



La demenza nel Parkinson e nei Parkinsonismi

Prof. Marco Onofrj

*Dipartimento di Oncologia e Neuroscienze, Neurofisiopatologia,
Centro Disturbi del Movimento, UVA
Università "G.D'Annunzio", Chieti-Pescara*

Neuropsychiatry of the basal ganglia

HA Ring, J Serr-Mertes JNNP Jan 2002

Mind & Movement: the Neuropsychiatry of Movement Disorders

BL Lennox, G Lennox, JNNP Mar. 2002 S.1

Parkinson's Disease: Advances in Neurology, Vol. 91.
 Edited by Ariel Gordon, Seppo Kaakkola,
 and Heikki Teräväinen
 Lippincott Williams & Wilkins, Philadelphia © 2003

37

Parkinson's Disease Is a Neuropsychiatric Disorder

*†‡Y. Agid, §I. Arnulf, **P. Bejjani, †F. Bloch, *†‡A. M. Bonnet, ¶P. Damier, ||B. Dubois, ‡C. François, *†‡J. L. Houeto, †D. Iacono, ‡C. Karachi, *†‡V. Mesnage, †O. Messouak, *‡M. Vidailhet, *†‡M. L. Welter, and ‡J. Yelnik

Mental and Behavioral Dysfunction in Movement Disorders

Edited by

Marc-André Bédard, MSc, PhD

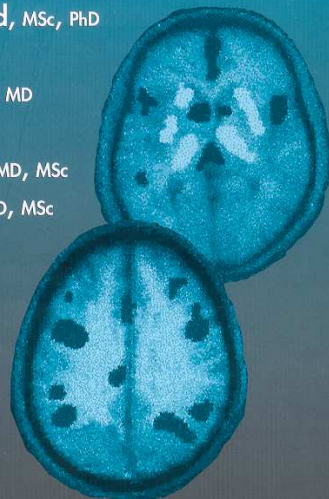
Yves Agid, MD, PhD

Sylvain Chouinard, MD

Stanley Fahn, MD

Amos D. Korczyn, MD, MSc

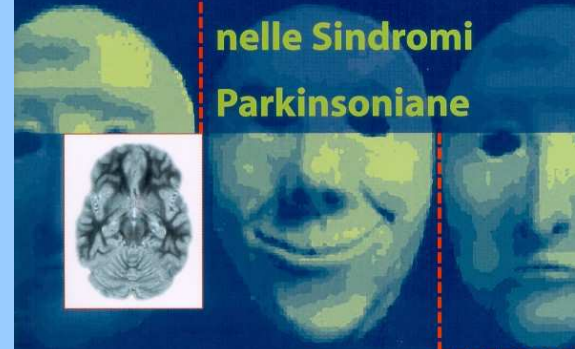
Paul Lespérance, MD, MSc



 HUMANA PRESS

MARCO ONOFRI

Disturbi Mentali nelle Sindromi Parkinsoniane



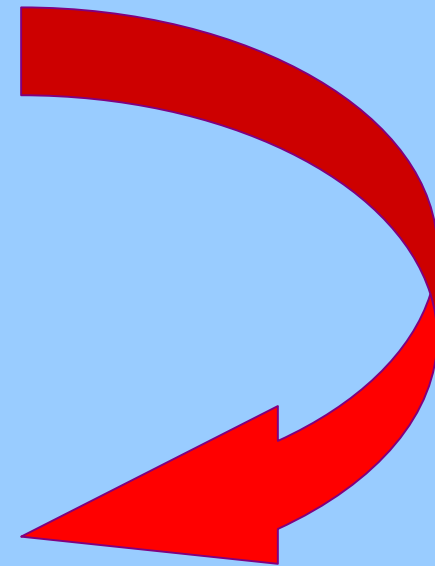
 Springer

Disordini Cognitivi nella Malattia di Parkinson

Identificabile settoriale 90%
grave 25%

Rischio X 3 popolazione normale
Incidenza 5% anno > 65aa

Prevalenza 15-40%



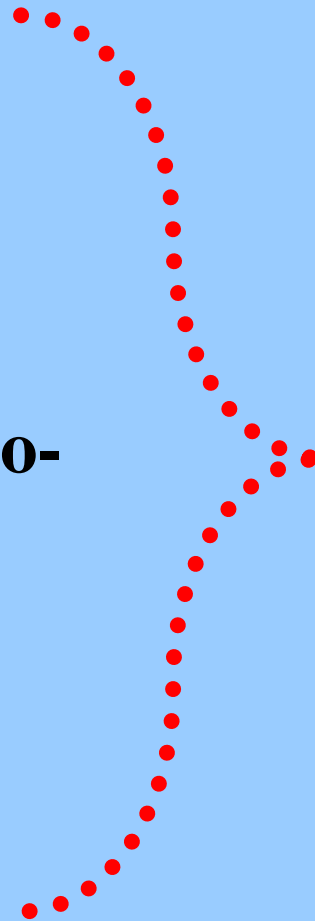
Bradifrenia

Disordine Disesecutivo

**Alterazioni delle funzioni visuo-
spaziali**

Memoria (retrieval)

Apatia



**19 % PD
senza
demenza**

Disturbo cognitivo

Disordine Disesecutivo Frontale:

astrazione

fluenza

giudizio

attenzione

capacità adattative

pogrammazione

Cascata dei deficit prefrontali nell'uomo

Primari

Deficit dei controlli inibitori

Deficit del riconoscimento di novità

Secondari

Distraibilità

Rumore di fondo interno

Ridotta attenzione fasica e tonica

Scarsa codificazione temporale degli eventi

Terziari

Comportamento legato allo stimolo IB-UB

Insicurezza nelle decisioni

Perseverazione

Ridotta pianificazione e organoizzazione della memoria

Disturbo nella generazione di nuove idee

Disturbo di organizzazione temporale (passato, presente, futuro)

Disturbo di confronto di realtà (reality cheking o monitoring)

Disturbo di creazione di ipotesi alternative (counterfactual scenarios)



Jonathan Franzen
Le correzioni



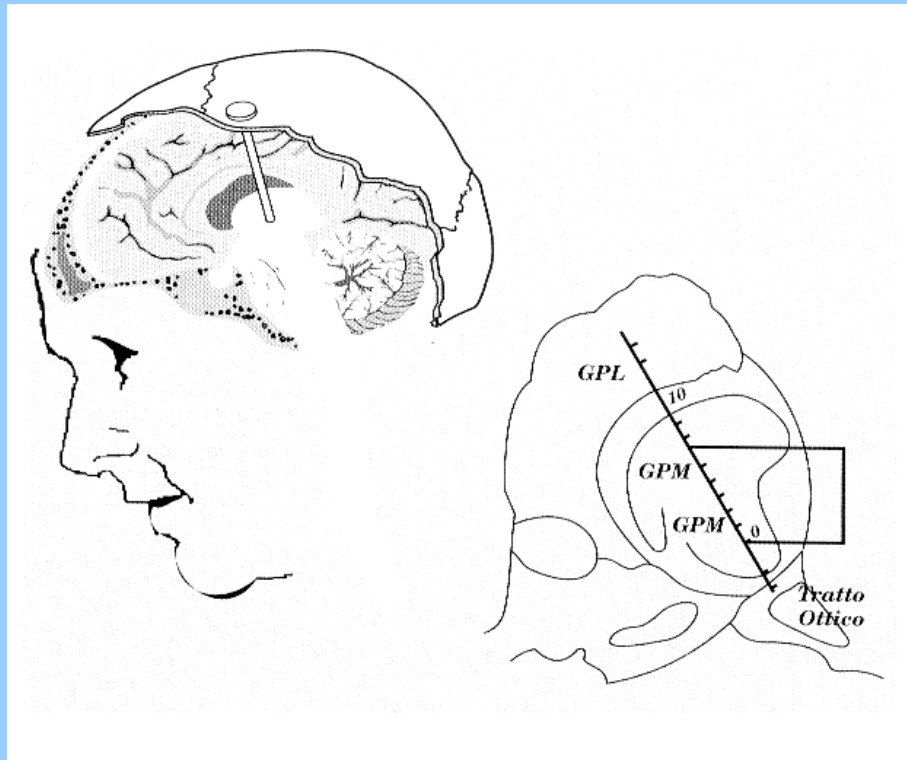
– Al? Cosa stai facendo?

Si voltò verso la soglia dove era apparsa Enid. Cominciò una frase: – Sto... – ma quando veniva colto di sorpresa ogni frase diventava un'avventura nella foresta; non appena perdeva di vista la luce della radura da cui era entrato, si accorgeva che le briciole che aveva seminato per orientarsi erano state mangiate dagli uccelli, esseri che sfrecciavano silenziosi nelle tenebre e che lui non poteva vedere ma che si accalcavano così numerosi per la fame da sembrare tenebra *loro stessi*, come se l'oscurità non fosse uniforme, non fosse assenza di luce ma una cosa brulicante e corpuscolare, e in ef-

Escape from Linear Time:
Prefrontal Cortex and
Conscious Experience

Robert T. Knight and Marcia Grabowecy

Rappresentazione dell'elettrodo per la stimolazione cerebrale profonda

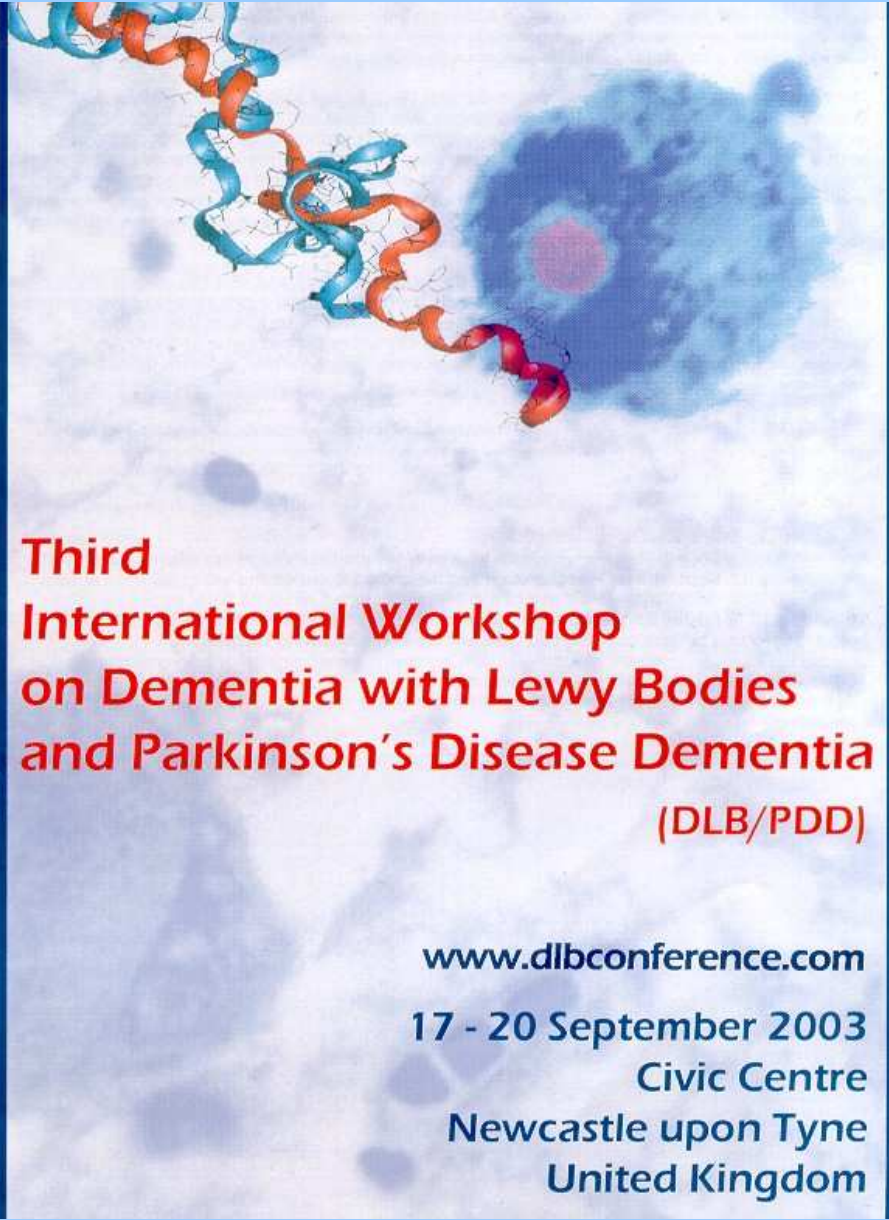


Perché ci sono disordini mentali nella Malattia di Parkinson

- Tentato suicidio da elettrostimolazione
- Allucinazione da elettrostimolazione
- Riso gioioso da elettrostimolazione
- Disordine disesecutivo da elettrostimolazione
- Abulia o acinesia psichica da lacune del Nucleo lenticolare
- Ipomania in lacune dei Nuclei subtalamici

Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): Report of the consortium on DLB intranational workshop (McKeith IG et al., Neurology 47, Nov 1996)

1. **The central feature required for a diagnosis of DLB is progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational function.
Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression. Deficits on tests of attention and of frontal-subcortical skills and visuospatial ability may be especially prominent.**
2. **Two of the following core features are essential for a diagnosis of probable DLB, and one is essential for possible DLB:**
 - a. **Fluctuating cognition with pronounced variations in attention and alertness**
 - b. **Recurrent visual hallucinations that are typically well formed and detailed**
 - c. **Spontaneous motor features of parkinsonism**
3. **Features supportive of the diagnosis are**
 - a. **Repeated falls**
 - b. **Syncope**
 - c. **Transient loss of consciousness**
 - d. **Neuroleptic sensitivity**
 - e. **Systematized delusions**
 - f. **Hallucinations in other modalities**
4. **A diagnosis of DLB is less likely in the presence of**
 - a. **Stroke disease, evident as focal neurologic signs or on brain imaging**
 - b. **Evidence on physical examination and investigation of any physical illness or other brain disorder sufficient to account for the clinical picture**

The image shows a microscopic view of a neuron with a prominent nucleus. Overlaid on the neuron is a 3D ribbon model of a protein structure, colored in blue, orange, and red. The protein structure is positioned diagonally across the upper left portion of the neuron. The background is a light, grainy texture, likely representing the cytoplasm or extracellular space.

**Third
International Workshop
on Dementia with Lewy Bodies
and Parkinson's Disease Dementia
(DLB/PDD)**

www.dlbconference.com
17 - 20 September 2003
Civic Centre
Newcastle upon Tyne
United Kingdom

Introduzione

3

Tabella 2. Classificazione anatomico-clinica dei disordini del movimento

Patologia	Categoria	Gruppo
Malattie di Parkinson monogeniche	Park 1-8	
Sinucleinopatie	Malattia di Parkinson idiopatica	Malattia a corpi di Lewy troncoencefalica Malattia a corpi di Lewy diffusa
	Parkinson con demenza	Malattia a corpi di Lewy diffusa Parkinson iniziale con demenza tardiva
	Atrofie multisistemiche	Degenerazione olivo-ponto-cerebellare Degenerazione striato-nigrica Ipotensione ortostatica idiopatica

Systematic Review and Meta-Analysis Show that Dementia with Lewy Bodies Is a Visual-Perceptual and Attentional-Executive Dementia

Daniel Collerton^a David Burn^b Ian McKeith^c John O'Brien^c

^aBensham Hospital, Gateshead, and ^bRegional Neurosciences Centre and ^cWolfson Research Unit, Institute for Aging and Health, Newcastle General Hospital, Newcastle upon Tyne, UK

Table 2. Description of studies included in systematic review

Authors	Year of publication	Diagnosis	Clinical (C) or pathological (P) diagnosis	Quality score	Controls		DLB		AD/PD				
					n	age, years	n	age, years	n	age, years			
					mean	SD	mean	SD	mean	SD			
<i>Comparisons with AD</i>													
Hansen et al. [6]	1990	LBV	P	4			9	80.1	7.8	9	74.8	5.8	
Saghal et al. [20]	1992	SDLT	C	2	16	74.8	1.3	7	77.3	3.1	10	78	1.7
Saghal et al. [21]	1992	SDLT	C	2	16	74.8	1.3	7	77.3	3.1	10	78	1.7
Galkoway et al. [22]	1992	SDLT	C	2	16	74.8	1.3	7	77.3	3.1	10	78	1.7
Forstl et al. [23]	1993	LBV	P	3			8	73.3	6.0	8			
Saghal et al. [8]	1995	SDLT	C	2	16	74.8	5.2	10	78.4	5.4	9	75	5.6
Salmon et al. [5]	1996	DLBD	P	3			5	72.6	0.9	5	77	2.4	
Galasko et al. [24]	1996	LBV	P	4			13	73.3	5.6	13	72.8	5	
Gnanalingham et al. [25]	1996	LBD	C	3	16	75.6		14	77.2		14	76.1	
Gnanalingham et al. [7] ¹	1997	LBD	C	4	22	73.3	6.1	16	76.4	7.2	25	75.7	7
Walker et al. [26]	1997	SDLT	C	4			17	73.1	8	17	73.1	5.5	
Shimomura et al. [27]	1998	DLB(c)	C	3			26	73.6	5.1	52	73.7	5.1	
Connor et al. [28]	1998	LBV	P	5			23	75.9	5.2	23	76.7	5.7	
Walker et al. [13] ²	2000	DLB(c)	C	2	10	77.5	4.5	15	78.7	6.6	15	78.8	3.9
Calderon et al. [29]	2000	DLB(c)	C	3	17	68.3	5.3	10	72.5	9.6	9	71.2	5.2
Mori et al. [30]	2000	DLB(c)	C	3			24	74	5.8	48	74	7.2	
Lambon Ralph et al. [9]	2001	DLB(c)	C	3	15	71.5	3.5	10	76.4	9.1	10	71.7	5.1
Ballard et al. [31]	2001	DLB(c)	C	2	35	73.9	7.4	84	78	6.3	75	79.3	6.8
Ata et al. [32]	2001	DLB(c)	P	2			17	75	7.2	27	79.7	7.6	
<i>Comparisons with PD</i>													
Gnanalingham et al. [7] ¹	1997	LBD	C	4	22	73.3	6.1	16	76.4	7.2	13	72.6	8.13
Downes et al. [34] ³	1999	DLB(c)	C	3	10	64.7	2	10	66.4	3.84	20	60.6	9.17
Molloy et al. [unpubl.]	2002	DLB(c)	C	2			22	74		32	76		

¹ Gnanalingham et al. [7] included both AD and PD groups.

² Walker et al. [13] reported only variability; therefore included in the variability but not in the effect size analyses.

³ Downes et al. [34] used two PD comparison groups: early and late.

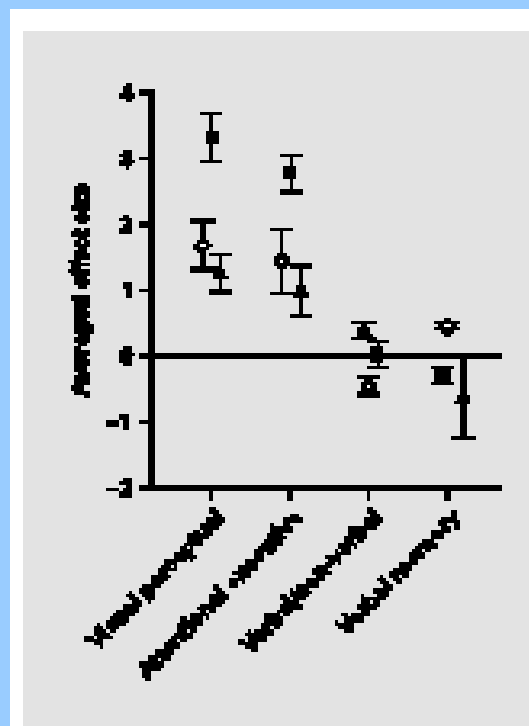
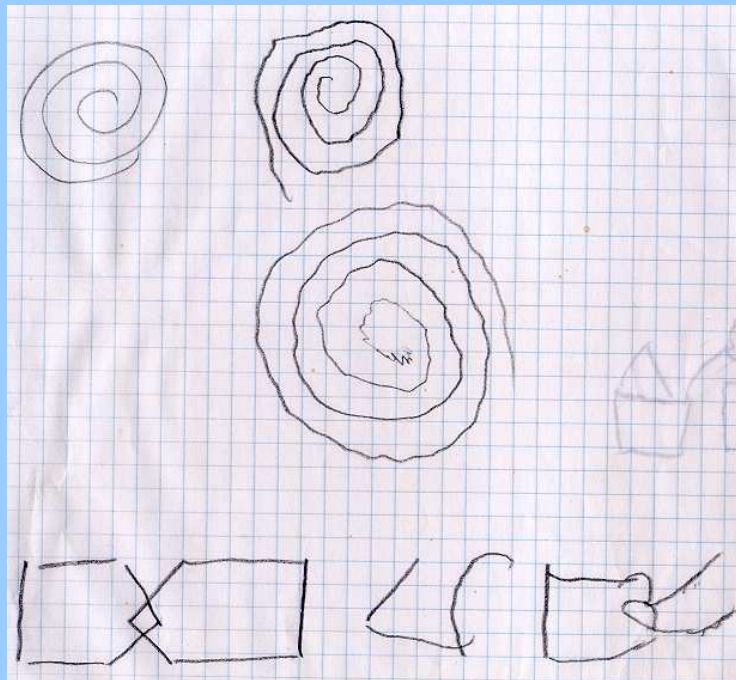
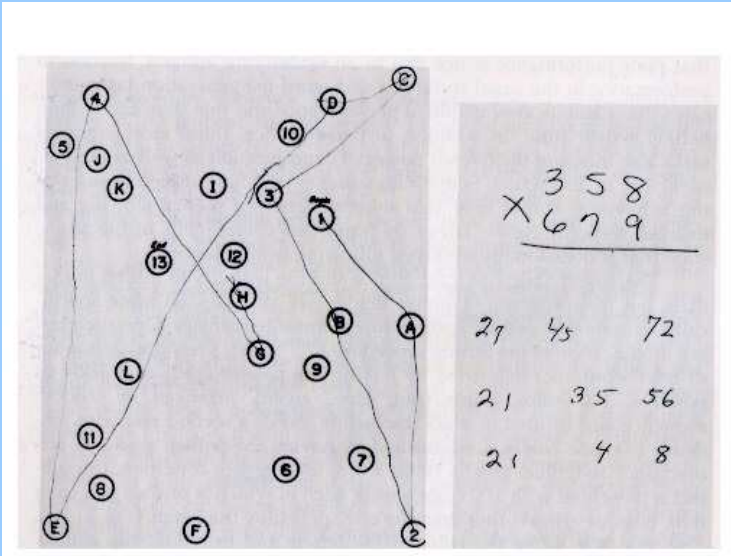
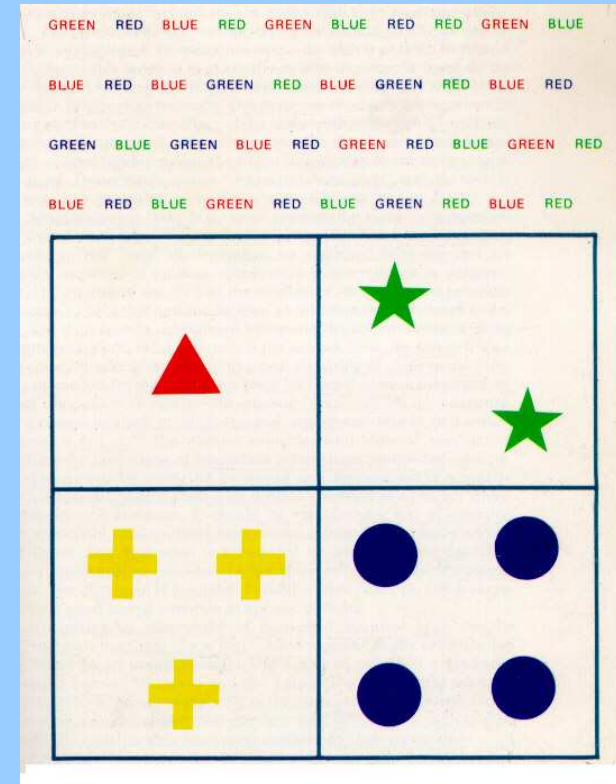


Fig. 1. Results of comparisons between DLB and controls, AD, and PD patients on factors. ■ = DLB compared to controls; ◇ = DLB compared to AD; ▲ = DLB compared to PD. Values are mean and 95% CI.

Trail-Making Test

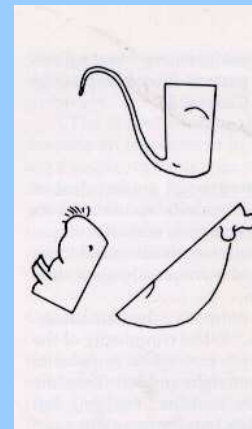


Stroop

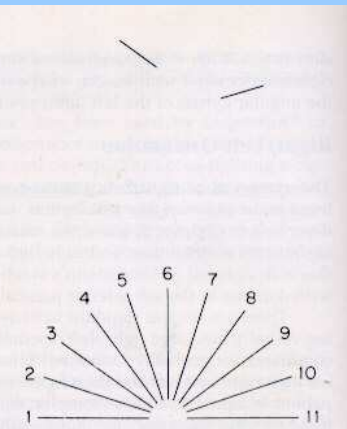


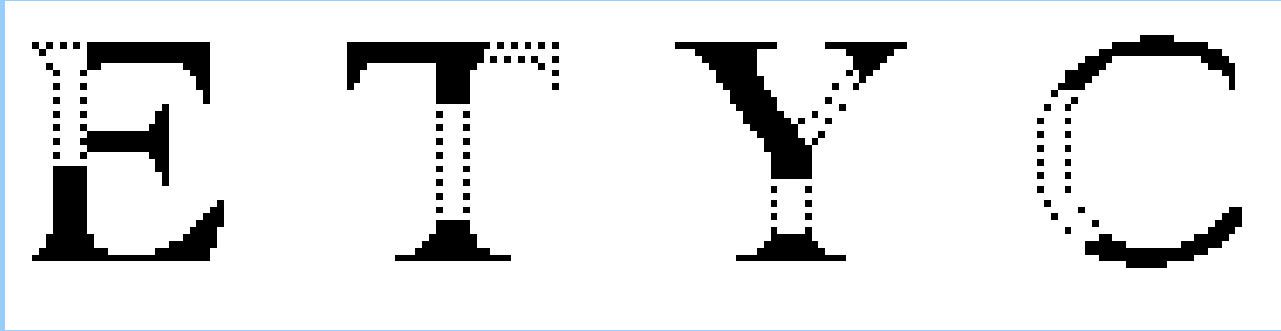
Wisconsin Card Sorting

Hooper visual organization test



Benton Judgment of Line Orientation Test





J Darymple-Alford JNNP Feb 2001

	LBD	AD
Attention:	sustained devided	set shifting selective attention
Memory:	recall recognition	delayed recall

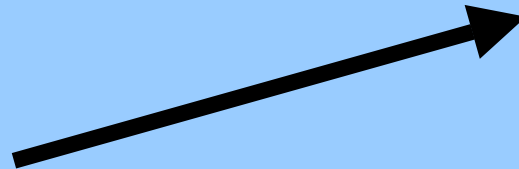
Dementia with Lewy bodies

Improving diagnostic criteria

Carol F. Lippa, MD; and Ian McKeith, MD



Fluttuazioni Cognitive



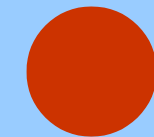
LBD

Ci



sono

nella



PDD?

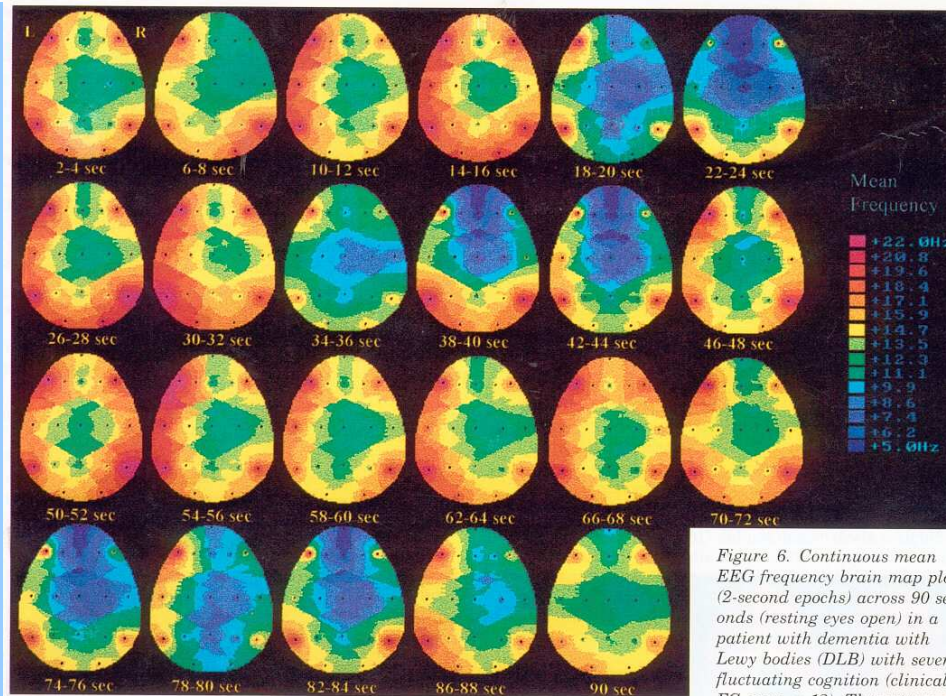
Allucinazioni – Psicosi – Ipersensibilità ai Neurolettici

Cognitive Fluctuations in AD – LBD – VaD

NEUROLOGY 2000;54:1616–1624

Quantifying fluctuation in dementia with Lewy bodies, Alzheimer's disease, and vascular dementia

M.P. Walker, PhD; G.A. Ayre, PhD; J.L. Cummings, MD; K. Wesnes, PhD; I.G. McKeith, MD;
J.T. O'Brien, DM; and C.G. Ballard, MD

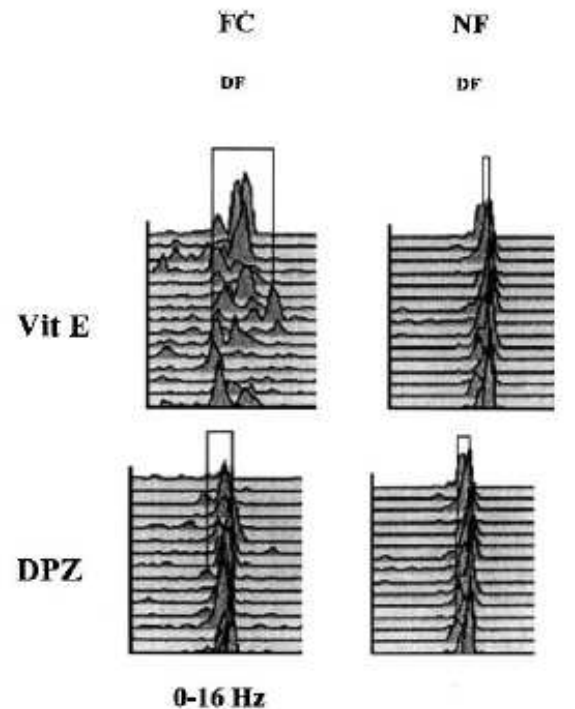


Abnormality of
electrocortical arousal

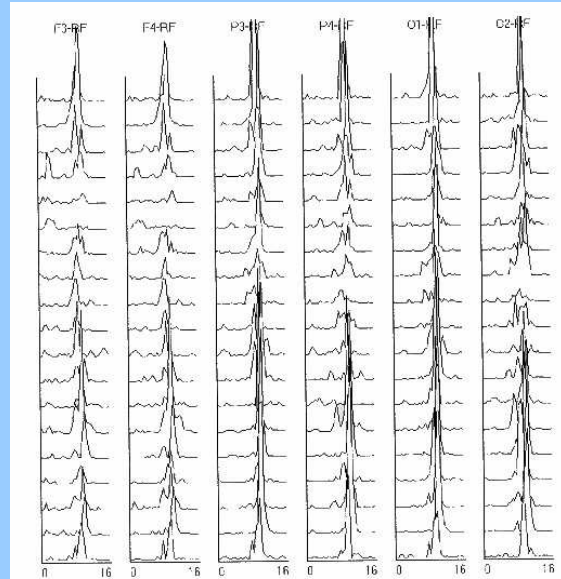
The Effects of a Cholinesterase Inhibitor Are Prominent in Patients With Fluctuating Cognition: A Part 3 Study of the Main Mechanism of Cholinesterase Inhibitors in Dementia

*Marco Onofrj, *Astrid Thomas, *Diego Iacono, *Anna Lisa Luciano, and †Angelo Di Iorio

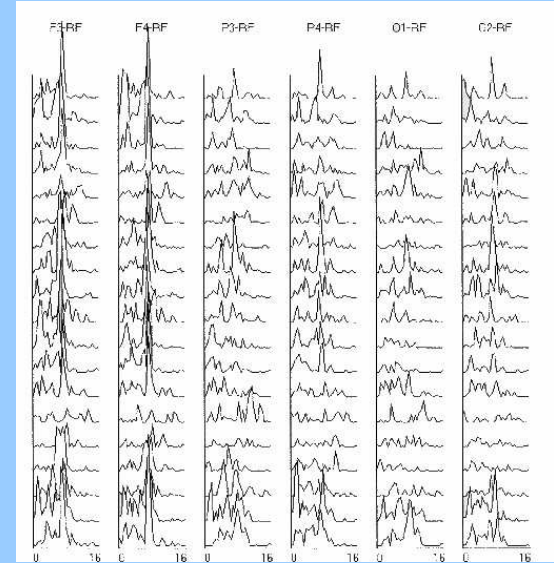
**Department of Oncology and Neuroscience, Institute of Neurophysiopathology, †Department of Medicine and Ageing, Geriatric Unit, University "G.D'Annunzio," Italy*



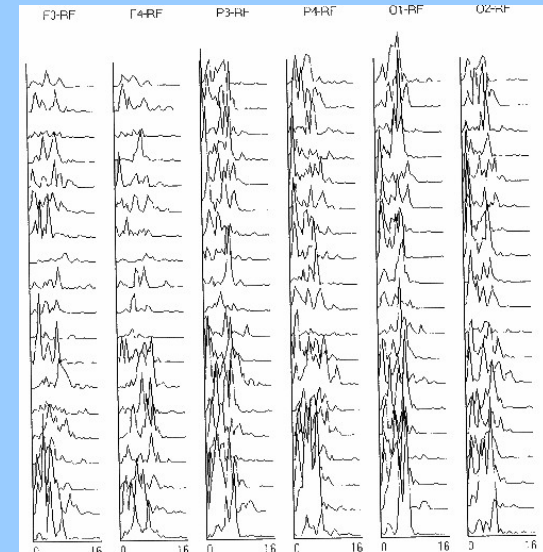
PDD AD type



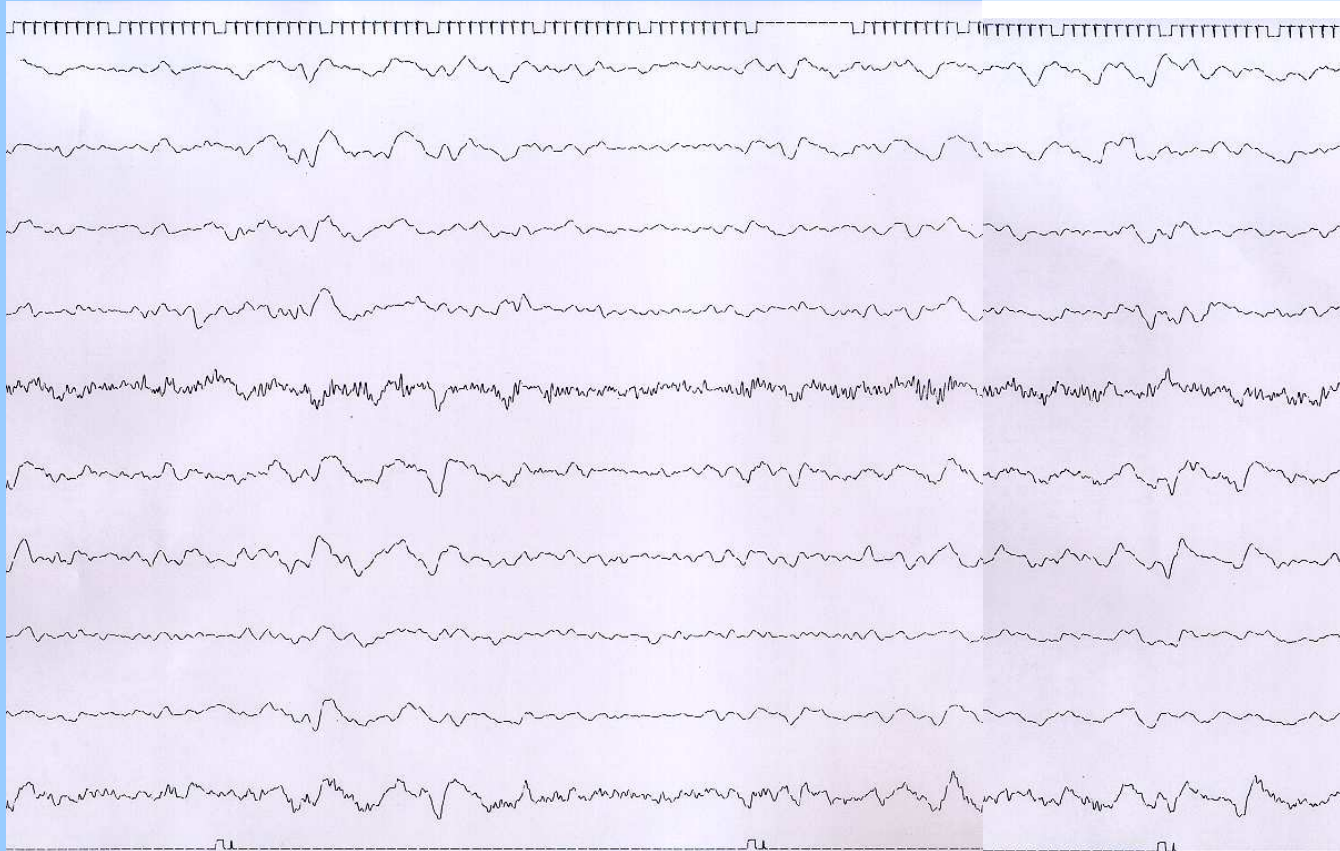
PDD LBD-type

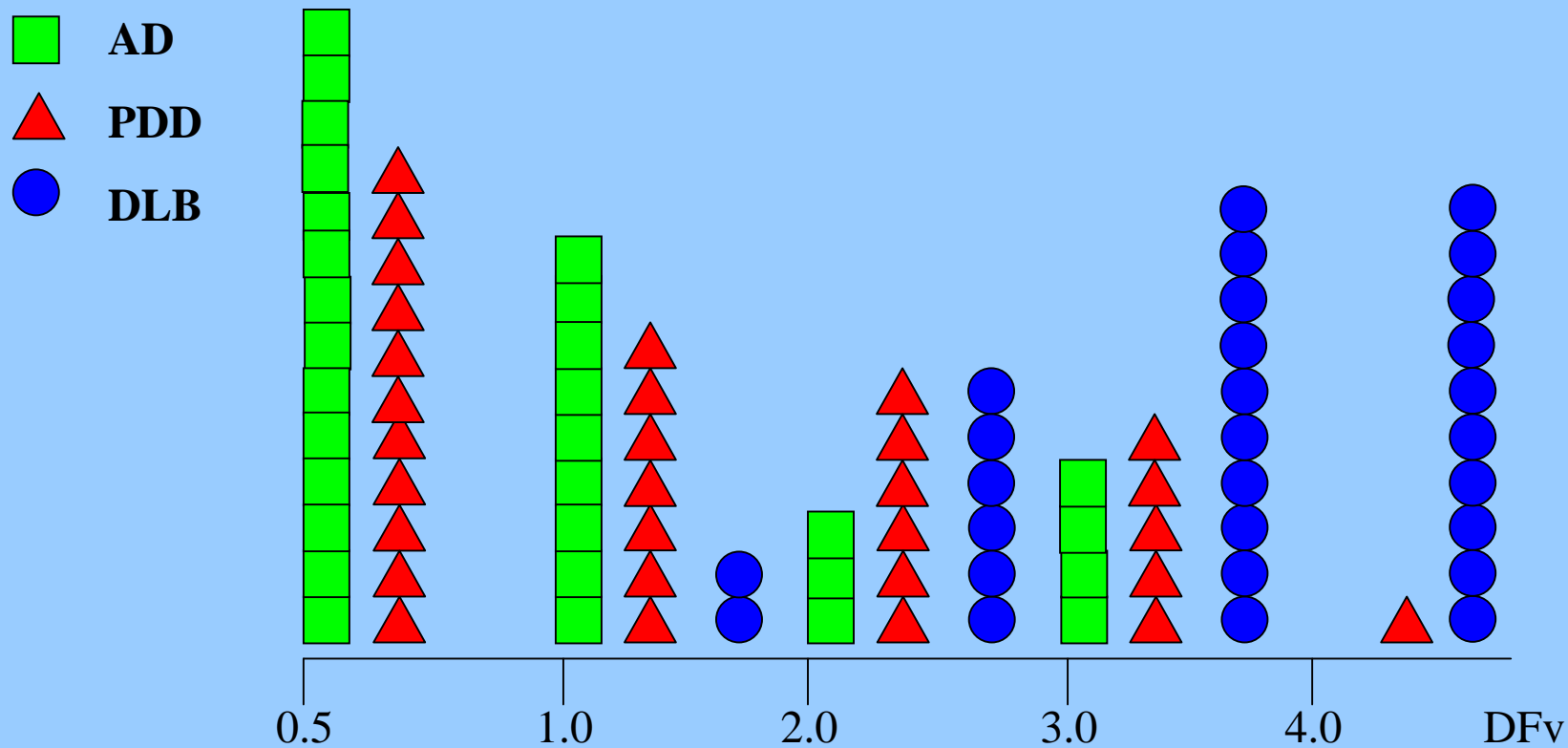


Severe-PPD LBD-type



EEG





- If cut-offs are based on LBD features only 46% of PDD have features of LBD
- In this group cluster highest NPI, CAF scores, RBD positive patients

Registrazione polisonnografica di un paziente con RBD

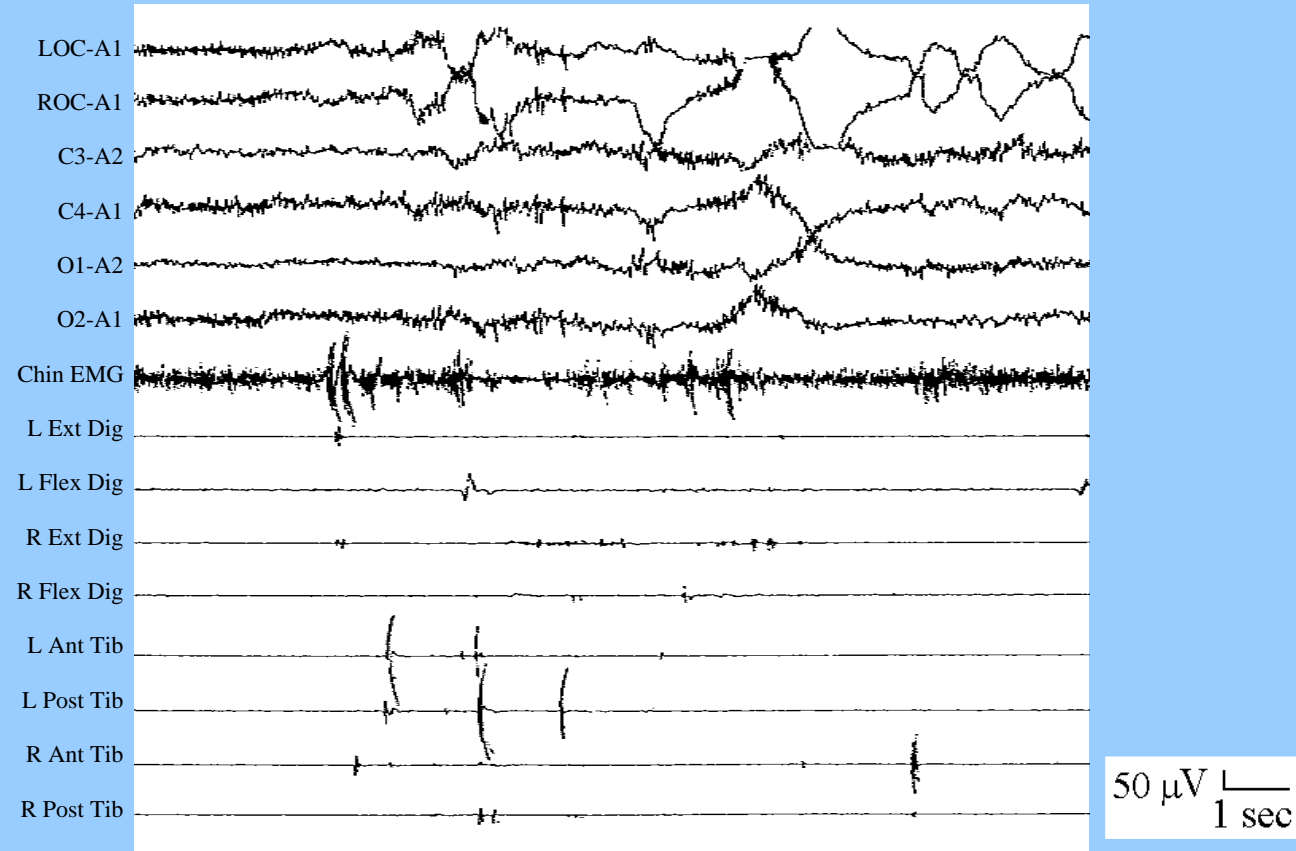


FIG. *La polisonnografia mostra la presenza di attività in diversi distretti muscolari (in particolare a livello degli arti inferiori) durante la fase REM del sonno in un soggetto con Malattia di Parkinson Idiopatica ed RBD*

Comella CL, Tanner CM, Ristanovic RK. **Polysomnographic sleep measures in Parkinson's Disease patients with treatment induced hallucinations.** *Ann Neurol* 1993;34:710-714

Schenk CH, Scott RB, Mahowald MW. **Delayed emergence of parkinsonian disorder in 38% of older men initially diagnosed with idiopathic rapid eye movement sleep behavior disorder.** *Neurology* 1996;46:388-393

Plazzi G, Corsini R, Provini F, Pierangeli G, Martinelli P, Montagna P, Lugaresi E, Cortelli P. **REM sleep behavior disorders in multiple system atrophy.** *Neurology* 1997;48:1094-1097

Comella CL, Nardine TM, Diederich NJ, Stebbins GT. **Sleep-related violence, injury and REM sleep behaviour disorder in Parkinson's Disease.** *Neurology* 1998;51:526-529.

Boeve BF, Silber MH, Ferman TJ, Kokmen E, Smith GE, Ivnik RJ, Parisi JE, Olson EJ, Petersen RC. **REM sleep behavior disorder and degenerative dementia.** *Neurology* 1998;51:363-370

Boeve BF, Silber MH, Ferman TJ, Kokmen E, Smith GE, Ivnik RJ, Parisi JE, Olson EJ, Petersen RC. **REM sleep behavior disorder and degenerative dementia: an association likely reflecting Lewy body disease.** *Neurology*. 1998 Aug;51(2):363-70.

Olson EJ, Boeve BF, Silber MH. **Rapid eye movement sleep behaviour disorder: demographic, clinical and laboratory findings in 93 cases.** *Brain*. 2000 Feb;123 (Pt 2):331-9.

Boeve BF, Silber MH, Ferman TJ, Lucas JA, Parisi JE. **Association of REM sleep behavior disorder and neurodegenerative disease may reflect an underlying synucleinopathy.** *Mov Disord*. 2001 Jul;16(4):622-30.

Ferman TJ, Boeve BF, Smith GE, Silber MH, Lucas JA, Graff-Radford NR, Dickson DW, Parisi JE, Petersen RC, Ivnik RJ. **Dementia with Lewy bodies may present as dementia and REM sleep behavior disorder without parkinsonism or hallucinations.** *J Int Neuropsychol Soc*. 2002 Nov;8(7):907-14.

REM sleep behavior disorder and dementia

Cognitive differences when compared with AD

T.J. Ferman, PhD, B.F. Boeve, MD, G.E. Smith, PhD, M.H. Silber, MB, ChB, E. Kokmen, MD, R.C. Petersen, MD, and R.J. Ivnik, PhD

Article abstract—Objective: To determine whether the dementia associated with REM sleep behavior disorder (RBD) differs from Alzheimer's disease (AD) and, if so, whether differences in cognitive performance between RBD/dementia and AD resemble reported differences between dementia with Lewy bodies (DLB) and AD. **Methods:** This retrospective study compares neurocognitive performance between 51 patients with degenerative dementia and polysomnography-confirmed RBD and 51 patients without brainstem/Lewy body pathology who met Consortium to Establish a Registry for Alzheimer's Disease (CERAD) clinical and neuropathologic criteria for AD. The patient groups did not differ in dementia severity (based on Global Deterioration Scale score) or duration. **Results:** RBD preceded or coincided with the onset of cognitive decline in 94% of the patients. All but one patient with RBD/dementia had one or more of the following clinical features of DLB: visual hallucinations, extrapyramidal signs, or fluctuating cognition/alertness. The data revealed significantly worse performance on attention, perceptual organization, visual memory, and letter fluency for the RBD/dementia group, whereas the AD group showed significantly worse performance on confrontation naming and verbal memory. **Conclusions:** Patients with RBD and degenerative dementia demonstrate a significantly different pattern of cognitive performance from patients with AD. Most of the patients in the RBD/dementia sample also meet criteria for possible or probable DLB, and the pattern of cognitive differences from AD is similar to reported comparisons between DLB and AD. The cognitive and clinical data provide evidence to suggest that the dementia associated with RBD may represent DLB.

NEUROLOGY 1996;52:561-567

Synucleinopathy pathology and REM sleep behavior disorder plus dementia or parkinsonism

B.F. Boeve, MD, M.H. Silber, MBChB, J.E. Parisi, MD, D.W. Dickson, MD, T.J. Ferman, PhD, E.E. Benarroch, MD, A.M. Schulz, PhD, G.E. Smith, PhD, R.C. Petersen, PhD, M.D., J.E. Ahlskog, PhD, MD, J.Y. Matsumoto, MD, D.S. Knopman, MD, C.H. Schenk, MD, and M.W. Mahowald, MD

Abstract—Objective: To determine if synucleinopathy pathology is related to REM sleep behavior disorder (RBD) plus dementia or parkinsonism. **Methods:** The clinical and neuropathologic findings were analyzed on all autopsied cases evaluated at Mayo Clinic Rochester from January 1990 to April 2003 who were diagnosed with RBD and a neurodegenerative disorder. Ubiquitin and/or α -synuclein immunocytochemistry was used in all cases. The clinical and neuropathologic diagnoses were based on published criteria. **Results:** Fifteen cases were identified (14 men). All had clear histories of dream enactment behavior, and 10 had RBD confirmed by polysomnography. RBD preceded dementia or parkinsonism in 10 (66.7%) patients by a median of 10 (range 2 to 29) years. The clinical diagnoses included dementia with Lewy bodies (DLB) (n = 6); multiple-system atrophy (MSA) (n = 2); combined DLB, AD, and vascular dementia (n = 1); dementia (n = 1); dementia with parkinsonism (n = 1); PD (n = 1); PD with dementia (n = 1); dementia/parkinsonism/rastor neuron disease (n = 1); and AD/Binswanger's disease (n = 1). The neuropathologic diagnoses were Lewy body disease (LBD) in 12 (neocortical in 11 and limbic in 1) and MSA in 3. Three also had argyophilic grain pathology. In the LBD cases, concomitant AD pathology was present in six (one also with Binswanger's pathology, and one also with multiple subcortical infarcts). **Conclusion:** In the setting of degenerative dementia or parkinsonism, RBD often reflects an underlying synucleinopathy.

NEUROLOGY 2003;61:40-45

Mirtazapine induces REM sleep behavior disorder (RBD) in parkinsonism

M. Onofri, MD; A.L. Luciano, MD; A. Thomas, MD, PhD; D. Iacono, MD, PhD; and G. D'Andreamatteo, MD

Correspondence

Mirtazapine induces REM sleep behavior disorder (RBD) in parkinsonism

To the Editor: We read with interest the report of Onofri et al.¹ linking REM sleep behavior disorder (RBD) to the antagonist action of mirtazapine at $\alpha 2$ -adrenoceptors. We describe a case of confirmed RBD responding to the $\alpha 2$ -adrenoceptor agonist clonidine that supports the role of these receptors in the pathology of this disorder.

A healthy 85-year-old man with no history of neurologic disorder had for 18 years suffered sleep disruption with episodes of violent behavior and accompanying dream imagery. Our clinical diagnosis of RBD was confirmed by polysomnography. He had found little benefit from prior treatments including amitriptyline, nefazodone, vortioxetine, trazodone, clonazepam and zopiclone. We prescribed clonidine, as this drug is known to reduce REM sleep time, increase sleep continuity and reduce phasic EMG activity during REM sleep in healthy volunteers.²³ The episodes of violence were immediately reduced and sleep quality improved. Although the effects diminished after 2 weeks, they returned following a drug holiday, and we instituted a treatment plan of clonidine 100 μ g nocte for a week, then 200 μ g nocte for a week, and then a week without clonidine. The benefits have been sustained for several months and this regime has been preferable to all others tried.

RBD may be caused either by disruption of the process preventing REM atonia or by excessive locomotor drive during REM sleep. Animal studies implicate pontine and medullary structures in the maintenance of REM atonia. Active inhibition of motor activity is mediated by centers in the peri-locus caeruleus region via the nucleus reticularis magnocellularis in the medulla, leading to hyperpolarization of spinal motor neurons. A condition similar to RBD was produced in rats by bilateral puzosine tegmental section.⁴ Loss of noradrenergic brainstem nuclei was found at post mortem examination of a human case of RBD.⁵ The association of RBD with neurodegenerative disorders such as Progressive Supranuclear Palsy and Multiple System Atrophy suggests that the disorder could be caused by destruction or functional depression of the peri-locus caeruleus nuclei.

Clonidine is a relatively selective partial agonist at central and peripheral $\alpha 2$ -adrenoceptors. This receptor is chiefly found at presynaptic sites on noradrenaline-releasing neurones, and stimulation inhibits noradrenaline release, leading to reduced arousal and improved sleep continuity. We suggest that clonidine has a direct effect on the maintenance of REM atonia via noradrenergic transmission. Our findings, taken with those of Onofri,¹ strengthen the theory that central $\alpha 2$ -adrenoceptors are involved in the pathogenesis of RBD.

Jon E. Nash, MD, Sus J. Wilson, PhD, John P. Peitkar, MD, David J. Nutt, MD, Bristol, UK

Reply from the Authors: We thank Nash et al. for their comments. The suggestion that the partial $\alpha 2$ -adrenoceptor agonist clonidine might reduce RBD has important therapeutic implications. We are already testing the effect of clonidine in three patients with RBD with episodes of violent behavior during dream imagery who had transient Parkinson's symptoms only when typical neuroleptics were administered. These patients and the one described by Nash et al. are similar to those in a report of pure

RBD disorder without parkinsonism or dementia with Lewy bodies at autopsy.⁶

We also note that presynaptic $\alpha 2$ adrenoceptor antagonist activity, disinhibiting noradrenergic neurotransmission, is present for molecules other than the antidepressant mirtazapine, including the atypical antipsychotics clozapine,⁷ the antiparkinsonian piribedil,⁸ and the analgesic tramadol.⁹

In our first patient, we noted that episodes interpretable as RBD-onirid confusion were precipitated by the IV administration of tramadol, a drug used in post-surgical analgesia that has $\alpha 2$ -adrenoceptor antagonist and serotonin reuptake inhibitor properties⁹ like mirtazapine. Tramadol should be tested for its effect on REM sleep and RBD in patients, or in experimental settings, in order to further assess the role of $\alpha 2$ -adrenoceptors.

Even though we believe that studies of the effect of drugs on REM sleep and RBD are promising, the induction of RBD by drugs poses more questions than answers, and is difficult to explain using REM models.¹⁰ This model includes double inhibitory and facilitatory action of cholinergic transmission on the mesopontine tegmentum and inhibitory action of noradrenergic transmission on the peri-locus caeruleus nucleus.

The induction of RBD by anticholinergic drugs in our view does not fit with earlier models focused on pedunculopontine cholinergic activity, as anticholinergic drugs should reduce rather than induce RBD.

We look forward to new explanations and suggest that the effect of the long or short half-life cholinesterase inhibitors on REM sleep and confusional states be investigated.

Marco Onofri, MD, Astrid Thomas, MD, Palermo, Italy

Copyright © 2003 by AAN Enterprises, Inc.

References

1. Onofri M, Luciano AL, Thomas A, Iacono D, D'Andreamatteo G. Mirtazapine induces REM sleep behavior disorder (RBD) in parkinsonism. *Neurology* 2003;60:110-112.
2. Anttilä A, Miettinen M, Hellenäs T, Oksala HP, Schmitt H. Effect of clonidine on sleep patterns in man. *Eur J Clin Pharmacol* 1977;12:319-322.
3. Gerthi A, Godschalk MF, Gheorgiu D, Nelson K, Julius DA, Mulligan T. Effect of clonidine and reboxetine on sleep in healthy man: a double-blind, randomized, controlled trial. *Eur J Clin Pharmacol* 1996;50:463-465.
4. Hendrichs JC, Morrison AR, Meiss GL. Different behaviors during paradoxical sleep without atonia depend on pontine locus sites. *Brain Res* 1982;252:1-105.
5. Turner EH, Damsis CJ, Charvin ED, Hobbs M. The pathology of REM sleep behavior disorder with comorbid Lewy body dementia. *Neurology* 2003;61:1714-1718.
6. Uchiyama M, Iseki K, Tanaka K, et al. Incidental Lewy body disease in a patient with REM sleep behavior disorder. *Neurology* 2003;61:709-712.
7. Kulkarni HO, Lovelace E. $\alpha 2$ -Adrenoceptor blockade by clozapine and other antipsychotic drugs. *Eur J Pharmacol* 2002;442:35-40.
8. Gobert A, Di Ciano P, Cistarelli L, Miles MJ, Piribedil enhance frontocortical and hippocampal release of acetylcholine in freely moving rats by blockade of alpha 2-adrenoceptors: a dialysis comparison to haloperidol and quipazine in the absence of acetylcholinesterase inhibitor. *J Pharmacol Exp Ther* 2002;305:338-346.
9. Leo CH, McTavish D, Serkin EM. Tramadol. Preliminary review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential in acute and chronic pain states. *Drugs* 1999;163:310-340.
10. Puro-Scott EP, Hobson A. The biology of sleep: genetics, cellular physiology and subcortical networks. *Nature Reviews Rev* 2002;3:5291-535.

Abstract—Shortly after initiation of mirtazapine (a noradrenergic and serotonergic antidepressant) treatment in four patients with parkinsonism, the authors observed the appearance of REM sleep behavior disorder (RBD). In the two patients with severe motor symptoms, RBD was accompanied by hallucinations and confusion. These disturbances resolved with drug discontinuation, and remained resolved by 12- to 24-month follow-up, suggesting that RBD can be triggered by a drug lacking anticholinergic activity.

NEUROLOGY 2003;60:110-112

Incidence of RBD and hallucination in patients affected by Parkinson's disease: 8-

year follow-up. Onofri M, Thomas A, D'Andreamatteo G, Iacono D, Luciano AL, Di Rollo A, Di Mascio R, Ballone E, Di Iorio A. *Neurol Sci*. 2002 Sep;23 Suppl 2:S91-4.

Movement Disorders
Vol. 18, No. 3, 2003, pp. 337-349
© 2002 Movement Disorder Society

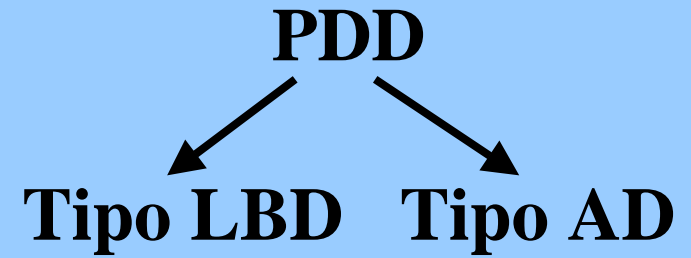
Clinical/Scientific Notes

HLA Typing Does Not Predict REM Sleep Behaviour Disorder and Hallucinations in Parkinson's Disease

Marco Onofri, MD,^{1*} Anna Lisa Luciano, MD,¹ Diego Iacono, MD, PhD,¹ Astrid Thomas, MD, PhD,¹ Fabrizio Stocchi, MD,¹ Franco Papola, PhD,² Domenico Adorno, MD,² and Rocco Di Mascio, MD, PhD³

Prevalenza di LBD in Demenza

25-34% vs NIL < 1%



Operating Definition

Consensus:



+

Visual hallucinations

Neuroleptic sensitivity

Parkinsonism < 2 years

RBD

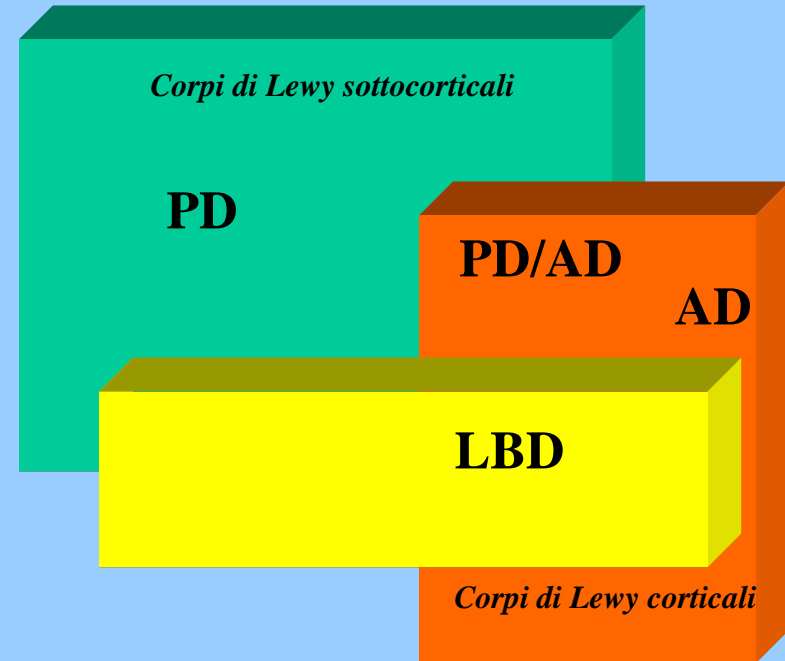
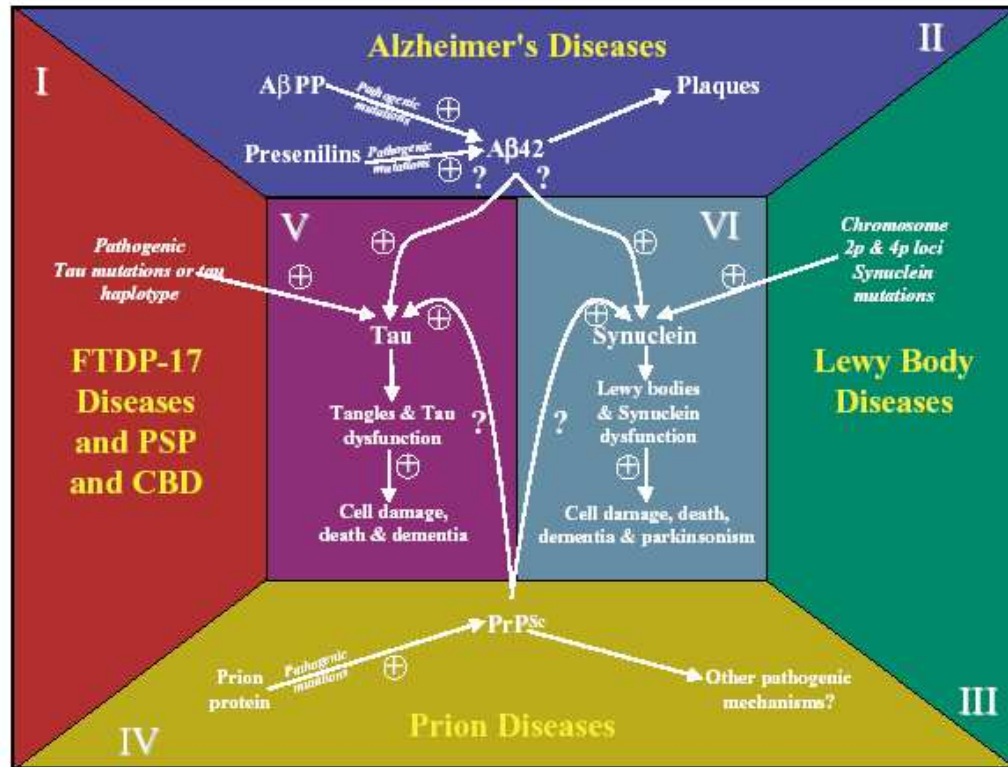
Cognitive Fluctuations

Clinical CAF- ODFAS

EEG - QEEG

Adapted from: Hardy J. Homologies between the genetic etiology and pathogenesis of synucleinopathies and Taupathies. *Mental and Behavioural Dysfunction in Movement Disorders*. 2003,255- 258

Adapted from: Grabowski TJ and Damasio AR, 1998



TERAPIA

L'ipotesi colinergica:

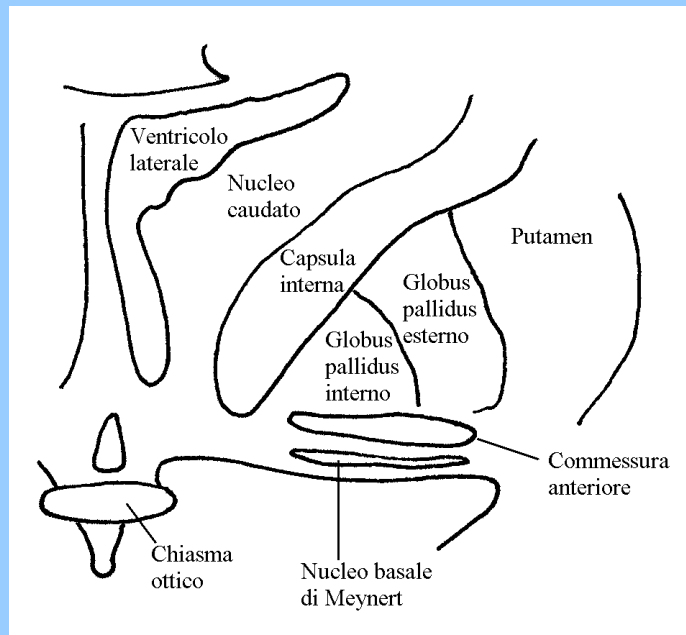
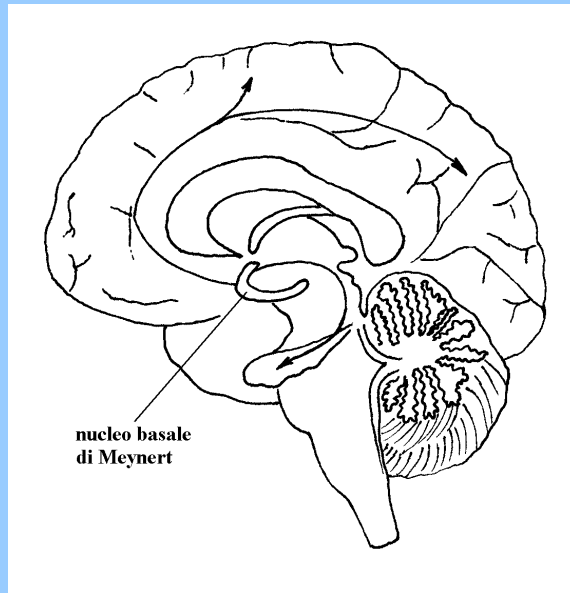
Maclean et al Int Psychogeriat	2001 – LBD
McKeith et al: Int J Geriat Psy	2000 - LBD
Lancet	2000 - LBD
Reading et al Mov Disord	2001 - PD

ma

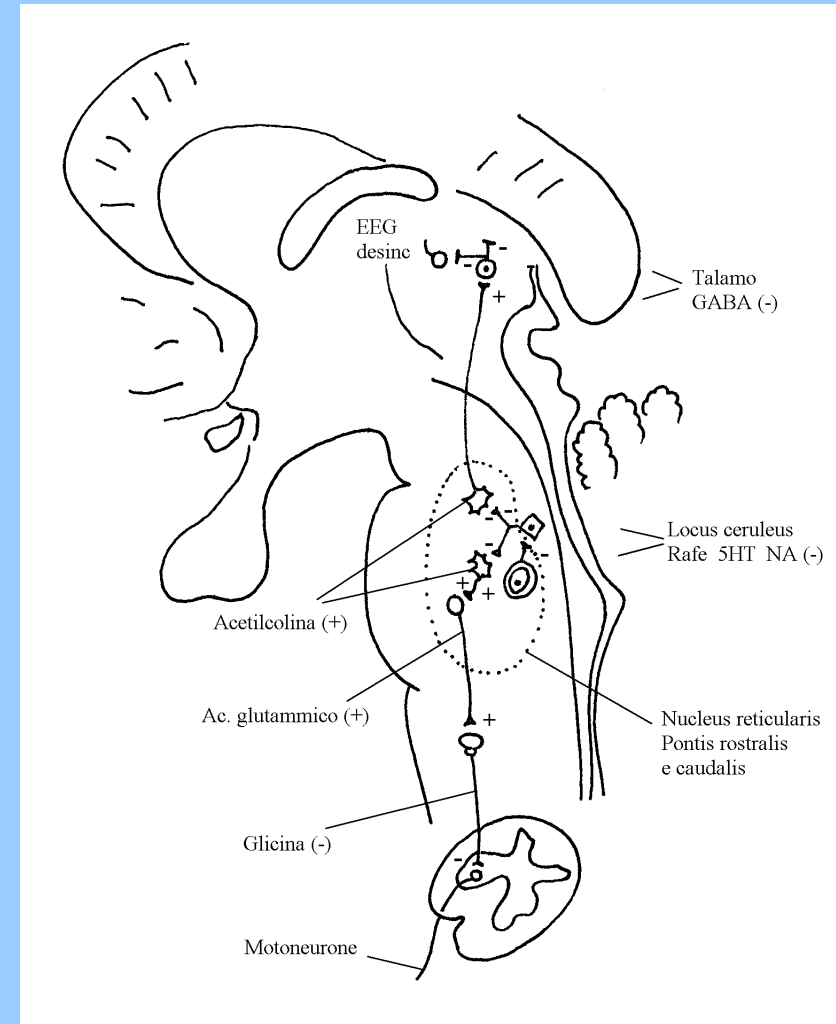
Agitazione, confusione, allucinazioni, psicosi

Rivastigmina	5%
Eptastigmina	15 %
Donepezil	9%
Galantamina	8%

Vie colinergiche e Nucleo basale di Meynert



Via colinergica pontina



Aricept® Global Advisory Board
6 – 8 November 2003
The Grand Hotel Timeo and Villa Flora
Taormina, Italy

Advisors

Professor Sube Banerjee

The David Goldberg Centre
PO 26, Health Services Research
De Crespigny Park, Denmark Hill
London, United Kingdom SE58AF
Ph: 44 0 20 7836 5454
Fax: 44 0 20 7848 0012
spjussb@top.kcl.ac.uk

Dr. Howard Chertkow

McGill University
Room 408, Lady David Institute
8755 Chemin de la Cote, St. Catherine
Montreal, Quebec Canada H3T1E2
Ph: 514 340 8260 ext. 5116
Fax: 514 340 8295
howard.chertkow@mcgill.ca

Professor Murat Emre

Istanbul Faculty of Medicine
Department of Neurology
Capa
Istanbul, Turkey 34390
Ph: 90 212 533 8575
muratemre@superonline.com

Dr. Howard Feldman

University of British Columbia
Division of Neurology
Room S-192 2211 Wesbrook Mall
Vancouver, B.C. Canada V6T 2B5
Ph: 604 822 7697
Fax: 604 822 7703
hfeldman@interchange.ubc.ca

Professor Hans Förstl

Klinikum rechts der Isar
Department of Psychiatry
Ismaninger Str. 22
Munich, Germany 81675
Ph: 49 89 4140 4200
Fax: 49 89 4140 4837
hans.foerstl@lrz.tum.de

Professor Harald Hampel

Ludwig-Maximilian University
Department D2
Nussbaumstr. 7
Munich, Germany 80336
Ph: 49 89 5160 5877
Fax: 49 89 5160 5856
hampel@psy.med.uni-muenchen.de

Dr. Peter Johannsen

Viborg Hospital
Department of Neurology, N09
Heibergs Alle 4
Viborg, Denmark DK 8800
Ph: 45 8927 2391
Fax: 45 8927 3469
peterj@dadlnet.dk

Dr. Secundino Lopez-Pousa

Hospital Santa Caterina
Plaza Hospital 5
Girona, Spain 17002
Ph: 34 972 18 25 95
uvamid@ias.scs.es

Professor Marco Onofri

Universita G. D'Annunzio
Chieti-Pescara
Ospedale Civile Via Fonte Romana
Pescara, Italy 65100
Ph: 39 085 425 2881
Fax: 39 085 34178
onofri@unich.it

Dr. Leonardo Pantoni

University of Florence
Dept. of Neurology & Psychiatric
Sciences
Viale Morgagni 85
Florence, Italy 50134
Ph: 39 055 4277 995
Fax: 39 055 4298 461
pantoni@neuro.unifi.it

Dr. Norman Relkin

Weill Medical College
Cornell University
428 E. 72nd Street
Suite 500
New York, NY United States 10021
Ph: 212 746 2441
Fax: 212 746 5584
nrelkin@med.cornell.edu

Professor Andrzej Szczudlik

Jagiellonian University
Institute of Neurology
3 Botaniczna Str.
Krakow, Poland 31503
Ph: 48 12 421 4069
szczudlik@neuro-cm-uj.krakow.pl

Professor Bruno Vellas

Hospital de Toulouse
Dept. of Internal and
Geriatric Medicine
170 Avenue de Casselardit
Toulouse, France 31300
Ph: 33 5 61 77 76 49
Fax: 33 5 61 49 71 09
velas.b@chu-toulouse.fr

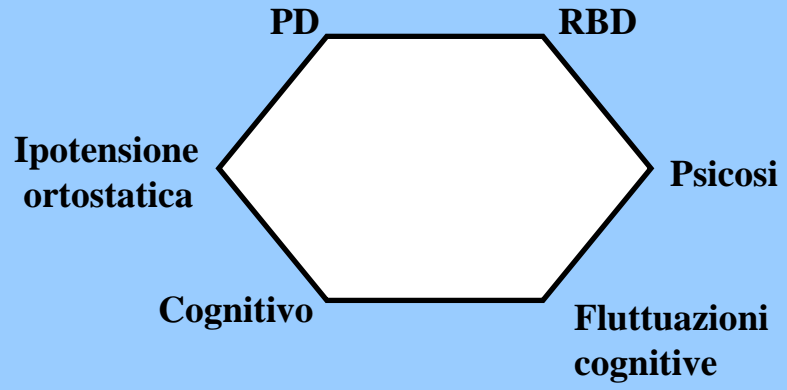
Professor Gunhild Waldemar

Memory Disorders Research
Unit, Section 6702, Rigshospitalet
9 Blegdamsvej
Copenhagen, Denmark DK2100
Ph: 45 354 52580
Fax: 45 354 52446
waldemar@dadlnet.dk

Dr. David Wilkinson

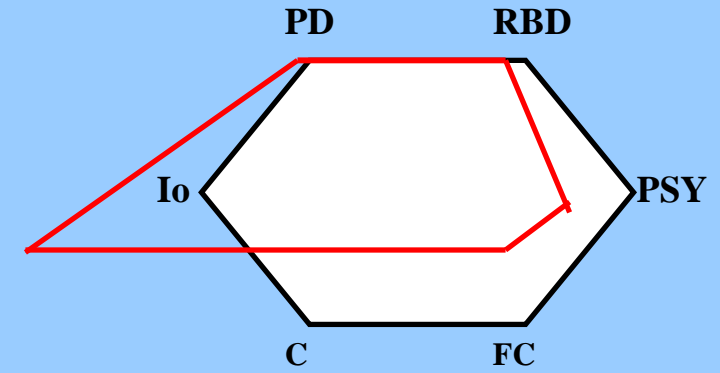
Moorgreen Hospital
Memory Assessment & Research
Botley Road, West End
South Hampton, United Kingdom
SO30 3JB
Ph: 44 2380 475205
Fax: 44 2380 463 022
david.wilkinson@wht.nhs.uk

Inibitori delle Colinesterasi




Terapia o Politerapia Ideale

Ipotesi A



Ipotesi B

