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Beyond the Symptom: The Biology of Fatigue
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Fatigue in Autoimmune disorders

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Disclaimer and Disclosures

Disclaimer
This certifies that the views expressed in this presentation are those of the author and do not reflect the official policy of the NIH.

Disclosure
This certifies that I, Lauren Krupp, have received royalties for the fatigue severity scale from biotechnology and pharmaceutical companies.

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Fatigue and autoimmune disorders

- Fatigue is a shared feature of many immune mediated disorders
  - Most common symptom in multiple sclerosis (MS)
  - Frequent in rheumatoid arthritis (RA), systemic lupus erythematosus (SLE)
  - Key feature in post-infectious disorders e.g. Post Lyme Syndrome, COVID long haulers

- Fatigue often heralds a flare in systemic lupus erythematosus (SLE)

- Patients with fatigue associated with SLE or MS both note the adverse impact of fatigue on daily living (e.g. failing to meet responsibilities, experiencing fatigue as a frequent problem) – such features less likely among healthy volunteers

- Heat worsens MS fatigue but has little effect on fatigue in SLE or on fatigue among healthy volunteers
- Mood, pain, sleep disturbance exacerbate fatigue across autoimmune disorders

Zielinski MR, et al. Fatigue, Sleep, and Autoimmune and Related Disorders. Front Immunol. 2019;10:1827, Krupp LB et al. Krupp LB, et al.. The Fatigue Severity Scale: Application to Patients With Multiple Sclerosis and Systemic Lupus Erythematosus. *Arch Neurol.* 1989;46(10):1121–1123.; Monahan RC, et al. Fatigue in patients with systemic lupus erythematosus and neuropsychiatric symptoms is associated with anxiety and depression rather than inflammatory disease activity. Lupus. 2021;30(7):1124-1132.

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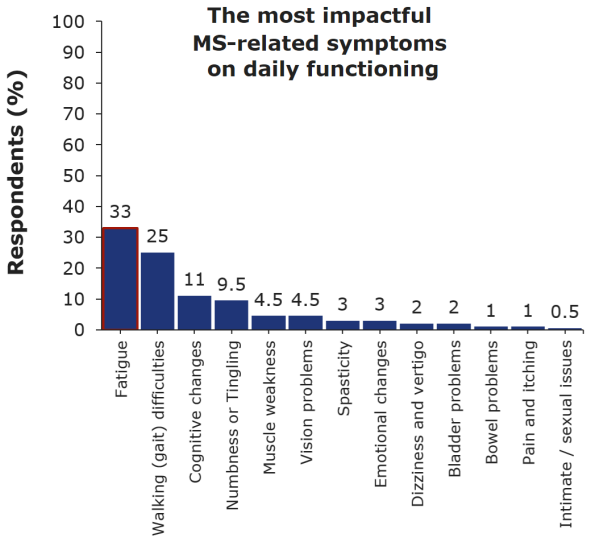
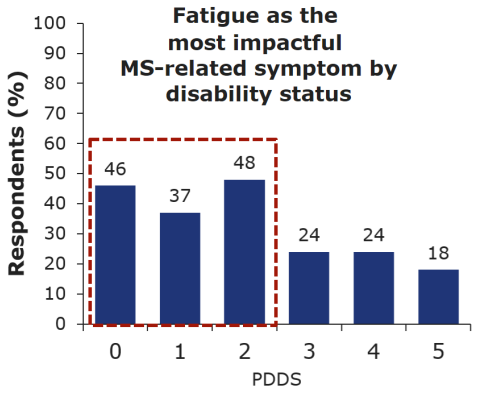
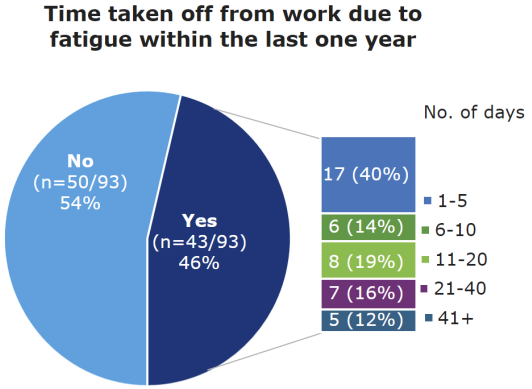
How fatigue affects individuals with MS

Impact of MS-related symptoms on daily functioning







- Fatigue was rated as the most impactful symptom on daily functioning, followed by walking difficulties
- Patients with lower disability (PDDS 0-2) tended to rate fatigue as the most impactful symptom on daily functioning
- Nearly half of the patients had to take time off work because of fatigue within the last one year, with most patients taking 1-5 days off

MS, multiple sclerosis; PDDS, Patient Determined Disease Steps Poster presented at ACTRIMS 2020

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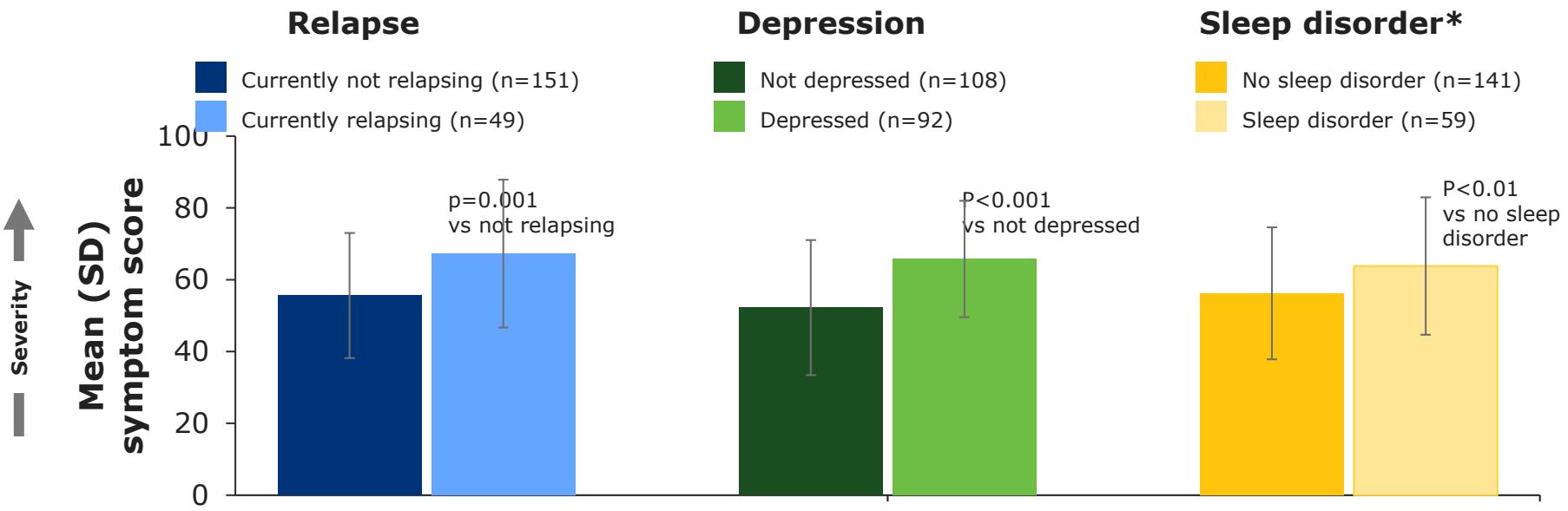
Fatigue worsens during relapse, depression, and impaired sleep

FSIQ-RMS – Symptoms score by subgroups



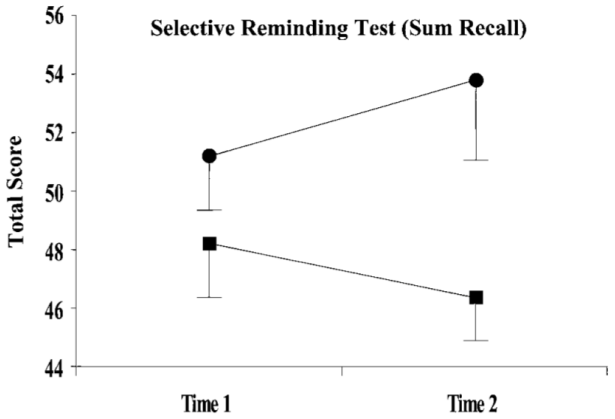
- Fatigue levels were significantly more severe in patients with relapse, depression, and/or sleep disorder than in patients without these characteristics.

*Sleep disorder: narcolepsy, restless leg syndrome or sleep apnea
FSIQ-RMS, Fatigue Symptoms and Impacts Questionnaire – Relapsing Multiple Sclerosis
Statistical comparisons were performed by Student's t-test. P<0.05 was considered as statistically significant.

Fatigue and Fatigability

- Self reported fatigue is measured by questionnaires, scales
  - “Subjective”
  - Variable
  - Influenced by context

- Performance based fatigue “fatigability” is measured by declines in performance over time
  - Readily measurable
  - “Objective”
  - But, often does NOT correlate with self-reported fatigue



BM, Krupp LB, Enoka RM. Fatigue and fatigability in neurologic illnesses: proposal for a unified taxonomy. Neurology. 2013 Jan 22;80(4):409-16.
doi:. Krupp, LB Elkins LE. Neurology 2000; 55:934-939; Saberi A. NeuroReport 2021, Vol 32 No 6

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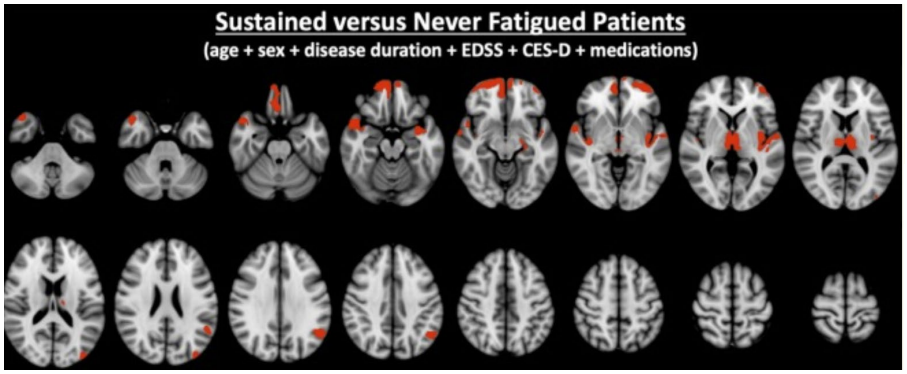
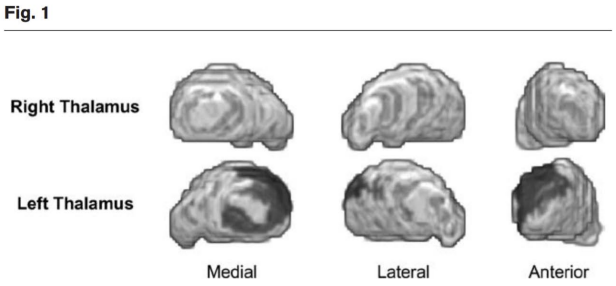
Loss of grey matter volume or change in shape associated with MS fatigue



Many more grey matter regions show atrophy among MS patients with sustained fatigue vs. MS patients with no history of fatigue

Thalamic shape abnormalities in MS patients with multiple sclerosis – related fatigue



Inward thalamic shape deformation (dark grey) in patients with higher cognitive fatigue.

Palotai M, et al. History of fatigue in multiple sclerosis is associated with grey matter atrophy. *Sci Rep*. 2019;9(1):14781. ; Saberi A. NeuroReport 2021, Vol 32 No

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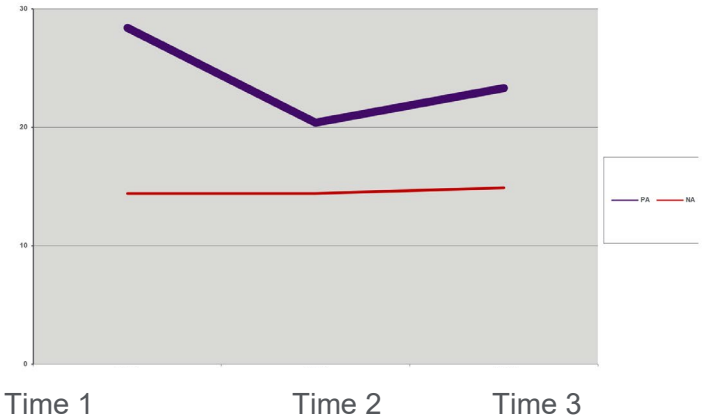
- Fatigue can be associated with cytokine therapy
- Being able to predict fatigue onset, provides an opportunity for research

Positive and Negative Affect For Fatigue Group



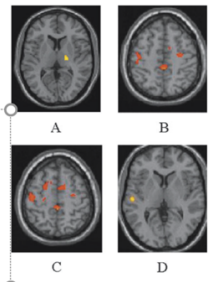
Change over time PA=.03
Change over time NA=.81

"Reversible fatigue" in MS

fMRI Changes in Relapsing-Remitting Multiple Sclerosis Patients Complaining of Fatigue after IFNβ-1A Injection

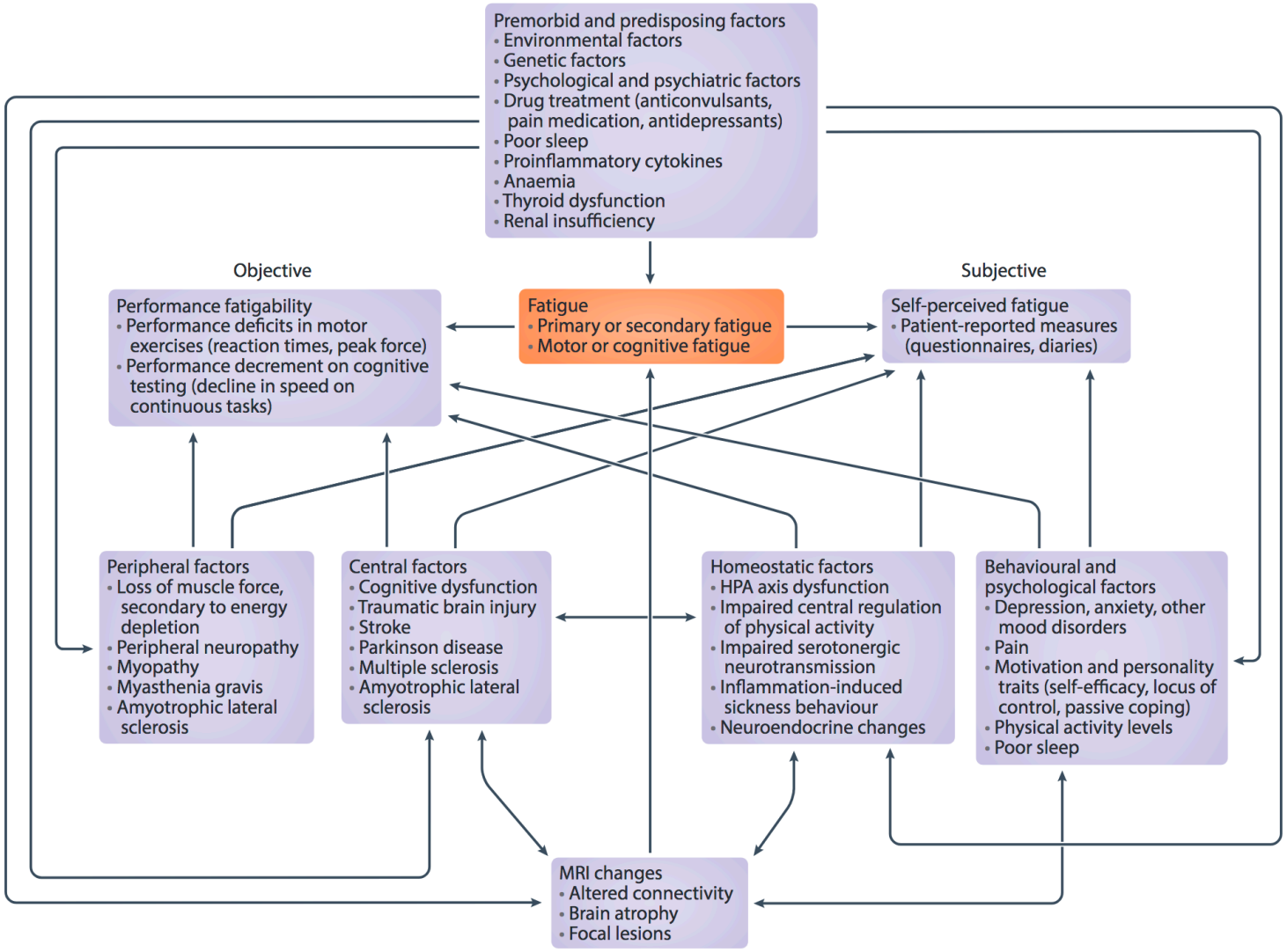
MS patients with reversible fatigue showed an increased activation of the thalamus bilaterally, MS patients with reversible fatigue had increased activations of the thalamus and of several regions of the frontal lobes.

An abnormal recruitment of the fronto-thalamic circuitry is associated with IFN-1a-induced fatigue in MS



Rocca M.A. et al. Hum Brain Mapp 28:373–382, 2007.

Mechanisms of fatigue



Penner & Paul, *Nat Rev Neurol 2017*

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Targets for fatigue in autoimmune disease

TABLE 1 | Potential target areas, molecular pathways, cellular targets, and target molecules for understanding fatigue in individuals with autoimmune and related disorders.

Potential target areas	Related molecular pathways	Cellular targets	Target molecules
Inflammatory-related molecules	- AP-1 pathway - B-cell receptor signaling - COX-2/prostaglandins - NLRP3 inflammasome pathways - JAK/STAT pathway - MAPK pathway - NF-κB - T-cell receptor signaling - Vagal afferents - Vagal efferents	- Astrocytes - B-cells - Endothelial cells - Macrophages - Microglia - Neurons - Pericytes - Perivascular macrophages - T-cells	- IL-1β - IL-6 - IL-18 - IFN-γ - TNF-α - Other cytokines/ chemokines
Metabolic-related molecules	- Brain glymphatic system - Citric acid cycle - Gluconeogenesis - Glycolysis - Oxidative phosphorylation - NLRP3 inflammasome pathways - Pentose phosphate pathway	- Astrocytes - Microglia - Neurons - Pericytes - Perivascular macrophages	- Acetyl-CoA - ATP - Hexokinase - NADH - Purinergic receptors
Sleep-related molecules	- ARAS - Neurotransmitter pathways - NLRP3 inflammasome pathways	- Astrocytes - Microglia - Neurons	- IL-1β - Neurotransmitters - TNF-α
Circadian-related molecules	- CLOCK pathway	- Astrocytes - Microglia - Neurons	- BMAL1 - CLOCK - PERIOD
Stress-related molecules	- HPA-axis pathway - Sympathomedullary pathway	- Astrocytes - Macrophages - Microglia - Neurons	- Adrenocorticotrophic hormone - Catecholamines - Corticosteroids - Corticotrophin - IL-1β - TNF-α
Vasoregulatory-related molecules	- Adrenergic cAMP and protein kinase A - cGMP - Protein kinase G - Neurotransmitter pathways - Voltage-sensitive calcium channels	- Astrocytes - Endothelial cells - Interneurons - Microglia - Neurons - Perivascular macrophages - Pericytes	- Adenosine - Dopamine - Epinephrine - IL-1β - Nitric oxide - Norepinephrine - TNF-α

What can be learned from clinical trials

- Pharmacologic strategies largely unsuccessful
- In contrast, behavioral approaches and neuromodulation show more promise. Positive trials include:
  - Mindfulness, yoga, cognitive behavioral therapy, exercise
  - Online fatigue management programs,
  - At home transcranial direct current stimulation (tDCS) of dorsal lateral frontal cortex

- Which pathways, circuits, molecular complexes do these strategies target in such a way to lower fatigue?

THANK YOU

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