



FATIGUE SLEEPINESS AND AGING

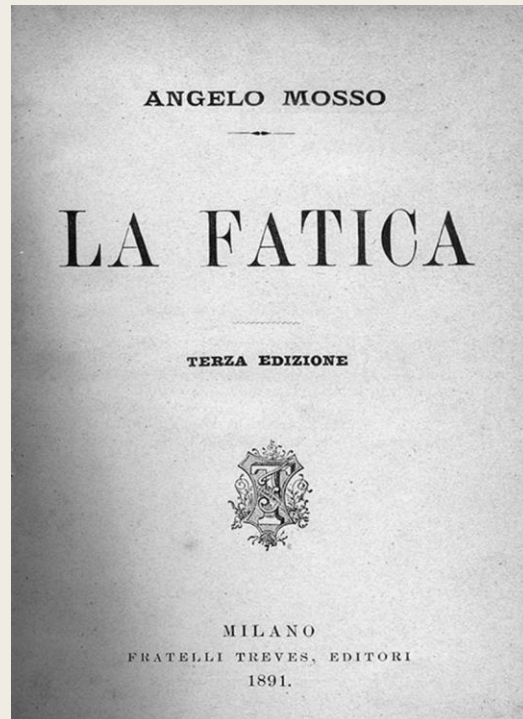
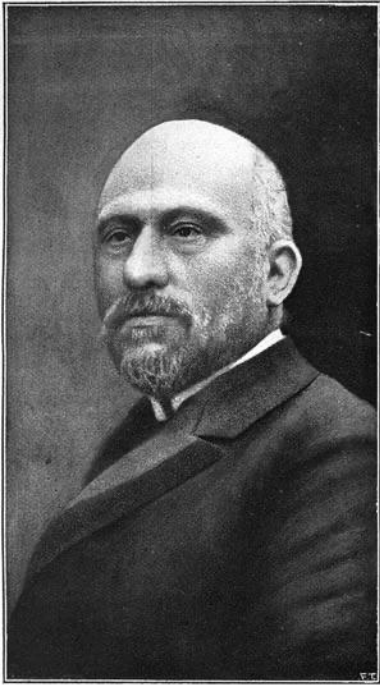
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10/25/2024

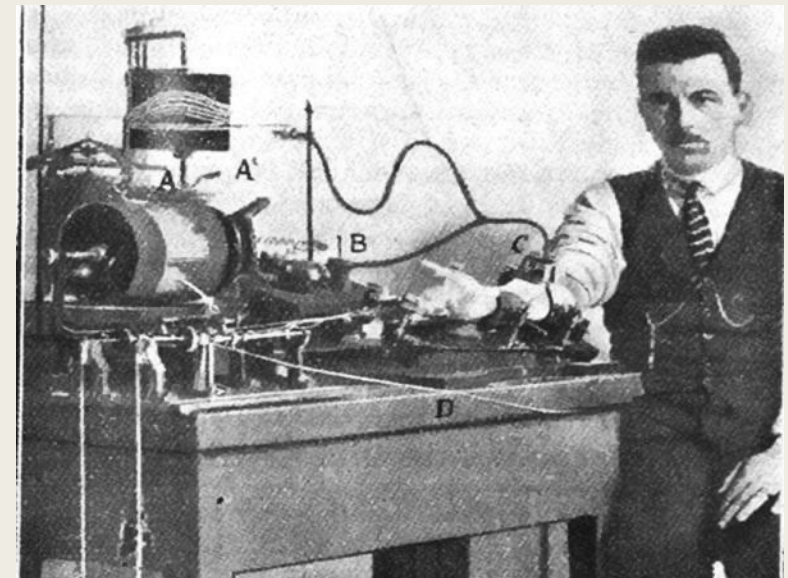
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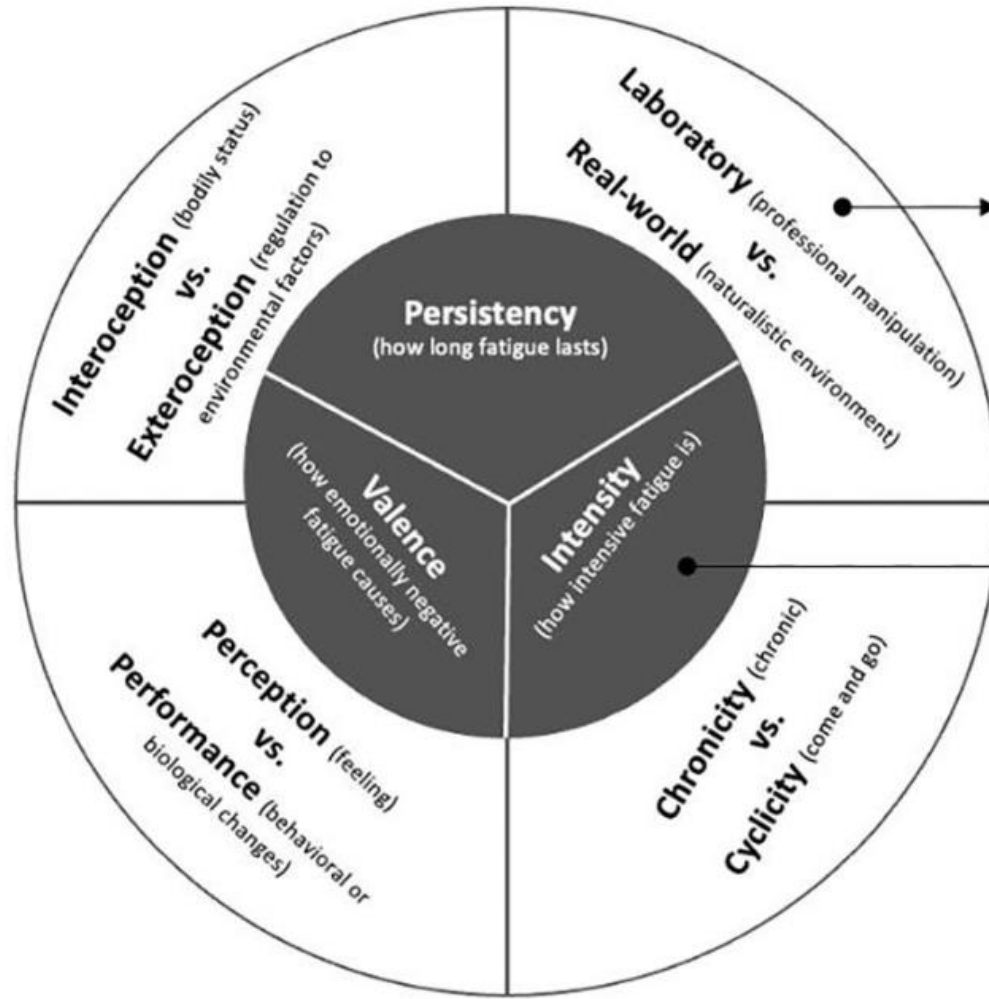
- No financial conflicts of interest

First steps



Peripheral fatigue: repeated muscle movements decrease over time

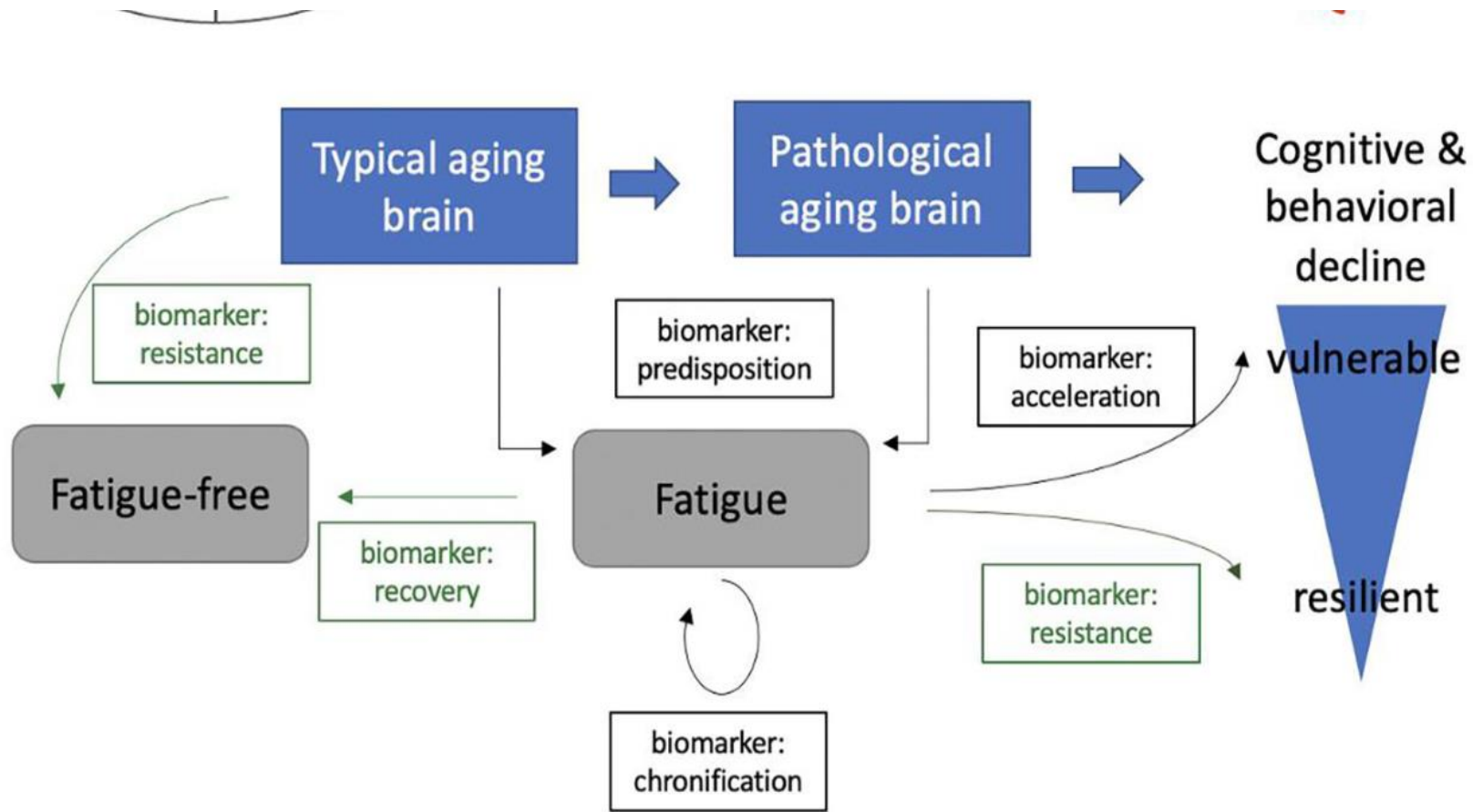




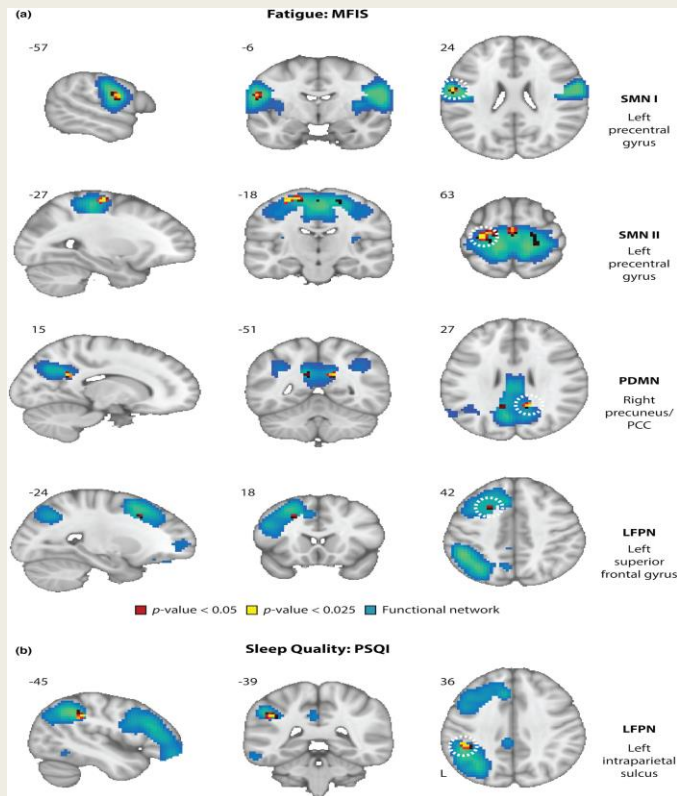
Multidimensional Model of Fatigue vs Age

- Localized nodes (regions)
 - -Insula – response to salient events
 - -Striatum – motivation
- Edges (connections)
 - -Striatum- Prefrontal Cortex
 - (Perception of fatigue)
- Large scale networks
 - -Information processing efficiency
- Posterior to Anterior Shift (PASA)
- Frontal regions neural compensation

C



Sleep and Fatigue localization



- Fatigue and poor sleep do not localize to the same areas
- Fatigue leads to poor sleep
- Fatigue: primary motor cortex (precentral gyrus), right posterior cingulate cortex, fronto-parietal network
- Poor sleep quality: left intraparietal sulcus

CENTRAL FATIGUE

- The failure to initiate and/or sustain attentional tasks and physical activities requiring self motivation
- Tasks of cognitive **vigilance** (effort) rather than those performed over prolonged period of time
- Patients may **report** fatigue and low performance with no objective performance difference (Parmenter, 2003)
- Perceived **interference** with daily activities



Subjective experience of fatigue



- subjective “feeling” of lacking energy vs objective measured (muscular, cardiovascular)
- What patients say vs. what they mean
- Cognitive fatigue is not cognitive impairment
- Experience
 - during sustained mental effort?
 - After mental exertion?
 - Alertness and vigilance?
 - Is impact on cognitive function or everyday life?

Primary vs. Secondary Fatigue

■ Primary causes

- *Grey matter atrophy (hippocampal) correlation*
- *Hypometabolism (fMRI) in prefrontal, premotor cortices*
- *Basal ganglia (connection to limbic system – cortically driven voluntary activities)*

■ Secondary causes

- Sleep related (OSA, RLS, insomnia, nocturia)
- Mood disorders (depression, anxiety)
- Medications
- Vitamin deficiencies
- Anemia
- Autoimmune and endocrine disorders
- Deconditioning, diet

Sample PROMIS Fatigue Short Form

In the past 7 days ...		Never	Rarely	Some- times	Often	Always
FATEXP 20	How often did you feel tired?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
FATEXP 5	How often did you experience extreme exhaustion?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
FATEXP 18	How often did you run out of energy?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
FATIMP 33	How often did your fatigue limit you at work (include work at home)?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
FATIMP 30	How often were you too tired to think clearly?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
FATIMP 21	How often were you too tired to take a bath or shower?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
FATIMP 40	How often did you have enough energy to exercise strenuously?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5



Patient-Reported Outcomes Measurement Information System
Dynamic Tools to Measure Health Outcomes From the Patient Perspective

SCALES
PROMIS - DOMAIN
FOCUSED, NOT
DISEASE
FOCUSED

Domain is a feeling, function or perceptions we want to measure

Sleep and fatigue

- Fatigue correlates with worse sleep quality (Ruiz-Rizzo, 2022)
- Sleepiness does increase with age, but not fatigue
- Fatigue does not serve a basic homeostatic role (unlike sleep)
- Causes of poor sleep:
 - *Obstructive sleep apnea (central OSA rarely)*
 - *Restless legs syndrome*
 - *Pain*
 - *Hormonal changes*
 - *Anxiety*
 - *Medications and substances*

MOOD DISORDERS

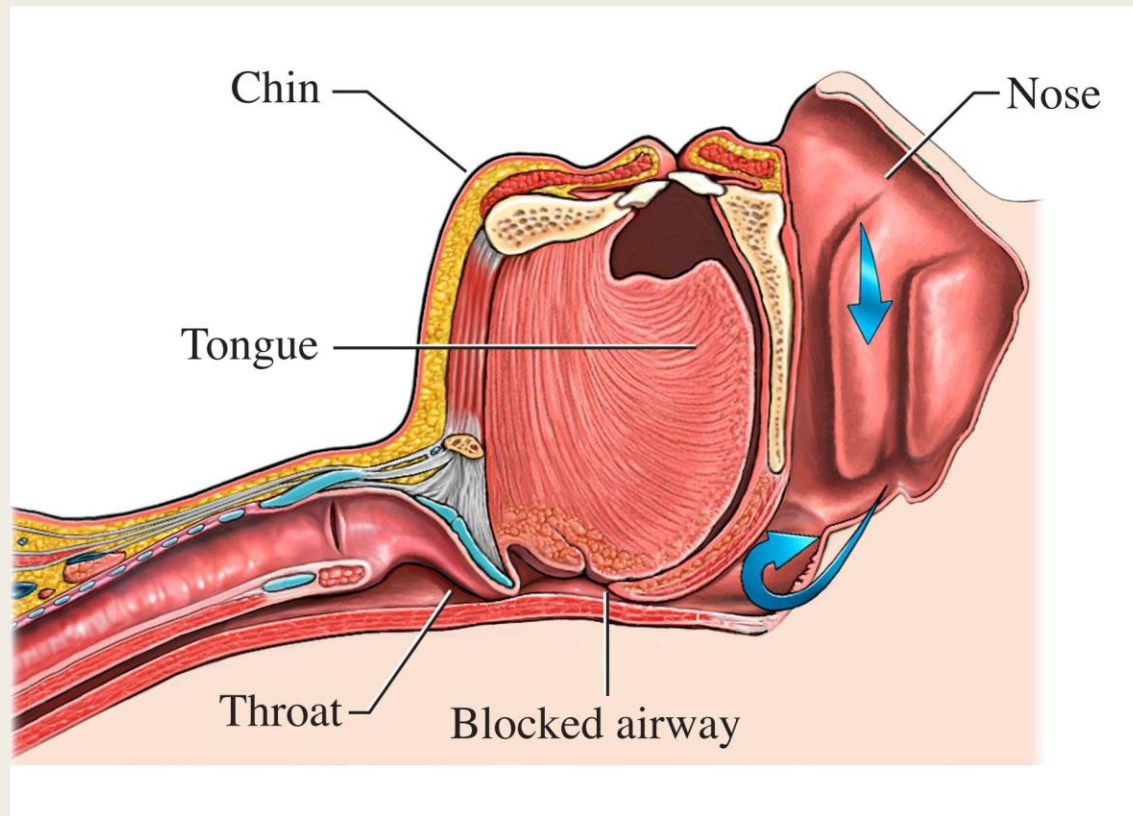
- Major depressive disorder
 - *Negative self evaluation, lack of motivation, anhedonia*
 - *Sleep disruption*
 - *Scales (PHQ 2, PHQ 9 – pay attention to question 9)*
 - *May be exacerbated by medications*
- Antidepressants can be sedating
 - *Less sedating: SSRI: Fluoxetine DNRI: Bupropion*
 - ***Antidepressants are not effective at treating fatigue in neurodegenerative disorders in absence of co-existing depression***
- Generalized anxiety disorder (persistent activation, insomnia)
 - *GAD 7*
 - *SSRI, SNRI before benzodiazepine*

MEDICATIONS, SUBSTANCES and FATIGUE



- Betablockers
- Muscle relaxants, pain medications
- Benzodiazepines
- SSRIs (some)
- Steroids (effect on sleep)
- Alcohol – effect also on sleep
- Cannabis – effect on motivation, mood?
- Supplements – Ashwaganda, magnesium

SLEEP APNEA



- Snoring (STOP BANG)
- Gasping for air, pauses
- Waking up in panic
- *Frequent awakenings**
- *Morning headaches***
- Obesity is a risk factor
- **Home sleep testing!**

STOP BANG

STOP

SNORE (loudly)

TIRED (daytime)

OBSERVED (stop breathing)

PRESSURE (Blood pressure)

YES *THREE* OR MORE TIMES

BANG

BMI (greater than 35)

AGE (over 50)

Neck (circumference 40 cm+)

GENDER (male)

= HIGH RISK OF OSA

RESTLESS LEGS SYNDROME

1. Urge to move: irresistible, involves legs but may involve arms and trunk
2. Worsening AT REST (body position should not matter)
3. Relief with movement (no symptoms during movement)
4. Worsening in the evening or at night
5. "Aching", "jumpiness", "crawliness", "itchiness"

RLS TREATMENT

- Check: Ferritin
 - *Therapy target ferritin >75 nG/mL (AAN guideline) [normal >15]*
- Avoid: Nicotine, Caffeine, Alcohol
 - *TCA's and SSRI's/SNRI's nighttime*
 - *Antihistamines*
 - *Reglan, Compazine*
 - *Caution with **SSRI's/SNRI's** and Antipsychotics*
- Treatment
 - *Dopamine agonists: Pramipexole, Ropinirole, Rotigotine patch*
 - Most common side effect is nausea (10-40%)
 - AUGMENTATION: RLS symptoms worsen – frequency, duration, body parts affected, intensity
 - *Horizant (Gabapentin Enacarbil) – Gabapentin Prodrug*
 - *Pregabalin*

Pharmacological interventions and supplements

- Modafinil/Armodafinil
- Stimulant (methylphenidates, amphetamines)
- Activating antidepressants (if mood symptoms are present)
 - *DNRI: Bupropion*
 - *SSRI: Fluoxetine, Escitalopram*
- Supplements: Vitamin B12
 - *Only if it is in the lower range of normal (200-1000 mG/L)*
 - *Use sublingual formulations/ injections/intranasal*
- Iron deficiency (ferritin level; % saturation)
- Vitamin D

ALTERNATIVES TO MEDICATIONS

Journal of Clinical and Translational Research 2021; 7(4): 575-620



Journal of Clinical and Translational Research

Journal homepage: <http://www.jctres.com/en/home>



REVIEW ARTICLE

The effects of twenty-one nutrients and phytonutrients on cognitive function: A narrative review

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ARTICLE INFO

Article history

Received: January 24, 2021

Revised: June 17, 2021

Accepted: July 09, 2021

Published online: August 4, 2021

Key words:

Alzheimer's disease

cognitive function

cognitive impairment

memory

nutrients

phytonutrients

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ABSTRACT

Background and Aim: Brain health is becoming more important to the average person as the number of people with cognitive impairments, such as Alzheimer's disease (AD), is rising significantly. The current Food and Drug Administration-approved pharmacotherapeutics for dementia neither cure nor halt cognitive decline; they just delay the worsening cognitive impairment. This narrative review summarizes the effects of nutrients and phytonutrients on cognitive function.

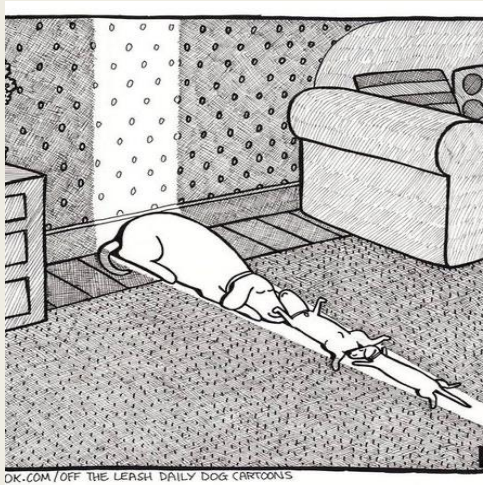
Methods: A comprehensive literature search of PubMed was performed to find clinical trials in humans that assessed the effects of nutrients and phytonutrients on cognitive function published in English between 2000 and 2021. Six independent reviewers evaluated the articles for inclusion in this review.

Results: Ninety-six articles were summarized in this narrative review. In total 21 categories of nutrients and phytonutrients were included, i.e., α -lipoic acid, *Bacopa monnieri*, B vitamins, cholinergic precursors, vitamin D, vitamin E, *Ginkgo biloba*, ginseng, lion's mane mushroom, N-acetyl cysteine, omega-3 fatty acids, aloe polysaccharides, *Rhodiola rosea*, rosemary, saffron, tart cherries, turmeric, wild yam, *Withania somnifera*, xanthines, and zinc. Particular noteworthy effects on cognition included memory, recollection, attention, intelligence, vocabulary, recognition, response inhibition, arousal, performance enhancement, planning, creative thinking, reaction time, vigilance, task switching, orientation to time, place, and person, reading, writing, comprehension, accuracy, learning, information processing speed, executive function, mental flexibility, daily functioning, decrease in mental fatigue, and freedom from distractibility. Some nutrients and phytonutrients also improved mood and contentedness and reduced anxiety and the need for caregiving. These effects are not completely consistent or ubiquitous across all patient populations or health statuses. Adverse effects were minimal or nonexistent.

Conclusion: Due to the growing population of people with cognitive impairment and the lack of effective pharmacotherapeutics, it is prudent for those afflicted or their caregivers to find alternative treatments. Our narrative review shows that many of these nutrients and phytonutrients may be promising for treating some aspects of cognitive impairment, especially for people afflicted with AD.

Relevance for Patients: As demonstrated in a number of clinical trials, healthy adults and patients with various health challenges (e.g., AD, mild cognitive impairment, multiple sclerosis, and Parkinson's disease) exhibiting a wide range of severity in cognitive defects would be best served to consider multiple nutrients and phytonutrients to improve aspects of their cognitive function.

Behavioral approaches to fatigue management



- Rewarded behavior leads to decrease in task fatigue
- Intrinsically rewarding tasks (the flow)
- Exercise – **aerobic** more than resistance exercise improves fatigue
- Light therapy (?)



THANK YOU!

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