Simposio – La Fatica nella Sclerosi Multipla

Correlati clinici

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DISCLOSURES (alphabetical order):

Letitia Leocani:

- Advisory board/Consultancies: Abbvie, Biogen, Merck Serono, Novartis, Roche, Bristol-Myers Squibb, Janssen-Cilag
- Travel support: Almirall, Biogen, Genzyme, Merck, Novartis, Roche, Teva
- Research support: Almirall, Biogen, Merck, Novartis
- Speakers bureau: Almirall, Biogen, Excemed, Merck, Novartis, Roche, Teva, Bristol-Myers Squibb, Janssen Cilag

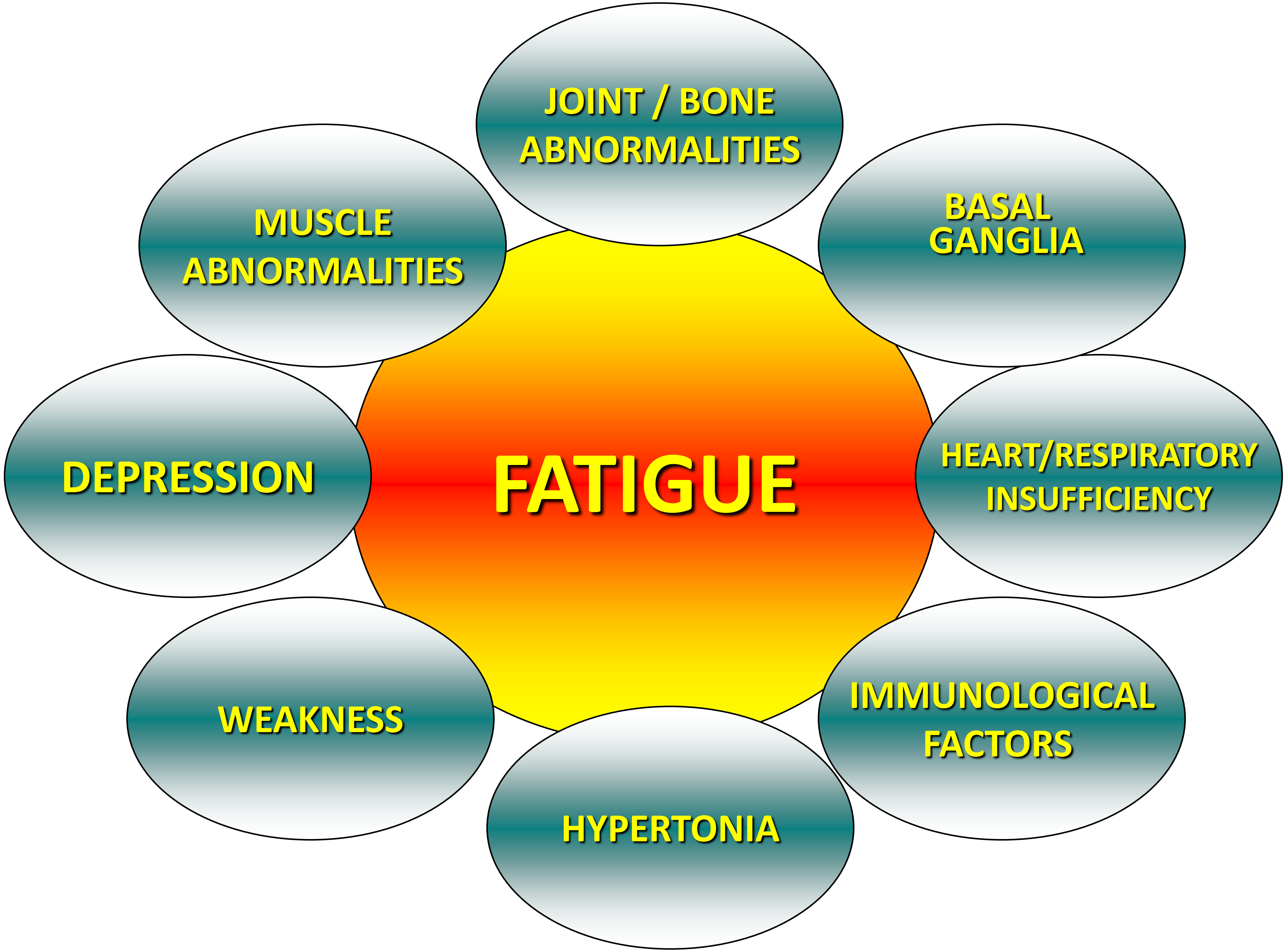
Fatigue in MS

- One of the most disabling symptoms
- Affects about 50-80% of the patients
- May be the onset symptom
- Transient or chronic
- May occur at any stage of the disease

Fatigue in MS

- Fatigue: overwhelming sense of tiredness, lack of energy, or feeling of exhaustion, already present at rest
- Fatigability: generalised sensation of exhaustion, not present at rest, affecting the patient after a few minutes of physical activity, that disappears after a short rest
- Fatigue and fatigability are not correlated although they can occur in the same individual

Pathophysiology of MS fatigue



The Fatigue Severity Scale

The Fatigue Severity Scale

Application to Patients With Multiple Sclerosis and Systemic Lupus Erythematosus

Lauren B. Krupp, MD; Nicholas G. LaRocca, PhD; Joanne Muir-Nash, RN; Alfred D. Steinberg, MD

Table 2 The FSS: each patient is asked to respond to the following nine statements by choosing a number between one and seven, where one indicates strongly disagree and seven indicates strongly agree

Statement	*Score*
1. My motivation is lower when I am fatigued	____
2. Exercise brings on my fatigue	____
3. I am easily fatigued	____
4. Fatigue interferes with my physical functioning	____
5. Fatigue causes frequent problems for me	____
6. My fatigue prevents sustained physical functioning	____
7. Fatigue interferes with carrying out certain duties and responsibilities	____
8. Fatigue is among my three most disabling symptoms	____
9. Fatigue interferes with my work, family, or social life	____
Total Score	____

Krupp et al Arch Neurol. 1989;46:1121-1123

Are questionnaires adequate for quantification of fatigue severity?

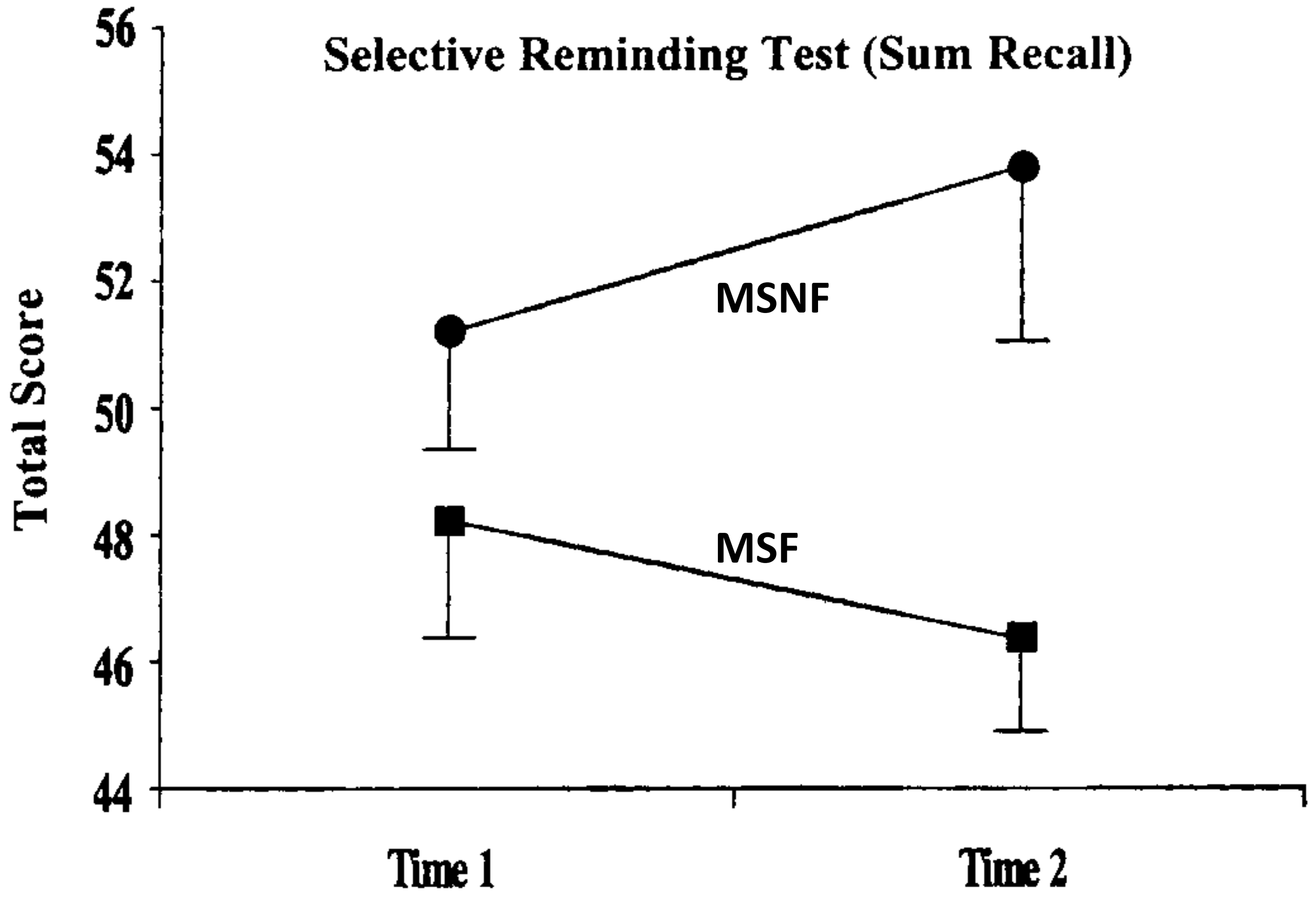
- They can be confounded by other symptoms of MS
- They are entirely subjective
- They require patients to make difficult retrospective assessments

Fatigue & disability correlations

Kroencke et al. 2000

Pyramidal	0.33	<0.001
Cerebellar	0.29	<0.001
Brain stem	0.24	<0.001
Sensory	0.29	<0.001
Bowel and bladder	0.30	<0.001
Visual	0.12	NS
Cerebral	0.23	0.001
Other	0.01	NS
EDSS	0.33	<0.001

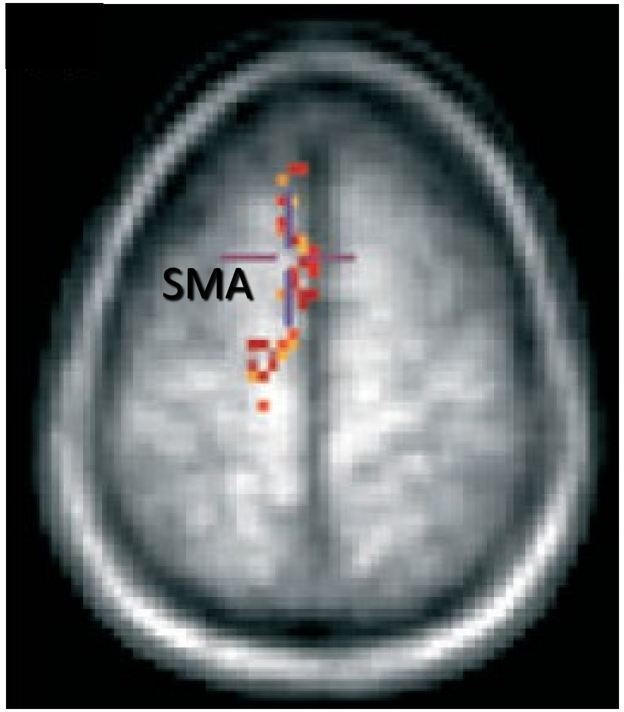
Verbal learning before-after effortful cognitive task



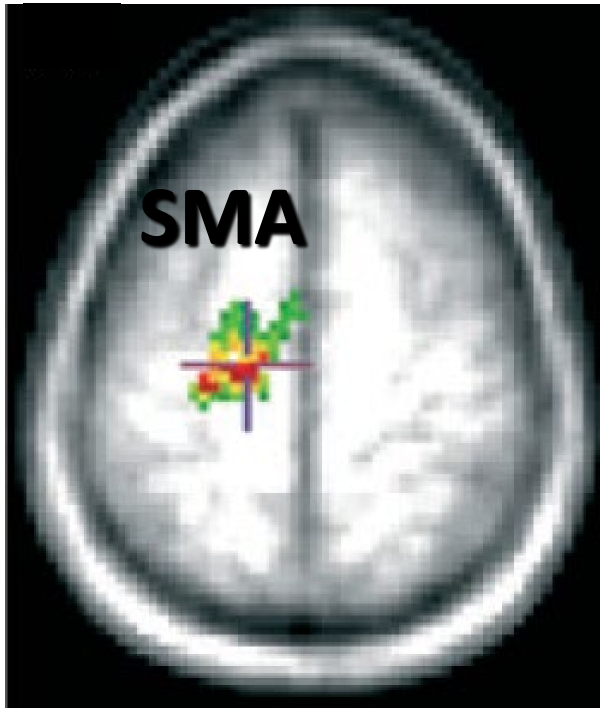
Krupp et al. 2000

SMA overactivation to MOVEMENT after COGNITIVE fatigue in pwMS (FSS > 5)

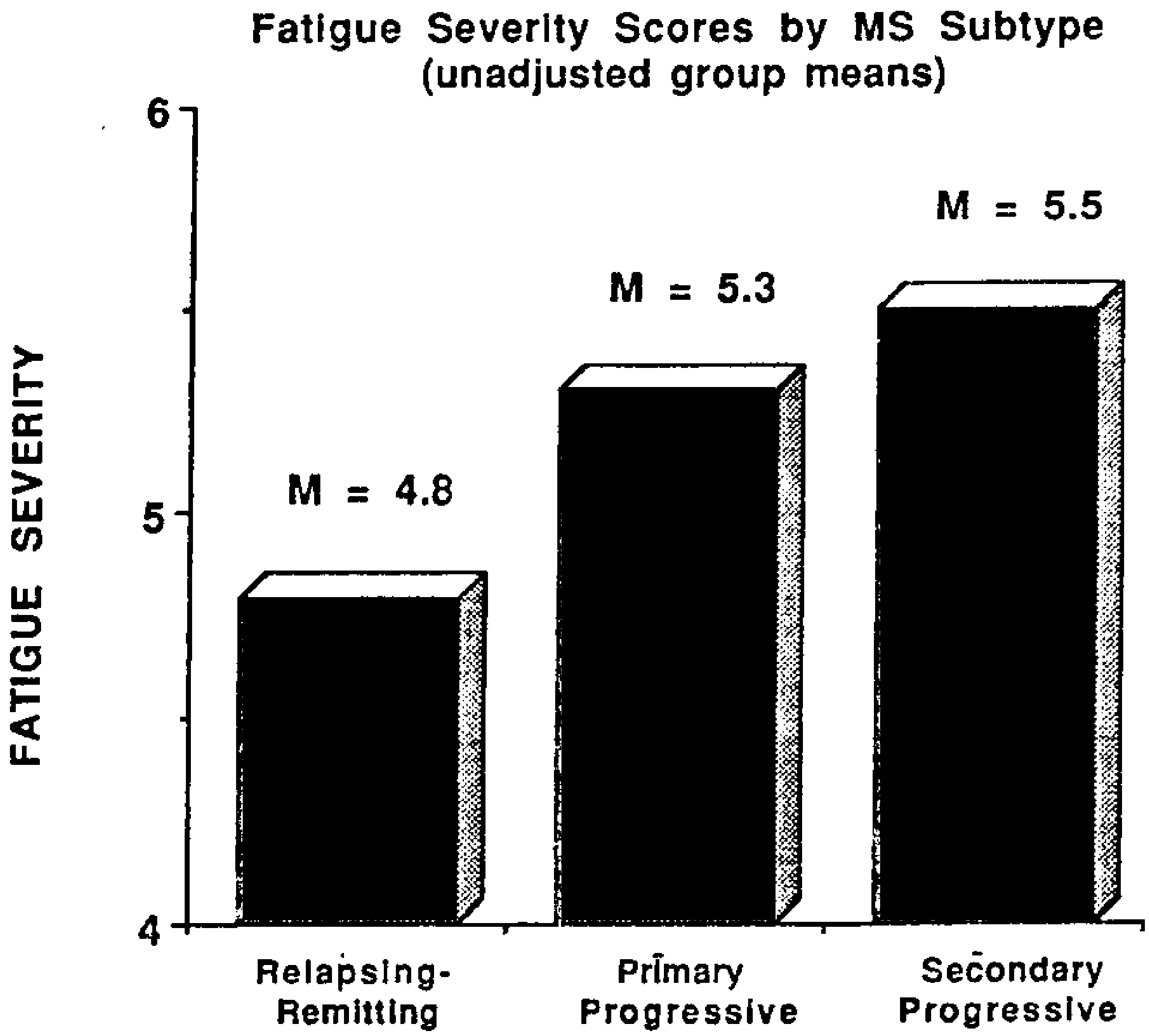
Pz *vs* controls
pre-PASAT



Pz *vs* controls
post-PASAT

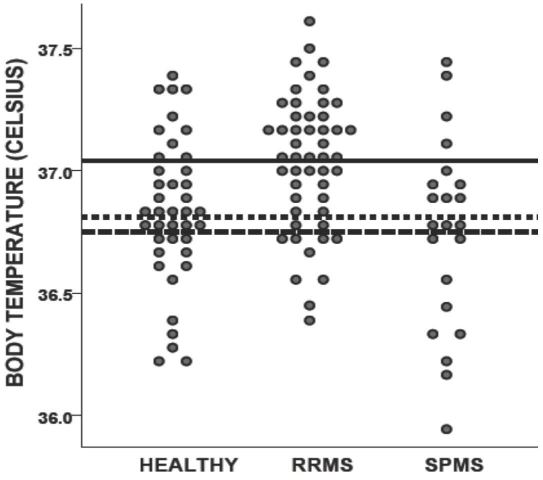


Tartaglia et al 2008

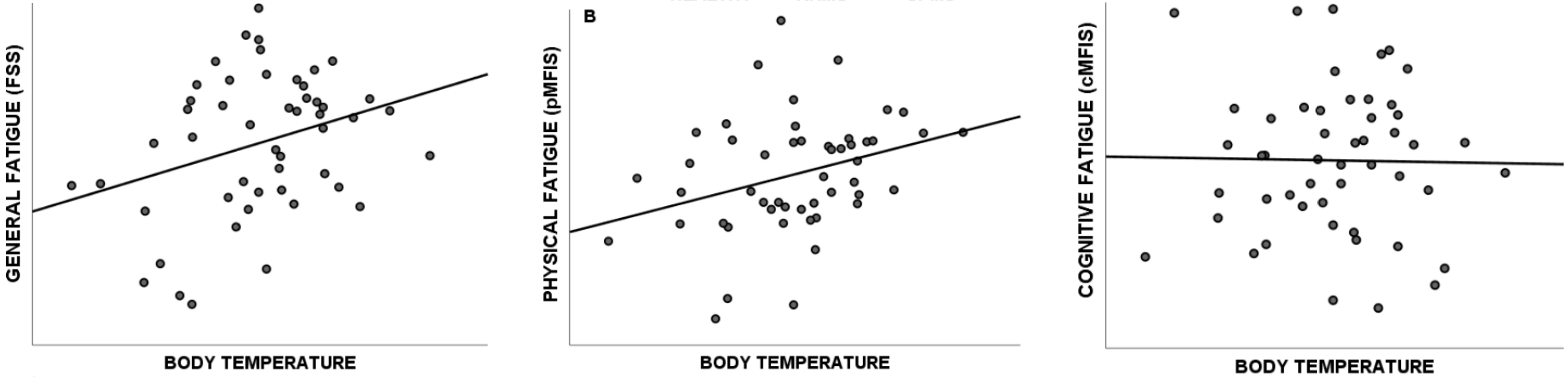


Kroencke et al. 2000

Body temperature is elevated and linked to fatigue in relapsing-remitting multiple sclerosis, even without heat exposure



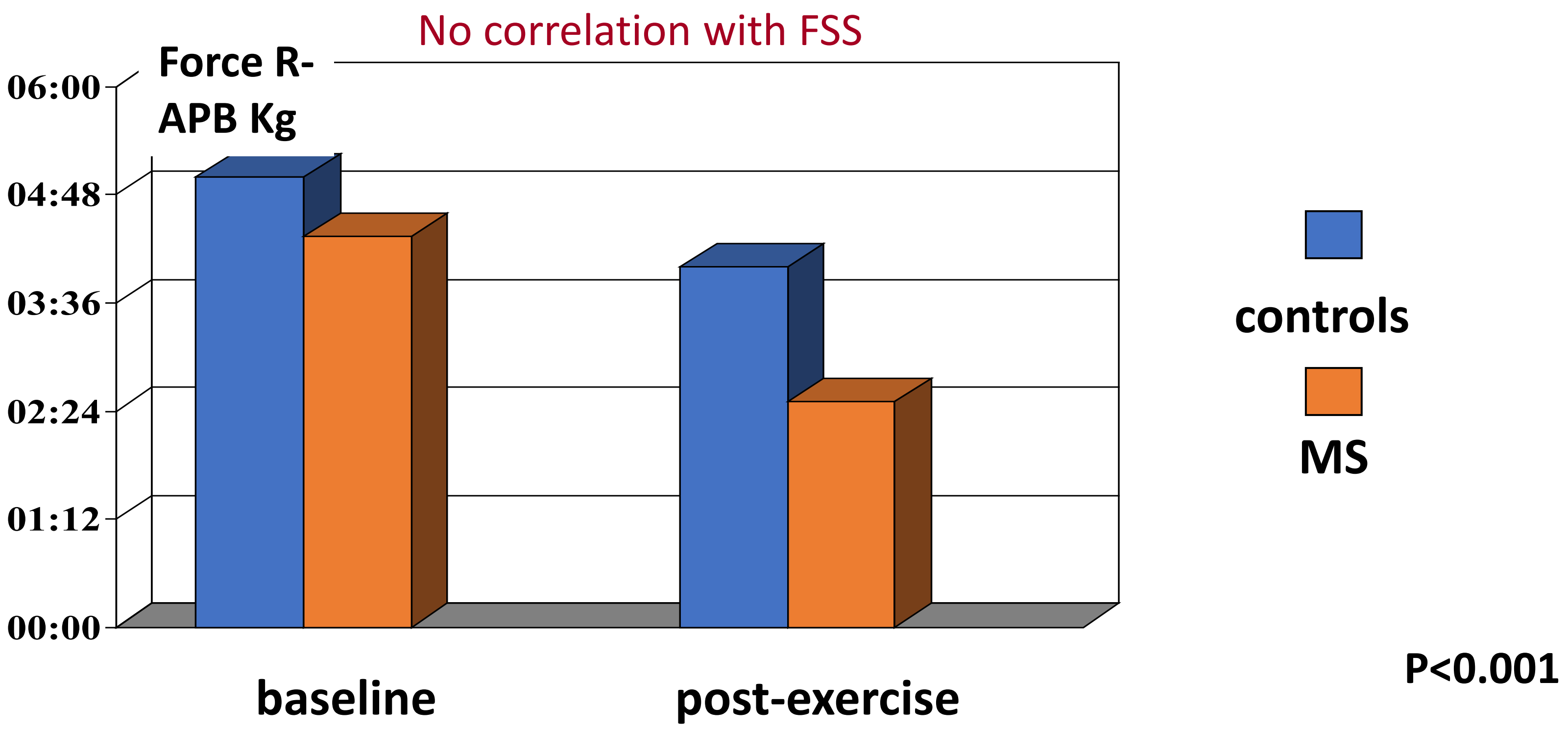
Archives of Physical Medicine and Rehabilitation



Sumowski & Leavitt, 2014

Force pre- and post-fatiguing exercise in pwMS

pwMS & subjective fatigue - no severe UL weakness *Sheean et al. 1997*



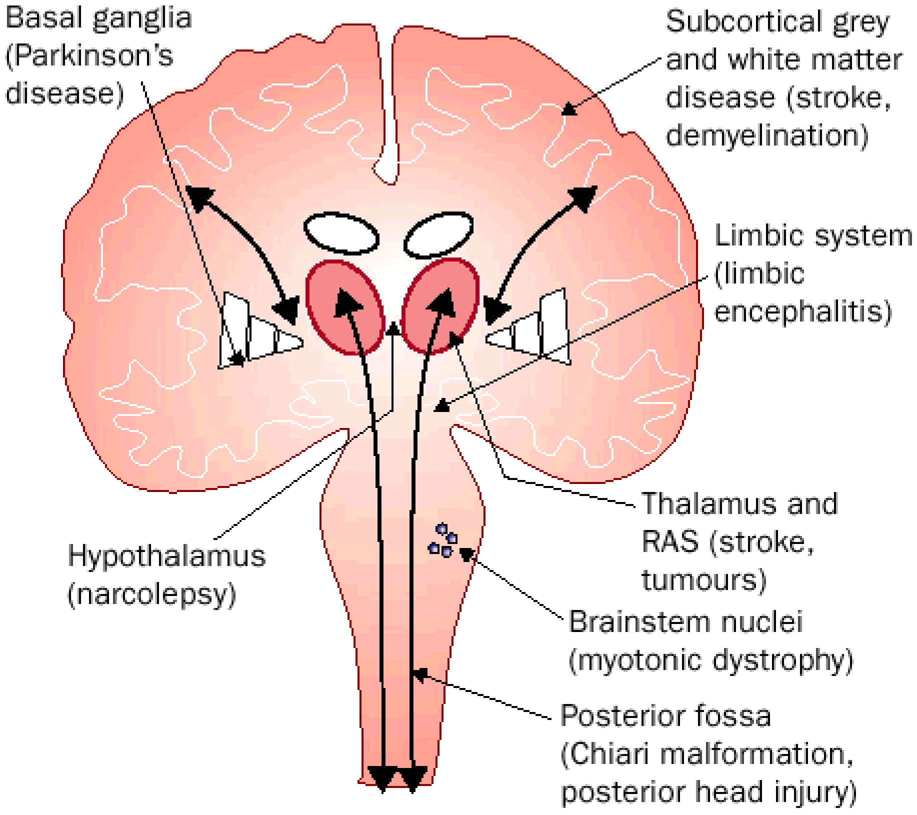
Fatigue as a movement disorder?

Increase of complex reaction times not related to slowing of conduction along the primary afferent or efferent pathways *(Sandroni et al., 1992)*

Role of the circuits related to motor planning:
basal ganglia-thalamus-cortex

These circuits may be studied by means of functional techniques: EEG and fMRI

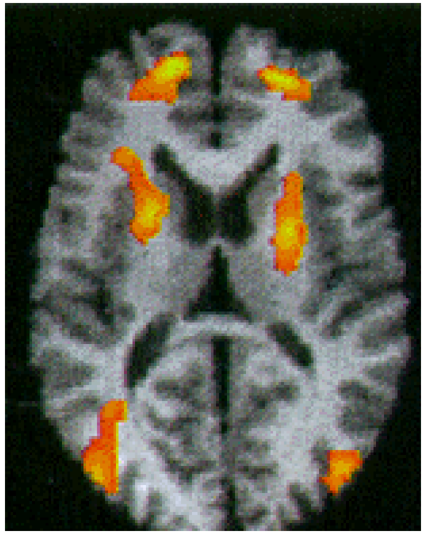
Basal ganglia participate in several functions -motor, cognitive, limbic- due to parallel circuitries



Chaudry and Behan 2004

MS-FAT vs No-FAT (FSS)

↓rCBF lat/medial PF, PM, SMA, putamen, caudate



Roelcke et al. 1997

Neuroradiology (2008) 50:17–23
DOI 10.1007/s00234-007-0304-3

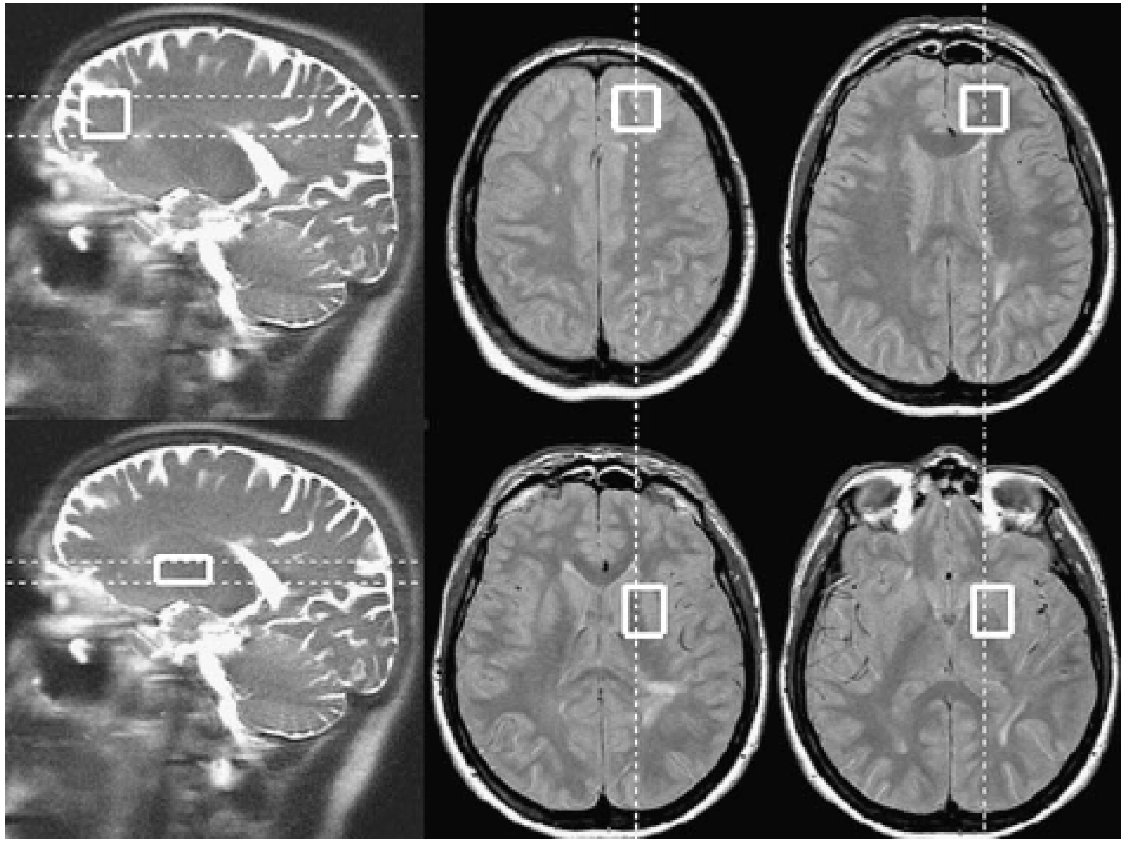
DIAGNOSTIC NEURORADIOLOGY

The basal ganglia: a substrate for fatigue in multiple sclerosis

N. Téllez • J. Alonso • J. Río • M. Tintoré • C. Nos •
X. Montalban • A. Rovira

MS Fatigue (≥ 5) vs non fatigue (<4)

Frontal wm
n.s.



Lentiform
nucleus
p=0.04

significant NAA/Cr decrease in the lentiform nucleus

No differences in the frontal white matter

Posterior cingulate and left parietal wm: n.s. *(Pokryszko-Dragan et al. J Neurol Sci 2014)*

But also higher Beck Depression score in Fat vs NFat

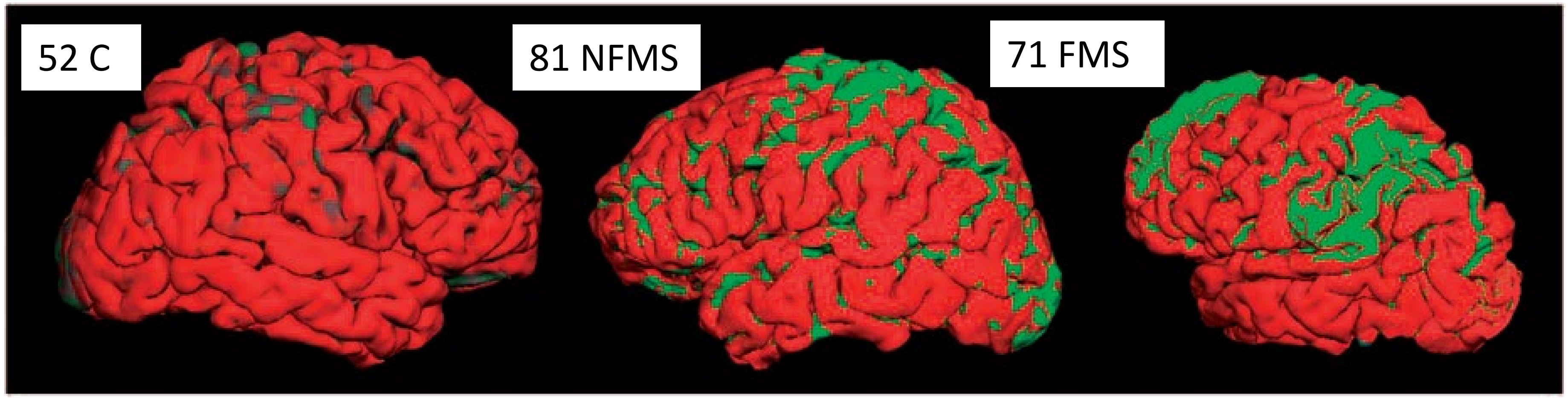
Fatigue in MS & tissue damage

Journal of the Neurological Sciences 263 (2007) 15 – 19

Correlation between fatigue and brain atrophy and lesion load in multiple sclerosis patients independent of disability

Gioacchino Tedeschi [a,b,*], Daria Dinacci [a], Luigi Lavorgna [a], Anna Prinster [c],

Basal ganglia and frontal/parietal cortical atrophy



Severe depression (BDI > 18) exclluded –max 21

Calabrese et al Mult Sclerosis 2010

Fatigue in Multiple Sclerosis Is Associated with Abnormal Cortical Activation to Voluntary Movement—EEG Evidence

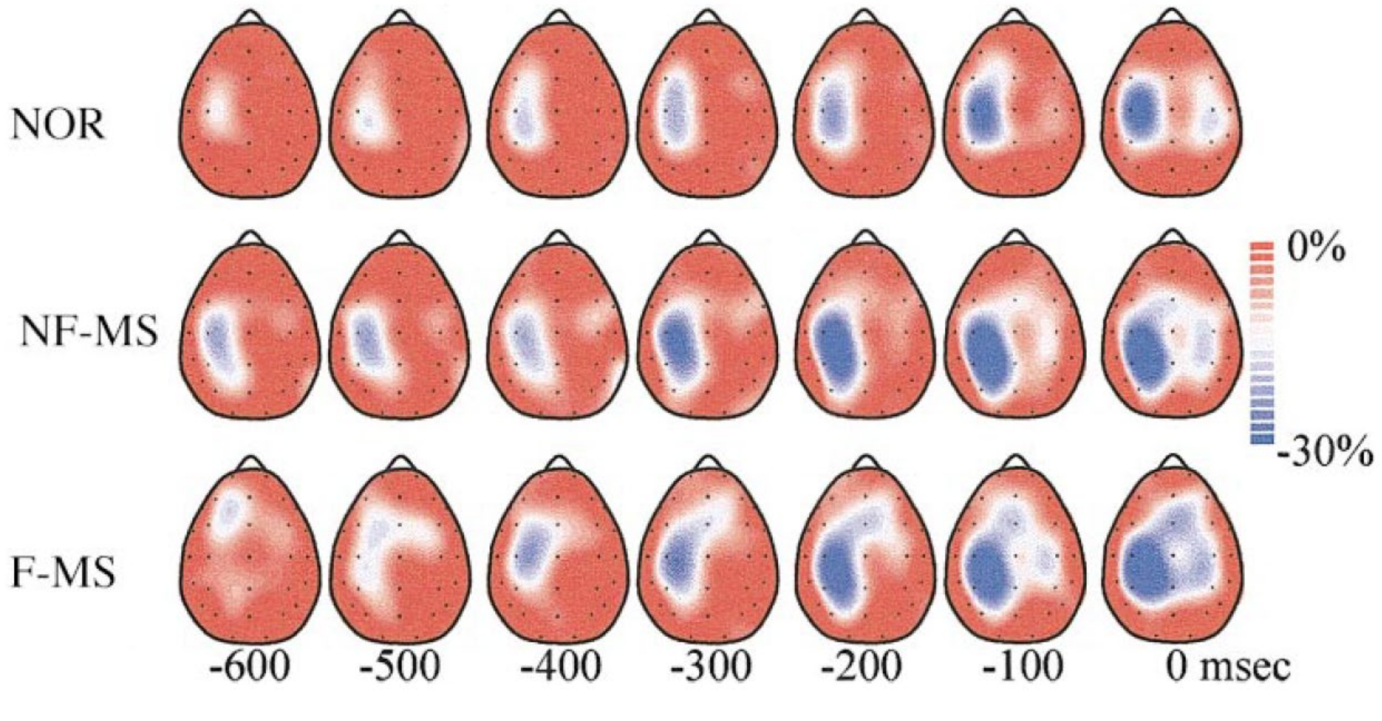
Letizia Leocani,* Bruno Colombo,† Giuseppe Magnani,† Filippo Martinelli-Boneschi,† Marco Cursi,*
Paolo Rossi,† Vittorio Martinelli,† and Giancarlo Comi*,†

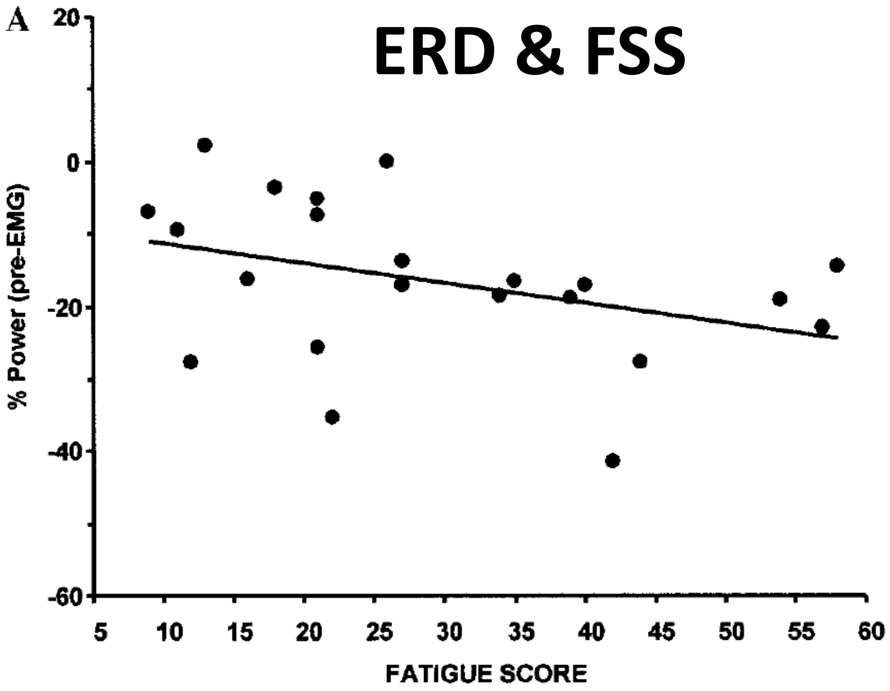
*Department of Neurophysiology and †Department of Neurology, Scientific Institute H. San Raffaele, Milan, Italy

Received September 6, 2000

Increased cortical Event-Related Desynchronization (ERD) of EEG rhythms in pwMS & fatigue

LEOCANI ET AL.





Fatigue treatment in MS: a complex scenario

- Symptomatic Drugs
  - Modafinil, Amantadine, Aminopyridines, Methylphenidate
- Disease-modifying Drugs
  - Ponesimod (RCT)
- Cognitive behavioural therapy
- Physical activity
- Non-invasive brain stimulation

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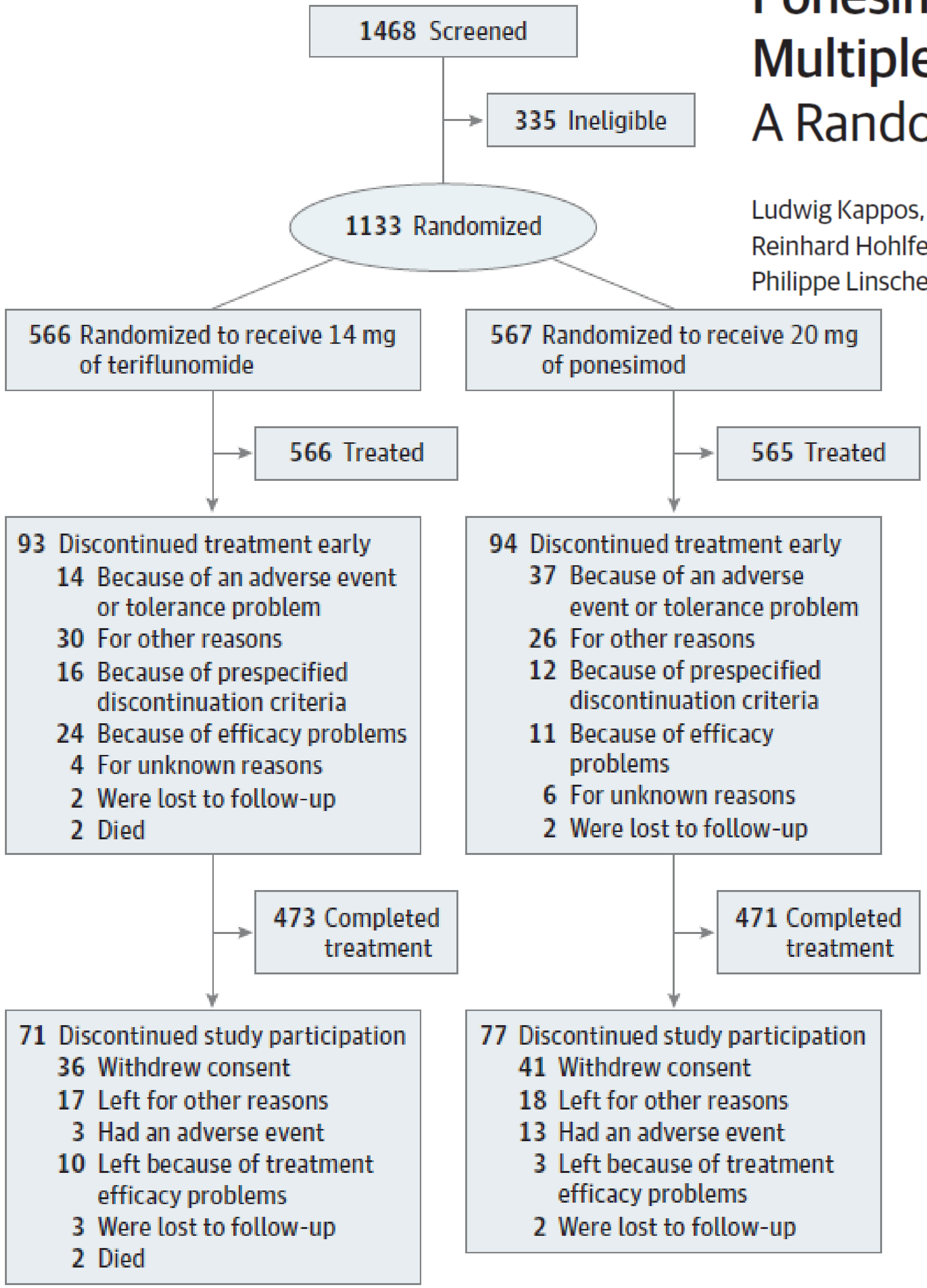
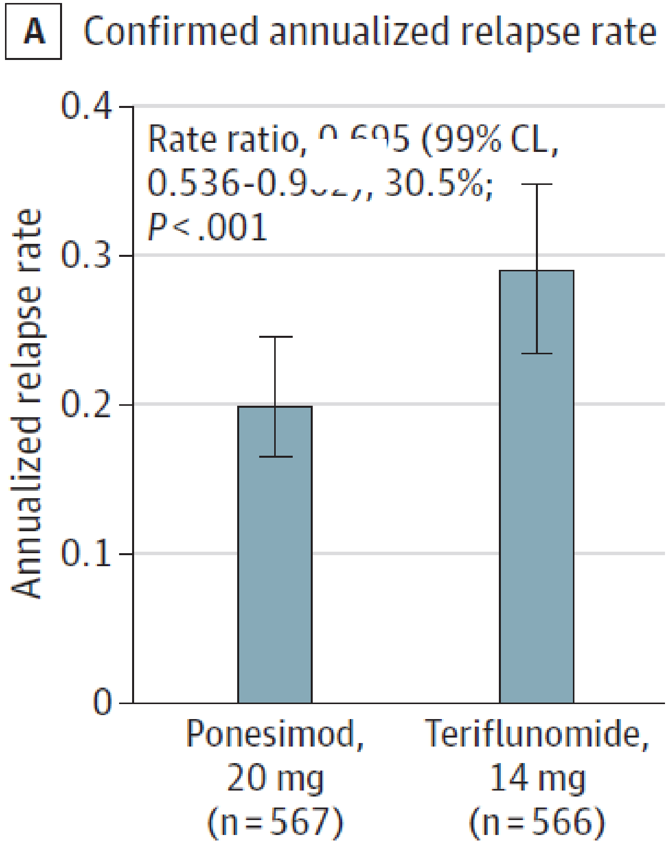
JAMA Neurology | Original Investigation

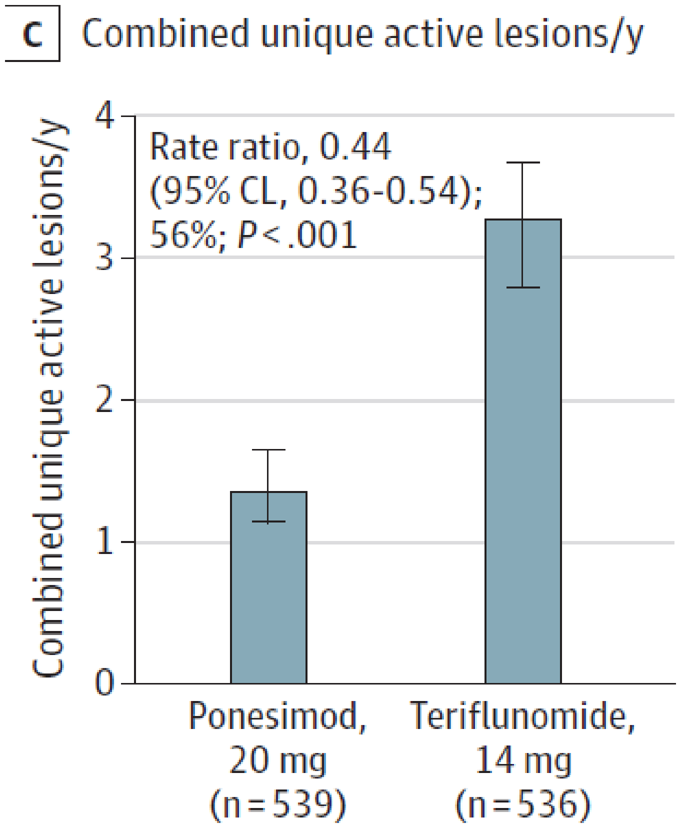
Ponesimod Compared With Teriflunomide in Patients With Relapsing Multiple Sclerosis in the Active-Comparator Phase 3 OPTIMUM Study
A Randomized Clinical Trial

Ludwig Kappos, MD; Robert J. Fox, MD; Michel Burcklen, PhD; Mark S. Freedman, MSc, MD; Eva K. Havrdová, MD, PhD; Brian Hennessy, MSc; Reinhard Hohlfeld, MD; Fred Lublin, MD; Xavier Montalban, MD, PhD; Carlo Pozzilli, MD, PhD; Tatiana Scherz, MD, PhD; Daniele D'Ambrosio, MD, PhD; Philippe Linscheid, PhD; Andrea Vaclavkova, MD; Magdalena Pirozek-Lawniczek, MD; Hilke Kracker, PhD; Till Sprenger, MD



1133 patients randomized in a 1:1 ratio to ponesimod 20 mg or teriflunomide 14 mg





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Agenzia Italiana del Farmaco

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Neurological Sciences
https://doi.org/10.1007/s10072-022-06080-1

ORIGINAL ARTICLE

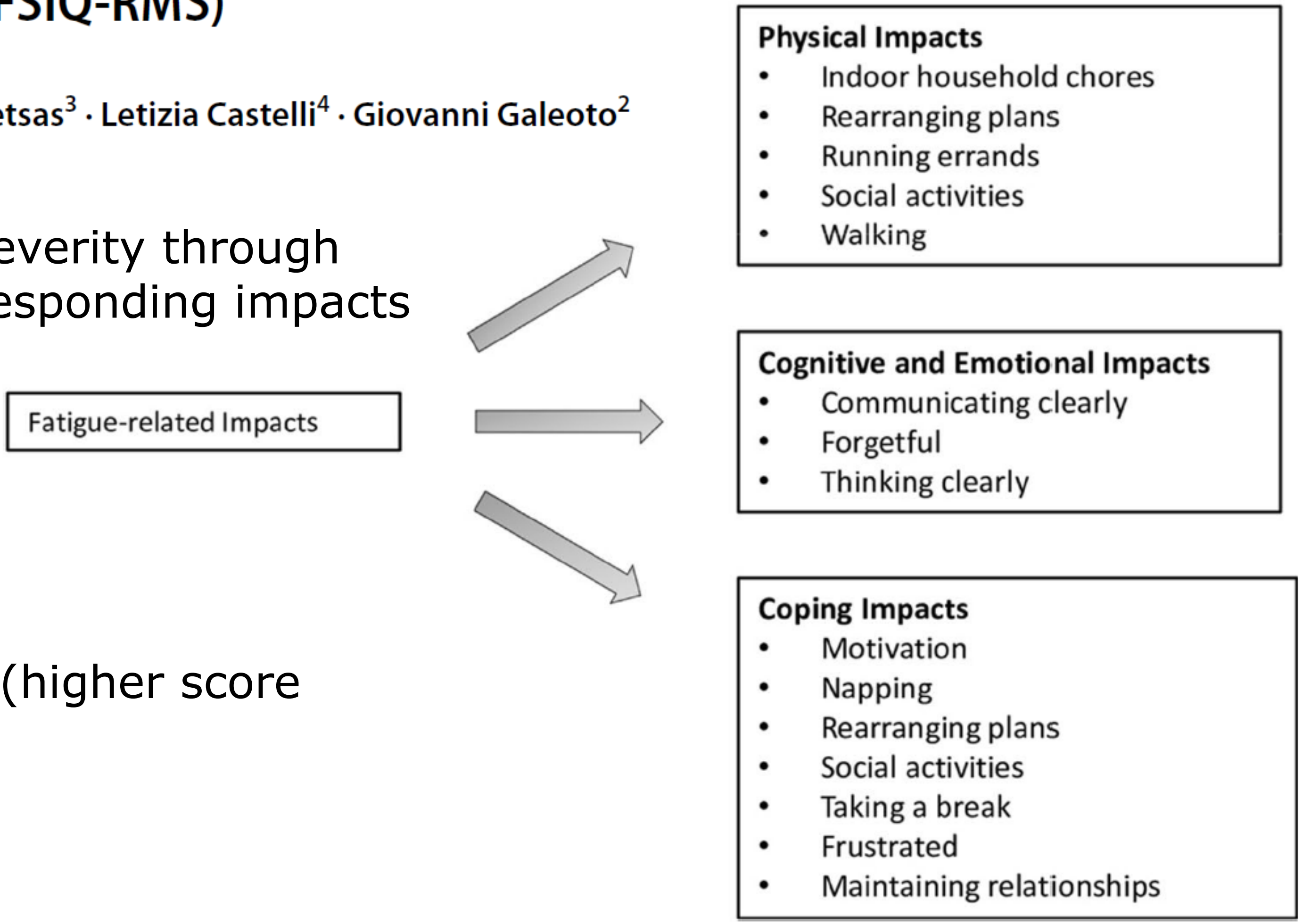
Italian translation and validation of fatigue symptoms and impacts questionnaire in relapsing multiple sclerosis (FSIQ-RMS)

Ilaria Ruotolo[1] · Giovanni Sellitto[1] · Antonio Ianniello[2] · Nikolaos Petsas[3] · Letizia Castelli[4] · Giovanni Galeoto[2] · Anna Berardi[2] · Valeria Barletta[2] · Antonella Conte[2,3] · Carlo Pozzilli[1,2]

20-item FSIQ-RMS which assesses fatigue severity through mean daily ratings over 7 days and the corresponding impacts of fatigue on three subdomains:

Physical
cognitive/emotional
Coping

FSIQ-RMS domain scores range from 0-100 (higher score indicates greater severity)



Fatigue and disease-modifying drugs – a complex scenario: the example of ponesimod

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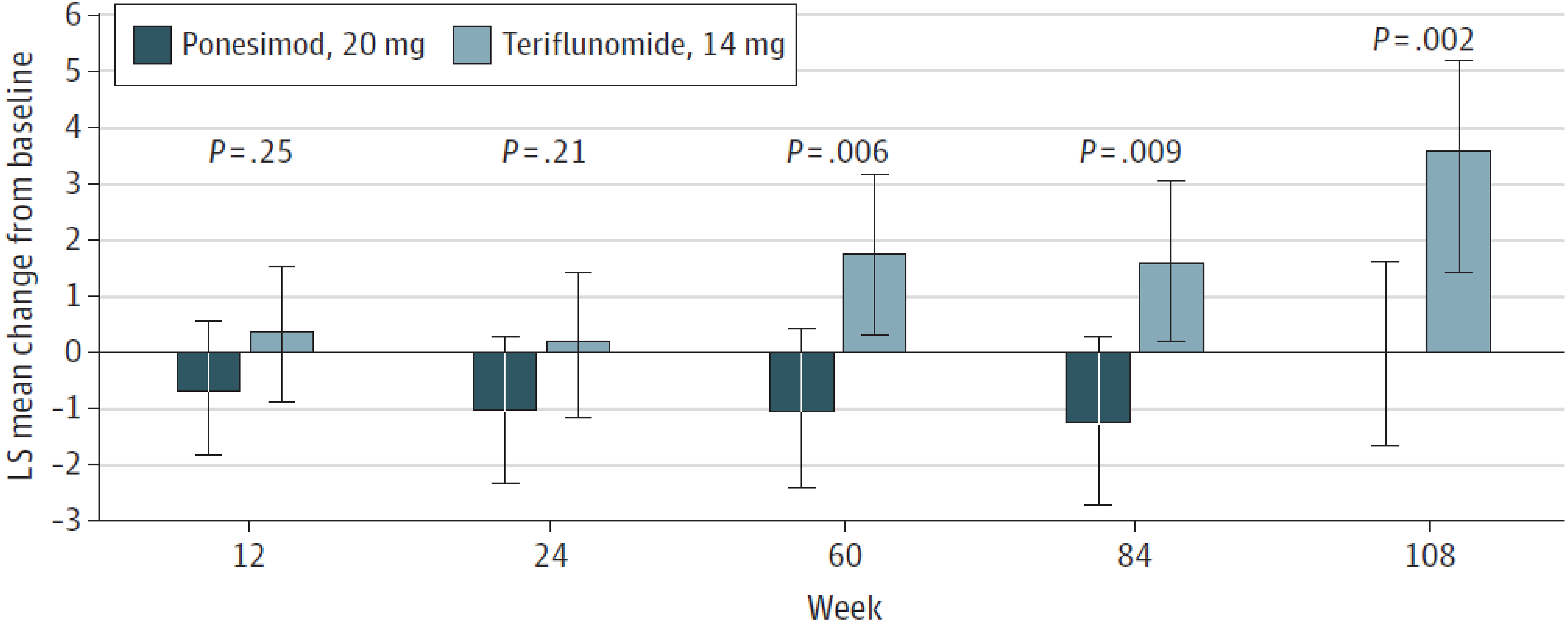
Fatigue Symptom and impact questionnaire score

FSIQ-RMS symptoms score



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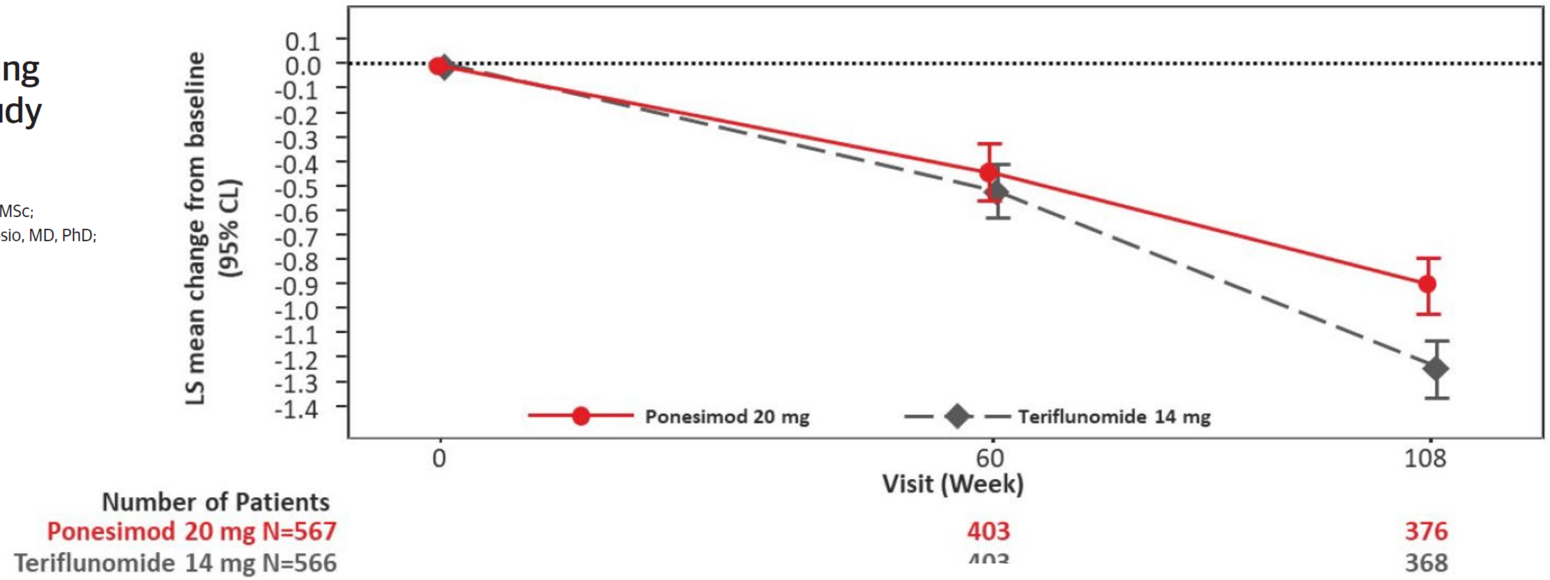

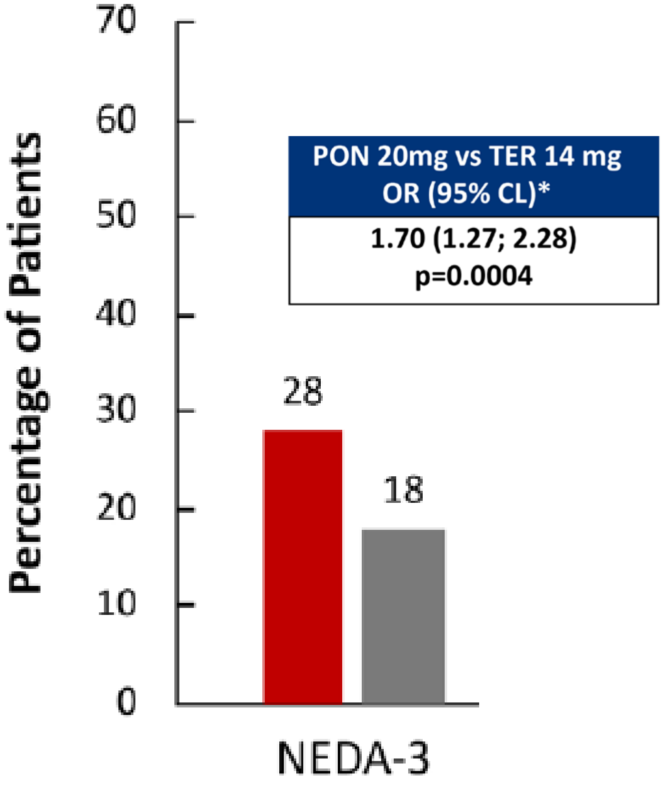

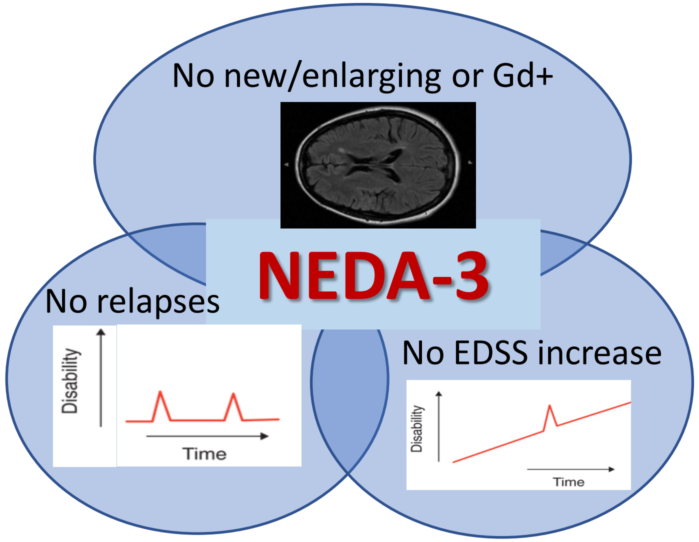

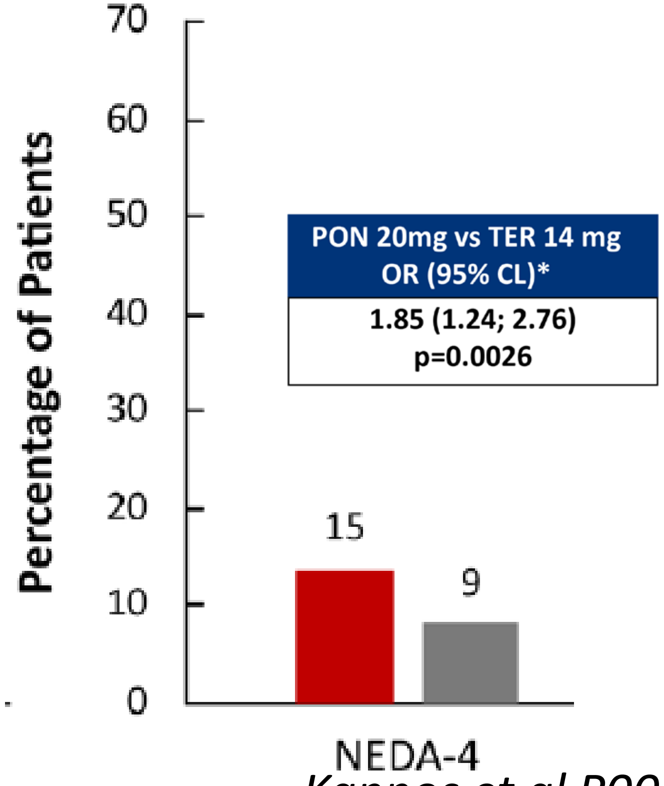

Kappos et al P007 ECTRIMS 2020

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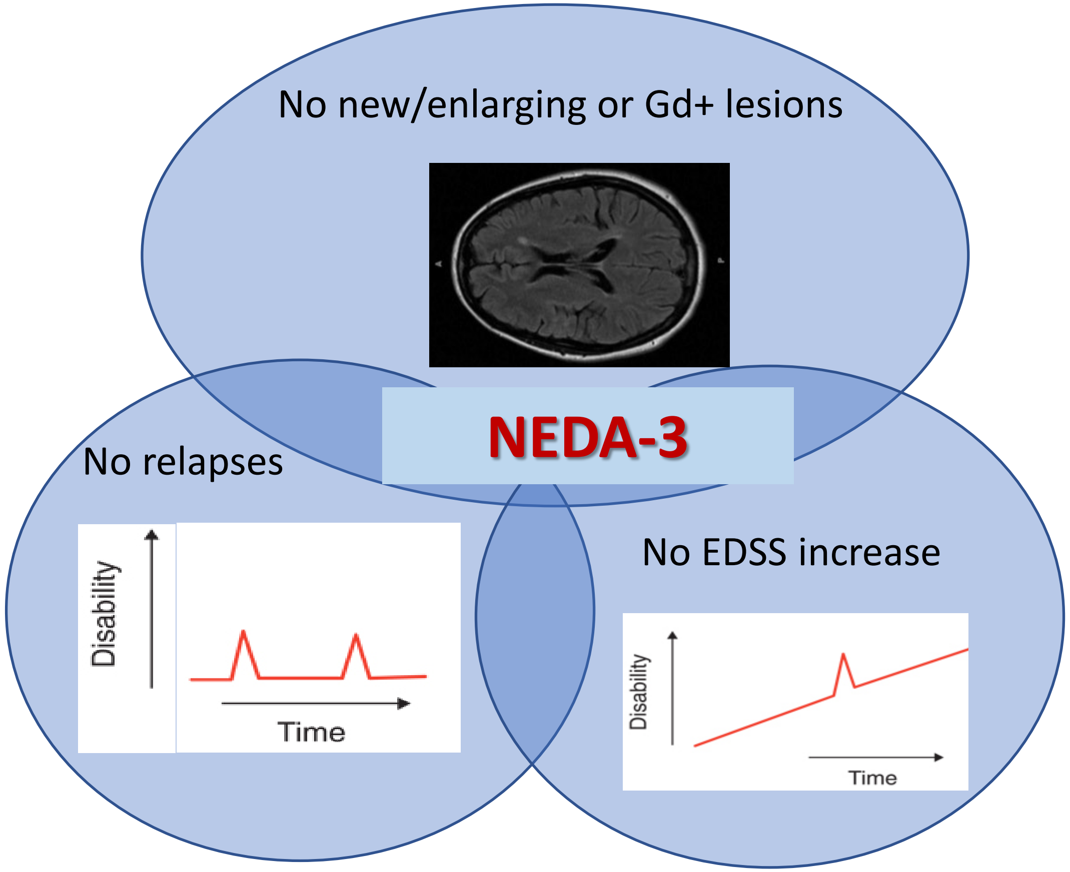
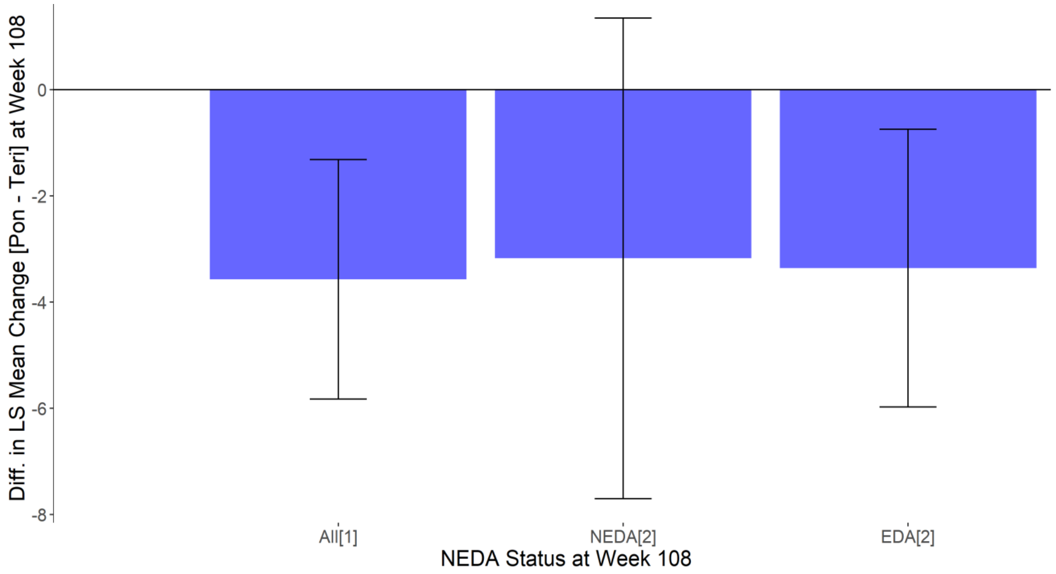


FSIQ-RMS symptoms score

Change from baseline to week 108 in FSIQ-RMS mean daily ratings over 7 days.

•Proportion of patients achieving NEDA-3 at End of Study (defined by the absence of confirmed relapse, Gd+ T1 lesions, new or enlarging T2 lesions, and 12-week CDA).



Difference PON-TER in change from baseline to week 108 in FSIQ-RMS weekly score: -3.17 (NEDA) vs. -3.36 (EDA), both favoring ponesimod

Fatigue treatment in MS: a complex scenario

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- Disease-modifying Drugs
  - Ponesimod (RCT)
- Cognitive behavioural therapy
- Physical activity
- Non-invasive brain stimulation

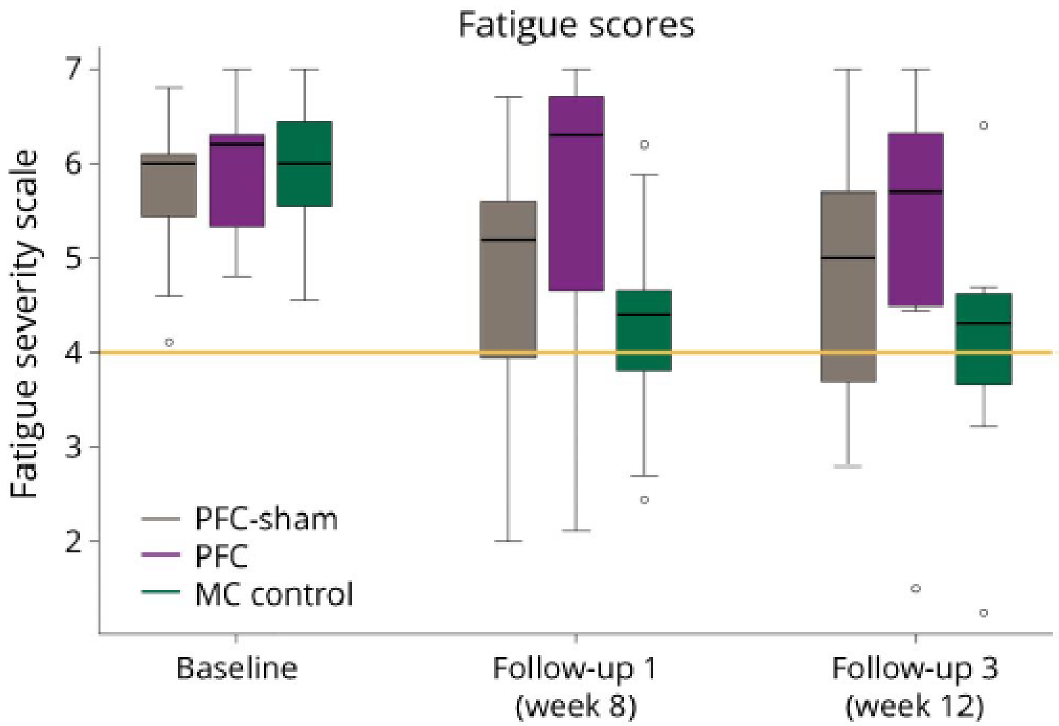
Fatigue treatment in MS: non invasive brain stimulation

Repetitive Transcranial Magnetic Stimulation - rTMS

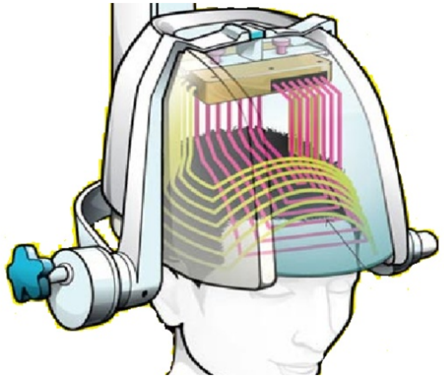
Safety and preliminary efficacy of deep transcranial magnetic stimulation in MS-related fatigue

Gunnar Gaede, MD
Marina Tiede, MD
Ina Lorenz, MD
Alexander U. Brandt, MD
Caspar Pfueller, MD
Jan Dörr, MD
Judith Bellmann-Strobl, MD
Sophie K. Piper, PhD
Yiftach Roth, PhD
Abraham Zangen, PhD
Sven Schippling, MD
Friedemann Paul, MD

Changes in fatigue under treatment

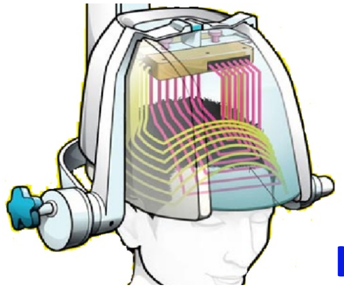


Motor cortex (Lower Limb rTMS)



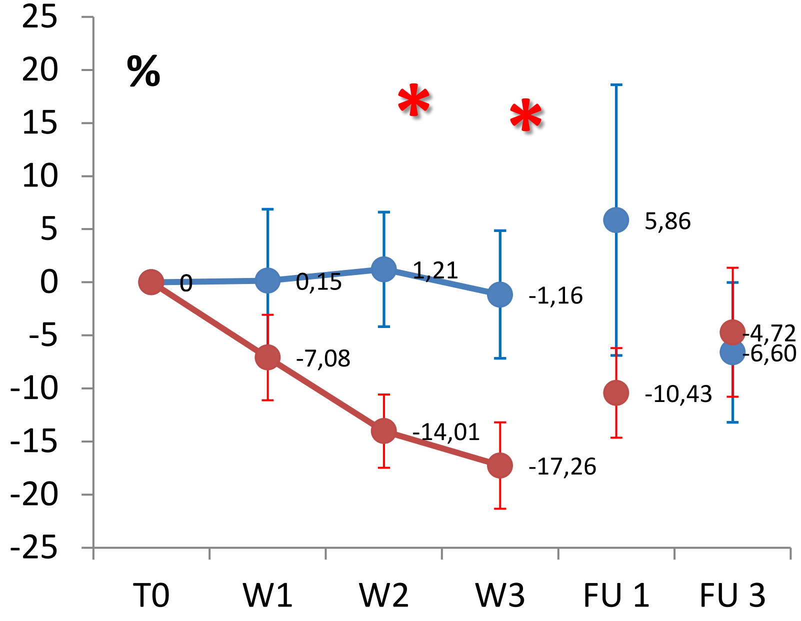
Gaede et al. Neurol Neuroim Neuroinfl 2018

Motor cortex rTMS & walking in MS (Lower Limb rTMS)



Walking speed

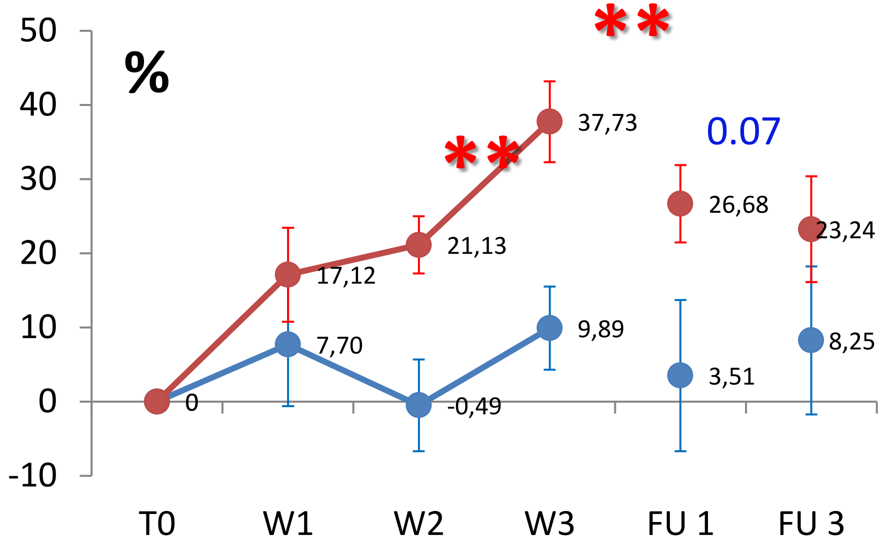
10 mt walk *sec*



% of pts improved at W3
63% sham
90% real

Walking endurance

6 min walk *sec*



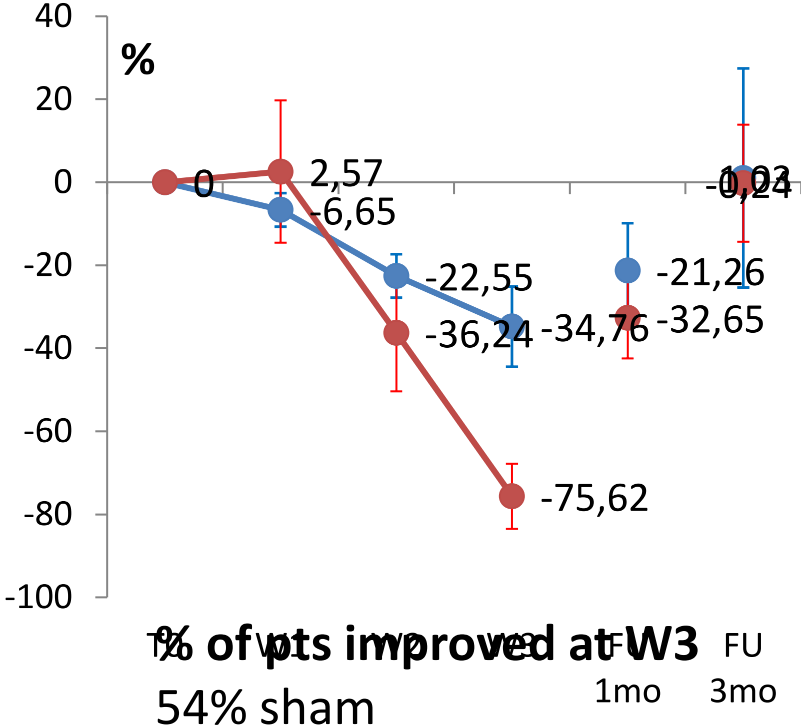
ANOVA post-hoc unpaired t P<0.05*; P<0.01**

sham real

% of pts improved at W3
54% sham
100% real

Spasticity

m.Ashworth *hip-knee*



% of pts improved at W3
54% sham
100% real

Leocani et al submitted

Fatigue treatment in MS: non invasive brain stimulation

Transcranial direct current stimulation - tDCS

Effects of Transcranial Direct Current Stimulation on Cognition, Mood, Pain, and Fatigue in Multiple Sclerosis: A Systematic Review and Meta-Analysis

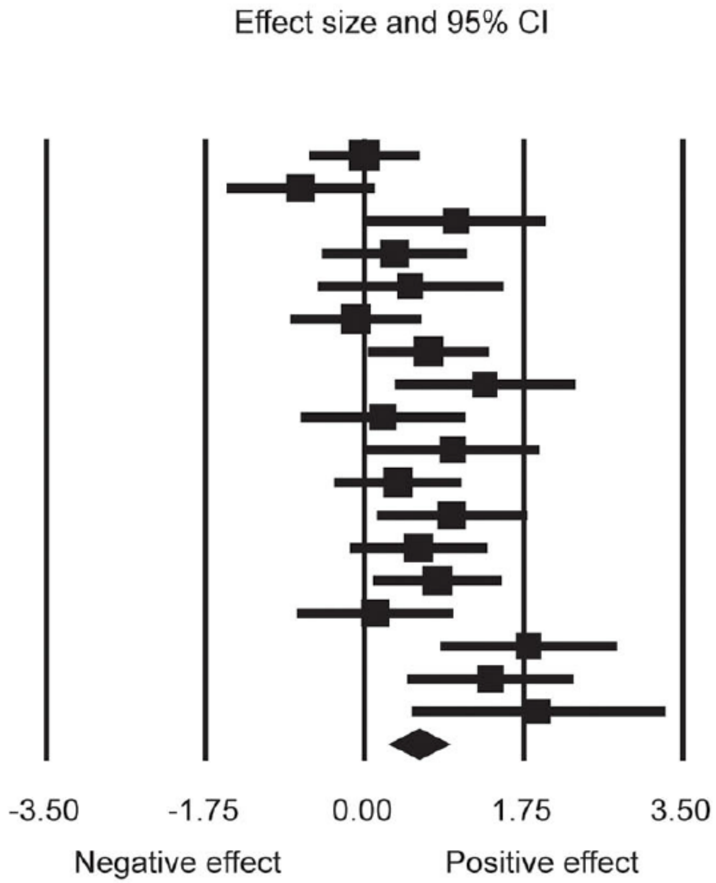
Wan-Yu Hsu[1], Chia-Hsiung Cheng[2,3,4,5], Theodore P. Zanto[1,6], Adam Gazzaley[1,6,7,8] and Riley M. Bove[1]*

Fatigue ++

But ≠ outcome, brain region, dose, duration

statistics for each study

	Effect size	Lower limit	Upper limit	p-Value	Relative weight
Ferrucci et al (2014) [25]	0.00	-0.57	0.57	1.00	7.25
Saiote et al (2014) [30]	-0.70	-1.49	0.08	0.08	5.76
Tecchio et al (2014) [41]	1.00	0.05	1.96	0.03	4.80
Tecchio et al (2015) (SI) [33]	0.33	-0.44	1.10	0.40	5.88
Tecchio et al (2015) (SM1) [33]	0.50	-0.48	1.50	0.31	4.60
Ayache et al (2016) [22]	-0.09	-0.79	0.59	0.78	6.42
Hanken et al (2016) [26]	0.70	0.06	1.34	0.03	6.81
Chalah et al (2017) (DLPFC) [24]	1.32	0.35	2.29	0.00	4.74
Chalah et al (2017) (PPC) [24]	0.20	-0.67	1.07	0.65	5.24
Cancelli et al (2018) [39]	0.96	0.04	1.89	0.04	4.96
Charvet et al (2018) (OLS) [34]	0.36	-0.30	1.04	0.28	6.55
Charvet et al (2018) (RCT) [34]	0.95	0.15	1.76	0.01	5.71
Fiene et al (2018) [35]	0.59	-0.13	1.32	0.11	6.16
Porcaro et al (2019) [36]	0.80	0.12	1.48	0.02	6.52
Chalah et al (2020) [40]	0.11	-0.71	0.95	0.78	5.49
Mortezanejad et al (2020) (MC) [32]	1.80	0.85	2.75	0.00	4.84
Mortezanejad et al (2020) (DLPFC) [32]	1.38	0.49	2.27	0.00	5.16
Workman et al (2020) [42]	1.91	0.54	3.27	0.00	3.09
Pooled effect size (random effects model)	0.60	0.31	0.89	0.00	



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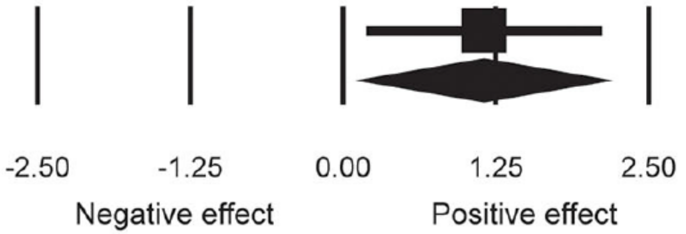
Wan-Yu Hsu[1], Chia-Hsiung Cheng[2,3,4,5], Theodore P. Zanto[1,6], Adam Gazzaley[1,6,7,8] and Riley M. Bove[1]*

Cognition ± (outcome)

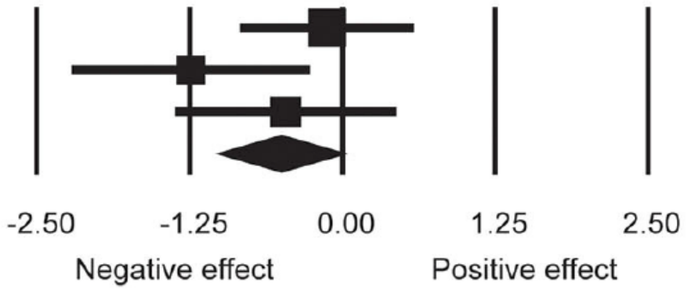
Study name	Cognition (SDMT) statistics for each study				
	Effect size	Lower limit	Upper limit	p-Value	Relative weight
Mattioli et al (2016) [21]	1.15	0.20	2.10	0.01	100.00
Pooled effect size (fixed effects model)	1.15	0.20	2.10	0.01	

Effect size and 95% CI



Study name	Cognition (ANT) statistics for each study				
	Effect size	Lower limit	Upper limit	p-Value	Relative weight
Ayache et al (2016) [22]	-0.12	-0.82	0.56	0.72	46.84
Chalah et al (2017) (DLPFC) [24]	-1.24	-2.19	-0.28	0.01	24.60
Chalah et al (2017) (PPC) [24]	-0.46	-1.35	0.42	0.30	28.56
Pooled effect size (fixed effects model)	-0.49	-0.97	-0.02	0.04	

Effect size and 95% CI



Journal of Neurology (2018) 265:607–617
https://doi.org/10.1007/s00415-018-8754-6

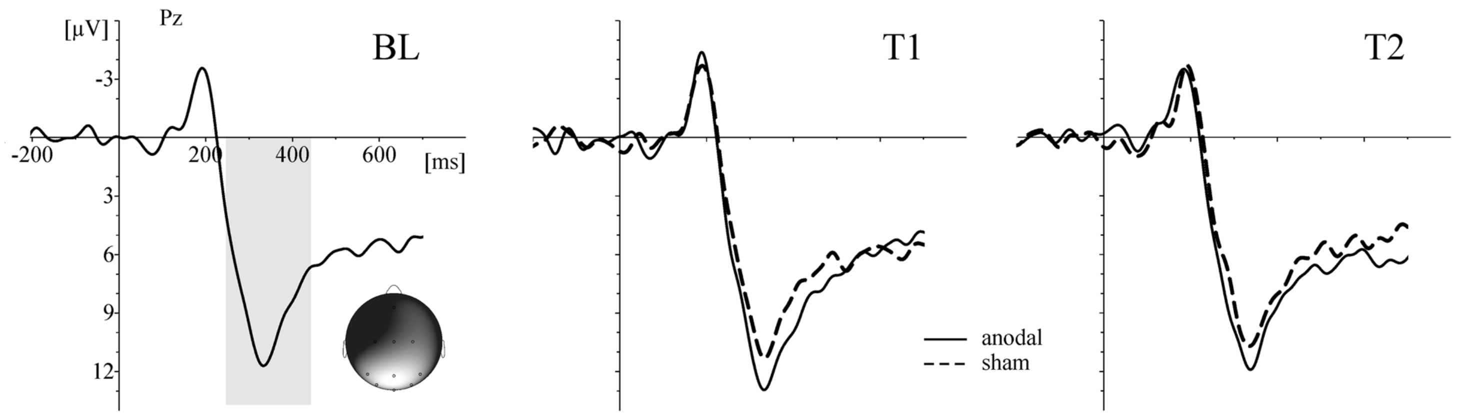
ORIGINAL COMMUNICATION

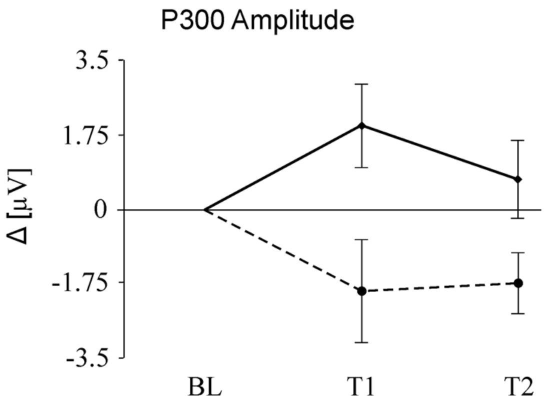
CrossMark

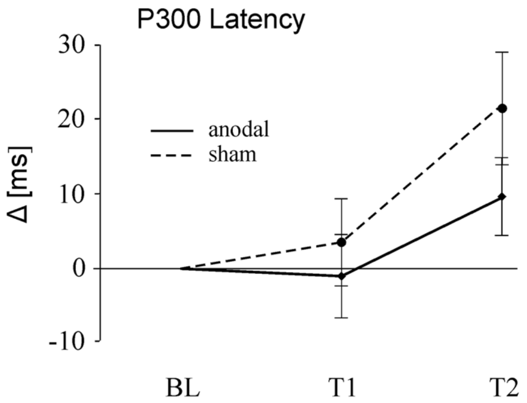
Left DLPF cortex

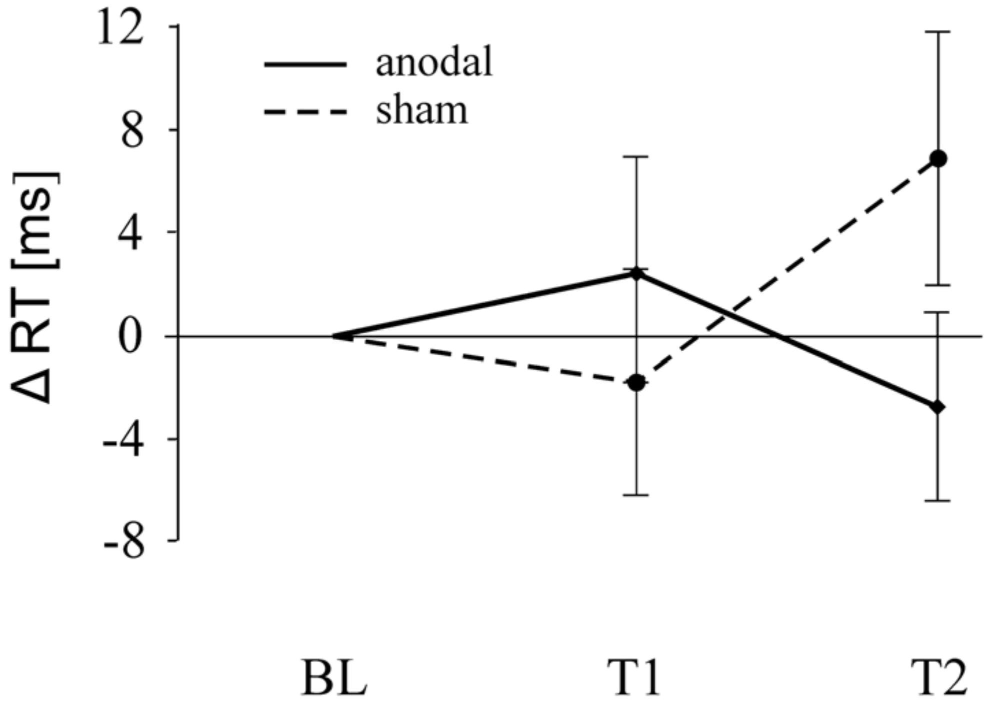
Electrophysiological and behavioral effects of frontal transcranial direct current stimulation on cognitive fatigue in multiple sclerosis

Marina Fiene[1,2] · Katharina S. Rufener[1,3] · Maria Kuehne[1] · Mike Matzke[1] · Hans-Jochen Heinze[1,3] · Tino Zaehle[1,3]









Neuromodulation: Technology at the Neural Interface

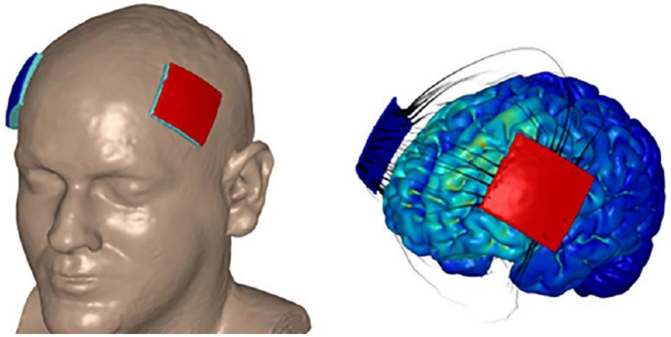
Received: October 7, 2016 Revised: January 3, 2017 Accepted: January 6, 2017

(onlinelibrary.wiley.com) DOI: 10.1111/ner.12583

Left DLPF cortex

Remotely Supervised Transcranial Direct Current Stimulation Increases the Benefit of At-Home Cognitive Training in Multiple Sclerosis

Leigh Charvet, PhD*; Michael Shaw, BS*; Bryan Dobbs, MS*; Ariana Frontario, BS†; Kathleen Sherman, MS*; Marom Bikson, PhD‡; Abhishek Datta, PhD§; Lauren Krupp, MD*; Esmail Zeinapour, MS‡; Margaret Kasschau, BS¶



Remotely supervised transcranial direct current stimulation for the treatment of fatigue in multiple sclerosis: Results from a randomized, sham-controlled trial

Multiple Sclerosis Journal

2018, Vol. 24(13) 1760–1769

Leigh E Charvet, Bryan Dobbs, Michael T Shaw, Marom Bikson, Abhishek Datta and Lauren B Krupp

Therapy That Just Might Beat MS Fatigue

OCTOBER 6, 2017 BY ED TOBIAS
IN COLUMNS, THE MS WIRE - A COLUMN BY ED TOBIAS.

Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): An update (2014–2018)

Jean-Pascal Lefaucheur[a,b,*], André Aleman[c], Chris Baeken[d,e,f], David H. Benninger[g], Jérôme Brunelin[h], Vincenzo Di Lazzaro[i], Saša R. Filipović[j], Christian Grefkes[k,l], Alkomiet Hasan[m], Friedhelm C. Hummel[n,o,p], Satu K. Jääskeläinen[q], Berthold Langguth[r], Letizia Leocani[s], Alain Londero[t], Raffaele Nardone[u,v,w], Jean-Paul Nguyen[x,y], Thomas Nyffeler[z,aa,ab], Albino J. Oliveira-Maia[ac,ad,ae], Antonio Oliviero[af], Frank Padberg[m], Ulrich Palm[m,ag], Walter Paulus[ah], Emmanuel Poulet[h,ai], Angelo Quartarone[aj], Fady Rachid[ak], Irena Rektorová[al,am], Simone Rossi[an], Hanna Sahlsten[ao], Martin Schecklmann[r], David Szekely[ap], Ulf Ziemann[aq]

Clinical Neurophysiology 131 (2020) 474–528

A panel of experts examined publications until the end of 2018 **[rTMS real vs placebo]**

Level A evidence (definite efficacy):

- rTMS of the left dorsolateral prefrontal cortex (DLPFC) for depression (high frequency, figure-of-8 or a H1-coil)
- rTMS of the primary motor cortex (M1) contralateral to the painful side for neuropathic pain (High-frequency)
- rTMS of contralesional M1 for hand motor recovery in the post-acute stage of stroke (Low-frequency)

NIH Public Access
Author Manuscript
Brain Stimul. Author manuscript; available in PMC 2015 November 01.

Published in final edited form as:
Brain Stimul. 2014 ; 7(6): 773–783. doi:10.1016/j.brs.2014.10.003.

The uncertain outcome of prefrontal tDCS

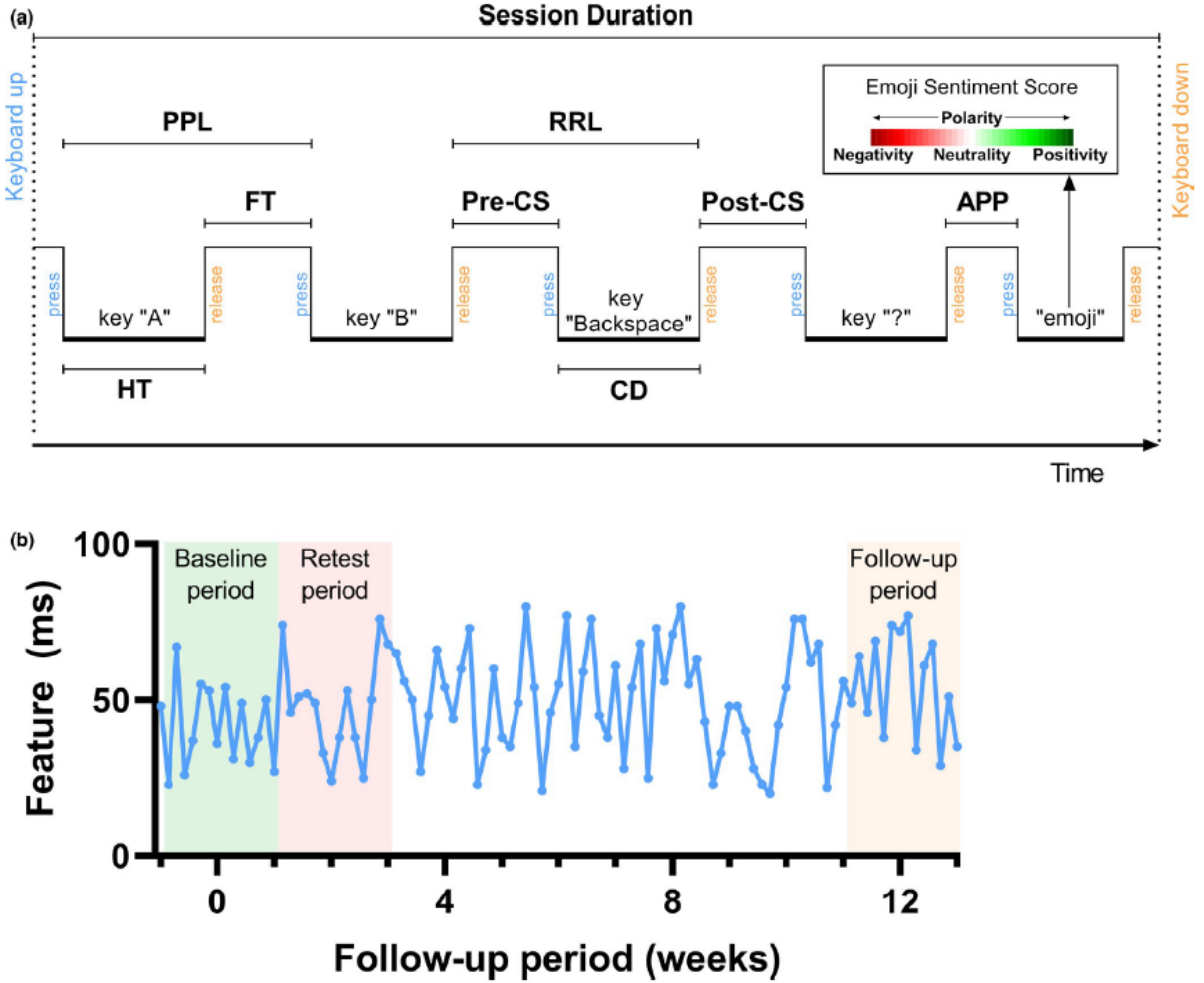
Sara Tremblay[1,2], **Jean-François Lepage**[3], **Alex Latulipe-Loiselle**[1,2], **Felipe Fregni**[3], **Alvaro Pascual-Leone**[4], and **Hugo Théoret**[1,2]

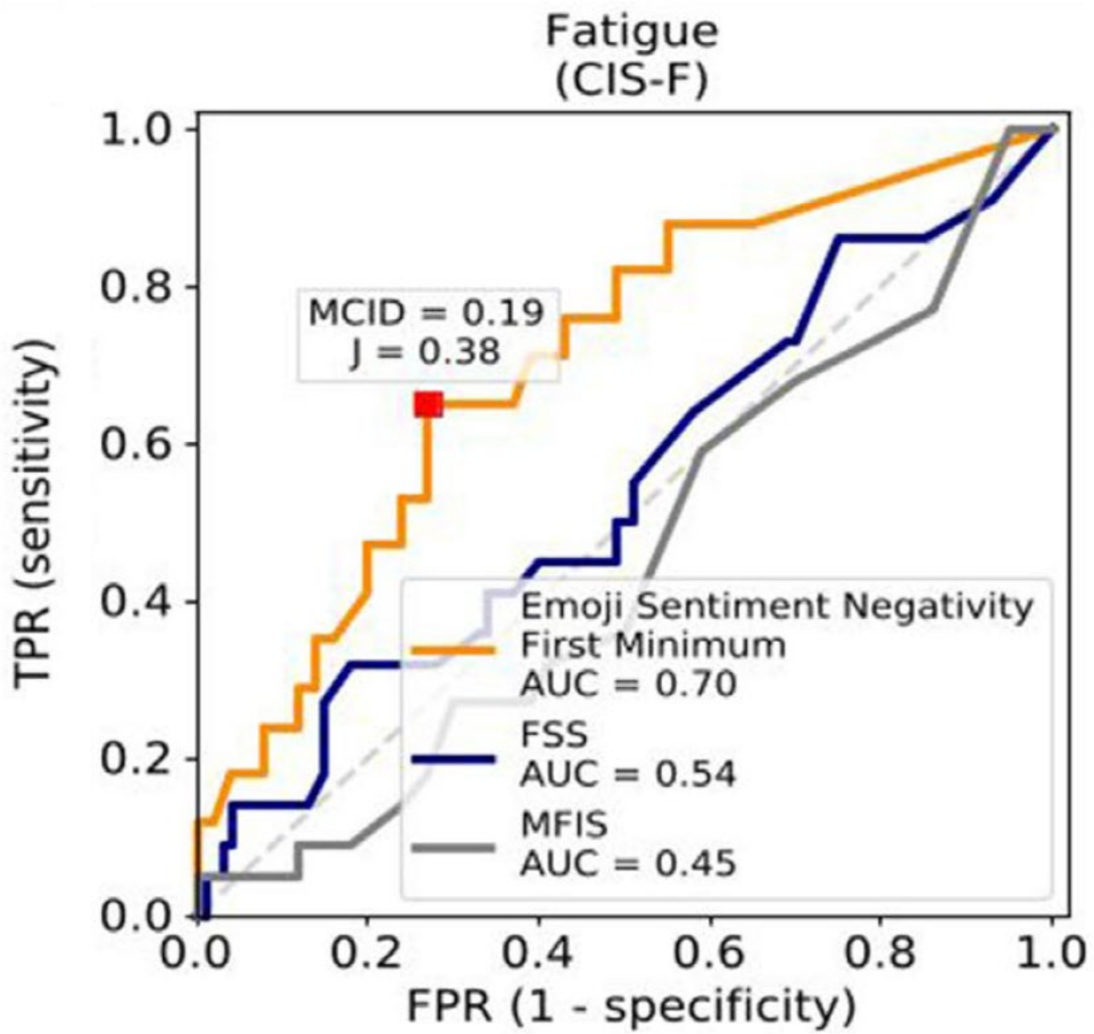
Prefrontal tDCS has the potential to modulate numerous cognitive functions simultaneously, but to properly interpret the results, a clear a priori hypothesis is necessary, careful technical consideration are mandatory, further insights into the neurobiological impact of tDCS are needed, and consideration should be given to the possibility that some behavioral effects may be partly explained by parallel modulation of related functions.

Smartphone-derived keystroke dynamics are sensitive to relevant changes in multiple sclerosis

european journal of neurology
the official journal of the european academy of neurology

Ka-Hoo Lam[1] | James Twose[2] | Hannah McConchie[2] | Giovanni Licitra[2] | Kim Meijer[2] | Lodewijk de Ruiter[1] | Zoë van Lierop[1] | Bastiaan Moraal[3] | Frederik Barkhof[3,4] | Bernard Uitdehaag[1] | Vincent de Groot[5] | Joep Killestein[1]



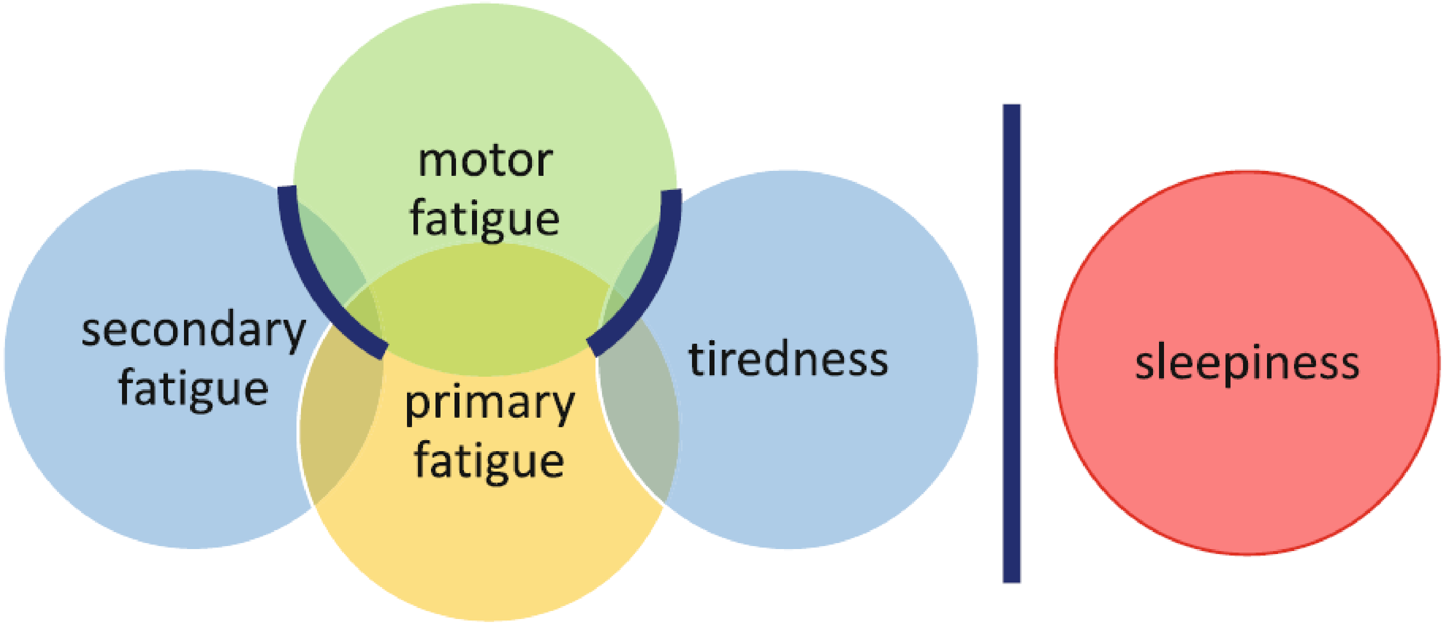


ROC curves of change in keystroke dynamics (orange) and classification of clinically relevant change

Lam et al 2021

The Berlin Treatment Algorithm: recommendations for tailored innovative therapeutic strategies for multiple sclerosis-related fatigue

Christian Veauthier[1,2*], Helge Hasselmann[2,3], Stefan M. Gold[3,4] and Friedemann Paul[2,5,6]



Veauthier et al. The EPMA Journal (2016) 7:25