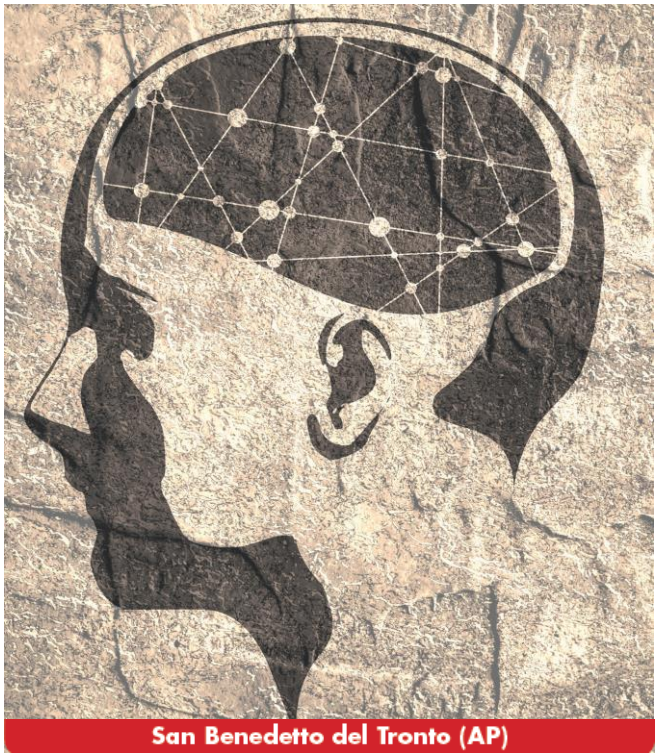
Azienda Ospedaliera - Università di Perugia
Clinica Neurologica - Dir: prof. P. Calabresi
Centro Disturbi del Movimento



6-7-8 NOVEMBRE 2017

Feattori di rischio cardiovascolare e malattie neurodegenerative

Nicola Tambasco

outline

I. Basi vascolari delle malattie degenerative

II. Malattia di Parkinson e fattori di rischio cardiovascolari

III. Il parkinsonismo vascolare

Patologie neurodegenerative

Progressiva degenerazione neuronale
in specifiche aree cerebrali

→ Coinvolgimento progressivo di funzioni cognitive e motorie

Principali forme primitive

- Malattia di Alzheimer
- Malattia di Parkinson
- Demenza Frontotemporale
- Demenza a Corpi di Lewy
- Sclerosi Laterale Amiotrofica
- Corea di Huntington

Forme secondarie
ad altra condizione patologica

- Demenza vascolare e mista
- Parkinsonismo vascolare
- Parkinsonismo iatrogeno

Ipotesi eziologiche delle patologie neurodegenerative

- **Ipotesi genetica**
- **Agenti infettivi/Traumi ripetuti/Sostanze tossiche**
- **Stress ossidativo e alterazione mitocondriale**
- **Proteinopatie**
  - Alterata aggregazione
  - Neurotossiità di forme fibrillari o oligomeriche
- **Neuroinfiammazione**
- **Alterazioni vascolari**

Rapporto tra patologia cerebrovascolare e neurodegenerazione nel **declino cognitivo**

› 45% dei casi di Demenza associati primariamente o secondariamente a malattia cerebrovascolare

Già da Alzheimer (1907) ipotizzato ruolo trigger di alterazione vascolare nella Malattia di Alzheimer

Successivamente da vari studi progressive conferme

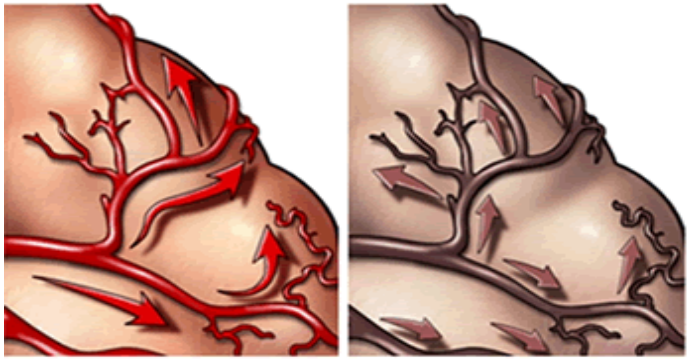
Rilevata correlazione tra riduzione dell'incidenza di demenza e riduzione di incidenza di stroke (Norton, 2016)

Per tutte le forme di Demenza rapporto di **influenza reciproca** con la disfunzione vascolare. . .

. . . per i “Vascular Cognitive Disorders”(VCDs)

Eziologia

- Malattia dei grandi vasi
- Malattia cardioembolica
- **Malattia dei piccoli vasi**



Presenza di sangue circolante nel cervello

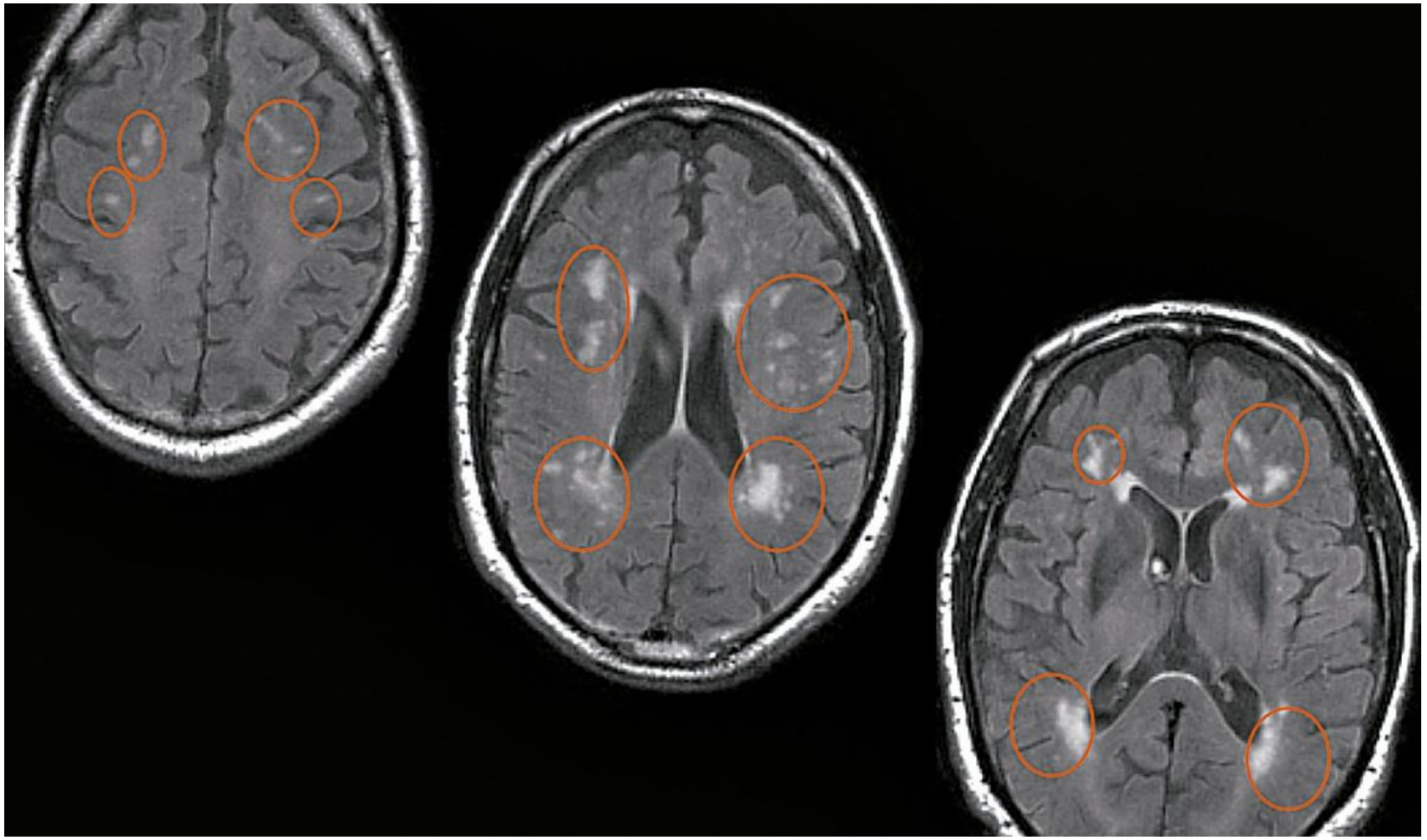
Mancanza di sangue circolante nel cervello

Forme cliniche

Impairment Cognitivo Vascolare

Vascular Dementia (VaD):
seconda forma di demenza
più frequente dopo Malattia di Alzheimer

- Demenza multinfartuale
- Demenza da infarti strategici
- Demenza emorragica
- Demenza vascolare ischemica sottocorticale
- Demenza mista



Multiple lesioni iperintense in FLAIR,
esiti di danni vascolari sottocorticali in paziente con Demenza Vascolare

. . . e per le **Demenze Primariamente Degenerative**

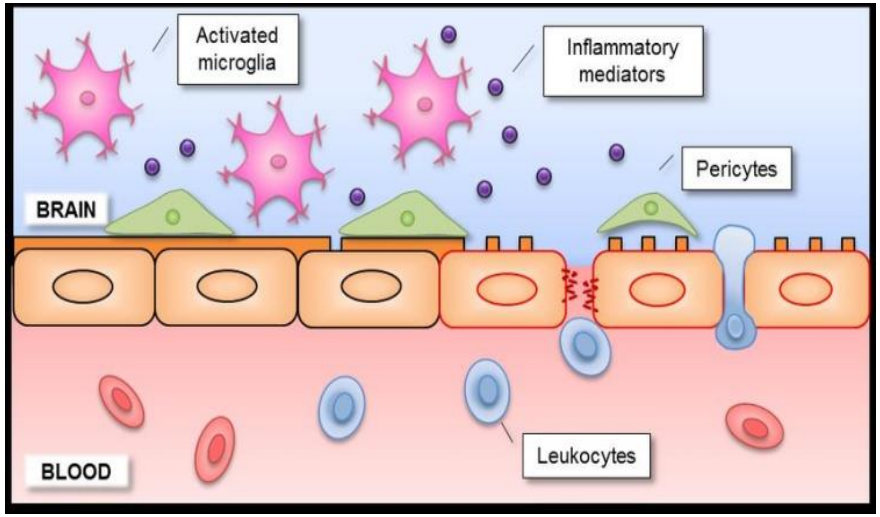
Meccanismi patogenetici

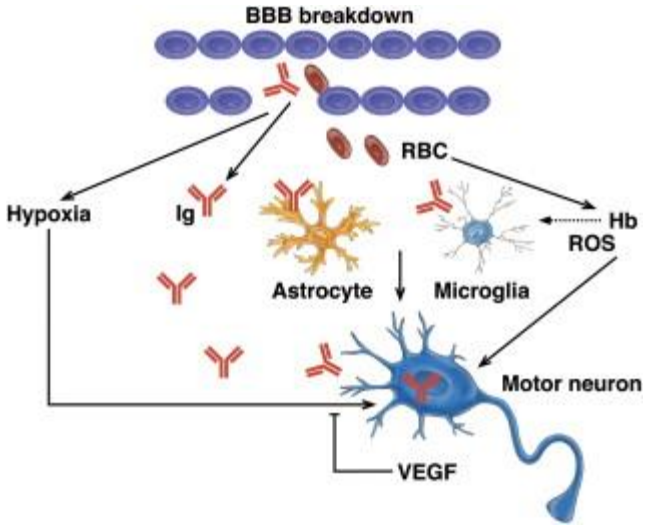
- Ipossia
- Stress ossidativo e alterazione mitocondriale
- Alterata permeabilità della BEE

- Deterioramento della parete capillare
- Alterazioni della membrana basale
- Degenerazione dei periciti

Neuroinfiammazione

Alterata integrità di barriera

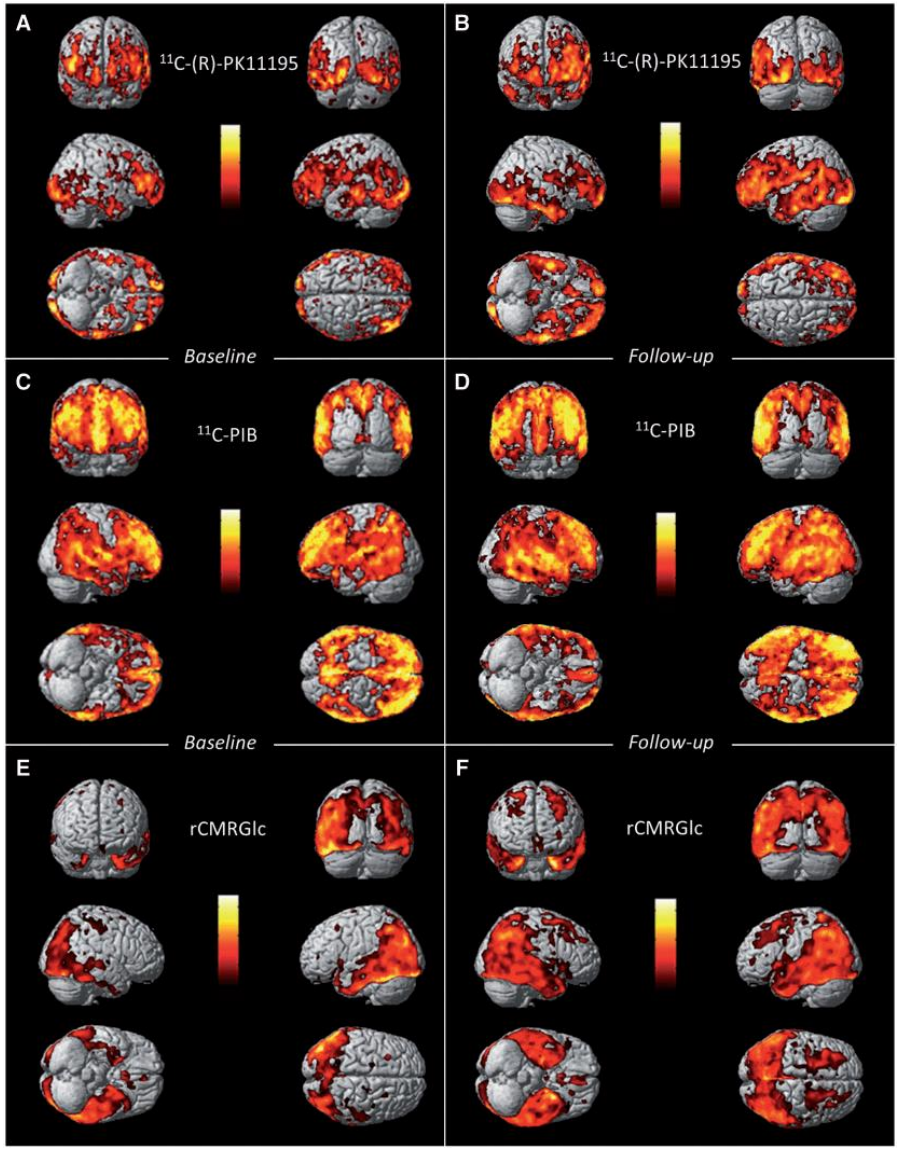




BRAIN
A JOURNAL OF NEUROLOGY
BRAIN 2015: 138; 3685–3698 | 3685

Longitudinal influence of microglial activation and amyloid on neuronal function in Alzheimer's disease

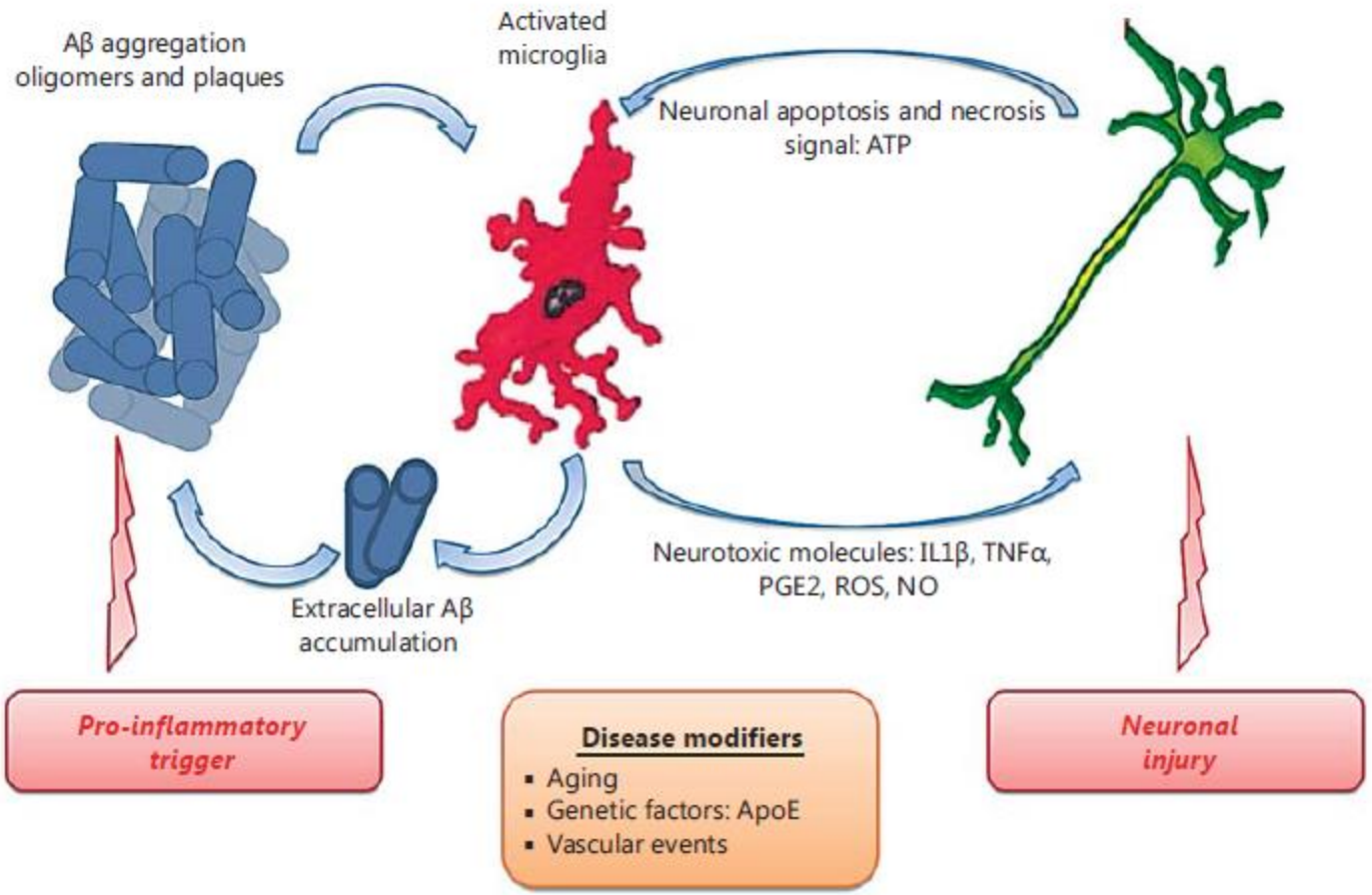
Zhen Fan,[1] Aren A. Okello,[1] David J. Brooks[1,2] and Paul Edison[1]



This study demonstrates that there is persistent neuroinflammation throughout the Alzheimer's disease process with associated synaptic dysfunction and reduced glucose metabolism.

Voxel-wise correlation analysis suggests that neuroinflammation is associated with localized amyloid deposition and glucose metabolism over time, however, the level of inflammation could also occur independently of amyloid pathology, especially in the later stages of Alzheimer's disease.

Amyloid accumulation forms aggregates that activate microglia. This phenomenon induces the production of reactive oxygen species (ROS), nitric oxide (NO) and the expression of cytokines.



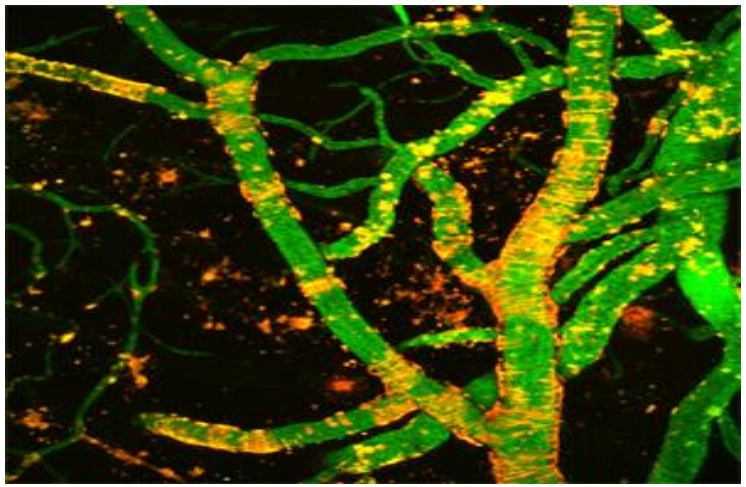
Microglial activation and astrocytosis are potentially early phenomena in AD. However, the individual levels of amyloid deposition and microglial activation were not correlated.

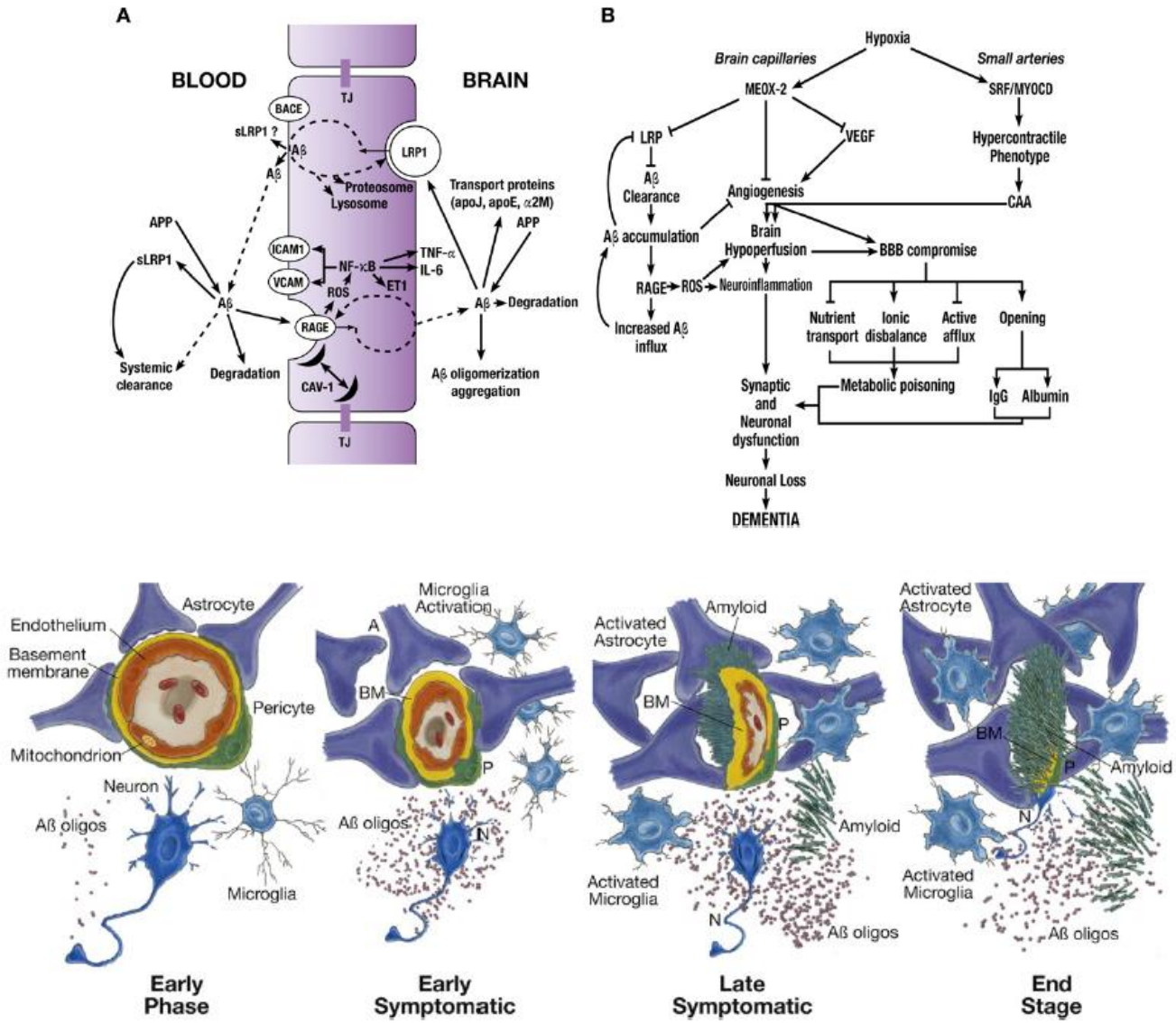
Hommet C, Dem Ger Cogn Dis 2014

Malattia di Alzheimer

Effetti cerebrovascolari dell'amiloide

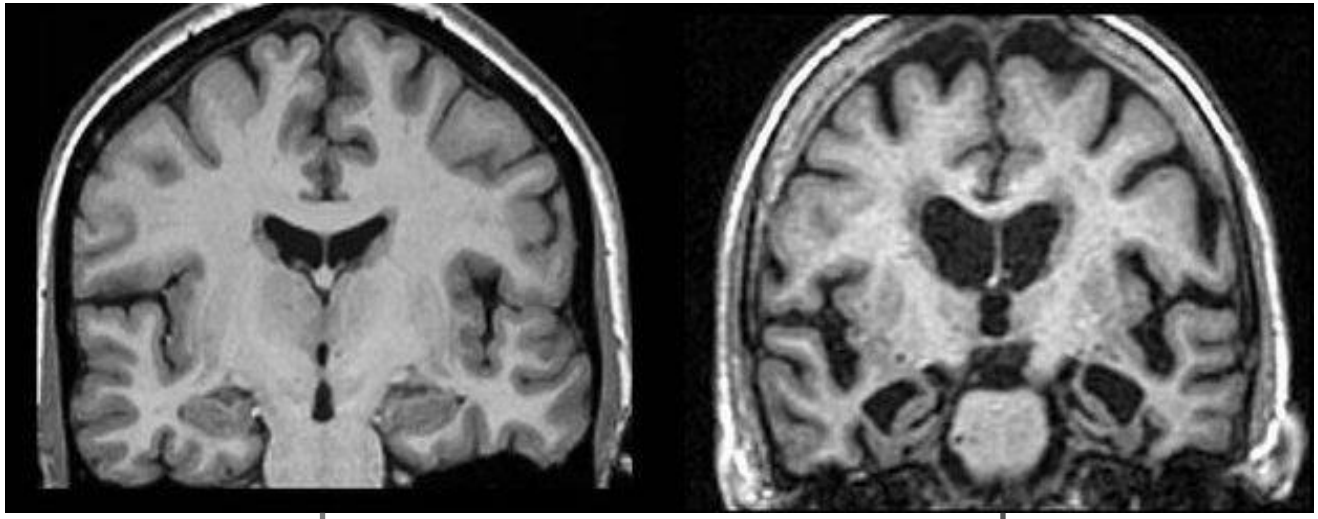
- Alterazione della morfologia vascolare → **Ridotta densità** ed **aumentata tortuosità** dei vasi del microcircolo
- Depositi di frammenti di amiloide $A\beta_{1-40}$ nella parete dei vasi
- Ridotta rappresentazione delle cellule muscolari lisce → **Indebolimento di parete** con **maggior rischio di emorragia**
- Depositi di frammenti $A\beta_{1-40}$ e $A\beta_{1-42}$ → **Alterata reattività vascolare** con **aumento delle resistenze**





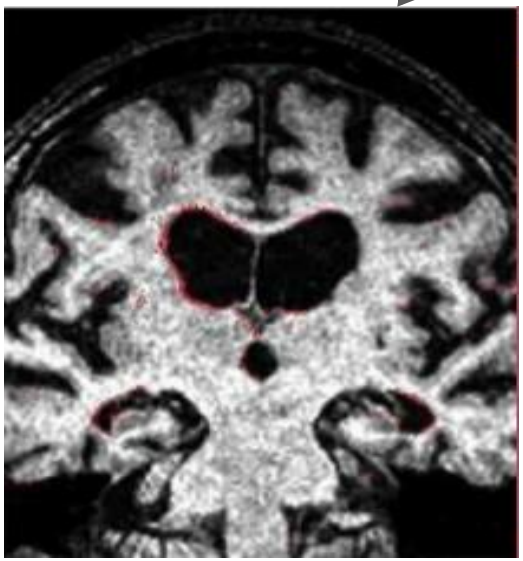
BBB breakdown, due to disruption of the tight junctions, altered transport of molecules between blood and brain and brain and blood, aberrant angiogenesis, vessel regression, brain hypoperfusion, and inflammatory responses, may initiate and/or contribute to a ‘‘vicious circle’’ of the disease process,

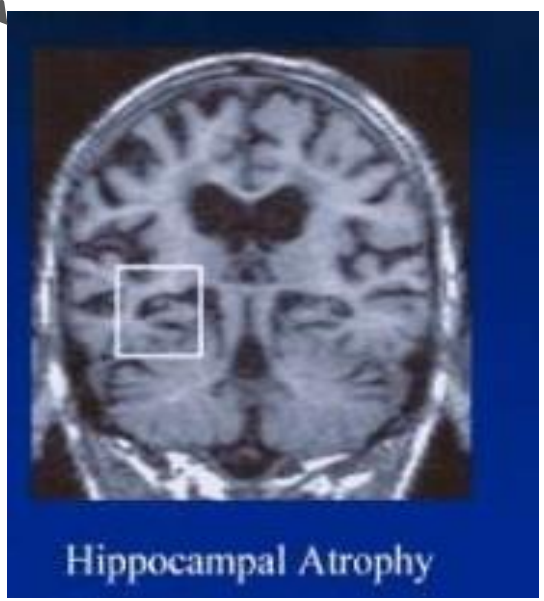
Zlokovic BV, Neuron 2008



Cervello normale

Malattia di Alzheimer





Jama Neurol. 2016 October 01; 73(10): 1231-1237

The Role of Cardiovascular Risk Factors and Stroke in Familial Alzheimer Disease

Tosto G. et al.

Analisi di associazioni tra Malattia di Alzheimer ad Esordio Tardivo (LOAD) e fattori di rischio cardiovascolare

1) **Valutazione dei risultati degli studi autoptici di Toledo et al. Del 2013**

- In pazienti con LOAD **maggiori anomalie vascolari**

- In pz con comorbidità vascolare, minori anomalie di amiloide e proteina tau

Abbassamento della soglia?

2) Relazione tra ipertensione e LOAD

Associata a **minor rischio**
Tosto et al., (2016)

- In età avanzata maggior rischio da ipotensione
- Effetto protettivo di diuretici, betabloccanti, calcioantagonisti, ACE inibitori,e sartani

Rischio di LOAD maggiore se storia di patologia cerebrovascolare associata a ipertensione

Alterazioni della sostanza bianca alla MRI precedono LOAD

3) Ruolo del Diabete Mellito tipo 2

Associato a:

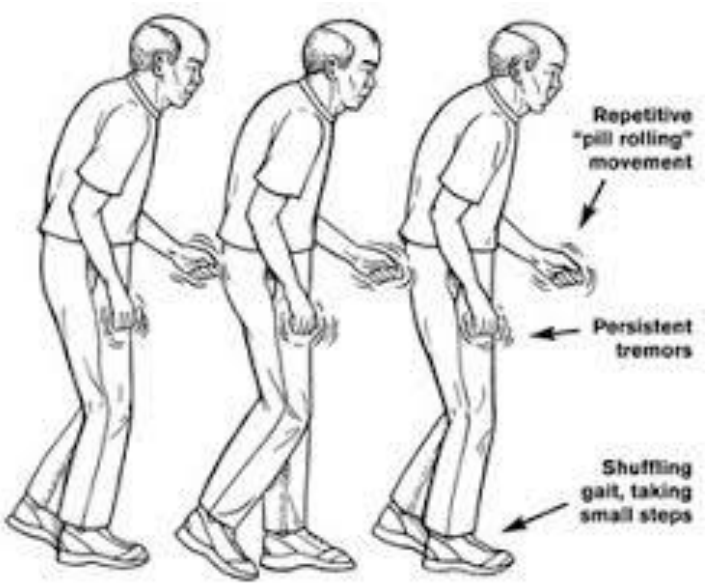
- maggiori anomalie cerebrovascolari
- aumentati livelli liquorali di proteina tau

Non associato a:

- riduzione dei livelli liquorali di βamiloide
- placche e grovigli

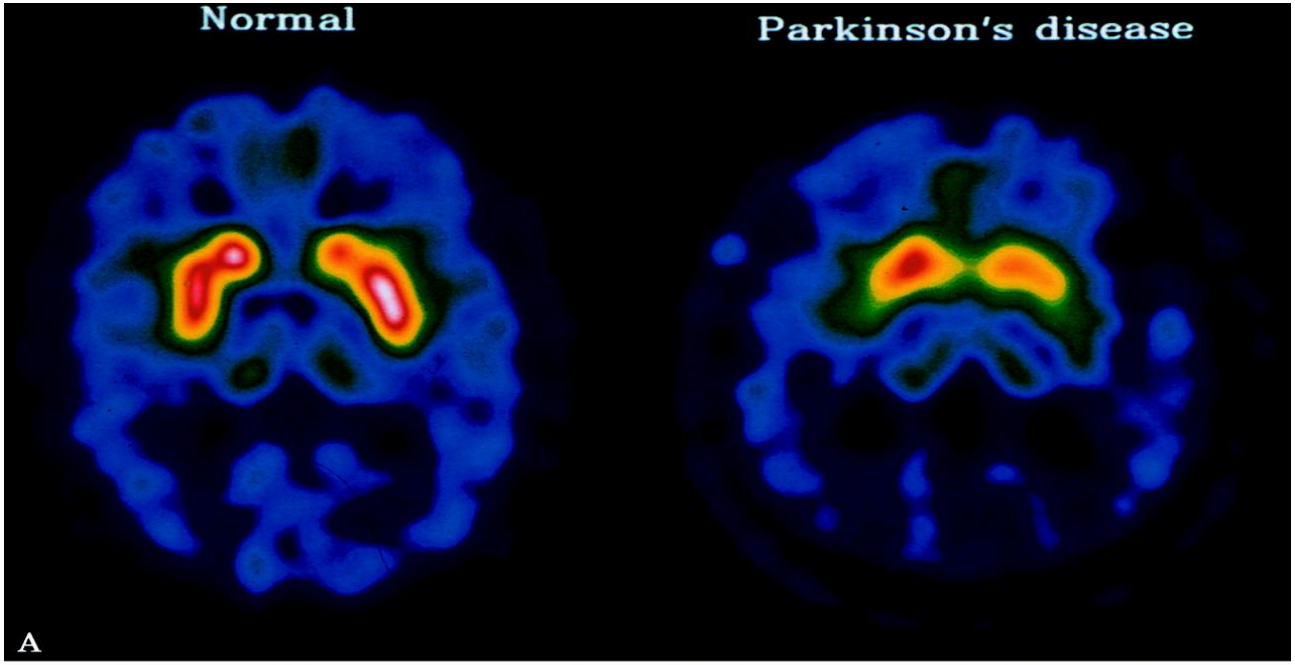
Probabile coinvolgimento generico in processi di neurodegenerazione

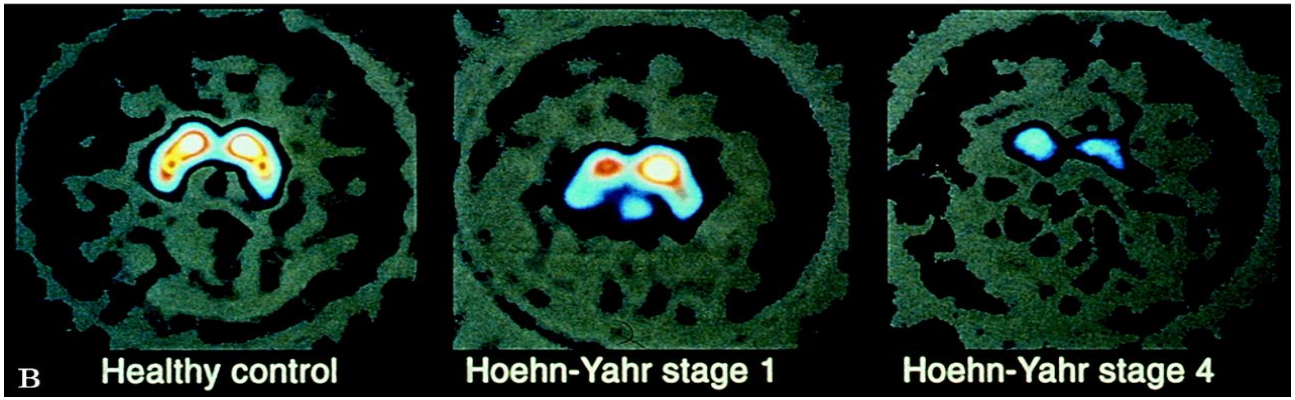
Malattia di Parkinson idiopatica



Quadro sindromico caratterizzato da:

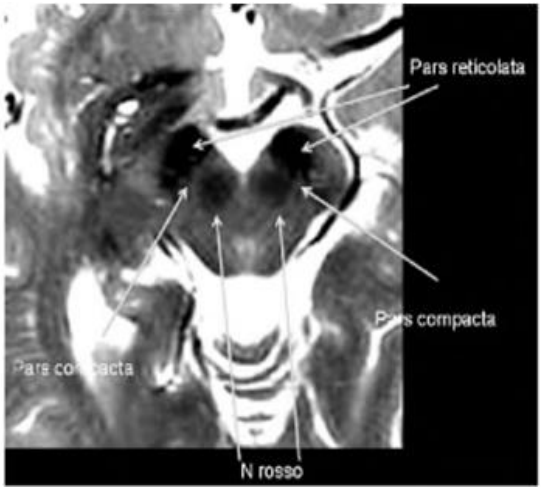
- Bradicinesia
- Rigidità plastica
- Tremore a riposo
- Asimmetria delle manifestazioni
- Alterazioni della postura
(atteggiamento camptocormico)
- Compromissione dei riflessi posturali
- Alterazioni della marcia
(freezing, festinatio)
- Manifestazioni disautonomiche
- Disturbi del sonno
- Iposmia
- Ipomimia
- Disturbi dell'umore e comportamentali
- Possibili disfunzioni cognitive



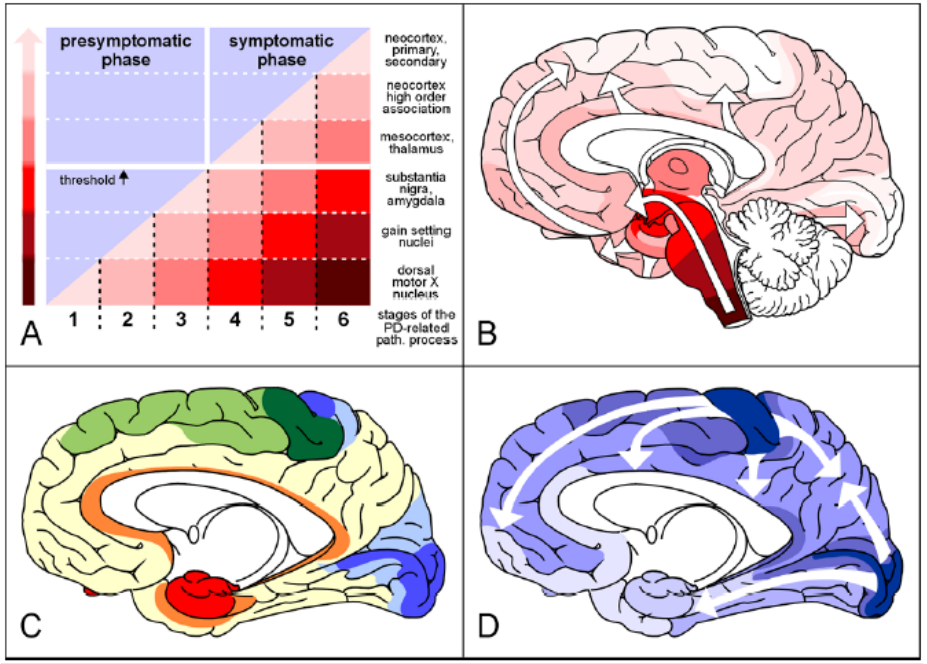


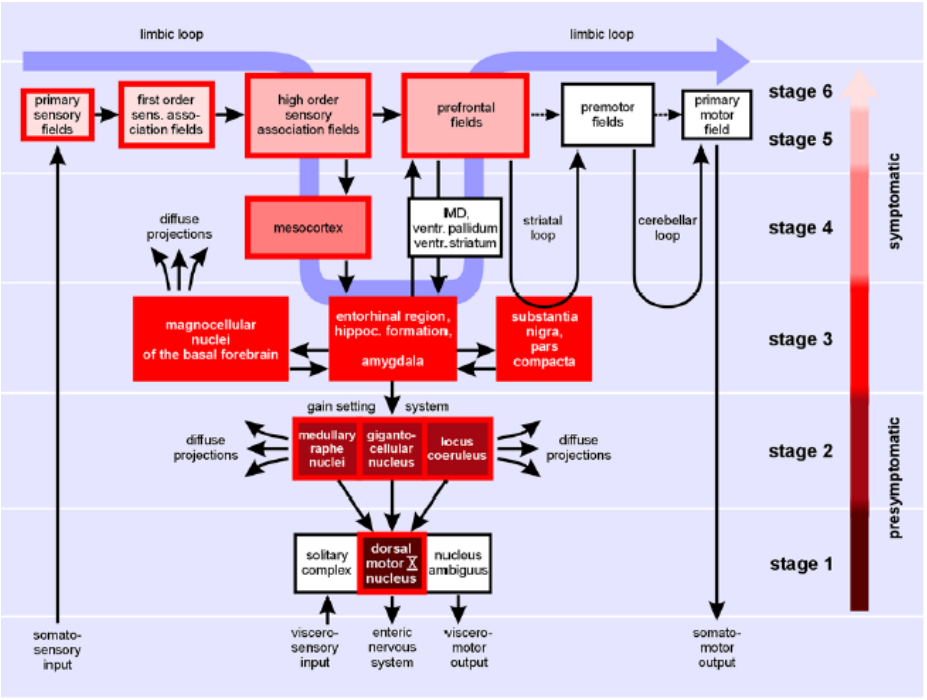
DATSCAN in soggetto normale

DATSCAN nella Malattia di Parkinson

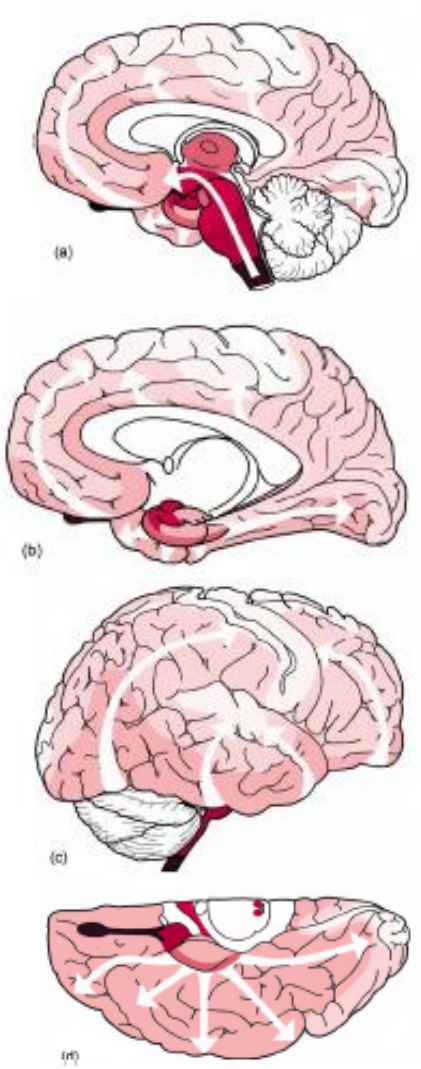


Degenerazione della pars compacta della Sostanza Nera prevalentemente a sinistra, in paziente con Malattia di Parkinson

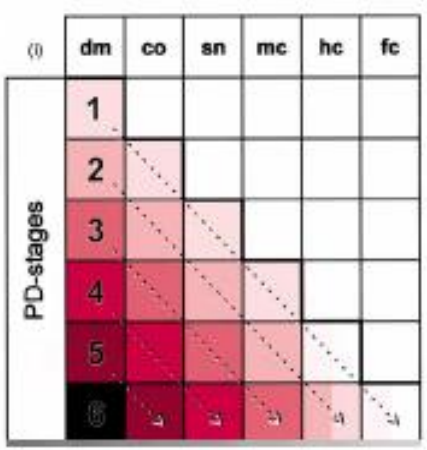


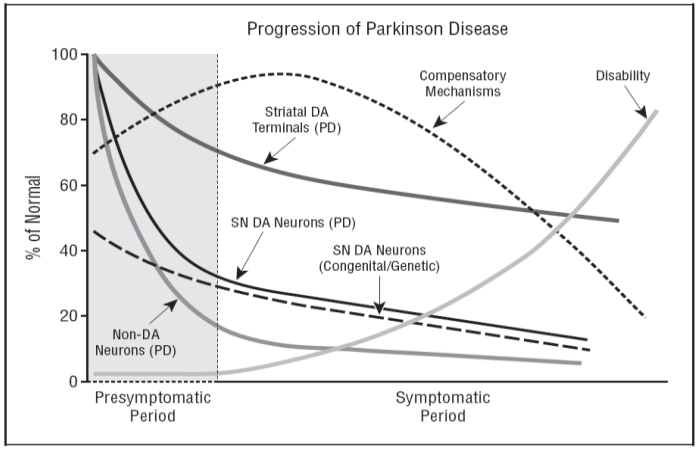


Following Synucleinopathy Progression



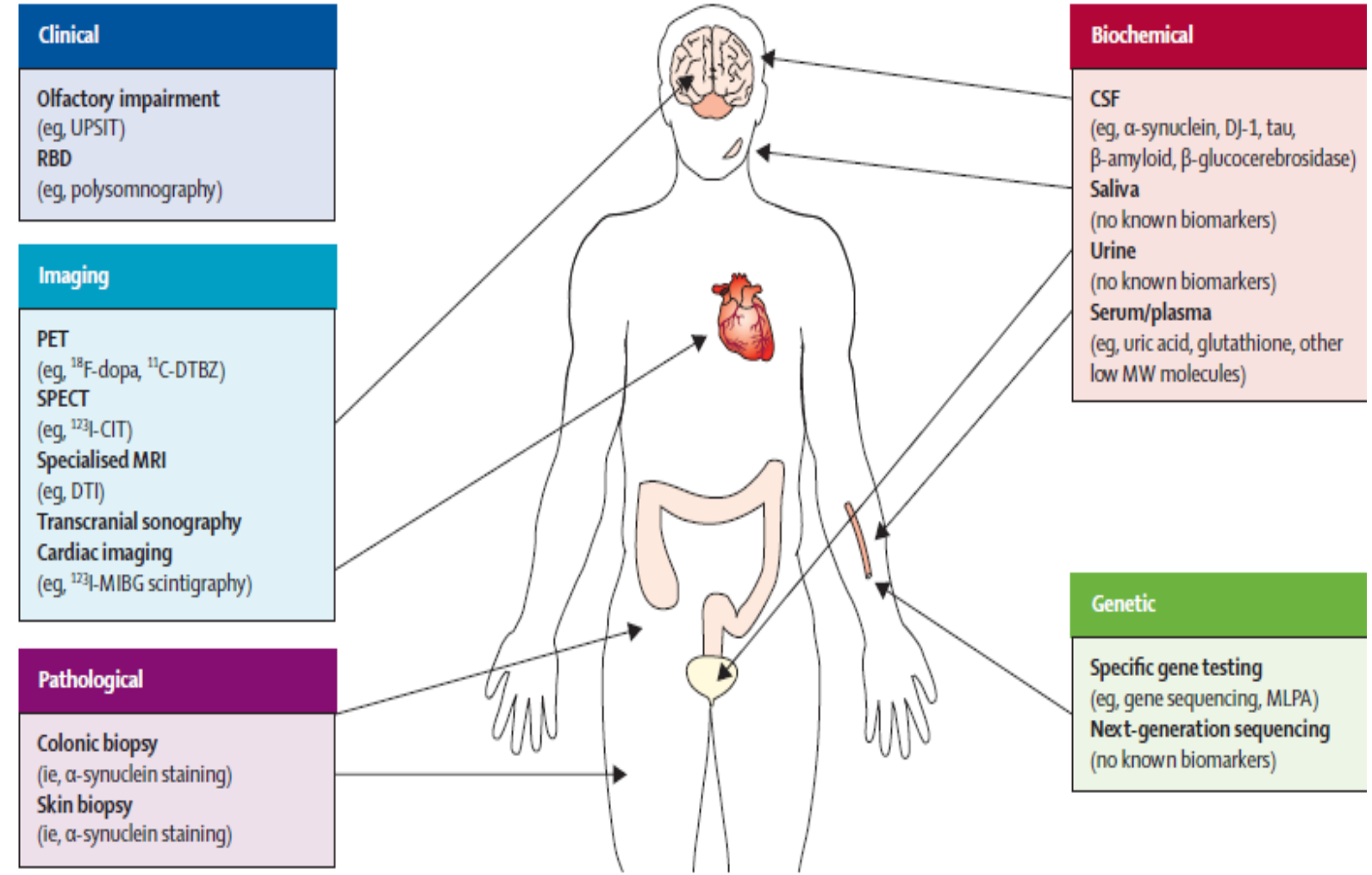
Braak' stages





….. the key lesions in PD begin developing—as in other neurodegenerative diseases—a considerable time prior to the appearance of somato-motor dysfunctions.

The vulnerable nerve cell types most likely vary in their proclivities to undergo the pathological changes and, as such, become involved at different times in the course of the disease.



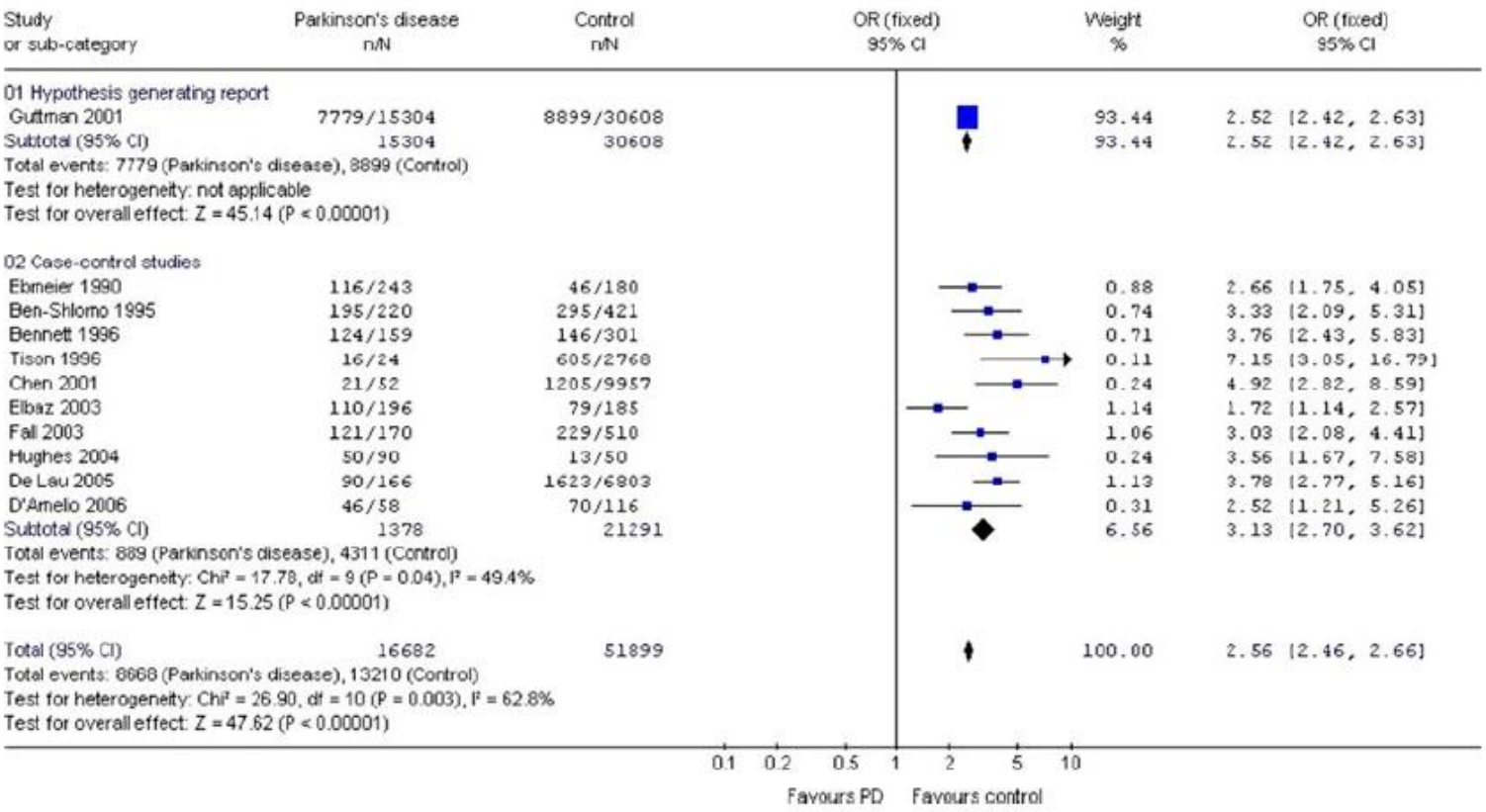
Potential biomarkers for diagnosis of Parkinson's disease

Lorraine V Kalia, Anthony E Lang. Parkinson's Disease. Lancet 2015; 386: 896–912

J Neurol (2010) 257 (Suppl 2):S262–S267
DOI 10.1007/s00415-010-5716-z

Has drug therapy changed the natural history of Parkinson's disease?

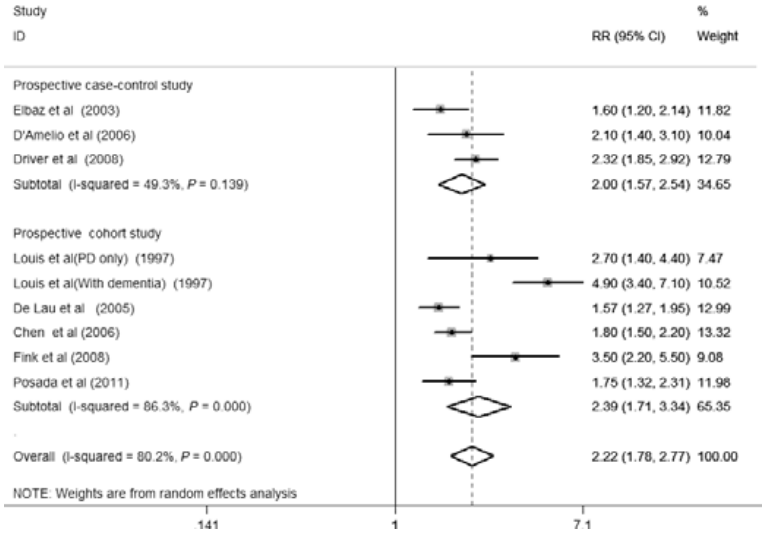
C. E. Clarke



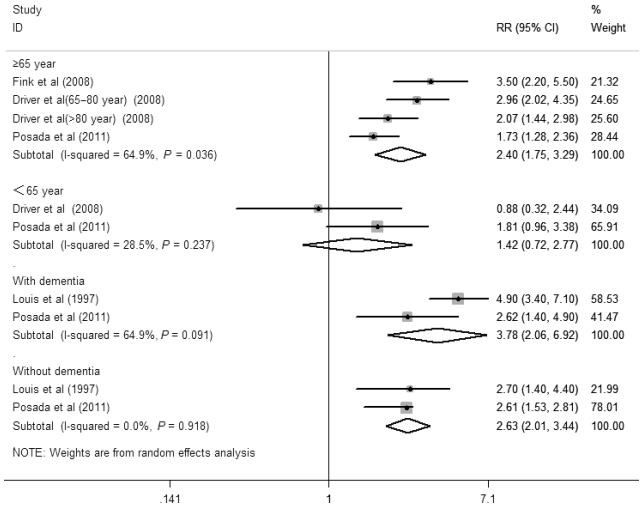
Meta-analysis of all of these results continues to show an excess mortality in Parkinson's disease with an odds ratio of 2.56 (95% CI 2.46, 2.66; p\0.00001). This is in keeping with the raised standardized mortality ratio in the seminal pre-levodopa Hoehn and Yahr study of 2.9

Mortality in Parkinson's disease

Parkinson's disease



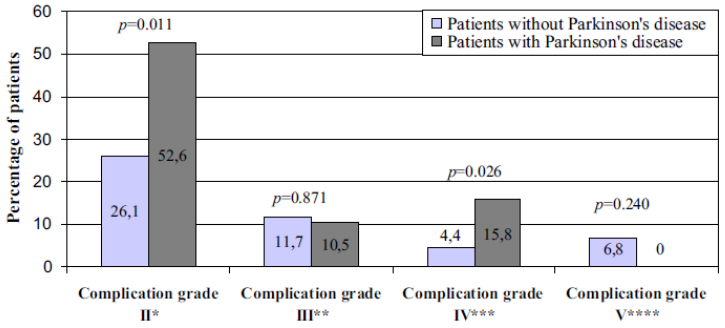
Parkinson's disease with dementia



- Among patients with PD, the all-cause mortality increased by 2.22-fold compared with the general population.
- PD patients with dementia particularly had higher risks of mortality

Xu J, Acta Neurol Scand 2014

Frattura del femore nella malattia di Parkinson



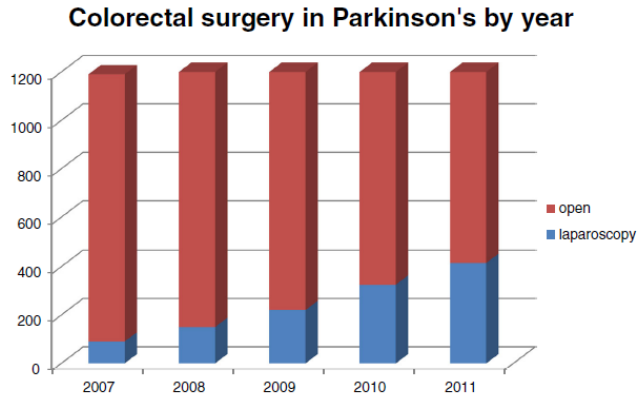
Patients with PD are at risk for specific complications and longer hospitalization at the time of transfer from acute care so as for reduced abilities in activities of daily living in the medium term.

Table 2 Perioperative clinical course and functional outcome parameters for patients with and without PD

	Whole study population	Patients with PD	Patients without PD	*p* value
Perioperative clinical course				
Period of time (h) from admission to surgical treatment	18 ± 13	19 ± 14	18 ± 13	0.883
Surgical treatment				
Prosthesis (%)	165 (41)	9 (47)	156 (41)	0.566
Internal fixation (%)	237 (59)	10 (53)	227 (59)	
Length of stay in hospital (days)	14 ± 6	17 ± 10	14 ± 6	0.034
In-hospital mortality (%)	25 (6.2)	0 (0)	25 (6.8)	0.240
Functional outcome at discharge				
BI at discharge	49 ± 29	38 ± 24	49 ± 29	0.103
TT balance at discharge	4.4 ± 4.4	2.5 ± 3.1	4.5 ± 4.4	0.062
TT gait at discharge	5.0 ± 4.2	3.6 ± 4.2	5.0 ± 4.2	0.147
TUG performance possible at discharge (%)	43.0	27.8	43.8	0.226
TUG at discharge (s)	41 ± 48	40 ± 18	41 ± 44	0.978
Functional outcome at 6-month follow-up				
BI	69 ± 30	45 ± 31	71 ± 29	0.001
TT balance	7.7 ± 4.9	4.6 ± 3.2	7.9 ± 5.0	0.002
TT gait	8.2 ± 4.3	6.6 ± 4.4	8.3 ± 4.3	0.160
TUG (s)	25 ± 15	33 ± 20	25 ± 15	0.104
Mortality rate (%)	81 (20.1)	2 (10.5)	79 (20.6)	0.388

Bliemel C, Arch Orthop Trauma Surg 2015

Chirurgia colorettale nella malattia di Parkinson



PD patients have high rates of morbidity and mortality after colorectal surgery; this may be because more than half of all patients in this population undergo emergent surgery. The laparoscopic approach appears to have short term benefits in this patient population.

Hwang GS, Int J Colorechtal Dis 2015

Movement Disorders, Vol. 31, No. 10, 2016

Vascular Disease and Vascular Risk Factors in Relation to Motor Features and Cognition in Early Parkinson's Disease

Malek M.D.et al. (1759 pazienti)

Studio dell'influenza di fattori di rischio e precedenti malattie vascolari sulla Malattia di Parkinson

Fattori di rischio:
Fumo di sigaretta
Ipertensione
Ipercolesterolemia
Diabete Mellito
BMI>30
QRISK2 score

Maggiore gravità clinica associata a:
- Diabete Mellito
- Copresenza di >2 fdr
- QRISK2 score>20

Declino cognitivo associato a
- Diabete Mellito

Neuroimaging cerebrale
(MRI) in 842 pz

Correlazione significativa tra Leucoaraiosi e
- Impairment Cognitivo
- Fenotipo clinico PIGD
(postural instability gait difficulty)

Ipotesi patogenetiche

1) Da **Instabilità Neurocardiovascolare** tipica della Malattia di Parkinson determinato **danno cerebrovascolare**

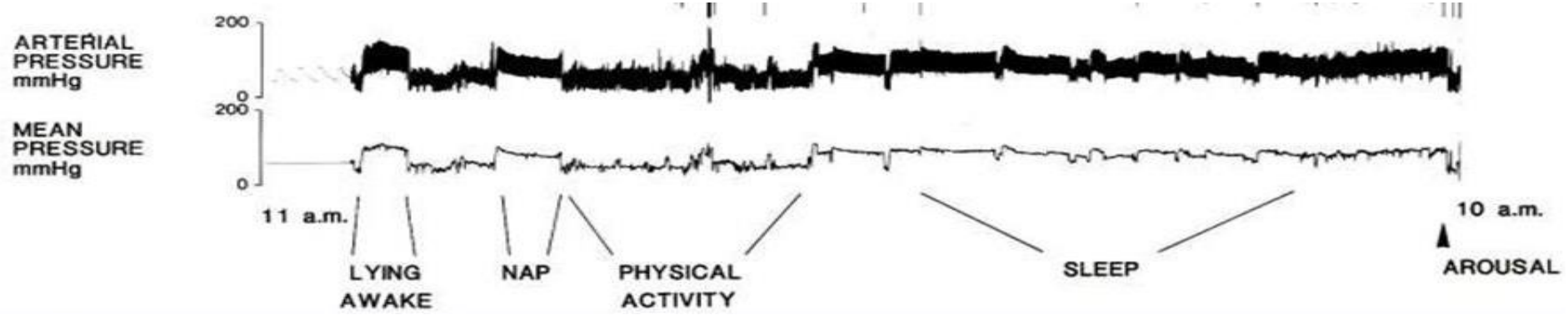
Ipotensione ortostatica

Presente in 58% dei pz con PD

- Sofferenza ischemica della Sostanza Bianca per ipoperfusione
- fattore di rischio indipendente per mortalità, eventi coronarici e stroke

Ipertensione clinostatica

- Effetti dannosi su parete vascolare con sviluppo Malattia dei Piccoli Vasi (SVD)
- causate Lesioni della Sostanza Bianca, ischemie cerebrali silenti, microsanguinamenti e dilatazione degli spazi perivascolari



FEATURED ARTICLE

Is Cardiac Function Impaired in Premotor Parkinson's Disease? A Retrospective Cohort Study

Jose-Alberto Palma, MD, PhD,[1]* Maria-Mar Carmona-Abellan, MD,[1] Noelia Barriobero, MD,[1] Cristina Trevino-Peinado, MD,[1] Martin Garcia-Lopez, MD,[2] Elena Fernandez-Jarne, MD, PhD,[2] and Maria R. Luquin, MD, PhD[1]*

[1]*Department of Neurology, University Clinic of Navarra, Pamplona, Spain*
[2]*Department of Cardiology, University Clinic of Navarra, Pamplona, Spain*

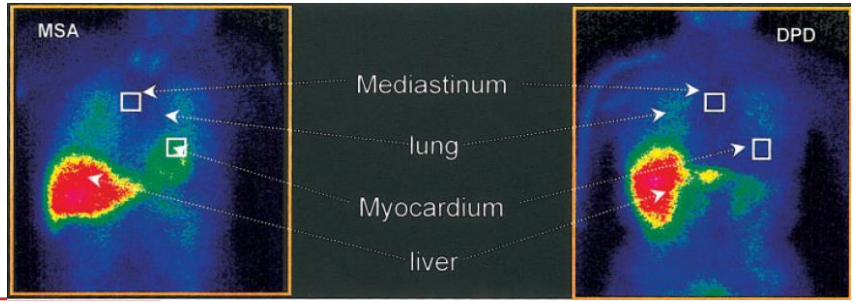


TABLE 2. Cardiac stress testing and heart rate variability measures

	Mean ± SD			
Measure	PD the same day of CST, n = 14	PD after CST, n = 18	Controls, n = 18	*P* (ANOVA)
Measures at rest				
Basal HR, bpm	76.83 ± 14.91	77.78 ± 17.74	75.98 ± 15.95	0.9
Basal SBP, mm Hg	122.5 ± 11.58	127.22 ± 8.44	128.1 ± 14.86	0.43
Basal DBP, mm Hg	67.5 ± 9.65	80.56 ± 7.53	77.78 ± 11.14	0.002[a]
Basal MBP, mm Hg	92.95 ± 9.73	96.11 ± 7.36	94.53 ± 11.2	0.009[a]
Measures at peak exercise				
Maximum HR, bpm	124.5 ± 18.48	130.94 ± 33.14	152.89 ± 12.24	0.004[a]
Percentage of theoretical MHR	81.5 ± 9.61	84.11 ± 14.98	98 ± 6.9	<0.001[a]
Maximum SBP, mm Hg	169.58 ± 18.89	185.83 ± 16.82	184.72 ± 23.23	0.071
Maximum DBP, mm Hg	81.67 ± 3.25	90.83 ± 9.73	87.5 ± 12.51	0.055
Maximum MPB, mm Hg	110.97 ± 7.46	122.5 ± 10.94	119.9 ± 12.87	0.023[a]
Δ SBP, mm Hg	47.08 ± 20.93	55.83 ± 22.24	60 ± 22.75	0.3
Δ DBP, mm Hg	9.99 ± 9.1	9.72 ± 7.5	9.72 ± 7.9	0.51
HR variability measures				
Mean R-R interval, msec	725 ± 113	821 ± 79	843 ± 110	0.29
SDNN, msec	78.8 ± 5.9	81.2 ± 5.5	87.6 ± 4.5	0.06

SD, standard deviation; PD, Parkinson's disease; CST, cardiac stress testing; ANOVA, analysis of variance; MBP, mean blood pressure; HR, heart rate; bpm, beats per minute; MHR, maximum heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; Δ, increment; SDNN, standard deviation of normal R-R intervals.
[a]These are statistically significant *P* values.

The results from this exploratory study demonstrate that chronotropic insufficiency may constitute an early sign of Parkinson's disease during the premotor phase, serving as potential risk factor for its diagnosis.

2) Ruolo dello **stress ossidativo** nella patogenesi della PD e nel danno vascolare

Fonti di ROS e RNS:
- metabolismo della dopamina
- disfunzione mitocondriale
- accumulo di ferro
- disregolazione dei livelli intracellulari di calcio
- perossidazione lipidica
- neuroinfiammazione
- disfunzioni del sistema ubiquitina-proteasoma
- invecchiamento

Stress ossidativo e nitrosativo

alterazione di numerosi processi biologici nei neuroni della SNc

Degenerazione dei neuroni dopaminergici

- migrazione di cellule muscolari lisce vascolari e cellule infiammatorie
- alterazione della matrice extracellulare
- apoptosi delle cellule endoteliali
- attivazione di fattori di trascrizione (NFkB, AP-1)
- espressione di citochine infiammatorie e molecole di adesione (ICAM-1, VCAM-1, E-selectina)

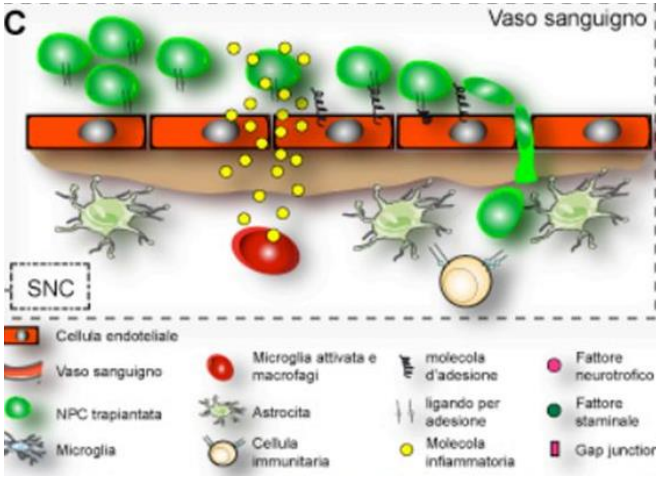
Progressivo danno endoteliale

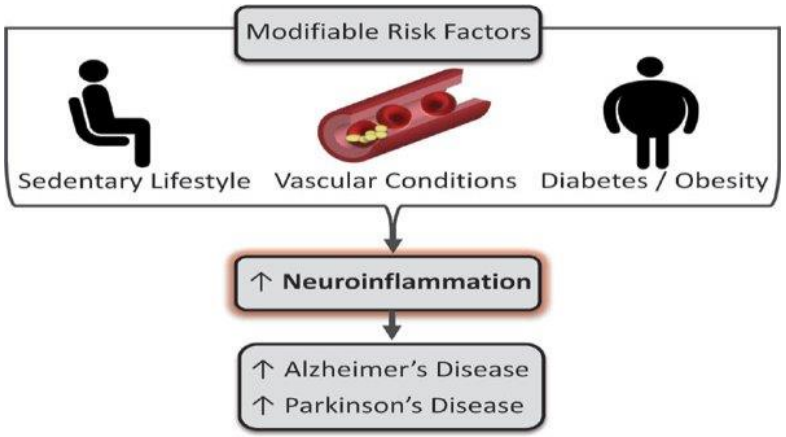
3) Ruolo della **neuroinfiammazione** in neurodegenerazione e danno vascolare

Sostenuta da attivazione di astrociti, oligodendrociti e cellule della microglia

Da cellule e mediatori neuroinfiammatori determinati danno endoteliale ed aterosclerosi

Neuroinfiammazione a sua volta **favorita da vita sedentaria, diabete mellito, obesità e dislipidemia**
(fattori di rischio vascolari)





Correlazione tra Patologia cerebrovascolare e malattia di Parkinson

Ipotizzata associazione ma differenti risultati da vari studi

Associata a **minor rischio cerebrovascolare**

Ipotizzato ruolo protettivo di ridotti livelli di dopamina

Associata a **rischio maggiore**

- Terapia con L-DOPA
- Ipotizzato aumento dei livelli di omocisteina da catabolismo di L-DOPA dalle COMT

Da risultati più recenti **associazione positiva con Lesioni Ischemiche Cerebrali** (Song, 2017; Malek, 2016))

Coinvolta specialmente malattia dei piccoli vasi

RESEARCH ARTICLE

Glitazone Use Associated With Reduced Risk of Parkinson's Disease

Brage Brakedal, BA, MD,[1,2] Irene Flønes, MD,[1,2] Simone F. Reiter, MD, PhD,[1,2] Øivind Torkildsen, MD, PhD,[1,2] Christian Dölle, PhD,[1,2] Jörg Assmus, PhD,[3] Kristoffer Haugarvoll, MD, PhD,[1,2†] and Charalampos Tzoulis, MD, PhD[1,2†*]

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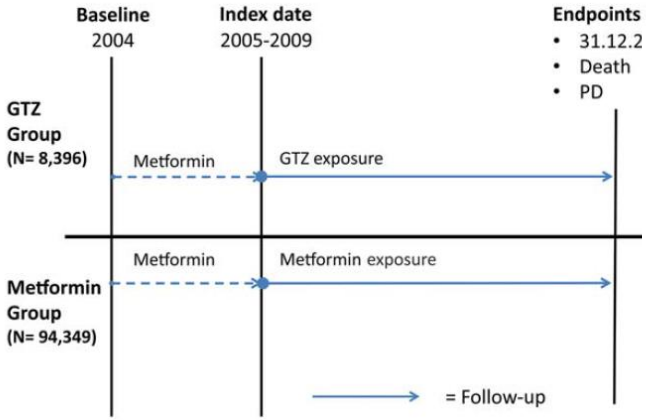
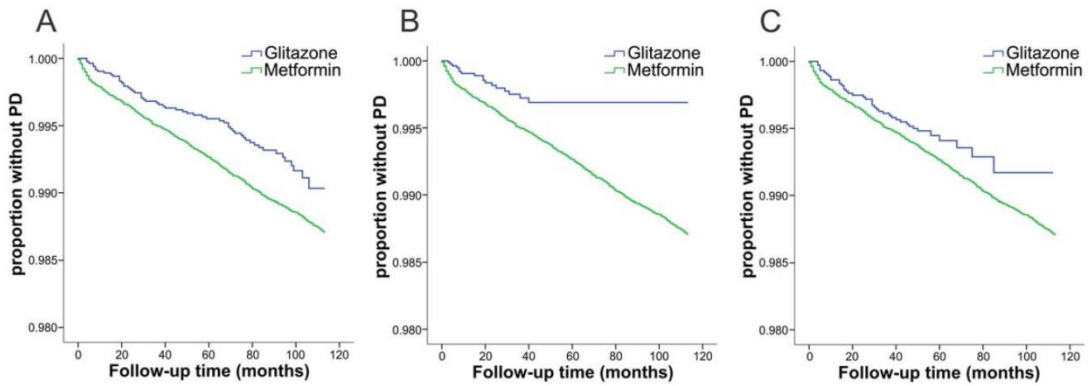
[3]*Centre for Clinical Research, Haukeland University Hospital, Bergen, Norway*





Kaplan-Meier survival curves. (A-C) Kaplan-Meier estimators of time to PD diagnosis as a function of treatment duration (in months) with GTZ (blue) and metformin (green).

(A) GTZ users (current and past), (B) current GTZ exposure, (C) past GTZ users.

Conclusions: The use of glitazones is associated with a decreased risk of incident PD in populations with diabetes.

Contents lists available at SciVerse ScienceDirect

Parkinsonism and Related Disorders

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

Diabetes is associated with postural instability and gait difficulty in Parkinson disease

Vikas Kotagal [a,*], Roger L. Albin [a,b], Martijn L.T.M. Müller [c], Robert A. Koeppe [c], Kirk A. Frey [a,c], Nicolaas I. Bohnen [a,b,c]

	Mean ± SD		Group comparison [significance]
	PD subjects with diabetes ($n = 13$)	PD subjects without diabetes ($n = 26$)	
Gender (M/F)	11/2	22/4	$\chi^2 = 0.00$, $p = 1.00$
Mean age (yrs)	66.5 ± 6.4	66.3 ± 5.1	$t = 0.14$, $p = 0.89$
Mean duration of disease (yrs)	6.84 ± 4.7	6.98 ± 4.4	$t = 0.09$, $p = 0.93$
Mean Hoehn & Yahr scale	2.7 ± 0.72	2.3 ± 0.58	$t = 1.62$, $p = 0.11$
Mean striatal DTBZ DVR	2.10 ± 0.51	1.84 ± 0.26	$t^a = 1.77$, $p = 0.10$
Body mass index (BMI)	33.4 ± 6.0	27.6 ± 3.7	$t = 3.73$, $p = 0.0006$
History of statin use	46.2%	34.6%	$\chi^2 = 0.49$, $p = 0.49$
History of hypertension	69.2%	34.6%	$\chi^2 = 4.2$ $p = 0.04$
Levodopa dose equivalency	784.2 ± 745.0	886.8 ± 681.0	$t = 0.43$, $p = 0.67$
Supratentorial white matter hyperintensity burden ($n = 36$)	−5.37 ± 2.3	−5.24 ± 1.6	$t = 0.12$, $p = 0.91$
Brainstem white matter hyperintensity burden ($n = 35$)	−3.75 ± 4.4	−3.78 ± 4.3	$t = 0.08$, $p = 0.93$
Mean vibratory sense duration (seconds)	8.4 ± 4.5	8.8 ± 4.0	$t = 0.29$, $p = 0.77$
Mean global cognitive Z-score ($n = 37$)	−0.94 ± 0.85	−0.39 ± 0.95	$t = 1.70$, $p = 0.10$

PD = Parkinson disease, DTBZ DVR = [^{11}C]dihydrotetrabenazine distribution volume ratio.
[a] Satterthwaite t-test due to unequal variance.

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Parkinsonism and Related Disorders

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Diabetes is associated with postural instability and gait difficulty in Parkinson disease

Vikas Kotagal [a,*], Roger L. Albin [a,b], Martijn L.T.M. Müller [c], Robert A. Koeppe [c], Kirk A. Frey [a,c], Nicolaas I. Bohnen [a,b,c]

UPDRS motor subscore categories	Total score for PD subjects with diabetes (±SD)	Total score for PD subjects without diabetes (±SD)	Overall model	Diabetes status	Striatum DTBZ DVR
Bradykinesia	13.7 ± 6.2	12.3 ± 6.2	$F = 7.25$, $p = 0.0023$	$t = 1.99$, $p = 0.055$	$t = -3.73$, $p = 0.0007$
Rigidity	5.0 ± 2.6	4.6 ± 2.5	$F = 3.32$, $p = 0.048$	$t = 1.38$, $p = 0.176$	$t = -2.51$, $p = 0.017$
PIGD	5.0 ± 2.5	3.6 ± 2.0	$F = 14.1$, $p < 0.0001$	$t = 3.81$, $p = 0.0005$	$t = -4.75$, $p < 0.0001$
Tremor	5.2 ± 4.2	3.9 ± 3.6	$F = 0.48$, $p = 0.62$	NA	NA

PD = Parkinson disease, DTBZ DVR = [^{11}C]dihydrotetrabenazine distribution volume ratio, N.A. = Not applicable.

We report that a history of diabetes in PD is associated with increased PIGD motor feature severity.

Clinical features of Parkinson disease when onset of diabetes came first

A case-control study

E. Cereda, MD, PhD
M. Barichella, MD
E. Cassani, MD
R. Caccialanza, MD
G. Pezzoli, MD

Table 2 Characteristics of the patients included in the study according to the presence or absence of diabetes preceding PD diagnosis[a]

Variable[a]	Diabetes (n = 89)	No diabetes (n = 89)	p Value[b]
Male, n (%)	58 (65.1)	58 (65.1)	1.000
Previous or current smoking, n (%)	23 (25.8)	20 (22.5)	0.726
Sedentary, n (%)	65 (73)	61 (68.5)	0.621
Education, y, mean (SD)	8.4 (3.7)	9.2 (3.9)	0.162
Body weight, Kg, mean (SD)	77.1 (12.4)	78.4 (12.3)	0.483
Body mass index, Kg/m^2, mean (SD)	27.7 (3.9)	27.6 (3.3)	0.854
Age, y, mean (SD)			
At inclusion	70.7 (7.7)	69 (7.9)	0.123
At onset of disease	66.9 (8.0)	65.1 (8.2)	0.140
Length of disease, y, mean (SD)	3.8 (3.5)	3.9 (3.4)	0.847
Positive family history for PD, n (%)	12 (13.5)	9 (10.1)	0.643
Positive history for hydrocarbon exposure, n (%)	21 (23.6)	16 (18.0)	0.460
Main symptom at diagnosis, n (%)			0.771
Resting tremor	45 (50.6)	52 (58.4)	
Bradykinesia	30 (33.7)	27 (30.3)	
Rigidity	4 (4.5)	4 (4.5)	
Postural instability	4 (4.5)	3 (3.4)	
Others	6 (6.7)	3 (3.4)	
Levodopa at inclusion, mg/d, mean (SD)[c]	448 (265)	300 (213)	<0.0001
mg/Kg/d, mean (SD)	5.8 (4.0)	3.8 (2.9)	<0.0001
Inception of levodopa therapy, y, mean (SD)	2.3 (2.3)	2.1 (2.2)	0.554
Dopamine-agonist therapy at inclusion, n (%)	38 (42.7)	43 (48.3)	0.547
Total levodopa equivalent at inclusion, mg/d, mean (SD)[d]	503 (292)	350 (206)	<0.0001
mg/Kg/day, mean (SD)	6.5 (4.2)	4.5 (2.8)	<0.0001
Hypertension, n (%)	32 (36)	27 (30.3)	0.524
Use of statins, n (%)	16 (18)	3 (3.4)	0.003

Clinical features of Parkinson disease when onset of diabetes came first

A case-control study

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G. Pezzoli, MD

Table 3 Clinical rating scales in patients with PD at entry to the study

	Diabetes (n = 89)	No diabetes (n = 89)	p Value[a]
Hoehn & Yahr stage, n (%)			0.009
I	18 (20.2)	29 (32.6)	
II	51 (57.4)	54 (60.7)	
III	18 (20.2)	4 (4.5)	
IV	2 (2.3)	2 (2.2)	
V	0 (0)	0 (0)	
UPDRS score, mean (SD)			
Part I	1.7 (1.8)	1.2 (1.5)	0.046
Part II	9.7 (5.1)	8.3 (4.3)	0.049
Part III	22.3 (9.0)	19.3 (7.9)	0.019
Total	33.7 (15.0)	28.8 (13.8)	0.024
Part IV	1.1 (1.7)	0.8 (1.3)	0.188

Clinical features of Parkinson disease when onset of diabetes came first

A case-control study

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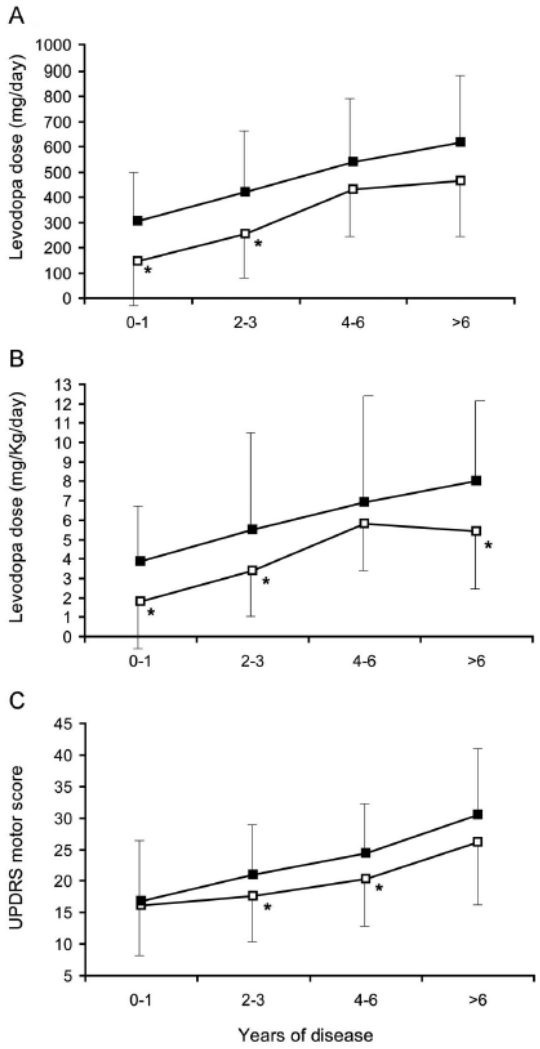
Figure Levodopa dosage from levodopa-containing medications and severity of motor symptoms by preceding diabetes (■, diabetes; □, no diabetes) and duration of Parkinson disease (analysis of variance)

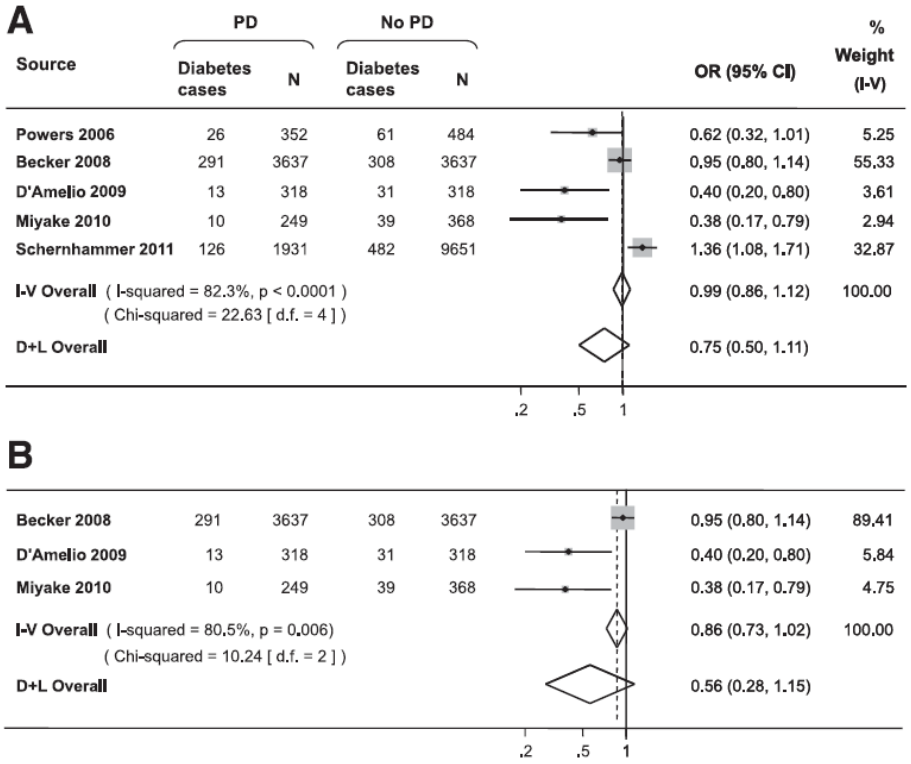


In the present study we showed that patients in whom the onset of diabetes occurs before the onset of PD experience more severe PD symptoms and reduced efficacy of levodopa therapy. These findings provide further support to the hypothesis that diabetes is a risk factor for PD.

Diabetes and Risk of Parkinson's Disease

A systematic review and meta-analysis

EMANUELE CEREDA, MD, PHD[1,2]
MICHELA BARICHELLA, MD[2]
CARLO PEDROLLI, MD[3]
CATHERINE KLERSY, MD, MSC[4]
ERICA CASSANI, MD[2]
RICCARDO CACCIALANZA, MD[1]
GIANNI PEZZOLI, MD[2]



CONCLUSIONS—Although data from cohort studies suggest that diabetes is a risk factor for PD, there is no conclusive evidence on this association. Further prospective studies focused on putative pathogenic pathways and taking a broad range of confounders into account is required to clarify this relationship.

Parkinsonism and Related Disorders 43 (2017) 27–32

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Parkinsonism and Related Disorders

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

Subclinical vascular disease and the risk of parkinsonism: The Rotterdam Study

Vanja Vlasov [a], Sirwan K.L. Darweesh [a, b, c], Bruno H. Stricker [a, d], Oscar H. Franco [a], M.Kamran Ikram [a, b], Maryam Kavousi [a], Daniel Bos [a, c, e], Caroline C.W. Klaver [a, f], M.Arfan Ikram [a, b, e, *]

Overview of incident clinical diagnoses of parkinsonism.

	All-cause PS patients (n = 211)
Parkinson disease	110 (52.1%)
Unspecified parkinsonism	61 (28.9%)
Drug-induced parkinsonism	20 (9.5%)
Vascular parkinsonism	8 (3.8%)
Multiple system atrophy	4 (1.9%)
Lewy body dementia	1 (0.5%)
Secondary to dementia	4 (1.9%)
Secondary to a tumor	2 (0.9%)
Progressive supranuclear palsy	1 (0.5%)

These are clinical diagnoses; no histologic confirmation was obtained.
n, number of cases during follow-up.

Our report suggest that systemic vascular pathology does not play a large role in the etiology of parkinsonism in the general population

Reduced Risk Factors for Vascular Disorders in Parkinson Disease Patients

A Case-Control Study

Giulio Scigliano, MD; Massimo Musicco, MD, PhD; Paola Soliveri, MD, PhD; Immacolata Piccolo, MD; Gabriele Ronchetti; Floriano Girotti, MD

Stroke. 2006;37:1184-1188

TABLE 2. Crude and Multivariable Risk Estimates (ORs) for IPD Patients Compared to non-IPD Controls

	Controls	IPD	Crude OR** (95% CI)	Multivariable OR*** (95% CI)
History of smoking	294 (55.2%)	74 (41.6%)	0.54 (0.37–0.78) *P*=0.001	*
Diabetes	58 (10.9%)	6 (3.4%)	0.30 (0.13–0.72) *P*=0.007	*
Hypertension	134 (25.1%)	28 (15.7%)	0.59 (0.37–0.92) *P*=0.022	*
Blood glucose, mg/dl				
Mean (No. of cases)	91.5 (533)	85 (178)	0.71 (0.57–0.88) *P*=0.002§	0.69 (0.52–0.93) *P*=0.015§
1st tertile [52–82]‡	182 (34.1%)	78 (43.8%)	1	1
2nd tertile [83–91]	173 (32.6%)	67 (37.6%)	0.89 (0.60–1.31)	0.79 (0.45–1.36)
3rd tertile [92–233]	172 (32.3%)	33 (18.5%)	0.47 (0.29–0.75) *P*=0.001	0.47 (0.26–0.86) *P*=0.015
Cholesterol, mg/dl				
Mean (No. of cases)	230.6 (345)	220 (111)	0.89 (0.68–1.15) *P*>0.05	
1st tertile [93–208]	119 (34.5%)	46 (41.4%)	1	*
2nd tertile [209–251]	112 (32.5%)	30 (27.0%)	0.70 (0.41–1.18)	*
3rd tertile [252–464]	114 (33.0%)	35 (31.5%)	0.79 (0.48–1.33)	*
Triglycerides, mg/dl				
Mean (No. of cases)	151.0 (322)	134 (100)	0.65 (0.49–0.87) *P*=0.004§	0.71 (0.53–0.95) *P*=0.021§
1st tertile [45–116]	111 (34.5%)	48 (48.0%)	1	1
2nd tertile [117–160]	104 (32.3%)	31 (31.0%)	0.70 (0.41–1.19)	0.76 (0.44–1.31)
3rd tertile [161–535]	107 (33.2%)	21 (21.0%)	0.42 (0.23–0.76) *P*=0.004	0.49 (0.27–0.89) *P*=0.019
Total lipids, mg/dl				
Mean (No. of cases)	828.2 (299)	761 (94)	0.71 (0.53–0.95) *P*=0.010§	
1st tertile [433–717]	99 (33.1%)	42 (44.7%)	1	*
2nd tertile [718–867]	101 (33.8%)	32 (34.0%)	0.79 (0.46–1.37)	*
3rd tertile [868–1700]	99 (33.1%)	20 (21.3%)	0.49 (0.27–0.90) *P*=0.021	*
Systolic blood pressure, mm Hg				
Mean (No. of cases)	145.9 (530)	142 (177)	0.80 (0.64–0.99) *P*=0.041§	0.73 (0.55–0.97) *P*=0.029§
1st tertile [95–130]	173 (32.6%)	74 (41.8%)	1	1
2nd tertile [131–150]	151 (28.5%)	51 (28.81%)	0.84 (0.54–1.29)	0.76 (0.43–1.35)
3rd tertile [151–240]	206 (38.9%)	52 (29.4%)	0.63 (0.41–0.98) *P*=0.041	0.52 (0.29–0.92) *P*=0.025
Diastolic blood pressure, mm Hg				
Mean (No. of cases)	89.0 (530)	87 (177)	0.84 (0.69–1.03) *P*>0.05§	
1st tertile [50–80]	206 (38.9%)	76 (42.9%)	1	*
2nd tertile [81–90]	118 (22.3%)	53 (29.9%)	1.28 (0.84–1.96)	*
3rd tertile [91–140]	206 (38.9%)	48 (27.1%)	0.68 (0.44–1.04)	*

Diabetes, history of smoking, high blood pressure, high blood glucose, high blood cholesterol, and triglycerides were significantly less frequent in IPD than controls.

We interpret the association of untreated IPD with reduced vascular diseases risk factors as attributable to reduced autonomic activity, suggesting that autonomic hyperactivity may be involved in the pathogenesis of vascular disorders.

RESEARCH ARTICLE

Obesity, Diabetes, and Risk of Parkinson's Disease

Natalia Palacios, ScD,[1*] Xiang Gao, MD, PhD,[1,5] Marjorie L. McCullough, ScD,[2] Eric J. Jacobs, PhD,[2] Alpa V. Patel, PhD,[2] Tinisha Mayo, MPH,[2] Michael A. Schwarzschild, MD, PhD,[3] and Alberto Ascherio, MD, DPH[1,4,5]

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[3]*Massachusetts General Hospital, Boston, Massachusetts, USA*
[4]*Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts, USA*
[5]*Channing Laboratory, Department of Medicine, Brigham and Women's Hospital, and Harvard Medical School, Boston, Massachusetts, USA*

- 147,096 participants in the Cancer Prevention Study II Nutrition Cohort from 1992 to 2005 were prospectively followed.
- Assessment of BMI, Body Composition (waist circumference, weight change), and Diabetes

In this large, prospective cohort of U.S. men and women, we did not find any significantly altered risk of PD when examining BMI, weight change, tendency for central weight gain, or baseline diabetes.

Movement Disorders, Vol. 26, No. 12, 2011

Movement Disorders
Vol. 21, No. 4, 2006, pp. 446–455

Comorbid Conditions Associated With Parkinson's Disease: A Population-Based Study

Cynthia L. Leibson, PhD,[1]* Demetrius M. Maraganore, MD,[2] James H. Bower, MD,[2] Jeanine E. Ransom, BS,[1] Peter C. O'Brien, PhD,[1] and Walter A. Rocca, MD, MPH[1,2]

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1759 PD cases
mean age 67.5 years
mean disease duration 1.3 years
65.2% men

TABLE 1. *Characteristics of Parkinson's disease (PD) cases: stratified by time from onset of PD symptoms and age at onset of PD symptoms*

Age group or time period	Cases (n)	Gender (% male)	Age at PD onset, yr (mean ± SD)
5 yr before onset	197	61	70 ± 11
At onset	197	61	70 ± 11
5 yr after onset	139	60	67 ± 10
10 yr after onset	66	56	64 ± 10
<70 yr at onset[a]	89	66	60 ± 7
≥70 yr at onset[a]	108	57	77 ± 6

[a]The mean age at onset was 70 years.

TABLE 2. *Comparisons between Parkinson's disease (PD) cases and referent subjects for the likelihood of having a clinical diagnosis within specific disease categories*

	All ages (N = 197)			Age at index < 70 years (N = 89)			Age at index ≥ 70 years (N = 108)		
Conditions	Cases, n (%)	Referent subjects, n (%)	RR (95% CI)	Cases, n (%)	Referent subjects, n (%)	RR (95% CI)	Cases, n (%)	Referent subjects, n (%)	RR (95% CI)
Dementia	22 (11)	13 (7)	1.8 (0.9–3.6)	7 (8)	2 (2)	3.7 (0.7–18.3)[c]	15 (14)	11 (10)	1.4 (0.6–3.3)
Bone breaks	73 (37)	46 (23)	1.9 (1.2–3.0)[a]	35 (39)	20 (23)	2.2 (1.1–4.2)[b]	38 (35)	26 (24)	1.7 (0.9–3.1)[c]
Hip fracture	25 (13)	5 (2)	5.6 (2.1–15.0)[a]	12 (13)	1 (1)	14.0 (1.7–107.0)[a]	13 (12)	4 (4)	3.6 (1.1–11.0)[b]
Myocardial infarction	23 (12)	26 (13)	0.9 (0.5–1.6)	8 (9)	9 (10)	0.9 (0.3–2.4)	15 (14)	17 (16)	0.9 (0.4–1.8)
Ischemic heart disease	73 (37)	78 (40)	0.9 (0.6–1.4)	28 (31)	34 (39)	0.7 (0.4–1.4)	45 (42)	44 (40)	1.1 (0.6–1.8)
Stroke	21 (11)	14 (7)	1.6 (0.8–3.2)	11 (12)	4 (5)	3.0 (0.8–9.7)[c]	10 (9)	10 (9)	1.0 (0.4–2.5)
Diabetes	18 (9)	24 (12)	0.7 (0.4–1.4)	12 (13)	10 (11)	1.2 (0.5–3)	6 (6)	14 (13)	0.4 (0.2–1.1)[c]
Cancer	72 (37)	59 (30)	1.4 (0.9–2)	37 (42)	24 (27)	1.9 (1.0–3.6)[b]	35 (32)	35 (32)	1.0 (0.6–1.8)

For all ages and stratified by ages <70 and ≥70 years as of the index year. Index year was defined as the year of PD onset for each case and the same year for the referent subject.
[a]$P < 0.01$. [b]$0.01 \leq P < 0.05$. [c]$0.05 \leq P < 0.1$. The alpha level for our primary analyses was set at < 0.01.

This population-based historical cohort study revealed that PD is accompanied by significant comorbidity and that both the extent and the type of comorbidity vary as a function of PD duration and age at symptom onset. In the 5 years preceding onset of symptoms, PD cases exhibited levels of comorbidity similar to their unaffected age- and sex-matched peers. The excess comorbidity was most apparent in the later time periods, i.e., 5 to 10 and 10 to 15 years after onset of PD symptoms, and *was largely confined to conditions associated with recognized PD symptoms, sequelae, and complications.*

Movement Disorders
Vol. 24, No. 15, 2009, pp. 2233–2241

Brain Atrophy and White Matter Hyperintensities in Early Parkinson's Disease[a]

Turi O. Dalaker, MD,[1,2,3] Jan P. Larsen, MD, PhD,[3,4,5] Niels Bergsland, BA,[1] Mona K. Beyer, MD, PhD,[2,3] Guido Alves, MD, PhD,[3,4] Michael G. Dwyer, BS,[1] Ole-Bjorn Tysnes, MD, PhD,[5,6] Ralph H.B. Benedict, PhD,[1,7] Arpad Kelemen, PhD,[1] Kolbjorn Bronnick, PhD,[3] and Robert Zivadinov, MD, PhD[1,7]*

MRI characteristics	PD	NC	*P*-value
WMH volume (mL)			
mean ± SD	8.2 ± 14.8	7.4 ± 13.3	0.662
median (min/max)[a]	2.6 (0/88.1)	2.1 (0/62.2)	
	n = 155	n = 98	
WMH volume as percentage of normalized brain volume (%)			
mean ± SD	0.6 ± 1.0	0.5 ± 0.9	0.973
median (min/max)[a]	0.2 (0/5.7)	0.1 (0/4.0)	
	n = 155	n = 98	
Normalized brain parenchymal volume (mL)			
mean ± SD[a]	1517.2 ± 80.1	1520.9 ± 63.4	0.688
	n = 155	n = 101	
Normalized lateral ventricle volume (mL)			
mean ± SD	53.5 ± 19.1	48.9 ± 20.3	0.059
median (min/max)[a]	49,498 (20,471/113,710)	46,327 (16,453/124,630)	
	n = 155	n = 101	
Normalized total gray matter volume (mL)			
mean ± SD	854.6 ± 49.8	867.9 ± 51.6	0.506
median (min/max)[b]	847.5 (759.3/946.1)	860.1 (801.8/1017.9)	
	n = 37	n = 37	
Normalized neocortical volume (mL)			
mean ± SD[c]	656.7 ± 39.4	666.9 ± 42.1n = 37	0.286
	n = 37		
Normalized deep gray matter volume (mL)			
mean ± SD[b]	197.9 ± 14.3	200.1 ± 13.2n=37	0.325
	n = 37		
Normalized white matter volume (mL)			
mean ± SD[c]	662.1 ± 40.0	672.0 ± 38.4	0.285
	n = 37	n = 37	

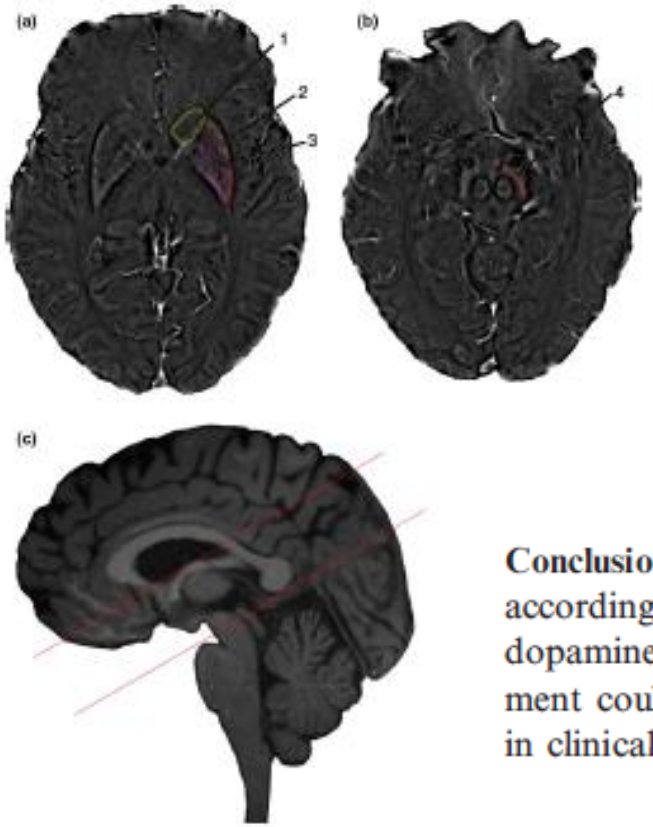
There was no evidence of brain atrophy or higher WMH volume in PD compared to NC, and MRI volumetric measurements were not significant predictors of cognitive functions in PD patients.

We conclude that global structural brain changes are not a major feature in patients with incident PD.

ORIGINAL ARTICLE

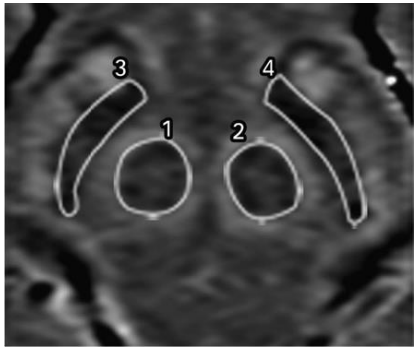
Motor associations of iron accumulation in deep grey matter nuclei in Parkinson's disease: a cross-sectional study of iron-related magnetic resonance imaging susceptibility

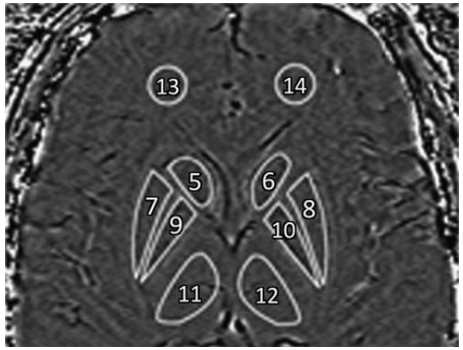
A. Martin-Bastida[a], N. P. Lao-Kaim[a,*], C. Loane[a,b,*], M. Politis[a,c], A. A. Roussakis[a], N. Valle-Guzman[d], Z. Kefalopoulou[a], G. Paul-Visse[e], H. Widner[g], Y. Xing[h], S. T. Schwarz[h], D. P. Auer[h], T. Foltynie[a], R. A. Barker[i,j] and P. Piccini[a]



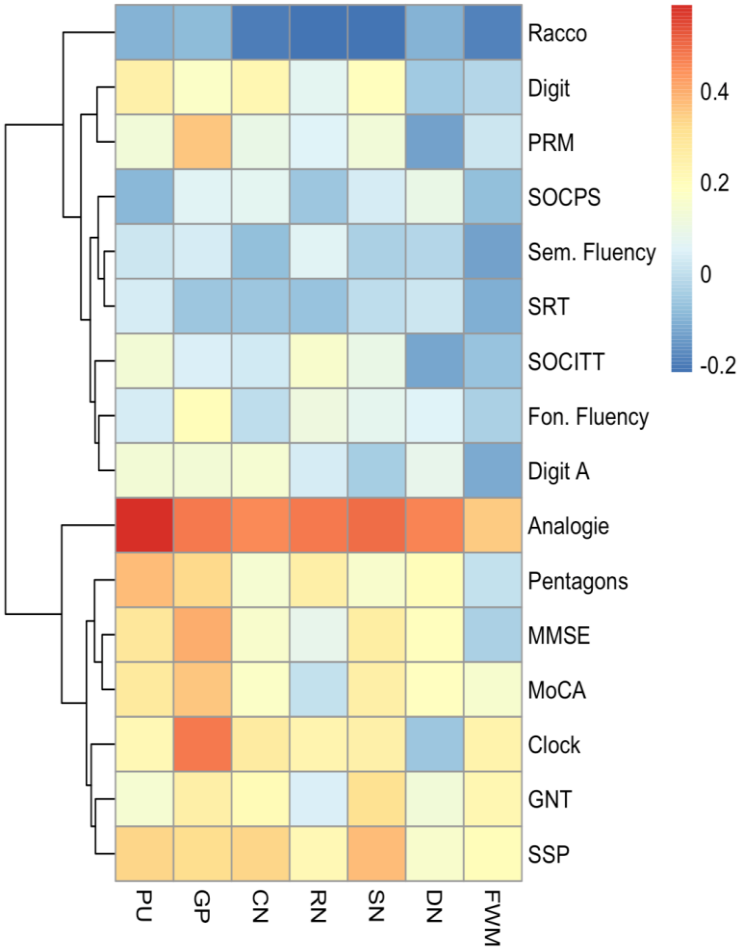
		Mean ± SD	Controls (N = 20)	PD group 1 (N = 23)	PD group 2 (N = 22)	PD group 3 (N = 25)	ANOVA
Putamen[a]	Controls	0.130 ± 0.052					F = 6.346 (3, 82)
	PD group 1	0.181 ± 0.035					P = 0.001
	PD group 2	0.195 ± 0.036					
	PD group 3	0.172 ± 0.054					
Globus pallidus[b]	Controls	−1.621 ± 0.176					F = 7.993 (3, 82)
	PD group 1	−1.488 ± 0.153					P < 0.001
	PD group 2	−1.413 ± 0.123					
	PD group 3	−1.441 ± 0.143					
Substantia nigra	Controls	0.027 ± 0.021					F = 65.008 (3, 82)
	PD group 1	0.094 ± 0.017					P < 0.001
	PD group 2	0.111 ± 0.021					
	PD group 3	0.117 ± 0.023					

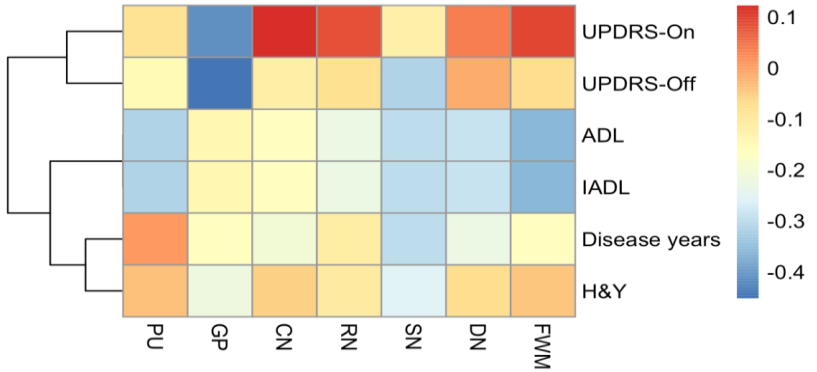
Conclusions: Increased nigral iron accumulation in PD appears to be stratified according to disease motor severity and correlates with symptoms related to dopaminergic neurodegeneration. This semi-quantitative *in vivo* iron assessment could prove useful for objectively monitoring PD progression, especially in clinical trials concerning iron chelation therapies.





	COGNITIVE DOMAIN	TEST
FIRST LEVEL	Global Cognitive Functioning	*MoCA*
SECOND LEVEL	Attention and working memory	*Digit Span forwards/backwards* *Spatial Span* *Simple Reaction Time*
	Executive functions	*Verbal fluency test* *Semantic fluency test* *Tower of London*
	Language	*WAIS-IV Similiraties* *Graded Naming Test*
	Memory	*WMS-IV Logical Memory subtest* *Pattern Recognition Memory*
	Visuospatial function	*Clock drawing test*





Mechanisms of Dementia in Synucleinopathies

SHORT REPORT

Cortical cholinergic denervation is associated with depressive symptoms in Parkinson's disease and parkinsonian dementia

N I Bohnen, D I Kaufer, R Hendrickson, G M Constantine, C A Mathis, R Y Moore

J Neurol Neurosurg Psychiatry 2007;78:641–643. doi: 10.1136/jnnp.2006.100073

AChE PET and brain MRI

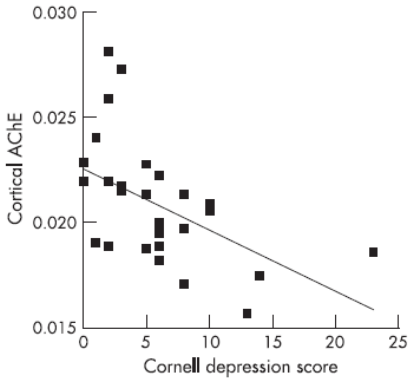


Table 1 Results of the multiple regression analysis using cortical acetylcholinesterase as a dependent parameter and scores for the Cornell Scale for Depression in Dementia and Mini-Mental State Examination as regressors

Subjects	CSDD Score	MMSE Score	Overall model
Patients and controls	$F=5.8$, $p<0.05$	$F=7.8$, $p<0.01$	$F=9.4$, $p<0.001$
Patients only	$F=3.6$, $p<0.05$	$F=3.2$, $p<0.05$	$F=3.7$, $p<0.05$

CSDD, Cornell Scale for Depression in Dementia; MMSE, Mini-Mental State Examination.

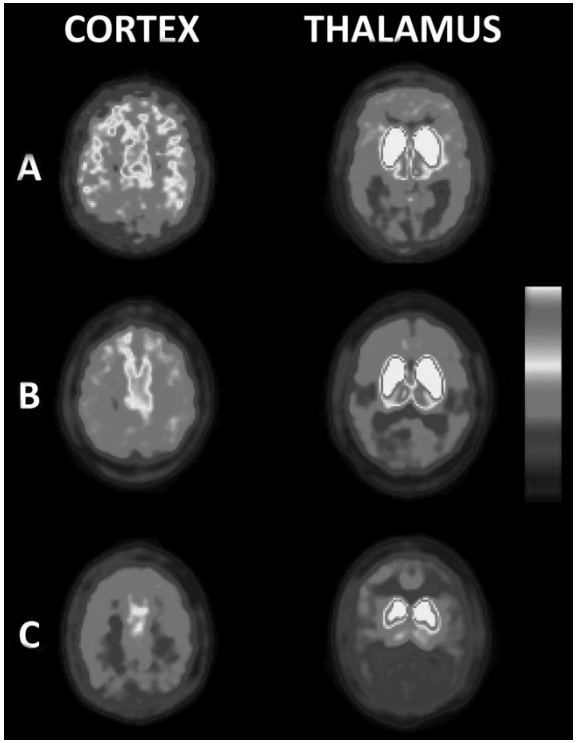
Depressive symptomatology is associated with cortical cholinergic denervation in PD that tends to be **more prominent when dementia is present**

Mechanisms of Dementia in Synucleinopathies

[11C]PMPAChE PET

Cognitive test	Correlation coefficient, significance
CVLT-STM	Rs = 0.13, ns
CVLT-LTM	Rs = 0.20, ns
JOLO	Rs = 0.43 ($P < 0.05$)
SCWT	Rs = 0.46 ($P < 0.05$)
TMT BA	Rs = 0.44 ($P < 0.05$)
Digit Span	Rs = 0.57 ($P < 0.005$)

California Verbal Learning Test, CVLT-STM and LTM, Judgement of Line Orientation Test, JOLO, Stroop Color Word Test, SCWT, Trail Making Test B-A, and WAIS-III Digit Span



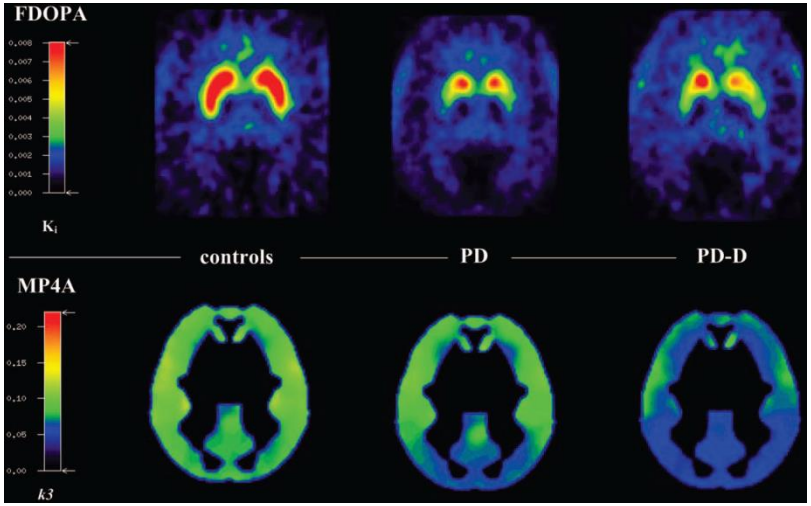
Averaged radioactivity from 40- to 70-min frames of dynamic [11C]PMP PET for a subject with normal cortical and thalamic cholinergic innervation (row A), a subject with cortical-only cholinergic deficits (row B), and a subject with combined cortical and thalamic cholinergic deficits (row C).

Bohnen NI, 2006

Muller LTM, 2015

Mechanisms of Dementia in Synucleinopathies

18fluorodopa (FDOPA)



N-[11C]-methyl-4-piperidyl actetate (MP4A)

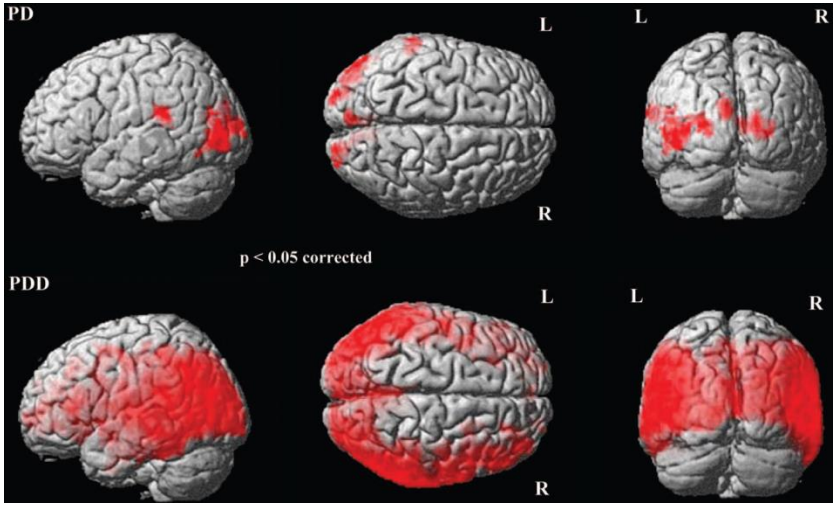


Table 5 *Regions with significant covariance of cortical MP4A k_3 reduction and right-to-left averaged caudate and putaminal FDOPA K_i values in PD and PDD patients*

	Talairach coordinates					
	x	y	z	z_{max}	Voxels pc	*p*
PD						
Putamen						
R middle frontal gyrus	32	52	-2	4.58	125	0.001
Caudate						
R middle frontal gyrus	30	44	22	4.61	102	<0.001
PDD						
Putamen						
L postcentral gyrus	−42	−22	60	4.60	381	<0.001
R precuneus	24	−76	42	5.32	247	<0.001
L superior temporal gyrus	−46	−28	16	4.74	559	<0.001
R middle frontal gyrus	36	28	42	4.28	126	<0.011

While nondemented patients with Parkinson disease had a **moderate cholinergic dysfunction**, subjects with Parkinson disease associated dementia (PDD) presented with a **severe cholinergic deficit in various cortical regions**. The finding of a closely associated striatal FDOPA and cortical MP4A binding reduction suggests a common disease process leading to a complex transmitter deficiency syndrome in PDD.

Hilker R, 2005

Parkinsonismo vascolare

Jean-Martin Charcot (1825-1893)

In 1925, Garrison described Charcot as "*so sedentary that his very gait was regarded as that of a man who could not walk properly because he had forgotten how. With bent back and head thrust forward, he seemed to propel himself by short, quick, shuffling steps. Toward the last, when he mimicked the propulsion in* paralysis agitans*, he seemed to be a patient»*

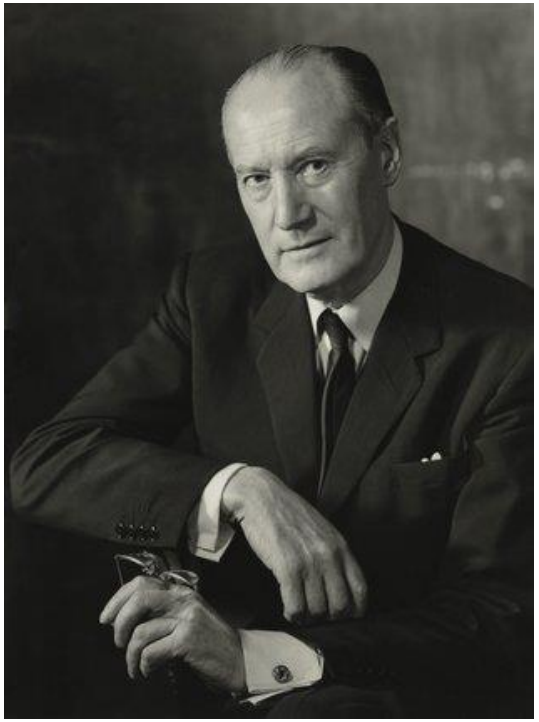
CHARCOT

A L'AMPHITHÉATRE DE LA SALPÊTRIÈRE

ARTERIOSCLEROTIC PARKINSONISM.[1]

BY MACDONALD CRITCHLEY.

CONTENTS.



1929 Dr Macdonald Critchley
(King's College Hospital, London)

Rapporto tra patologia cerebrovascolare e neurodegenerazione **nell'ambito motorio**

Parkinsonismo vascolare (PV)
(2,5- 3,6% di tutti parkinsonismi fino a 22%)

↓

Da encefalopatia multinfartuale o infarti lacunari coinvolgenti
neuroni dopaminergici della SNc e/o connessioni del sistema extrapiramidale

- Progressione a gradini
- Precoce compromissione di equilibrio mediolaterale e andatura
- Prevalente interessamento degli AAII
- Assenza o scarsità del tremore a riposo
- Possibili segni pseudobulbari, piramidali e cerebellari
- Presenza di fattori di rischio e precedenti cerebrovascolari
- Minore risposta alla levodopa
- **Frequente associazione con disfunzioni cognitive**

Parkinsonismo vascolare (PV)

ad esordio insidioso (PVi)
- estese lesioni SB sottocorticale
- esordio con alterazioni cognitive e del cammino

ad esordio acuto (PVa)
- Infarti strategici nei circuiti dei gangli della base
- rigidità , bradicinesia ed alterazioni del cammino

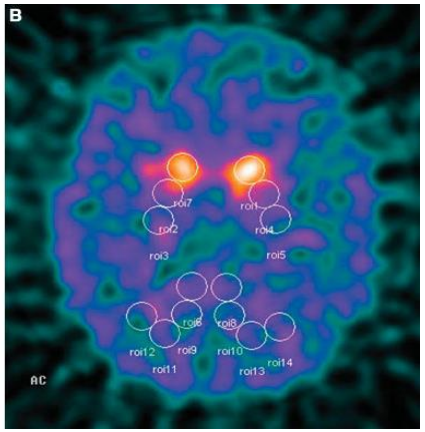
entro un anno dall'infarto

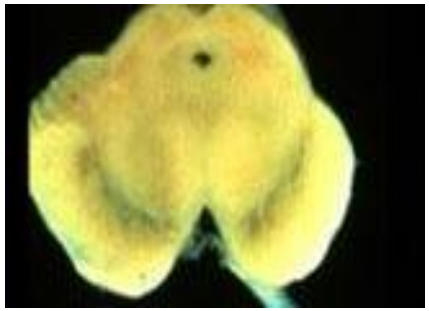
Malattia dei Piccoli Vasi (SVD)
(evidenze TC-MRI-istopatologiche)

Ipotizzata conseguente neurodegenerazione

^{123}I-FP-CIT SPECT :
ipocaptazione nei Gangli della Base sia in VPi che in VPa
come in PD idiopatica
ma con minore asimmetria

Sezioni istologiche della SNc:
rarefazione cellulare e gliosi
come in PD idiopatica





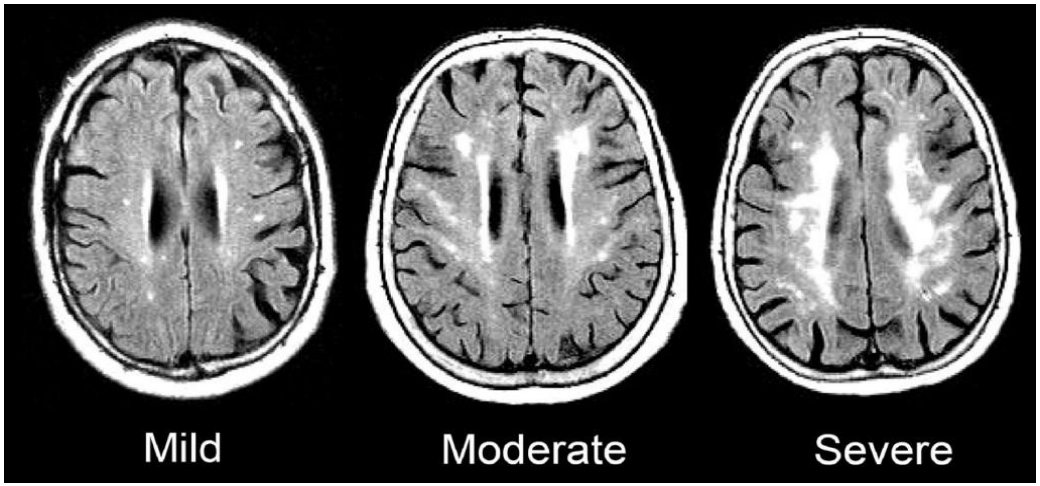
Leucoaraiosi e Parkinsonismo Vascolare

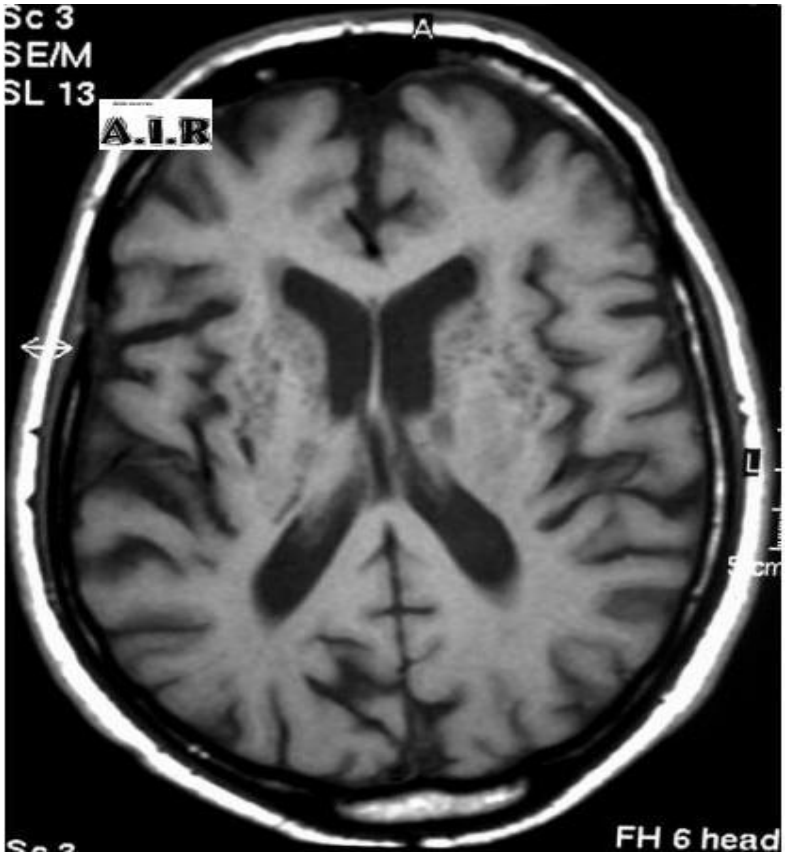
Leucoaraiosi:
Lesioni lacunari o diffuse della Sostanza Bianca causate da arteriolosclerosi delle arterie penetranti
(determinata da vari fattori di rischio vascolari)

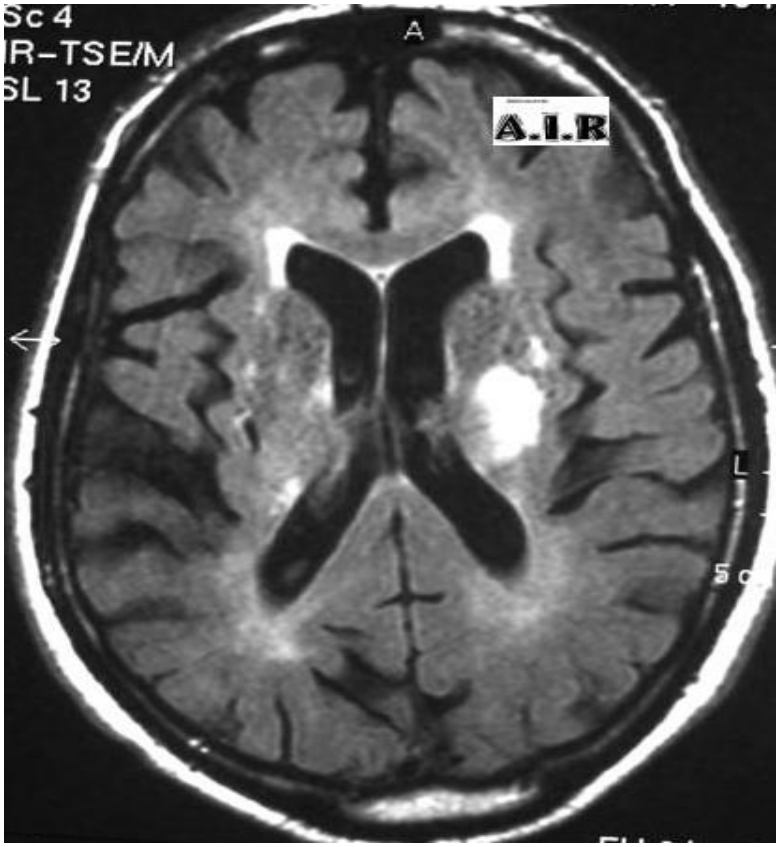
Associata a:

Maggiore gravità clinica motoria e mortalità nel PV
(Rektor et al., 2012; Chen et al., 2014)

Alterazioni cognitive, comportamentali e del tono dell'umore nei pz con PV







Esiti di **infarti multipli dei nuclei della base** con lesioni nodulari ipointense in T1 e iperintense in FLAIR per gliosi reattiva e spazi perivascolari dilatati ipointensi sia in T1 che in FLAIR

TABLE 1. Most common causes of the syndrome of lower-body parkinsonism

Most Common Causes of Lower-Body Parkinsonisms		
Clinical Presentation	Suspected Syndrome	Actual Diagnosis
Acute onset of hemiparkinsonism + midbrain stroke/hemorrhage	VaP	Stroke ("definite" VaP)
LBP + diffuse and confluent hyperintensities on brain MRI	VaP (pseudobulbar palsy, pyramidal features)	Binswanger's disease[a]; multiple lacunar infarcts
LBP + hyperintensities on brain MRI, especially in striatum, external capsule, and temporal lobes	VaP	CADASIL (*NOTCH3*)
Porencephalic cavities, calcifications, and microbleeds; sparing of temporal poles	Apathetic depression, abulia, migraine	*COL4A1*-related disorders
Frontal lobe predominance of WM hyperintensities	Same as above VaP	Hereditary diffuse leukoencephalopathy with axonal spheroids (*CSF1R*)
LBP + enlarged perivascular spaces in striatum on MRI	VaP	SCS (also common in CADASIL)
LBP + hydrocephalus	NPH	Idiopathic communicating hydrocephalus; secondary hydrocephalus (meningitis, head trauma)
LBP + hydrocephalus + periventricular and/or deep WM hyperintensities	NPH + VaP	NPH or microangiopathic brain disease or both (scant clinicopathological correlations)
LBP + falls + "unremarkable" MRI (early on)	Richardson syndrome	PSP
Primary progressive freezing of gait	Richardson syndrome VaP	PSP; striatonigroluysian degeneration; Alzheimer's disease
LBP + frontal lobe lesions	Akinesia, abulia, apathetic depression VaP	Tumors; ischemia; demyelination

Lower-body parkinsonism (LBP) has been defined for a syndrome of reduced gait mobility, with shortened stride length, diminished step height, increased step width, and freezing of gait episodes, with poor response to external cues and L-dopa.
[a]Binswanger's disease (most often defined by neuroimaging than pathology) has also been referred to as subcortical arteriosclerotic encephalopathy.
CADASIL, cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy.

Vizcarra et al, 2015

Rapporto tra patologia cerebrovascolare e neurodegenerazione **nell'ambito motorio**

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Da encefalopatia multinfartuale o infarti lacunari coinvolgenti
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- Minore risposta alla levodopa
- **Frequente associazione con disfunzioni cognitive**

Ictus ischemico/emorragico

Distruzione SN o
vie dopaminergiche →

Sintomatologia parkinsoniana

CT e SPECT →

Parkinsonismo vascolare definito

MDS Clinical Diagnostic Criteria for Parkinson's Disease

Ronald B. Postuma, MD, MSc,[1†*] Daniela Berg, MD,[2†*] Matthew Stern, MD,[3] Werner Poewe, MD,[4] C. Warren Olanow, MD, FRCPC,[5] Wolfgang Oertel, MD,[6] José Obeso, MD, PhD,[7] Kenneth Marek, MD,[8] Irene Litvan, MD,[9] Anthony E. Lang, OC, MD, FRCPC,[10] Glenda Halliday, PhD,[12] Christopher G. Goetz, MD,[13] Thomas Gasser, MD,[2] Bruno Dubois, MD, PhD,[14] Piu Chan, MD, PhD,[15] Bastiaan R. Bloem, MD, PhD,[16] Charles H. Adler, MD, PhD,[17] and Günther Deuschl, MD[18]

The first essential criterion is parkinsonism, which is defined as bradykinesia, in combination with at least 1 of rest tremor or rigidity. Examination of all cardinal manifestations should be carried out as described in the MDS–Unified Parkinson Disease Rating Scale.[30] Once parkinsonism has been diagnosed:

Diagnosis of **Clinically Established PD** requires:

1. Absence of absolute exclusion criteria
2. At least two supportive criteria, and
3. No red flags

Diagnosis of **Clinically Probable PD** requires:

1. Absence of absolute exclusion criteria
2. Presence of red flags counterbalanced by supportive criteria
   If 1 red flag is present, there must also be at least 1 supportive criterion
   If 2 red flags, at least 2 supportive criteria are needed
   No more than 2 red flags are allowed for this category

Supportive criteria
(Check box if criteria met)

- ☐ 1. Clear and dramatic beneficial response to dopaminergic therapy. During initial treatment, patient returned to normal or near-normal level of function. In the absence of clear documentation of initial response a dramatic response can be classified as:
  - a) Marked improvement with dose increases or marked worsening with dose decreases. Mild changes do not qualify. Document this either objectively (>30% in UPDRS III with change in treatment), or subjectively (clearly-documented history of marked changes from a reliable patient or caregiver).
  - b) Unequivocal and marked on/off fluctuations, which must have at some point included predictable end-of-dose wearing off.
- ☐ 2. Presence of levodopa-induced dyskinesia
- ☐ 3. Rest tremor of a limb, documented on clinical examination (in past, or on current examination)
- ☐ 4. The presence of either olfactory loss or cardiac sympathetic denervation on MIBG scintigraphy

Absolute exclusion criteria: The presence of any of these features rules out PD:

- ☐ 1. Unequivocal cerebellar abnormalities, such as cerebellar gait, limb ataxia, or cerebellar oculomotor abnormalities (eg, sustained gaze evoked nystagmus, macro square wave jerks, hypermetric saccades)
- ☐ 2. Downward vertical supranuclear gaze palsy, or selective slowing of downward vertical saccades
- ☐ 3. Diagnosis of probable behavioral variant frontotemporal dementia or primary progressive aphasia, defined according to consensus criteria[31] within the first 5 y of disease
- ☐ 4. Parkinsonian features restricted to the lower limbs for more than 3 y
- ☐ 5. Treatment with a dopamine receptor blocker or a dopamine-depleting agent in a dose and time-course consistent with drug-induced parkinsonism
- ☐ 6. Absence of observable response to high-dose levodopa despite at least moderate severity of disease
- ☐ 7. Unequivocal cortical sensory loss (ie, graphesthesia, stereognosis with intact primary sensory modalities), clear limb ideomotor apraxia, or progressive aphasia
- ☐ 8. Normal functional neuroimaging of the presynaptic dopaminergic system
- ☐ 9. Documentation of an alternative condition known to produce parkinsonism and plausibly connected to the patient's symptoms, or, the expert evaluating physician, based on the full diagnostic assessment feels that an alternative syndrome is *more likely* than PD

Red flags

- ☐ 1. Rapid progression of gait impairment requiring regular use of wheelchair within 5 y of onset
- ☐ 2. A complete absence of progression of motor symptoms or signs over 5 or more y unless stability is related to treatment
- ☐ 3. Early bulbar dysfunction: **severe** dysphonia or dysarthria (speech unintelligible most of the time) or severe dysphagia (requiring soft food, NG tube, or gastrostomy feeding) within first 5 y
- ☐ 4. Inspiratory respiratory dysfunction: either diurnal or nocturnal inspiratory stridor or frequent inspiratory sighs
- ☐ 5. Severe autonomic failure in the first 5 y of disease. This can include:
  - a) Orthostatic hypotension[32]—orthostatic decrease of blood pressure within 3 min of standing by at least 30 mm Hg systolic or 15 mm Hg diastolic, in the absence of dehydration, medication, or other diseases that could plausibly explain autonomic dysfunction, or
  - b) Severe urinary retention or urinary incontinence in the first 5 y of disease (excluding long-standing or small amount stress incontinence in women), that is not simply functional incontinence. In men, urinary retention must not be attributable to prostate disease, and must be associated with erectile dysfunction
- ☐ 6. Recurrent (>1/y) falls because of impaired balance within 3 y of onset
- ☐ 7. Disproportionate anterocollis (dystonic) or contractures of hand or feet within the first 10 y
- ☐ 8. Absence of any of the common nonmotor features of disease despite 5 y disease duration. These include sleep dysfunction (sleep-maintenance insomnia, excessive daytime somnolence, symptoms of REM sleep behavior disorder), autonomic dysfunction (constipation, daytime urinary urgency, symptomatic orthostasis), hyposmia, or psychiatric dysfunction (depression, anxiety, or hallucinations)
- ☐ 9. Otherwise-unexplained pyramidal tract signs, defined as pyramidal weakness or clear pathologic hyperreflexia (excluding mild reflex asymmetry and isolated extensor plantar response)
- ☐ 10. Bilateral symmetric parkinsonism. The patient or caregiver reports bilateral symptom onset with no side predominance, **and** no side predominance is observed on objective examination

Criteria Application:

1. Does the patient have parkinsonism, as defined by the MDS criteria? Yes ☐ No ☐
   If no, *neither* probable PD nor clinically established PD can be diagnosed. *If yes:*
2. Are any absolute exclusion criteria present? Yes ☐ No ☐
   If "yes," *neither* probable PD nor clinically established PD can be diagnosed. *If no:*
3. Number of red flags present ____
4. Number of supportive criteria present ____
5. Are there at least 2 supportive criteria *and* no red flags? Yes ☐ No ☐
   If yes, patient meets criteira for **clinically established PD**. *If no:*
6. Are there more than 2 red flags? Yes ☐ No ☐
   If "yes," probable PD *cannot* be diagnosed. *If no:*
7. Is the number of red flags equal to, or less than, the number of supportive criteria? Yes ☐ No ☐
   If yes, patient meets criteria for **probable PD**

The first essential criterion is parkinsonism, which is defined as bradykinesia, in combination with at least 1 of rest tremor or rigidity. Examination of all cardinal manifestations should be carried out as described in the MDS–Unified Parkinson Disease Rating Scale.

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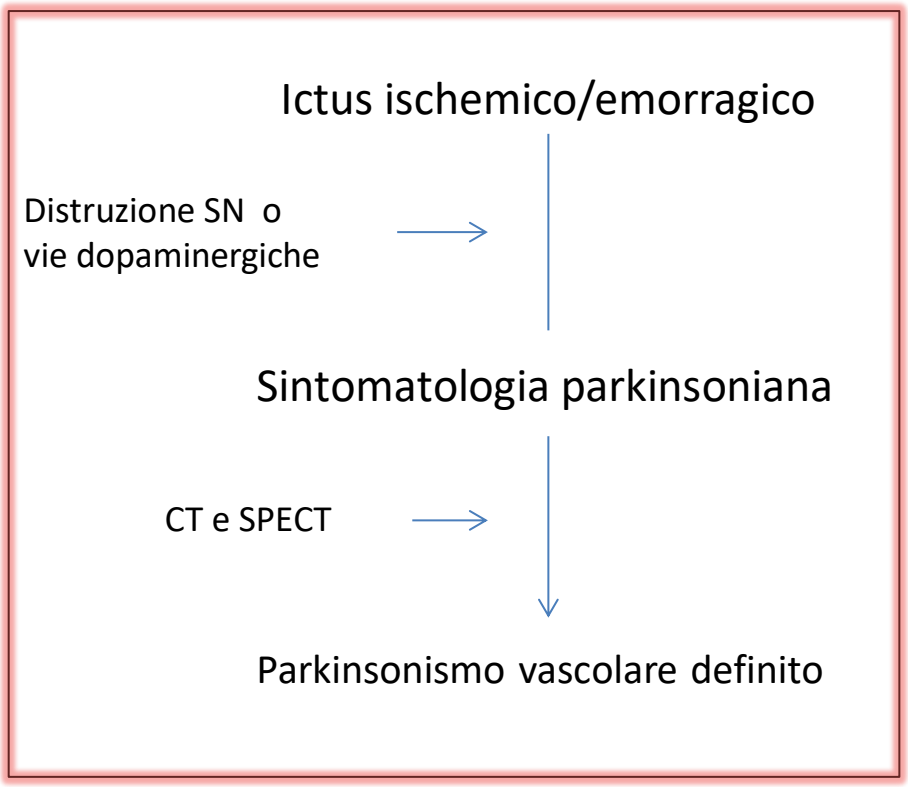
3.4 FINGER TAPPING

Instructions to examiner: Each hand is tested separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to tap the index finger on the thumb 10 times as quickly AND as big as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude.

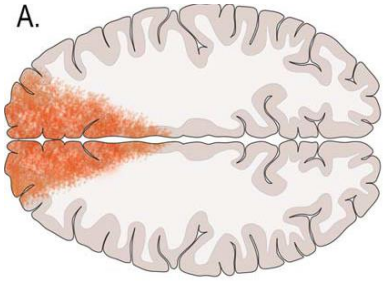
0: Normal:	No problems.	
1: Slight:	Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the tapping movement; b) slight slowing; c) the amplitude decrements near the end of the 10 taps.	☐ R
2: Mild:	Any of the following: a) 3 to 5 interruptions during tapping; b) mild slowing; c) the amplitude decrements midway in the 10-tap sequence.	☐ L
3: Moderate:	Any of the following: a) more than 5 interruptions during tapping or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) the amplitude decrements starting after the 1st tap.	
4: Severe:	Cannot or can only barely perform the task because of slowing, interruptions or decrements.	

Parkinsonismo vascolare



Vascular pseudoparkinsonism

A.



strokes resulting from anterior cerebral artery territory infarcts

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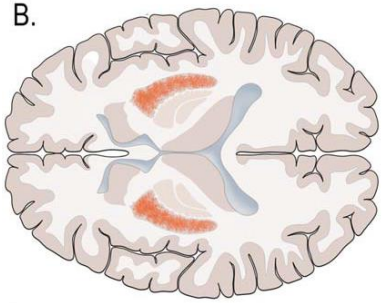
akinetic mutism

B.

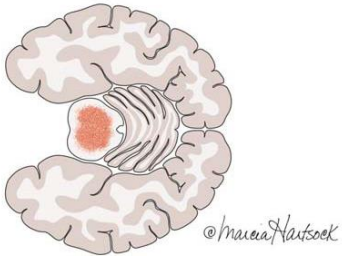


bilateral striatal lacunar infarctions

↓

apathetic depression

C.



Small vessel ischemic disease of the pons

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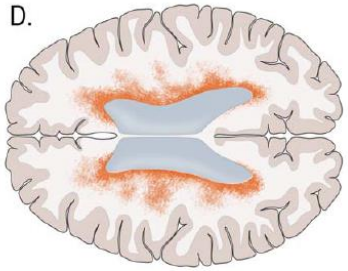
Pyramidal weakness and slowness

Vizcarra et al, 2015

Pseudovascular pseudoparkinsonism

D.

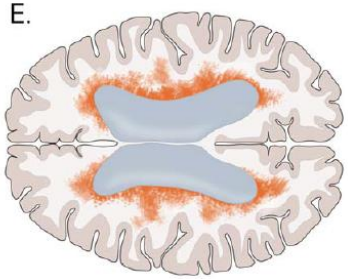


periventricular and deep WM signal abnormalities in isolation

↓

higher-level gait disorder

E.



periventricular and deep WM signal abnormalities in association with ventriculomegaly

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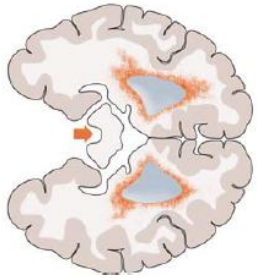
higher-level gait disorder in NPH

Pseudovascular parkinsonism



Pseudovascular parkinsonism can be documented in patients with PD (with a pattern similar to D) or PSP

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atrophic midbrain

Interessanti relazioni tra
Patologia cerebrovascolare e Neurodegenerazione

Importanti risvolti concreti in prospettiva preventiva e terapeutica

Grazie per l’attenzione