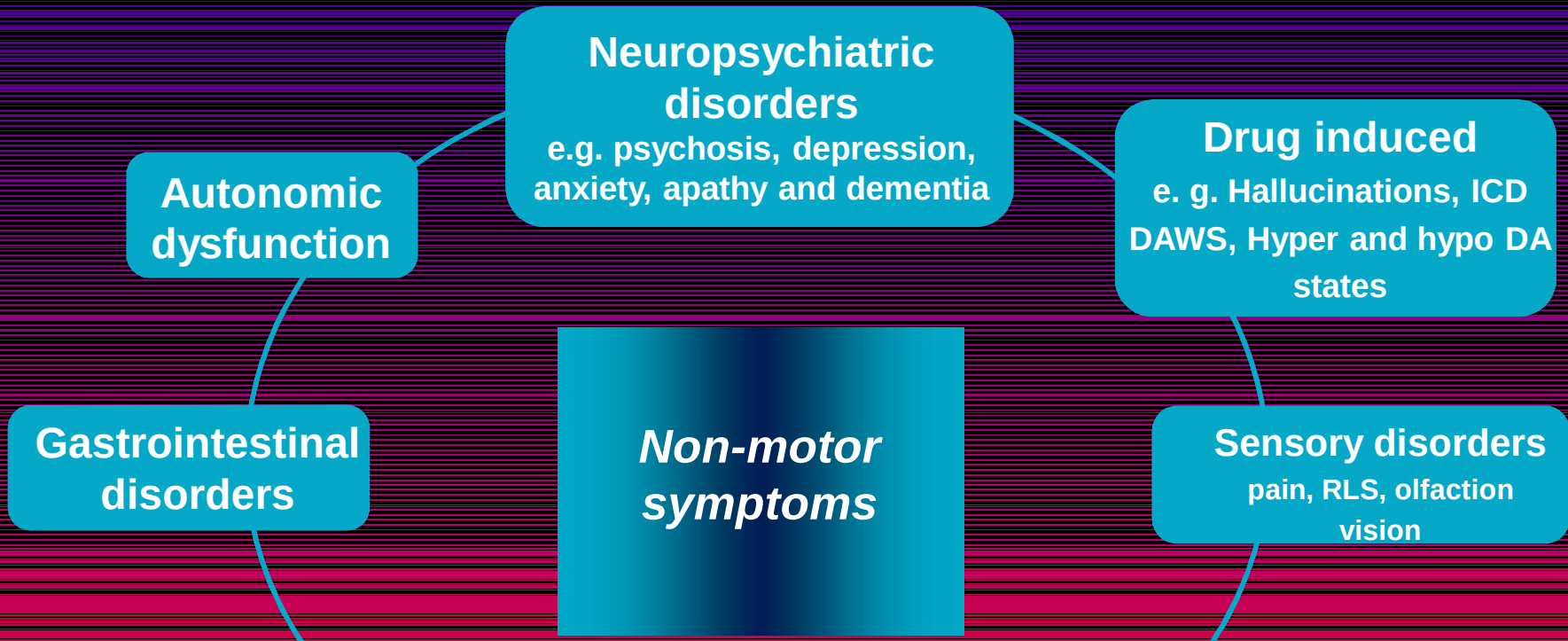
NMS Phenomenology

PD is more than just a motor disorder

Parkinson's disease (PD), one of the most frequent neurodegenerative disorders, is no longer considered a complex motor disorder characterized by extrapyramidal symptoms, but a progressive multisystem or—more correctly—multiorgan disease with variegated neurological and nonmotor deficiencies.

K Jellinger . Mov Disord 2012

Non-motor symptoms of PD cause morbidity, mortality and quadruples cost of care of advanced Parkinson's and are common across all stages of PD



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Chaudhuri et al. Lancet Neurology 2006;5:235-245
Chaudhuri, Tolosa, Schapira, Poewe. NMS in PD. Oxford University Press. 2010

A description of the range of Non-motor symptoms in PD
Sauerbier and Chaudhuri. BJHM 2013 In Press

Cognitive and Neuropsychiatric symptoms	**Related to PD Pathophysiology**	**Related to drug therapy**	**Contribution from both**
Cognitive impairment (ranging from mild cognitive impairment to frank Dementia)	**++**	**-**	**-**
Anxiety	**+/-**	**++**	**+**
Major Depression	**++**	**+/-**	**+/-**
Apathy	**++**	**-**	**-**
Delirium	**+/-**	**++**	**+/-**
Hallucinations, delusions, illusions	**+**	**++**	**+**
Panic attacks (could be “off” period related)	**+**	**++**	**+**
Sleep disorders and dysfunctions			
Excessive daytime somnolence, sudden onset of sleep (narcolepsy without cataplexy)	**++**	**++**	**++**
Insomnia (onset and maintenance)	**++**	**+**	**+**
Non-REM parasomnias (confusional wandering sleep talking)	**++**	**-**	**-**
REM sleep behavior disorder	**++**	**-**	**-**
Restless legs syndrome	**+**	**+**	**+**
Periodic leg movements	**+**	**+**	**+**
Sleep disordered breathing	**++**	**-**	**-**

++ = strong contribuition, - = no contribution likely, ± = uncertain contribution

A description of the range of Non-motor symptoms in PD

Autonomic Dysfunction			
Bladder urgency, frequency, nocturia	**++**	**+/-**	**+/-**
Orthostatic hypotension	**++**	**+**	**++**
Post-prandial hypotension	**++**	**+/-**	**+/-**
Sexual dysfunction	**++ (?Ç**	**++(?Ç**	**++**
Erectile dysfunction	**+**	**-**	**-**
Thermoregulatory abnormalities (Hyperhidrosis)	**++**	**+**	**+**
Gastrointestinal symptoms			
Dribbling of saliva	**++**	**+/-**	**+/-**
Dysphagia	**++**	**+/-**	**+/-**
Ageusia (change in taste sensation)	**++**	**+/-**	**+/-**
Constipation	**++**	**+/-**	**+/-**
Fecal incontinence	**++**	**+/-**	**+/-**
Nausea	**+/-**	**++**	**+/-**
Reflux	**+/-**	**++**	**+/-**
Vomiting	**+/-**	**++**	**+/-**
Other NMS			
Central fatigue	**++**	**+/-**	**+/-**
Functional anosmia/ Hypoamia	**++**	**-**	**-**
Pain (off period related and central)	**NMF**		
Visual disturbances (blurred vision, transient diplopia), impaired contrast-sensitivity (colour vision)	**++**	**+/-**	**+/-**
Weight gain (could be related to impulse control disorders)	**++**	**+**	**+**
Weight loss	**++**	**+/-**	**+/-**

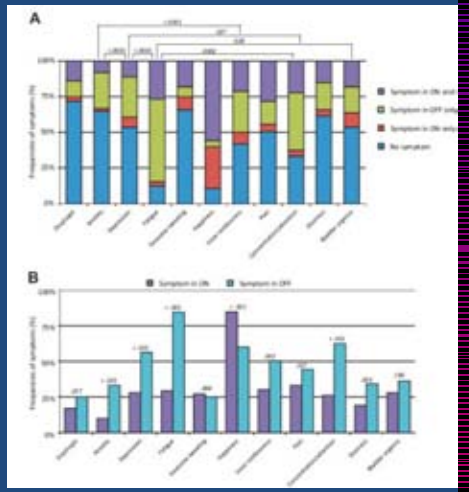
A description of the range of Non-motor symptoms in PD

Dopaminergic drug-induced behavioural NMS
Dopamine dysregulation syndrome (usually linked to levodopa intake associated with obsessional "pill popping")
Impulse control disorders (e.g. compulsive gambling, hypersexuality, binge eating)
Hallucinations, delusions, psychosis
Dopaminergic drug-induced “other” NMS
Ankle swelling
Dopamine agonist withdrawal syndrome (DAWS)
NMS linked to acute parkinsonian emergencies such as Parkinson hyperprexia syndrome
Non-motor fluctuations occurring as a complication of dopaminergic drug therapy
Cognitive/Psychiatric (Depression, Anxiety, Anxious-depressed)
Dysautonomic
Sensory/Pain
Visual blurring

Non Motor Fluctuation in PD

Storch et al Neurology 2013

- NM symptoms shown to be worse during off periods:
- Fatigue (p=0.001)
- Depression (p=0.001)
- Anxiety (p=0.001)
- Inner restlessness (p=0.002)
- Concentration/attention (p=0.001)
- NM symptoms declared only/exclusively during off periods:
- Fatigue
- Depression
- Anxiety
- Lack of concentration
- Inner restlessness



- Anxiety, depression, fatigue and pain had a negative impact on health related quality of life (Storch et al,2013).

NMS in PD

Why ?

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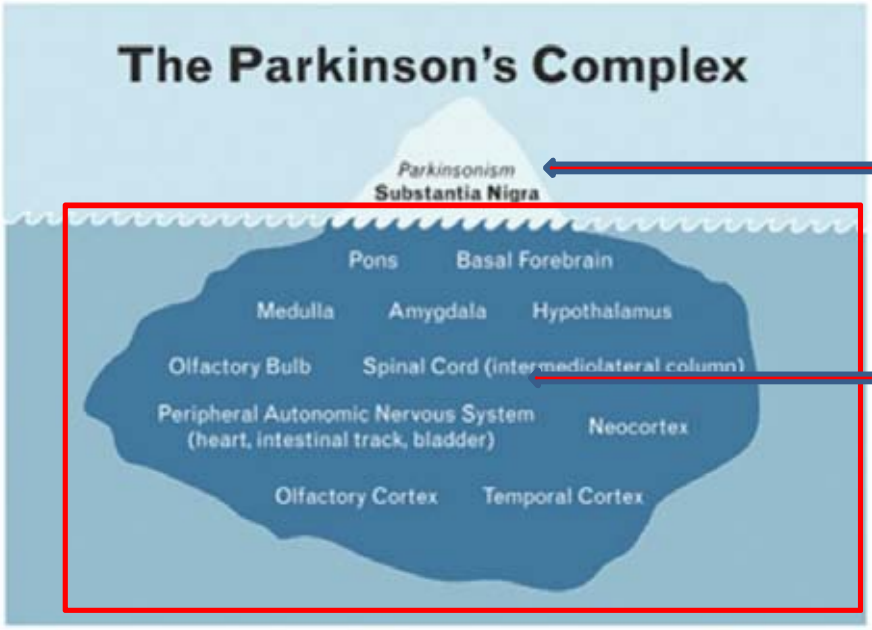
POINTS OF VIEW

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

J. William Langston, MD

Annals of Neurology Vol 59 No 4 April 2006



Motor

Non Motor

Fig 1. Parkinson's disease as typically viewed by both clinicians and researchers (the tip of the iceberg). However, the disease process as measured by neuronal degeneration and Lewy body and neuritic pathology is widespread in the central and peripheral nervous systems (the body of the iceberg). There is increasing recognition that many of these nonnigral sites also produce clinical signs and symptoms.

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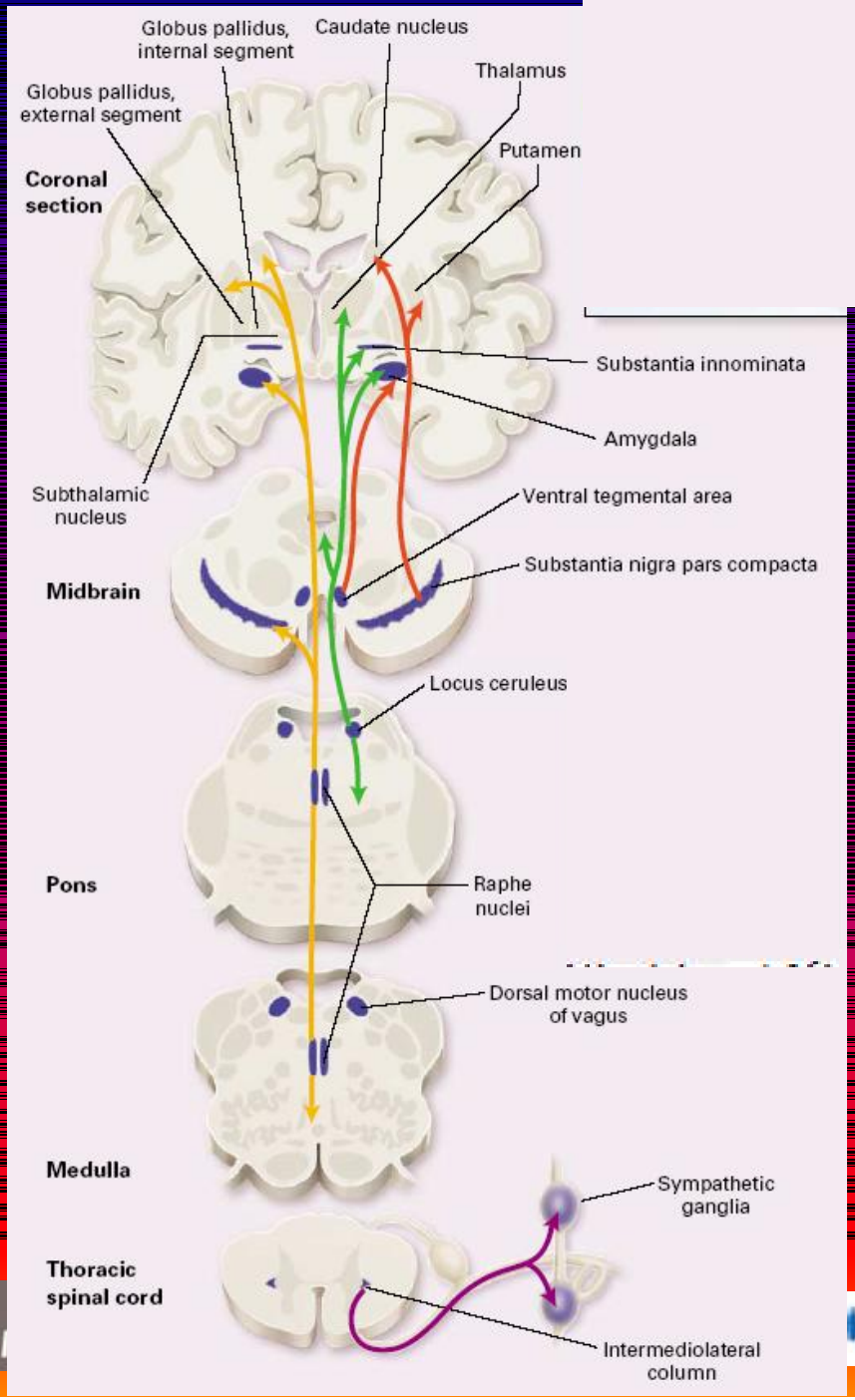

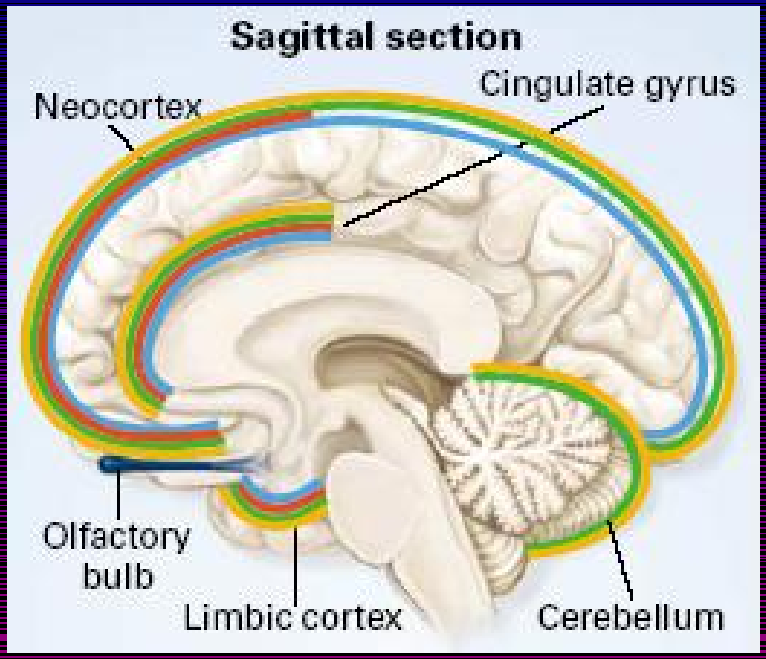

Sites of neurodegeneration

Neurochemical pathways

- Dopamine
- Norepinephrine
- Serotonin
- Acetylcholine

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VIEWPOINT

Toward a Redefinition of Parkinson's Disease

Matthew B. Stern, MD,[1*] Anthony Lang, MD,[2] and Werner Poewe, MD[3]

Movement Disorders, Vol. 27, No. 1, 2012

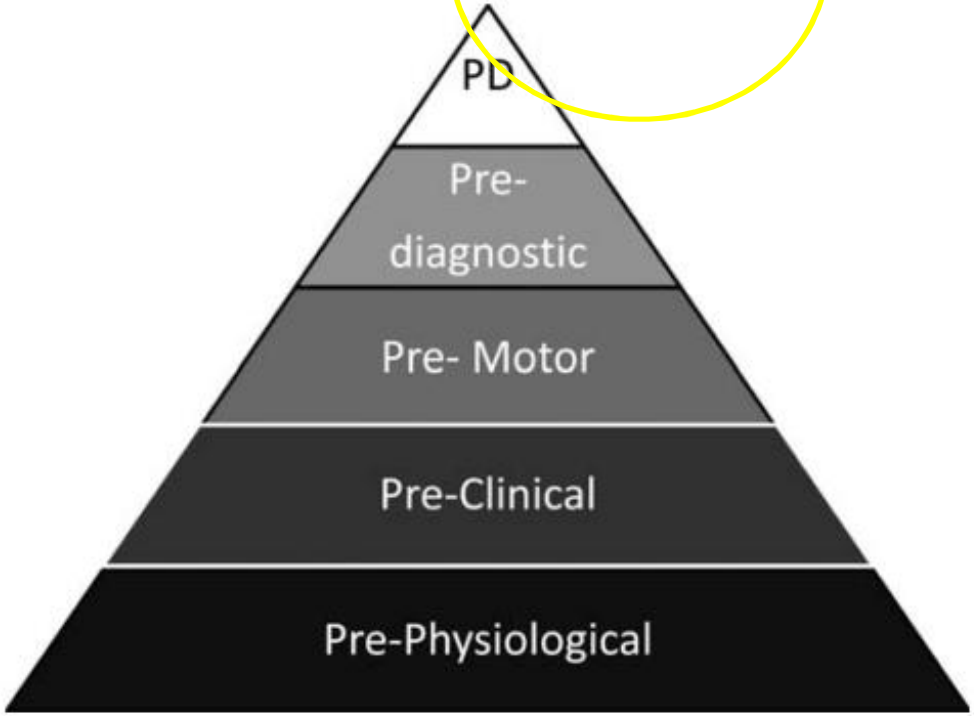
PHASE 1	PRECLINICAL PD	PD-specific pathology assumed to be present, supported by molecular or imaging markers, no clinical signs and symptoms
PHASE 2	PREMOTOR PD	Presence of early non-motor signs and symptoms due to extranigral PD pathology
PHASE 3	MOTOR PD	PD pathology involves substantia nigra leading to nigrostriatal dopamine deficiency sufficient to cause classic motor manifestations followed by later nonmotor features due to extention of the pathology

Premotor Parkinson's Disease: Concepts and Definitions

Andrew Siderowf, MD, MSCE[1]* and Anthony E. Lang, MD[2]

[1]Parkinson's Disease and Mov Disord. Center, Department of Neurology, University of Pennsylvania, Philadelphia, Pennsylvania, USA
[2]Moverment Disorders Center and the Edmond J. Safra Program in Parkinson's Disease, Toronto Western Hospital and the Department of Medicine, University of Toronto, Toronto, Ontario, Canada

PrePhysiological
Genetic
• Preclínical:
• Premotor:
tic:



Movement Disorders, Vol. 27, No. 5, 2012

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Sauerbier and Chaudhuri. BJHM 2013. In Press; Lang 2012; Korczyn and Gurevitch, 2010; Tolosa and Pont-Sunyer 2011; Chaudhuri et al. 2011

	NMS cited	Relevant findings reported
Commonly associated	Late onset hyposmia	Hyposmia + abnormal DATscan may suggest 50% develop motor PD in 4 years (Siderowf et al, 2012)
	Rapid eye movement sleep behavior disorder	17.7% at 5 years, 40.6%at10 years, 52.4%12years, Risk higher if coupled with abnormal DATscan (Postuma et al, 2009)
	Constipation	18,9/ 10.000 person years in men <1 bowel movements/ day (Abbott et al, 2001)
	Depression	Increased risk of developing PD(Nilsson et al, 2001)
Association described	Excessive daytime sleepiness	3 times excess in the risk of PD in men with EDS versus men without EDS 55.3 versus 17.0/10,000 person-years (Abbott et al, 2005)
	Erectile dysfunction	3.8 times more likely to develop PD (Gao et al, 2007)
	Pain (unilateral and usually in affected limb)	Retrospective studies (Negre-Pages et al, 2008)
	Fatigue	Retrospective studies: -study 1: Fatigue in 48%
		-study 2: Fatigue in 43% (15% worst symptom, 50% premotor)(van Hilten et al, 1993)
	Visual impairment (Contrast sensitivity, Color vision etc.)	Case studies (Diederich et al, 2010)
	Pre morbid personality traits	Retrospective studies (Todes et al, 1985)

- Olfaction ~ 4 years
- Constipation ~ 12 years
- REM SBD/ EDS ~ 12 years

NMS

Epidemiology

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Movement Disorders
Vol. 22, No. 11, 2007, pp. 1623–1629

Prevalence of Nonmotor Symptoms in Parkinson's Disease in an International Setting; Study Using Nonmotor Symptoms Questionnaire in 545 Patients

Pablo Martinez-Martin, PhD, MD,[1] Anthony H.V. Schapira, FRCP, MD, DSc, FmedSci,[2] Fabrizio Stocchi, MD,[3] Kapil Sethi, MD, FRCP,[4] Per Odin, MD,[5] Graeme MacPhee, FRCP,[6] Richard G. Brown, PhD,[7] Yogini Naidu, BSc, RGN,[8] Lisa Clayton, BSC,[9] Kazuo Abe, MD,[10] Yoshio Tsuboi, MD,[11] Dough MacMahon, FRCP,[12] Paolo Barone, MD,[13] Martin Rabey, MD,[14] Ubaldo Bonuccelli, MD,[15] Alison Forbes, RGN,[16] Kieran Breen, MRCP,[17] Susanne Tluk, RGN,[8] C. Warren Olanow, MD,[18] Sue Thomas, RGN,[19] David Rye, MD,[20] Annette Hand, RGN, MSc,[21] Adrian J. Williams, FRCP,[22] William Ondo, MD,[23] and K. Ray Chaudhuri, MD, FRCP, DSc[24]*

PDNMG International 2007

Movement Disorders
Vol. 24, No. 11, 2009, pp. 1641–1649

The Priamo Study: A Multicenter Assessment of Nonmotor Symptoms and Their Impact on Quality of Life in Parkinson's Disease

Paolo Barone, MD,[1] Angelo Antonini, MD,[2*] Carlo Colosimo, MD,[3] Roberto Marconi, MD,[4] Letterio Morgante, MD,[5] Tania P. Avarello, MD,[6] Eugenio Bottacchi, MD,[7] Antonino Cannas, MD,[8] Gabriella Ceravolo, MD,[9] Roberto Ceravolo, MD,[10] Giulio Cicarelli, MD,[11] Roberto M. Gaglio, MD,[12] Rosa M. Giglia, MD,[13] Francesco Iemolo, MD,[14] Michela Manfredi, MD,[15] Giuseppe Meco, MD,[3] Alessandra Nicoletti, MD,[16] Massimo Pederzoli, MD,[17] Alfredo Petrone, MD,[18] Antonio Pisani, MD,[19] Francesco E. Pontieri, MD,[20] Rocco Quatrale, MD,[21] Silvia Ramat, MD,[22] Rosanna Scala, MD,[23] Giuseppe Volpe, MD,[24] Salvatore Zappulla, MD,[25] Anna Rita Bentivoglio, MD,[26] Fabrizio Stocchi, MD,[27] Giorgio Trianni, MD,[28] and Paolo Del Dotto, MD[29] on behalf of the PRIAMO study group

PRIAMO Italian 2009

PDNMG International 2010

Movement Disorders
Vol. 25, No. 6, 2010, pp. 704–709

The Nondeclaration of Nonmotor Symptoms of Parkinson's Disease to Health Care Professionals: An International Study Using the Nonmotor Symptoms Questionnaire

K. Ray Chaudhuri, MD, DSc,[1*] Cristina Prieto-Jurcynska, MD,[2,3] Yogini Naidu, MSc,[4] Tanya Mitra, BSc,[5] Belen Frades-Payo, MSc,[6] Susanne Tluk, RGN,[4] Anne Ruessmann, RGN,[7] Per Odin, PhD,[7] Graeme Macphee, MD,[8] Fabrizio Stocchi, MD,[9] William Ondo, MD,[10] Kapil Sethi, MD, FRCP,[11] Anthony H.V. Schapira, MD, DSc,[12] Juan Carlos Martinez Castrillo, MD, PhD,[13] and Pablo Martinez-Martin, MD, PhD[6]

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National Parkinson Foundation

Mov Disord 2009; 24: 1641-1649

The Priamo Study: A Multicenter Assessment of Nonmotor Symptoms and Their Impact on Quality of Life in Parkinson's Disease

P. Barone et al.

Frequency of NMS increased along with the disease severity

TABLE 3. *Prevalence of NMS domains and disease stage*

		Disease Stage (Hoehn and Yahr scale)			
	All	1	1.5–2	2.5–3	4–5
NMS domains	N = 1,072 (%)	N = 167 (%)	N = 515 (%)	N =325 (%)	N = 49 (%)
Gastrointestinal	654 (61.0)	76 (45.5)	280 (54.4)	250 (76.9)	36 (73.5)
Pain	653 (60.9)	85 (50.9)	302 (58.6)	218 (67.1)	39 (79.6)
Urinary	614 (57.3)	72 (43.1)	266 (51.7)	222 (68.3)	44 (89.8)
Cardiovascular	158 (14.7)	22 (13.2)	70 (13.6)	53 (16.3)	11 (22.5)
Sleep	687 (64.1)	80 (47.9)	312 (60.6)	245 (75.4)	40 (81.6)
Fatigue	623 (58.1)	63 (37.7)	291 (56.5)	224 (68.9)	40 (81.6)
Apathy	328 (30.6)	41 (24.6)	138 (26.8)	119 (36.6)	24 (49.0)
Attention/memory	479 (44.7)	63 (37.7)	208 (40.4)	168 (51.7)	32 (65.3)
Skin	260 (24.3)	24 (14.4)	102 (19.8)	112 (34.5)	16 (32.7)
Psychiatric	716 (66.8)	102 (61.1)	326 (63.3)	238 (73.2)	41 (83.7)
Respiratory	191 (17.8)	16 (9.6)	80 (15.5)	74 (22.8)	15 (30.6)
Miscellaneous	515 (48.0)	62 (37.1)	247 (48.0)	168 (51.7)	29 (59.2)

Cochran-Armitage trend test <0.0045 (with Bonferroni's correction) for all NMS except cardiovascular symptoms ($P = 0.0774$).

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J Neural Transm
DOI 10.1007/s00702-012-0928-2

Non-motor symptoms of Parkinson's disease: the patient's perspective

Kieran C. Breen · Gerda Drutyte

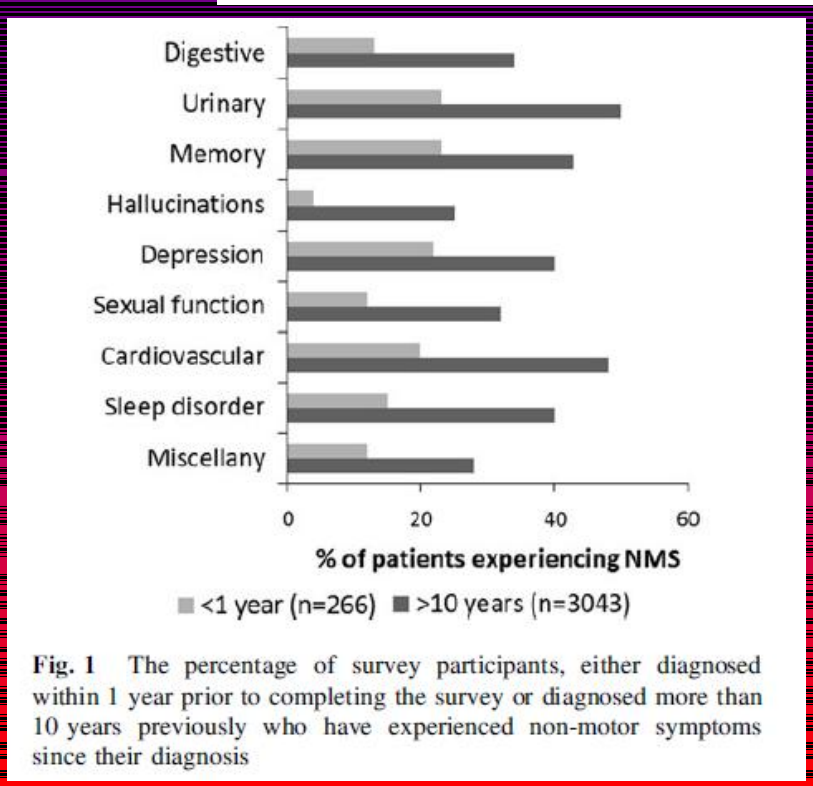

Fig. 1 The percentage of survey participants, either diagnosed within 1 year prior to completing the survey or diagnosed more than 10 years previously who have experienced non-motor symptoms since their diagnosis

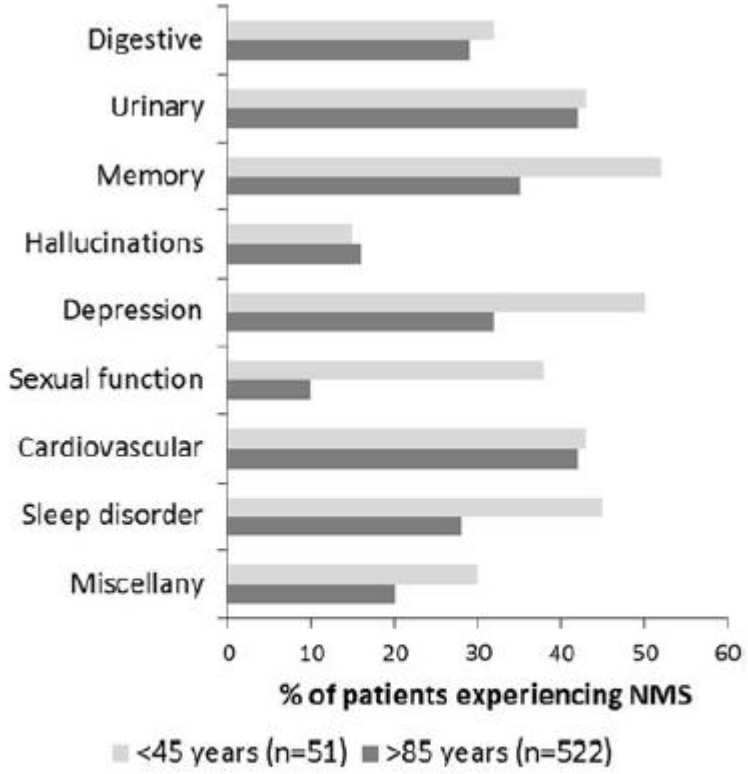

Fig. 2 The percentage of survey participants, either under the age of 45 prior to completing the survey or over the age of 85, experiencing non-motor symptoms since their diagnosis

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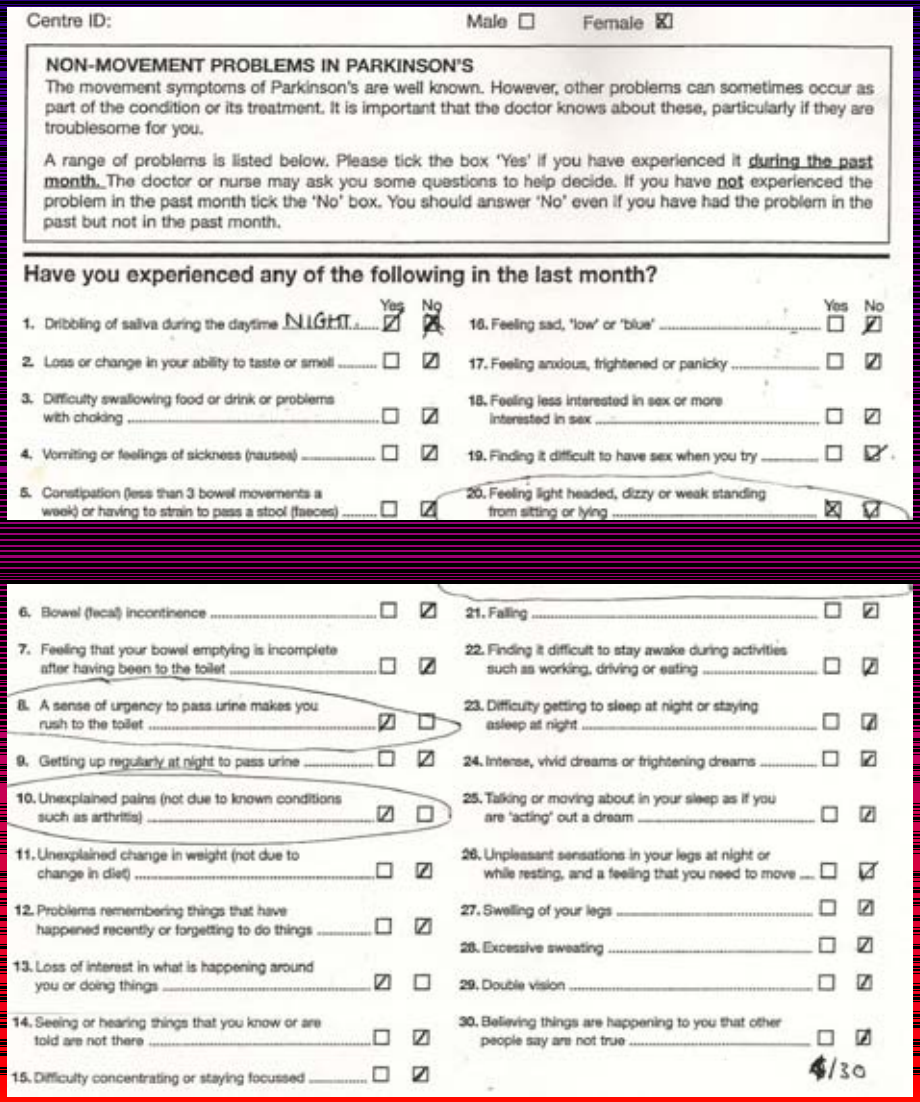
Fig : 4A . A NMSQuest completed by a drug naive PD patient at first consultation. HY stage 1 and NMSQ score is 5/30.



Centre ID: Male ☐ Female ☒

NON-MOVEMENT PROBLEMS IN PARKINSON'S

The movement symptoms of Parkinson's are well known. However, other problems can sometimes occur as part of the condition or its treatment. It is important that the doctor knows about these, particularly if they are troublesome for you.

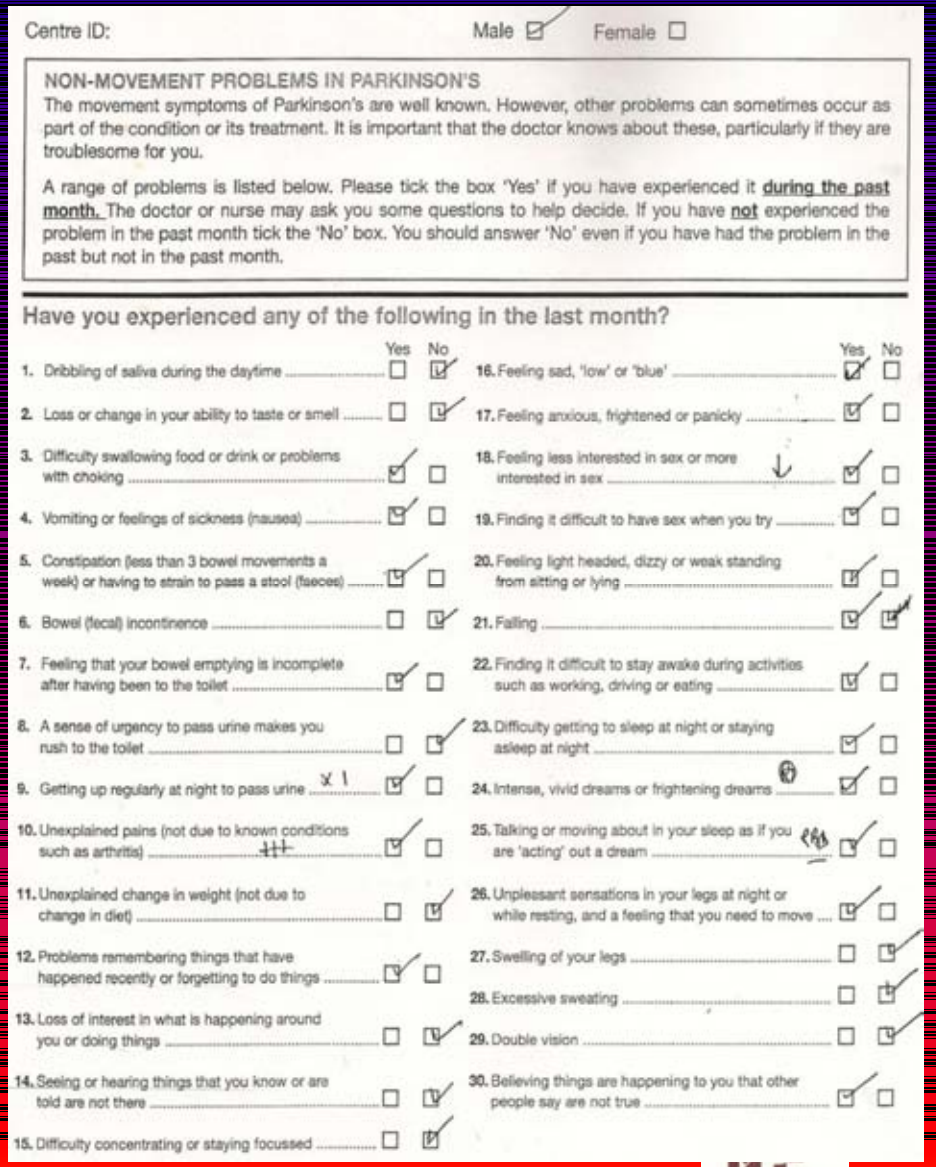
A range of problems is listed below. Please tick the box 'Yes' if you have experienced it **during the past month.** The doctor or nurse may ask you some questions to help decide. If you have **not** experienced the problem in the past month tick the 'No' box. You should answer 'No' even if you have had the problem in the past but not in the past month.

Have you experienced any of the following in the last month?

	Yes	No
1. Dribbling of saliva during the daytime NIGHT	☑	☒
2. Loss or change in your ability to taste or smell	☐	☑
3. Difficulty swallowing food or drink or problems with choking	☐	☑
4. Vomiting or feelings of sickness (nausea)	☐	☑
5. Constipation (less than 3 bowel movements a week) or having to strain to pass a stool (faeces)	☐	☑
6. Bowel (fecal) incontinence	☐	☑
7. Feeling that your bowel emptying is incomplete after having been to the toilet	☐	☑
8. A sense of urgency to pass urine makes you rush to the toilet	☑	☐
9. Getting up regularly at night to pass urine	☐	☑
10. Unexplained pains (not due to known conditions such as arthritis)	☑	☐
11. Unexplained change in weight (not due to change in diet)	☐	☑
12. Problems remembering things that have happened recently or forgetting to do things	☐	☑
13. Loss of interest in what is happening around you or doing things	☑	☐
14. Seeing or hearing things that you know or are told are not there	☐	☑
15. Difficulty concentrating or staying focussed	☐	☑
16. Feeling sad, 'low' or 'blue'	☐	☑
17. Feeling anxious, frightened or panicky	☐	☑
18. Feeling less interested in sex or more interested in sex	☐	☑
19. Finding it difficult to have sex when you try	☐	☑
20. Feeling light headed, dizzy or weak standing from sitting or lying	☒	☑
21. Falling	☐	☑
22. Finding it difficult to stay awake during activities such as working, driving or eating	☐	☑
23. Difficulty getting to sleep at night or staying asleep at night	☐	☑
24. Intense, vivid dreams or frightening dreams	☐	☑
25. Talking or moving about in your sleep as if you are 'acting' out a dream	☐	☑
26. Unpleasant sensations in your legs at night or while resting, and a feeling that you need to move	☐	☑
27. Swelling of your legs	☐	☑
28. Excessive sweating	☐	☑
29. Double vision	☐	☑
30. Believing things are happening to you that other people say are not true	☐	☑

4/30

Fig : 4B . A NMSQuest completed by a drug naive PD patient at first consultation. HY stage 1 and NMSQ score is 19/30. Park sleep + Park autonomic



Centre ID: Male ☑ Female ☐

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Have you experienced any of the following in the last month?

	Yes	No
1. Dribbling of saliva during the daytime	☐	☑
2. Loss or change in your ability to taste or smell	☐	☑
3. Difficulty swallowing food or drink or problems with choking	☑	☐
4. Vomiting or feelings of sickness (nausea)	☑	☐
5. Constipation (less than 3 bowel movements a week) or having to strain to pass a stool (faeces)	☑	☐
6. Bowel (fecal) incontinence	☐	☑
7. Feeling that your bowel emptying is incomplete after having been to the toilet	☑	☐
8. A sense of urgency to pass urine makes you rush to the toilet	☐	☑
9. Getting up regularly at night to pass urine x 1	☑	☐
10. Unexplained pains (not due to known conditions such as arthritis)	☑	☐
11. Unexplained change in weight (not due to change in diet)	☐	☑
12. Problems remembering things that have happened recently or forgetting to do things	☑	☐
13. Loss of interest in what is happening around you or doing things	☐	☑
14. Seeing or hearing things that you know or are told are not there	☐	☑
15. Difficulty concentrating or staying focussed	☐	☑
16. Feeling sad, 'low' or 'blue'	☑	☐
17. Feeling anxious, frightened or panicky	☑	☐
18. Feeling less interested in sex or more interested in sex	☑	☐
19. Finding it difficult to have sex when you try	☑	☐
20. Feeling light headed, dizzy or weak standing from sitting or lying	☑	☐
21. Falling	☑	☑
22. Finding it difficult to stay awake during activities such as working, driving or eating	☑	☐
23. Difficulty getting to sleep at night or staying asleep at night	☑	☐
24. Intense, vivid dreams or frightening dreams	☑	☐
25. Talking or moving about in your sleep as if you are 'acting' out a dream	☑	☐
26. Unpleasant sensations in your legs at night or while resting, and a feeling that you need to move	☑	☐
27. Swelling of your legs	☐	☑
28. Excessive sweating	☐	☑
29. Double vision	☐	☑
30. Believing things are happening to you that other people say are not true	☑	☐

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	NMSQ study 2006 n = 123	NMSQ 2007 n = 545	PRIAMO study 2009 n = 1072	NMSQ 2010 n = 242	Dutch study NMSQ 2012 n = 215	NMSQ 2012 n = 200	Icicle PD study NMSQ N=159
Cognitive							
Memory	43.9	44.8	25.1	51.2	37.9	62.5	55.3
Concentration	37.4	45.7	31.4	50	45.5	31.5	29.6
Depression							
Sadness	44.7	50.1	22.5	48.8	38.6	56	37.1
Anxiety	39.9	45.3	55.8	41.7	30.7	47.5	42.8
Sleep							
EDS	28.4	31.1	21.2	34.7	29	32.5	37.1
Insomnia	40.6	45.7	36.9	47.3	45.8	52.5	17.6
RBD	32.5	35.6	29.6	38.7	34.8	33.5	34.6
RLS	37.4			41.1	32.4	41	27.7
Fatigue		31.1	58.1	35			
Pain	27.6	28.7	20.8	45.9	18.2	38.8	37.7
GIT							
Swallowing	26.3	28.3	16.1	27	29.9	30.3	20.1
Constipation	46.7	52.4	27.5	47.5	38.6	71.7	42.1
Urinary							
Urgency	61	55.8	35	59.9	59.2	56.5	46.5
Nocturia	66.7	61.9	34.6	64.9	56.9	65.4	26.4

N = 2556

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Non-motor findings and diagnostic results in de novo Parkinson's disease subjects of the DeNoPa study

Brit Mollenhauer[#] [1,2,5], MD; Ellen Trautmann [#1,3], PhD; Friederike Sixel-Döring[1], MD; Tamara Wicke[1], MS; Jens Ebentheuer[1], MD; Martina Schaumburg[1], MS; Elisabeth Lang[1], BS; Niels K. Focke[2], MD; Kishore R. Kumar[4], PhD; Katja Lohmann[4], PhD; Christine Klein[4], MD; Michael G. Schlossmacher[6], MD; Ralf Kohnen[7], PhD; Tim Friede[8], PhD; Claudia Trenkwalder [1,2], MD & the DeNoPa Study Group**

Neurology In Press

Table 2.1: Subjective non-motor features of *de-novo* PD patients assessed by validated self-rating scales (the same table including subitems of the NMSS can be found in the Supplementary material eTable2)

	PD N=159	HC N=110	Mean difference (95% CI)	p-value	Un adjusted p-value
NMSQuest	n=159 7.5 (4.05, 0-19.00)	n=110 3.7 (2.54, 0-12.00)	-3.79 (-4.63, -2.97)	<.001	<.001
NMSS	n=156 37.4 (30.72, 0-150.00)	n=110 13.1 (13.38, 0-70.00)	-24.35 (-30.30, -18.40)	<.001	<.001
Scopa-AUT	n=155	n=110			
Gastro intestinal	2.7 (2.30, 0-12.00)	0.7 (1.08, 0-5.00)	-1.95 (-2.41, -1.50)	<.001	<.001
Urinary	5.0 (3.37, 0-16.00)	4.1 (2.84, 0-13.00)	-0.91 (-1.66, -0.17)	.023	.032
Cardiovascular	0.7 (0.92, 04.00)	0.17 (0.45, 0-2.00)	-0.50 (-0.69, -0.31)	<.001	<.001
Thermo regulatory	1.8 (1.84, 0-9.00)	1.3 (1.62, 0-8.00)	-0.52 (-0.95, -0.10)	.017	.025
Pupillomotor	0.6 (0.79, 0-3.00)	0.3 (0.72, 0-3.00)	-0.25 (-0.44, -0.07)	.007	.009
Sexual dysfunction man	1.9 (2.01, 0-6.00)	1.2 (1.65, 0-8.00)	-0.78 (-1.35, -0.20)	.009	.044
Sexual dysfunction woman	0.9 (1.31, 0-5.00)	0.78 (1.19, 0-4.00)	-0.10 (-0.68, 0.48)	.711	.483
PDQ-39 Total score	n=122 15.0 (10.36, 0-41.00))	n=73 3.6 (3.76, 0-14.00)	-10.08 (-12.31, -7.85)	<.001	<.001
PDSS Total score	n=152 15.3 (8.55, 0-41.00)	n=107 10.2 (6.34, 0-44.50)	-5.31 (-7.23, -3.40)	<.001	<.001
RBD-SQ	n=125 3.8 (2.8, 0-13.00)	n=92 2.2 (2.1, 0-8.00)	-1.61 (-2.305, -0.909)	<.001	.001

Table 2.2: Technical investigations: Olfactory test, electrocardiogram (ECG), serum cholesterol, presence of REM-sleep behavior disorder (RBD) in polysomnography (PSG) and transcranial sonography

	PD n=159	HC n=110	Mean difference (95% CI)	p-value	Un adjusted p-value
Olfactory testing	n=159	n=110			
Threshold	3.1 (3.62, 0-16.00)	7.1 (3.69, 0-16.00)	3.89 (3.01, 4.77)	<.001	<.001
Discrimination	8.3 (3.52, 0-15.00)	12.0 (2.52, 0-16.00)	3.63 (2.87, 4.38)	<.001	<.001
Identification	7.2 (3.52, 0-15.00)	12.0 (2.65, 0-16.00)	4.70 (3.93, 5.47)	<.001	<.001
ECG	n=159	n=110			
Heart rate [1/min]	68.9 (11.34, 44.00-95.00)	61.5 (9.36, 44.00-88.00)	-7.76 (-10.16, -5.17)	<.001	<.001
Total serum cholesterol [mg/dL]	n=159 212.7 (39.97, 119.00-320.00)	n=110 233.2 (40.27, 151.00-354.00)	19.87 (10.11, 29.63)	<.001	<.001
PSG RBD yes/ no (%)	81/ 77 (51/ 49)	17/ 93 (15/ 85)	5.72 (4.46, 7.33)	<.001	<.001
Transcranial sonography*	n=141	n=104			
Substantia nigra Echogenicity Bilateral mean [cm^2]	0.3 (0.20, 0.10-0.47)	0.1 (0.07, 0.02-0.41)	-0.136 (-0.18,-0.10)	<.001	<.001

Data are mean (SD, range) or number (%). Mean difference (95% CI) and p- values with multiple imputation and adjustment for age, gender and education.
*Only performed in sufficient bone window

Table 3: Performance of individual questionnaires and tests including area under the receiver-operating curve (ROC) (AUC) including the confidence interval (CI), optimal cut-off-values as determined by Youden Index[34] and sensitivity preferred strategy[35] and sensitivity and specificity.

		Maximizing Youden Index			Sensitivity preferred strategy with sensitivity of at least 85%		
	AUC (95% CI)	Cut-off value	Sensitivity	Specificity	Cut-off value	Sensitivity	Specificity
NMSQuest	0.748 (0.690 - 0.806)	5.7	0.67	0.78	2.9	0.89	0.35
Scopa-AUT gastrointestinal	0.723 (0.660 - 0.786)	2.0	0.67	0.84	1.0	0.85	0.59
Smell identifiation test	0.836 (0.785 - 0.886)	10.0	0.82	0.81	11.0	0.88	0.70
ECG (heart rate)	0·692 (0·629-0·755)	67.0	0.55	0.75	52	0.85	0.36
Serum cholesterol	0·633 (0·566-0·700)	251.5	0.85	0·36	281.5	0.85	0.36
TCS (hyperechogenic substantia nigra)	0.897 (0.854 - 0.940)	0.22	0.87	0.85	0.22	0.87	0.85
RBD*			0.51 (0.43-0.59)	0.85 (0.78-0.91)			

NMS-Q: Non-motor Symptoms Questionnaire; Scopa-AUT: Assessment of autonomic dysfunction in Parkinson's disease; TCS: transcranial sonography; RBD: REM-sleep behavior disorder

NMS

A range of NMS are prevalent in untreated or early PD

An average patients would exhibit 8-12 different NMS

Listing of NMSQ in official and UK related agencies

Parkinson´s UK: NMSQuest: http://www.parkinsons.org.uk/PDF/nms_questionnaire.pdf and http://www.parkinsons.org.uk/default.aspx?page=12523
The Professional´s Guide to Parkinson´s Disease (pp 3,22,26.60) http://www.parkinsons.org.uk/pdf/B126_Professionalsguide.pdf
European Parkinson´s Disease Association. Life with Parkinson´s: http://www.epda.eu.com/en/parkinsons/life-with-parkinsons/part-2/introduction/
The Movement Disorders Society: www.movementdisorders.org/publications/rating_scales/
Map of Medicine for PD: http://healthguides.mapofmedicine.com/choices/pdf/parkinson_s_disease1.pdf
Elective Care Commissioning Pathway - Parkinson´s Disease 2008: http://webarchive.nationalarchives.gov.uk/20130107105354/http:www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/@ps/documents/digitalasset/dg_122474.pdf
DoH`s Best Practice Tariff http://www.ncsupport.org.uk/parkinsons-best-practice-tariff-announced/
American Academy of Neurology. Http://journals.lww.com/neurotodayonline/Fulltext/2010/04010/New_Parameter_for_Nonmotor_Pd_Symptoms.2.aspx
National Institue of Neurological Disorders and Stroke Parkinson´s Disease CDE Working Group: http://www.commondataelements.ninds.nih.gov/PD.aspx#tab=Data_Standards
Parkinson Society Canada, Physician Guide Non-motor symptoms of Parkinson´s Disease (pp 3,41,42): http://www.parkinsonclinicalguidelines.ca/sites/defaults/files/PhysicianGuide_Non-motor_EN.pdf

Sauerbier and Chaudhuri. BJHM 2013 In Press

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Motor vs Non Motor Parkinson's

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Motor Endophenotypes

TD
AKD
PIGD
Mixed

RESEARCH ARTICLE

The Motor Phenotype of Parkinson's Disease in Relation to Age at Onset

Mirdhu M. Wickremaratchi, PhD, MRCP,[1] M. Duleeka W. Knipe, BSc, MPH,[1] B.S. Dwarakanath Sastry, MBBS, FRCPI, FRCP,[2] Elizabeth Morgan, BSc RGN,[2] Anne Jones, RGN,[2] Rachel Salmon, BSc, RGN,[1] Richard Weiser, FRCP,[3] Maralyn Moran, BN, RGN,[3] Debbie Davies, BSc, RGN,[4] Louise Ebenezer, RGN, MSc,[5] Sandip Raha, BSc, MBBS,[5] Neil P. Robertson, MD, FRCP,[1] Christopher C. Butler, FRCGP, MD,[6] Yoav Ben-Shlomo, MD, PhD,[7] and Huw R. Morris, FRCP, PhD[1,8]*

RESEARCH ARTICLE

Akinetic-Rigid and Tremor-Dominant Parkinson's Disease Patients Show Different Patterns of FP-CIT Single Photon Emission Computed Tomography

Carsten Eggers, MD,[1] Deniz Kahraman, MD,[2] Gereon R. Fink, MD,[1,3] Matthias Schmidt, MD,[2] and Lars Timmermann, MD[1]*

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Table 1 Parkinson's disease subtypes identified by data driven studies

Author, year	Subtypes identified
Graham 1999[3]	Short duration (mean 5 years): 1. Good motor control without cognitive impairment 2. Good motor control, executive cognitive deficits 3. Older age at onset, poor motor control + complications, mild cognitive impairment Longer duration (mean 14 years): 1. Poor motor control, no cognitive impairment 2. Poor motor control, moderately severe cognitive impairment
Gasparoli 2002[4]	1. Rapid progression 2. Slow progression
Dujardin 2004[5]	1. Mild motor impairment, relatively preserved cognition 2. 'Reduced overall cognitive efficiency', subcorticofrontal syndrome and more severe motor dysfunction
Lewis 2005[6]	1. Young onset 2. Non-tremor dominant, cognitive impairment and depression 3. Rapid progression without cognitive impairment 4. Tremor dominant
Schrag 2006[7]	1. Young onset 2. Older onset, more rapid [illegible] and fluctuations
Post 2008[8]	1. Young onset with slow 2. Intermediate age onset with anxiety and depression 3. Oldest onset
Reijnders 2009[9]	1. Rapid progression 2. Young onset with motor complications 3. Non-tremor dominant and psychopathology 4. Tremor dominant
Van Rooden 2011[10]	1. Mild all domains, young 2. Severe motor complications, sleep and depressive symptoms, youngest 3. Medium severity, older 4. Most severe, except mild tremor, prominent motor complications, older
Liu 2011[11]	1. Non-tremor dominant 2. Rapid disease progression 3. Young onset 4. Tremor dominant

All motor and no non motor !!!

REVIEW

Parkinson's disease subtypes: lost in translation?

Connie Marras,[1,2] Anthony Lang[1,2]

J Neurol Neurosurg Psychiatry 2013;**84**:409–415. doi:10.1136/jnnp-2012-303455

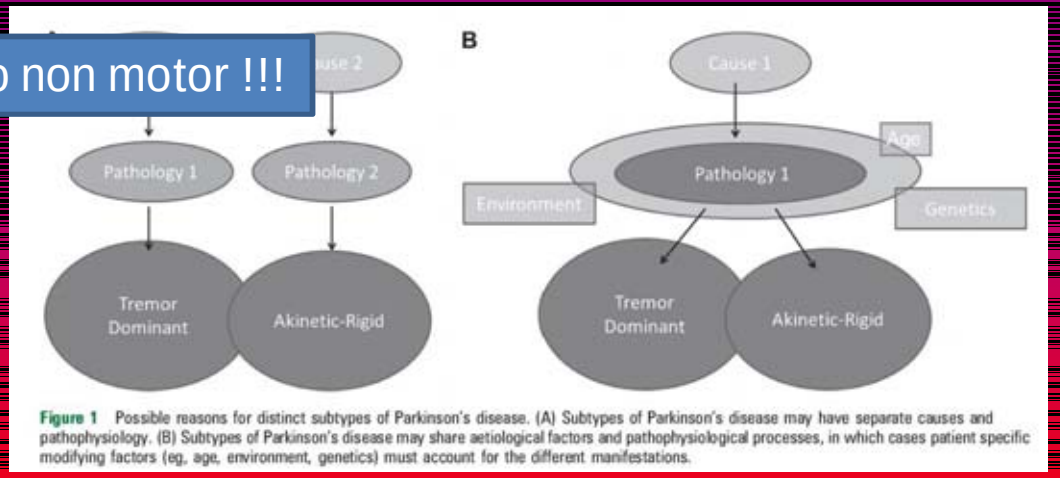

Figure 1 Possible reasons for distinct subtypes of Parkinson's disease. (A) Subtypes of Parkinson's disease may have separate causes and pathophysiology. (B) Subtypes of Parkinson's disease may share aetiological factors and pathophysiological processes, in which cases patient specific modifying factors (eg, age, environment, genetics) must account for the different manifestations.

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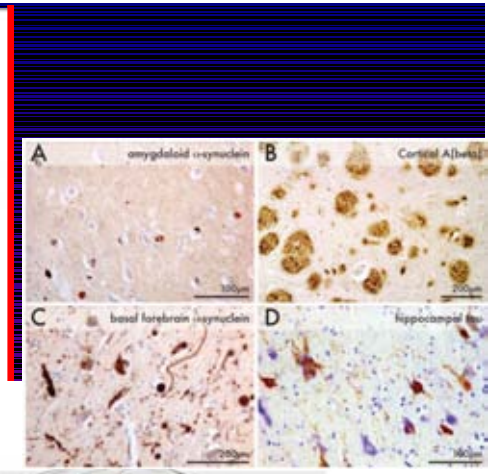
REVIEW

Milestones in Parkinson's Disease—Clinical and Pathologic Features

Glenda Halliday, PhD,[1] Andrew Lees, MD, FRCP,[2*] and Matthew Stern, MD[3]

[1]Neuroscience Research Australia and the University of New South Wales, Sydney, Australia
[2]University College London, Reta Lila Weston Institute of Neurological Studies, London, United Kingdom



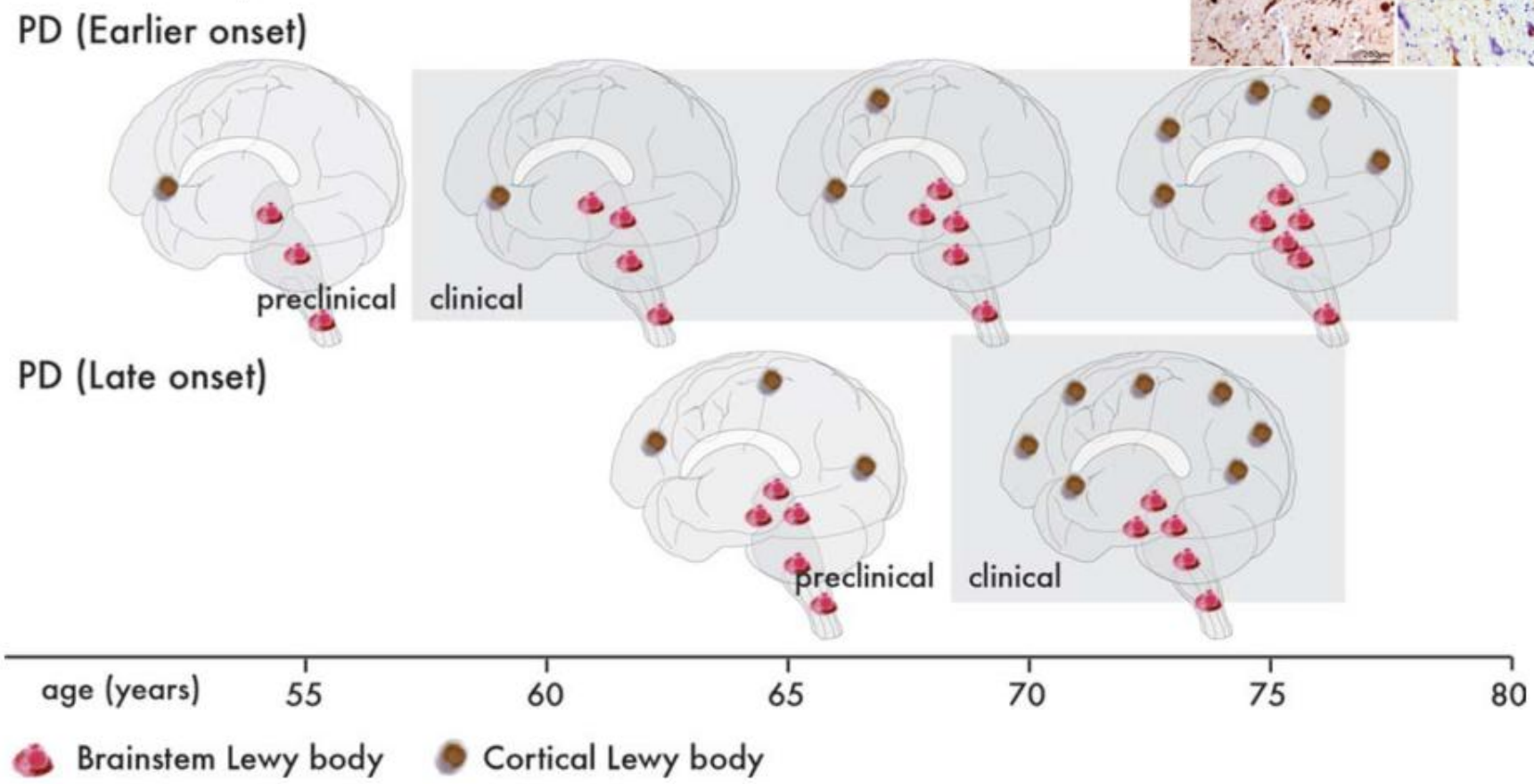


TABLE 1. Neuropathological staging of Lewy body disease

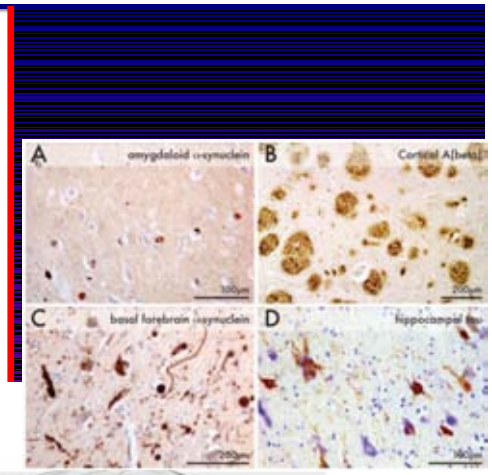
Kosaka LBD stage	Braak PD stage	Anatomical distribution of Lewy bodies
Brain stem–predominent type	1	Medulla oblongata: lesions in the dorsal IX/X motor nucleus and/or intermediate reticular zone, enteric and peripheral autonomic nervous system, spinal cord, and anterior olfactory nucleus.
	2	Medulla oblongata and pontine tegmentum: pathology of stage 1 plus lesions in the caudal raphe nuclei, gigantocellular reticular nucleus, and ceruleus-subceruleus complex; involvement of the olfactory bulb.
	3	Midbrain: pathology of stage 2 plus midbrain lesions, particularly in the pars compacta of the substantia nigra.
Transitional (limbic) type	4	Basal prosencephalon and mesocortex: pathology of stage 3 plus prosencephalic lesions. Cortical involvement confined to temporal mesocortex (transentorhinal region) and allocortex (CA2 plexus).
Diffuse cortical type	5	Neocortex: pathology of stage 4 plus lesions in high-order sensory association areas of the neocortex and prefrontal neocortex.
	6	Advanced neocortex: pathology of stage 5 plus lesions in first-order sensory association areas of the neocortex and premotor areas; occasionally, mild changes in primary sensory areas and the primary motor field. Metabolic and functional abnormalities already occur in brain regions in early stages of PD that are not accompanied by Lewy pathology.

REVIEW

Milestones in Parkinson's Disease—Clinical and Pathologic Features

Glenda Halliday, PhD,[1] Andrew Lees, MD, FRCP,[2*] and Matthew Stern, MD[3]

[1]Neuroscienc… …ney, Australia
[2]University College… …United Kingdom



Brainstem NMS endophenotype

Limbic NM endophenotype

Cortical NM endophenotype

PD (Earlier onset)

preclinical clinical

PD (Late onset)

preclinical clinical

age (years) 55 60 65 70 75 80

Brainstem Lewy body Cortical Lewy body

NM Endophenotypes/Subtypes

Chaudhuri et al. PLOS One. 2013

Chaudhuri et al. MDS Sydney 2013

- Park Cognitive
- Park Depression/Anxiety
- Park Sleep
- Park Pain
- Park Fatigue
- Park Autonomic

OPEN ACCESS Freely available online

PLOS ONE

A Proposal for a Comprehensive Grading of Parkinson's Disease Severity Combining Motor and Non-Motor Assessments: Meeting an Unmet Need

Kallol Ray Chaudhuri[1], Jose Manuel Rojo[2], Anthony H. V. Schapira[3], David J. Brooks[4], Fabrizio Stocchi[5], Per Odin[6], Angelo Antonini[7], Richard J. Brown[8], Pablo Martinez-Martin[9]*

Table 3. Variables in the study broken down by the NMS burden levels and Hoehn and Yahr staging*.

	Non-Motor Symptoms Burden Levels				
	No	**Mild**	**Moderate**	**Severe**	**Very severe**
Level	**0**	**1**	**2**	**3**	**4**
NMSS score	0	1–20	21–40	41–70	≥71
n (935)	5	244	233	218	235
PD Duration	2.80±2.49	5.88±4.68	7.84±4.99	8.58±5.21	10.16±7.12
SCOPA-Motor					
A. Examination	4.00±1.87	9.54±5.16	10.35±5.56	12.16±6.11	14.89±7.94
B. ADL	0.00±0.00	4.70±3.11	5.93±3.12	7.33±3.72	9.65±4.72
C. Complications	0.40±0.89	1.43±2.27	2.28±2.55	3.07±2.80	4.11±3.57
Total score	4.40±2.07	15.68±8.85	18.55±9.04	22.56±10.68	28.57±14.35
CISI-PD Total	1.80±1.10	5.52±3.19	7.19±3.55	9.02±4.04	11.55±5.04
EQ-5D Index	1.00±0.00	0.78±0.23	0.68±0.28	0.60±0.29	0.36±0.38
EQ-VAS	75.80±37.43	66.73±22.65	65.08±20.86	63.11±20.86	54.35±21.62
PDQ-8 Index	6.25±10.60	19.88±17.85	25.80±15.89	31.51±16.87	45.70±19.05

Hoehn and Yahr Stages	Non-Motor burden levels					Total
	0	**1**	**2**	**3**	**4**	
1	3	45	48	19	9	124
2	2	104	144	77	77	404
3	0	34	77	75	94	280
4	0	6	17	24	59	106
5	0	0	1	1	17	19
Total	5	189	287	196	256	933*

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

Unveiling relevant non-motor Parkinson's disease severity symptoms using a machine learning approach

Rubén Armañanzas[a,*], Concha Bielza[a], Kallol Ray Chaudhuri[b], Pablo Martinez-Martin[c], Pedro Larrañaga[a]

Table 7
Individual non-motor symptoms most commonly selected by the feature selection process in the classification of `moderate` and `severe` instances. The *selection* column lists the number of times each item was selected for HY[a] and CISI-PD[b] classes, respectively. The `moderate` and `severe` columns report the average value of each item for the respective cases and problems. Statistically significant differences between the values of the two groups for each classification problem using a signed rank sum test with $\alpha = 0.01$ and $\alpha = 0.05$ are marked with the † and ‡ symbols, respectively.

Item	Description	Selection		Moderate		Severe	
		HY	CISI-PD	HY	CISI-PD	HY	CISI-PD
scpc2	Illusions and misidentification of persons	3	3	0.2679	0.2991	0.6957	1.2083†
nms14	Does the patient believe in unlikely facts	2	4	0.5179	0.6667	1.9565	3.9583†
nms9	Nervousness or frightened for no reason	3	1	2.5268	3.0085	3.9565	5.0417
nms19	Drooling during the day	4	0	2.0000	2.6410	4.8478	6.0000†
nms25	Altered interest in sex	4	0	2.5893	2.7009	1.5435	1.7917
nms2	Fainting	0	3	0.3482	0.3761	1.5000	2.9583†
nms23	Void within 2 h of last voiding	3	0	2.8482	3.2650	5.0000	5.2500‡
nms24	Pass urine regularly at night	3	0	3.6161	4.6068	6.5870	6.5833‡

[a] Hoehn & Yahr index.
[b] Clinical impression of severity index for Parkinson's disease.

NMS

Biomarkers ??

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Chaudhuri, Todorova, Jenner. Pract Neurol. In Press.

Biochemical/histopathology markers:	
Rectal/Colonic biopsy	Phosphorylated ?/-SNC positive Lewy neurites; ?ø-SNC positive nerve fibres
Skin biopsy	?-SNC accumulation
Gastric biopsy	Phosphorylated ?á-SNC positive Lewy neurites
Salivary glands	?Ñ-SNC accumulation
Low Uric acid	
Low LDL	
Genetic Markers:	
LRRK2	
GBA	
Imaging Markers:	
Transcranial USS	
DAT Scan	
The above two can be used in conjunction with clinical symptoms such as hyposmia or RBD.	

Impaired Olfaction and Other Prodromal Features in the Parkinson At-Risk Syndrome Study

Andrew Siderowf, MD, MSCE,[1*] Danna Jennings, MD,[2] Shirley Eberly, MS,[3] David Oakes, PhD,[3] Keith A. Hawkins, PsyD,[4] Albert Ascherio, MD, PhD,[5] Matthew B. Stern, MD,[1] and Kenneth Marek, MD[2], the PARS Investigators

Movement Disorders, Vol. 27, No. 3, 2012

Hyposmics are more likely to:

- **Endorse non-motor symptoms (RBD, constipation, depression, anxiety)**
- **Endorse subtle motor symptoms**
- **Have DAT deficit on imaging**

GI-Tract: Entry Zone and/or Window

-Pathological View-

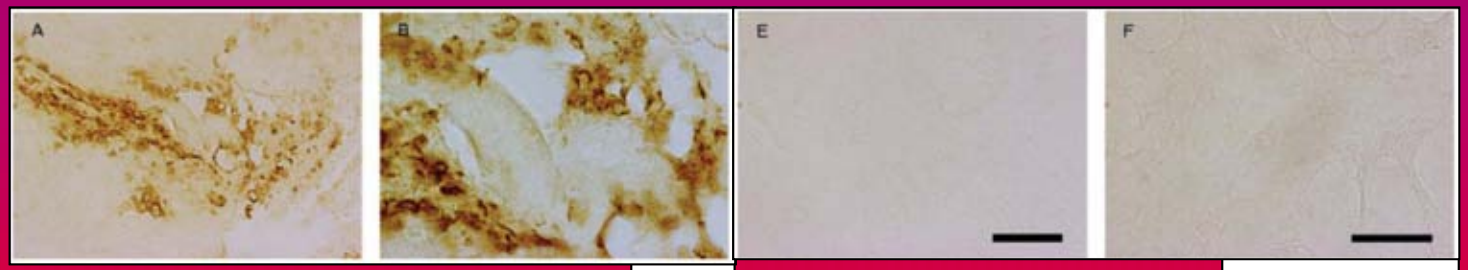
Courtesy D Woitalla

RESEARCH ARTICLE

Alpha-Synuclein in Colonic Submucosa in Early Untreated Parkinson's Disease

Kathleen M. Shannon, MD,[1]* Ali Keshavarzian, MD,[2] Ece Mutlu, MD,[2] Hemraj B. Dodiya, MS,[3] Delia Daian,[2] Jean A. Jaglin, RN,[1] and Jeffrey H. Kordower, PhD[3]

Mov Disord 2012: 27:709-715



PD **Controls**

- 10 untreated Parkinson patients ; all positive for Alpha-Synuclein
- Sigmoidoscopie and Bx: alpha-Synuclein and 3-Nitro-Tyrosin (marker for mitochondrial stress)

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NMS

Endophenotype specific markers ?

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Patients and PET protocol

- **Scans:**

^{18}F-dopa (monoamine storage capacity)

AND

^{11}C-DASB (SERT marker)

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Brain Advance Access published September 30, 2010

doi:10.1093/brain/awq268 Brain 2010: Page 1 of 10 | 1

BRAIN
A JOURNAL OF NEUROLOGY

Fatigue in Parkinson's disease is linked to striatal and limbic serotonergic dysfunction

Nicola Pavese,[1] Vinod Metta,[2] Subrata K. Bose,[1] Kallol Ray Chaudhuri[2] and David J. Brooks[1]

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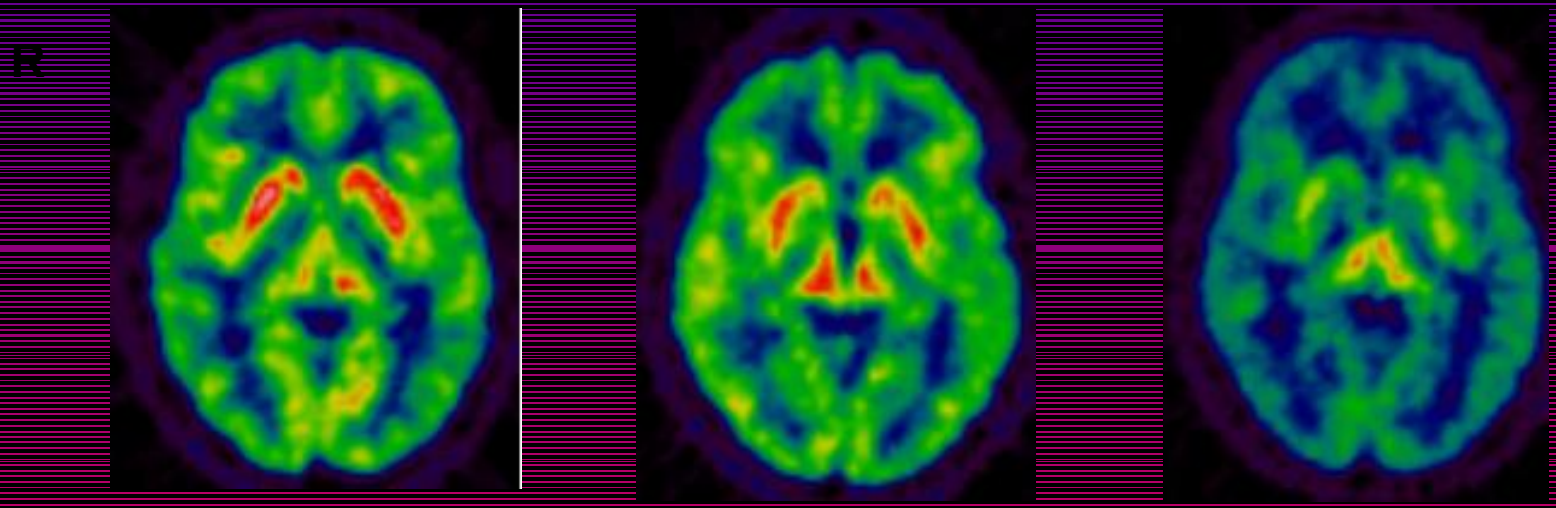
^{11}C-DASB binding in PD



Healthy volunteer

PD without fatigue

PFS-16 = 2

PD with fatigue

PFS-16 = 15

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NPF NATIONAL PARKINSON FOUNDATION

NeuroImage 59 (2012) 1080–1084

Contents lists available at SciVerse ScienceDirect

NeuroImage

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

[^{18}F]FDOPA uptake in the raphe nuclei complex reflects serotonin transporter availability. A combined [^{18}F]FDOPA and [^{11}C]DASB PET study in Parkinson's disease

N. Pavese [a,*], B.S. Simpson [a], V. Metta [b], A. Ramlackhansingh [a], K. Ray Chaudhuri [b], D.J. Brooks [a]

Sleep regulatory centres dysfunction in Parkinson's disease patients with excessive daytime sleepiness. An in vivo PET study

Nicola Pavese[1], Vinod Metta[2], Benjamin S Simpson[1], Tytus A Murphy[1], A Ramlackhansingh[1], K Ray Chaudhuri[2], and David J Brooks[1]

[1] Centre for Neuroscience, Faculty of Medicine, Hammersmith Hospital, Imperial College, London, UK;
[2] Kings College and Lewisham Hospitals, Kings College, London, UK

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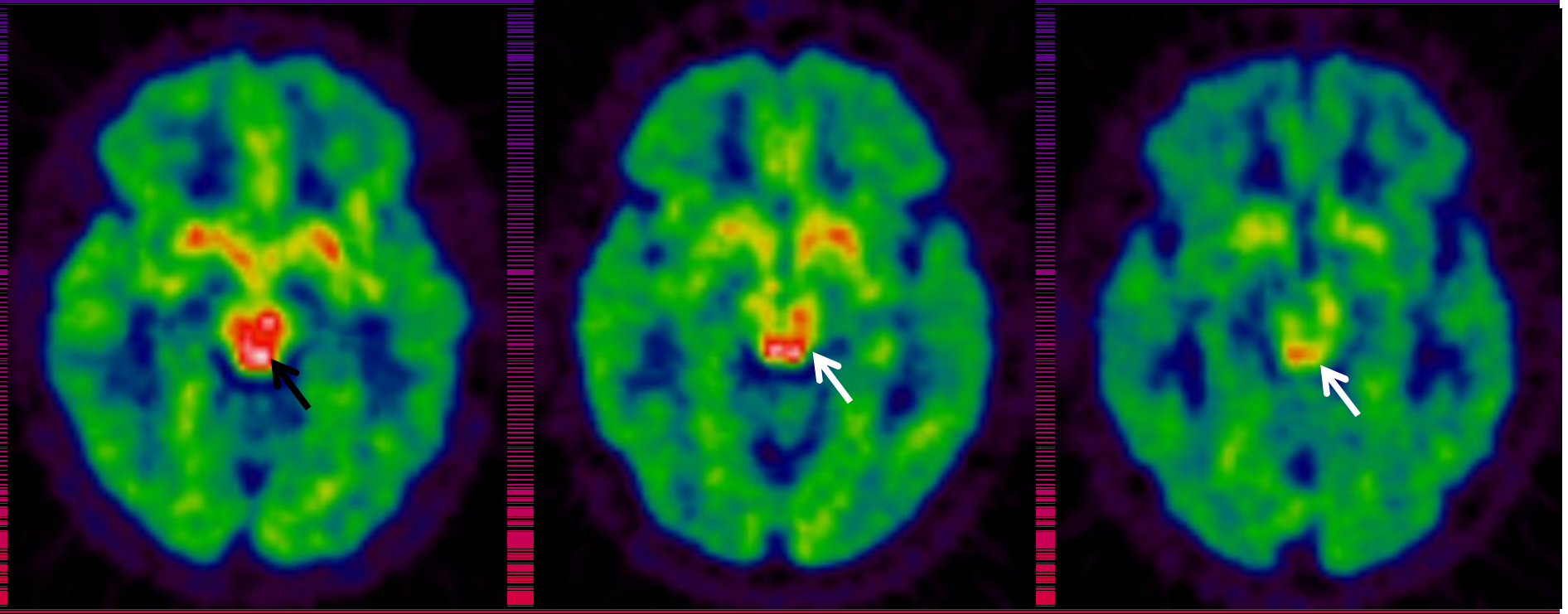
^{11}C-DASB – Rostral Raphe



Control

PD without excessive daytime somnolence ESS < 10

PD with excessive daytime somnolence ESS >10

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ARTNERS

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RESEARCH PAPER

Impulse control disorders in Parkinson's disease: decreased striatal dopamine transporter levels

Valerie Voon,[1,2,3] Alexandra Rizos,[4] Riddhika Chakravartty,[4] Nicola Mulholland,[4] Stephanie Robinson,[4] Nicholas A Howell,[1,5] Neil Harrison,[6] Gill Vivian,[7] K Ray Chaudhuri[4]

Table 2 Binding values

	PD−ICD	PD+ICD	Error	F	p Value
R striatum	1.43 (0.68)	0.91 (0.41)	27	6.22	0.02
L striatum	1.45 (0.67)	0.98 (0.47)	27	4.87	0.04
R caudate	1.68 (0.71)	1.06 (0.63)	27	6.12	0.02
L caudate	1.57 (0.60)	1.13 (0.62)	27	3.77	0.06
R putamen	1.14 (0.68)	0.63 (0.41)	27	5.80	0.02
L putamen	1.23 (0.75)	0.70 (0.48)	27	5.14	0.03
R caudate:putamen ratio	1.70 (0.55)	1.78 (0.57)	27	0.15	0.71
L caudate:putamen ratio	1.54 (0.56)	1.81 (0.61)	27	1.45	0.24

All values reported as mean (SD).

We show that PD+ICD subjects have lower DAT binding compared to PD−ICD subjects. An effect on DAT regulation is consistent with observations in substance use disorders. Decreased reuptake may account for some of the enhancement in dopamine activity beyond that of dopamine release and may also contribute to the behavioural effects.

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Subtype/ Phenotype	Possible biomarkers
Park Cognitive	Clinical: Akinesia dominant phenotype Imaging: fMRI/VBM: Cortical thinning PET: Genetic: *MAPT* H1/H1 genotype GBA: Carrier G2019S LRRK2 Carrier
Park Depression/ Anxiety	Imaging: PET: ?ô ^{11}C-RTI-32 : LC/Amygdala ?ë ^{18}[F]MPPF binding (5HT1A): Striatal ?â F-Dopa SPECT: ?ÙDAT – striatum, thalamus, midbrain Genetic: G2019S LRRK2 Carrier
Park Sleep	Imaging: ^{11}C-DASB PET: ?ó ^{11}C-RTI-32 ?á dorsal and ventral raphe 5HT DTI: ?Ï &?????????????????????– PAG/ viPAG ?½^{18} F-Dopa – striatum, midbrain Neuropathology/Biochemical: ?2 d?2222?22 ?2222222?2222222 ? s??????? , ??????? ????
Park Fatique	Imaging: ^{11}C-DASB PET:: ?™limbic 5HT

NMS

HrQol and progression

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RESEARCH ARTICLE

The Impact of Non-Motor Symptoms on Health-Related Quality of Life of Patients with Parkinson's Disease

Pablo Martinez-Martin, MD, PhD,[1,2]* Carmen Rodriguez-Blazquez, BS,[1] Monica M. Kurtis, MD,[3] K. Ray Chaudhuri, MD, FRCP, DSC,[4,5] on Behalf of the NMSS Validation Group

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[3]Movement Disorders Unit, Department of Neurology, Ruber International Hospital, Madrid, Spain
[4]Nation
[5]Dep

TABLE 6. Multiple linear regression models of HRQoL scales

	Adjusted R^2	Standardized beta	t	Sig.
PDQ-39 SI model	0.59			
(Constant)		(23.76)	5.55	0.000
NMSS total		0.52	13.64	0.000
SCOPA-motor complications		0.20	4.81	0.000
SCOPA-motor examination		0.17	4.15	0.000
EQ-5D index model	0.53			
(Constant)		(0.83)	9.24	0.000
SCOPA-motor examination		−0.38	−9.11	0.000
NMSS total		−0.37	−8.74	0.000
SCOPA-motor complications		−0.12	−2.71	0.000

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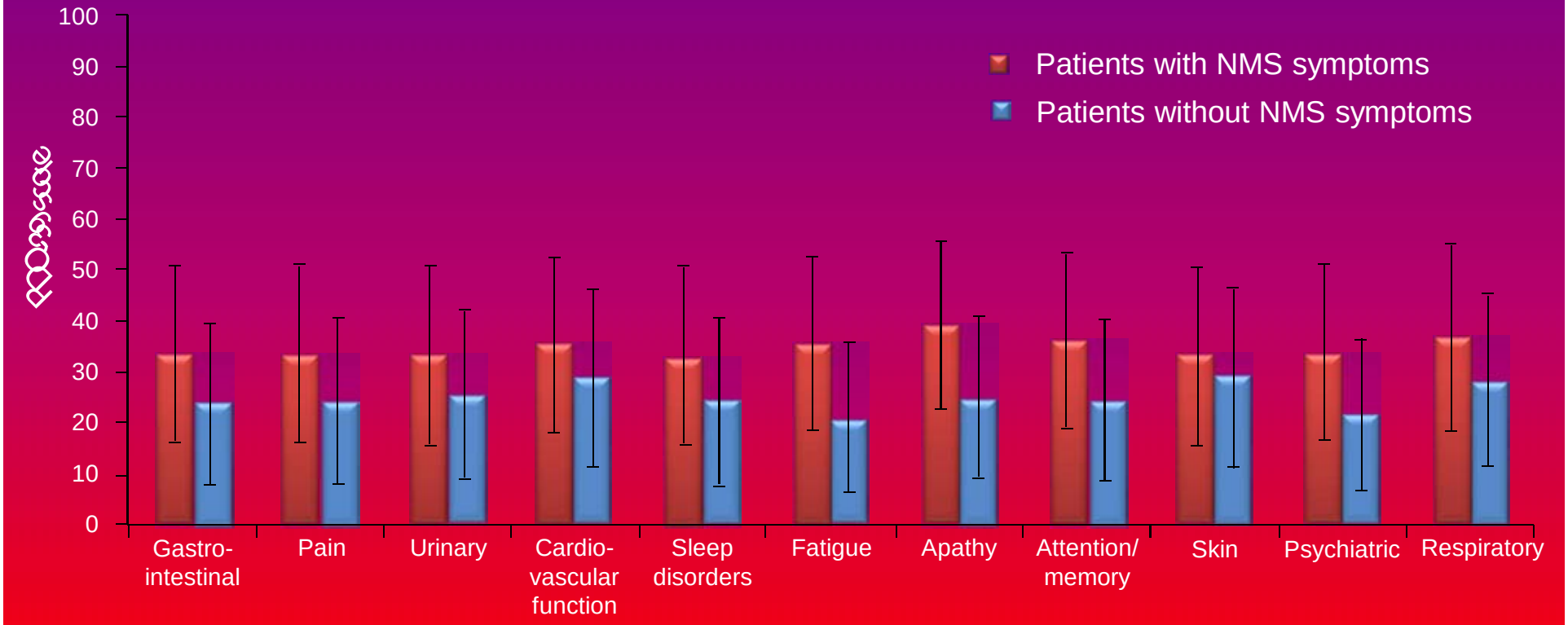
Patients who have NMS have worse quality of life (PDQ-39 scores) than those without

Adapted from:
Antonini A *et al.*. *Neurol Sci* 2008;29(2):61-65. Barone P *et al*.. *Mov Disorders* 2009;15;24(11):1641-9.



N=1072; score range between 0 (best health state) and 100 (worst health state)

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The Sydney Multicenter Study of Parkinson's Disease: The Inevitability of Dementia at 20 years

Hely et al.

Movement Disorders
Vol. 23, No. 6, 2008, pp. 837–844

Drug induced dyskinesia and end of dose failure were experienced by most patients, but the main current problems relate to the non-levodopa responsive features of the disease. Dementia is present in 83% of 20-year survivors.

Excessive daytime sleepiness is noted in 70%, falls have occurred in 87%, ... symptomatic postural hypotension in 48%, urinary incontinence in 71%, moderate dysarthria in 81%, choking in 48%, and hallucinations in 74%.

The challenge is to understand the cellular mechanisms underlying the diverse features of advanced PD that go far beyond a lack of dopamine.

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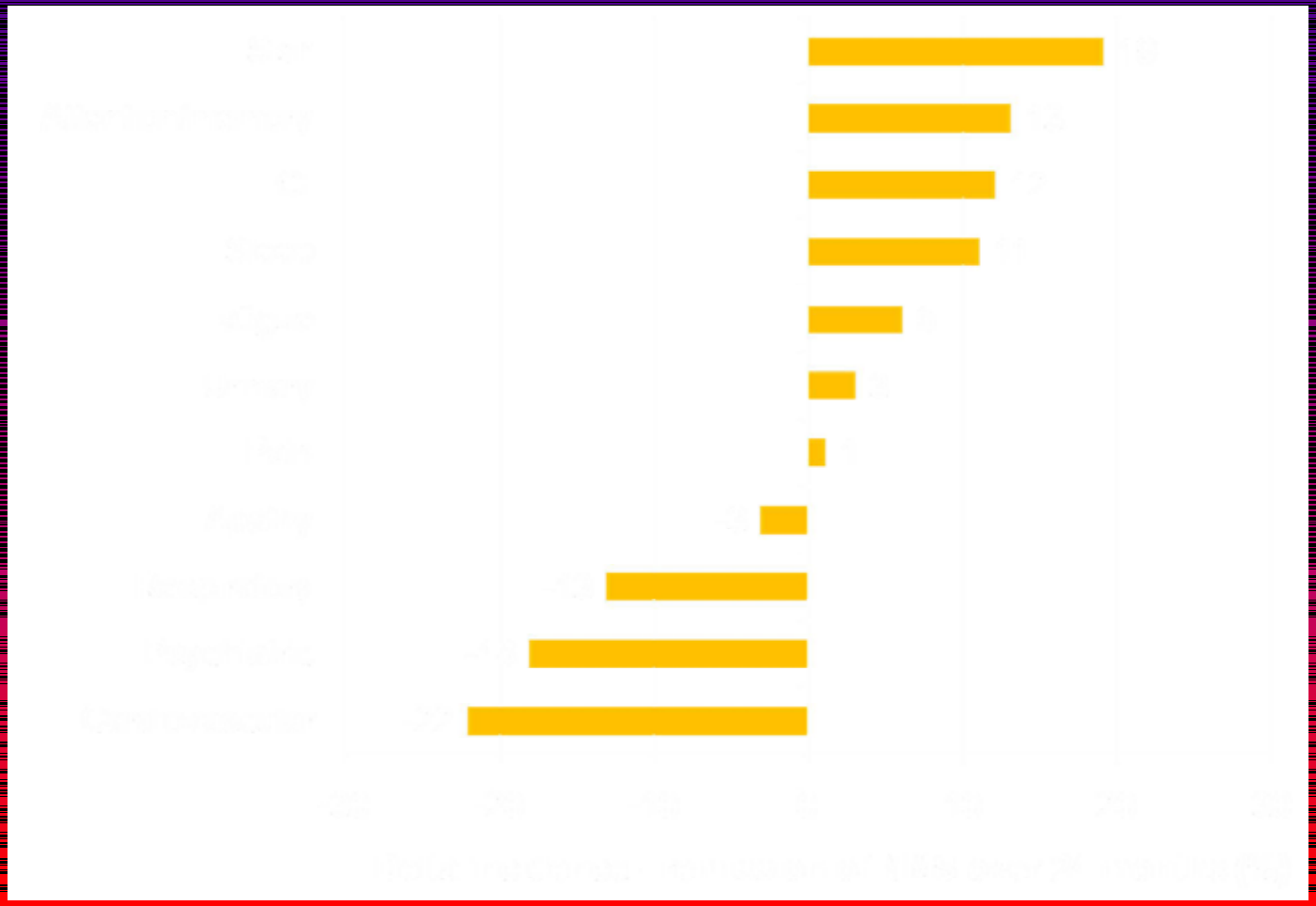
Progression of non-motor disability over 24 months in PD varies by domain

Antonini *et al.* Two-year clinical follow-up of a cohort with Parkinson's disease and other parkinsonisms: the PRIAMO study. *Mov Disord* 24, Suppl 1, 434) *; J Neurol 2012*



N=134
N=176
N=163
N=199
N=202
N=177
N=207
N=173
N=113
N=213
N=103

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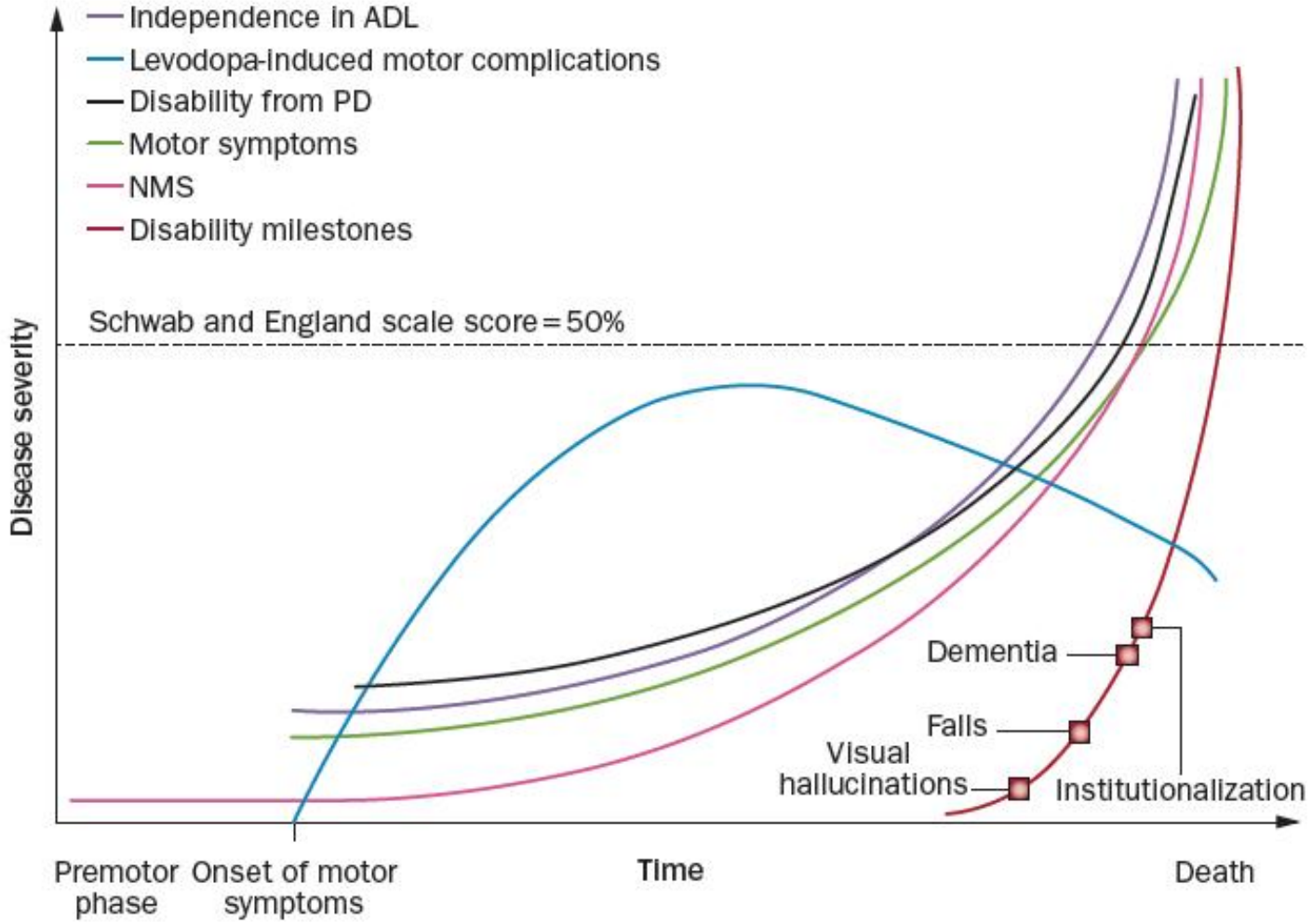
Progression of PD and Symptoms

Coelho, M. & Ferreira, J. J. *Nat. Rev. Neurol.* 8, 435–442 (2012)



NMS

Treatment

Remains a key UNMET need

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		Design	Patient Population
Cholinesterase inhibitor	Donepezil	Phase II double-blind crossover single center	PD with falls or near falls ≥2/week excluding FOG
A_1/A_{2A} receptor antagonist	Caffeine	Phase II/III double-blind three centers	PD with excessive daytime somnolence
A_{2A} receptor antagonist	Istradefylline (KW-6002)	Phase II double-blind multicenter	Mild to moderate PD; not on dopaminergic medications

CME

tor Features of
cent Trials

H. Fox, MRCP(UK), PhD[1,2*]

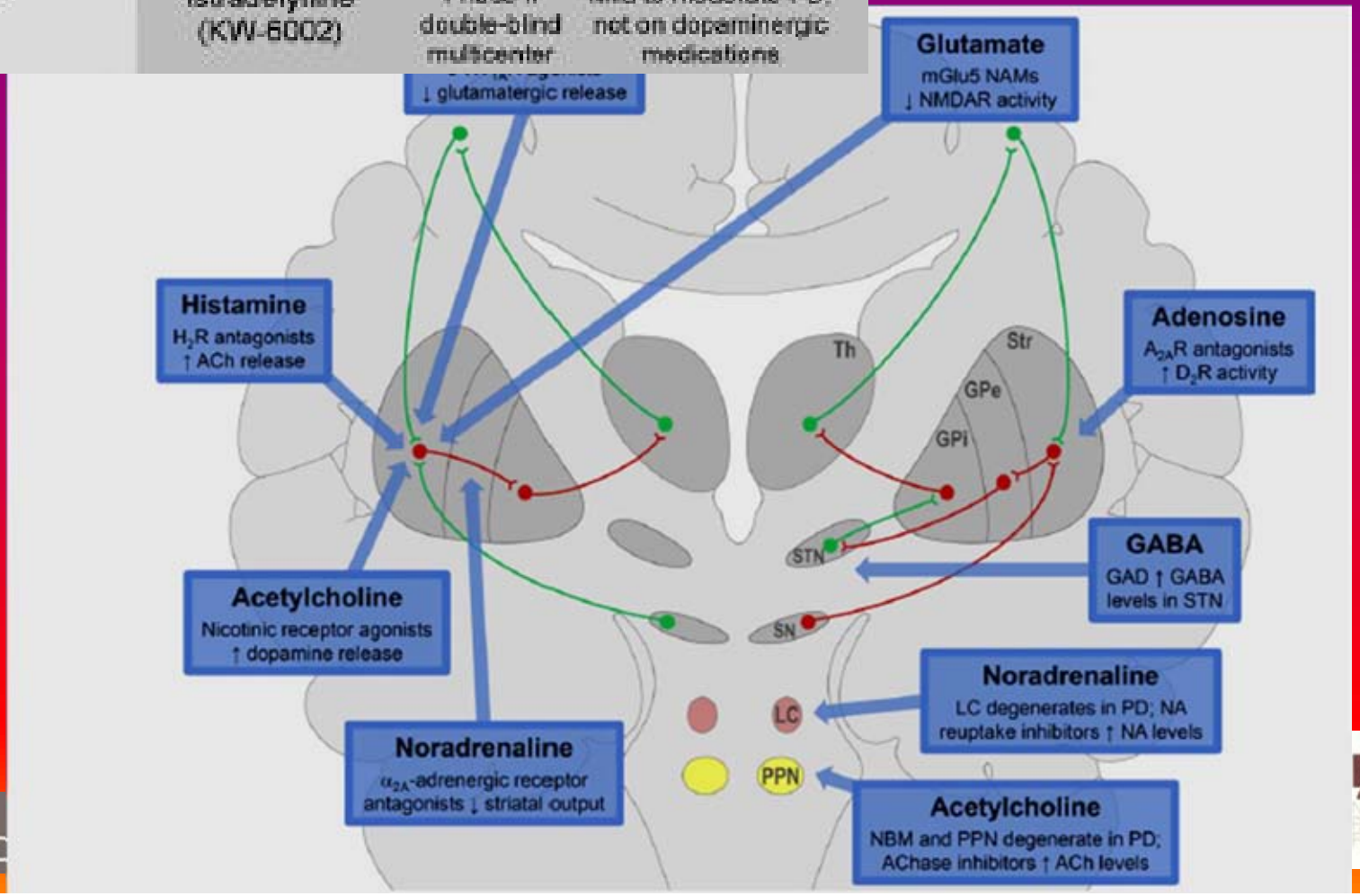

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Table 4. Non Motor PD subtyping by staging
Staging by NMSQuest (can be performed by HCP based on patient responses using NMSQ) Chaudhuri et al. 2009 **Stage 1** NMSQ – **0-5** **Stage 2** NMSQ – **6-12**
Stage 3 NMSQ – **13-20** **Stage 4** NMSQ – **21-30**
Staging by NMSS (to be used for clinical and research based studies) (PLOS ONE) Chaudhuri et al 2013 **Stage 1** NMSS **– 1-20**
Stage 2 NMSS **– 21-40** **Stage 3** NMSS **– 41-70** **Stage 4** NMSS - **?ž71**

Sauerbier and Chaudhuri . 2013. BJHM In Press

Clinical Consultation:

Patient and carer complete NMSQuest in the waiting area

Self reported 30 NMS in the last month

Grade NMSQuest scores

NMSQuest 0-5: stage 1 n significant burden of NM

NMSQuest 6-12: stage 2 mild

NMSQuest 13-20: stage 3 moderate

NMSQuest >20: stage 4

severe

Ask patient to classify the top 4 NMS causing poor quality of life

Those in NMSQuest stage3/4 seek hospital specialist referral and screen using other scales such as PDSS, HADS

Modify therapy addressing reported NMS


The *Movement* Disorder Society Evidence-Based Medicine Review Update: Treatments for the Non-Motor Symptoms of Parkinson's Disease


SPECIAL ARTICLE

Practice Parameter: Treatment of nonmotor symptoms of Parkinson disease

Report of the Quality Standards Subcommittee of the American Academy of Neurology

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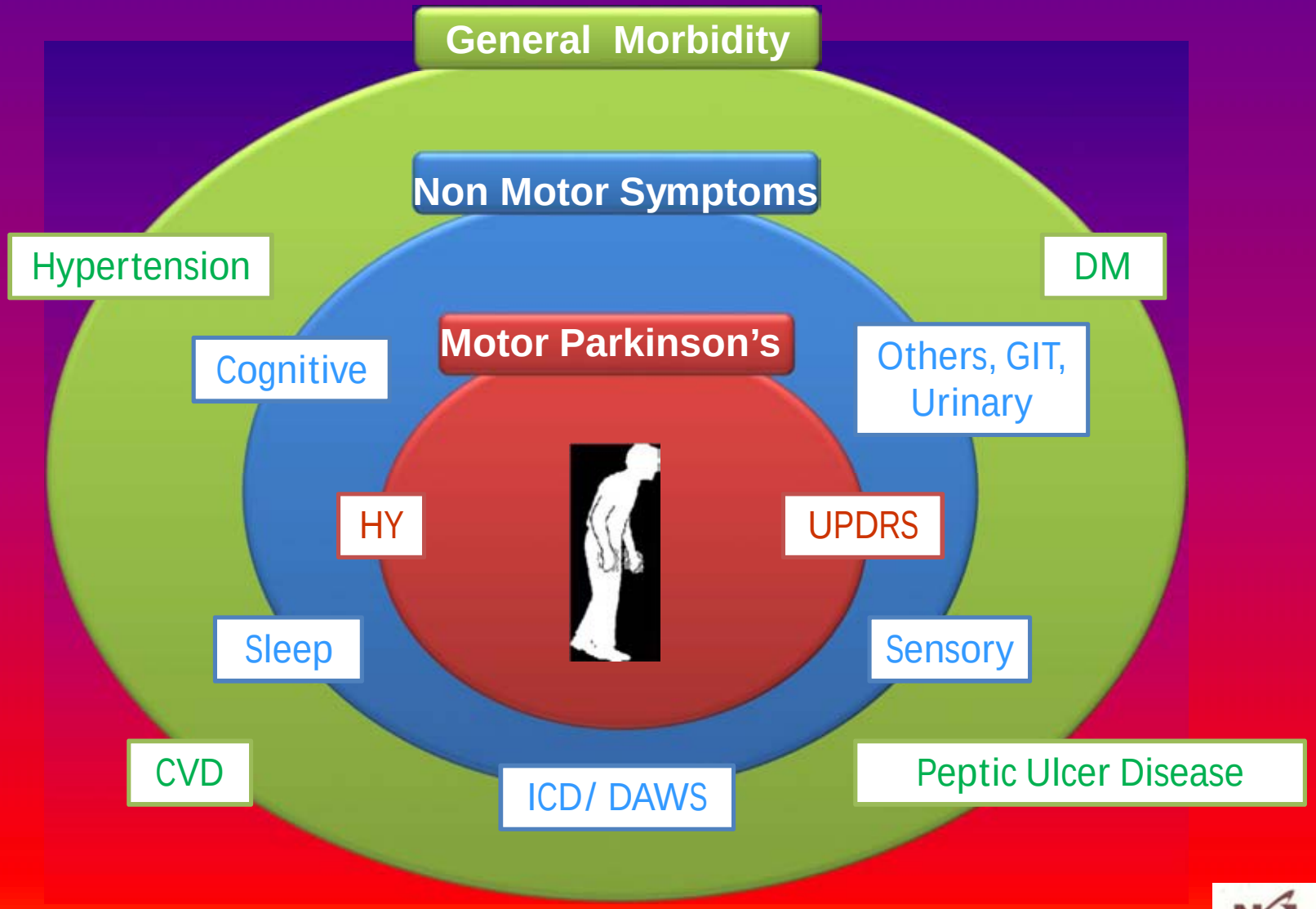
The Multi-Morbid PD



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Kings Parkinson's Centre of Excellence Research Team

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