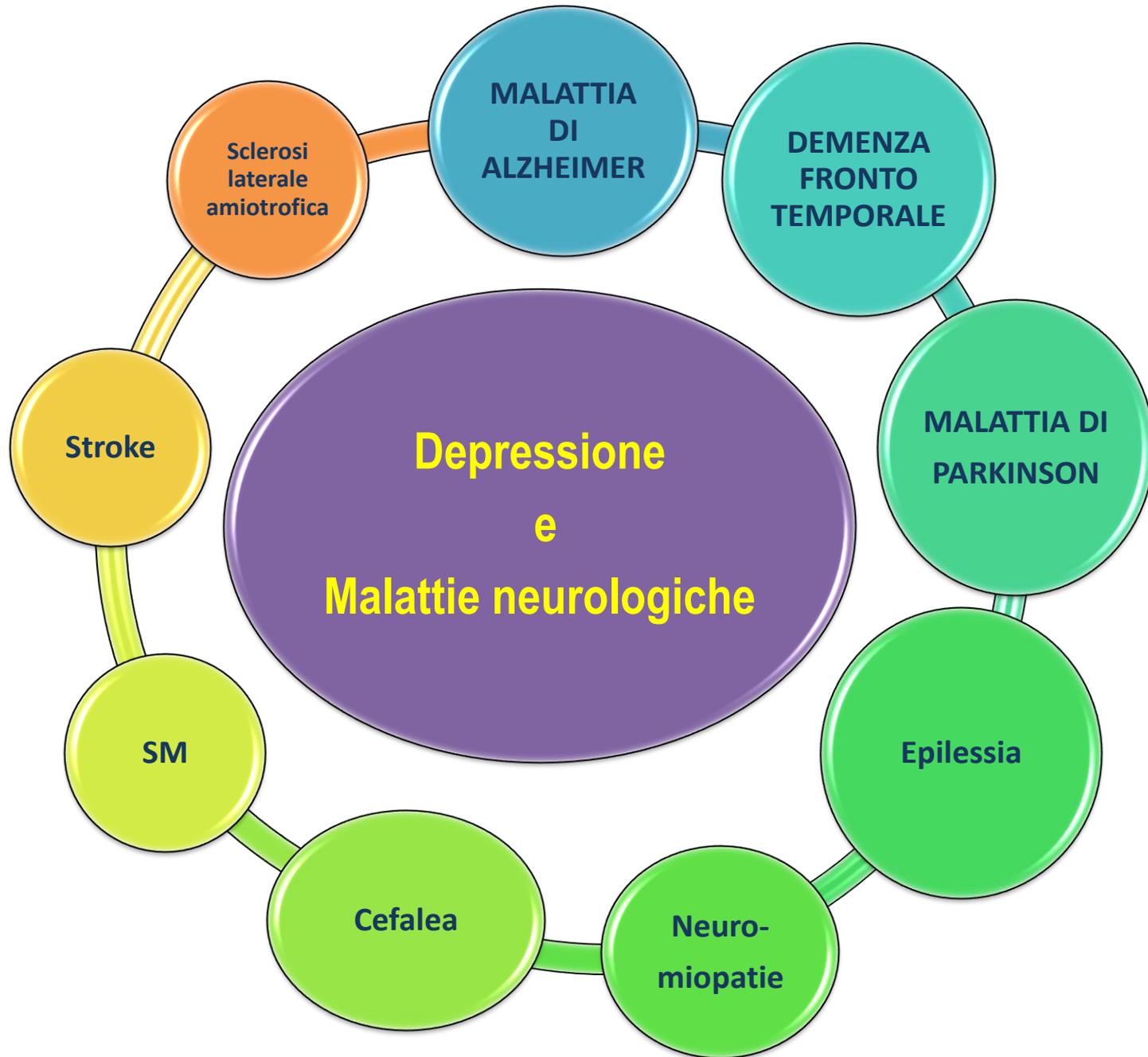


La depressione nelle malattie neurologiche

Roberto Ceravolo,

Department of Clinical and Experimental Medicine
University of Pisa

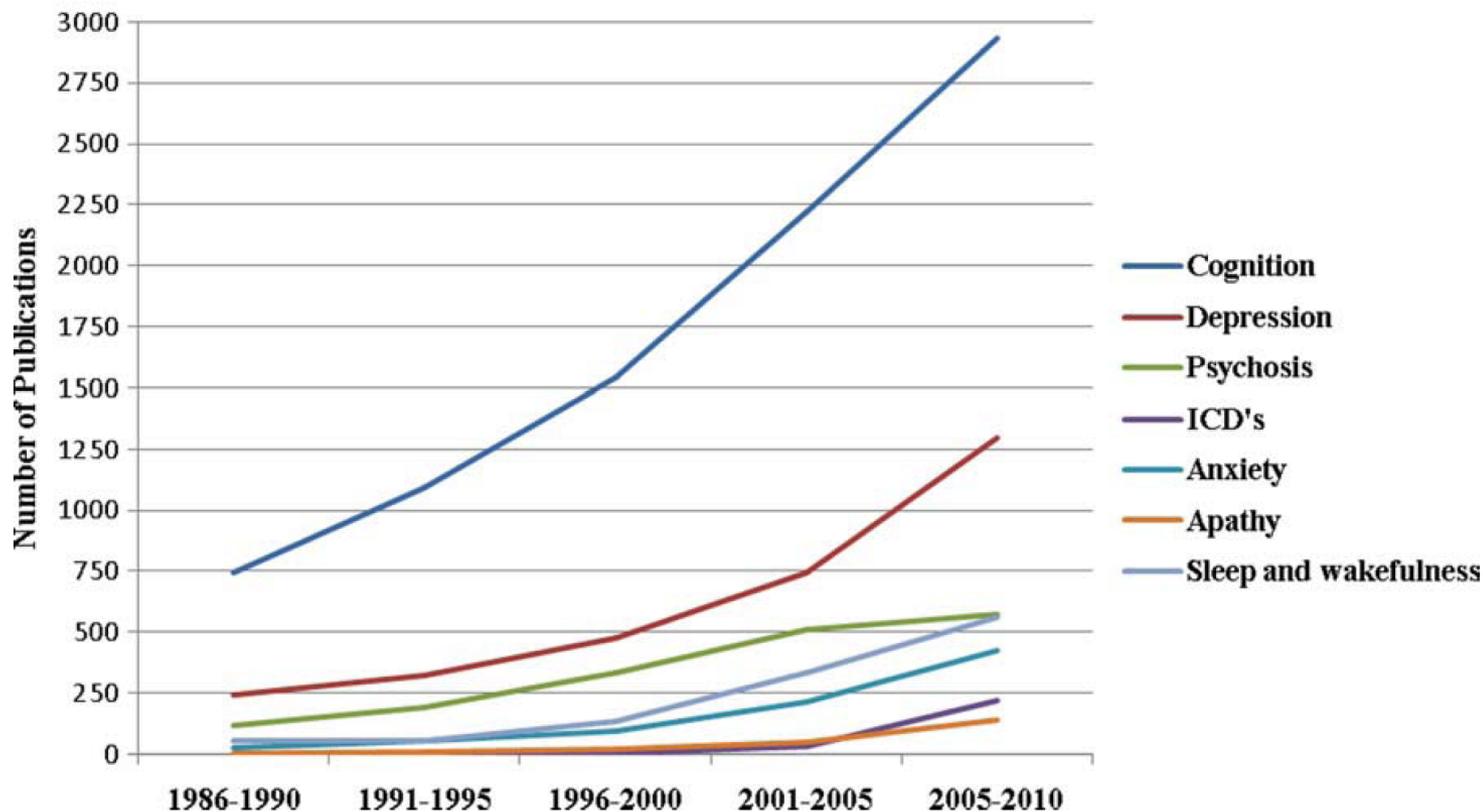




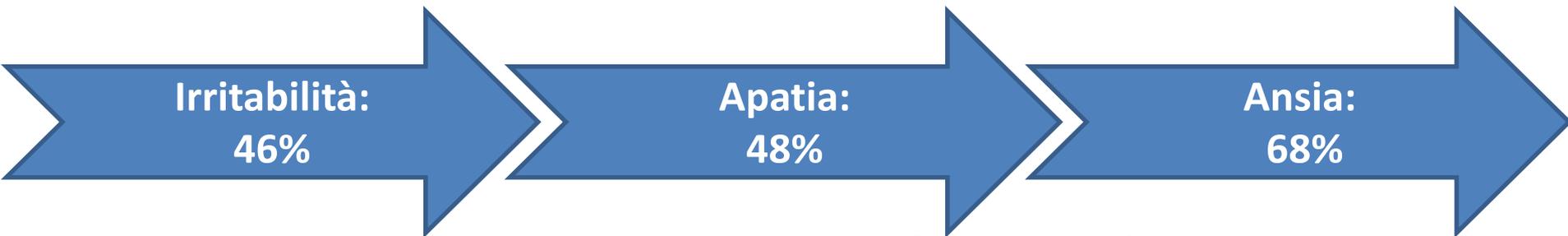
Parkinson's Disease: The Quintessential Neuropsychiatric Disorder

Daniel Weintraub, MD,^{1,2*} and David J. Burn, MD^{3,4}

Number of Publications 1986-2010



Prevalence and Correlates of Neuropsychiatric Symptoms in Parkinson's Disease Without Dementia



hanno almeno 1 sintomo neuropsichiatrico, in una popolazione con età media di 70 aa e una durata media di malattia di 5 aa

Depression in PD

Unmet needs

- ❖ Depression is the factor most significantly associated with QoL and is an important contributor to caregiver distress (Hobson *et al.*, 1999; Schrag *et al.*, 2000)
- ❖ In general practice registries, 64% of PD patients reported clinically significant depression on GDS scale but only 7% were treated with ADs (Meara *et al.*, *Age Ageing* 1999;28:38)
- ❖ In a movement disorder clinic, 34% of patients met diagnostic criteria for depressive disorder, but 65% were not treated with ADs (Weintraub, *J Geriatr Psych Neurol*, 2003;16:178-83)
- ❖ Over 1000 PD patients in 6 countries, 50% had significant depression as measured by BDI, however only 1% of patients had revealed depressive symptoms to the clinicians (GPDS, *Mov Disord* 2002;17:60-67)

Antidepressant Studies in Parkinson's Disease: A Review and Meta-Analysis

Daniel Weintraub, MD,^{1-4*} Knashawn H. Morales, ScD,⁵ Paul J. Moberg, PhD,^{1,3}
Warren B. Bilker, PhD,⁵ Catherine Balderston, MS,¹ John E. Duda, MD,^{2,3} Ira R. Katz, MD, PhD,^{1,4}
and Matthew B. Stern, MD^{2,3}

- ❖ Inclusion criteria: Antidepressant treatment in PD reporting outcome measure
- ❖ 27 studies from 1965 to 2003; total patient population=772 subjects
- ❖ 16/27 were specifically designed for depression in PD
- ❖ Only 11/27 studies suitable for meta-analysis
- ❖ Only 2 studies with Double Blind versus placebo design

Despite the high prevalence of depression and antidepressant use in PD, controlled treatment research has been almost non-existent. Meta-analysis results suggest a large but nonspecific effect for depression treatment in PD. In addition, PD patients may benefit less from antidepressant treatment, particularly selective serotonin reuptake inhibitors, than do elderly patients without PD. © 2005 Movement Disorder Society



Depression in PD

Under recognized

Misdiagnosed

Under treated

BASTOGNE 505 Km

COPENHAGUE 1490 Km

MOSCOU 3160 Km

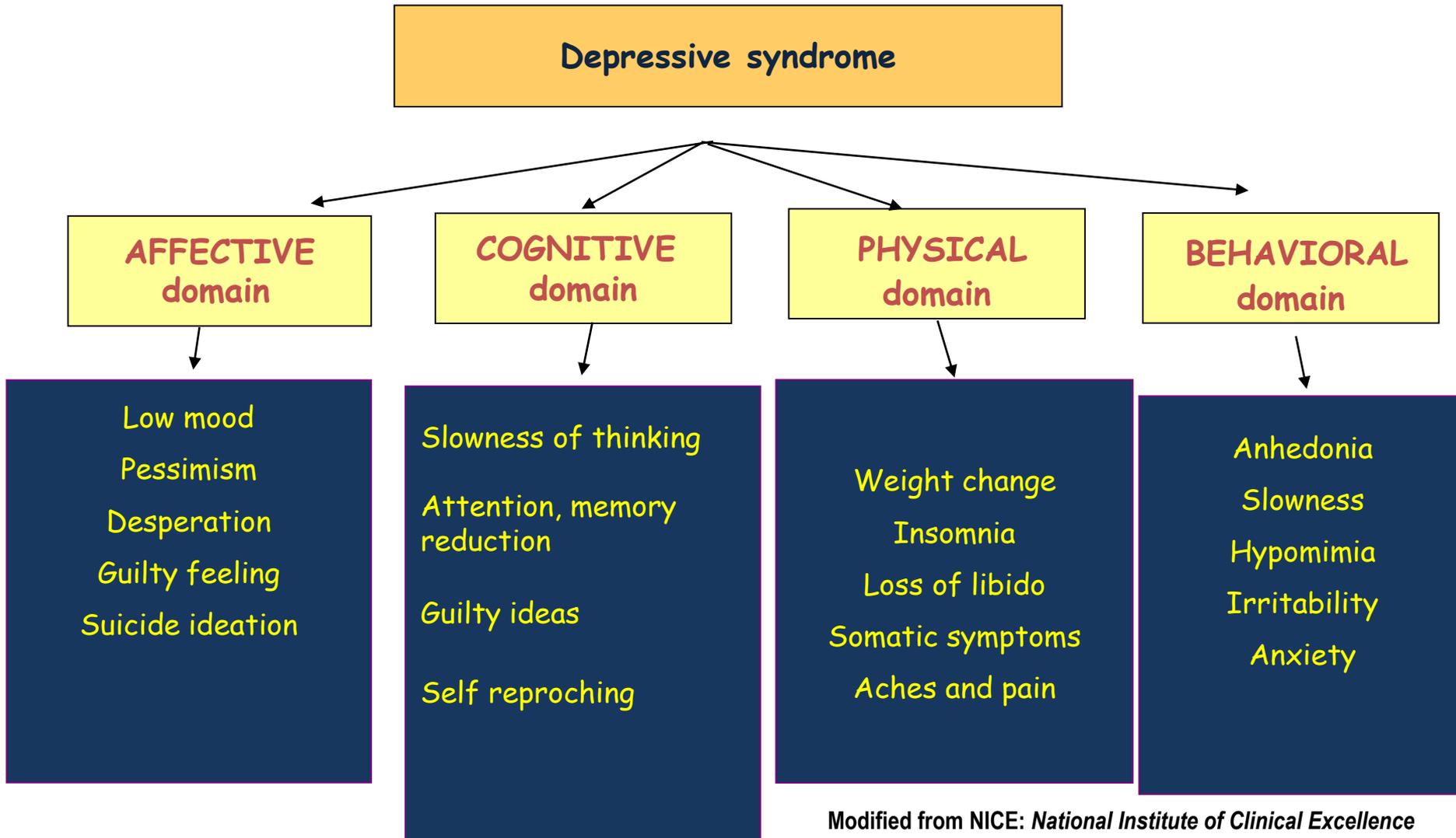
LE CAIRE 3460 Km

MADRID 1362 Km

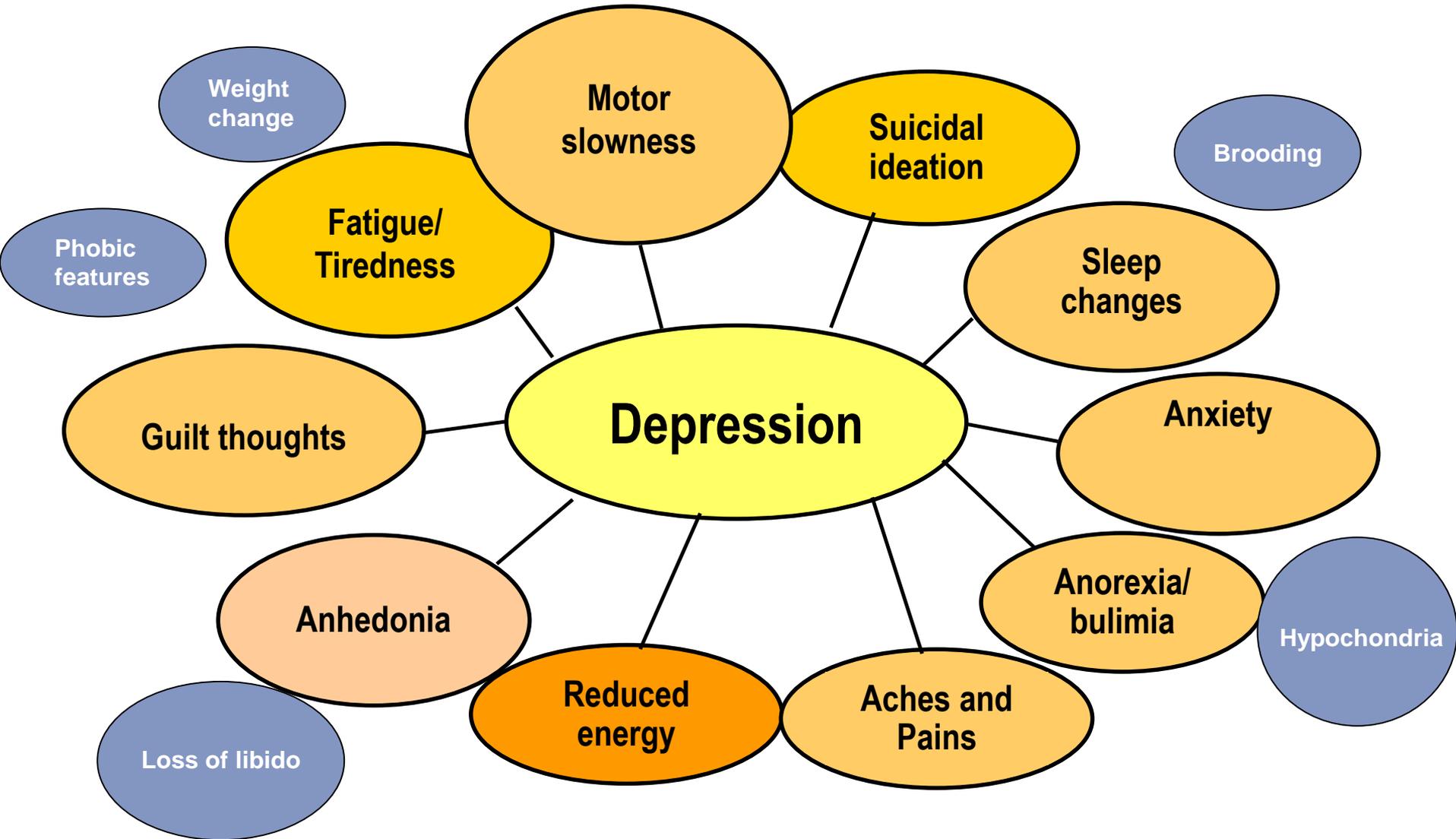
TOBROUK 2780 Km

BAR 0.015 Km

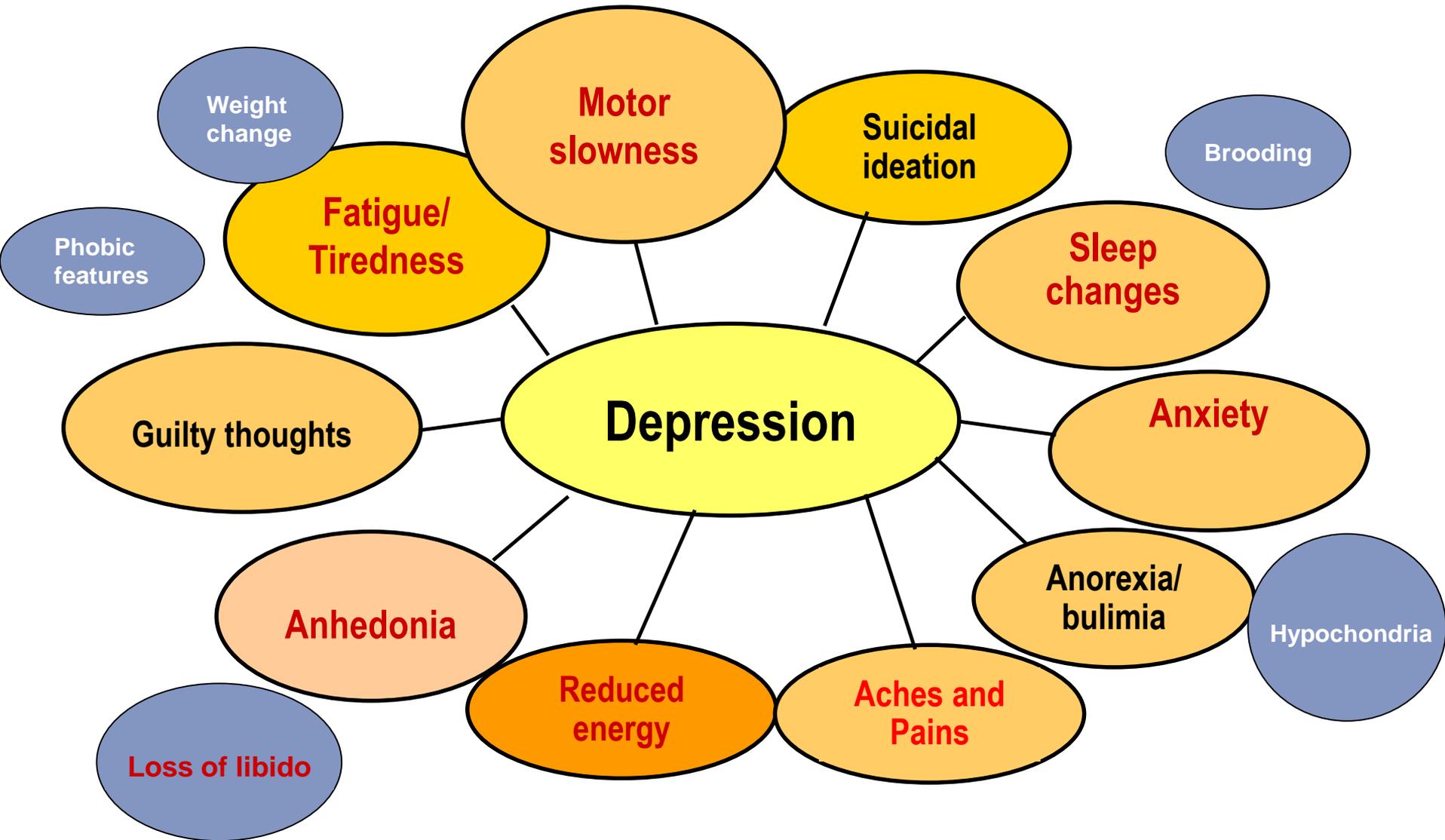
Depression: NICE criteria



DEPRESSION GALAXY



PD DEPRESSION GALAXY

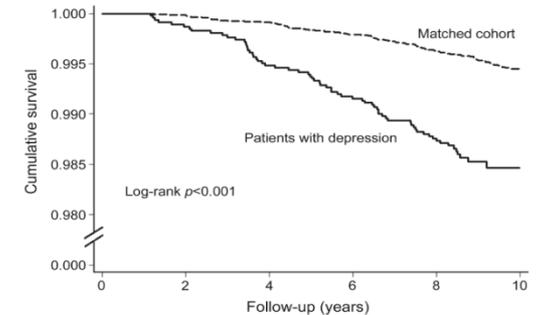


Risk of Parkinson disease after depression

A nationwide population-based study

	Adjusted HR (95% CI, p value)
Including all patients diagnosed with PD in the study period	
Sex (male = 1, female = 0)	0.99 (0.72-1.35, 0.941)
Age	1.09 (1.08-1.10, <0.001 ^a)
Depression (1 = depression, 0 = control)	3.24 (2.36-4.44, <0.001^a)
Excluding patients diagnosed with PD in the first 2 y after enrollment	
Sex (male = 1, female = 0)	0.91 (0.66-1.26, 0.576)
Age	1.09 (1.08-1.10, <0.001 ^a)
Depression (1 = depression, 0 = control)	3.10 (2.23-4.30, <0.001^a)
Excluding patients diagnosed with PD in the first 5 y after enrollment	
Sex (male = 1, female = 0)	1.05 (0.71-1.55, 0.794)
Age	1.08 (1.07-1.10, <0.001 ^a)
Depression (1 = depression, 0 = control)	2.84 (1.89-4.27, <0.001^a)

Rischio di MP



Periodo di follow-up



4,636 p. con depressione → Malattia di Parkinson 1,42% ($p < 0,001$)

18,544 controlli

Rischio di MP aumenta quando c'è una diagnosi di depressione HR=3.24

l'età è più alta nei pazienti con depressione e PD rispetto ai pazienti depressi non PD;

Depressione difficile da trattare è un fattore di rischio per MP indipendente

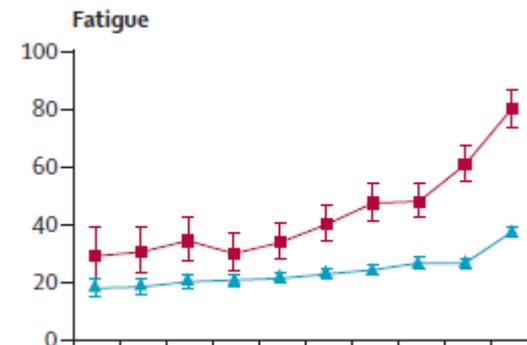
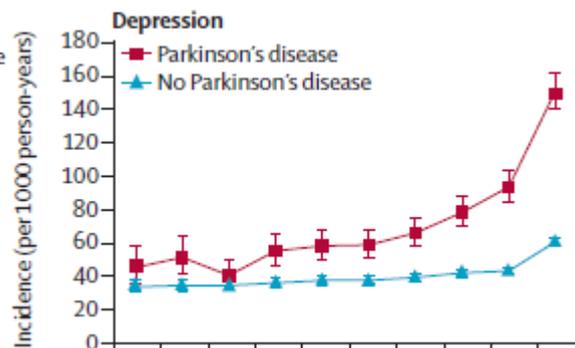
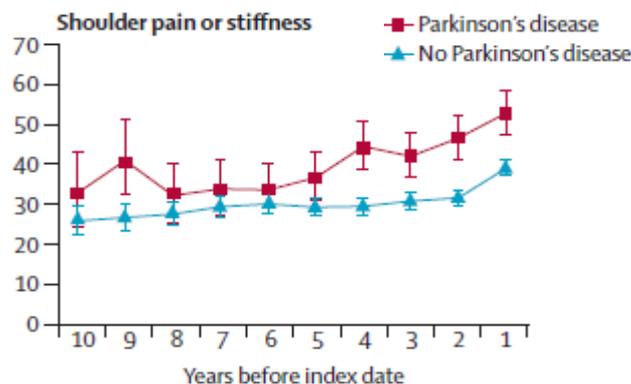
Prediagnostic presentations of Parkinson's disease in primary care: a case-control study

Anette Schrag, Laura Horsfall, Kate Walters, Alastair Noyce, Irene Petersen

Lancet Neurol 2014; 14: 57-64

	Within 0 to <2 years		≥2 years to <5 years		≥5 years to <10 years	
	Parkinson's disease (n=7232)	Controls (n=40 541)	Parkinson's disease (n=4769)	Controls (n=25 544)	Parkinson's disease (n=1680)	Controls (n=8305)
Tremor	2946 (41%)	184 (<1%)	311 (7%)	118 (<1%)	29 (2%)	41 (<1%)
Constipation	2326 (32%)	7598 (19%)	1196 (25%)	3890 (15%)	335 (20%)	1202 (14%)
Fatigue	761 (11%)	2129 (5%)	430 (9%)	1472 (6%)	180 (11%)	618 (7%)
Dizziness	725 (10%)	2411 (6%)	486 (10%)	1629 (6%)	206 (12%)	723 (9%)
Depression	696 (10%)	1724 (4%)	312 (7%)	1035 (4%)	94 (6%)	409 (5%)
Shoulder pain or stiffness	528 (7%)	2263 (6%)	407 (9%)	1729 (7%)	175 (10%)	803 (10%)
Anxiety	624 (9%)	1505 (4%)	333 (7%)	1039 (4%)	136 (8%)	504 (6%)
Neck pain or stiffness	301 (4%)	1613 (4%)	224 (5%)	1301 (5%)	128 (8%)	667 (8%)
Urinary dysfunction	338 (5%)	815 (2%)	167 (4%)	459 (2%)	53 (3%)	170 (2%)
Erectile dysfunction	293/4323 (7%)	1434/24 076 (6%)	242/2885 (8%)	1072/15 330 (7%)	116/1024 (11%)	416/5017 (8%)
Insomnia	314 (4%)	1286 (3%)	190 (4%)	850 (3%)	85 (5%)	386 (5%)
Balance impairments	300 (4%)	379 (1%)	78 (2%)	196 (1%)	21 (1%)	62 (1%)
Hypotension	153 (2%)	346 (1%)	80 (2%)	204 (1%)	27 (2%)	61 (1%)
Memory problems	197 (3%)	520 (1%)	61 (1%)	187 (1%)	8 (<1%)	47 (1%)
Rigidity	201 (3%)	52 (<1%)	11 (<1%)	36 (<1%)	3 (<1%)	16 (<1%)

8166 PD patients
46755 individuals without PD



The Onset of Nonmotor Symptoms in Parkinson's Disease (The ONSET PD Study)

Mov Dis 2014

NMS	Onset Before OMS n (% of All PD Subjects)	Timespans Before OMS ^a		
		<2 Years n (% ^a)	2 to 10 Years n (% ^a)	>10 Years n (% ^a)
Smell loss ^c	44 (88)	11 (25)	17(39)	16 (36)
Constipation ^c	33 (78)	7 (21)	5 (15)	21 (63)
Mood disturbances	32 (68)	9 (28)	12 (37.5)	11 (34.5)
H/C intolerance	31 (81)	9 (29)	9 (29)	13 (57)
Dream-enacting behavior ^c	24 (77)	3 (12.5)	9 (37.5)	12 (50)
Frequent nightmares ^c	21 (81)	3 (13)	4 (17)	14 (61)
Excessive sweating	20 (67)	5 (25)	7 (35)	8 (40)
Memory complains	19 (54)	11 (58)	8 (42)	0 (0)
Fatigue	19 (49)	7 (36.5)	10 (52.5)	2 (10)
Inattention	18 (60)	14 (78)	1 (5.6)	3 (16.6)
Anhedonia	18 (51)	12 (68)	3 (16)	3 (16)
Apathy	17 (50)	12 (71)	4(23)	1 (6)
Postprandial fullness	16 (64)	4 (25)	2 (12.5)	10 (62.5)
FDS	16 (52)	4 (25)	5 (31)	7 (44)
Unexplained pain	13 (59)	4 (31)	6 (46)	3 (23)
Taste loss ^c	11 (73)	0	10 (91)	1 (9)
Chest pain ^c	11 (100)	1 (9)	5 (45.5)	5 (45.5)

NON MOTOR SYMPTOMS were assessed by a custom-made questionnaire in **109 newly diagnosed untreated PD patients** and **107 controls**

	PD (n = 109)	Controls (n = 107)	OR	95% CI
Significant NMS	%	%		
Taste loss	14	1	16.9	2.1-130
Dream-enacting behavior	28	3	13.77	4.06-46.71
Anhedonia	32	6	7.96	3.18-19.90
Smell loss	46	11	6.7	3.3-13.6
Fatigue	36	9	5.4	2.5-11.5
Frequent nightmares	24	6	5.27	2.07-13.41
Unexplained pain	20	6	4.25	1.65-10.97
Constipation	38.5	13	4.1	2.1-8.2
Chest pain	10	3	3.89	1.0-14.36
Mood disturbances	43	19	3.29	1.78-6.10
Apathy	31	12	3.27	1.61-6.51
Inattention	28	11	3	1.44-6.25
Heat/cold intolerance	35	19	2.32	1.24-4.35
Excessive daytime sleepiness	28	15	2.26	1.15-4.43
Postprandial fullness	23	12	2.1	1.0-4.5
Excessive sweating	28	16	2.01	1.03-3.91
Memory complains	32	20	1.93	1.03-3.61

- Anhedonia, apathy, memory complaints and inattention occurred more frequently during the 2-year premotor period
- Smell loss, mood disturbances, taste loss, excessive sweating, fatigue, and pain were more frequently reported in the 2- to 10-year premotor period
- Constipation, dream-enacting behavior, excessive daytime sleepiness, and postprandial fullness were frequently perceived more than 10 years before motor symptoms.

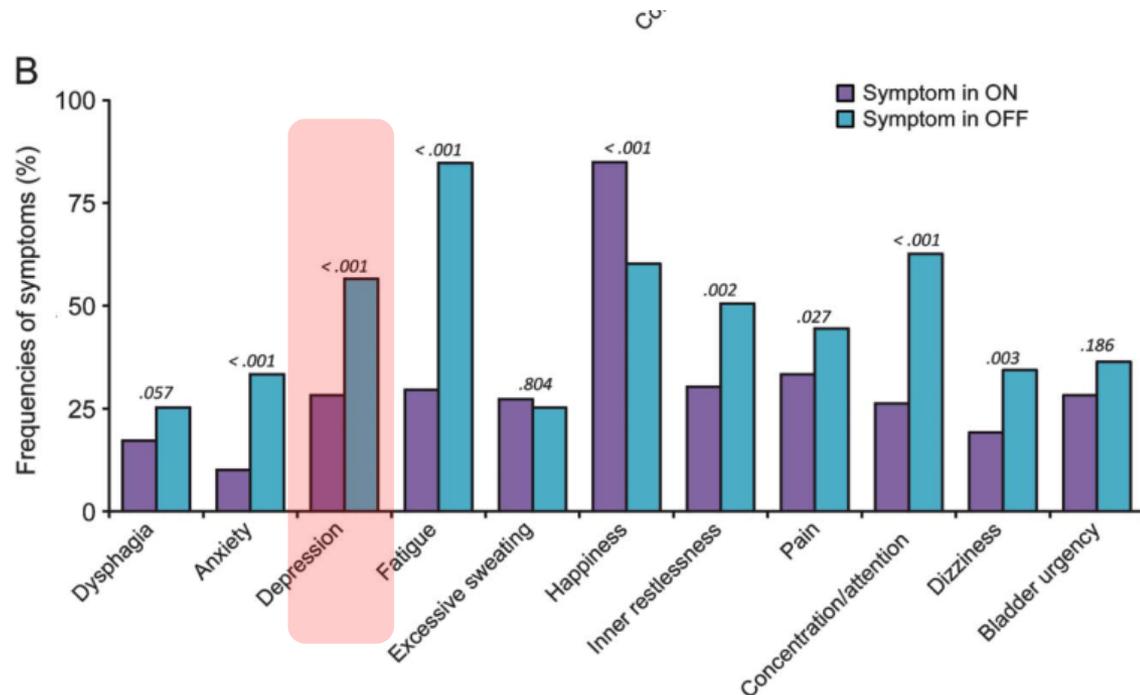
Nonmotor fluctuations in Parkinson disease

Severity and correlation with motor complications

Alexander Storch,
Neurology 2013

- Fluttuazioni non motorie (NMS) presenti nel 100% dei pz con fluttuazioni motorie, tutti i SNM sono peggiori nelle fasi OFF
- La gravità dei NMS non correla con l'entità delle variazioni motorie

in circa 2/3 dei pz
l'ansia e la
depressione erano
presenti solo in fase
off



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

Psychiatric symptoms (10)	Anhedonia	114 (10.6)
	Anxiety	598 (55.8)
	Panic attacks	45 (4.2)
	Aggressive behavior	38 (3.5)
	Suicidal ideas	16 (1.5)
	Nervousness	192 (17.9)
	Frightened without reason	58 (5.4)
	Sadness/depression	241 (22.5)
	Delirium	17 (1.6)
	Hallucinations	39 (3.6)

Depressione/MP

Research Review

Provisional Diagnostic Criteria for Depression in Parkinson's Disease: Report of an NINDS/NIMH Work Group

Laura Marsh, MD,^{1*} William M. McDonald, MD,² Jeffrey Cummings, MD,³ Bernard Ravina, MD,⁴ and the NINDS/NIMH Work Group on Depression and Parkinson's Disease

- **La diagnosi dovrebbe essere fatta seguendo i criteri DSM-V**
- **La depressione sub-sindromica dovrebbe essere inclusa come categoria diagnostica negli studi**
- **Il momento della valutazione dovrebbe essere (on o off)**
- **Per i paziente con demenza dovrebbero essere interrogati i caregivers**
- **L'anedonia dovrebbe essere considerata solo sulla base della perdita di piacere.**

Depressione/MP

I sintomi di depressione in MP sono diversi rispetto a quelli solitamente presenti nella depressione primaria: i pazienti con MP hanno meno senso di colpa, meno biasimo ma maggiore irritabilità, tristezza che correlano con lo stato di salute, raro il suicidio.

Depression in Parkinson's disease

Must be properly diagnosed and treated to avoid serious morbidity

BMJ VOLUME 320 13 MAY 2000

Depressione/MP

- Associata con aumento della disabilità
- Peggiora la qualità della vita
- Tende ad essere sottodiagnosticata
sottotrattata

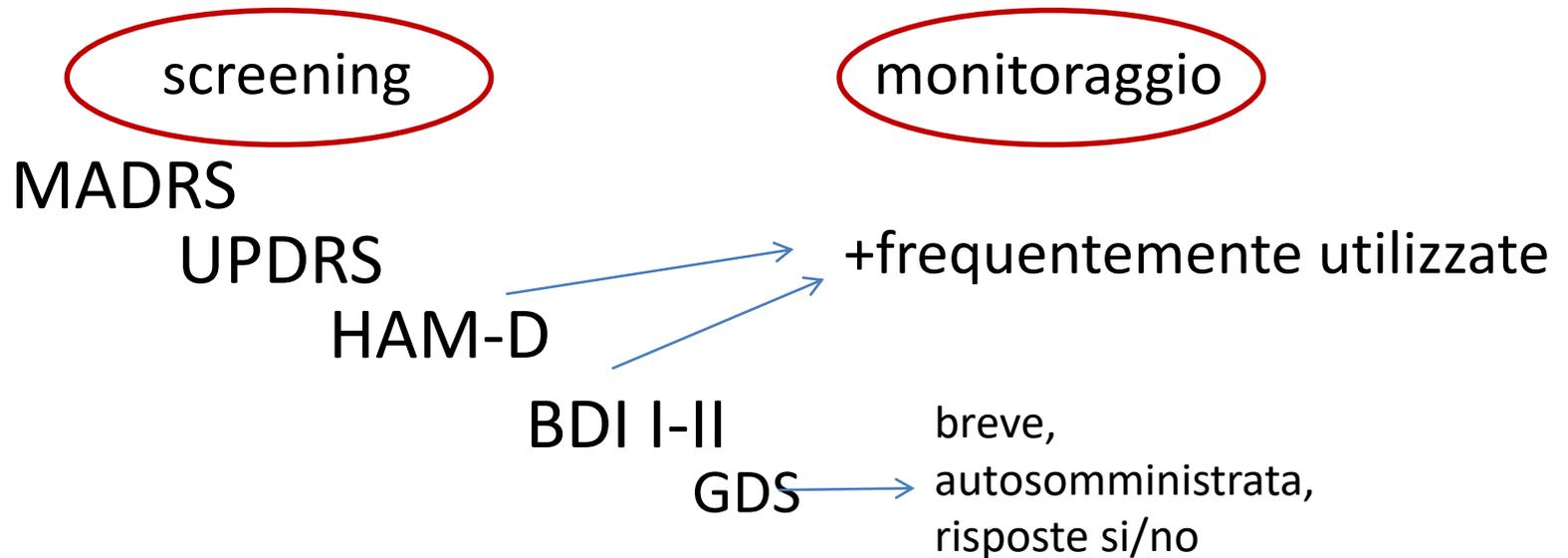


Solo 20-26% dei p. con MP
e depressione ricevono un
trattamento

([Richard IH, Neurology.](#) 1997 Oct)
(Weintraub D. J Geriatr Psyc Neurol 2003)

Depressione/MP

Scale cliniche depressione in MP



Scala clinica	Cut-off suggerito nella MP
Hamilton Depression (HAM-D)	9-10
Beck Depression Inventory (BDI)	13-14
Geriatric Depression Scale 30 (GDS 30)	9-10
Geriatric Depression Scale 15 (GDS 15)	4-5
Montgomery-Asberg Depression Rating Scale (MADRS)	14-15

Depression/PD

Prevalence of Depressive Disorder and Depressive symptoms in PD

TABLE 3. *Prevalence (%) of major depressive disorder and clinically relevant depressive symptoms in different settings*

Population	Major depressive disorder		Clinically relevant depressive symptoms	
	Number of studies	Prevalence	Number of studies	Prevalence
General population	4	8.1	5	10.8
General practice	0		2	42.3
Outpatient setting	11	24.0	25	40.4
Inpatient setting	1	21.7	3	54.3
Nursing home	0		1	32.7

Major depression: 17%
Minor depression: 22%
Dysthymia: 13%

Clinically significant depressive symptoms: 36.1%

“DEPRESSION” in PD: what should we treat?

❖ Depressive Disorder ?
(Major, Minor, Dysthymia)



❖ DSM-V criteria for
Diagnosis of depression

❖ Depressive Symptoms ?



❖ screening for depressive
symptoms

Depression in PD: not ONE disease



DEPRESSIONE E SEROTONINA

Pazienti con MP

Riduzione dei livelli di 5-HT e dei trasportatori SERT a livello striatale (soprattutto caudato)

(Kish S. Brain 2008)

Ridotti trasportatori SERT nella regione orbitofrontale, corteccia del cingolo, insula, amigdala e ippocampo

(Guttman Eur J. Neurol 2007)

(Albin J. Cereb. Blood Flow Metab 2008)

Pazienti con MP e depressione

Riduzione dei neuroni serotoninergici nucleo dorsale del rafe

(Pauls, J Neuropathol. Exp. Neurol. 1991)

Ridotta ecogenicità nel rafe mesencefalico alla sonografia transcranica

(Berg, J. Neurol. 1999)

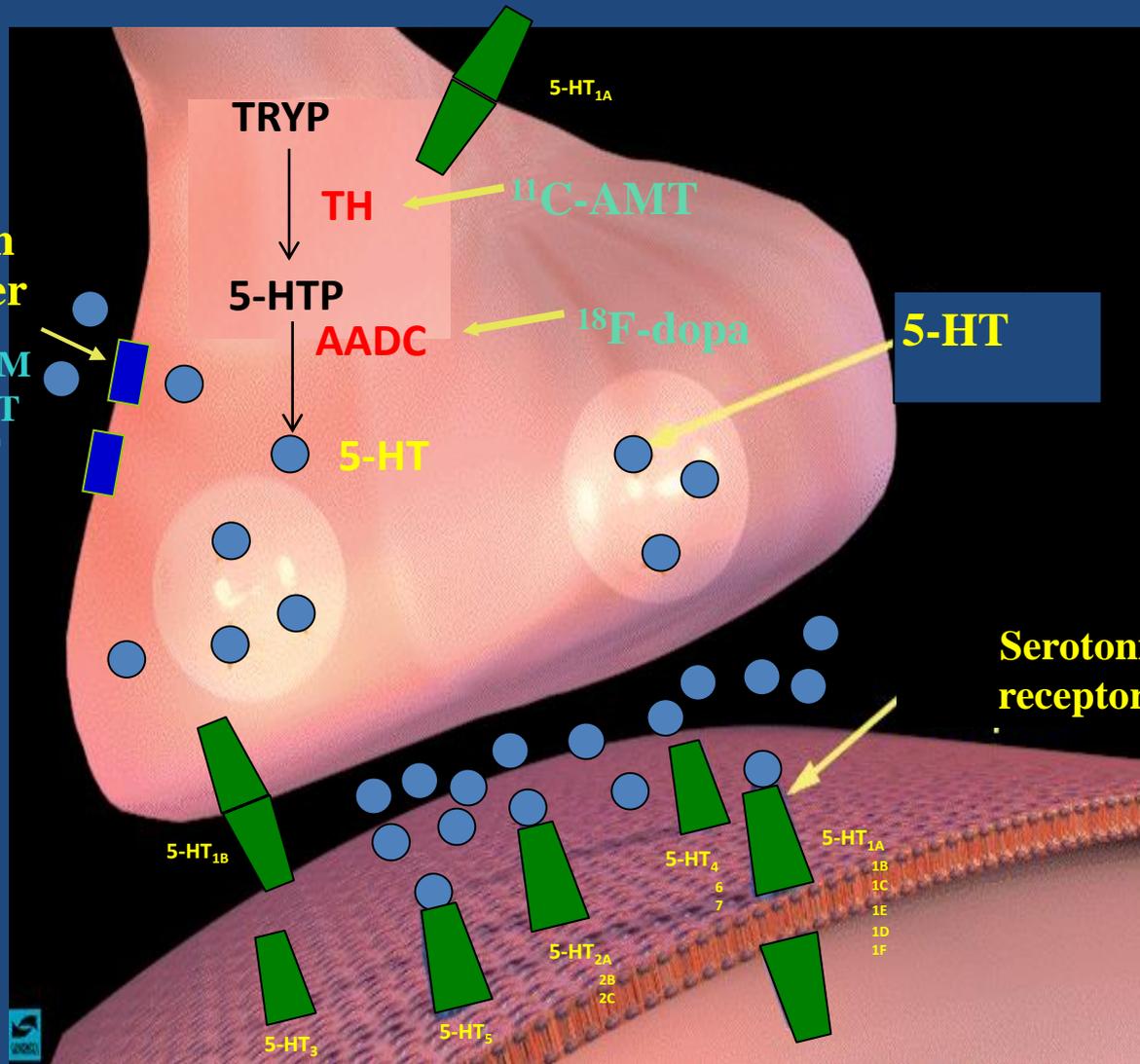
Natural history of degenerative parkinsonism

Possible correlation anatomo-clinic

	Presumed neuropathological substrate	Symptoms documented in the premotor phase	Braak stage
Loss of smell: impaired detection, identification, and discrimination of odours	Olfactory bulb, anterior olfactory nucleus, amygdala, perirhinal cortex	Hyposmia	1
Autonomic dysfunction: gastrointestinal disturbances (constipation), urinary dysfunction (urinary urgency), sexual dysfunction (erectile dysfunction in men), orthostatic hypotension	Dorsal motor nucleus of the vagus nerve, parasympathetic vagal output, enteric nervous system, sympathetic ganglia, intermediolateral column of the spinal cord	Constipation, urinary or erectile dysfunction	2
Sleep disturbances: REM sleep behaviour disorder, excessive daytime sleepiness	Subcoeruleus, pedunculopontine and magnocellularis nuclei, amygdala	REM sleep behaviour disorder, excessive daytime sleepiness	2, 3
Affective-behavioural disorders: depression, anxiety, apathy	Coeruleus-subcoeruleus complex, raphe nuclei, amygdala, mesocortical and mesolimbic dopaminergic systems, cingulate cortex	Depression, anxiety	2, 3

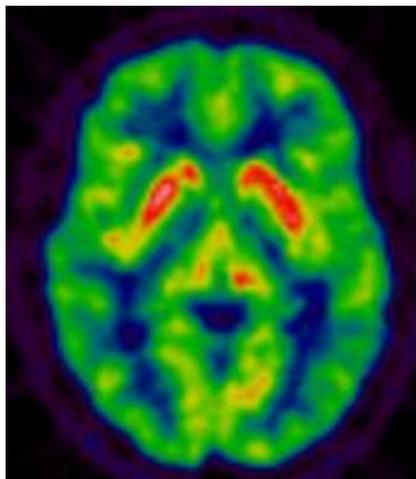
Imaging serotonin terminal function

**Serotonin
transporter**
¹¹C-DASB
¹¹C-MADAM
¹²³I-beta CIT
¹²³I-FP-CIT

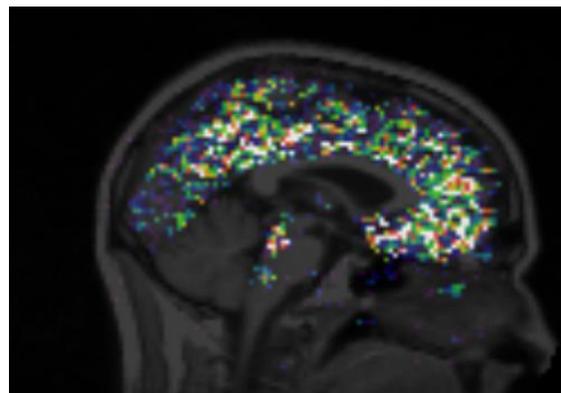


**Serotonin
receptors**

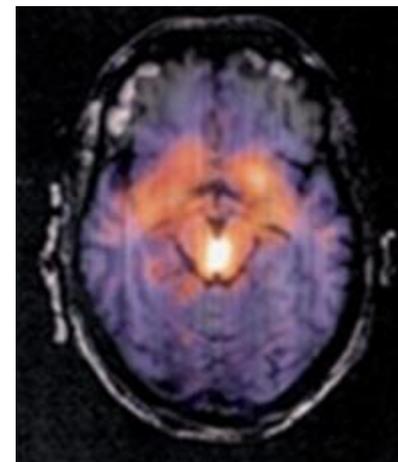
PET/SPECT ligands



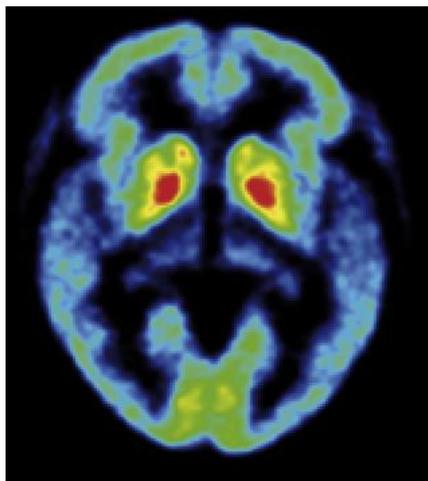
^{11}C -DASB
Serotonin transporter



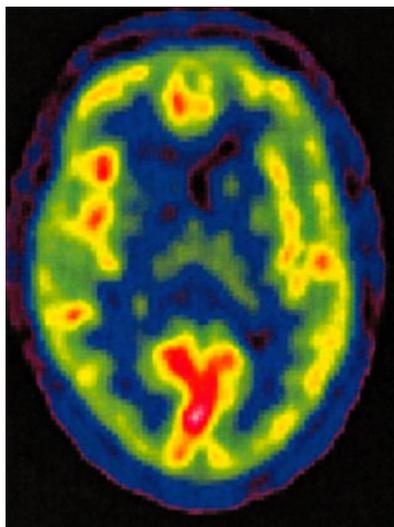
^{11}C -WAY100635
Serotonin HT_{1A} receptor



^{123}I -FP-CIT
Serotonin and Dopamine
transporter



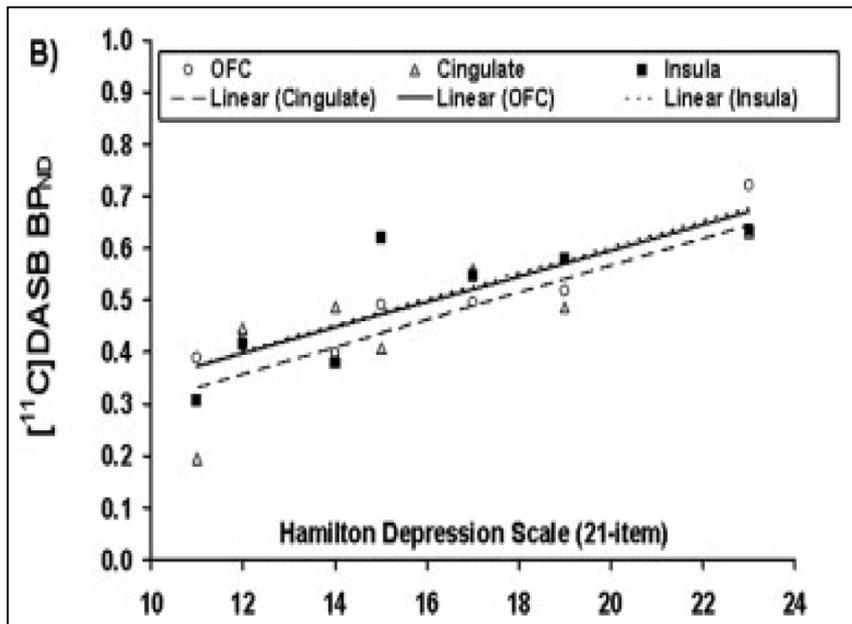
^{11}C -AZ10419369
Serotonin HT_{1B} receptor



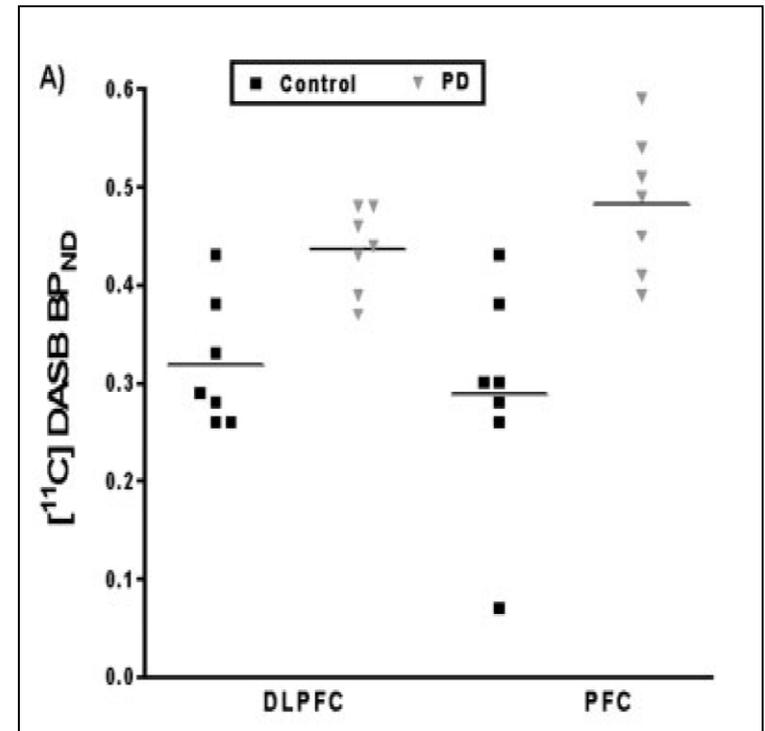
^{18}F -altanserin
Serotonin HT_{2A} receptor

Elevated Serotonin Transporter Binding in Depressed Patients with Parkinson's Disease: A Preliminary PET Study with [¹¹C]DASB

Isabelle Boileau, PhD,^{1*} Jerry J. Warsh, MD,²
 Mark Guttman, MD,^{1,3} Jean A. Saint-Cyr, PhD,^{1,4}
 Tina McCluskey, MSc,¹ Pablo Rusjan, PhD,⁵
 Sylvain Houle, MD,⁵ Alan A. Wilson, PhD,⁵
 Jeffrey H. Meyer, MD, PhD,⁵
 and Stephen J. Kish, PhD¹



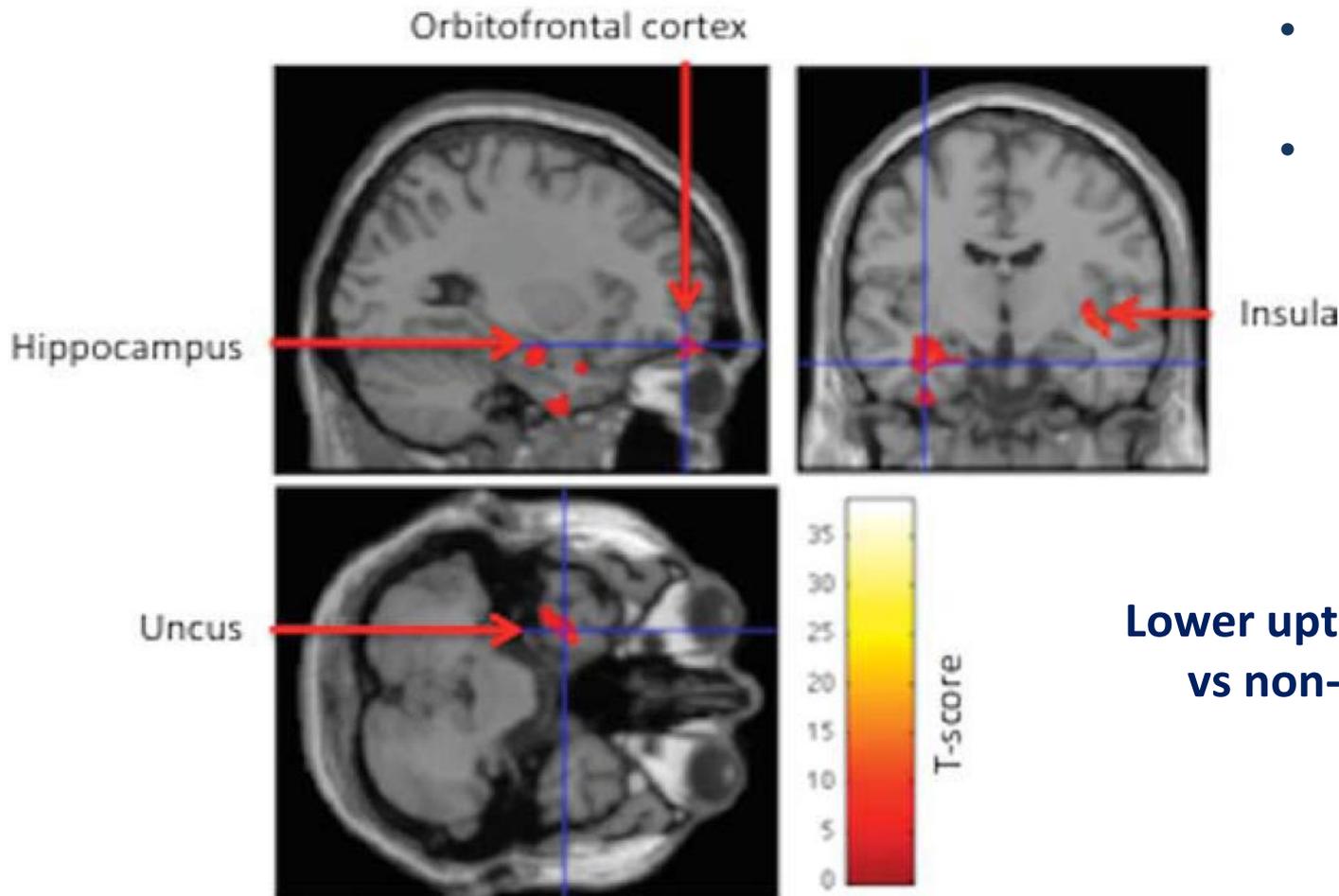
[¹¹C]DASB binding positively correlated with depression but not with disease severity/duration.



wide-spread increase in [¹¹C]DASB in PD/depression

1. dorsolateral cortices
2. prefrontal cortices

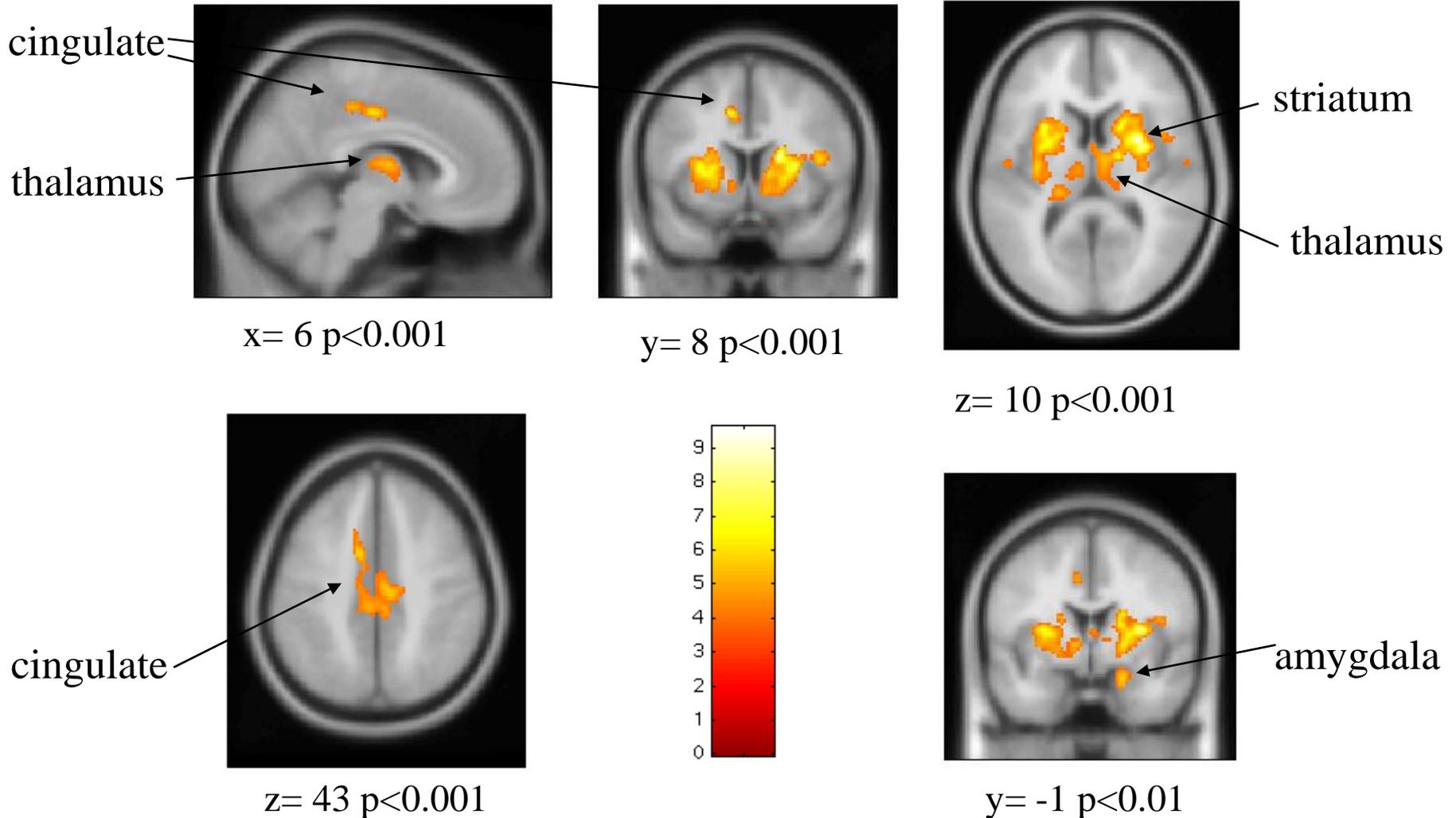
Role of Serotonergic 1A Receptor Dysfunction in Depression Associated with Parkinson's Disease



- 8 non depressed PD patients
- 4 depressed PD patients

Lower uptake in depressed vs non-depressed PD

Lower ^{11}C -DASB uptake in PD with depression



7 PD depr < 7 PD without depression

Studi sull'utilizzo di SSRI nei pazienti con Malattia di Parkinson e depressione (2003-2013)

Autore anno	Campione	Disegno	Farmaco	Scala usata	Risultati (decremento punteggio scala)	Follow up
Leentjens 2003 ³³	6 6	Doppio cieco	Sertralina Placebo	MADRS	-9 -11	10 settimane
Fregni 2004 ³⁴	21 21	Doppio cieco	Fluoxetina TMS	HAM D /BDI	-9 [§] /-8 [§] -10 [§] /-8 [§]	8 settimane
Serrano Duenas 2002 ³⁵	37 40	Randomizzato	Fluoxetina Amitriptilina	HAM D	Inefficace Efficace	12 mesi
Avila 2003 ³⁶	7 9	Randomizzato	Fluoxetina Nefazodone	BDI	Ugualmente efficaci [§]	12 settimane
Antonini 2006 ³⁷	12 11	Doppio cieco	Sertralina Amitriptilina	HAM D	-12 [§] -11 [§]	3 mesi
Barone 2006 ³⁸	33 34	Doppio cieco	Pramipexole Sertraline	HAM D	-10 [§] -9 [§]	12 settimane
Devos 2008 ²³	16 15 17	Doppio cieco	Placebo Citalopram Desimipramina	MADRS	-9 -14* -20*	4 settimane
Menza 2009 ²¹	17 18 17	Doppio cieco	Placebo Paroxetina Nortriptilina	HAM D	-4 -6 -11*	8 settimane
Richard 2012 ²⁴	39 42 34	Doppio cieco	Placebo Paroxetina Venlafaxina ER	HAM D	-6.8 -13* -11*	12 settimane

* differenza significativa rispetto al placebo

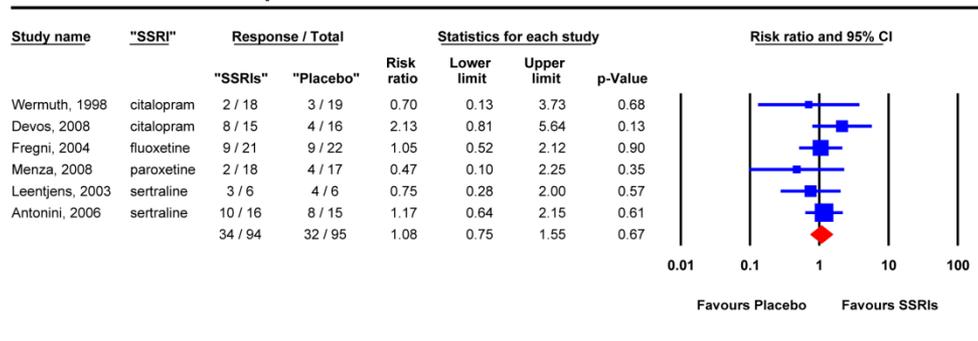
§ differenza significativa rispetto al basale

Depressione/MP

Trattamento della depressione in MP

Efficacy and Acceptability of selective serotonin reuptake inhibitors for the treatment of depression in Parkinson's disease: a systematic review and meta-analysis of randomized controlled trials
Petros Skapinakis et al.

Risk Ratio for response of SSRIs vs Placebo in Parkinson's Disease Patients



Meta Analysis (Random Effects)

- ***Il 63% degli antidepressivi prescritti sono SSRI e nel 7% sono TCA.***
- ***C'è ancora incertezza sull'efficacia degli SSRI nella depressione in MP.***
- ***I risultati di questo studio mostrano che la pratica clinica attuale non è supportata da forti evidenze.***

Depression and PD: clinical features

Core symptom

Anhedonia

Low mood and impaired interest or ability to experience pleasure

Other clinical features:

1. **Altered sleep patterns**
2. **Change in weight**
3. **Loss of libido**
4. **Psychomotor retardation**
5. **Reduced energy**

Does dopamine dysfunction drive depression?

Malhi GS, Berk M.

Objective: To examine the evidence that dopamine (DA) dysfunction contributes to melancholic depression.

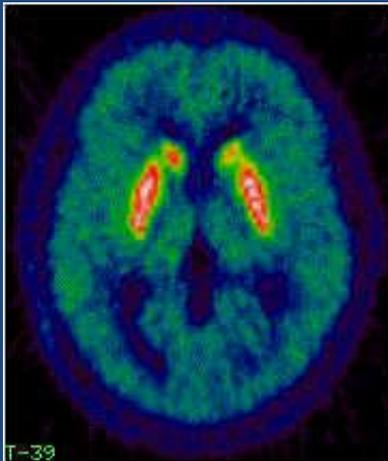
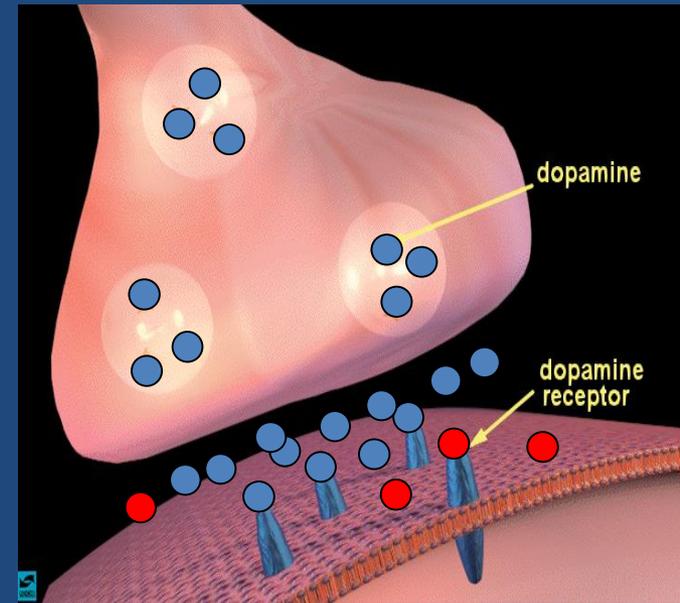
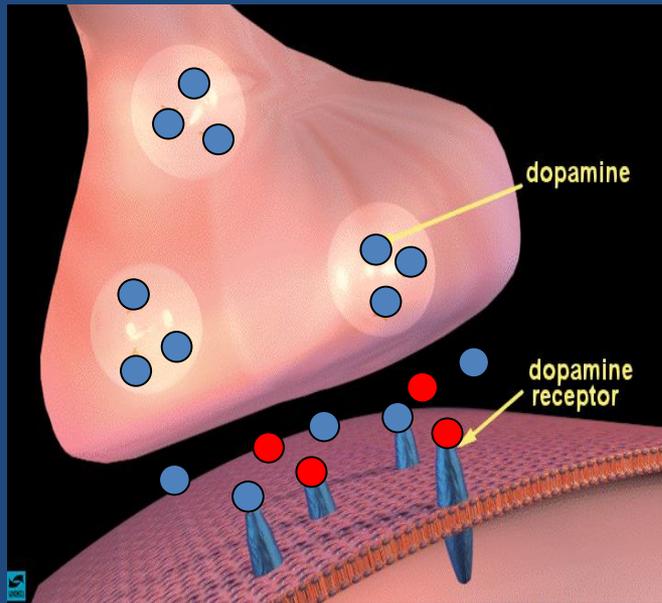
Method: Database (EMBASE, PsychLit and MEDLINE) searches using relevant key words were conducted and citations were scrutinized.

Results: In this paper, we assume that the definition of melancholia is contingent upon the presence of psychomotor disturbance (PMD). In melancholic depression PMD comprises both a cognitive and motor component and DA is found to be important in both. DA neurotransmission modulates cognition in particular in attention, adaptation and motivational processes and has a pivotal role in motor function.

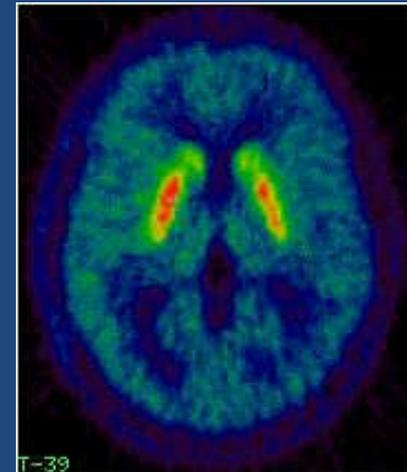
Conclusion: DA is a credible aetiological candidate for the PMD in melancholic depression. However, melancholia needs first to be characterized both clinically and in terms of its pathophysiology. In this regard, illnesses such as bipolar depression and Parkinson's disease warrant consideration as they provide suitable models of both the cognitive and motor aspects of PMD, and hold the necessary markers to better define melancholia.

Acta Psychiatr Scand 2007; 115 (Suppl. 433): 116–124

Imaging del rilascio di dopamina



**10% di riduzione
del ^{11}C raclopride
BP riflette un
incremento di 5
volte del rilascio di
Dopamina**



Striatal dopamine release after prefrontal repetitive transcranial magnetic stimulation in major depression: Preliminary results of a dynamic [^{123}I] IBZM SPECT study

Oliver Pogarell ^a, Walter Koch ^b, Gabriele Pöpperl ^b, Klaus Tatsch ^b, Franziska Jakob ^a, Peter Zwanzger ^a, Christoph Mulert ^a, Rainer Rupprecht ^a, Hans-Jürgen Möller ^a, Ulrich Hegerl ^a, Frank Padberg ^{a,*}

^a Department of Psychiatry, Ludwig-Maximilians-University, Nussbaumstr. 7, D-80336 Munich, Germany

^b Department of Nuclear Medicine, Ludwig-Maximilians-University, Munich, Germany

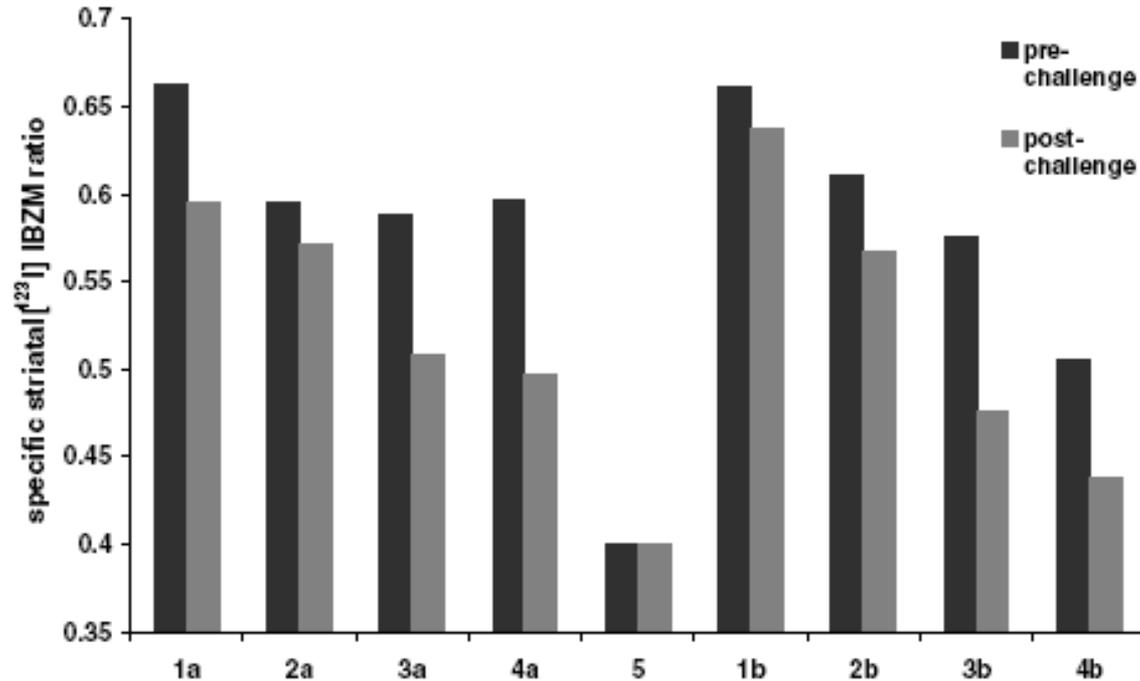
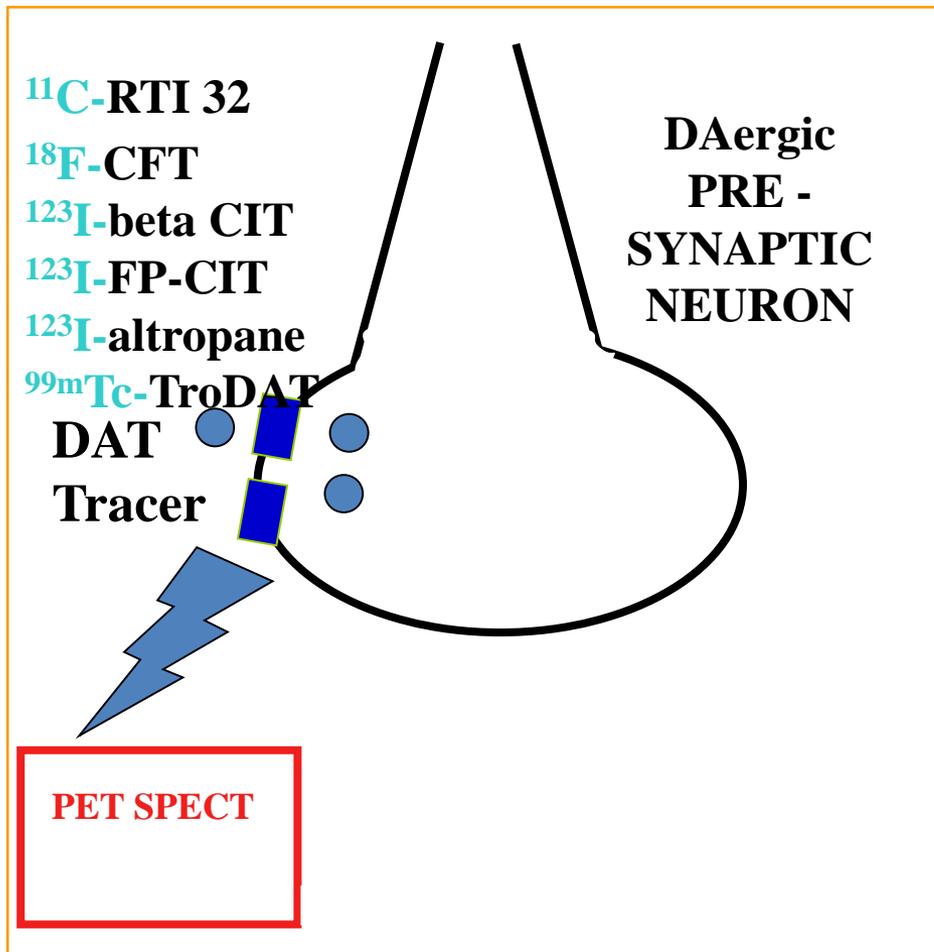
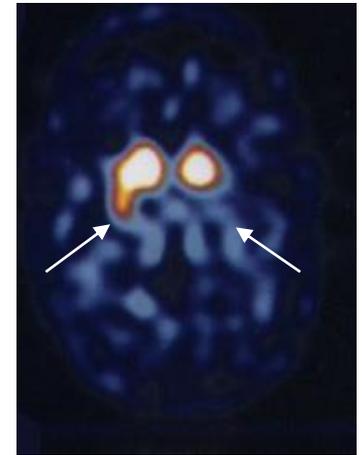


Fig. 1. Specific striatal to nonspecific [^{123}I] IBZM-binding ($[\text{striatal-occipital}/\text{occipital}]$) in nine SPECT studies each before and after rTMS-challenge (a) indicates the SPECT assessments at baseline; (b) SPECT studies upon completion of the scheduled three week treatment.

DAT TRACER BINDING = Density of DAergic terminals



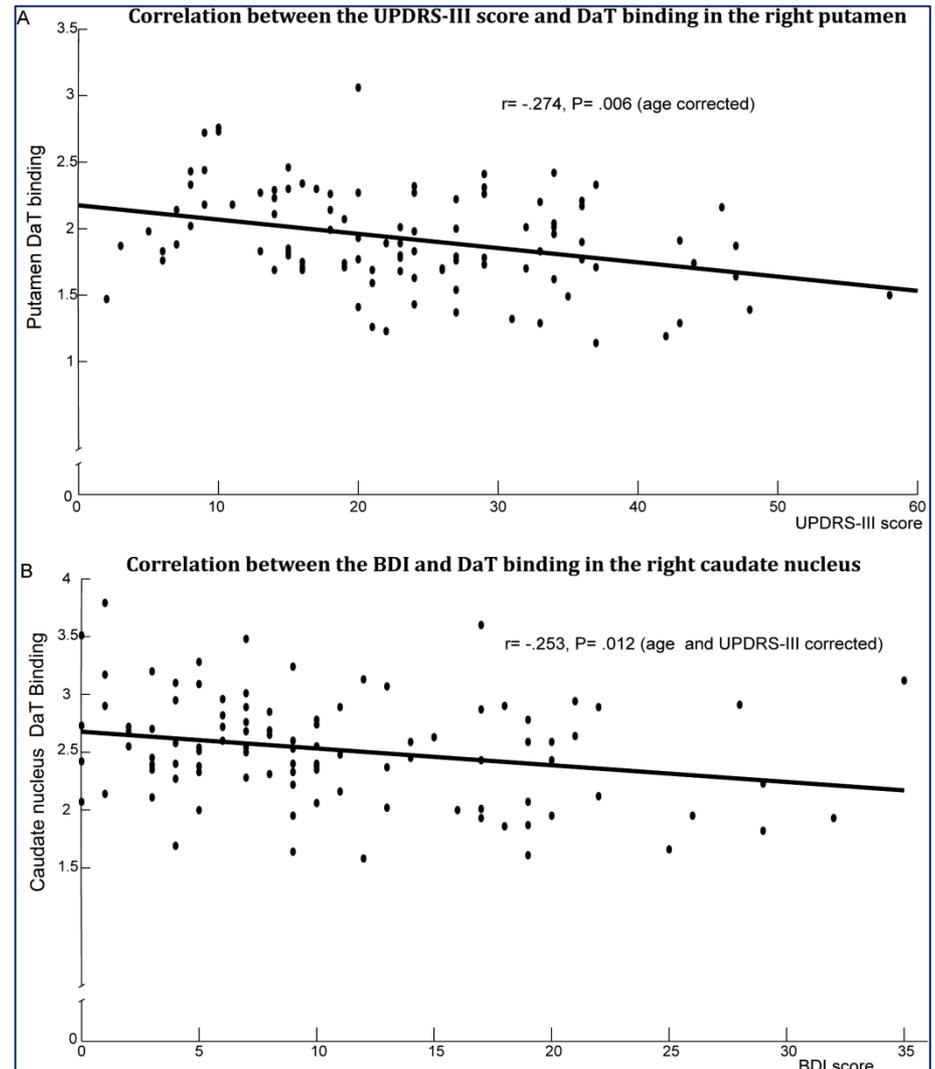
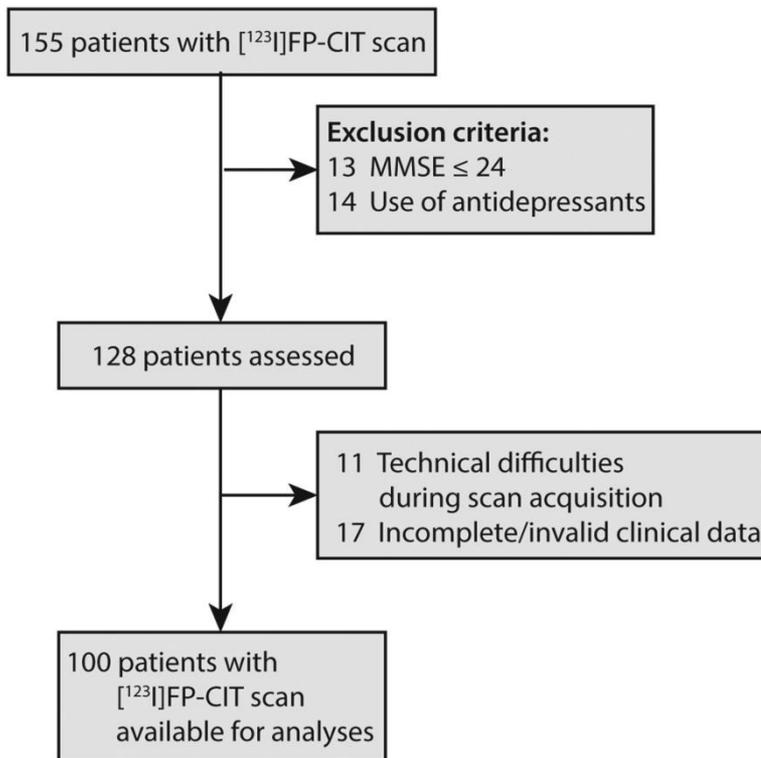
Healthy Control



Parkinson's disease

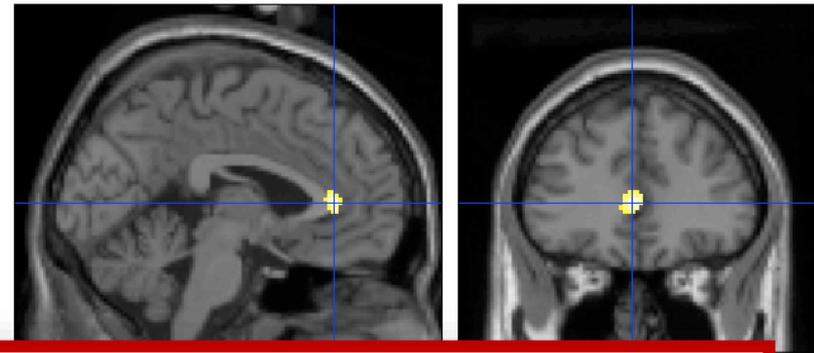
Depressive symptoms in Parkinson's disease are related to reduced [123I]FP-CIT binding in the caudate nucleus.

Flow Chart



Mesolimbic dopaminergic dysfunction in Parkinson's disease-depression: evidence from a 123I-FP-CIT SPECT investigation

	Pd-nd (35)	PD-d (15)
	Mean±SD	Mean±SD
Age at onset (years)	68.3±7.1	66.1±5.5
Disease duration (years)	1.2±1.0	1.0±0.5
Age at scan (years)	67.1±6.9	66.8±5.4
UPDRS II	5.8±3.6	7.0±3.4
UPDRS III	15.6±7.0	15.7±5.3
MMSE	27.9±1.7	27.5±1.3



Dopamine Agonist Withdrawal Syndrome in Parkinson Disease

Christina A. Rabinak, BSE; Melissa J. Nirenberg, MD, PhD

Depressione/MP

Trattamento della depressione in MP

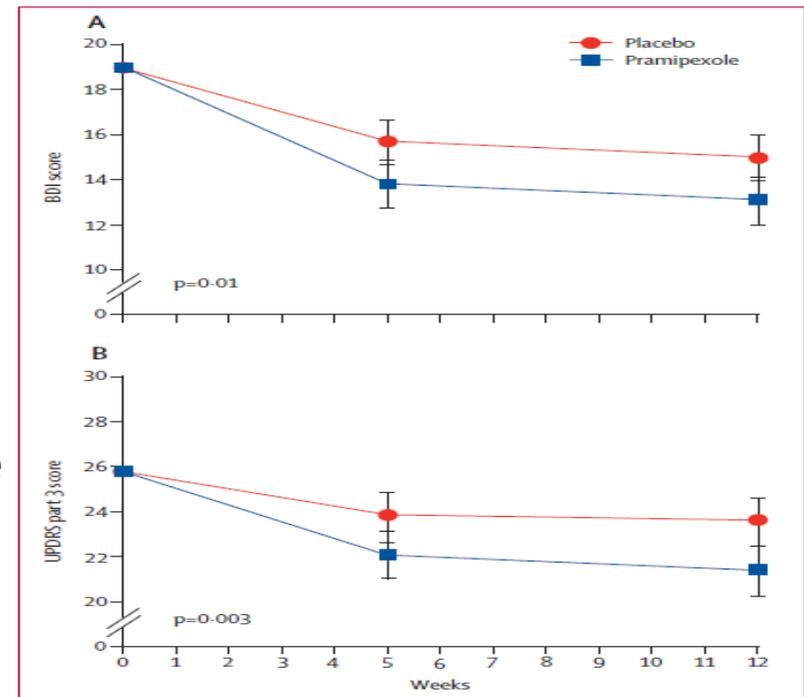
Pramipexole for the treatment of depressive symptoms in patients with Parkinson's disease: a randomised, double-blind, placebo-controlled trial

Paolo Barone, Werner Poewe, Stefan Albrecht, Catherine Debieuvre, Dan Massey, Olivier Rascol, Eduardo Tolosa, Daniel Weintraub

Lancet Neurol 2010; 9: 573–80

Miglioramento dello score Beck depression Inventory (BDI), Geriatric Depression Scale (GDS), UPDRS II e EQ-5D vs placebo

L'effetto del trattamento sui sintomi depressivi è stato per un **80%** diretto sulla depressione valutato con la BDI per un 20% indiretto legato ad un miglioramento dell' UPDRS III



Psychiatric comorbidity in a population of Parkinson's disease patients

A. Nuti^a, R. Ceravolo^a, A. Piccinni^b, G. Dell'Agnello^a, G. Bellini^a, G. Gambaccini^a, C. Rossi^a, C. Logi^a, L. Dell'Osso^b and U. Bonuccelli^a

^aDepartment of Neuroscience, Neurology Section and ^bDepartment of Psychiatry, University of Pisa, Pisa, Italy

	PD (#90) %	HC (#90) %
Major Depression	21.1*	3.3
Dysthymia	18.8*	4.4
DAP	30*	3.3
Anxiety	11.1	14.4
DOC	3.3	2.2

Anxious and Depressive Symptoms in Parkinson's Disease: The French Cross-Sectional DoPAMiP Study

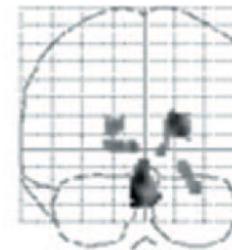
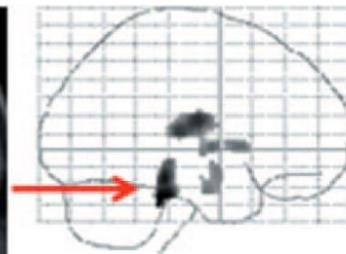
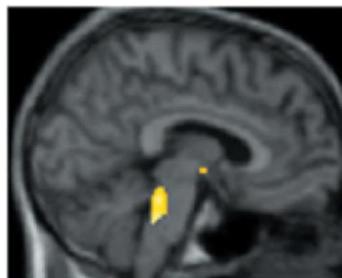
Laurence Nègre-Pagès, PhD,^{1,2} Hélène Grandjean, MD,³ Maryse Lapeyre-Mestre, MD,¹
Jean Louis Montastruc, MD,¹ Annie Fourier, MD,⁴ Jean Pierre Lépine, MD,⁵
and Oliver Rascol, MD,^{1,6*} on behalf of the DoPaMiP Study Group

TABLE 2. Anxious and depressive symptoms in PD and non-PD patients

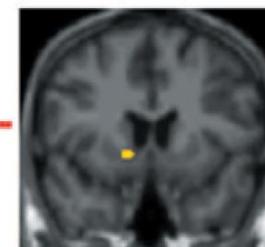
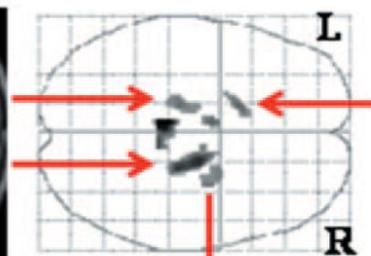
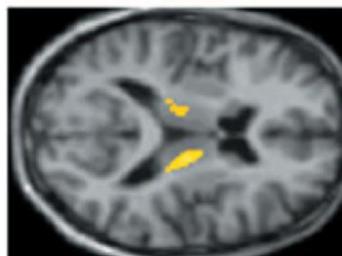
	PD Patients (n = 422)	Non-PD patients (n = 98)	P-value	OR (CI 95%)	aOR (CI 95%)	P-value
Anxious symptoms (HADS-A)						
Mean HADS-A score	8.2 ± 3.9	6.5 ± 3.2	<10 ⁻⁴			
No anxious symptoms (HADS-A ≤ 7)	49% (44–53)	72% (62–80)	0.0002	1	1	0.0003
Possible anxious symptoms (8 ≤ HADS-A ≤ 10)	24% (20–28)	16% (9–24)		2.3 (1.3 – 4.2)	2.4 (1.3 – 4.4)	
Probable anxious symptoms (HADS-A > 10)	27% (23–31)	12% (6–19)		3.7 (1.8 – 7.3)	3.6 (1.8 – 7.3)	
Possible/Probable anxious symptoms	51% (47–56)	29% (20–37)	<10 ⁻⁴	2.9 (1.8 – 4.9)	2.9 (1.7 – 4.8)	<10 ⁻⁴
Depressive symptoms (HADS-D)						
Mean HADS-D score	6.6 ± 3.8	3.9 ± 3.2	<10 ⁻⁴			
No depressive symptoms (HADS-D ≤ 7)	60% (55–65)	90% (84–96)	<10 ⁻⁴	1	1	<10 ⁻⁴
Possible depressive symptoms (8 ≤ HADS-D ≤ 10)	25% (21–29)	4% (0–8)		9.6 (3.4 – 26.8)	10.3 (3.6 – 28.8)	
Probable depressive symptoms (HADS-D > 10)	15% (11–18)	6% (1–11)		3.9 (1.6 – 9.4)	4.3 (1.8 – 10.6)	
Possible/probable depressive symptoms	40% (35–45)	10% (4–16)	<10 ⁻⁴	6.2 (3.1 – 12.3)	6.8 (3.4 – 13.6)	<10 ⁻⁴

Depressed compared to non depressed: dopaminergic and noradrenergic denervation

Locus coeruleus

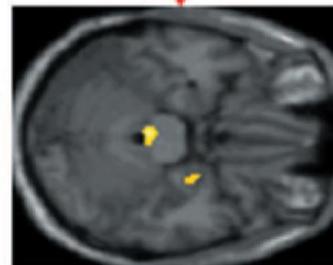


Medial thalamus



*Left
Ventral
striatum*

[¹¹C]RTI 32 PET



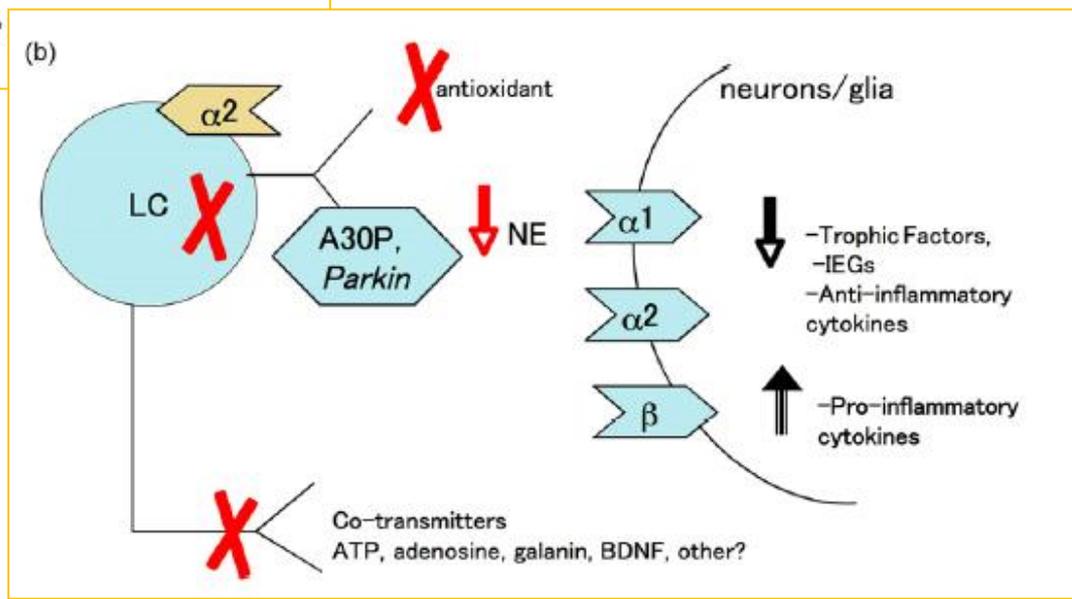
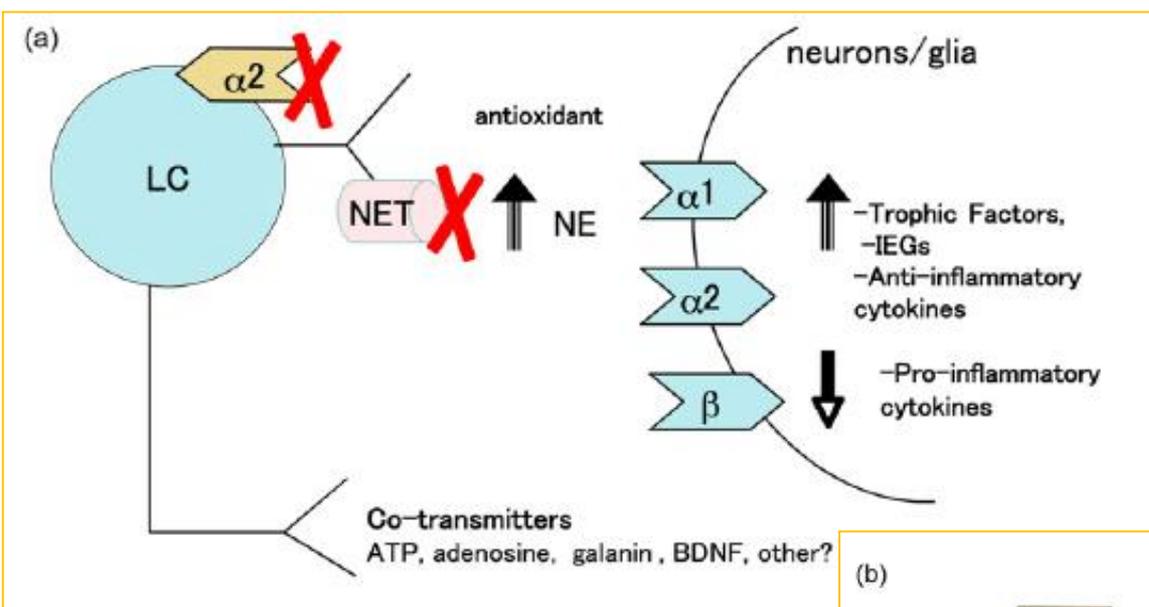
Right Amigdala



Region	Coordinates (x, y, z)	Z-score	Voxels (n)
Locus coeruleus L	-6, -32, -28	3.50	267
Locus coeruleus R	6, -34, -30	3.10	191
Thalamus R	16, -12, 16	3.10	532
Thalamus L	-16, -22, 14	2.68	454
Ventral striatum L	-16, 10, 2	2.68	480
Amygdala R	30, -6, -24	2.60	229

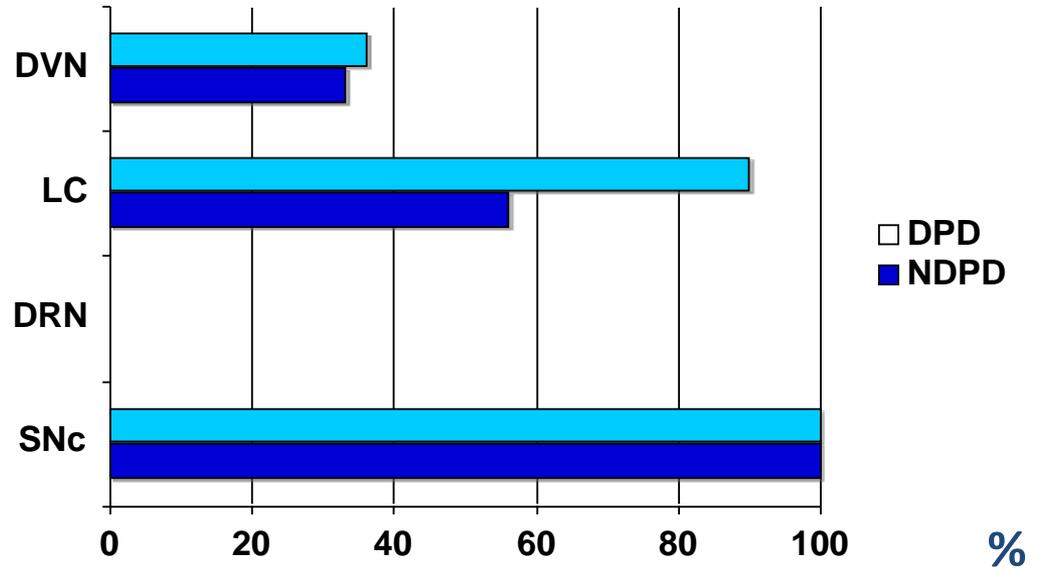
Norepinephrine: The redheaded stepchild of Parkinson's disease

K.S. Rommelfanger, D. Weinshenker*



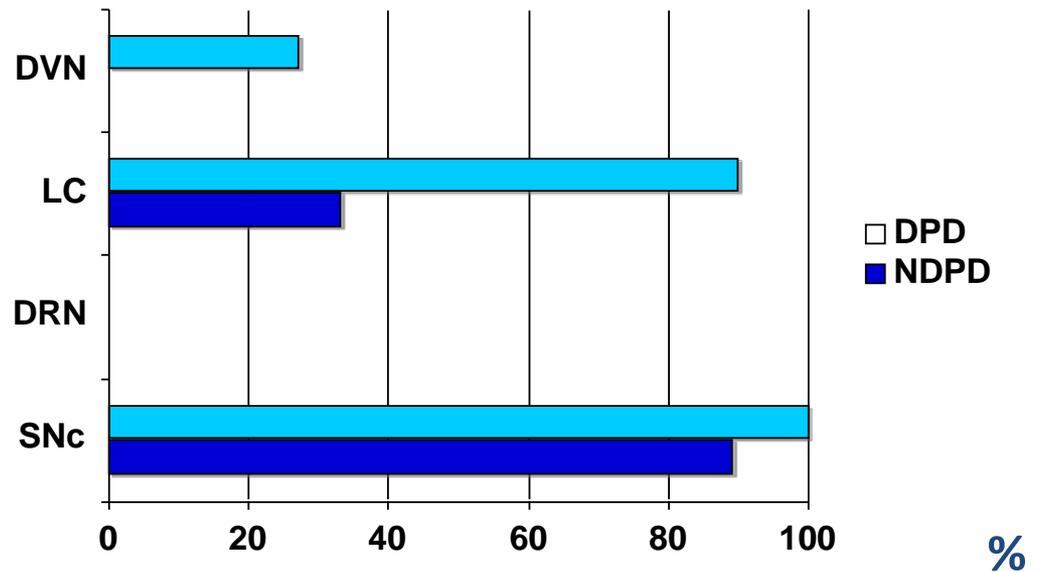
NEURONAL LOSS

DVN: dorsal vagus nerve
LC: locus coeruleus
DRN: dorsal raphe nuclei
SNc: substantia nigra c

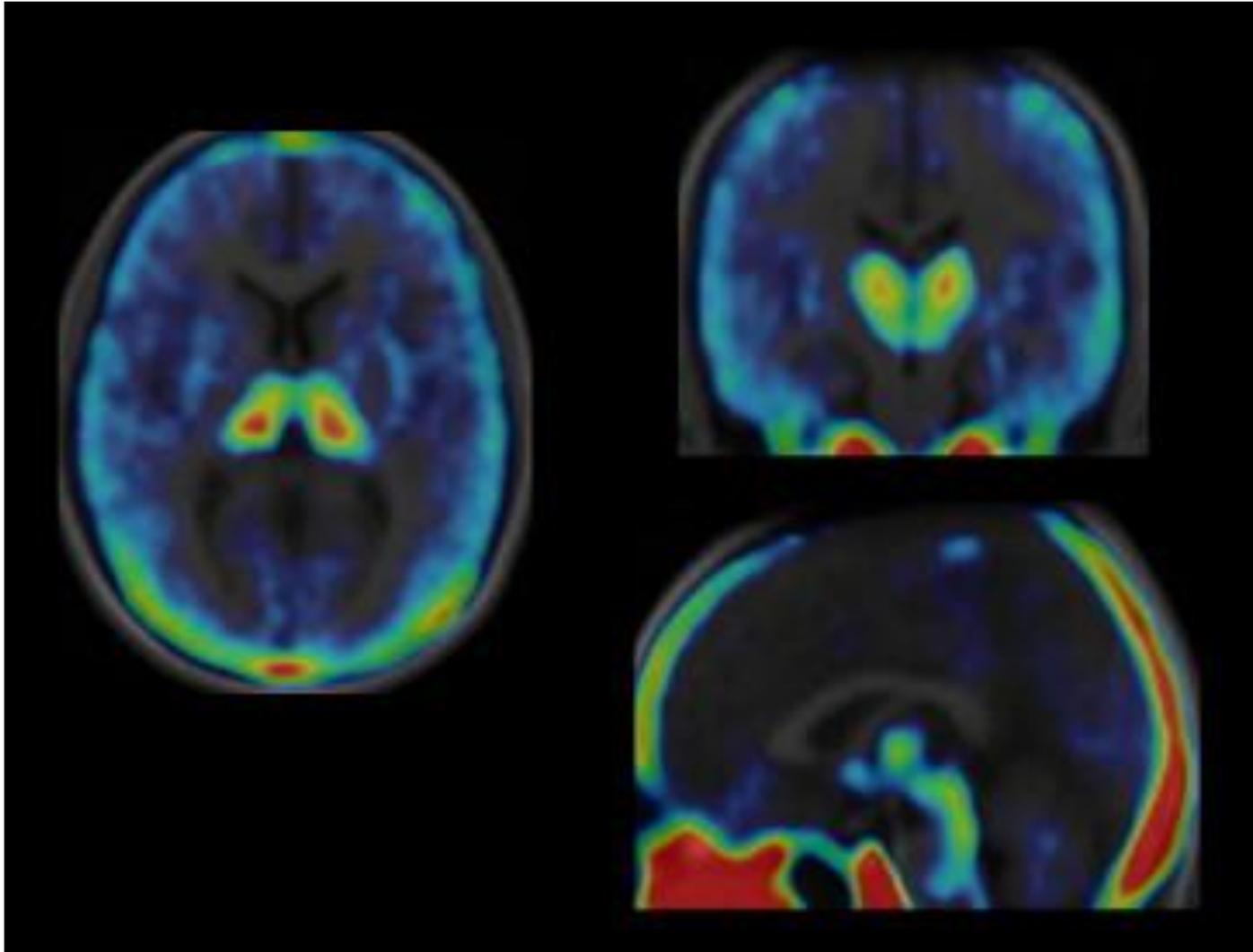


Frisina et al, 2009 modified

GLIOSIS



Mapping the norepinephrine transporter: NETSCAN



Atomoxetine for depression and other neuropsychiatric symptoms in Parkinson disease



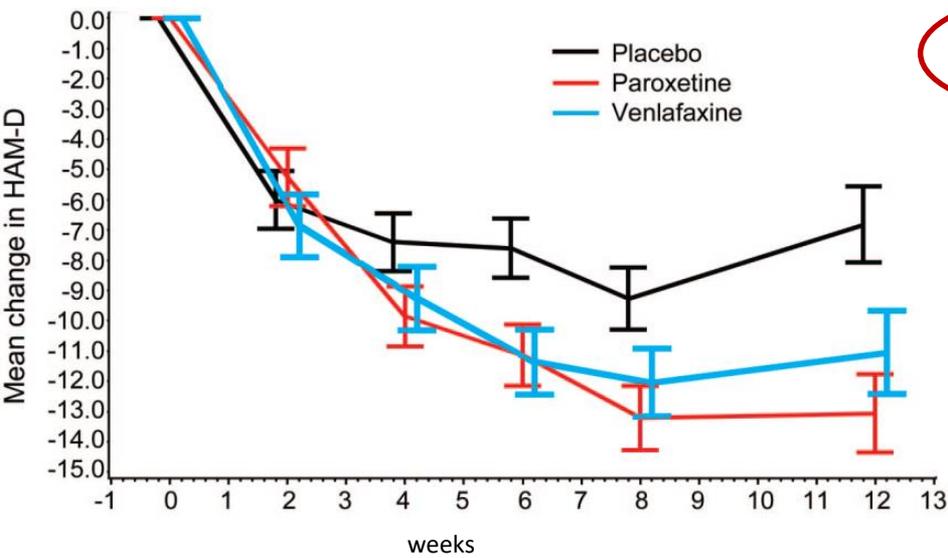
Atomoxetine treatment was not efficacious for the treatment of clinically significant depressive symptoms in PD, but was associated with improvement in global cognitive performance and daytime sleepiness

	Baseline	Week 2	Week 4	Week 8
Mini-Mental State Examination ^a				
Atomoxetine	28.12 (0.19)	—	—	28.92 (0.22)
Placebo	28.31 (0.19)	—	—	27.80 (0.22)
Effect (mean group difference in change since baseline, <i>p</i> value)	—	—	—	1.31 (0.41) <i>p</i> = 0.003

A randomized, double-blind, placebo-controlled trial of antidepressants in Parkinson disease

I.H. Richard,
Neurology 2012

Doppio cieco vs placebo, randomizzato 115 pazienti



venlafaxina

placebo

paroxetina

12 settimane

HAM-D

SSRI e SNRI sono più efficaci per il trattamento della depressione in MP del placebo

Trattamento della depressione in MP

A non-comparative assessment of tolerability and efficacy of duloxetine in the treatment of depressed patients with Parkinson's disease.

U. Bonuccelli Expert Opin Pharmacolther 2012

Studio multicentrico, non comparativo, open-label (151 pazienti)

tollerabilità

efficacia

sicurezza

Duloxetina 60mg 12 settimane

Pazienti con MP e depressione Maggiore

Miglioramento significativo

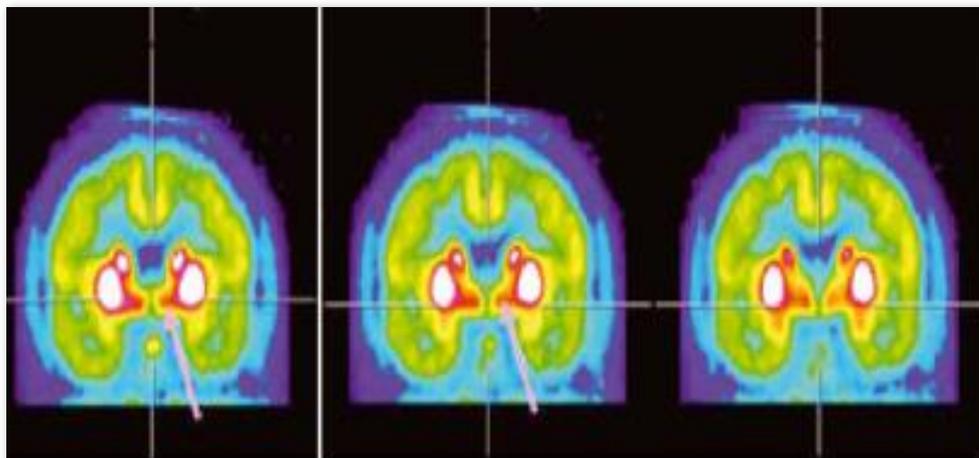


HAM-17, PDQ39

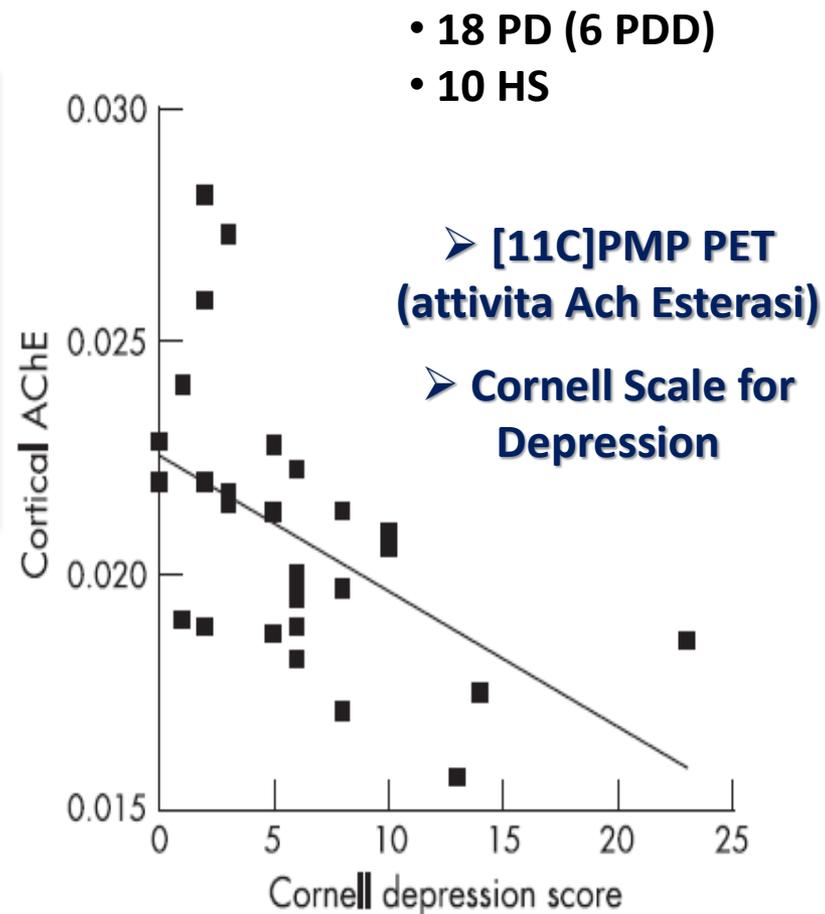
BDI, CGI-S, PGI-I

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



Depressive symptoms are associated with cholinergic deficit in PD (corrected for MMSe)



RESEARCH PAPER

Rivastigmine in apathetic but dementia and depression-free patients with Parkinson's disease: a double-blind, placebo-controlled, randomised clinical trial

David Devos,^{1,2,3} Caroline Moreau,^{2,3} David Maltête,⁴ Romain Lefaucheur,⁴ Alexandre Kreisler,^{2,5} Alexandre Eusebio,⁶ Gilles Defer,⁷ Thavarak Ouk,^{1,3} Jean-Philippe Azulay,⁶ Pierre Krystkowiak,^{8,9} Tatiana Witjas,⁶ Marie Delliaux,² Alain Destée,^{2,5} Alain Duhamel,¹⁰ Régis Bordet,^{1,3} Luc Defebvre,^{2,3} Kathy Dujardin^{2,3}



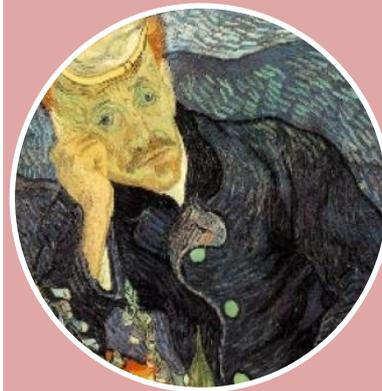
sadness



anxiety



anhedonia



apathy

SEROTONIN

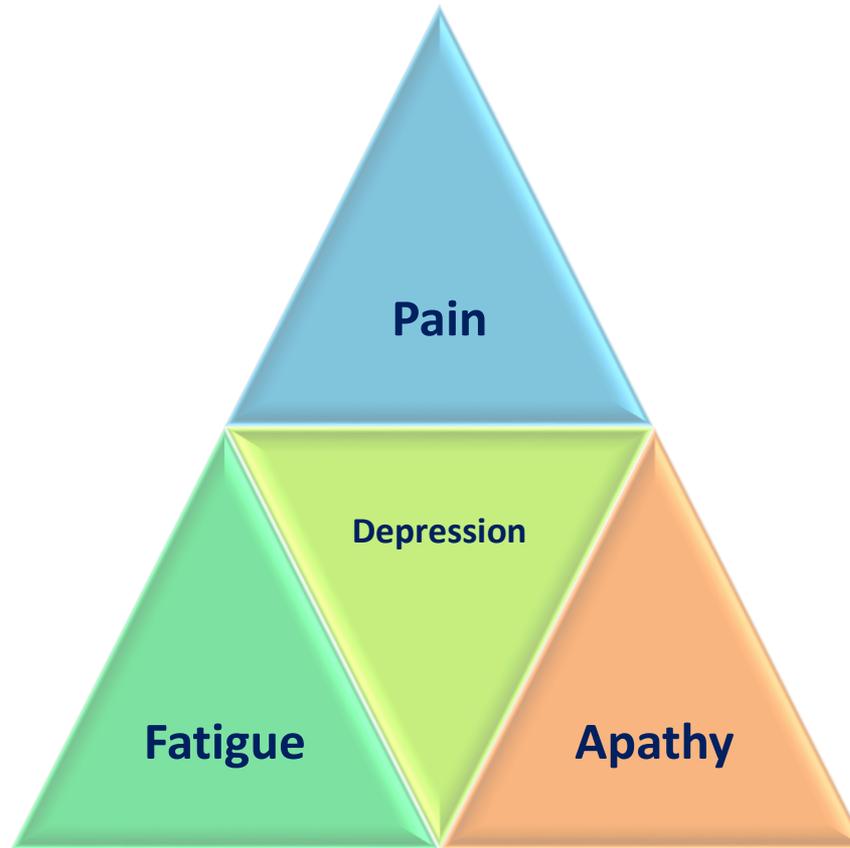
NORADRENALINE

DOPAMINE

ACETHYLCOLINE

DEPRESSION

Depression-Fatigue-Pain An unique syndrome?



NMS frequency (%) and PD severity: PRIAMO STUDY

Disease severity as Hoehn & Yahr score
N=1072

	1	1.5–2	2.5–3	4–5
Pain	50.9	58.6	67.1	79.6
Urinary	43.1	51.7	68.3	89.8
Sleep dysfunction	47.9	60.6	75.4	81.6
Fatigue	37.7	56.5	68.9	81.6
Apathy	24.6	26.8	36.6	49.0
Attention/memory	37.7	40.4	51.7	65.3
Skin	14.4	19.8	34.5	32.7
Psychiatric	61.1	63.3	73.2	83.7
Respiratory	9.6	15.5	22.8	30.6
Gastrointestinal	45.5	54.4	76.9	73.5

Adapted from:

Antonini A *et al.* The PRIAMO study: background, methods and recruitment. *Neurol Sci* 2008;29 (2):61–5.

Barone P *et al.* The PRIAMO study: A multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson's disease. *Mov Disorders* 2009;15;24(11):1641–9.

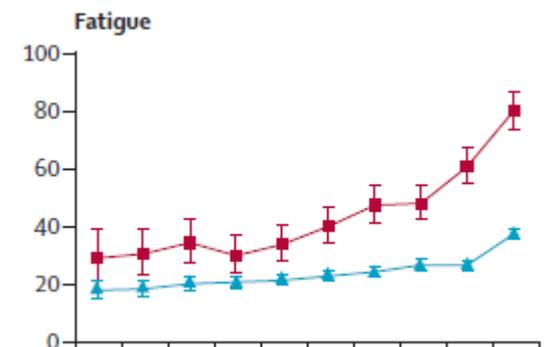
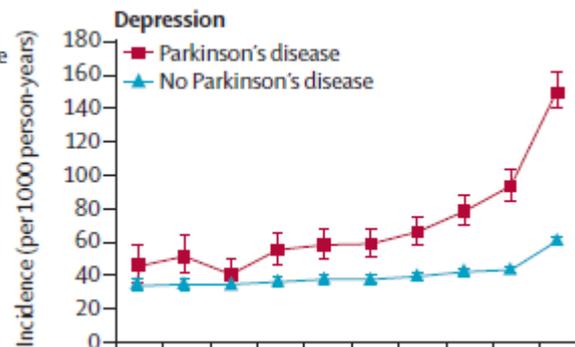
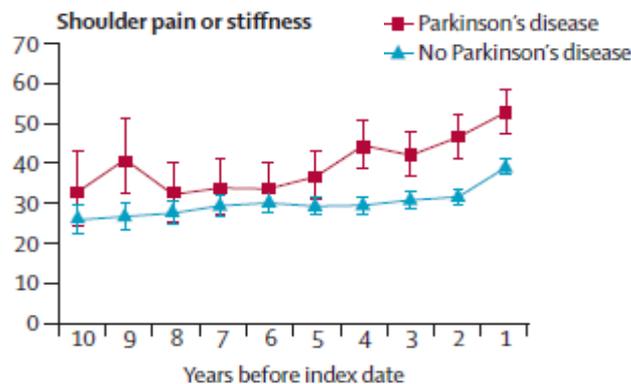
Prediagnostic presentations of Parkinson's disease in primary care: a case-control study

Anette Schrag, Laura Horsfall, Kate Walters, Alastair Noyce, Irene Petersen

Lancet Neurol 2014; 14: 57-64

	Within 0 to <2 years		≥2 years to <5 years		≥5 years to <10 years	
	Parkinson's disease (n=7232)	Controls (n=40 541)	Parkinson's disease (n=4769)	Controls (n=25 544)	Parkinson's disease (n=1680)	Controls (n=8305)
Tremor	2946 (41%)	184 (<1%)	311 (7%)	118 (<1%)	29 (2%)	41 (<1%)
Constipation	2326 (32%)	7598 (19%)	1196 (25%)	3890 (15%)	335 (20%)	1202 (14%)
Fatigue	761 (11%)	2129 (5%)	430 (9%)	1472 (6%)	180 (11%)	618 (7%)
Dizziness	725 (10%)	2411 (6%)	486 (10%)	1629 (6%)	206 (12%)	723 (9%)
Depression	696 (10%)	1724 (4%)	312 (7%)	1035 (4%)	94 (6%)	409 (5%)
Shoulder pain or stiffness	528 (7%)	2263 (6%)	407 (9%)	1729 (7%)	175 (10%)	803 (10%)
Anxiety	624 (9%)	1505 (4%)	333 (7%)	1039 (4%)	136 (8%)	504 (6%)
Neck pain or stiffness	301 (4%)	1613 (4%)	224 (5%)	1301 (5%)	128 (8%)	667 (8%)
Urinary dysfunction	338 (5%)	815 (2%)	167 (4%)	459 (2%)	53 (3%)	170 (2%)
Erectile dysfunction	293/4323 (7%)	1434/24 076 (6%)	242/2885 (8%)	1072/15 330 (7%)	116/1024 (11%)	416/5017 (8%)
Insomnia	314 (4%)	1286 (3%)	190 (4%)	850 (3%)	85 (5%)	386 (5%)
Balance impairments	300 (4%)	379 (1%)	78 (2%)	196 (1%)	21 (1%)	62 (1%)
Hypotension	153 (2%)	346 (1%)	80 (2%)	204 (1%)	27 (2%)	61 (1%)
Memory problems	197 (3%)	520 (1%)	61 (1%)	187 (1%)	8 (<1%)	47 (1%)
Rigidity	201 (3%)	52 (<1%)	11 (<1%)	36 (<1%)	3 (<1%)	16 (<1%)

8166 PD patients
46755 individuals without PD



The Onset of Nonmotor Symptoms in Parkinson's Disease (The ONSET PD Study)

Mov Dis 2014

NMS	Onset Before OMS n (% of All PD Subjects)	Timespans Before OMS ^a		
		<2 Years n (% ^a)	2 to 10 Years n (% ^a)	>10 Years n (% ^a)
Smell loss ^c	44 (88)	11 (25)	17(39)	16 (36)
Constipation ^c	33 (78)	7 (21)	5 (15)	21 (63)
Mood disturbances	32 (68)	9 (28)	12 (37.5)	11 (34.5)
H/C intolerance	31 (81)	9 (29)	9 (29)	13 (57)
Dream-enacting behavior ^c	24 (77)	3 (12.5)	9 (37.5)	12 (50)
Frequent nightmares ^c	21 (81)	3 (13)	4 (17)	14 (61)
Excessive sweating	20 (67)	5 (25)	7 (35)	8 (40)
Memory complains	19 (54)	11 (58)	8 (42)	0 (0)
Fatigue	19 (49)	7 (36.5)	10 (52.5)	2 (10)
Inattention	18 (60)	14 (78)	1 (5.6)	3 (16.6)
Anhedonia	18 (51)	12 (68)	3 (16)	3 (16)
Apathy	17 (50)	12 (71)	4(23)	1 (6)
Postprandial fullness	16 (64)	4 (25)	2 (12.5)	10 (62.5)
FDS	16 (52)	4 (25)	5 (31)	7 (44)
Unexplained pain	13 (59)	4 (31)	6 (46)	3 (23)
Taste loss ^c	11 (73)	0	10 (91)	1 (9)
Chest pain ^c	11 (100)	1 (9)	5 (45.5)	5 (45.5)

NON MOTOR SYMPTOMS were assessed by a custom-made questionnaire in **109 newly diagnosed untreated PD patients** and **107 controls**

Significant NMS	PD (n = 109)		Controls (n = 107)	
	%	%	OR	95% CI
Taste loss	14	1	16.9	2.1-130
Dream-enacting behavior	28	3	13.77	4.06-46.71
Anhedonia	32	6	7.96	3.18-19.90
Smell loss	46	11	6.7	3.3-13.6
Fatigue	36	9	5.4	2.5-11.5
Frequent nightmares	24	6	5.27	2.07-13.41
Unexplained pain	20	6	4.25	1.65-10.97
Constipation	38.5	13	4.1	2.1-8.2
Chest pain	10	3	3.89	1.0-14.36
Mood disturbances	43	19	3.29	1.78-6.10
Apathy	31	12	3.27	1.61-6.51
Inattention	28	11	3	1.44-6.25
Heat/cold intolerance	35	19	2.32	1.24-4.35
Excessive daytime sleepiness	28	15	2.26	1.15-4.43
Postprandial fullness	23	12	2.1	1.0-4.5
Excessive sweating	28	16	2.01	1.03-3.91
Memory complains	32	20	1.93	1.03-3.61

- Anhedonia, apathy, memory complaints and inattention occurred more frequently during the 2-year premotor period
- Smell loss, mood disturbances, taste loss, excessive sweating, fatigue, and pain were more frequently reported in the 2- to 10-year premotor period
- Constipation, dream-enacting behavior, excessive daytime sleepiness, and postprandial fullness were frequently perceived more than 10 years before motor symptoms.



Edgar Degas (1834-1917). *Melancholy*, late 1860s, French. Oil on canvas. Courtesy of The Phillips Collection, Washington, DC.

Prevalence of fatigue in Parkinson disease and its clinical correlates

Fabrizio Stocchi, MD
Giovanni Abbruzzese,
MD
Roberto Ceravolo, MD
Pietro Cortelli, MD, PhD
Marco D'Amelio, MD
Maria F. De Pandis, MD,
PhD
Giovanni Fabbrini, MD
Claudio Pacchetti, MD
Gianni Pezzoli, MD
Alessandro Tessitore,
MD, PhD
Margherita Canesi, MD
Claudio Iannaccone
Mario Zappia, MD
For the FORTE Study
Group

- A total of 402 patients were enrolled and 394 patients completed the PFS-16 questionnaire with a PFS-16 mean score of 2.87 ± 0.99 .
- 136 patients (33.8%) reported distressing fatigue (PFS-16 mean score ≥ 3.3)
- Patients with distressing fatigue were older and had a longer duration of PD than those without distressing fatigue.
- Female gender was a risk factor to develop fatigue

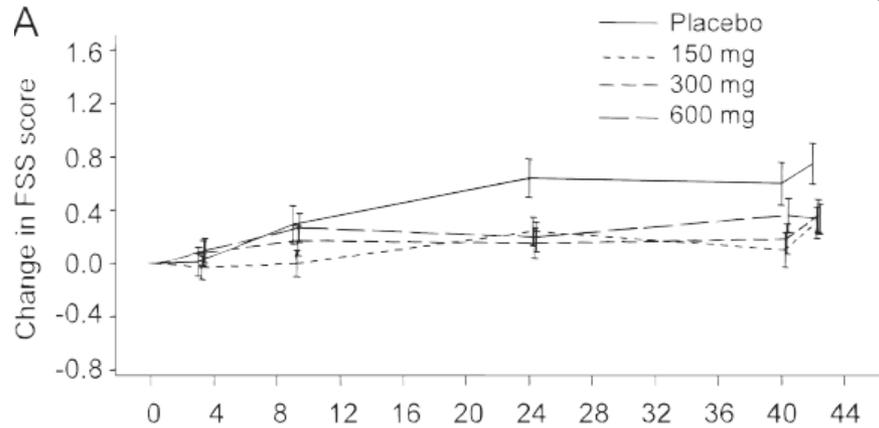
Prevalence of fatigue in Parkinson disease and its clinical correlates

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Marco D'Amelio, MD
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For the FORTE Study
Group

- The presence of distressing fatigue was associated with
- Higher total Unified Parkinson's Disease Rating Scale (UPDRS) scores
- Poorer quality of life (39-item Parkinson's Disease Questionnaire [PDQ-39])
- Worse social and psychological behaviors
- Higher severity of depressive symptoms
- Higher prevalence of sleep disorders

Fatigue in levodopa-naïve subjects with Parkinson disease

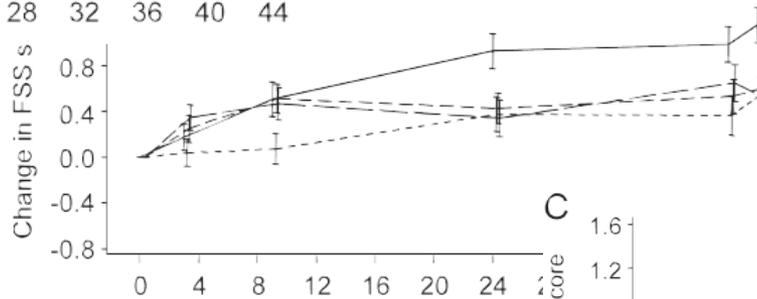
Neurology® 2008;71:481-485



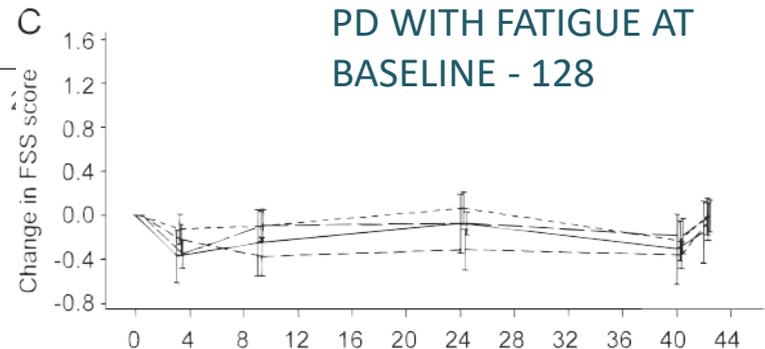
ALL SUBJECTS - 349

STUDIO ELLDOPA

Fatigue is a frequent symptom in early, untreated, non-depressed patients with Parkinson disease .



PD WITHOUT FATIGUE AT BASELINE - 221



PD WITH FATIGUE AT BASELINE - 128

Table 2 [¹²³I]-β-CIT uptake at baseline

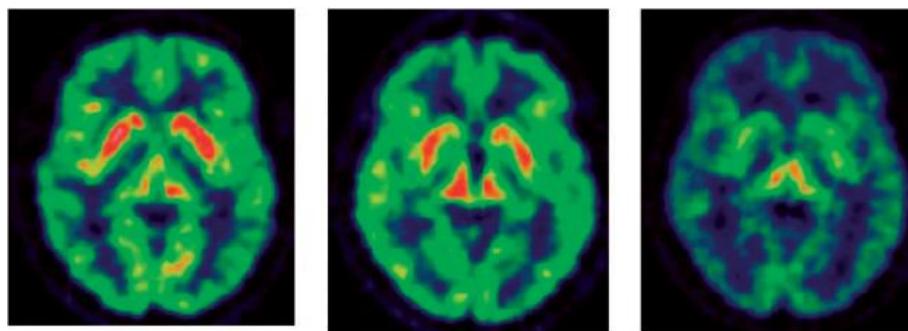
	Fatigued, n = 49	Nonfatigued, n = 82	p Value (age-adjusted)
Striatum	3.78 (1.72)	3.53 (1.14)	0.5515
Caudate nucleus	4.91 (1.88)	4.64 (1.29)	0.6056
Putamen	2.65 (1.61)	2.42 (1.09)	0.5156

Values are mean (SD).

Fatigue was associated with the severity of PD, and **progressed less in patients treated with levodopa.**

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 Chaudhuri² and David J. Brooks¹



Healthy volunteer

PD without fatigue

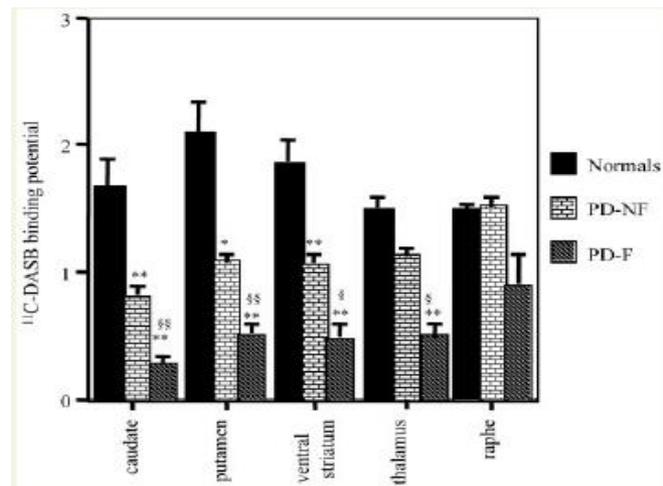
PFS-16 = 2

PD with fatigue

PFS-16 = 15

¹¹C-DASB uptake

- 10 healthy subjects
- 7 PD patients with fatigue
- 8 PD patients without fatigue



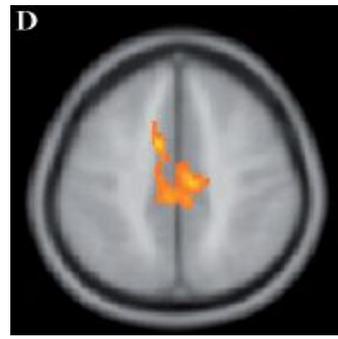
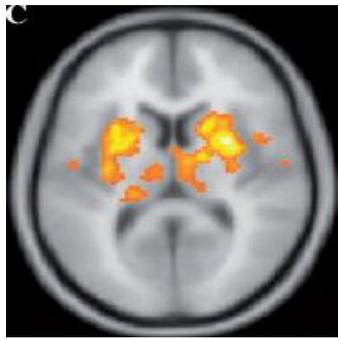
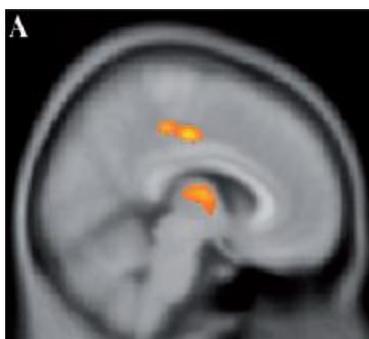
Right cingulate and right thalamus

Right and left striatum and left cingulate

Right and left striatum and right and left thalamus

Right and left cingulus

Right and left striatum and left amygdala



Take home message

- **La depressione nella MP è sindrome premotoria, molto frequente durante la malattia, e fattore di peggioramento della qualità della vita**
- **Il suo riconoscimento è cruciale : spesso sottodiagnosticata, e sottotrattata**
- **Piu che una diagnosi formale dovremo riconoscere I sintomi depressivi e trattarli in relazione al loro differente substrato neurochimico**
- **Necessario conoscere la multidimensionalità del quadro per un precoce ed efficace trattamento**