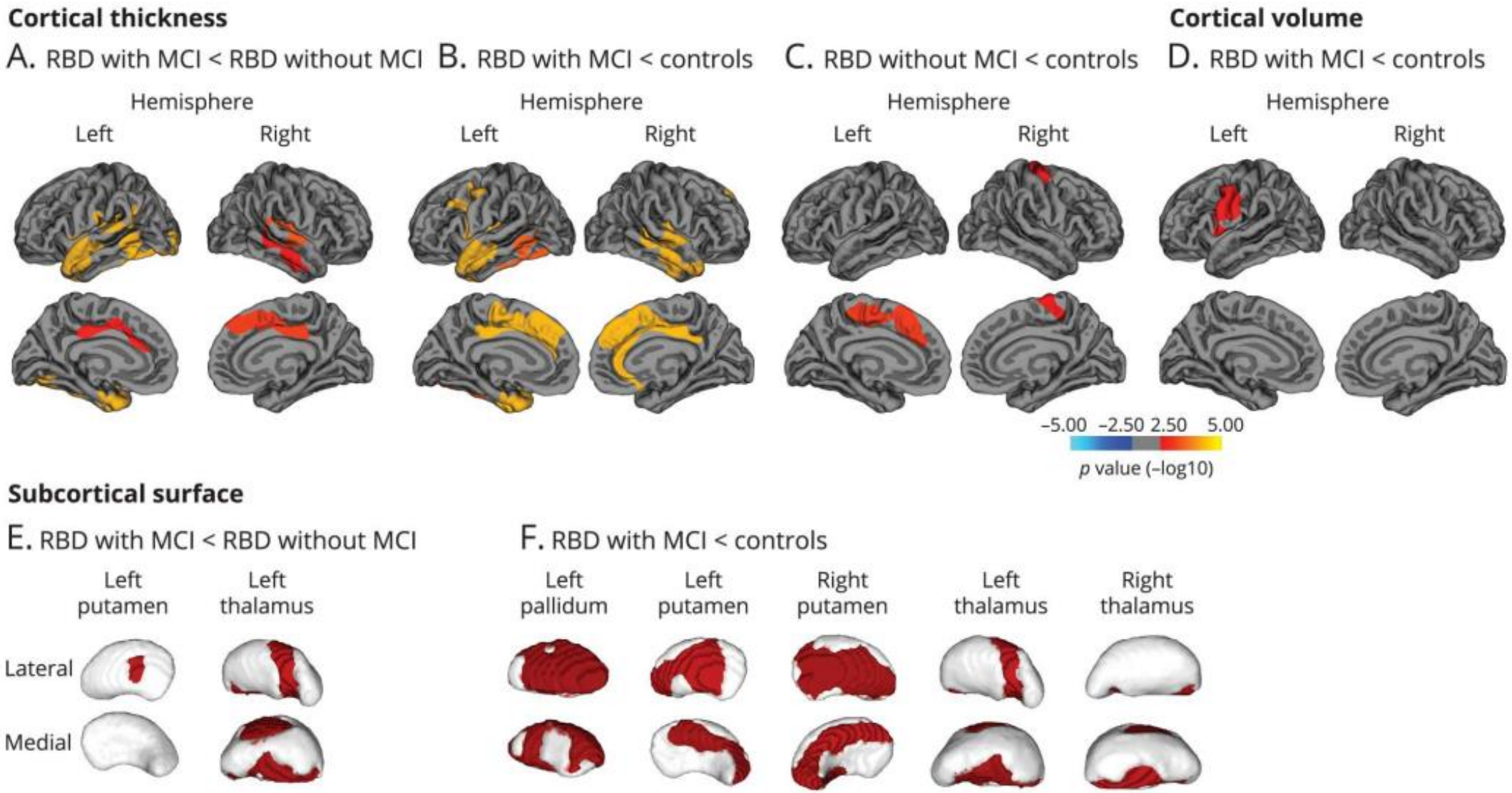


EXPERT REVIEW OF NEUROTHERAPEUTICS
2019, VOL. 19, NO. 11, 1069–1087
https://doi.org/10.1080/14737175.2019.1640603

L. FERINI-STRAMBI ET AL.

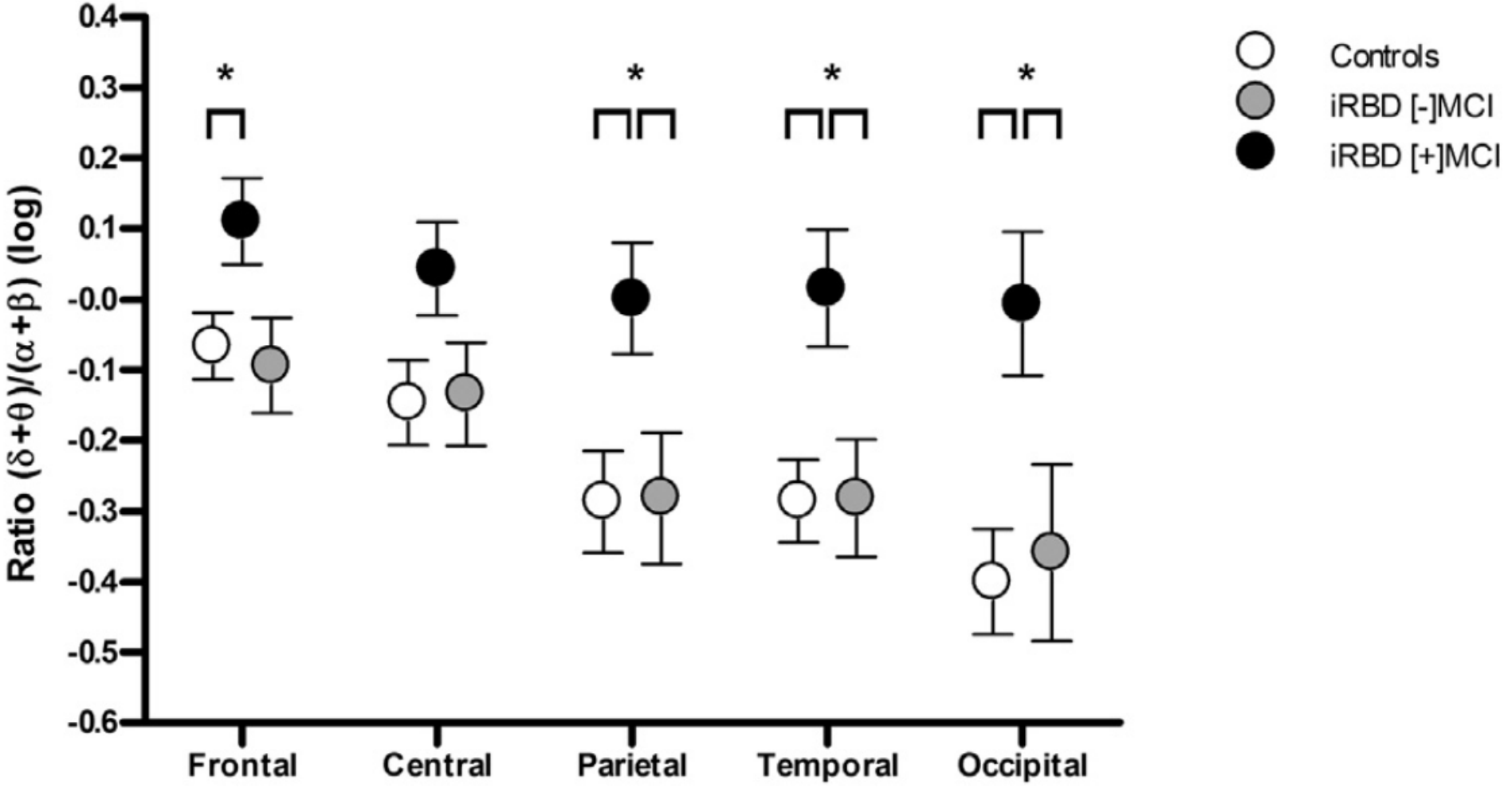
Cortical and subcortical gray matter bases of cognitive deficits in REM sleep behavior disorder

Neurology® 2018;90:e1759-e1770.



Electroencephalogram slowing in rapid eye movement sleep behavior disorder is associated with mild cognitive impairment

Jessica Rodrigues Brazète [a,b], Jacques Montplaisir [a,c], Dominique Petit [a], Ronald B. Postuma [a,d], Josie-Anne Bertrand [a,e], Daphné Génier Marchand [a,e], Jean-François Gagnon [a,e,*]

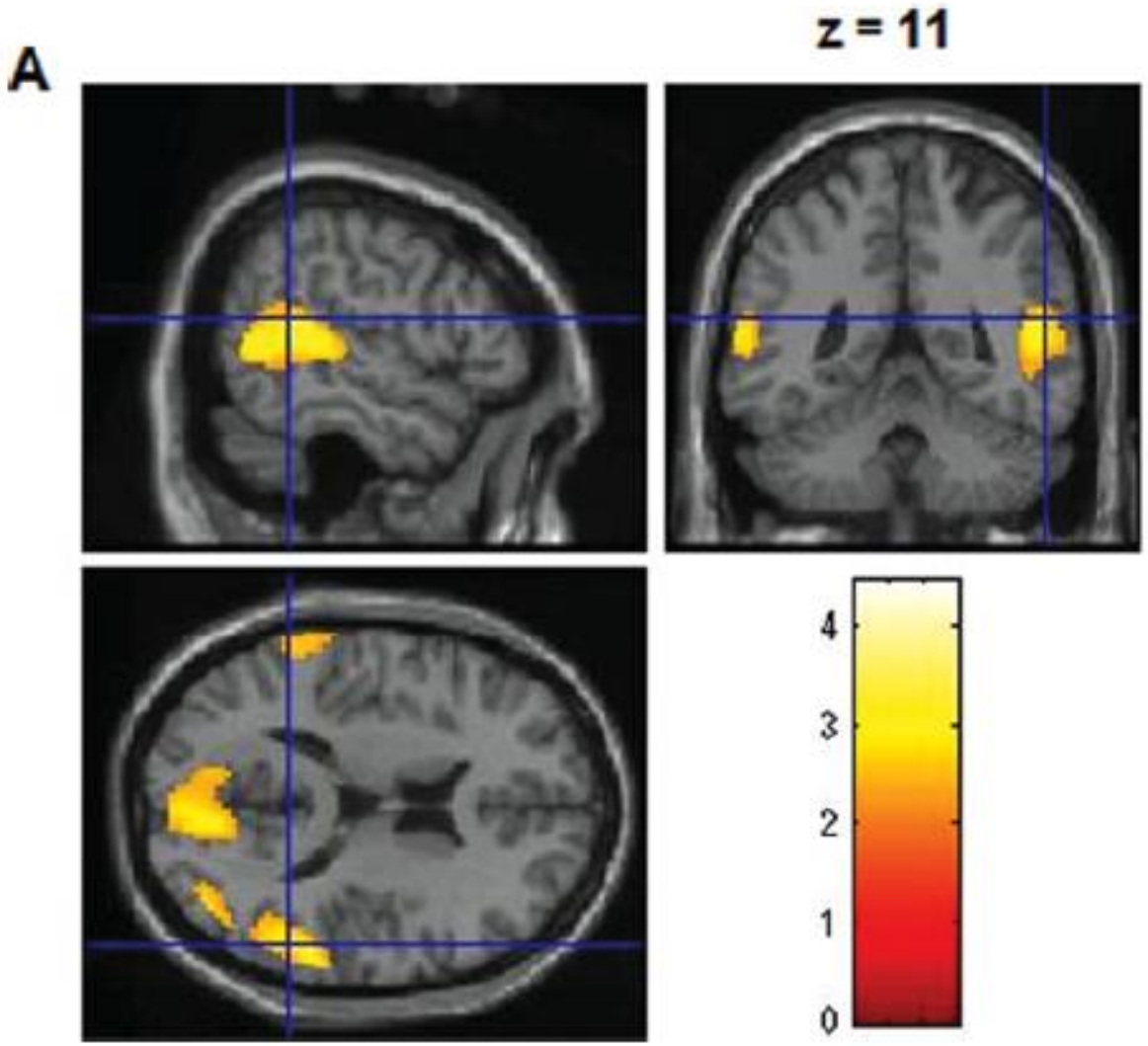


Sleep Medicine 14 (2013) 1059–1063

Brain Perfusion Anomalies in Rapid Eye Movement Sleep Behavior Disorder with Mild Cognitive Impairment

Mélanie Vendette, MSc,[1,2] Jacques Montplaisir, MD, PhD,[1,3] Nadia Gosselin, PhD,[1,3] Jean-Paul Soucy, MD, MSc,[4,5]
Ronald B. Postuma, MD, MSc,[6] Thien Thanh Dang-Vu, MD, PhD,[1,7] and Jean-François Gagnon, PhD[1,8*]

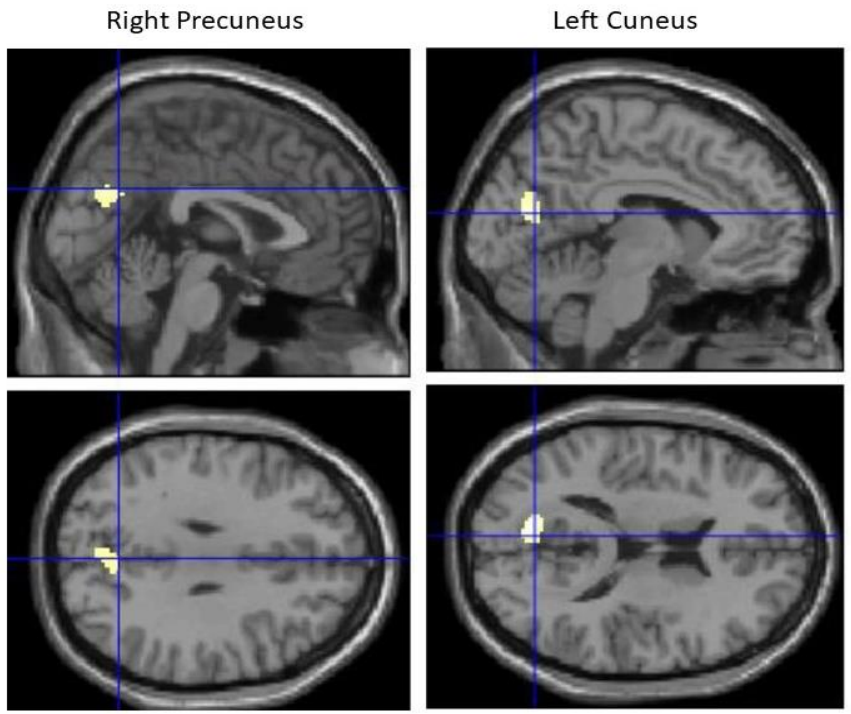
- I pazienti iRBD con MCI hanno ridotto flusso cerebrale rispetto ai pazienti iRBD con cognitività normale

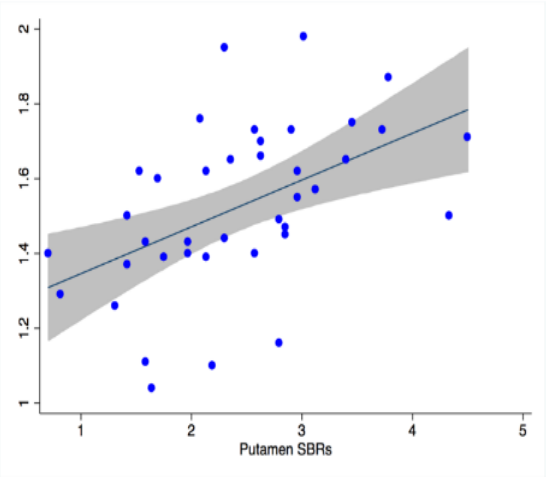


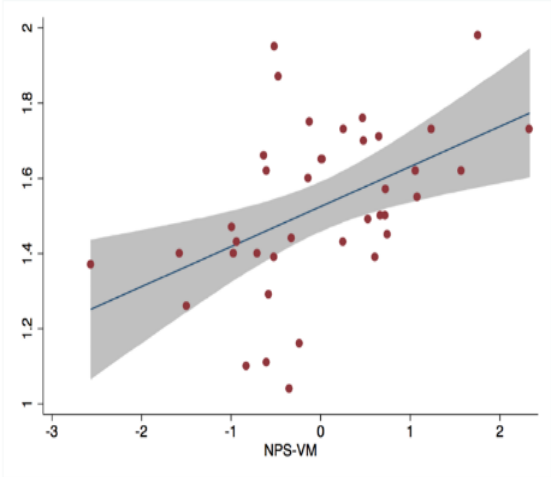
Movement Disorders, Vol. 27, No. 10, 2012

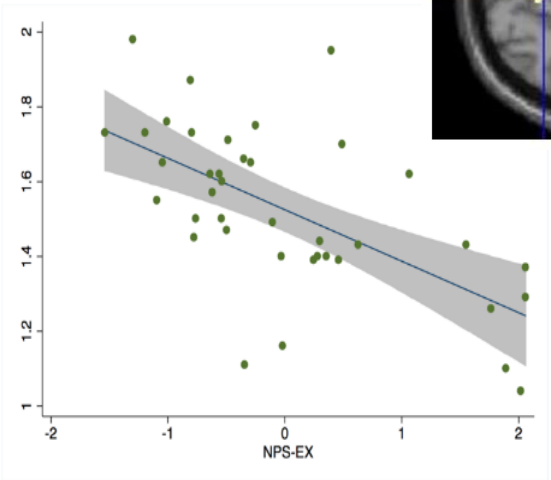
Metabolismo glucidico cerebrale nell'iRBD con MCI

- Cuneo/precuneo
  - Hub per la funzionalità cognitiva nell'iRBD
  - Correla con
    - DAT-SPECT
    - Funzioni esecutive
    - Memoria verbale









Mattioli et al. EJNMMI 2021

The fate of patients with REM sleep behavior disorder and mild cognitive impairment

Dario Arnaldi [a, b, *], Andrea Chincarini [c], Fabrizio De Carli [d], Francesco Famà [a, b], Nicola Girtler [a, b], Andrea Brugnolo [a, b], Matteo Pardini [a, b], Federico Massa [a, b], Riccardo Meli [a, b], Cristina Schenone [a, b], Matteo Bauckneht [e, b], Silvia Morbelli [e, b], Flavio Nobili [a, b]

- I pazienti iRBD con MCI hanno
  - Peggiori performance cognitive (per definizione)
  - Più severa disfunzione dopaminergica
  - Più alto rischio di conversione (DLB)

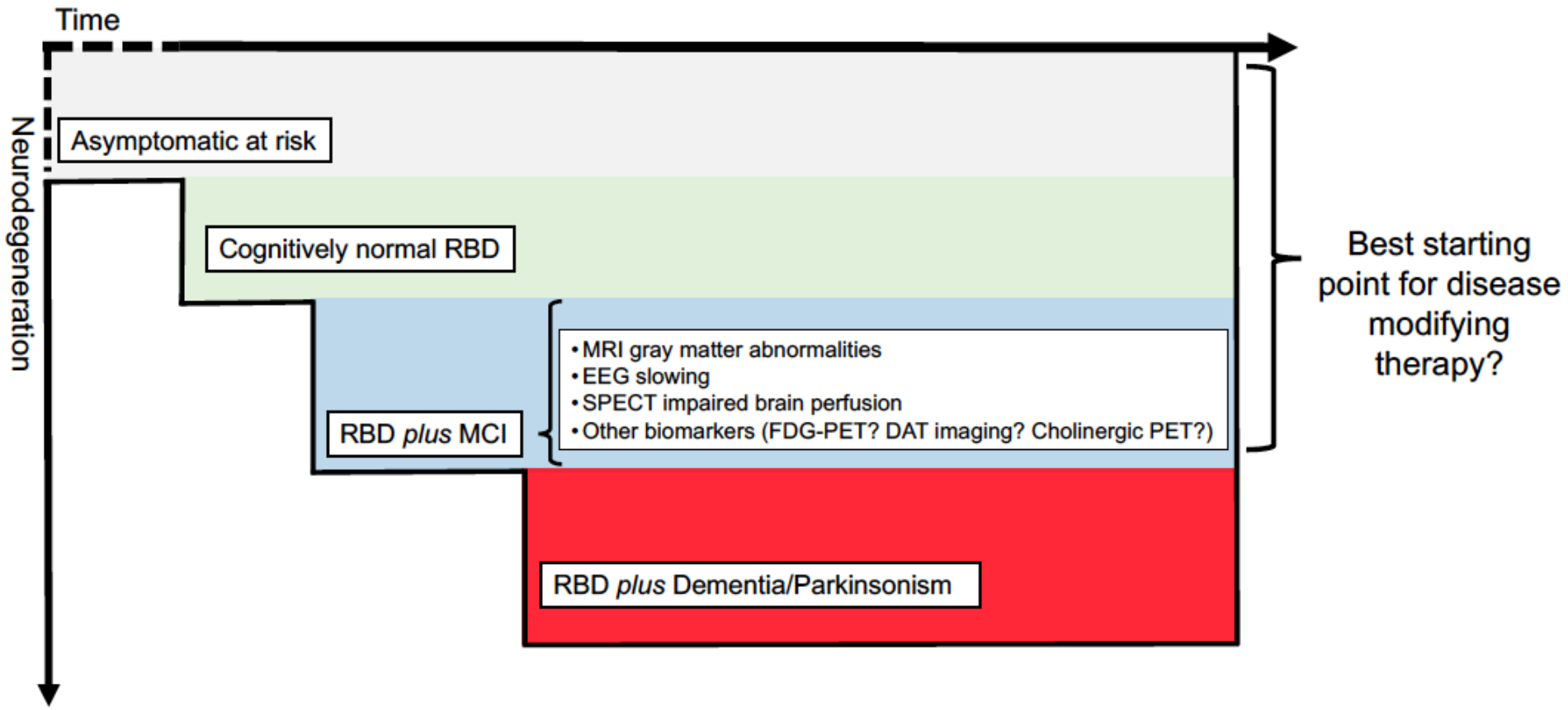
	iRBD-NC	iRBD-MCI	*p*
Baseline			
Patients number (%)	30 (68.2%)	14 (31.8%)	
Age, y	67.7 ± 7.6	70.3 ± 6.3	ns
Male/Female	27/3	11/3	ns
Education, y	10.0 ± 4.5	9.5 ± 4.3	ns
RBD duration (prior diagnosis), m	45.8 ± 37	30.9 ± 30.4	ns
MMSE	28.7 ± 1.3	27.6 ± 1.9	**0.025**
BDI-II	10.8 ± 7.8	11.6 ± 9	ns
Hyposmia	17 (56.7%)	6 (42.9%)	ns
Constipation	11 (36.7%)	9 (64.3%)	**0.043**
Orthostatic Hypotension	3 (10%)	3 (21%)	ns
MDS-UPDRS I	0.2 ± 0.4	0.4 ± 0.5	ns
MDS-UPDRS II	0.1 ± 0.3	0.1 ± 0.3	ns
MDS-UPDRS III	0.8 ± 1.7	1.8 ± 2	**0.029**
Tonic RWA, %	40.8 ± 23	50.7 ± 23	ns
Phasic RWA, %	51.0 ± 22	61.1 ± 20	ns
Any RWA, %	65.8 ± 19	70.7 ± 20	ns
^{123}I-FP-CIT-SPECT data			
Putamen SBRs	2.9 ± 0.9	2.0 ± 0.5	**0.0005**
Caudate SBRs	3.5 ± 1.0	3.0 ± 0.4	**0.037**
Neuropsychological (NPS) data			
NPS1-executive functions	0.51 ± 0.8	−0.59 ± 0.8	**0.0001**
NPS2-verbal memory/visuoconstruction	0.32 ± 0.6	−0.43 ± 1.2	**0.005**
NPS3-Attention	0.03 ± 1.1	0.34 ± 1.1	0.19
Follow-up data			
Converted patients	4 (13%)	6 (43%)	**0.015**
DLB	0 (0%)	5 (36%)	**0.0005**
PD	4 (13%)	1 (7%)	0.273
Conversion time (from iRBD diagnosis), m	38.5 ± 41	18.3 ± 7	0.131
Conversion time (from symptoms onset), m	86.5 ± 46	45.8 ± 16	**0.038**
Follow-up, m	31.5 ± 23	29.9 ± 19	0.409

Sleep Medicine 79 (2021) 205–210

The clinical relevance of cognitive impairment in REM sleep behavior disorder

Dario Arnaldi, MD, PhD, and Flavio Nobili, MD

Neurology® 2018;90:1-2. doi:10.1212/WNL.0000000000005508



Diagnosis and management of dementia with Lewy bodies

Fourth consensus report of the DLB Consortium

Neurology® 2017;89:88-100

Ian G. McKeith, MD, F Med Sci
Bradley F. Boeve, MD
Dennis W. Dickson, MD
Glenda Halliday, PhD
John-Paul Taylor, PhD, MRC Psych
Daniel Weintraub, MD
Dag Aarsland, MD
James Galvin, MD, MPH
Johannes Attems, MD
Clive G. Ballard, MRC Psych, MD
Ashley Bayston, BA, LLB
Thomas G. Beach, MD, PhD
Frédéric Blanc, MD, PhD
Nicolaas Bohnen, MD, PhD
Laura Bonanni, MD, PhD
Jose Bras, PhD
Patrik Brundin, MD, PhD
David Burn, MD, FRCP
Alice Chen-Plotkin, MD
John E. Duda, MD
Omar El-Agnaf, PhD
Howard Feldman, MD, FRCP
Tanis J. Ferman, PhD
Dominic ffytche, MD
Hiroshige Fujishiro, MD
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Jennifer G. Goldman, MD, MS
Stephen N. Gomperts, MD, PhD
Neill R. Graff-Radford, MD
Lawrence S. Honig, MD, PhD
Alex Iranzo, MD, PhD

- Essential
  - Dementia
- Core clinical features
  - Fluctuating cognition
  - Visual hallucinations
  - RBD
  - Parkinsonism
- Supportive clinical features
  - Sensitivity to antipsychotic; Postural instability; Repeated falls; Severe autonomic dysfunction; Hypersomnia; Hyposmia; Psychiatric symptoms.

Inclusion of RBD improves the diagnostic classification of dementia with Lewy bodies

Neurology® 2011;77:875-882

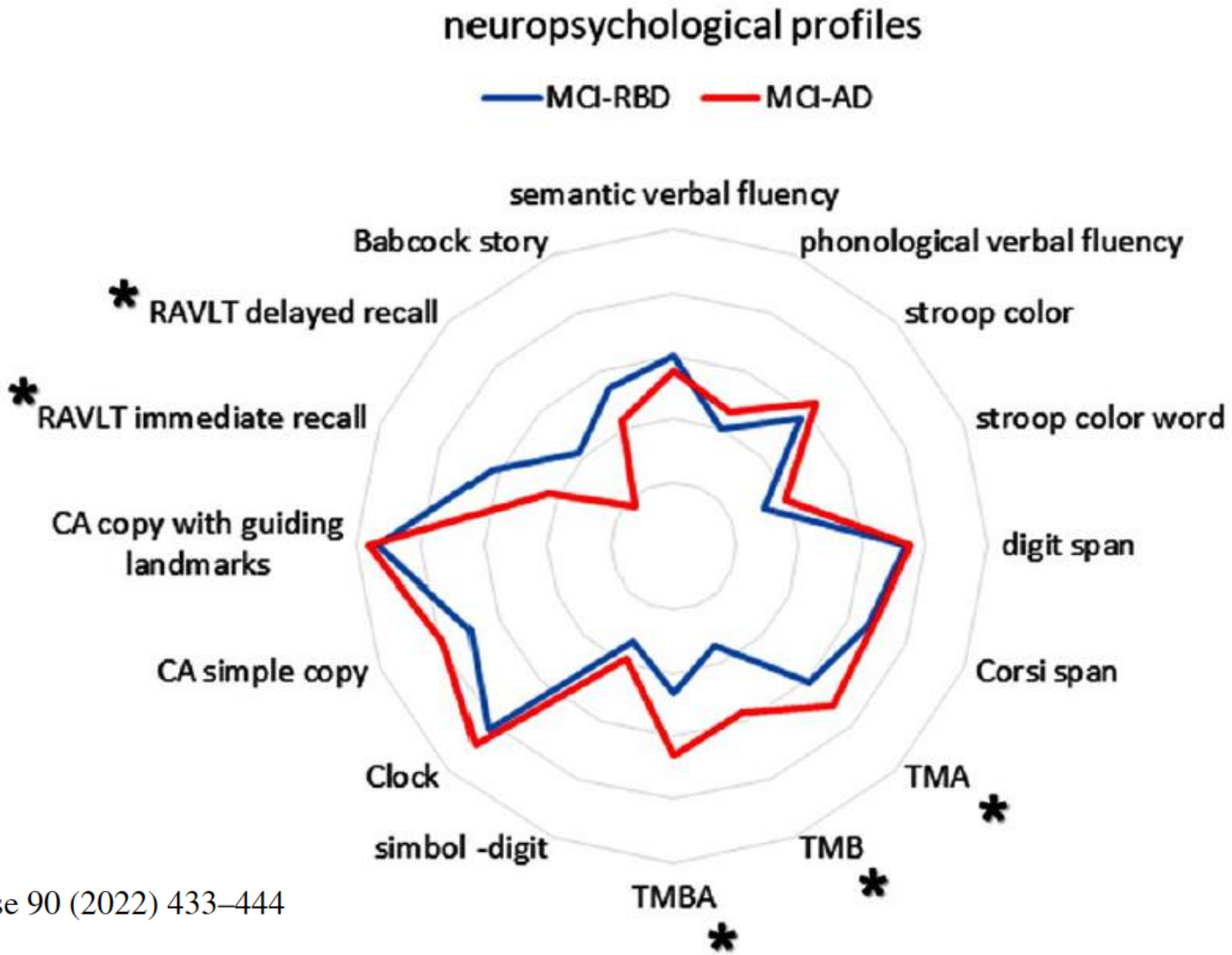
Table 4 Diagnostic accuracy of clinical feature combinations

Dementia plus clinical features	DLB intermediate-high	DLB no-low	χ^2	*p* Value	Sensitivity (95% CI)	Specificity (95% CI)	PPV, %	NPV, %
Two or more: visual hallucinations, parkinsonism, fluctuations								
Yes	83	37						
No	15	99	73	<0.01	85 (76-91)	73 (64-80)	69	87
Two or more: visual hallucinations, parkinsonism, fluctuations, RBD								
Yes	86	37						
No	12	99	82	<0.01	88 (79-93)	73 (64-80)	70	89
RBD as sole clinical feature or 2 or more: VH, parkinsonism, fluctuations, RBD								
Yes	88	37						
No	10	99	90	<0.01	90 (82-95)	73 (64-80)	70	91
Two or more: visual hallucinations, parkinsonism, RBD								
Yes	81	21						
No	17	115	102	<0.01	83 (73-89)	85 (77-90)	79	87

Abbreviations: CI = confidence interval; DLB = dementia with Lewy bodies; NPV = negative predictive value; PPV = positive predictive value; RBD = REM sleep behavior disorder.

Cognitive and Brain Metabolism Profiles of Mild Cognitive Impairment in Prodromal Alpha-Synucleinopathy

Pietro Mattioli[a,*], Matteo Pardini[a,b], Nicola Girtler[a,c], Andrea Brugnolo[a,c], Beatrice Orso
Andrea Donniaquio[a], Francesco Calizzano[a], Raffaele Mancini[a], Federico Massa[a],
Michele Terzaghi[d,e], Matteo Bauckneht[b,f], Silvia Morbelli[b,f], Gianmario Sambuceti[b,f],
Flavio Nobili[a,b] and Dario Arnaldi[a,b]



Journal of Alzheimer's Disease 90 (2022) 433–444
DOI 10.3233/JAD-220653

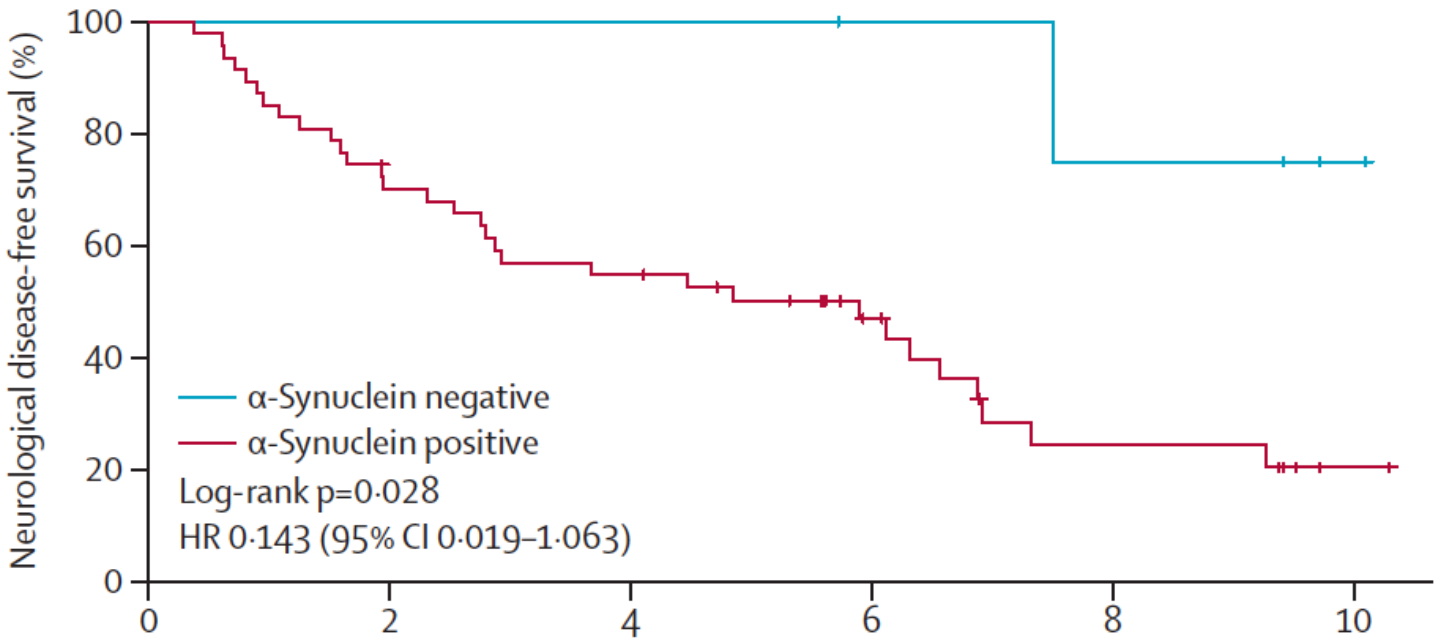
CSF – RT-QuIC

Detection of α-synuclein in CSF by RT-QuIC in patients with isolated rapid-eye-movement sleep behaviour disorder: a longitudinal observational study

90% iRBD → alpha-synuclein positive

Alex Iranzo, Graham Fairfoul, Anutra Chumbala Na Ayudhaya, Monica Serradell, Ellen Gelpi, Isabel Vilaseca, Raquel Sanchez-Valle, Carles Gaig, Joan Santamaria, Eduard Tolosa, Renata L Riha, Alison J E Green

Lancet Neurol 2021; 20: 203–12



Number at risk (number censored)						
α-Synuclein negative	5 (0)	5 (0)	5 (0)	4 (1)	3 (1)	1 (3)
α-Synuclein positive	47 (0)	32 (1)	25 (1)	14 (9)	6 (11)	1 (15)

Diagnostic value of cerebrospinal fluid alpha-synuclein seed quantification in synucleinopathies

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Variable\cohort	DeNoPa (*n* = 18)	Bologna (*n* = 11)	McGill (*n* = 10)	Oxford (*n* = 6)	*P*-value
RT-QuIC-positive response, *n* (%)	7 (38.9)	10 (90.9)	9 (90.0)	5 (83.3)	< 0.001***
Sex, male, *n* (%)	11 (61.1)	8 (72.7)	8 (80.0)	6 (100.0)	0.32
Age at lumbar puncture	64.7 ± 7.8 (51.0–77.0)	70.7 ± 6.5 (55.0–88.0)	63.0 ± 9.5 (46.0–76.0)	64.0 ± 9.9 (51.2–74.1)	0.15
Duration of disease	5.8 ± 4.3 (0.7–12.0)	3.3 ± 1.7 (1.5–7.0)	5.2 ± 6.4 (0.2–20.0)	3.0 ± 1.1 (1.4–4.4)	0.56
MDS-UPDRS part I	11.7 ± 4.8 (4–20)	NA	10.3 ± 5.9 (4.7–18.5)[a]	9.7 ± 5.6 (2–17)	0.64
MDS-UPDRS part II	2.8 ± 3.0 (0–10)	NA	1.8 ± 1.9 (0.2–6.3)[a]	2.5 ± 3.0 (0–8)	0.85
MDS-UPDRS part III	3.8 ± 3.2 (0–10)	1.9 ± 2.2 (0–5)	7.9 ± 3.7 (3.5–14.3)[a]	7.5 ± 4.4 (0–12)	0.002**
MMSE	28.9 ± 0.8 (27–30)	28.3 ± 1.2 (27–30)	28.1 ± 1.3 (26–30)	28.7 ± 0.8 (28–30)	0.34
MoCA	25.7 ± 2.5 (21–29)	NA	26.1 ± 1.3 (25–28)	26.3 ± 1.9 (24–29)	0.96
Urinary dysfunction, %	11/18 (61.1)	2/10 (20.0)	2/9 (22.2)	2/6 (33.3)	0.10
Constipation, %	10/18 (55.6)	5/10 (50.0)	3/10 (30.0)	4/6 (66.7)	0.53
Hyposmia, %	13/18 (72.2)		7/10 (70.0)	4/6 (66.7)	1.00
Family history, %	1/18 (5.6)	2/11 (18.2)	2/10 (20.0)	2.6 (33.3)	0.31

Data are mean ± SD (range) unless otherwise stated. *P*-values evaluated with a Fisher's exact test or Kruskal–Wallis test.

[a]UPDRS converted to MDS-UPDRS.[48]

**$P < 0.01$; ***$P < 0.005$.

BRAIN 2022: 145; 584–595

Skin biopsy

Biomarkers for REM sleep behavior disorder in idiopathic and narcoleptic patients

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Annals of Clinical and Translational Neurology 2019; 6(9): 1872–1876

86.7 % iRBD → alpha-synuclein positive

Immunohistochemical Detection of Synuclein Pathology in Skin in Idiopathic Rapid Eye Movement Sleep Behavior Disorder and Parkinsonism

CME

Ahmed Al-Qassabi, MD,[1,2] Tsu-Shuen Tsao, PhD,[3] Adriana Racolta, PhD,[3] Thomas Kremer, PhD,[4] Marta Cañamero, MD, PhD,[5] Anton Belousov, PhD,[4] Madison A. Santana, MA,[3] Rachel C. Beck, MPh,[3] Hongjun Zhang, MS,[3] Jeffrey Meridew, BS,[3] Judith Pugh, MD,[3] Fangru Lian, MD,[3] Mark D. Robida, PhD,[3] Mirko Ritter, PhD,[6] Christian Czech, PhD,[4] Thomas G. Beach, MD, PhD,[7] Lidija Pestic-Dragovich, PhD,[3] Kirsten I. Taylor, PhD,[4,8] Wagner Zago, PhD,[9] Lei Tang, PhD,[3] Sebastian Dziadek, PhD,[4] and Ronald B. Postuma, MD, MSc[1,10,11*]

Movement Disorders, Vol. 36, No. 4, 2021

82 % iRBD → alpha-synuclein positive

Esiste l'RBD 'idiopatico'?

- **80-90%** dei pazienti ha evidenze biologiche di alfa-sinucleinopatia *(Iranzo et al. 2021, Poggiolini et al. 2022, Antelmi et al. 2019, Al Qassabi et al. 2021)*
- Oltre il **70%** dei pazienti sviluppa parkinsonismo e/o demenza (se seguiti per follow-up sufficientemente lungo) *(Postuma et al. 2019)*

I pazienti con RBD (la maggior parte) sono già affetti da alfa-sinucleinopatia

Quando un paziente iRBD svilupperà parkinsonismo/demenza?

Disease-modifying therapies in synucleinopathy

TABLE 2. Treatments targeting α-synuclein active in patients with PD

Drug	Mechanism of action	Status
RO7046015	Passive immunization	Phase II
BIIB054	Passive immunization	Phase II
PD01A, PD03A	Active immunization	Phase I
Nilotinib	C-Abl inhibition	Phase II
NPT200-11	Inhibition of α-synuclein misfolding	Phase I
Ambroxol	Increases glucosylceramidase activity	Phase II
SAR40261	Glucosylceramide synthase inhibitor	Phase II

Movement Disorders, Vol. 33, No. 5, 2018

Where are we?

ORIGINAL ARTICLE

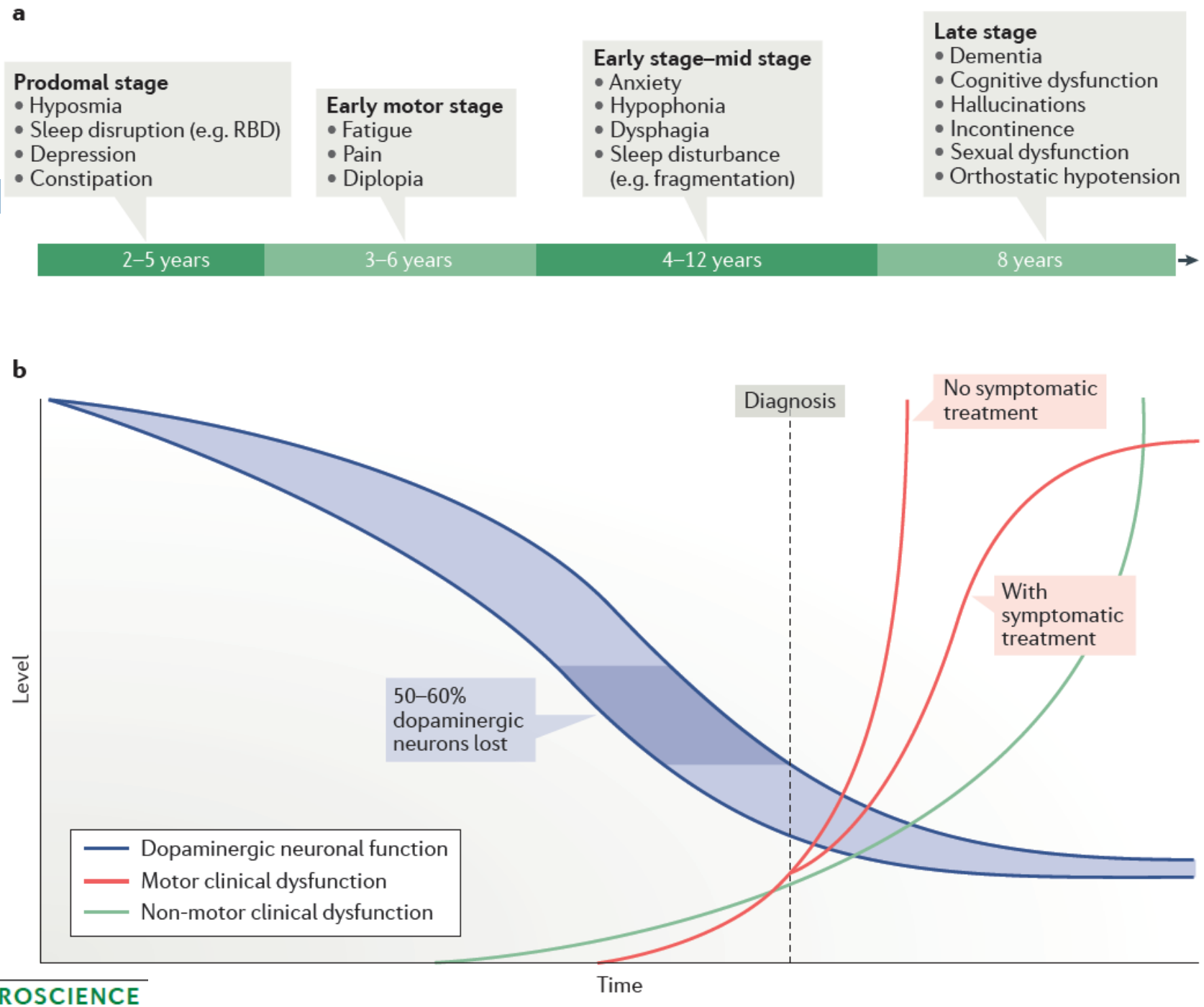
Trial of Prasinezumab in Early-Stage Parkinson's Disease

Gennaro Pagano, M.D., Ph.D., Kirsten I. Taylor, Ph.D., Judith Anzures-Cabrera, Ph.D., Maddalena Marchesi, M.D., Tanya Simuni, M.D., Kenneth Marek, M.D., Ph.D., Ronald B. Postuma, M.D., Nicola Pavese, M.D., Ph.D., Fabrizio Stocchi, M.D., Ph.D., Jean-Philippe Azulay, Ph.D., Brit Mollenhauer, M.D., Lydia López-Manzanares, M.D., et al., for the PASADENA Investigators and Prasinezumab Study Group*

ORIGINAL ARTICLE

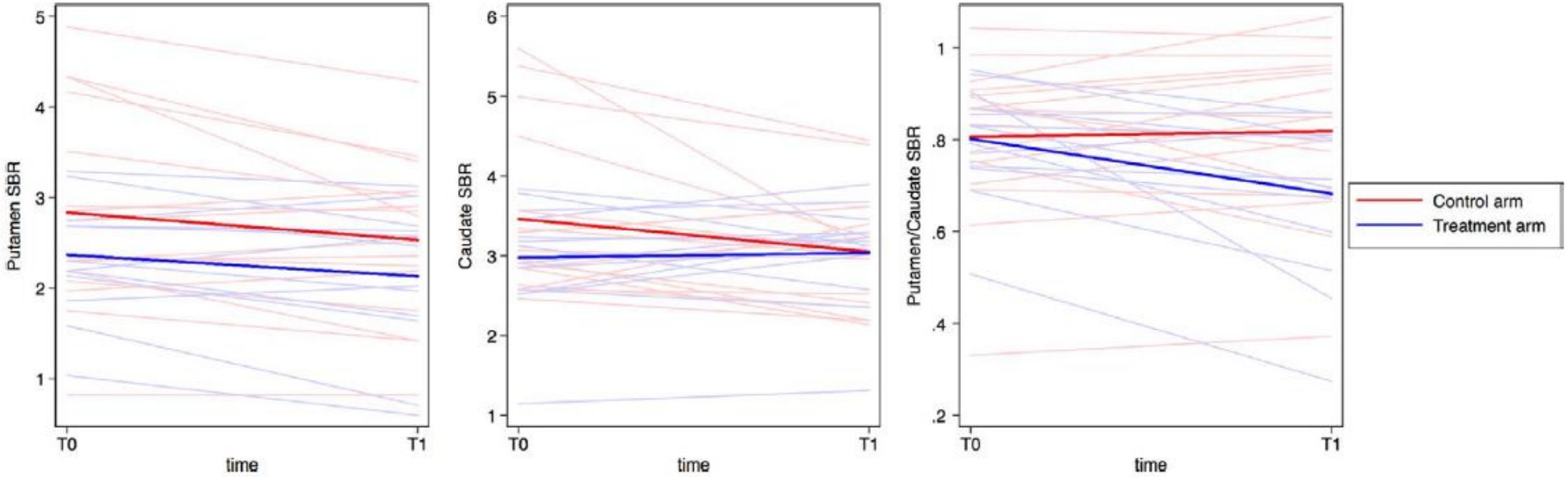
Trial of Cinpanemab in Early Parkinson's Disease

Anthony E. Lang, M.D., Andrew D. Siderowf, M.D., Eric A. Macklin, Ph.D., Werner Poewe, M.D., David J. Brooks, M.D., D.Sc., Hubert H. Fernandez, M.D., Olivier Rascol, M.D., Nir Giladi, M.D., Fabrizio Stocchi, M.D., Caroline M. Tanner, M.D., Ph.D., Ronald B. Postuma, M.D., David K. Simon, M.D., Ph.D., et al., for the SPARK Investigators*


a
Prodomal stage
• Hyposmia
• Sleep disruption (e.g. RBD)
• Depression
• Constipation
Early motor stage
• Fatigue
• Pain
• Diplopia
Early stage–mid stage
• Anxiety
• Hypophonia
• Dysphagia
• Sleep disturbance (e.g. fragmentation)
Late stage
• Dementia
• Cognitive dysfunction
• Hallucinations
• Incontinence
• Sexual dysfunction
• Orthostatic hypotension
2–5 years
3–6 years
4–12 years
8 years
b
Diagnosis
No symptomatic treatment
With symptomatic treatment
50–60% dopaminergic neurons lost
Level
Time
Dopaminergic neuronal function
Motor clinical dysfunction
Non-motor clinical dysfunction

Rapid eye movement sleep behavior disorder: A proof-of-concept neuroprotection study for prodromal synucleinopathies

Dario Arnaldi[1,2] | Francesco Famà[1,2] | Nicola Girtler[1,2] | Andrea Brugnolo[1,2] | Matteo Pardini[1,2] | Pietro Mattioli[1,2] | Riccardo Meli[1,2] | Federico Massa[1,2] | Beatrice Orso[1] | Maria Pia Sormani[3] | Maria Isabella Donegani[2,4] | Matteo Bauckneht[2,4] | Silvia Morbelli[2,4] | Flavio Nobili[1,2]



DAT-SPECT as a surrogate efficacy endpoint?

Eur J Neurol. 2020;00:1–9.

Grazie dell'attenzione!!!

SL&EP GRG

Sleep and Epilepsy
Genoa Research Group