BIOMARCATORI DIAGNOSTICI NELL MALATTIA DI PARKINSON E PARKINSONISMI

PROF. ALDO QUATTRONE

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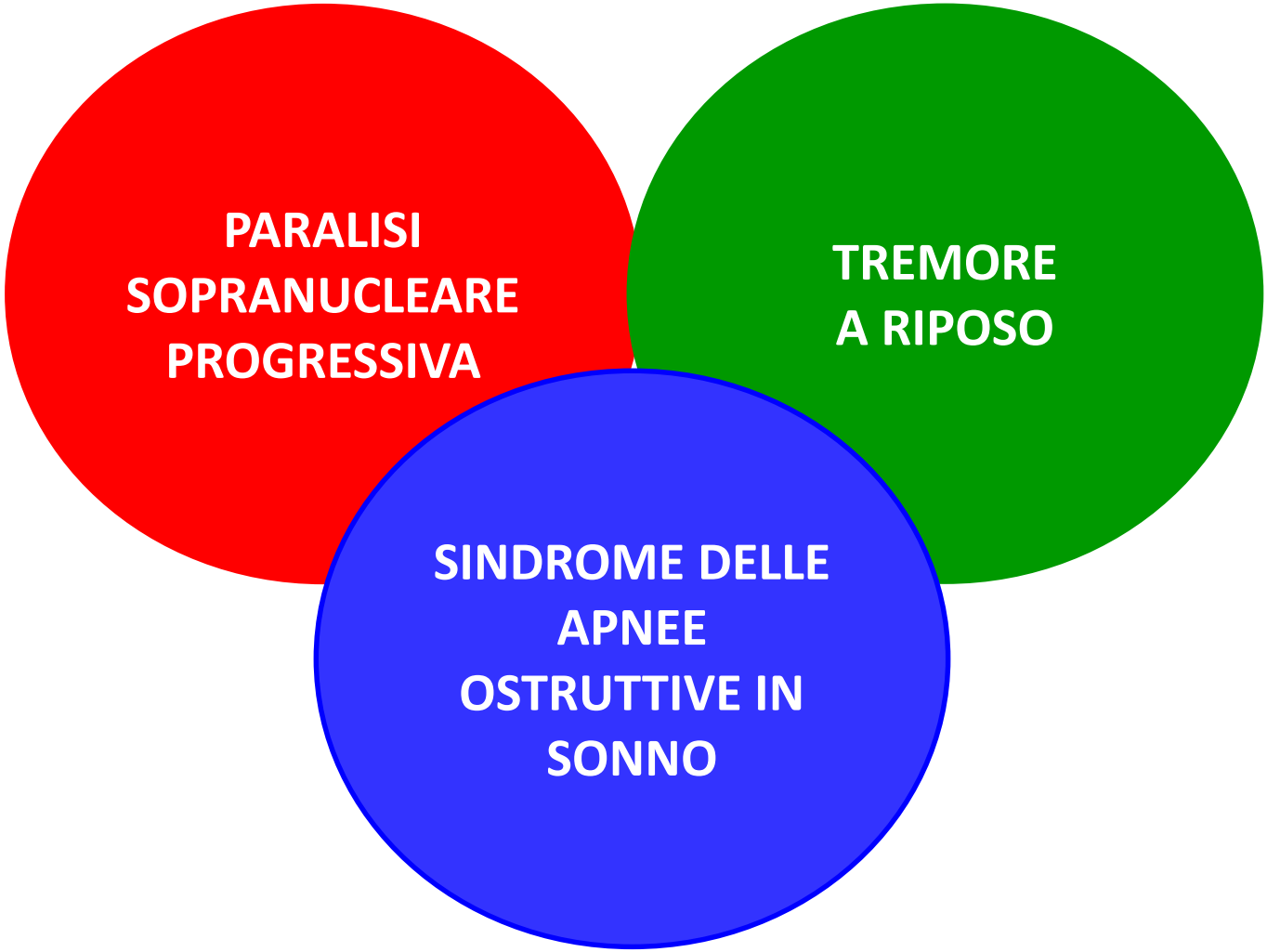
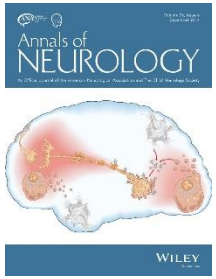
Catania **11 giugno 2019**

I BIOMARCATORI NEI DISORDINI DEL MOVIMENTO





NEUROLOGY GRAND ROUNDS

Neuroimaging Biomarkers for Parkinson Disease: Facts and Fantasy

Joel S. Perlmutter, MD[1] and Scott A. Norris, MD[2]

In this grand rounds, we focus on development, validation, and application of neuroimaging biomarkers for Parkinson disease (PD). We cover whether such biomarkers can be used to identify presymptomatic individuals (probably yes), provide a measure of PD severity (in a limited fashion, but frequently done poorly), investigate pathophysiology of parkinsonian disorders (yes, if done carefully), play a role in differential diagnosis of parkinsonism (not well), and investigate pathology underlying cognitive impairment (yes, in conjunction with postmortem data). Along the way, we clarify several issues about definitions of biomarkers and surrogate endpoints. The goal of this lecture is to provide a basis for interpreting current literature and newly proposed clinical tools in PD. In the end, one should be able to critically distinguish fact from fantasy.

ANN NEUROL 2014;76:769–783

I BIOMARCATORI NEI DISORDINI DEL MOVIMENTO

IL BIOMARCATORE IDEALE DEVE ESSERE IN GRADO DI DIFFERENZIARE FENOTIPI CLINICAMENTE INDISTINGUIBILI SU BASE INDIVIDUALE O CON ELEVATI LIVELLI DI SENSIBILITA' E SPECIFICITA' (ACCURATEZZA) NON INFERIORI AL 80%.

RISONANZA MAGNETICA:
MORFOMETRICA, DIFFUSIONE, VOLUMETRICA

RESEARCH ARTICLE

Clinical Diagnosis of Progressive Supranuclear Palsy: The Movement Disorder Society Criteria

Levels of Certainty	Ocular Motor Dysfunction	Postural Instability	Akinesia
Level 1	O1: Vertical supranuclear gaze palsy	P1: Repeated unprovoked falls within 3 years	A1: Progressive gait freezing within 3 years
Level 2	O2: Slow velocity of vertical saccades	P2: Tendency to fall on the pull-test within 3 years	A2: Parkinsonism, akinetic-rigid, predominantly axial, and levodopa resistant
Level 3	O3: Frequent macro square wave jerks or "eyelid opening apraxia"	P3: More than two steps backward on the pull-test within 3 years	A3: Parkinsonism, with tremor and/or asymmetric and/or levodopa responsive

Probable PSP-RS: (O1 or O2) + (P1 or P2)

Probable PSP-P: (O1 or O2) + (A2 or A3)

Hoglinger GU, et al 2017

RESEARCH ARTICLE

Clinical Diagnosis of Progressive Supranuclear Palsy: The Movement Disorder Society Criteria

Günter U. Höglinger, MD,[1,2*] Gesine Respondek, MD,[1,2] Maria Stamelou, MD,[3] Carolin Kurz, MD,[4] Keith A. Josephs, MD, MST, MSc,[5] Anthony E. Lang, MD,[6] Brit Mollenhauer, MD,[7] Ulrich Müller, MD,[8] Christer Nilsson, MD,[9] Jennifer L. Whitwell, PhD,[10] Thomas Arzberger, MD,[2,4,11] Elisabet Englund, MD,[12] Ellen Gelpi, MD,[13] Armin Giese, MD,[11] David J. Irwin, MD,[14] Wassilios G. Meissner, MD, PhD,[15,16,17] Alexander Pantelyat, MD,[18] Alex Rajput, MD,[19] John C. van Swieten, MD,[20] Claire Troakes, PhD, MSc,[21] Angelo Antonini, MD,[22] Kailash P. Bhatia, MD,[23] Yvette Bordelon, MD, PhD,[24] Yaroslau Compta, MD, PhD,[25] Jean-Christophe Corvol, MD, PhD,[26] Carlo Colosimo, MD, FEAN,[27] Dennis W. Dickson, MD,[28] Richard Dodel, MD,[29] Leslie Ferguson, MD,[19] Murray Grossman, MD,[14] Jan Kassubek, MD,[30] Florian Krismer, MD, PhD,[31] Johannes Levin, MD,[2,32] Stefan Lorenzl, MD,[33,34,35] Huw R. Morris, MD,[36] Peter Nestor, MD,[37] Wolfgang H. Oertel, MD,[38] Werner Poewe, MD,[31] Gil Rabinovici, MD,[39] James B. Rowe, MD,[40] Gerard D. Schellenberg, PhD,[41] Klaus Seppi, MD,[31] Thilo van Eimeren, MD,[42] Gregor K. Wenning, MD, PhD,[31] Adam L. Boxer, MD, PhD,[39] Lawrence I. Golbe, MD,[43] and Irene Litvan, MD[44]; for the Movement Disorder Society–endorsed PSP Study Group.

TABLE 5. Degrees of diagnostic certainty, obtained by combinations of clinical features and clinical clues

Diagnostic Certainty	Definition	Combinations	Predominance Type	Abbreviation
Definite PSP	Gold standard defining the disease entity	Neuropathological diagnosis	Any clinical presentation	def. PSP
Probable PSP	Highly specific, but not very sensitive for PSP *Suitable for therapeutic and biological studies*	(O1 or O2) + (P1 or P2)	PSP with Richardson's syndrome	prob. PSP-RS
		(O1 or O2) + A1	PSP with progressive gait freezing	prob. PSP-PGF
		(O1 or O2) + (A2 or A3)	PSP with predominant parkinsonism	prob. PSP-P
		(O1 or O2) + C2	PSP with predominant frontal presentation	prob. PSP-F

Mov Disord, 2017

2017

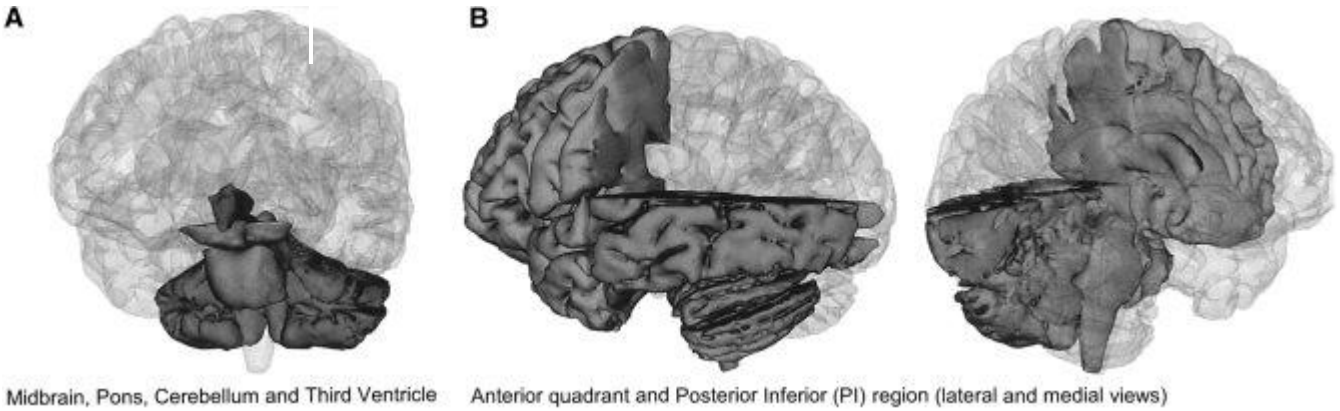
I BIOMARCATORI NELLA DIAGNOSI DI PSP: DEFINIZIONE

Levels of evidence for neuroimaging biomarkers in PSP

Level	Utility	PSP-RS	vPSP
1	Research tool	Group-level evidence that a biomarker is abnormal in PSP-RS	Group-level evidence that a biomarker is abnormal in vPSP
2	Supportive of clinical diagnosis	Individual-level data showing diagnostic value (high sensitivity + specificity) for PSP-RS	Individual-level data showing diagnostic value (high sensitivity + specificity) for vPSP
3	Supportive of early clinical diagnosis	Evidence for abnormalities before patients meet clinical criteria for PSP-RS	Evidence for abnormalities before patients meet clinical criteria for vPSP
4	Supportive of pathological diagnosis	Individual-level data showing diagnostic value for PSP pathology, regardless of syndrome	
5	Definitive	Biomarker of actual pathology	

Whitwell et al., for the Movement Disorder Society-endorsed PSP Study Group , Mov Disord. 2017

I BIOMARCATORI NELLA DIAGNOSI DI PSP



Midbrain, Pons, Cerebellum and Third Ventricle

Anterior quadrant and Posterior Inferior (PI) region (lateral and medial views)

LEVEL 1: RESEARCH TOOL
GROUP-LEVEL EVIDENCE THAT A BIOMARKER IS ABNORMAL IN PSP-RS

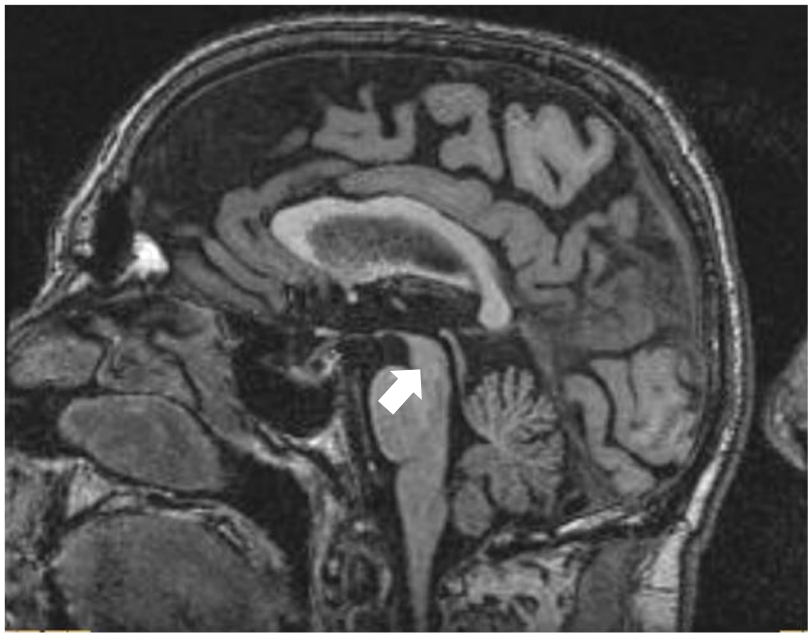
	PSP	MSA-P	PD	Control
Whole brain volume	1085.9 ± 57.2	1109.8 ± 59.9	1130.4 ± 78.7	1132.5 ± 74.3
Total frontal volume	**449.2 ± 26.8***	**474.8 ± 22.3**	**480.4 ± 35.0**	**484.2 ± 21.1**
Total PI volume	323.0 ± 21.6	314.9 ± 22.6	333.9 ± 20.8	337.2 ± 15.7
Cerebellar volume	**110.2 ± 15.9***	**90.2 ± 26.9**	**125.9 ± 13.1**	**119.9 ± 13.4**
Midbrain volume	**5.69 ± 1.1***	**7.08 ± 1.2**	**7.87 ± 1.1**	**8.33 ± 0.8**
Pons volume	12.8 ± 1.6	9.60 ± 4.3	15.4 ± 2.5	13.9 ± 1.5
SCP volume	**0.40 ± 0.08***	**0.54 ± 0.05**	**0.55 ± 0.05**	**0.55 ± 0.06**
LV volume	39.3 ± 14.9	34.4 ± 15.3	36.0 ± 18.0	26.7 ± 12.3
Third ventricle volume	**2.52 ± 0.8***	**1.93 ± 0.6**	**1.92 ± 0.8**	**1.59 ± 0.6**

Paviour et al., 2006

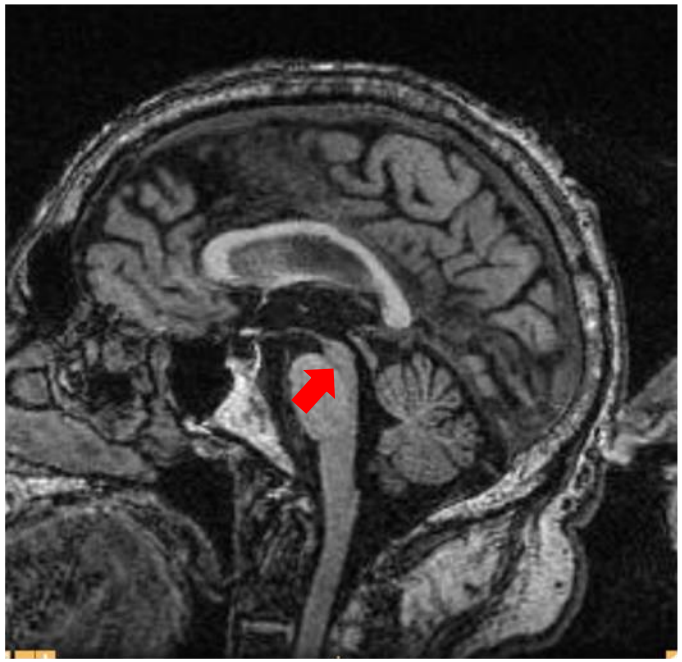
RISONANZA MAGNETICA CEREBRALE NELLA PARALISI SOPRANUCLEARE PROGRESSIVA E NELLA MALATTIA DI PARKINSON

RMN DI ROUTINE QUALITATIVA

Penguin silhouette sign



CONTROL



PSP

Oba et al,. 2006

Parkinsonism and Related Disorders 54 (2018) 90–94

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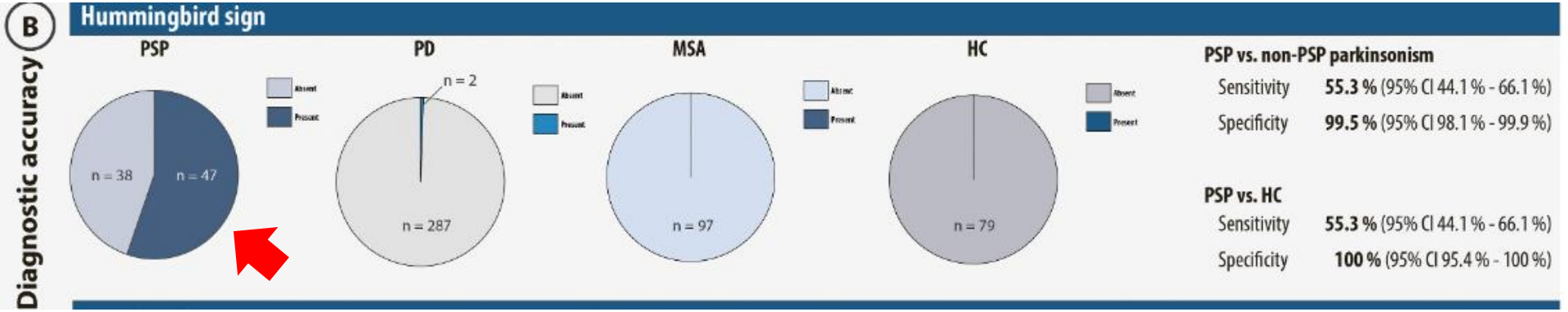
journal homepage: www.elsevier.com/locate/parkreldis

Short communication

The diagnostic accuracy of the hummingbird and morning glory sign in patients with neurodegenerative parkinsonism

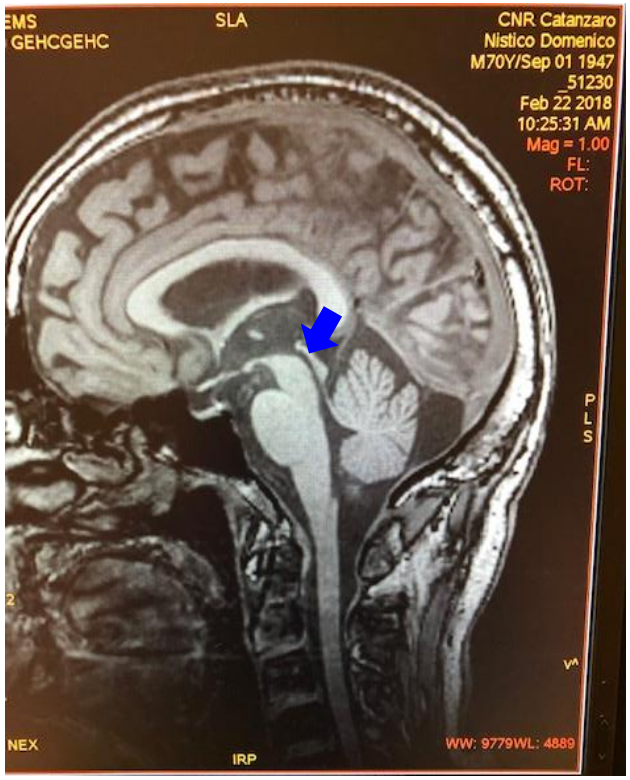


Midbrain atrophy patterns are useful in the differential diagnosis of neurodegenerative parkinsonism but the hummingbird sign suffers from low sensitivity, especially in early disease stages.

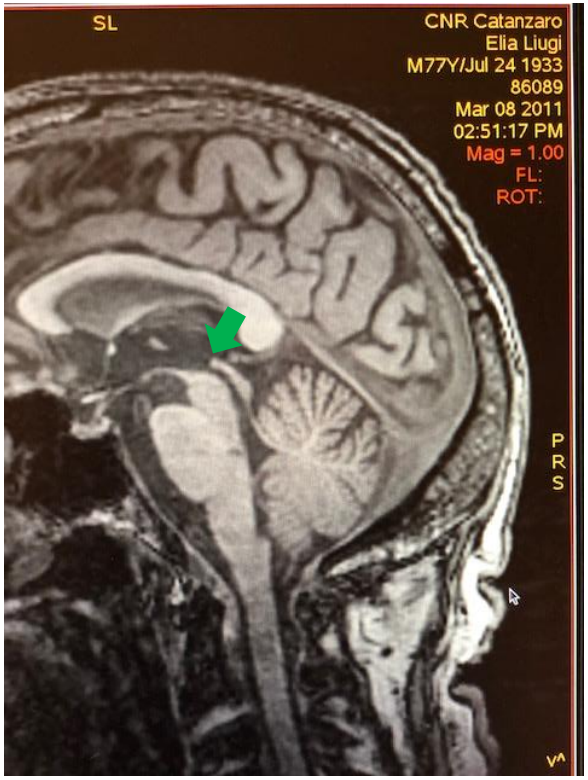
Mueller, 2018

QUALITATIVE MRI IN NPH: THE HUMMINGBIRD SIGN

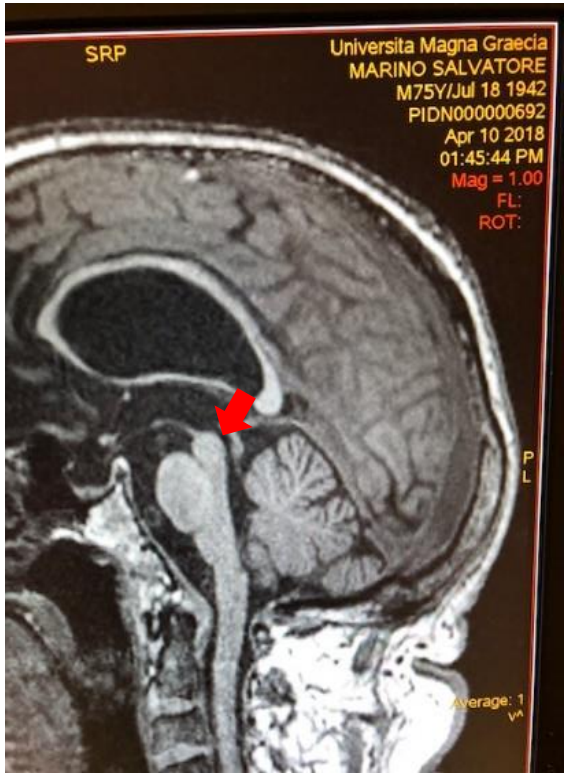
CONTROLLO



PSP



NPH



Quattrone, unpublished

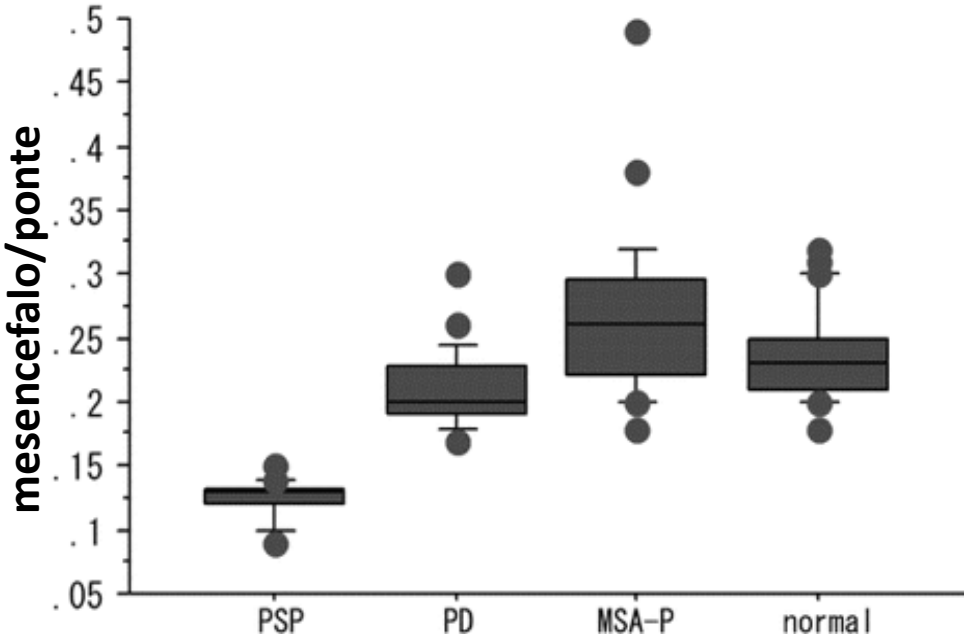
I BIOMARCATORI NELLA DIAGNOSI DI PSP

RM MORFOMETRICA

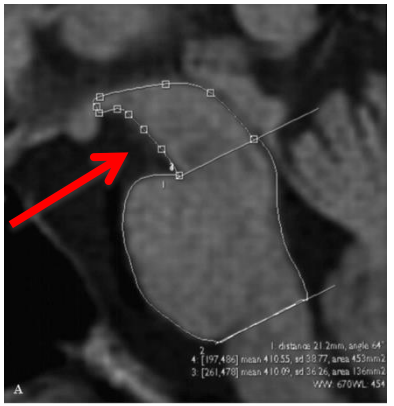
2005, 64:2050-55

LEVEL 2
INDIVIDUAL LEVEL
WITH HIGH ACCURACY IN
PSP-RS

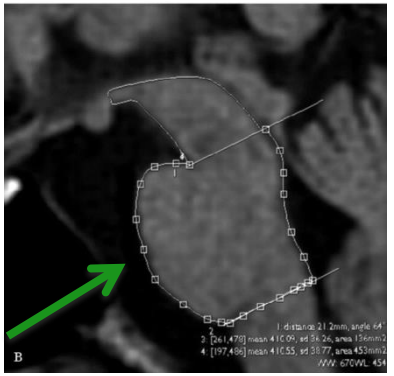
INDICE DI OBA
MESENCEFALO/PONTE



mesencefalo



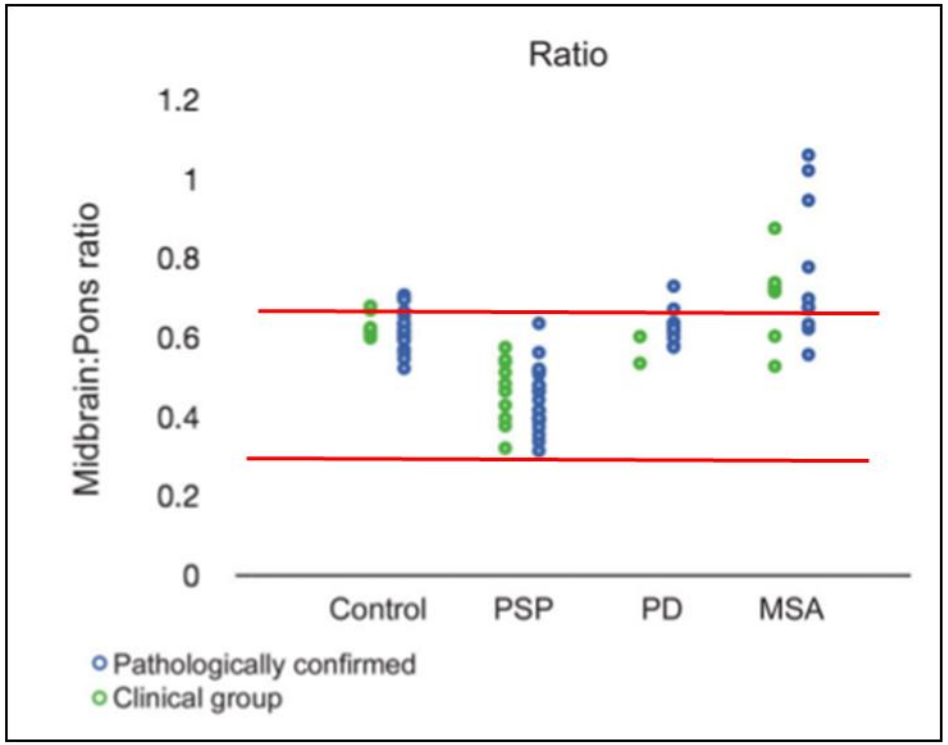
ponte

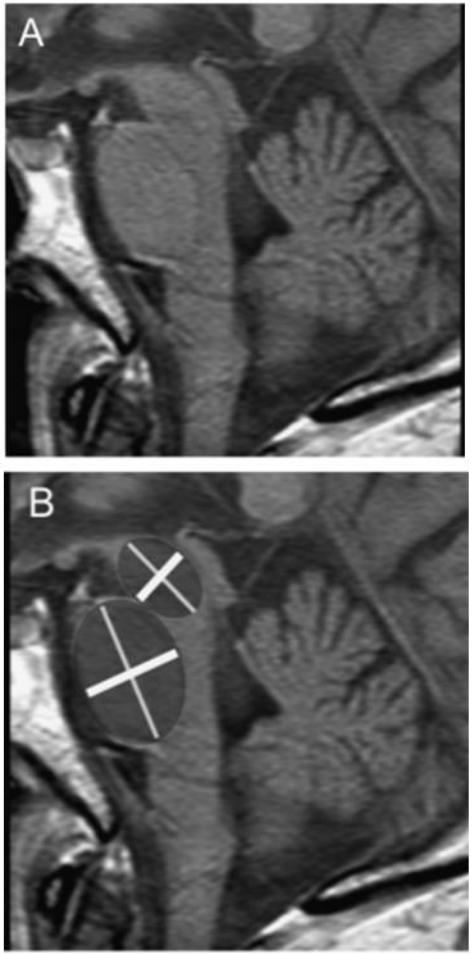


Oba et al 2005

The midbrain to pons ratio

A simple and specific MRI sign of progressive supranuclear palsy

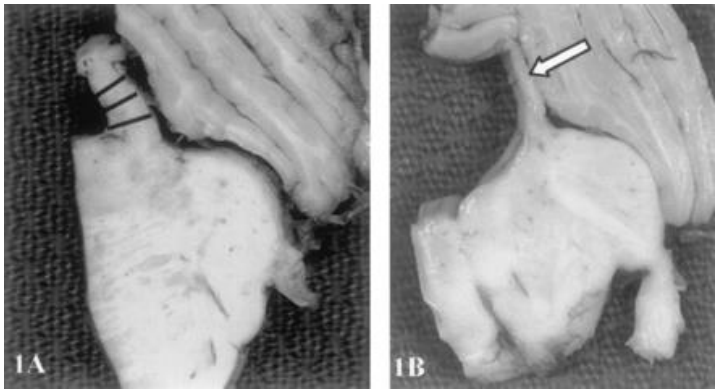




Massey, Neurology 2013;80:1-6

ATROPHY OF SUPERIOR CEREBELLAR PEDUNCLE IN PROGRESSIVE SUPRANUCLEAR PALSY

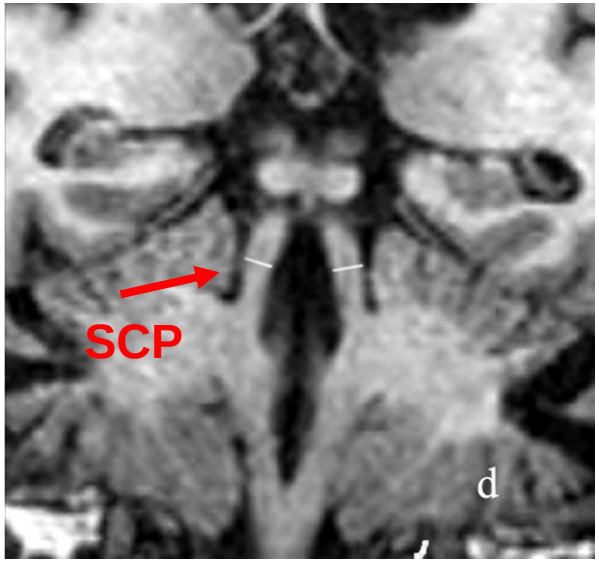
60:1766-1769, 2003



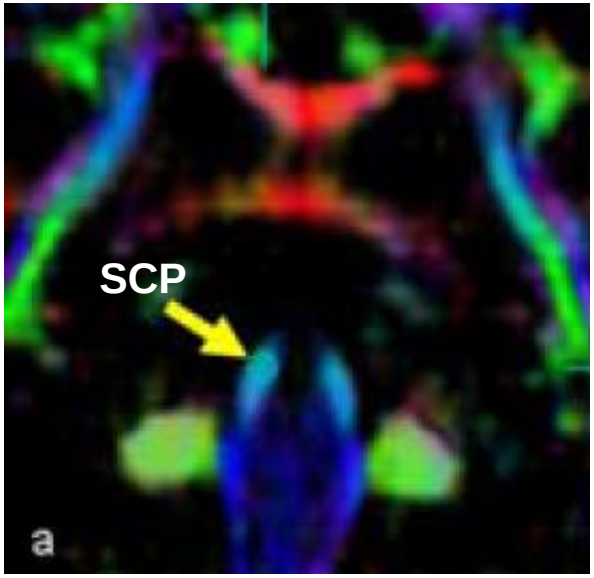
Superior cerebellar peduncle in a control case and in patient with PSP

Tsuboi et al., 2003

SUPERIOR CEREBELLAR PEDUNCLE



Quattrone et al., 2008

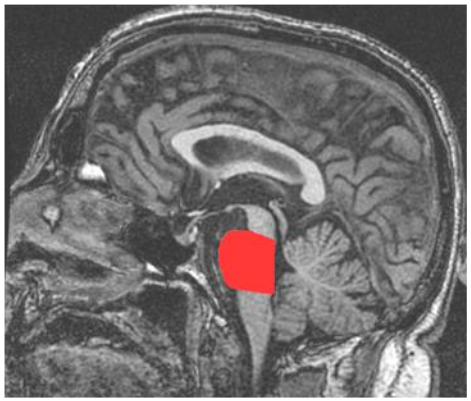


Taoka et al., 2007

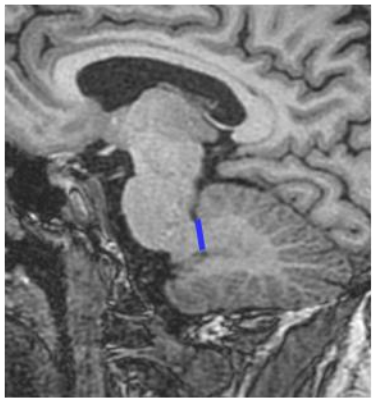
RAPPORTO MESENCEFALO/PONTE O MRPI PER LA DIAGNOSI DI PSP?

MRPI

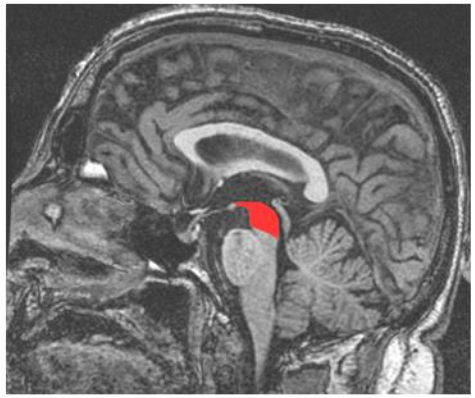
$$\frac{P/M}{MCP/SCP}$$



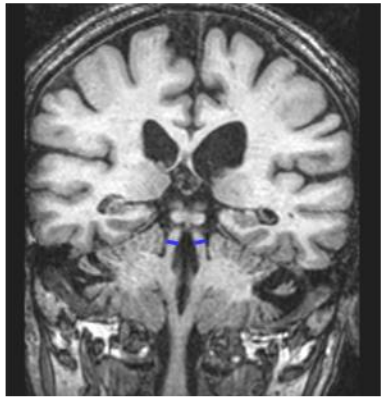
Pons



MCP



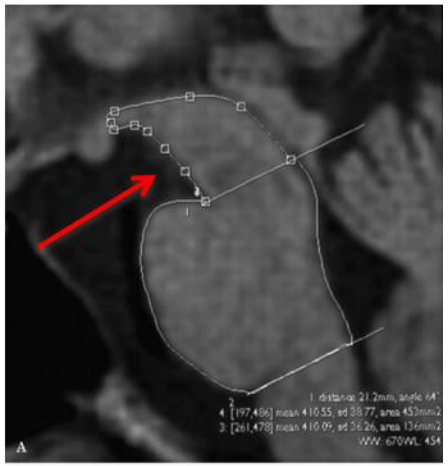
Midbrain

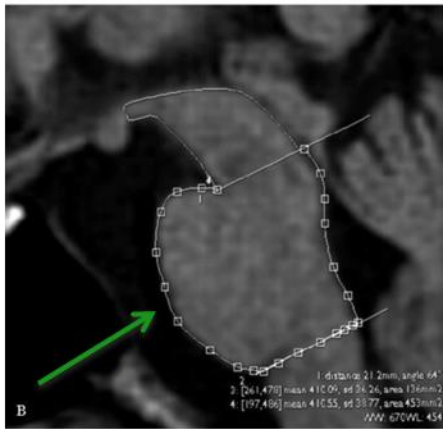


SCP

Quattrone et al, 2008

P/M





Oba et al. 2005

LEVEL 2: *SUPPORTIVE OF CLINICAL DIAGNOSIS*

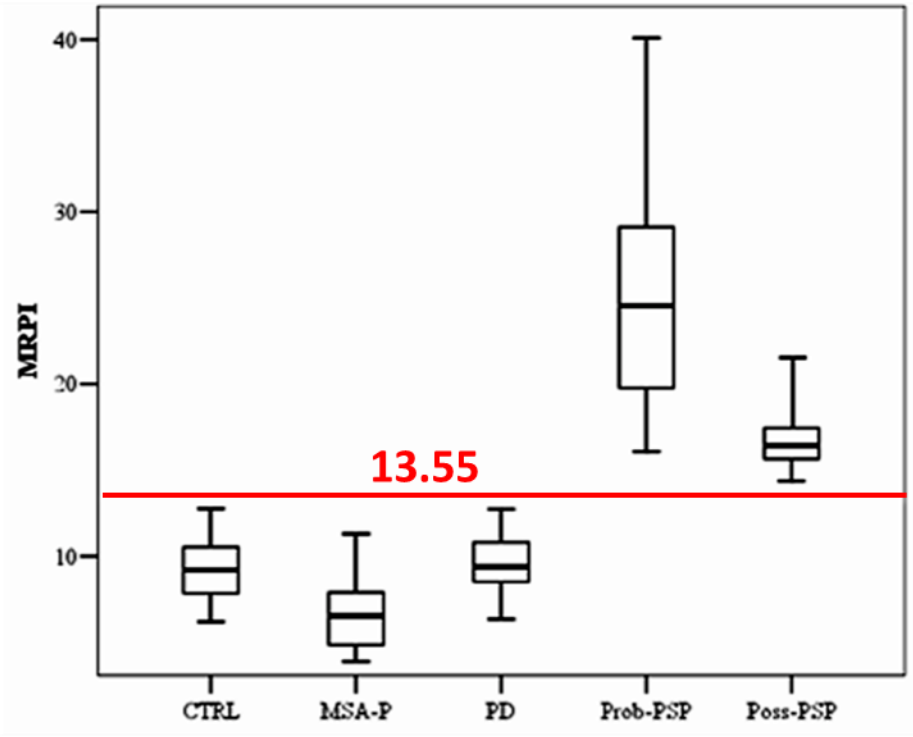
2008;246:214-221

MR Imaging Index for Differentiation of Progressive Supranuclear Palsy from Parkinson Disease and the Parkinson Variant of Multiple System Atrophy

A. Quattrone, G. Nicoletti, D. Messina, F. Fera, F. Condino, P. Pugliese, P. Lanza, P. Barone, L. Morgante, M. Zappia, U. Aguglia, O. Gallo

MR PARKINSONISM INDEX (MRPI)

$$\frac{\text{PONS AREA}}{\text{MIDBRAIN AREA}} \times \frac{\text{MIDDLE CEREBELLAR PEDUNCLE (MCP) WIDTH}}{\text{SUPERIOR CEREBELLAR PEDUNCLE (SCP) WIDTH}}$$



MRI measurements predict PSP in unclassifiable parkinsonisms

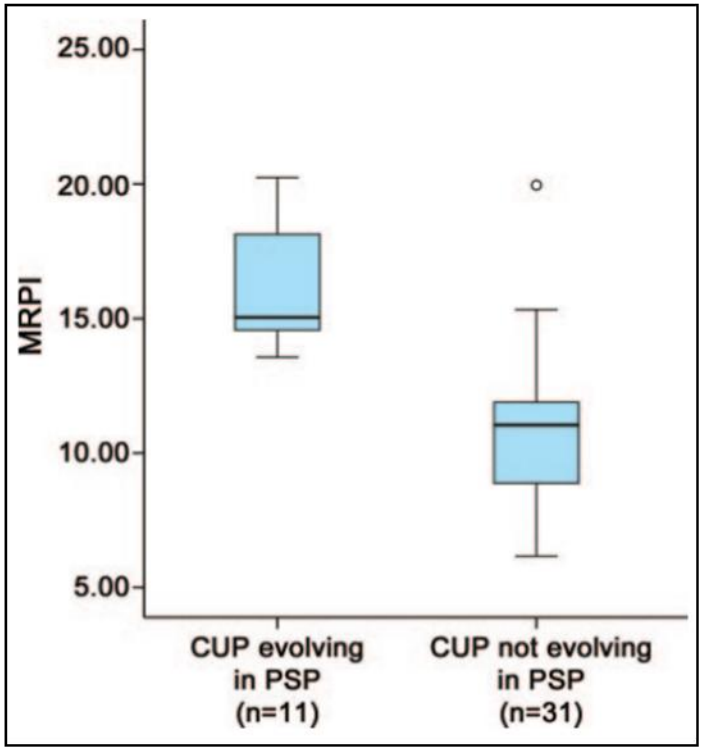
A cohort study

2011

M. Morelli, G. Arabia, F. Novellino, M. Salsone, L. Giofre, F. Condino, D. Messina, A. Quattrone

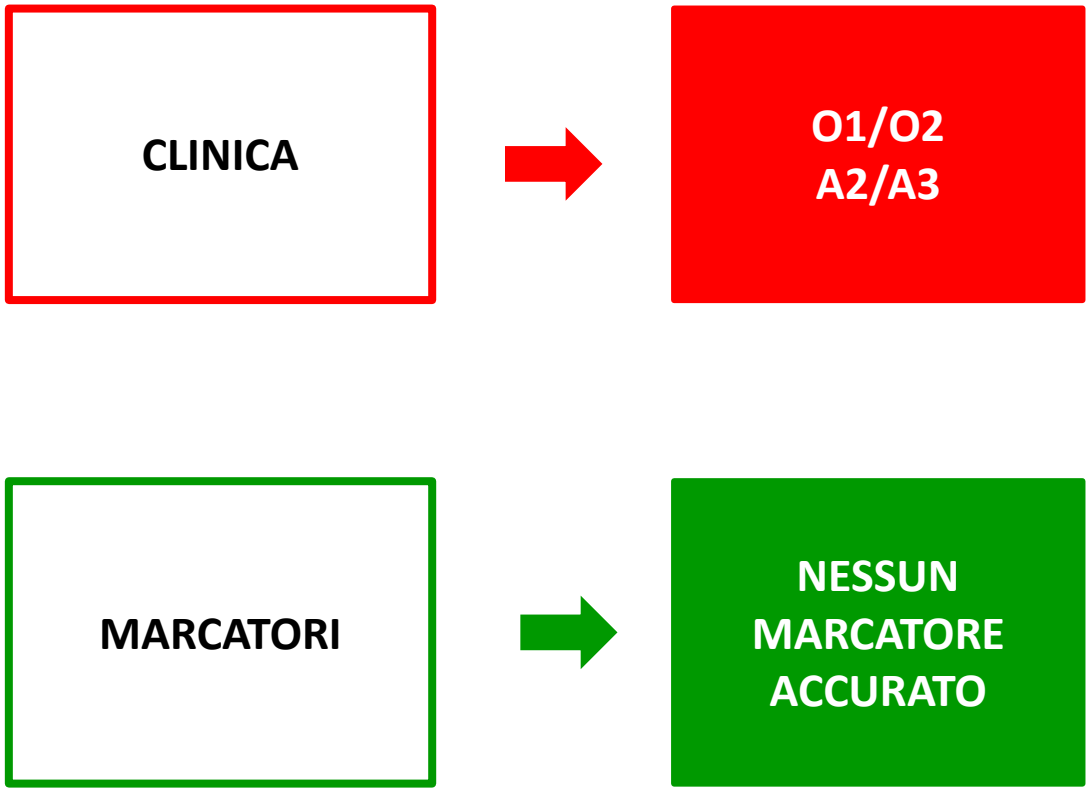
Table 2 Validity of clinical features and MRPI for PSP in patients with CUP

Baseline evaluation	Sensitivity, %	Specificity, %	PPV, %	NPV, %	Accuracy, %
Clinical features					
Isolated postural instability with falls in the first year of disease	45.4	83.9	50	81.2	73.8
Slowness of vertical saccades	18.2	77.4	22.2	72.7	61.9
Postural instability with falls after the first year of the disease and slowness of vertical saccades	27.3	93.5	60	78.4	76.2
Freezing in the first 3 years of disease	9.1	58.1	7.1	64.3	45.2
MRI features					
MRPI value ≥13.55	100	90.3	78.6	100	92.9



LEVEL 3: *SUPPORTIVE OF EARLY CLINICAL DIAGNOSIS*

DIAGNOSI DIFFERENZIALE TRA PARKINSON E PSP-P



Baseline and follow-up in a patient with PSP-P

Baseline
MRPI= 12.85

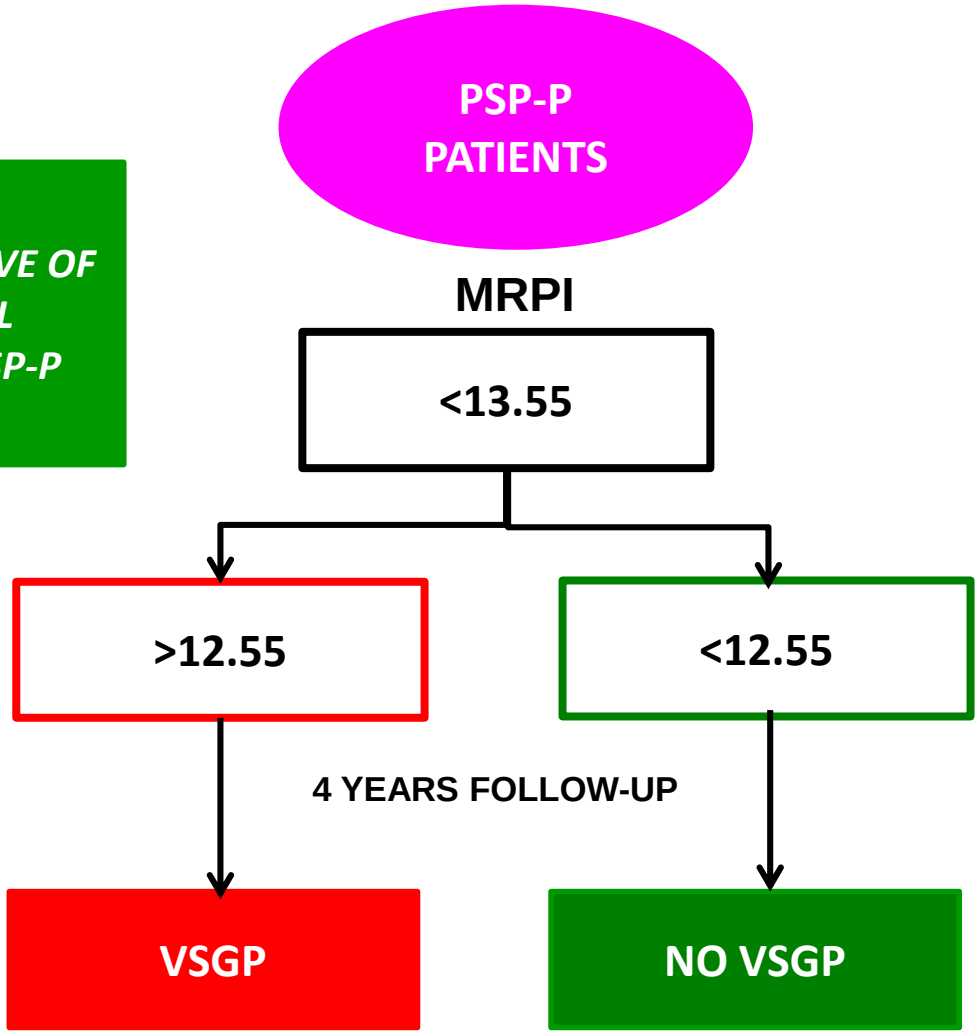
Follow-up 1.5 yrs
MRPI= 19.47

2016, 87:1266-1273

MRPI predicts vertical supranuclear gaze palsy (VSGP) in patients with PSP-P

Aldo Quattrone, MD,[1,2†] Maurizio Morelli, MD,[1] David R. Williams, PhD, FRACP,[3] Basilio Vescio, PhD,[2] Salvatore Nigro, PhD,[2] Giuseppe Nicoletti, MD,[2] Gennarina Arabia, MD,[1] Maria Salsone, MD,[2] Fabiana Novellino, MD,[2] Carmelina Chiriaco, PhD,[2] Sara Scannapieco, MD,[1] Pierfrancesco Pugliese, MD,[4] Domenico Bosco, MD,[5] Manuela Caracciolo, MD.[2]

LEVEL 3: *SUPPORTIVE OF EARLY CLINICAL DIAGNOSIS OF PSP-P*



Parkinsonism and Related Disorders 54 (2018) 3–8

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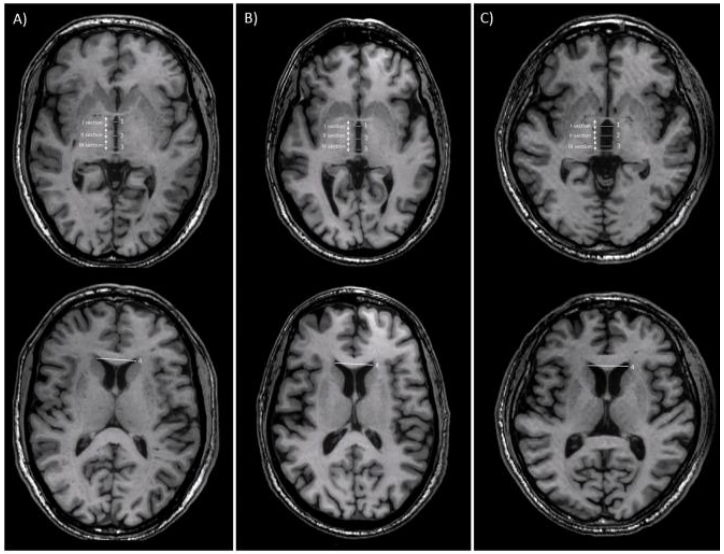
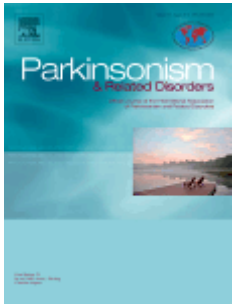
journal homepage: www.elsevier.com/locate/parkreldis

A new MR imaging index for differentiation of progressive supranuclear palsy-parkinsonism from Parkinson's disease

Aldo Quattrone[a,b,*], Maurizio Morelli[b,c], Salvatore Nigro[b], Andrea Quattrone[c], Basilio Vescio[d], Gennarina Arabia[b,c], Giuseppe Nicoletti[b], Rita Nisticò[b], Maria Salsone[b], Fabiana Novellino[b], Gaetano Barbagallo[c], Emilio Le Piane[e], Pierfrancesco Pugliese[f], Domenico Bosco[g], Maria Grazia Vaccaro[b], Carmelina Chiriaco[b], Umberto Sabatini[h], Virginia Vescio[h], Carlo Stanà[h], Federico Rocca[b], Domenico Gullà[a], Manuela Caracciolo[b]

MRPI +  = MRPI 2.0



2018

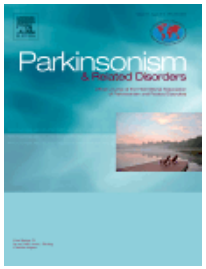
A new MR imaging index for differentiation of progressive supranuclear palsy-parkinsonism from Parkinson's disease

Aldo Quattronea,b,*, Maurizio Morellib,c, Salvatore Nigrob, Andrea Quattronec, Basilio Vesciod, Gennarina Arabiab,c, Giuseppe Nicolettib, Rita Nisticòb, Maria Salsoneb, Fabiana Novellinob, Gaetano Barbagalloc, Emilio Le Pianee, Pierfrancesco Pugliesef, Domenico Boscog, Maria Grazia Vaccarob, Carmelina Chiriacob, Umberto Sabatinih, Virginia Vescioh, Carlo Stanàh, Federico Roccab, Domenico Gullàa, Manuela Caracciolob

LEVEL 2: *SUPPORTIVE OF CLINICAL DIAGNOSIS OF PSP-P*

MRPI and MRPI 2.0 for differentiation of patients with PSP-P from patients with Parkinson's disease and control subjects.

Cutoff and statistical values	MRPI	MRPI 2.0
PSP-P patients vs. PD patients		
Cutoff value	≥12.38[a]	≥2.18[a]
Sensitivity (%)	73.5	100
Specificity (%)	98.1	94.3
PPV (%)	96.2	91.9
NPV (%)	85.2	100
Accuracy (%)	88.5	96.6



2018

A new MR imaging index for differentiation of progressive supranuclear palsy-parkinsonism from Parkinson's disease

Aldo Quattronea,b,*, Maurizio Morellib,c, Salvatore Nigrob, Andrea Quattronec, Basilio Vesciod, Gennarina Arabiab,c, Giuseppe Nicolettib, Rita Nisticòb, Maria Salsoneb, Fabiana Novellinob, Gaetano Barbagalloc, Emilio Le Pianee, Pierfrancesco Pugliesef, Domenico Boscog, Maria Grazia Vaccarob, Carmelina Chiriacob, Umberto Sabatinih, Virginia Vescioh, Carlo Stanàh, Federico Roccab, Domenico Gullàa, Manuela Caracciolob

O1= VSGP

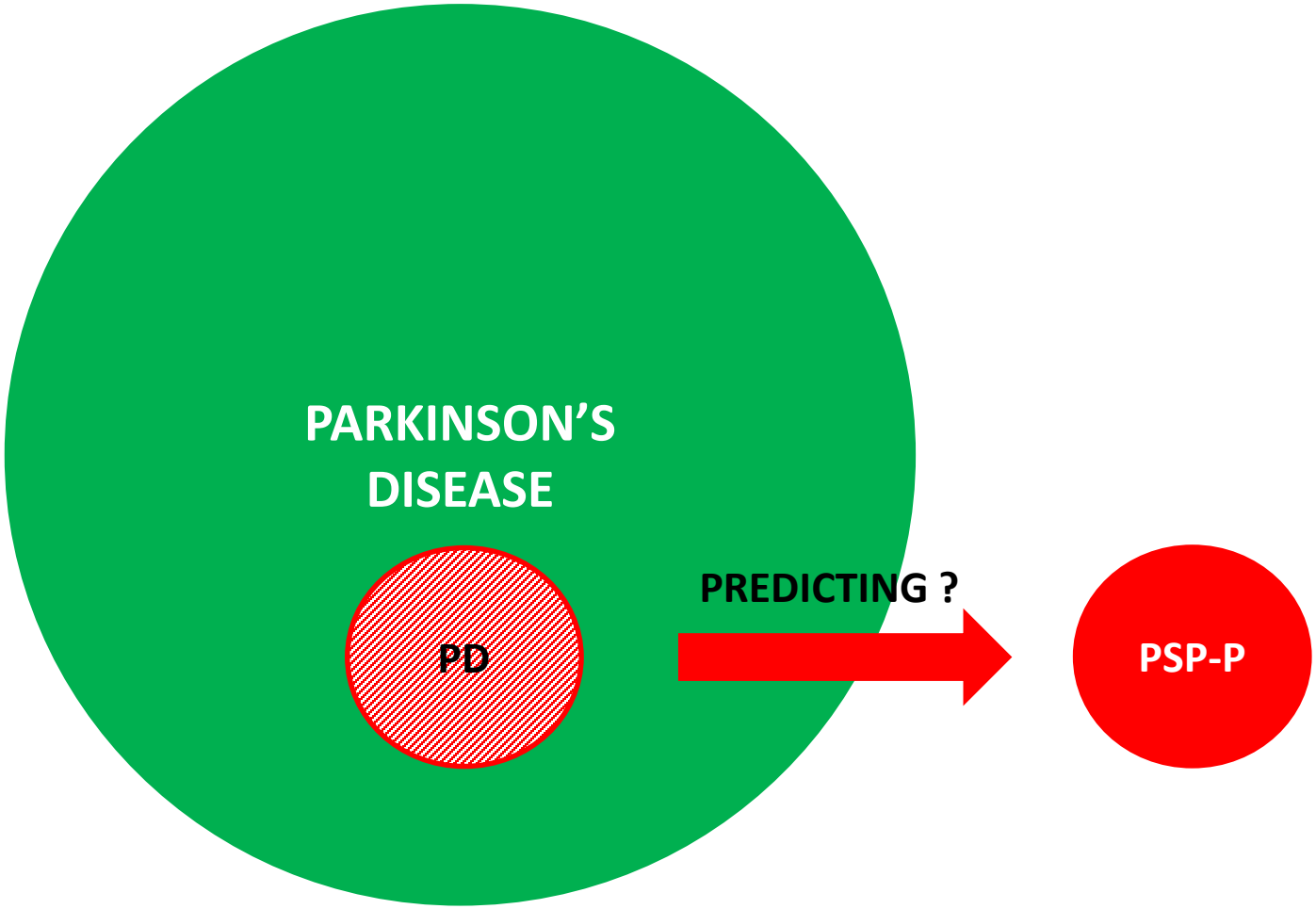
O2= vertical slowness

Cutoff and statistical values	MRPI	MRPI 2.0
PSP-P patients with O1 level vs. PD patients		
Cutoff value	≥12.38[a]	≥2.91[a]
Sensitivity (%)	100	100
Specificity (%)	98.1	100
PPV (%)	93.8	100
NPV (%)	100	100
Accuracy (%)	98.5	100
PSP-P patients with O2 level vs. PD patients		
Cutoff value	≥11.34[a]	≥2.18[a]
Sensitivity (%)	73.7	100
Specificity (%)	84.9	94.3
PPV (%)	63.6	86.4
NPV (%)	90.0	100
Accuracy (%)	81.9	95.8

LEVEL 2: *SUPPORTIVE OF CLINICAL DIAGNOSIS*

LEVEL 3: *SUPPORTIVE OF EARLY CLINICAL DIAGNOSIS*

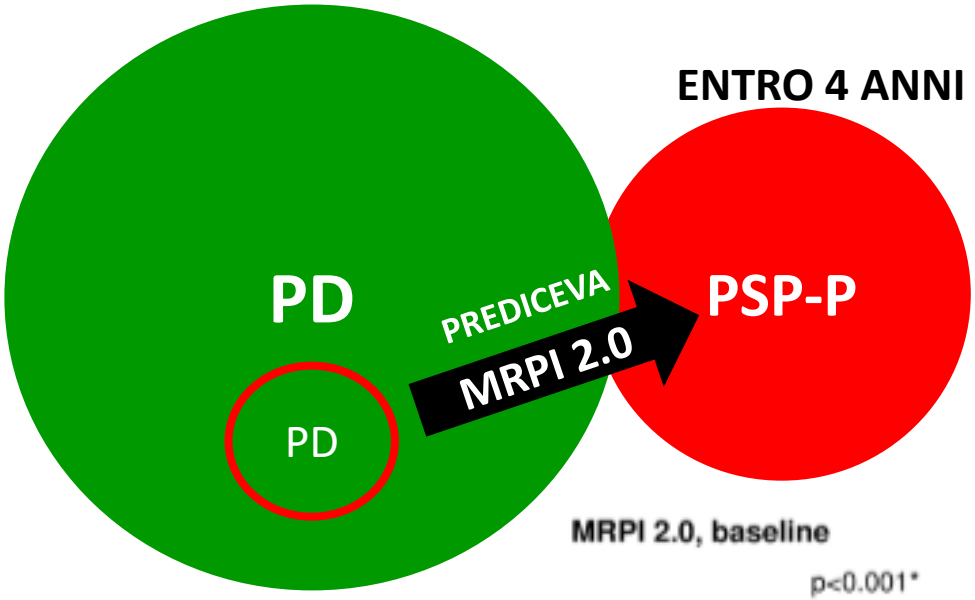
PSP-P MISDIAGNOSED AS PARKINSON'S DISEASE?

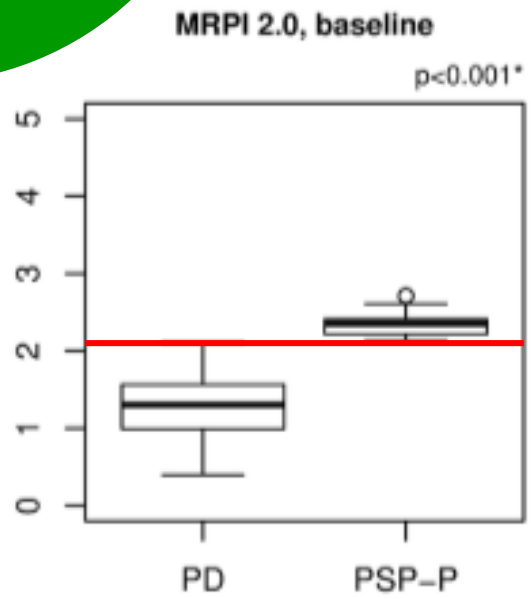


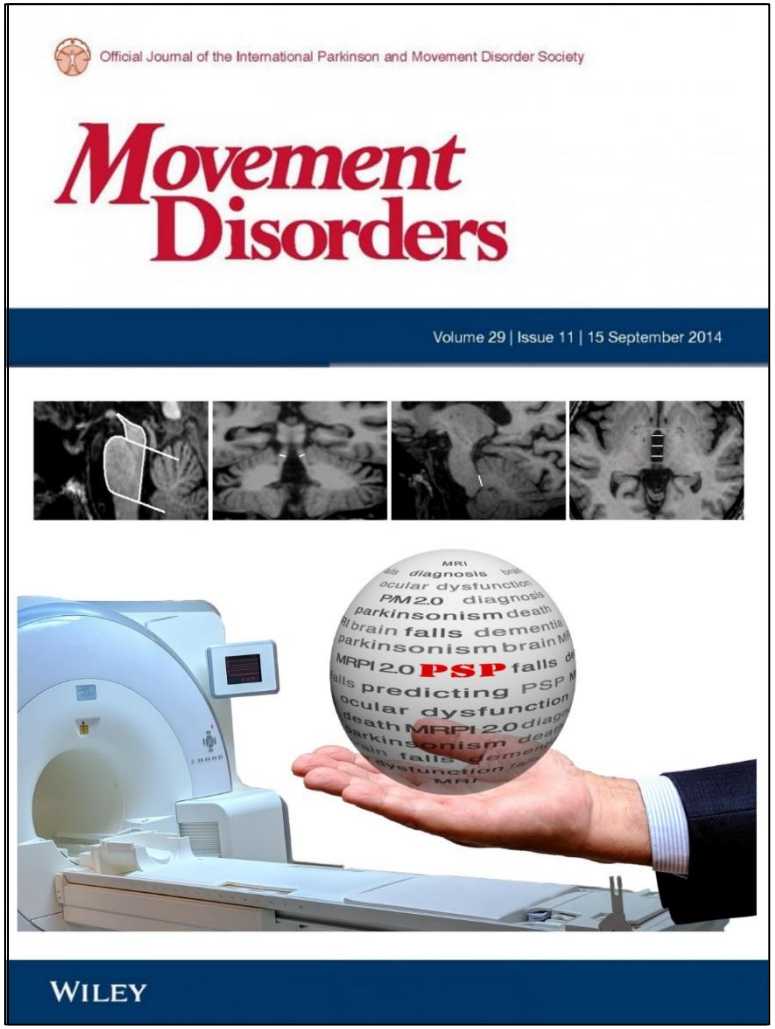
MARCATORI PREDITTIVI DI PSP-P: MRPI 2.0

ALL'ENTRATA NELLO STUDIO

ENTRO 4 ANNI



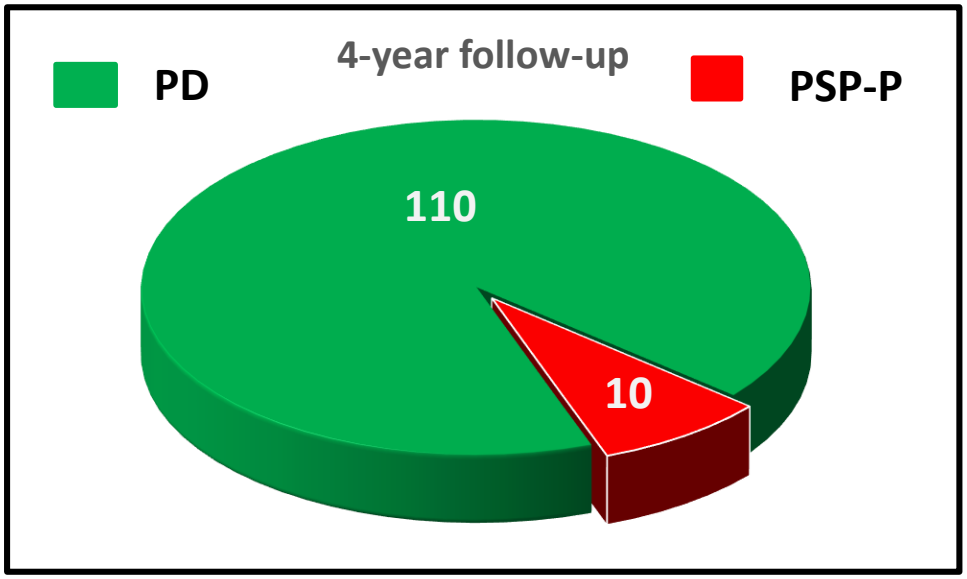


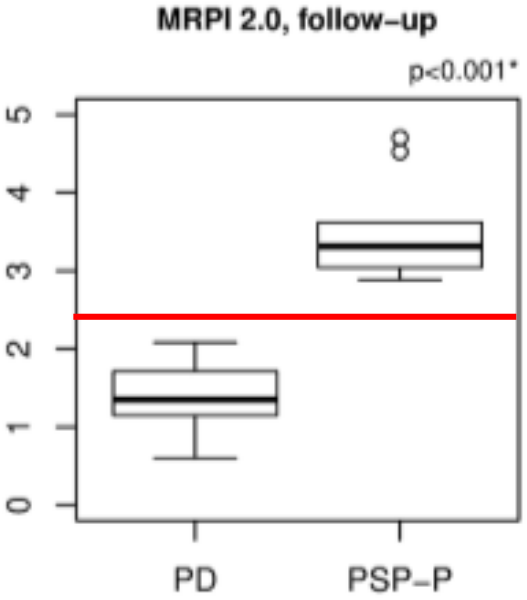


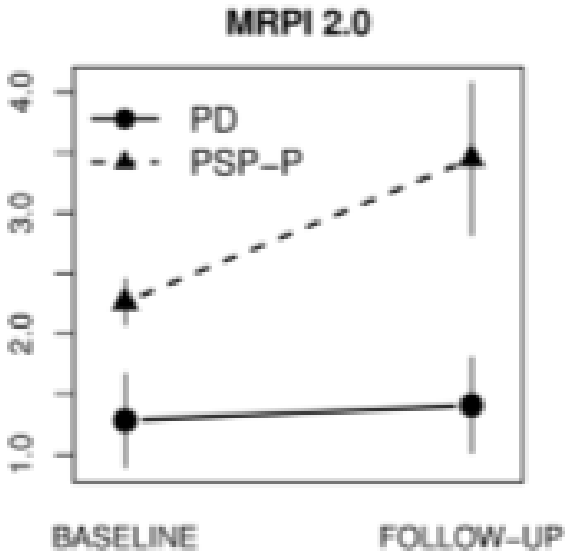
2019

Refining initial diagnosis of Parkinson's disease: a 4-year prospective clinical and MRI study

LEVEL 3: *SUPPORTIVE OF EARLY CLISNICAL DIAGNOSIS OF PP-P*







Quattrone et al. in press

2017

REVIEW

Radiological Biomarkers for Diagnosis in PSP: Where Are We and Where Do We Need to Be?

Jennifer L. Whitwell, PhD,[1*] Günter U. Höglinger, MD,[2,3] Angelo Antonini, MD,[4] Yvette Bordelon, MD, PhD,[5] Adam L. Boxer, MD, PhD,[6] Carlo Colosimo, MD, FEAN,[7] Thilo van Eimeren, MD,[3,8] Lawrence I. Golbe, MD,[9] Jan Kassubek, MD,[10] Carolin Kurz, MD,[11] Irene Litvan, MD,[12] Alexander Pantelyat, MD,[13] Gil Rabinovici, MD,[6] Gesine Respondek, MD,[2,3] Axel Rominger, MD,[14] James B. Rowe, MD, PhD,[15] Maria Stamelou, MD, PhD,[16] Keith A. Josephs, MD, MST, MSc,[17] and for the Movement Disorder Society-endorsed PSP Study Group

TABLE 3. Currently available neuroimaging biomarkers that fulfill each level of evidence in PSP

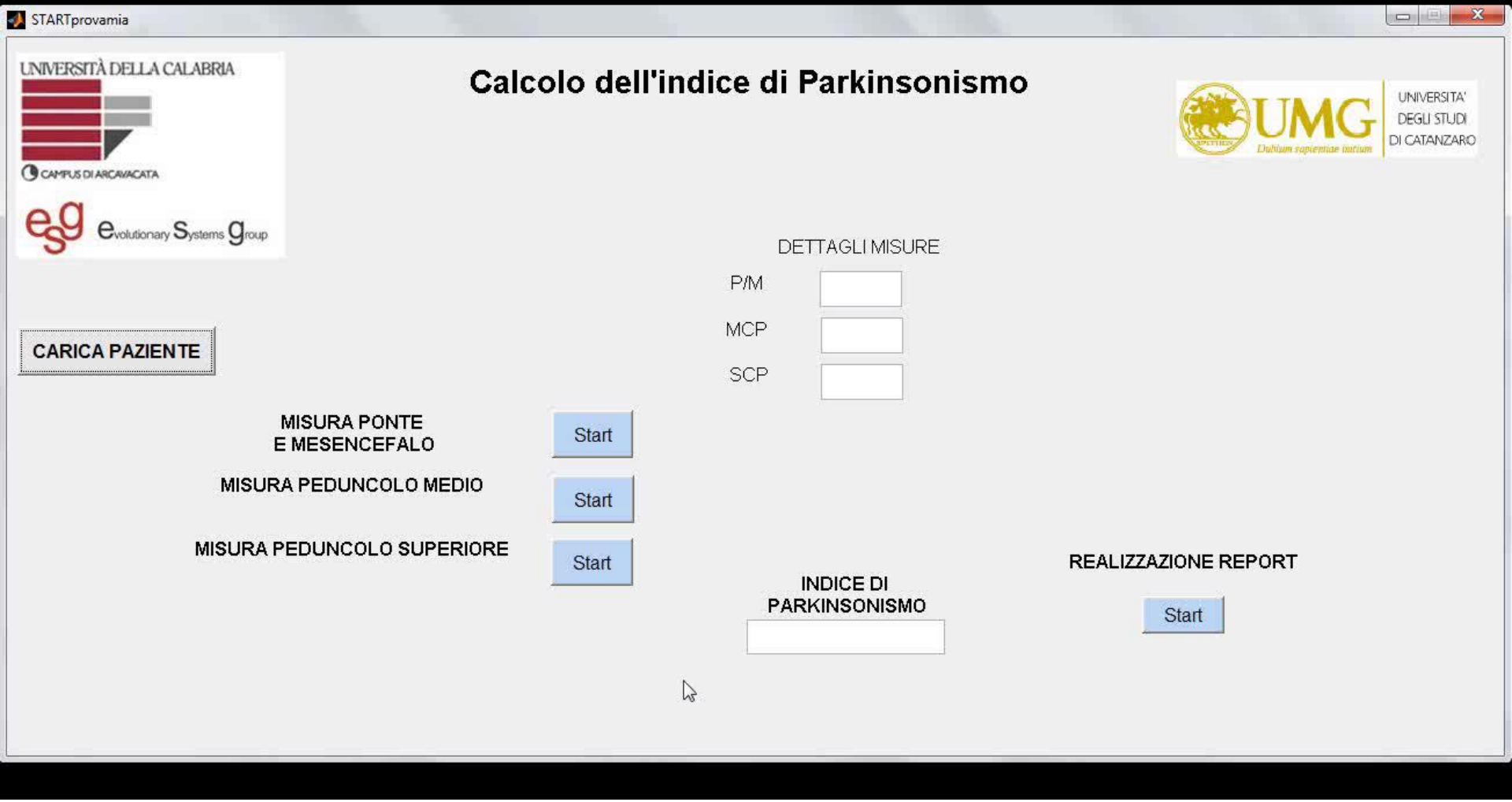
Level	Utility	PSP-RS	vPSP
1	Research tool	• Basal ganglia and thalamic atrophy • DTI abnormalities in the dentatorubrothalamic and frontal lobe tracts • THK-5351 uptake in midbrain and globus pallidus[a] • MRS metabolites • Rates of whole-brain and midbrain atrophy • Resting -fMRI[a] • SPECT frontal hypoperfusion	• Midbrain atrophy (PSP-SL, PSP-F, PSP-P) • Frontal atrophy (PSP-F, PSP-SL, PSP-CBS, PSP-PGF, PSP-P) • Basal ganglia atrophy (PSP-SL, PSP-CBS, PSP-PGF, PSP-P) • DTI abnormalities in frontal lobe tracts (PSP-P)a • Reduced striatal DAT (PSP-PGF, PSP-P)
2	Supportive of clinical diagnosis	• Midbrain area • Midbrain-pons area ratio • MRPI • Frontal atrophy in addition to midbrain atrophy[a] • DWI striatum[a] • DWI/DTI superior cerebellar peduncle[a] • FDG-PET frontal and midbrain hypometabolism[a] • [^{18}F]AV-1451 uptake in midbrain, thalamus, basal ganglia, dentate nucleus of the cerebellum[a] • Reduced striatal DAT/D2 receptor (sensitive only) • Reduced brain stem DAT[a]	
3	Supportive of early clinical diagnosis	• Midbrain-pons area ratio/MRPI • FDG-PET frontal hypometabolism[a]	• MRPI (PSP-P)[a]
4	Supportive of pathological diagnosis		None
5	Definitive		None

CONFRONTO TRA BIOMARCATORI

UN BIOMARCATORE SENSIBILE E SPECIFICO PER UNA DATA MALATTIA DEVE ESSERE FACILMENTE RIPRODUCIBILE ANCHE DA NON ESPERTI DEL SETTORE PER DIVENTARE AUSILIO ALLA DIAGNOSI

UN BIOMARCATORE SENSIBILE E SPECIFICO PER UNA DATA MALATTIA DOVREBBE ESSERE AUTOMATIZZATO PER MIGLIORARE LA RIPRODUCIBILITA' DEI RISULTATI

CALCOLO AUTOMATICO DEL MRPI


STARTprovamia
UNIVERSITÀ DELLA CALABRIA
CAMPUS DI ARCAVACATA
esg evolutionary Systems group
Calcolo dell'indice di Parkinsonismo
UMG
UNIVERSITA' DEGLI STUDI DI CATANZARO
DETTAGLI MISURE
P/M
MCP
SCP
CARICA PAZIENTE
MISURA PONTE E MESENCEFALO
Start
MISURA PEDUNCOLO MEDIO
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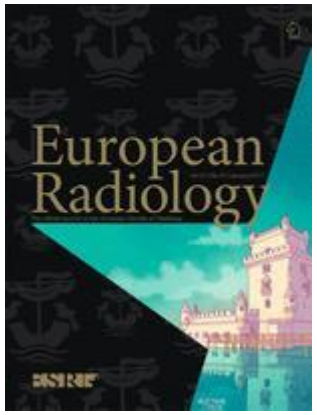
MISURA PEDUNCOLO SUPERIORE
Start
INDICE DI PARKINSONISMO
REALIZZAZIONE REPORT
Start



Eur Radiology 2016

Magnetic Resonance Parkinsonism Index: diagnostic accuracy of a fully automated algorithm in comparison with the manual measurement in a large Italian multicenter study in patients with Progressive Supranuclear Palsy.

Salvatore Nigro, Gennarina Arabia, Angelo Antonini, Luca Weis, Andrea Marcante, Alessandro Tessitore, Mario Cirillo, Giocchino Tedeschi, Stefano Zanigni, Giovanna Calandra-Buonaura Caterina Tonon, Gianni Pezzoli, Roberto Cilia, Mario Zappia, Alessandra Nicoletti, Edoardo Cicero, Michele Tinazzi, Pierluigi Tocco, Nicolò Cardobi, Aldo Quattrone

Scanner	Cutoff /Accuratezza	MRPI Automatico	MRPI Manuale
1.5T		PSP vs PD	PSP vs PD
	Cutoff value	13.46	13.58
	Accuratezza (%)	91.53	96.61
		PSP vs HC	
	Cutoff value	11.45	11.09
	Accuratezza (%)	95.24	98.41
3.0T		PSP vs PD	PSP vs PD
	Cutoff value	13.49	13.64
	Accuratezza (%)	96.35	100
		PSP vs HC	
	Cutoff value	13.49	13.64
	Accuratezza (%)	96.12	100

PD
234

PSP
88

CONFRONTO TRA BIOMARCATORI

UN BIOMARCATORE SENSIBILE E SPECIFICO PER UNA DATA MALATTIA IDENTIFICATO DA UN CENTRO DEVE ESSERE CONFERMATO IN ALTRI CENTRI CON COORTI DIVERSE DI PAZIENTI AFFETTI DALLA STESSA MALATTIA

UN BIOMARCATORE SENSIBILE E SPECIFICO PER UNA DATA MALATTIA DEVE ESSERE CONFRONTATO CON MARCATORI DIVERSI PER VALUTARE LA RELATIVA SENSIBILITA E SPECIFICITA'

Table 1. Number of submitted files on the online platform and number of failures in automated MRPI calculation.

Center	Submitted Jobs	Completed Jobs (%)	Failed Jobs (%)
University of Florida	236	218 (92,37 %)	18 (7,63%)
CEMIC, Argentina	21	16 (76,2%)	5 (23,8%)
University of Pisa	66	61 (93.84%)	5 (6.16%)
University of Cambridge	21	16 (76.19%)	5 (23.81%)
IRCCS S. Camillo - Venice	112	101 (87%)	11(13%)
University of Innsbruck	125	113 (90.4%)	12 (9.6%)
CEITEC MU Czech Republic	2	2 (100%)	0
Universisty Hospital Cologne	3	3 (100%)	0
University of Toronto	10	10 (100%)	0
University Magna Grecia	217	217 (100%)	0
	813	**757 (93%)**	**56 (7%)**

Table 2. Diagnostic properties of MRPI for the differentiation of patients with PSP from patients with PD and healthy controls

	Sensitivity	Specificity	Area under the ROC curve (AUC)	Cut-off
Non-PSP vs PSP (PSP-P + PSP-RS)	86,80%	92,50%	0,95	13,12
Non-PSP vs PSP-RS	100%	92,90%	0,99	13,31
Non-PSP vs PSP-P	88,90%	79,60%	0,9	11,31

MRI QUANTITATIVA: INDICI DIAGNOSTICI NEI PARKINSONISMI

REFERTO MORFOMETRIA

MRPI
MRPI 2.0

CNR

CONSIGLIO NAZIONALE DELLE RICERCHE
ISTITUTO DI BIOIMMAGINI E FISIOLOGIA MOLECOLARE
UNITA' ORGANIZZATIVA DI SUPPORTO "NEUROIMMAGINI"
Responsabile *Prof. Aldo Quattrone*

UMG

Data Esame 28/02/2019

Cognome Latella **Nome** Giuseppe **Data di nascita** 13/04/1933

Risonanza Magnetica GE modello Discovery MR 750 3Tesla

Tecnica: scansioni sagittali 3D T1-pesate acquisite con sequenza volumetrica SPGR

MORFOMETRIA CEREBRALE PER LA DIAGNOSI DEI PARKINSONISMI

	Valori del soggetto	Valori normali
Ponte	483 mm^2	*(372 - 615 mm^2)* [1]
Mesencefalo	96 mm^2	*(70 - 163 mm^2)* [1]
Peduncolo Cerebellare Medio (PCM)	8,1 *mm*	*(8,1 - 10,2 mm)* [1]
Peduncolo Cerebellare Superiore (PCS)	3,36 *mm*	*(3 - 4,8 mm)* [1]
Terzo Ventricolo (3° V)	8,88 *mm*	*(3,2 - 8,9 mm)* [2]
Ventricoli laterali (VL)	42,5 *mm*	*(26,8 - 43,1 mm)* [2]
Angolo Callosale	74,00 °	*(> 100 °)* [3]
Indice di Evans	0,33	*(< 0,32)* [3]
Magnetic Resonance Parkinsonism Index **(MRPI)**	12,13	*(6,37 - 12,47)* [2]
Z score	*1,59*	
Magnetic Resonance Parkinsonism Index 2.0 (MRPI 2.0)	2,53	*(0,60 - 2,38)* [2]
Z score	2,39	

I risultati vanno interpretati nell'ambito del contesto clinico

[1] *Quattrone et al., 2008, Radiology, 246, pp. 214-221.*
[2] *Quattrone et al., 2018, Park. Relat. Disord., 54, pp. 3-8.*
[3] *Mitkin et al., 2017, Radiology, 285, pp. 197-205.*

Ing. Salvatore Nigro
Prof. Aldo Quattrone

Campus Universitario Germaneto, Università degli Studi "Magna Graecia" (UMG) Viale Europa 88100 Catanzaro -
Tel. 0961/3695900 Fax 0961/3695919 email: germaneto@ibmf.cnr.it Partita IVA 02118311006 Codice Fiscale : 80054330586

BIOMARCATORI NEI DISORDINI DEL MOVIMENTO

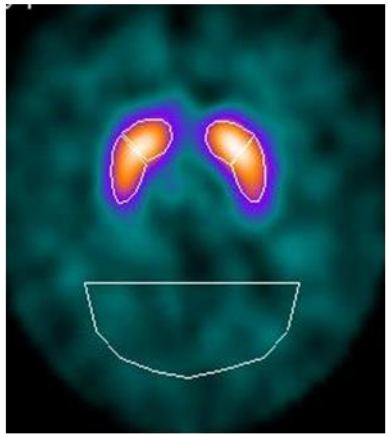
BIOMARCATORI SONO OTTENIBILI DA PROCEDURE TECNICHE MOLTO DIVERSE. BIOCHIMICHE, ELETTROFISIOLOGICHE, NEURORADIOLOGICHE

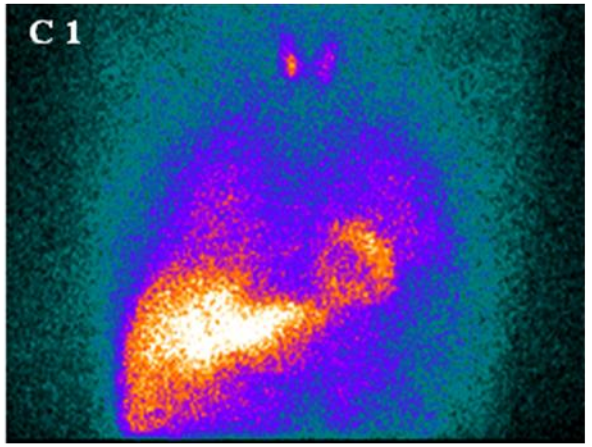
UN BIOMARCATORE DEVE ESSERE FACILMENTE RIPRODUCIBILE, OTTENIBILE IN POCO TEMPO, E POSSIBILMENTE POCO COSTOSO

DIAGNOSI DIFFERENZIALE TRA PARKINSON, TREMORE ESSENZIALE E PARKINSONIMSO FARMACOGENO

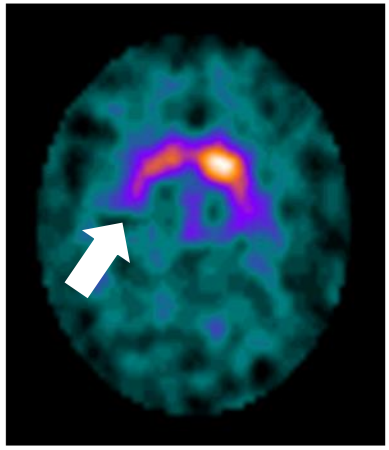
ESSENTIAL TREMOR WITH RESTING TREMOR (rET) vs TREMOR-DOMINANT PARKINSON DISEASE (TD-PD)

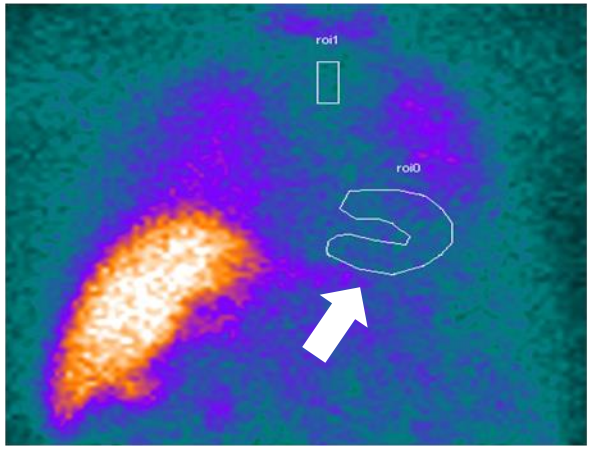
ESSENTIAL TREMOR WITH RESTING TREMOR (rET)





TREMOR DOMINANT PARKINSON DISEASE (TD-PD)





ESSENTIAL TREMOR WITH RESTING TREMOR OR TREMOR-DOMINANT PARKINSON DISEASE?

ESSENTIAL TREMOR WITH RESTING TREMOR OR TREMOR-DOMINANT PARKINSON DISEASE?

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

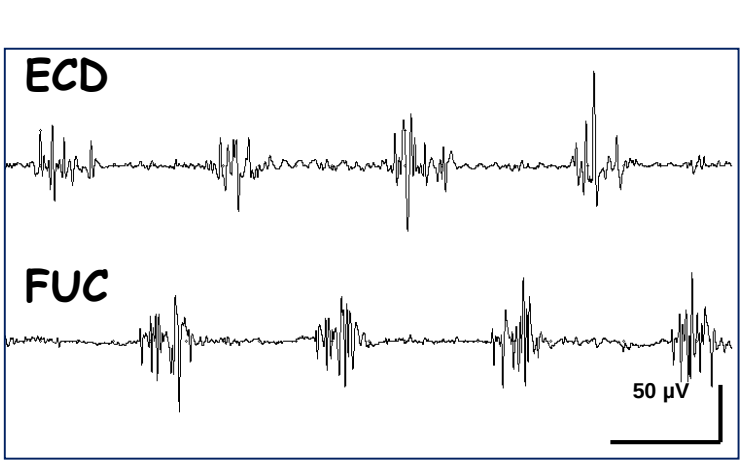
journal homepage: www.elsevier.com/locate/parkreldis

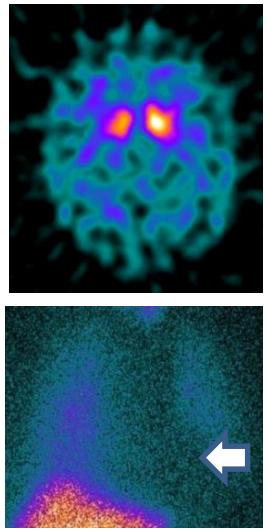
Synchronous pattern distinguishes resting tremor associated with essential tremor from rest tremor of Parkinson's disease☆

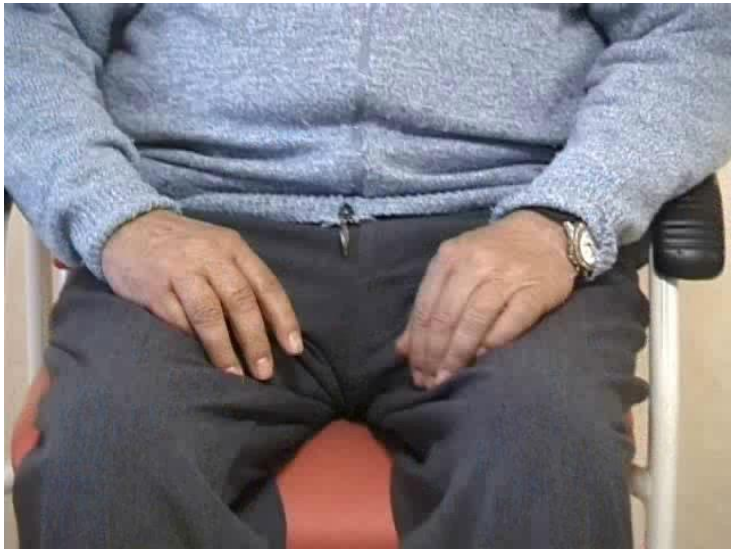
R. Nisticò [a,1], D. Pirritano [b,1], M. Salsone [b], F. Novellino [b], F. Del Giudice [b], M. Morelli [b], M. Trotta [b], G. Bilotti [b], F. Condino [c], A. Cherubini [a], P. Valentino [b], A. Quattrone [a,b,*]

2011; 17:30-33

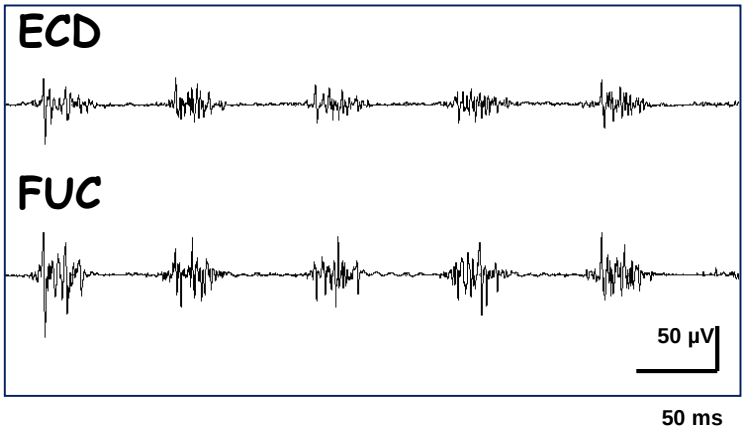
PARKINSON DISEASE

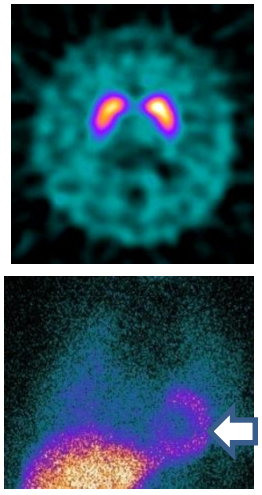


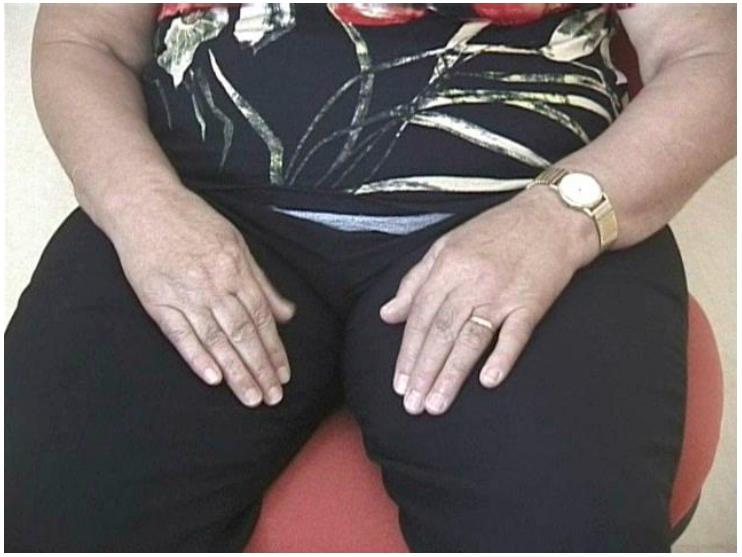




ESSENTIAL TREMOR





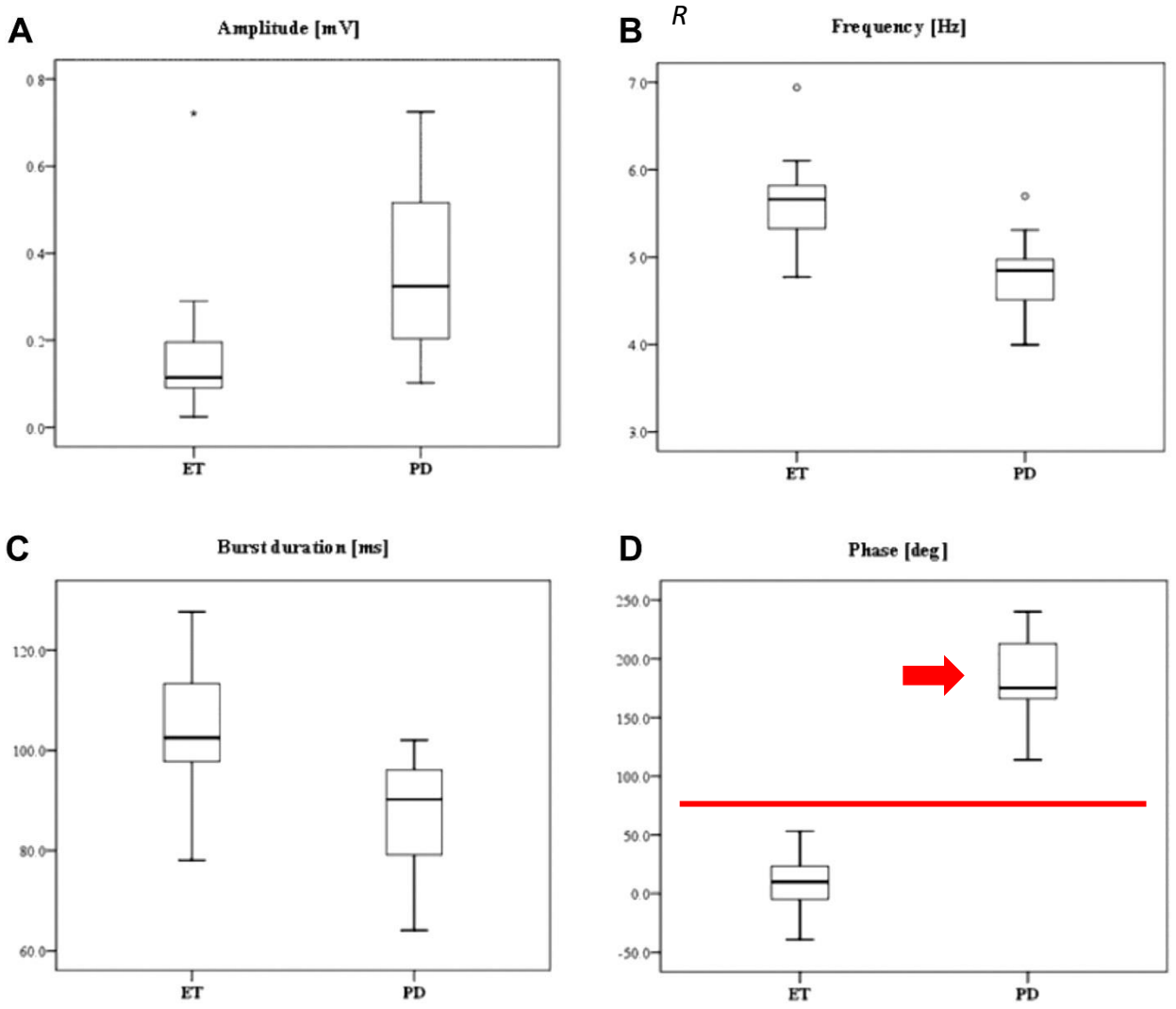


2011; 17: 30-33

Synchronous pattern distinguishes resting tremor associated with essential tremor from rest tremor of Parkinson's disease

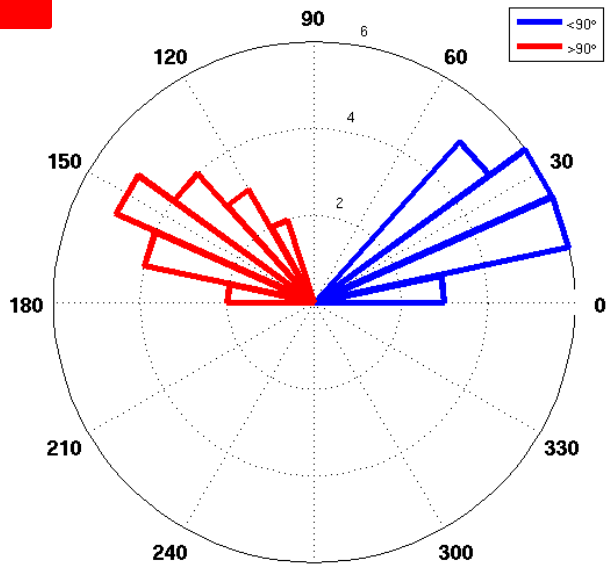
R. Nisticò[a, 1], D. Pirritano[b, 1], M. Salsone[b], F. Novellino[b], F. Del Giudice[b], M. Morelli[b], M. Trotta[b], G. Bilotti[b], F. Condino[c], A. Cherubini[a], P. Valentino[b], A. Quattrone[a, b],

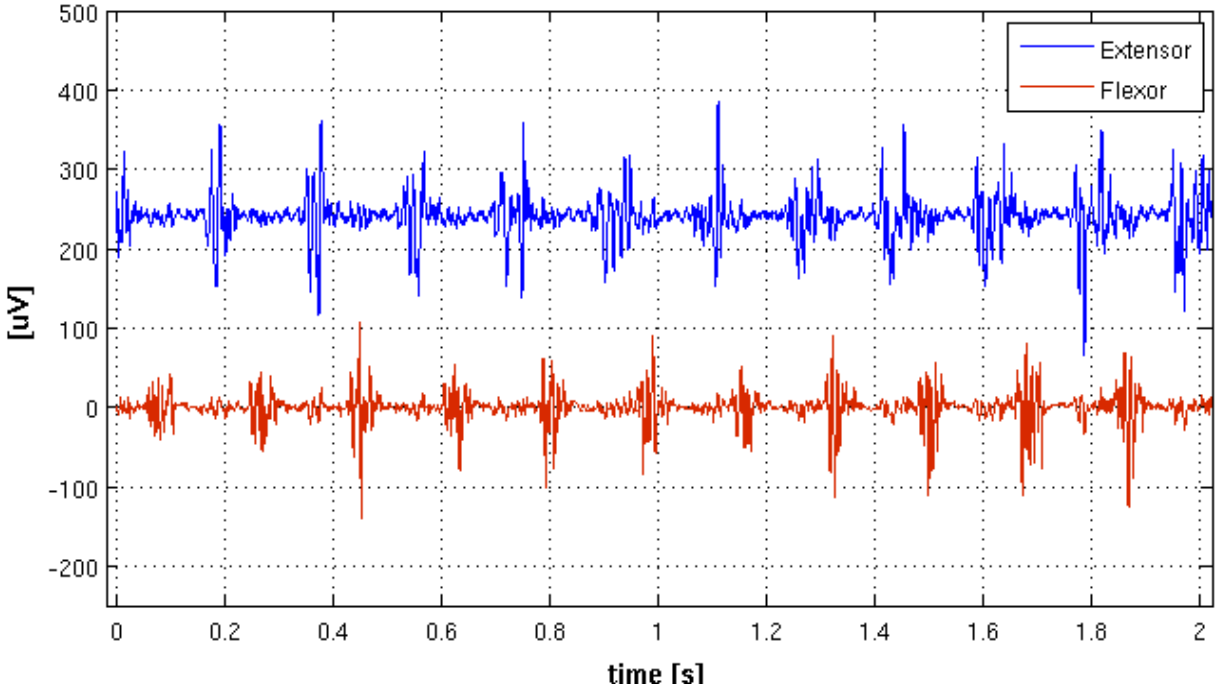
LEVEL 2: *SUPPORTIVE OF CLINICAL DIAGNOSIS* INDIVIDUAL LEVEL WITH HIGH ACCURACY



PATENT PENDING

Device per la registrazione del tremore



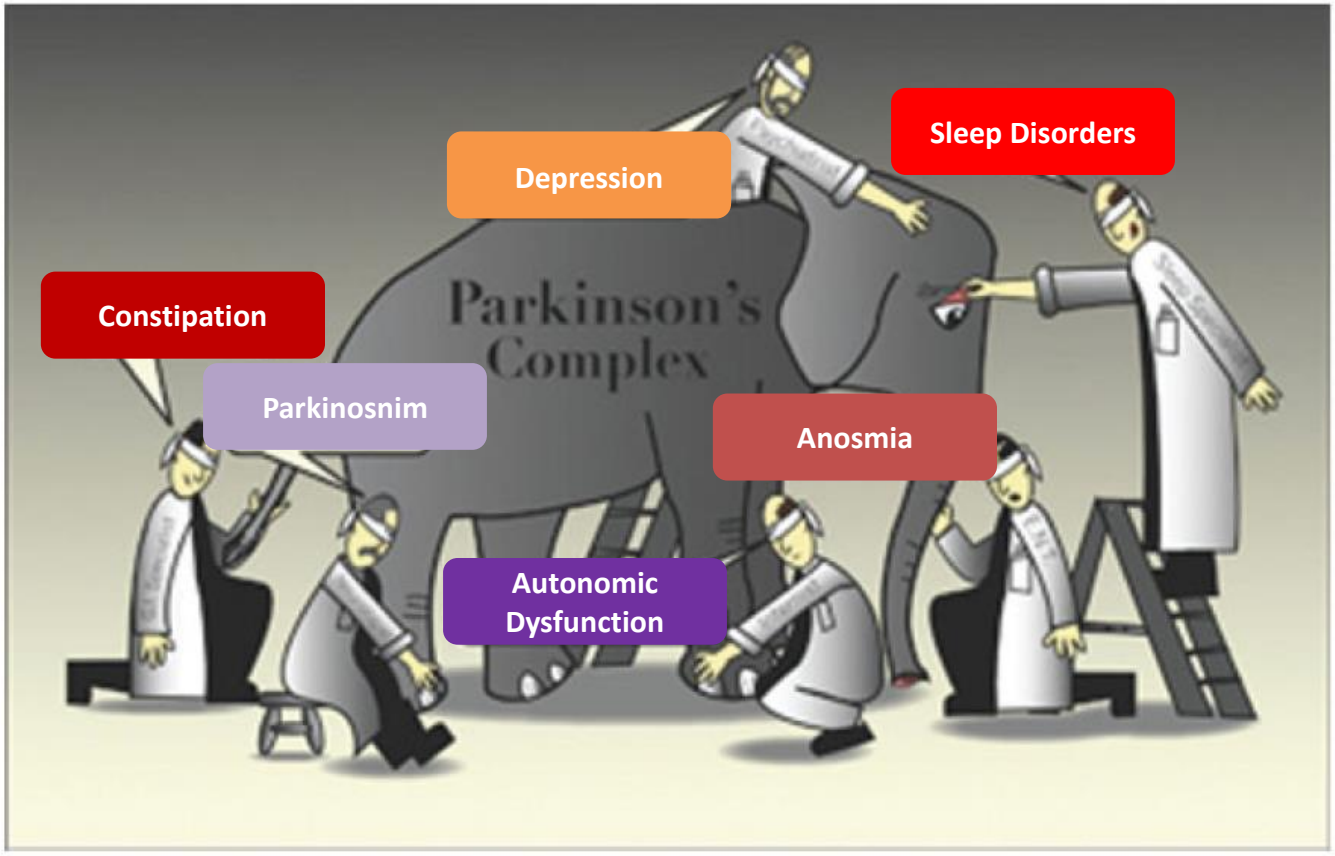


POINTS OF VIEW

The Parkinson's Complex: Parkinsonism Is Just the Tip of the Iceberg

J. William Langston, MD

2006



Contents lists available at ScienceDirect

Sleep Medicine Reviews

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

CLINICAL REVIEW

2018

Sleep disorders and Parkinson disease; lessons from genetics

Ziv Gan-Or [a, b, c, *], Roy N. Alcalay [d], Guy A. Rouleau [a, b, c], Ronald B. Postuma [c]

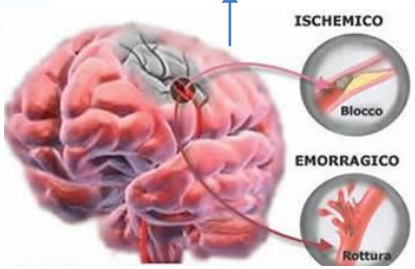
FATTORI DI RISCHIO OSAS: I CAMPANELLI D'ALLARME

OBESITA'

84.5%
dei medici ritiene indispensabile valutare OSA in presenza di:

DIABETE

CARDIOPATIA



ICTUS CEREBRALE

IPERTENSIONE ARTERIOSA

Osservatorio internazionale della salute- Indagine sulle Apnee Notturne

LA CLINICA

DI NOTTE

- -Russamento
- -Risvegli ricorrenti
- -Crisi di soffocamento
- -Nicturia
- -Sudorazione

DI GIORNO

- -Eccessiva sonnolenza diurna
- -Cefalea mattutina
- -allucinazioni ipnagogiche
- -Modificazioni della personalità
- -Deterioramento intelletivo

Contents lists available at ScienceDirect

Sleep Medicine

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

2016

Original Article

Obstructive Sleep Apnea and Cognition in Parkinson's disease

Alexandrea L. Harmell [a,b], Ariel B. Neikrug [c], Barton W. Palmer [a,b,d,e], Julie A. Avanzino [b,d], Lianqi Liu [b], Jeanne E. Maglione [b,d,e], Loki Natarajan [f], Jody Corey-Bloom [g], Jose S. Loredo [e,h], Sonia Ancoli-Israel [a,b,d,h,*]

The prevalence of OSA in PD is estimated to be around 20%–60%

Highlights

- Patients with Parkinson's disease and obstructive sleep apnea score significantly lower than those with Parkinson's disease without obstructive sleep apnea on tests of cognitive function.
- Obstructive sleep apnea is a significant predictor of poor cognition.
- Treating obstructive sleep apnea in Parkinson's disease does not result in improvements in cognition.

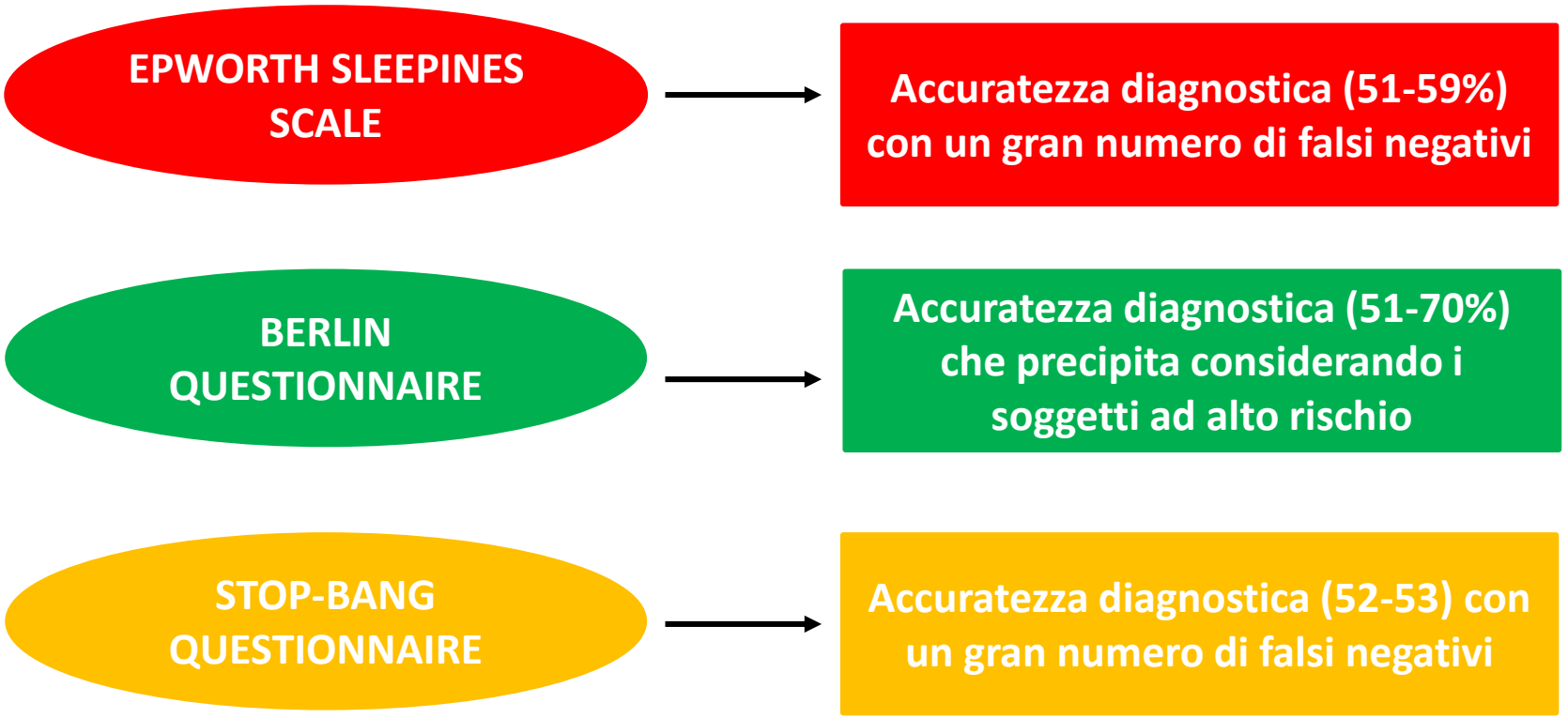
SCREENING E DIAGNOSI DI OSAS

QUESTIONARI

DIAGNOSI STRUMENTALE

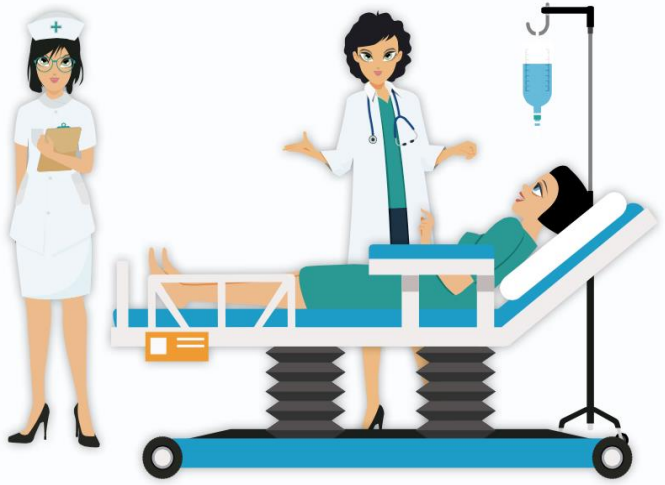
- **POLISONNOGRAFIA AMBULATORIALE**
- **HOME SLEEP APNEA TESTING**

QUESTIONARI DI SCREENING OSAS



Kapur et al.,J Clin Sleep Med. 2017;13:479-504.

POLISONNOGRAFIA AMBULATORIALE



COSTO PER IL SSN:

SALUTE | 15 novembre 2016

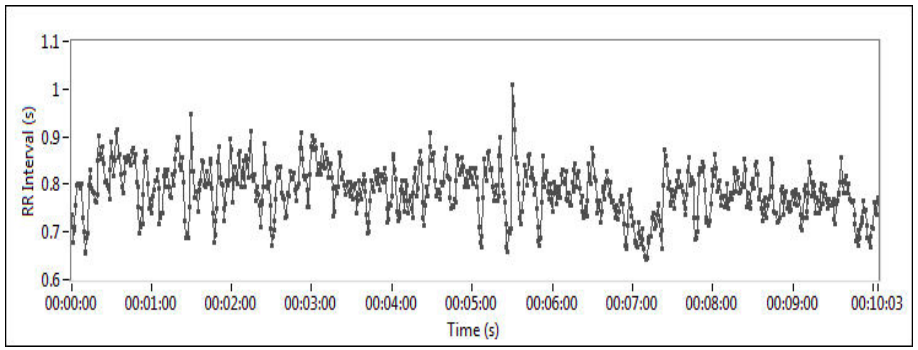
Osas, salgono costi e tempi d'attesa più lunghi. «Emergenza sovraffollamento ospedali si supera con la tecnologia»

L'opinione di Marco Brunori, odontostomatologo dell' "Umberto I" di Roma, tra i maggiori esperti della sindrome: «Esistono apparecchiature innovative che possono essere utilizzate da casa e forniscono dati precisi e utili al medico per assegnare terapie efficaci»

Heart Rate Variability (HRV) ANALISI

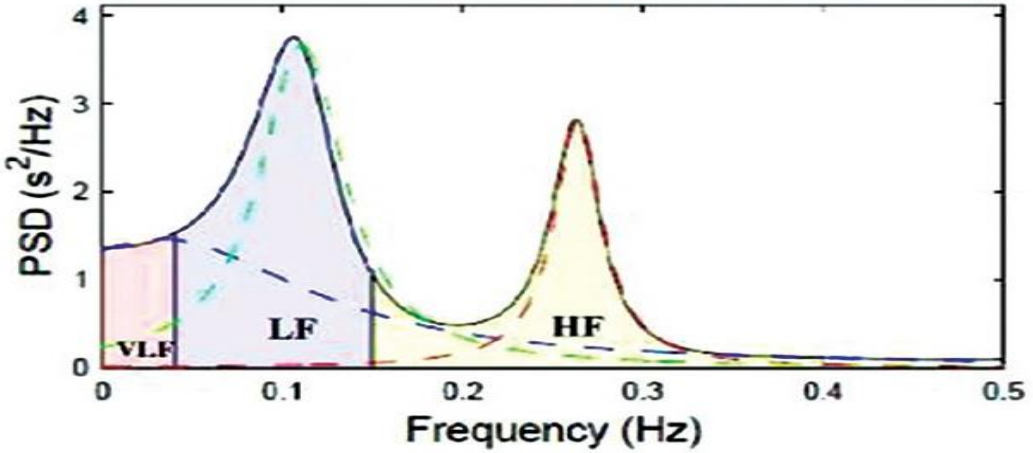
E’ una tecnica che consente di misurare la HRV (il segnale R-R, ovvero l’intervallo temporale tra un battito ed il successivo) espressione di un corretto bilanciamento tra Sistema Nervoso Simpatico e Parasimpatico cardiaco.

Tacogramma



Fourier Transform

Spettro di potenza

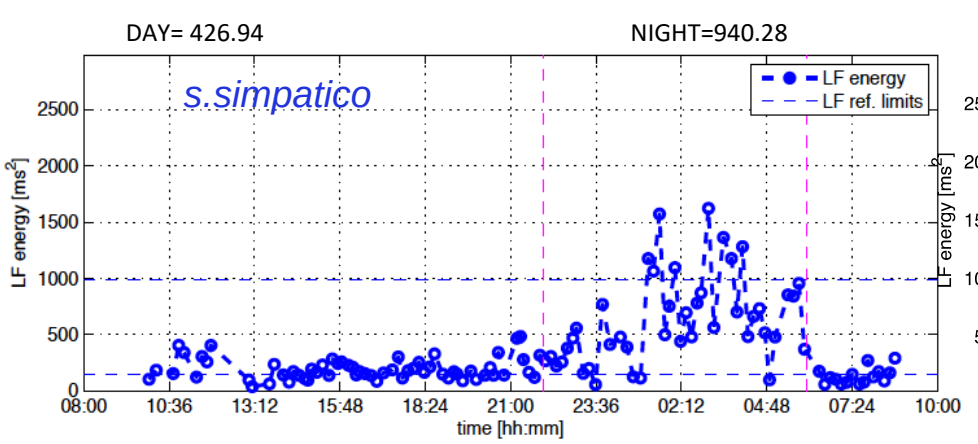


BANDE a BASSA FREQUENZA (LF)
Attività simpatica cardiaca

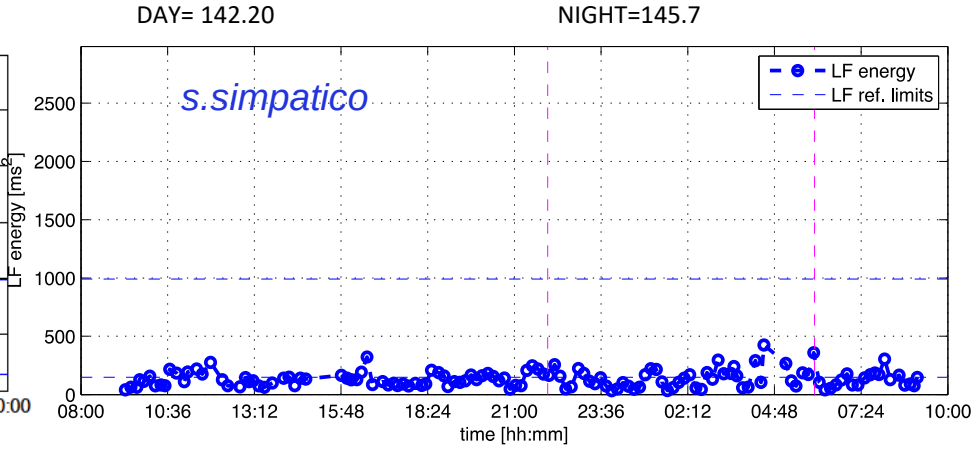
BANDE AD ALTA FREQUENZA (HF)
Attività parasimpatica casrdiaca

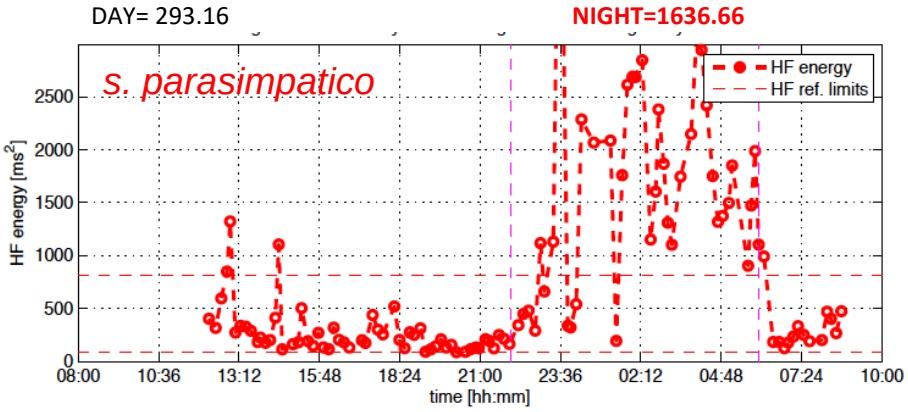
FLUTTUAZIONI AUTONOMICHE CIRCADIANE: NOTTE vs GIORNO

PAZIENTE CON OSA

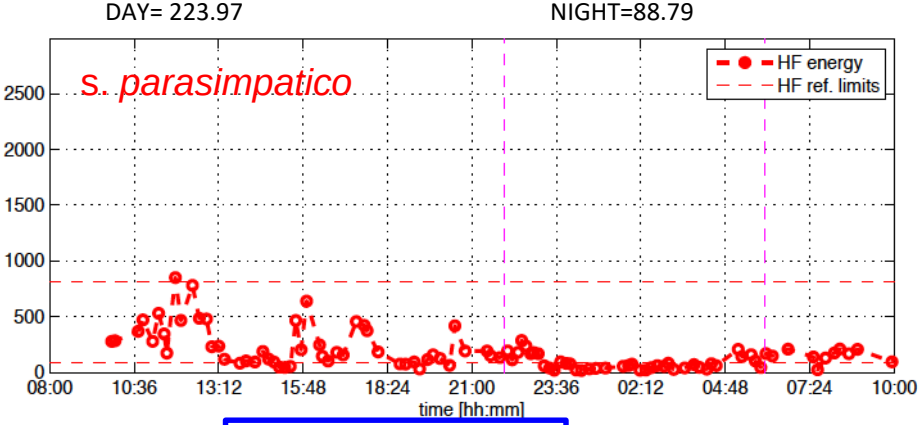


CONTROLLO





HF night/HF day
5.58



HF night/HF day
0.38

PLOS ONE

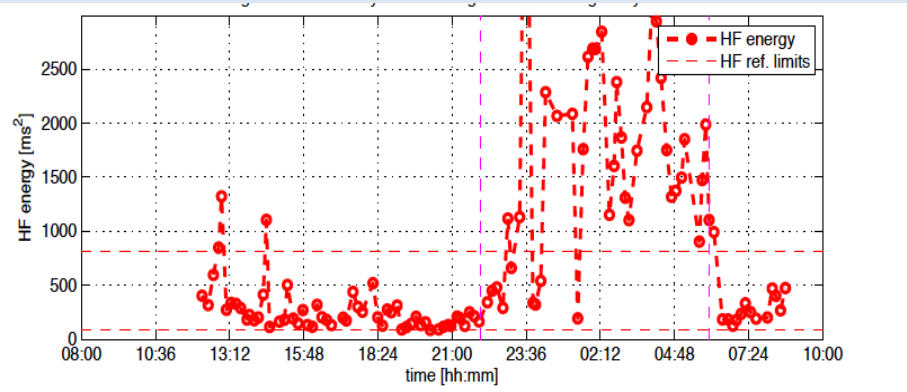
2018, 13: 18 (3) doi: 10.1371/journal.pone.0193879

RESEARCH ARTICLE

Cardiac parasympathetic index identifies subjects with adult obstructive sleep apnea: A simultaneous polysomnographic-heart rate variability study

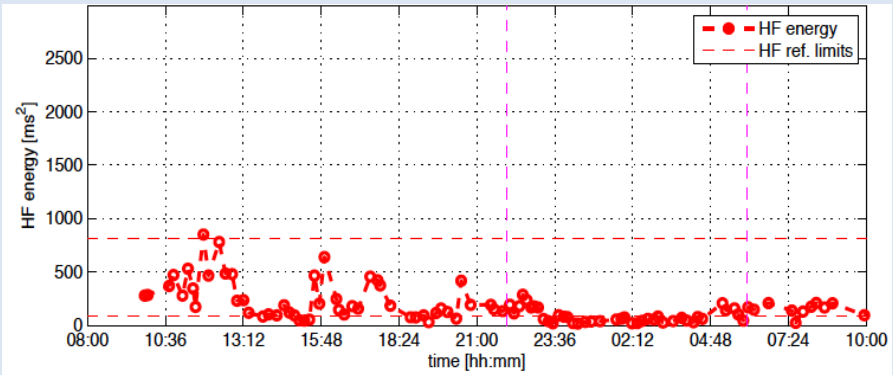
Maria Salsone[1], Basilio Vescio[2], Andrea Quattrone[3], Ferdinando Roccia[4], Miriam Sturniolo[3], Francesco Bono[3], Umberto Aguglia[3], Antonio Gambardella[3], Aldo Quattrone[1,5]*

PAZIENTE CON OSA



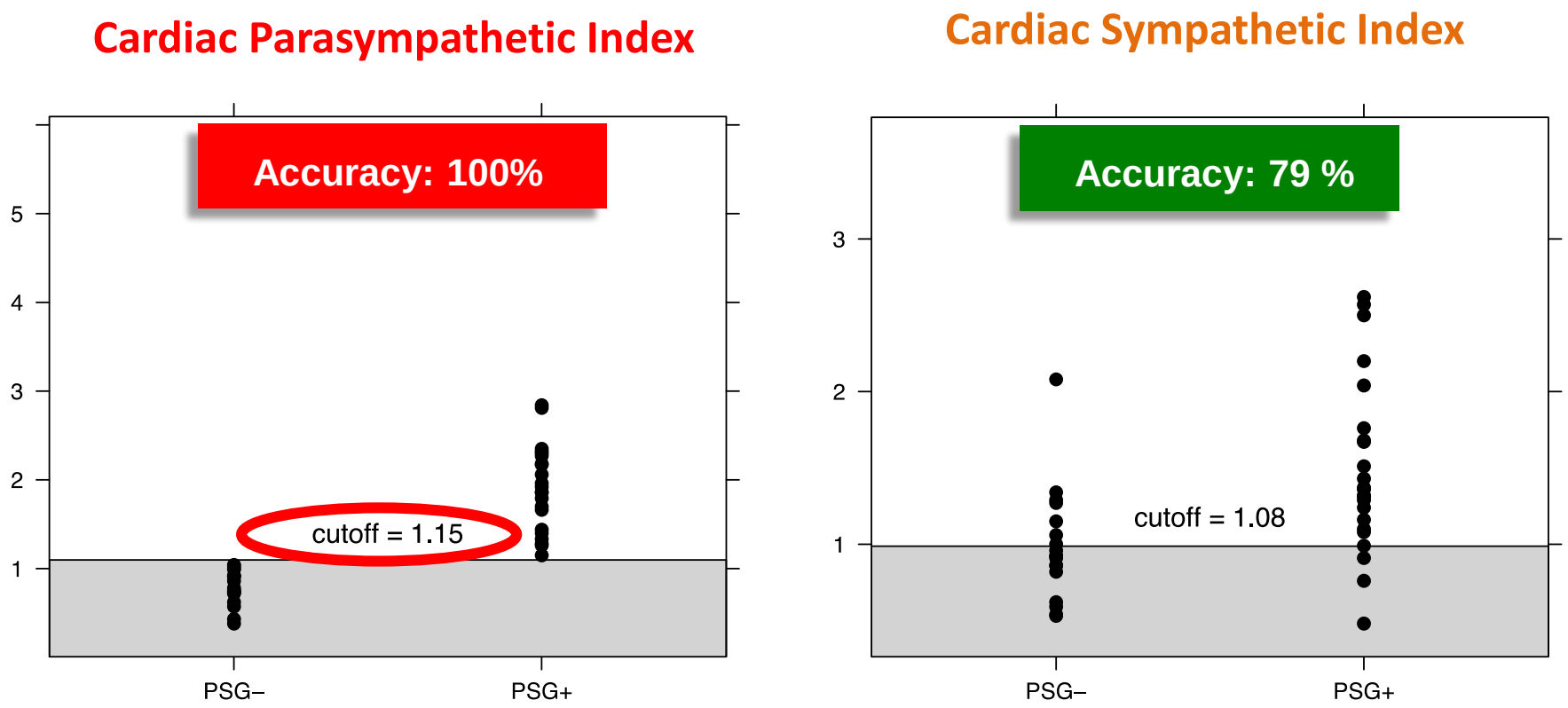
HF night/HF day
5.58

CONTROLLO SANO



HF night/HF day
0.38

GLI INDICI AUTONOMICI CARDIACI IN OSA E CONTROLLI



Upper limits of cardiac parasympathetic index (P-index, 1.15, light gray area) and cardiac sympathetic index (S-index, 1.08, light gray area) in PSG positive (PSG+) and PSG negative (PSG-) subjects (A and B respectively). The optimal cut-off levels were obtained as the points with the highest sum of sensitivity and specificity on ROC curves.

Salsone et al., PloS One 2018, 13: 18 (3)

INDICE CARDIACO AUTONOMICO VS ALTRI SISTEMI

Performances of Cardiac Autonomic Indexes, Epworth Sleepiness Scale, Nocturnal Oxymetry and portable Monitors in differentiating OSA patients from controls

OSA patients vs Controls	Cutoff	Sensitivity (%)	Specificity (%)	Accuracy (%)
Cardiac Parasympathetic Index*	≥1.15	**100**	**100**	**100**
Cardiac Sympathetic Index*	≥1.08	84	72.2	79.1
Epworth Sleepiness Scale*	≥11	56	83.3	67.4
Nocturnal Oxymetry **	-	55	88	
Portable Monitor II***	-	64-86	98-100	85
Portable Monitor III***	-	50-97	90-93	86-99

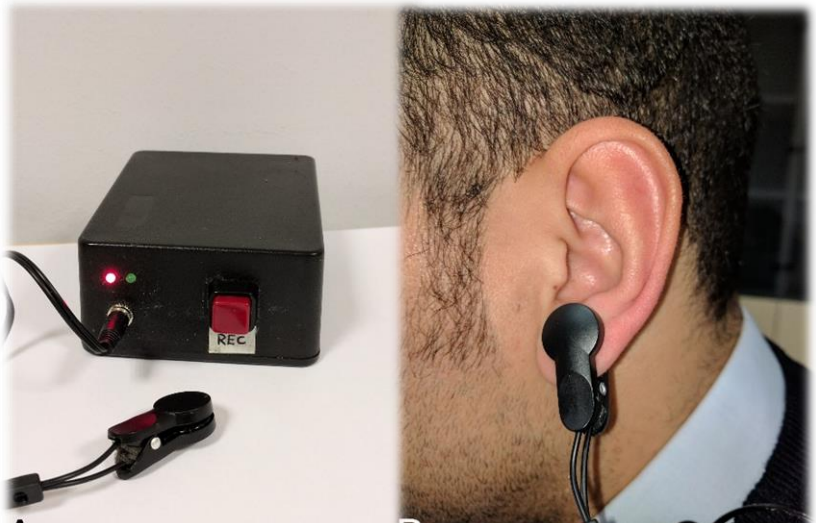
* Quattrone A et al., PloS One 2018; 13:18(3) doi:101371/Journal.pone.0193879.

** Van Eyck A et al, Sleep Med 2015; 16(11): 10.1016./J.Sleep.2015.07.023.

*** Jonas D. et al., JAMA 2017; 317 (4):415-433. doi:10.1001/Jama.2016.19635.

TECNOLOGIE INNOVATIVE PER LO SCREENING OSA

PROTOTIPO INIZIALE



sensors

Sensors. 2018;13:18(3)

MDPI

Article

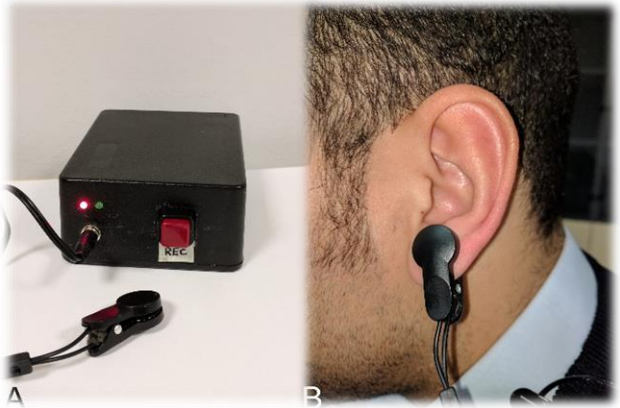
Comparison between Electrocardiographic and Earlobe Pulse Photoplethysmographic Detection for Evaluating Heart Rate Variability in Healthy Subjects in Short- and Long-Term Recordings

Basilio Vescio [1], Maria Salsone [2], Antonio Gambardella [3] and Aldo Quattrone [2,*]

REALIZZAZIONE PROTOTIPI

European Patent No. EP3267880

PROTOTIPO INIZIALE

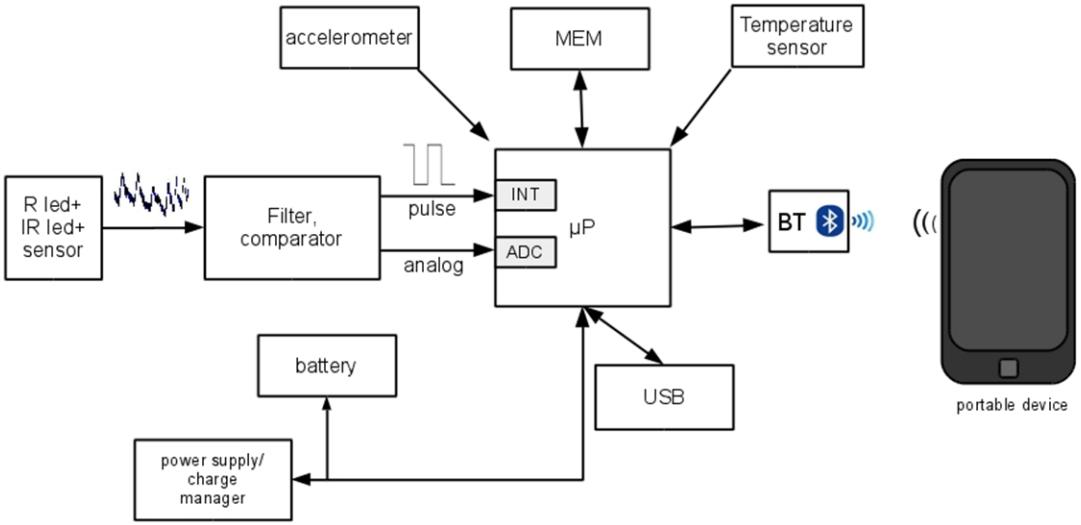


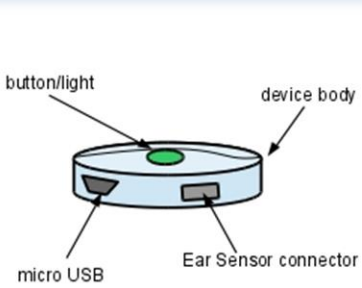
INVENTORI
Aldo Quattrone
Antonio Gambardella
Maria Salsone
Basilio Vescio

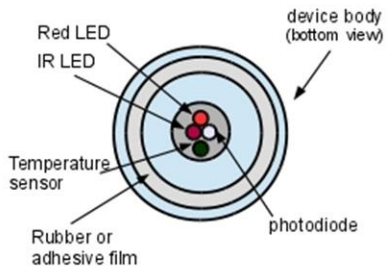
PROTOTIPO INTERMEDIO

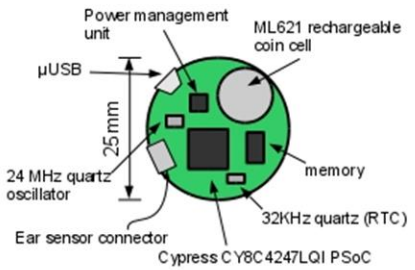
PROTOTIPO FINALE

MINIATURIZZAZIONE



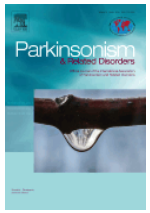






Patent Cooperation Treaty N.PCT/B 2016/050758

European Patent No. EP3267880



2016

DALLA RICERCA ALL'INNOVAZIONE TECNOLOGICA: MINI-HOLTER PER LO SCREENING DEI DISTURBI DEL SONNO

2018

2018

Patent Cooperation Treaty N.PCT/B 2016/050758
Brevetto Europeo EP 3267880

A. Quattrone, A. Gamblardella, M. Salsone, B.Vescio

Premi SIN per la ricerca ed innovazione tecnologica

REQUISITI PER UN BUON BIOMARCATORE

1. IL BIOMARCATORE DEVE ESSERE IN GRADO DI DIFFERENZIARE FENOTIPI CLINICAMENTE INDISTINGUIBILI SU BASE INDIVIDUALE CON ELEVATI LIVELLI DI SENSIBILITA' E SPECIFICITA' (ACCURATEZZA) NON INFERIORI AL 80-90%.

2. IL BIOMARCATORE PUO' ESSERE UTILIZZATO A SUPPORTO DELLA DIAGNOSI CLINICA IN FASE CONCLAMATA DI MALATTIA (LIVELLO 2, PSP PROBABILE) O A SUPPORTO DELLA DIAGNOSI IN FASE PRECOCE (LIVELLO 3, PSP POSSIBILE O CUP)

3. I LIVELLI DI CUI AL PUNTO 1) DEVONO ESSERE STATI OTTENUTI IN UN CAMPIONE SUFFICIENTEMENTE LARGO ANCHE IN CASO DI MALATTIE RARE

4. I LIVELLI DI CUI AL PUNTO 1) DEVONO ESSERE RIPRODUCIBILI NELLO STESSO CENTRO CON DATI APPARTENENTI A DIFFERENTI INDIVIDUI, ACQUISITI IN TEMPI DIVERSI

5. I LIVELLI DI CUI AL PUNTO 1) DEVONO ESSERE RICONFERMATI IN STUDI MULTICENTRICI NAZIONALI E/O INTERNAZIONALI O DEVONO PROVENIRE DA DATABASE DIVERSI

6. IL BIOMARCATORE IDEALE DEVE ESSERE DI FACILE USO, POCO COSTOSO, POSSIBILMENTE OTTENIBILE IN MODO AUTOMATICO

2008

2008

2009

2009

2010

2018

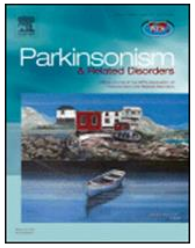
2019

2011

2011

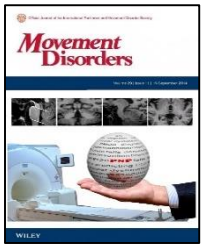
2011

2011

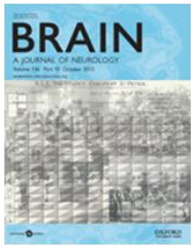


2011

2018

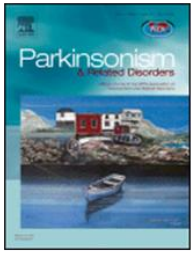


2019



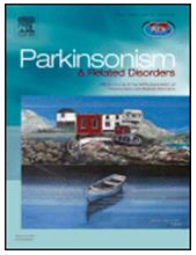
2011

2012



2012

2013



2013

2018

2018

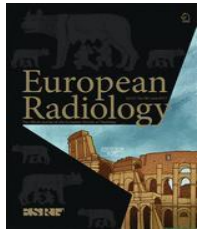
2013

2014

2014

2016

2016



2016

2017

CENTRO DI NEUROSCIENZE UMG-CNR

COORDINATORE. PROF. ALDO QUATTRONE

Consiglio Nazionale Ricerche

NEUROLOGI

G. Arabia
G. Barbagallo
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G. Nicoletti
R. Nisticò
F. Novellino
A. Quattrone
M. Salsone

PSICOLOGI

A. Cerasa
C. Chiriaco
I. Martino
M.G. Vaccaro

FISICI/ MATEMATICI

A. Cherubini
R. Vasta

INGEGNERI

A. Augimeri
M.G Bianco
M.E. Caligiuri
V. Gramigna
S. Nigro
F. Olivadese
A. Sarica
B. Vescio