

La fatica in neurologia

M. Pardini

DiNOGMI, Università di Genova

Organizzazione della presentazione

Come definire la fatica (isolata)?

Basi neurali della fatica

Approccio al paziente con fatica

Fatica e nel paziente neurologico: che fare?

Fatica... ma quale?

Fatigue and fatigability in neurologic illnesses

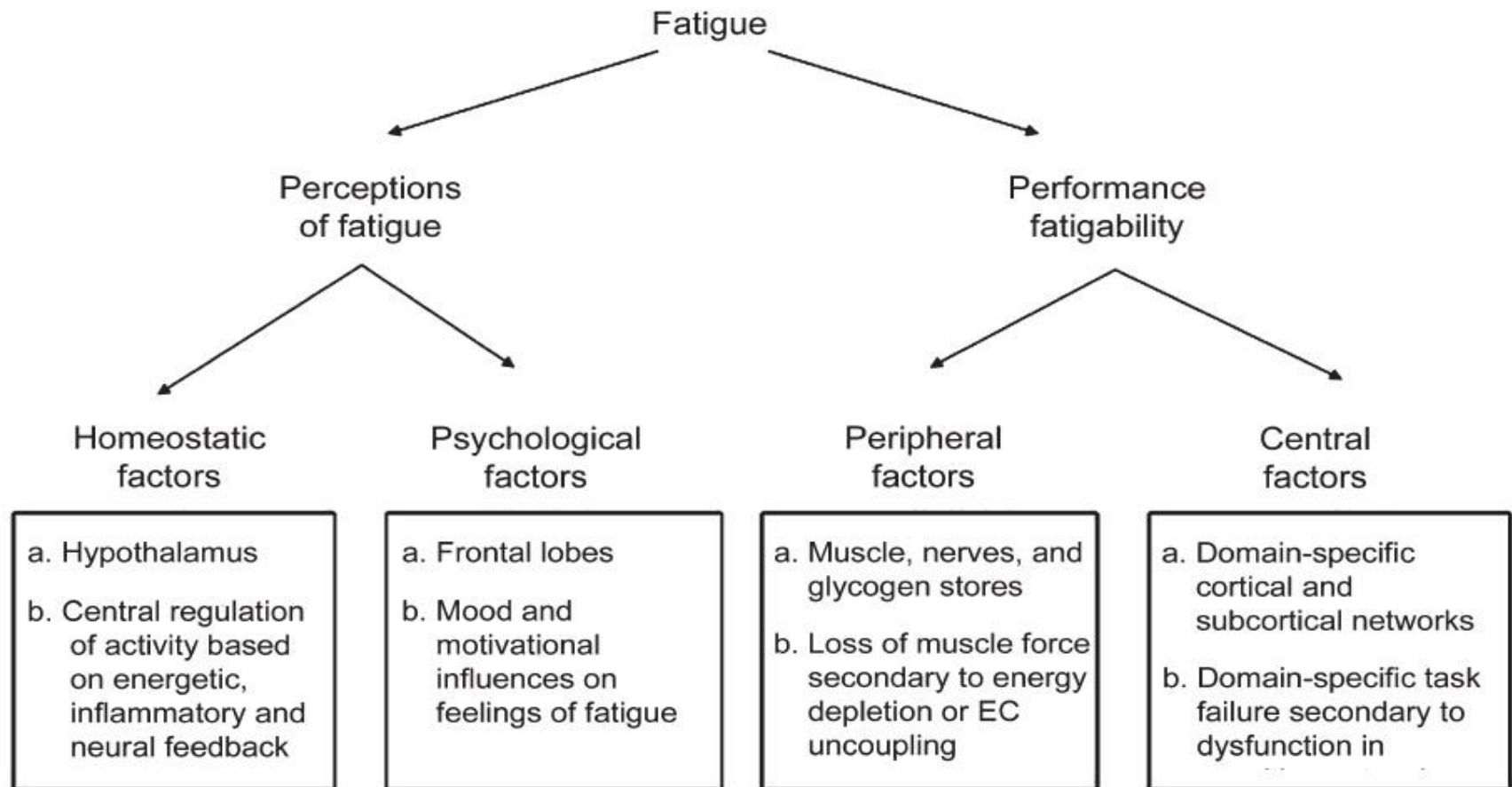
Neurology 80 January 22, 2013

Benzi M. Kluger, MD,
MS

Lauren B. Krupp, MD

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Proposal for a unified taxonomy



Fatica... ma quale?

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Table 1 Estimated prevalence of fatigue in selected neurologic illnesses

Population	Estimated prevalence, %
Multiple sclerosis	38–83 ^{e51–e53}
Parkinson disease	28–58 ^{12,20,32,e54}
Stroke	36–77 ^{15,e55–e57}
Myasthenia gravis	75–89 ^{14,e58,e59}
Postpolio syndrome	27–91 ^{74,e60,e61}
Amyotrophic lateral sclerosis	44–83 ^{16,e62}
Traumatic brain injury	45–73 ^{e63,e64}

Quali confini?

A Community-based Study of Prolonged Fatigue and Chronic Fatigue


Leonard A. Jason, Karen M. Jordan, Judith A. Richman, Alfred W. Rademaker, Cheng-Fang Huang, William McCreedy, Jennifer Shlaes, Caroline P. King, Dana Landis, Susan Torres, Trina Haney-Davis and Erin L. Frankenberry
J Health Psychol 1999 4: 9
DOI: 10.1177/135910539900400103

Table 5. Point prevalence of chronic fatigue

	<i>n</i>	<i>Conservative estimate Prevalence (95% CI)</i>	<i>Upper estimate Prevalence (95% CI)</i>
Prolonged fatigue	1435	5.00% (4.75–5.26)	7.68% (7.38–7.99)
CFS-like	408	1.42% (1.29–1.56)	2.18% (2.02–2.35)
ICF	304	1.06% (0.94–1.18)	1.63% (1.48–1.77)
CF-explained	68	0.24% (0.18–0.29)	0.36% (0.29–0.43)

Fenomenologia della fatica

Fatigue Severity Scale (FSS, English version)*

	<div><div><i>strongly disagree</i></div><div></div><div><i>strongly agree</i></div></div>						
	1	2	3	4	5	6	7
1. My motivation is lower when I am fatigued.	0	0	0	0	0	0	0
2. Exercise brings on my fatigue.	0	0	0	0	0	0	0
3. I am easily fatigued.	0	0	0	0	0	0	0
4. Fatigue interferes with my physical functioning.	0	0	0	0	0	0	0
5. Fatigue causes frequent problems for me.	0	0	0	0	0	0	0
6. My fatigue prevents sustained physical functioning.	0	0	0	0	0	0	0
7. Fatigue interferes with carrying out certain duties and responsibilities.	0	0	0	0	0	0	0
8. Fatigue is among my three most disabling symptoms.	0	0	0	0	0	0	0
9. Fatigue interferes with my work, family, or social life.	0	0	0	0	0	0	0

**Patients are instructed to choose a number from 1 to 7 that indicates their degree of agreement with each statement where 1 indicates strongly disagree and 7, strongly agree. [Krupp et al, Arch Neurol 1989]*

Quali confini?

Sul versante fenomenologico i pazienti descrivono la fatica (percezione di mancanza di energia o della necessità di un impegno maggiore per svolgere le attività quotidiane) come diversa dalla **sonnolenza** (non sentono la necessità di dormire), **apatia** (presentano motivazione di svolgere le attività quotidiane) e dalla **depressione** (non è l'umore basso a scatenare la fatica) (Kluger et al., 2016)

Quali confini?

Temporal Associations between Fatigue, Depression, and Apathy after Stroke: Results of the Cognition and Affect after Stroke, a Prospective Evaluation of Risks Study

Elles Douven^a Sebastian Köhler^a Syenna H.J. Schievink^a

Robert J. van Oostenbrugge^b Julie Staals^b Frans R.J. Verhey^a Pauline Aalten^a

Cerebrovasc Dis 2017;44:330–337

DOI: 10.1159/000481577

Table 1. Baseline characteristics

Variable	Overall	No PSF	PSF
<i>n</i> (%)	243 (100.0)	124 (51.0)	119 (49.0)
PSA, <i>n</i> (%)	40 (16.5)	19 (15.3)	21 (17.7)
PSD, <i>n</i> (%)	94 (38.7)	32 (25.8)	62 (52.1) ^b

Quali confini?

Is fatigue an independent and persistent symptom in patients with Parkinson disease?

G. Alves, MD; T. Wentzel-Larsen, MSc; and J.P. Larsen, PhD

NEUROLOGY 2004;63:1908–1911

Independence of fatigue. Since the overlap in symptomatology of fatigue and other non-motor features could have caused the positive relationship between fatigue and depression and EDS, we excluded all patients who showed depressive symptoms (MADRS > 19, BDI > 18) and EDS in the study period. In this selected patient group the prevalence rate of fatigue was still high and increased from 32.1% in 1993 (95% CI 23% to 41%) to 38.9% in 2001 (95% CI 14% to 64%).

Quali confini?

Sleep Med Rev. 2017 Apr;32:95-108. doi: 10.1016/j.smrv.2016.03.004. Epub 2016 Mar 18.

Daytime sleepiness versus fatigue in patients with multiple sclerosis: A systematic review on the Epworth sleepiness scale as an assessment tool.

Popp RF¹, Fierbeck AK¹, Knüttel H², König N³, Rupprecht R¹, Weissert R³, Wetter TC⁴.

Table 1 Comparison of fatigue and sleepiness as two different domains

	Fatigue	Sleepiness
Definition	<i>"Fatigue is a subjective lack of physical and/or mental energy that is perceived by the individual or the caregiver to interfere with usual and desired activities."</i> (p. 2) [82]	<i>"Sleepiness is the inability to stay awake and alert during the major waking episodes of the day, resulting in periods of irrepressible need for sleep or unintended lapses into drowsiness or sleep."</i> (p. 143) [18]
Symptoms	<ul style="list-style-type: none">• Feelings of tiredness, exhaustion, weariness or lassitude• not necessarily associated with sleep pressure• no definite sleep drive when resting (e.g. lying down to relax)	<ul style="list-style-type: none">• Decreased level of alertness or wakefulness• increased tendency to fall asleep or doze off unintentionally• sleep drive when resting (e.g. lying down to nap)
Semantics	<ul style="list-style-type: none">• Tiredness is commonly used as synonym (e.g. by insomniacs)	<ul style="list-style-type: none">• Tiredness is commonly used as synonym (e.g. by narcoleptics)
Characteristics in MS	<ul style="list-style-type: none">• Common and most troublesome symptom• strong negative impact on social and occupational functioning	<ul style="list-style-type: none">• Not commonly associated with MS• often associated with sleep disorders

Organizzazione della presentazione

Come definire la fatica (isolata)?

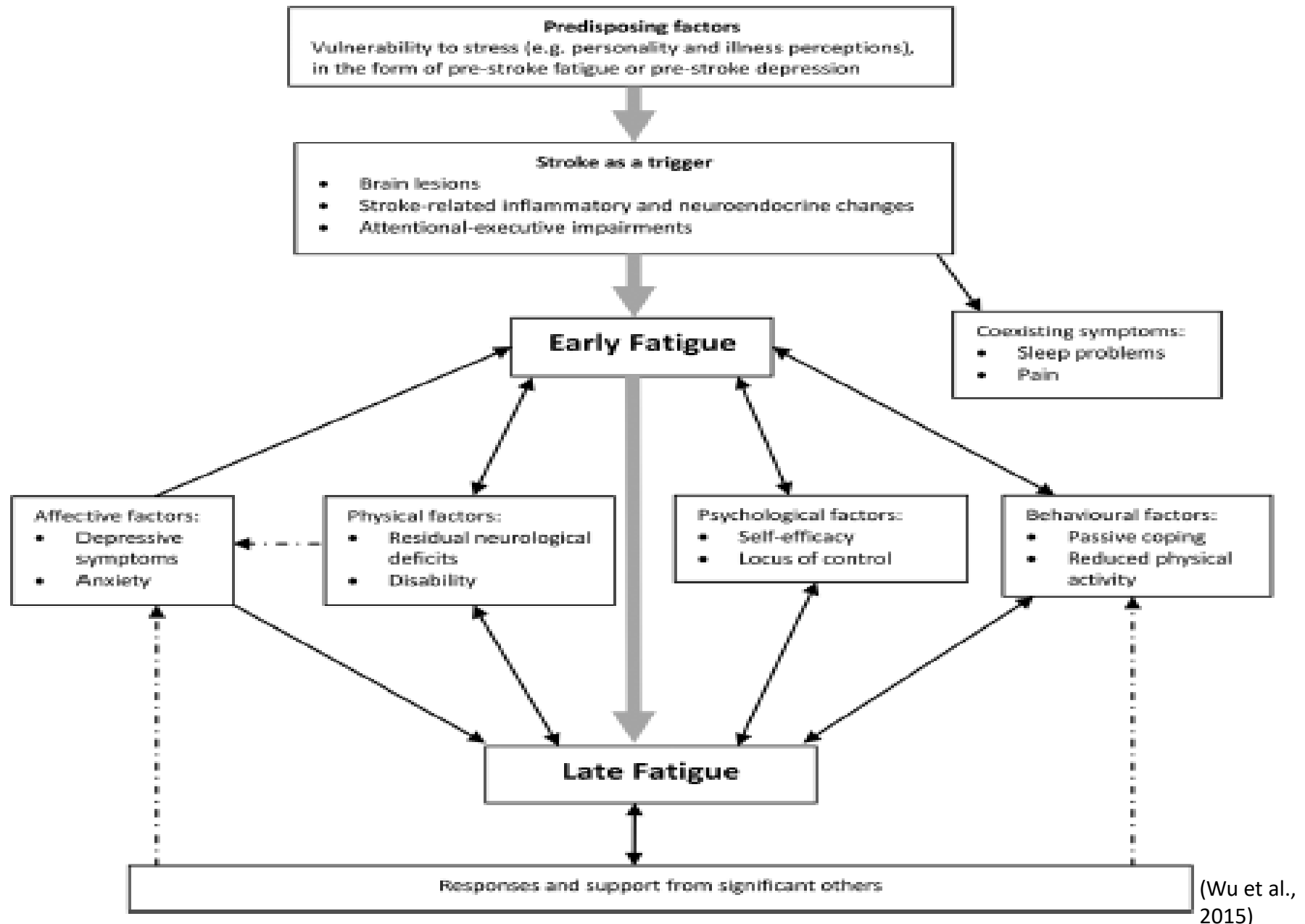
- *Fatica vs. faticabilità*
- *Costrutto indipendente da apatia, depressione, eccessiva sonnolenza*
 - *Frequente problema*

Basi neurali della fatica

Approccio al paziente con fatica

Fatica e nel paziente neurologico: che fare?

Modelli interpretativi e basi neurali



Fatica e mono-amine

Agomelatine but not melatonin improves fatigue perception: A longitudinal proof-of-concept study

M. Pardini^{a,b,*}, C. Cordano^a, F. Benassi^b, C. Mattei^c, D. Sassos^a, S. Guida^d, C. Serrati^e, A. Primavera^a, M. Amore^a, L. Cocito^a, L. Emberti Gialloreti^{b,f}

European Neuropsychopharmacology (2014) 24, 939-944

Reward responsiveness and fatigue in multiple sclerosis

Multiple Sclerosis Journal
19(2) 233–240
© The Author(s) 2012

Matteo Pardini¹, Elisabetta Capello¹, Frank Krueger², Gianluigi Mancardi¹ and Antonio Uccelli¹

Clinical correlates of raphe serotonergic dysfunction in early Parkinson's disease

FREE

Zahi Qamhawi, David Towey, Bina Shah, Gennaro Pagano, John Seibyl, Kenneth Marek, Per Borghammer, David James Brooks, Nicola Pavese

Brain, Volume 138, Issue 10, 1 October 2015, Pages 2964–2973,

Locus Coeruleus atrophy doesn't relate to fatigue in Parkinson's disease

Oleg Solopchuk^{1,3}, Moustapha Sebti¹, Céline Bouvy², Charles-Etienne Benoit¹, Thibault Warlop², Anne Jeanjean² & Alexandre Zénon^{1,3}

Fluoxetine Is Not Effective in the Treatment of Poststroke Fatigue: A Double-Blind, Placebo-Controlled Study

Choi-Kwon S.^a · Choi J.^a · Kwon S.U.^b · Kang D.-W.^b · Kim J.S.^b

Cerebrovasc Dis 2007;23:103–108

<https://doi.org/10.1159/000097045>

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

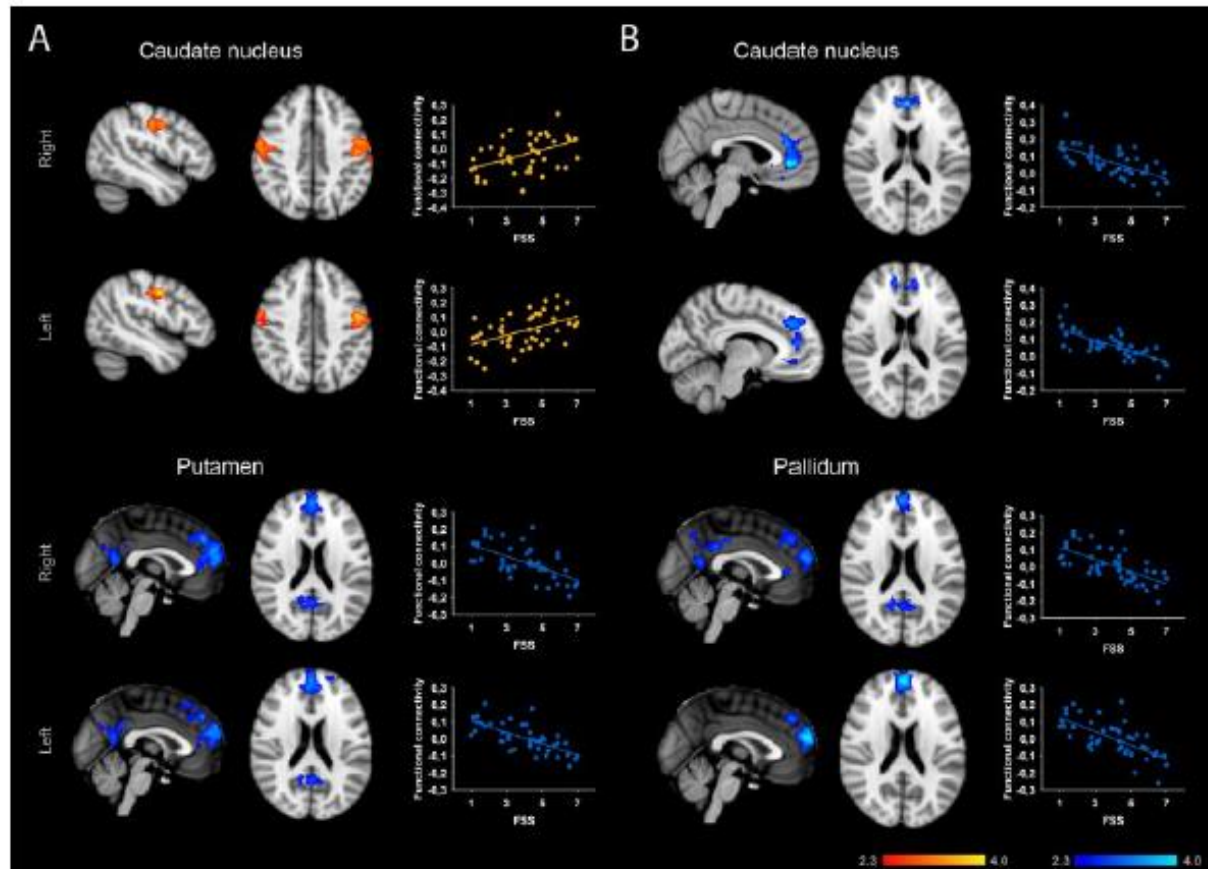
FREE

Nicola Pavese, Vinod Metta, Subrata K. Bose, Kallol Ray Chaudhuri, David J. Brooks

Brain, Volume 133, Issue 11, 1 November 2010, Pages 3434–3443,

Altered basal ganglia functional connectivity in multiple sclerosis patients with fatigue

C Finke, J Schlichting, S Papazoglou, M Scheel, A Freing, C Soemmer, LM Pech, A Pajkert, C Pfüller, JT Wuerfel, CJ Ploner, F Paul and AU Brandt

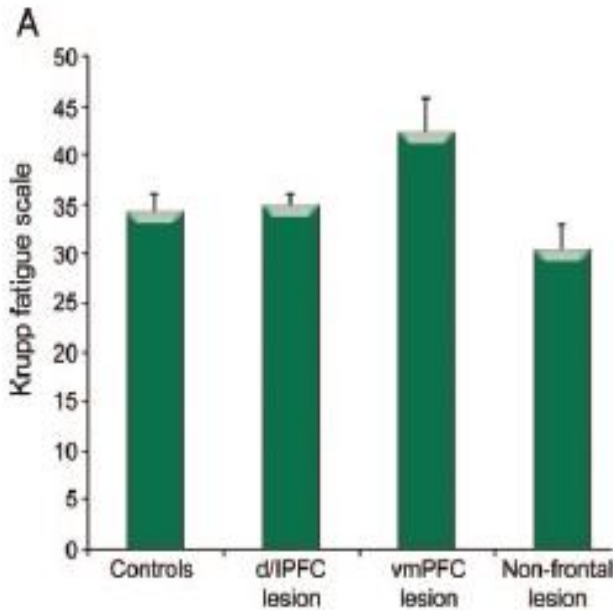


Fatica e neuroimmagini

Ventromedial prefrontal cortex modulates fatigue after penetrating traumatic brain injury

J. Neurology® 2010;74:749–754

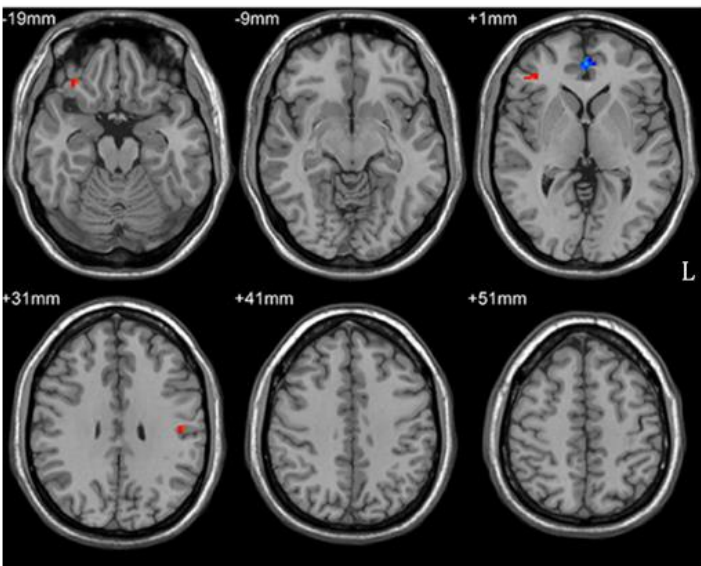
Matteo Pardini, MD
Frank Krueger, PhD
Vanessa Raymont, MD
Jordan Grafman, PhD



Alterations in regional homogeneity of resting-state brain activity in fatigue of Parkinson’s disease

Junyi Li¹ · Yongsheng Yuan¹ · Min Wang² · Jiejun Zhang¹ · Li Zhang¹ · Siming Jiang¹ · Jian Ding¹ · Kezhong Zhang¹

J Neural Transm (2017) 124:1187–1195
DOI 10.1007/s00702-017-1748-1



Anatomical region (AAL)

PD-F vs PD-NF

Cingulum_Ant_L
Frontal_Inf_Tri_R
Frontal_Sup_R
Frontal_Inf_Orb_R
Postcentral_L

PD-F vs HCs

Frontal_Mid_R
Precentral_R
Fusiform_R
Thalamus_L

PD-NF vs HCs

Frontal_Sup_R
Frontal_Mid_R
Parietal_Inf_R

Acute basal ganglia infarcts in poststroke fatigue: an MRI study

Wai Kwong Tang · Yang Kun Chen · Vincent Mok · Winnie C. W. Chu · Gabor S. Ungvari · Anil T. Ahuja · Ka Sing Wong

J Neurol (2010) 257:178–182
DOI 10.1007/s00415-009-5284-2

Organizzazione della presentazione

Come definire la fatica (isolata)?

- *Fatica vs. faticabilità*
- *Costrutto indipendente da apatia, depressione, eccessiva sonnolenza*
 - *Frequente problema*

Basi neurali della fatica

- *Quadro incompleto*
- *Ruolo per le vie dopaminergiche (meso-corticali?)*
- *Probabilmente coinvolte la corteccia prefrontale ventro-mediale, i gangli della base e le aree motorie)*

Approccio al paziente con fatica

Fatica e nel paziente neurologico: che fare?

The differential diagnosis of tiredness: a systematic review

Rebekka Stadje^{*}, Katharina Dornieden, Erika Baum, Annette Becker, Tobias Biroga, Stefan Bösner, Jörg Haasenritter, Christian Keunecke, Annika Viniol and Norbert Donner-Banzhoff

Results: We found considerable heterogeneity of estimates which was reduced by limiting our analysis to high quality studies. Prevalences were as follows-anaemia: 2.8 % (CI (confidence interval) 1.6–4.8 %); malignancy: 0.6 % (CI 0.3–1.3 %); serious somatic disease: 4.3 % (CI 2.7–6.7 %); depression 18.5 % (CI 16.2–21.0 %). Pooling was not appropriate for CFS.

In studies with control groups of patients without the symptom of tiredness, prevalence of somatic disease was identical to those complaining of tiredness. Depression, however, was more frequent among those with tiredness.

Approccio al paziente con fatica

Fatigue in neurological disorders

Lancet 2004; 363: 978–88

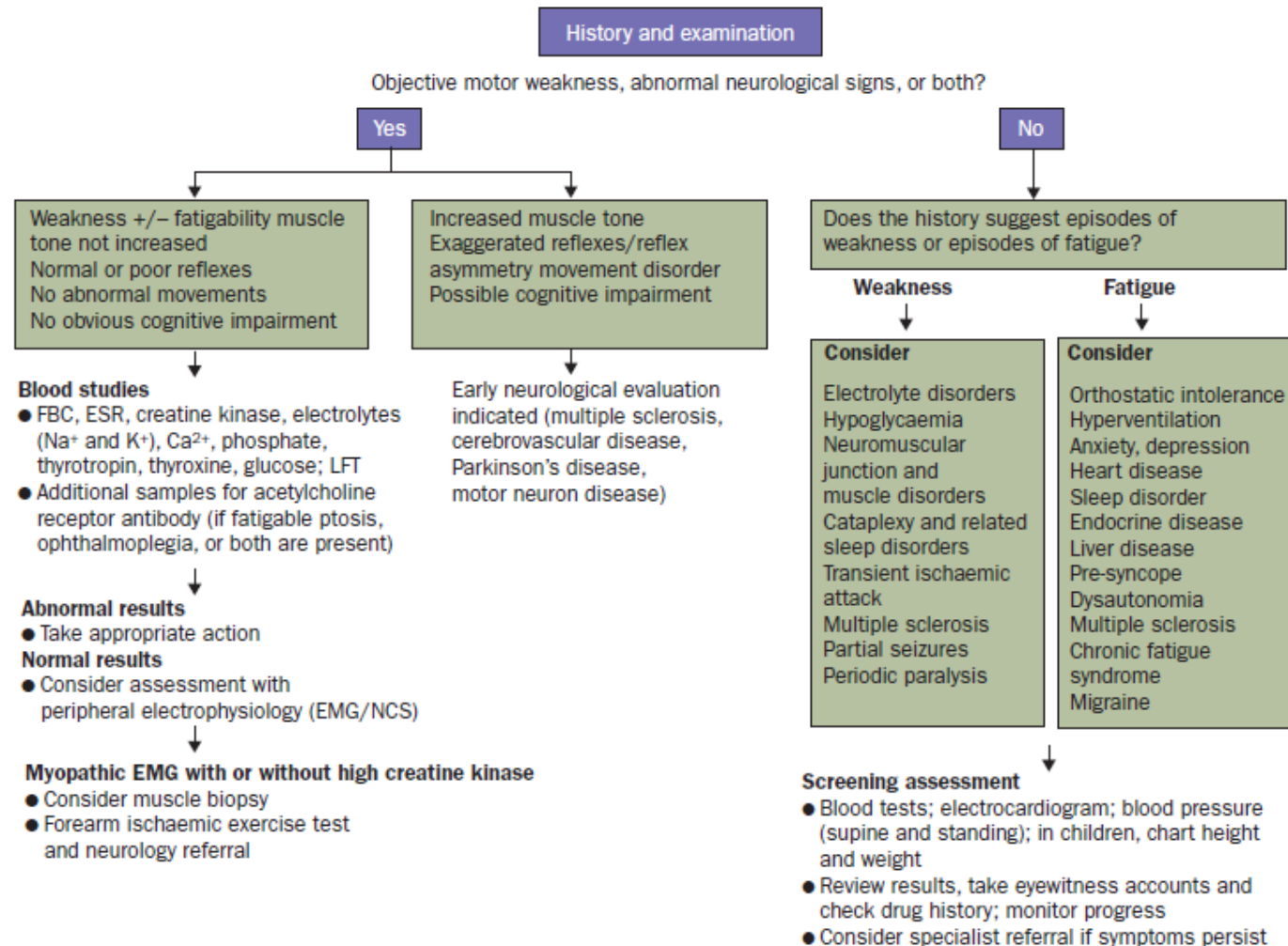


Figure 3: **Assessment of muscle fatigability and fatigue**

FBC=full blood count. ESR=erythrocyte sedimentation rate. LFT=liver function tests. EMG=electromyography. NCS=nerve conduction study.

Approccio al paziente (neurologico) con fatica

Parkinson's Disease-Related Fatigue: A Case Definition and Recommendations for Clinical Research

Movement Disorders, Vol. 31, No. 5, 2016

Proposed Criteria for diagnosis of Parkinson's Disease-related fatigue

Patients must report significantly diminished energy levels, or increased perceptions of effort which are disproportionate to attempted activities or general activity level. Symptoms must be present for most of the day, every day or nearly every day during the previous month. In addition, patients must have four or more of the symptoms from section A as well as meet criteria in sections B, C, and D.

A. Symptoms

1. Symptoms may be induced by routine activities of daily living.
2. Symptoms may occur with little or no exertion.
3. Symptoms limit the type, intensity or duration of activities performed by the patient.
4. Symptoms are not reliably relieved by rest or may require prolonged periods of rest.
5. Symptoms may be brought on by cognitive tasks or situations requiring sustained attention including social interactions.
6. Patients avoid rigorous activities due to fear of experiencing worsening of symptoms.
7. Mild to moderate exertion may induce a worsening of symptoms lasting hours to days.
8. Symptoms have a predictable diurnal pattern regardless of activities performed (e.g. worsening in the afternoon).
9. Symptoms are unpredictable and may have a sudden onset.

B. The patient experiences clinically significant distress or impairment in social, occupational or other important areas of function as a result of fatigue.

C. There is evidence from the history and physical examination suggesting fatigue is a consequence of PD.

D. The symptoms are not primarily a consequence of comorbid psychiatric disorders (e.g. depression), sleep disorders (e.g. obstructive sleep apnea) or medical conditions (e.g. anemia, congestive heart failure).

(Kluger et al., 2016)

Approccio al paziente (neurologico) con fatica

Assessment of Fatigue in Multiple Sclerosis

Sander C et al. Assessment of Fatigue in... Neurology International Open 2017; 1: E79–E85

► **Table 1** Criteria for the diagnosis of MS-related fatigue to based on criteria for determining fatigue in patients with Parkinson's disease according to Kluger et al. Parkinson's disease-related fatigue: a case definition and recommendations for clinical research. Mov Dis 2016; 31: 625–631 (5). [rerif] [5].

Criteria for the diagnosis of MS-related fatigue

Patients must report significantly diminished energy levels or increased perceptions of effort that are disproportionate to attempted activities or general activity level. Symptoms must be present for most of the day every day or nearly every day during the previous month. In addition, patients must have 4 or more of the symptoms from section A as well as meet criteria in sections B, C, and D.

A.	Symptoms
	1. Symptoms may be induced by routine activities of daily living.
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	7. Mild to moderate exertion may induce a worsening of symptoms lasting hours to days.
	8. Symptoms have a predictable diurnal pattern regardless of activities performed (eg., worsening in the afternoon).
	9. Symptoms are unpredictable and may have a sudden onset.
B.	Fatigue causes clinically-relevant stress in the patient or impairment of functional capacity in social, occupational or another important range of activities.
C.	There is evidence from the history and physical examination suggesting fatigue is a consequence of multiple sclerosis.
D.	Symptoms are not primarily a consequence of a comorbid psychiatric disturbance (e. g., depression), sleep impairment (e. g., obstructive sleep apnea) or other health issue (e. g., anemia, heart disease).

Approccio al paziente (neurologico) con fatica

3. Structured interview schedule for community patients

- 1a) Over the past month, have you experienced fatigue, a lack of energy or an increased need to rest?
- 1bi) Can you describe what your fatigue feels like, in your own words?
- 1bii) Is it a sleepy feeling, or is it more a lack of energy?
- 1ci) Over the past month, how much of the time do you feel fatigued?
- 1cii) How much of the day do you feel fatigued?
- 2a) Do you feel that fatigue is a problem for you?
- 2b) Is there anything else about your experience of fatigue that you feel is important?

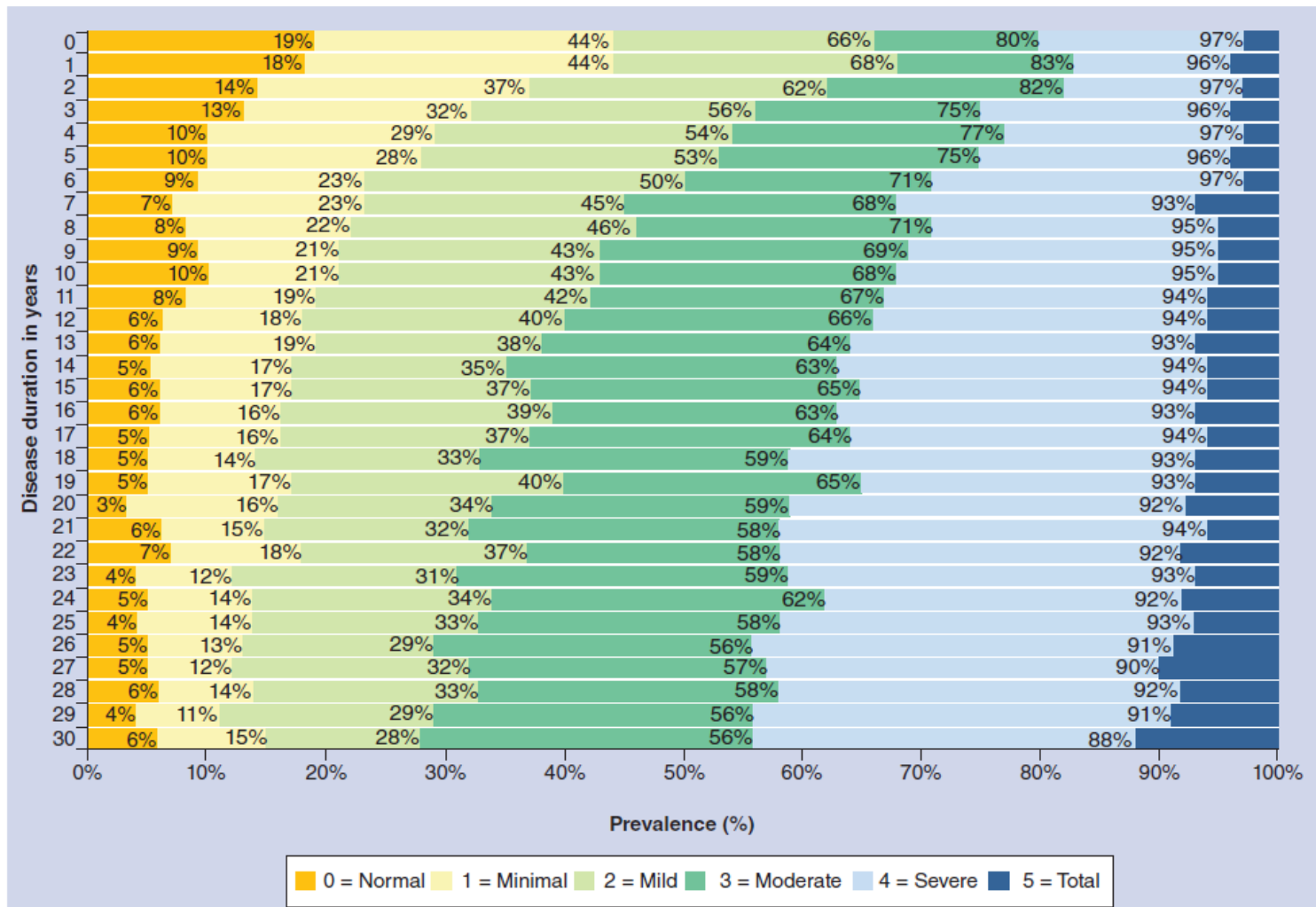
Probe	Criteria	Score
1a	Patient must answer yes to this question to fulfil the case definition. If patient answers no, go straight to question 2a.	Yes/no
1bi	Patient should describe feelings which are consistent with fatigue or lack of energy or increased need to rest rather than lack of motivation or boredom.	Yes/no
1bii	Patients should describe feelings of fatigue (or lack of energy or increased need to rest) rather than sleepiness	Yes/no
1ci)	Fatigue should have been present everyday or nearly everyday for at least two weeks in past month.	Yes/no
1cii)	Fatigue must be present for>50% of waking hours	Yes/no
2a	Fatigue must be perceived as a problem and affect everyday activities, e.g., activities of daily living, recreational activities such as reading or watching the television, and may or may not affect participation in therapy.	Yes/no
2b	Please note the patient's response.	

Storia naturale della fatica

Neurodegener Dis Manag. 2015;5(6 Suppl):3-10. doi: 10.2217/nmt.15.55.

Prevalence of multiple sclerosis symptoms across lifespan: data from the NARCOMS Registry.

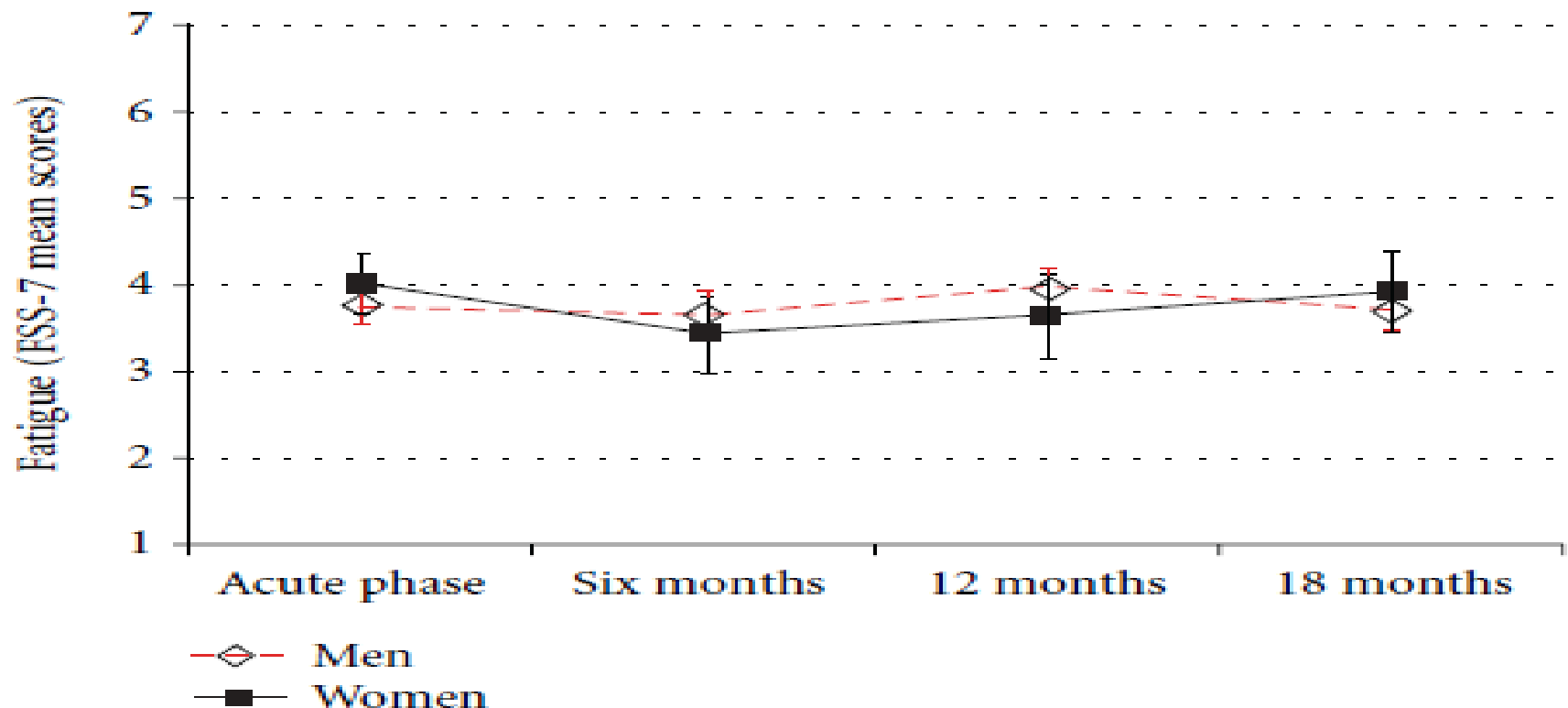
Fox RJ¹, Bacon TE², Chamot E³, Salter AR⁴, Cutter GR⁴, Kalina JT², Kister I².



The Course of Fatigue during the First 18 Months after First-Ever Stroke: A Longitudinal Study

**Anners Lerdal,^{1,2} Kathryn A. Lee,³ Linda N. Bakken,^{4,5}
Arnstein Finset,⁵ and Hesook Suzie Kim⁴**

Stroke Research and Treatment
Volume 2012, Article ID 126275, 8 pages
doi:10.1155/2012/126275



Organizzazione della presentazione

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- *Ruolo per le vie dopaminergiche (meso-corticali?)*
- *Probabilmente coinvolte la corteccia prefrontale ventro-mediale, i gangli della base e le aree motorie)*

Approccio al paziente con fatica

- *Sintomo assai aspecifico nel soggetto sano*
- *Nel malato neurologico enfasi su frequenza (quotidiana o semiquotidiana) e impatto ecologico*

Fatica e nel paziente neurologico: che fare?

Fatica nel paziente neurologico: che fare?

1. Eliminare cause concorrenti di fatica sia viscerali (anemia...) che psichiche (depressione...) nonché possibili sintomi concomitanti che impattano sui livelli di fatica percepita (disturbi del sonno, spasticità...)
2. Ottimizzare la terapia specifica per la patologia sottostante
3. Terapia sintomatica per la fatica (?)

Fatica nel paziente neurologico: che fare?

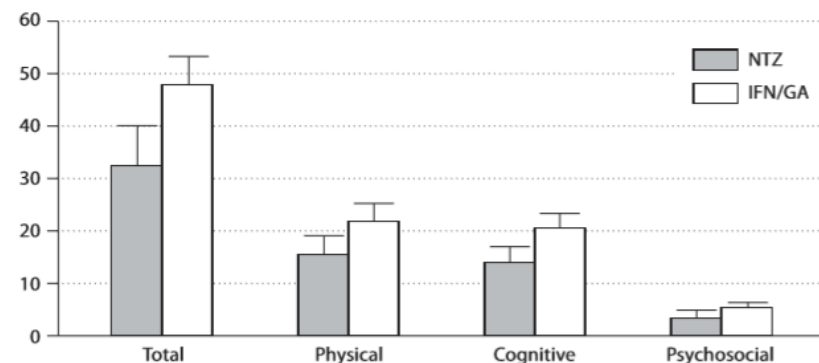
Multiple Sclerosis-Associated Fatigue during Disease-Modifying Treatment with Natalizumab, Interferon-Beta and Glatiramer Acetate

Murat Yildiz Barbara Tettenborn Norman Putzki

European
Neurology

Eur Neurol 2011;65:231–232

DOI: [10.1159/000324028](https://doi.org/10.1159/000324028)



Fatigue in early Parkinson’s disease: the Norwegian ParkWest study

S. O. Ongre^a, J. P. Larsen^b, O. B. Tysnes^c and K. Herlofson^a

*European Journal of
Neurology* 2017, **24**: 105–111

Table 3 Overview of antiparkinson medication and comparison of change in FSS mean sum score between baseline and the 1-year evaluation in patients with fatigue (FSS mean sum score ≥ 4) at baseline ($N = 98$)

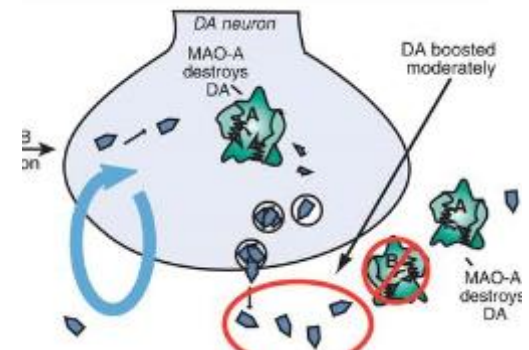
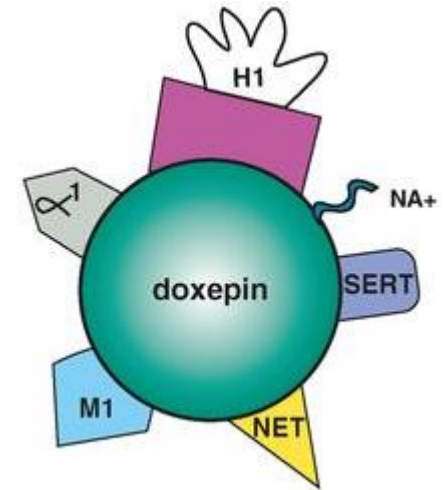
Medication	Yes		No		P value
	Number of patients	Change in FSS mean sum	Number of patients	Change in FSS mean sum	
Any PD medication (LD, DA, MAO-Bi)	83	−0.98	15	−0.72	0.52
Levodopa	51	−0.75	47	−1.2	0.17
Dopamine agonist	37	−1.4	61	−0.65	0.010 ^a
MAO-Bi	17	−1.38	81	−0.85	0.18
LED above 400	28	0.94	70	0.94	0.996

Fatica nel paziente neurologico: che fare?

PD: Based on the current evidence, **no clear recommendations** for the treatment of subjective fatigue in PD can be provided. **Doxepin** may reduce the impact of fatigue on ADL and fatigue severity; however, this finding has to be confirmed in high quality studies. **Rasagiline** may be effective in reducing levels of physical fatigue in PD. (Elbers RG et al., 2015)

Stroke: There was **insufficient evidence** on the efficacy of any intervention to treat or prevent fatigue after stroke. (Wu et al., 2015)

MS: **Exercise therapy**, and particularly endurance, mixed, or 'other' training, may reduce self reported fatigue (Heine et al., 2015). The efficacy of amantadine in reducing fatigue in people with MS is poorly documented, as well as its tolerability (Pucci et al., 2007). There is insufficient evidence that carnitine for the treatment of MS-related fatigue offers a therapeutic advantage over placebo (Tejani et al., 2012).

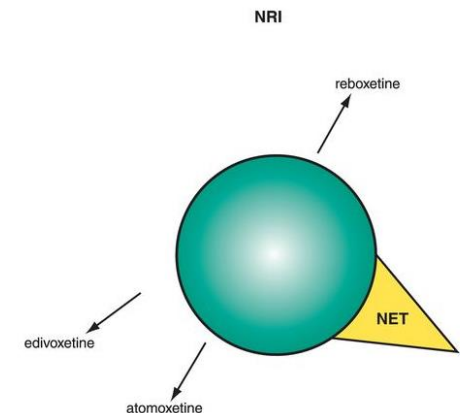
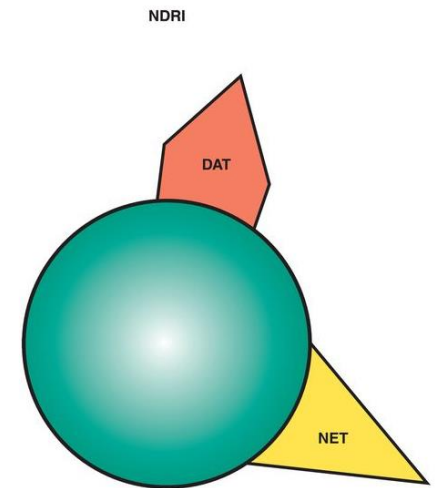


Fatica nel paziente neurologico: che fare?

Cancer: There is increasing evidence that **psychostimulant** trials provide evidence for improvement in CRF at a clinically meaningful level (Minton et al., 2010)

Palliative care: Based on limited evidence, we cannot recommend a specific drug for the treatment of fatigue in palliative care patients. Fatigue research in palliative care seems to focus on modafinil and methylphenidate, which may be beneficial for the treatment of fatigue associated with palliative care although further research about their efficacy is needed. (Muche et al., 2015)

Depression: There is some evidence that in the short-term, psychostimulants reduce symptoms of depression. A similar effect was found for fatigue (Candi et al., 2008)



Take home message

Come definire la fatica (isolata)?

- Fatica vs. faticabilità
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- Frequente problema

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Fatica e nel paziente neurologico: che fare?

- *Non evidenze solide*
- *Ottimizzare terapia specifica per condizione sottostante*
 - *Valutare noradrenergici/dopaminergici*