Probing the Energetic Basis of Mind-Body Processes through Mitochondria

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Chair in Energy and Health
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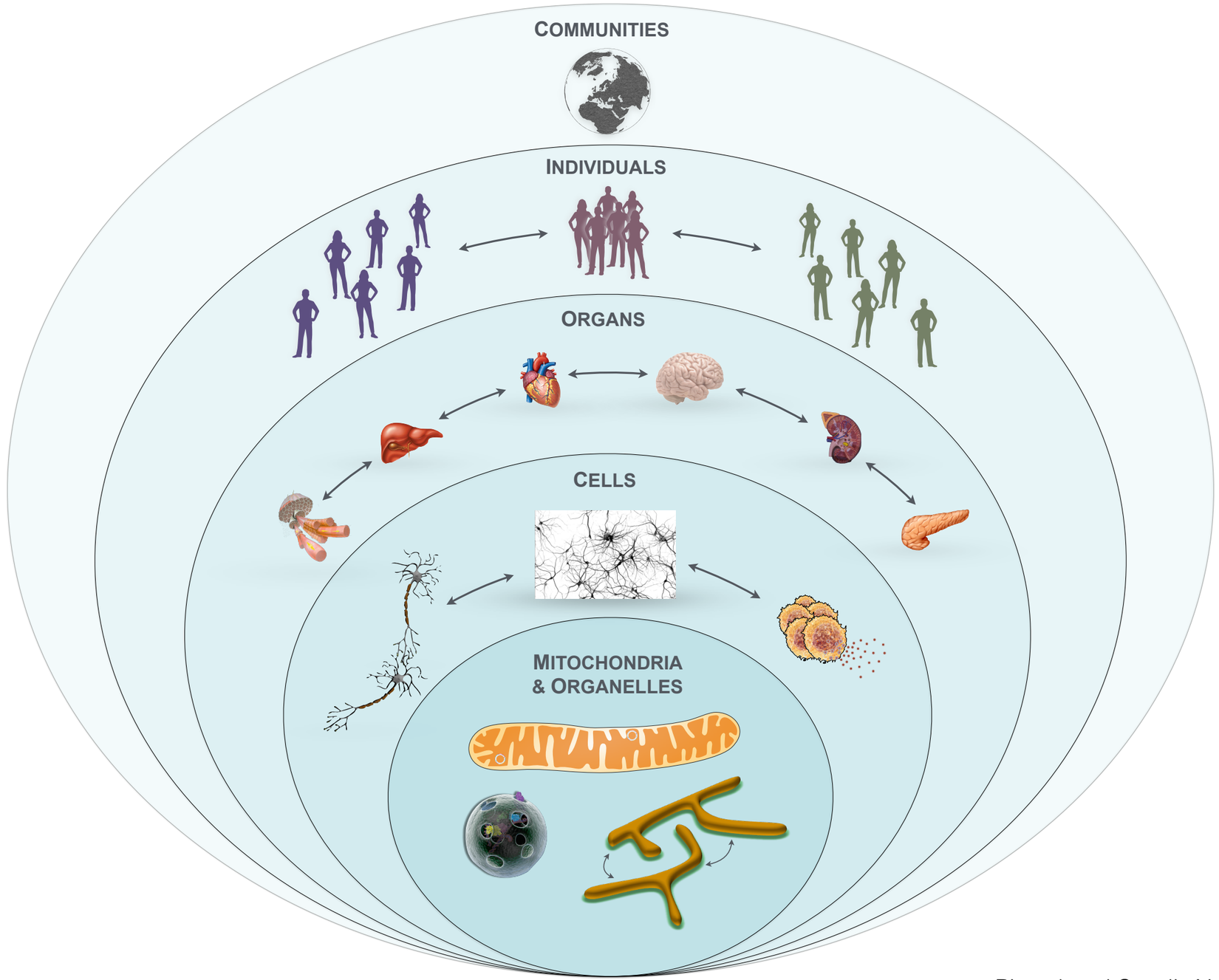
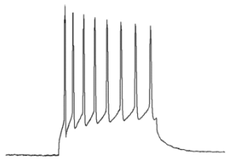
Mailman School of Public Health



Picard and Sandi. *Neurosci Biobehav Rev* (2021)

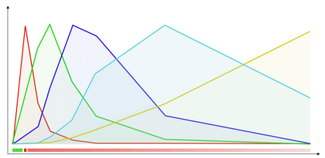
Brain function and cognition

Neural activity



Immune regulation

Stress responses

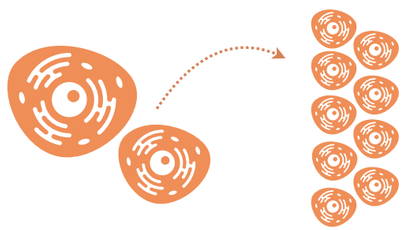


Wound healing

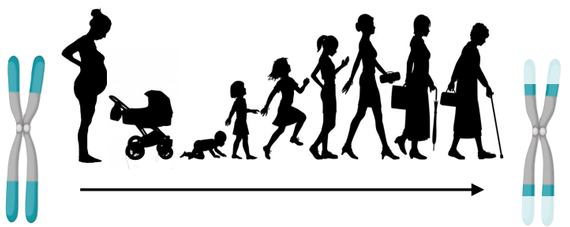
ENERGY

+ Body heat

Cell proliferation



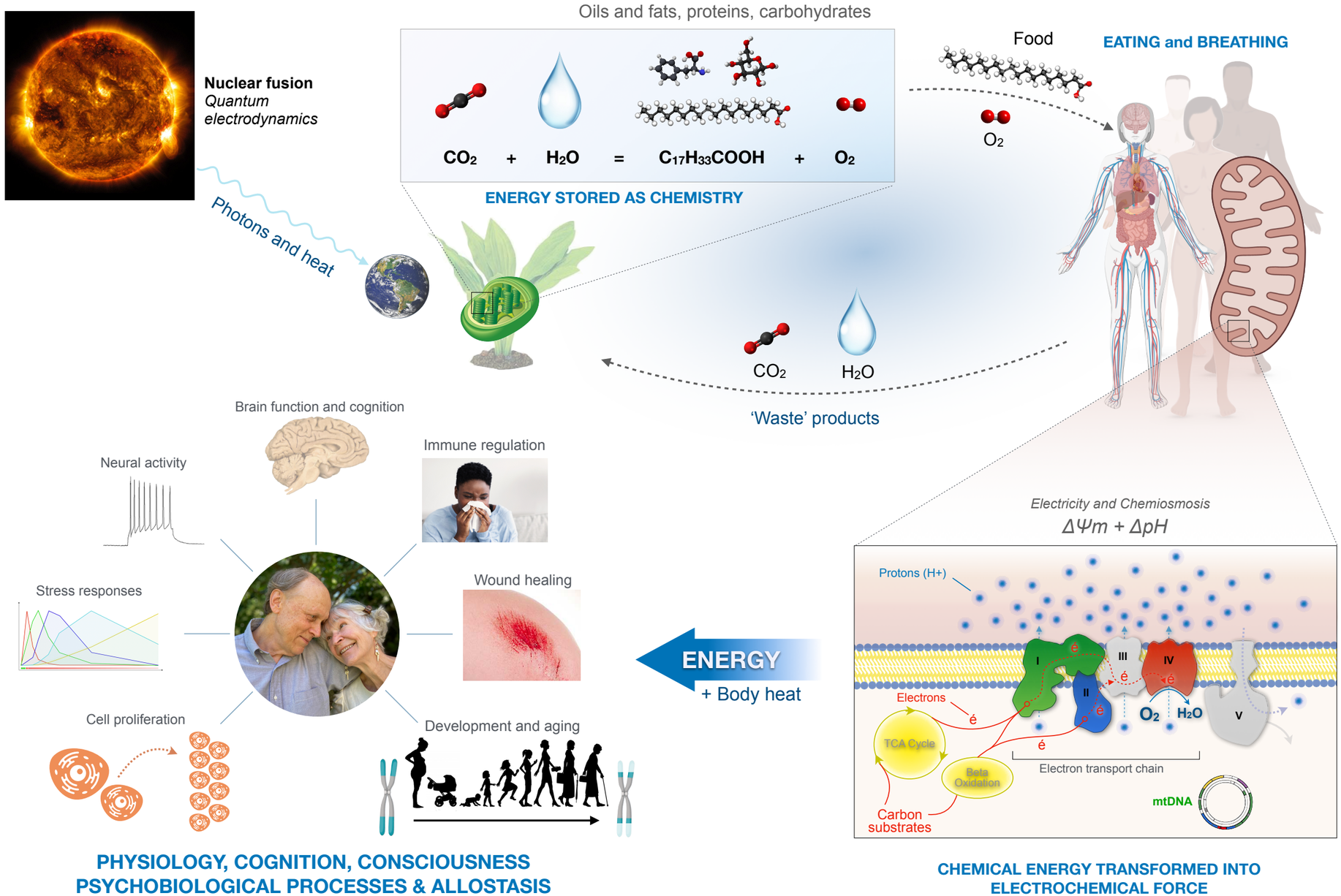
Development and aging



PHYSIOLOGY, COGNITION, CONSCIOUSNESS
PSYCHOBIOLOGICAL PROCESSES & ALLOSTASIS

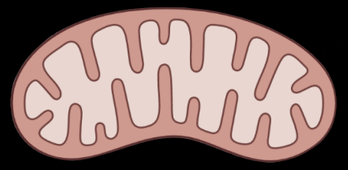
Biochemistry 2022

Mitochondrial PsychoBiology Lab



Biochemistry 2022

Organic
(carbon-based structure)



Consume O_2
Release CO_2

Flexible

Sensitive but resilient

Always in movement

Dynamic

Adaptable

Warm

Bright quality

Ephemeral and
finite lifespan

The vital ingredient of life

Cadaver

✅ ~20,000 genes ✅

✅ ~30 trillion cells ✅

✅ Heart, liver, … ✅

✅ Neurons, glia ✅

✅ Intact skin ✅

✅ Immune cells ✅

✅ Mitochondria ✅

❌ **Energy flow** ✅

Thinking, feeling, breathing, conscious person

What is Energy ?

Energy is the *potential for change*

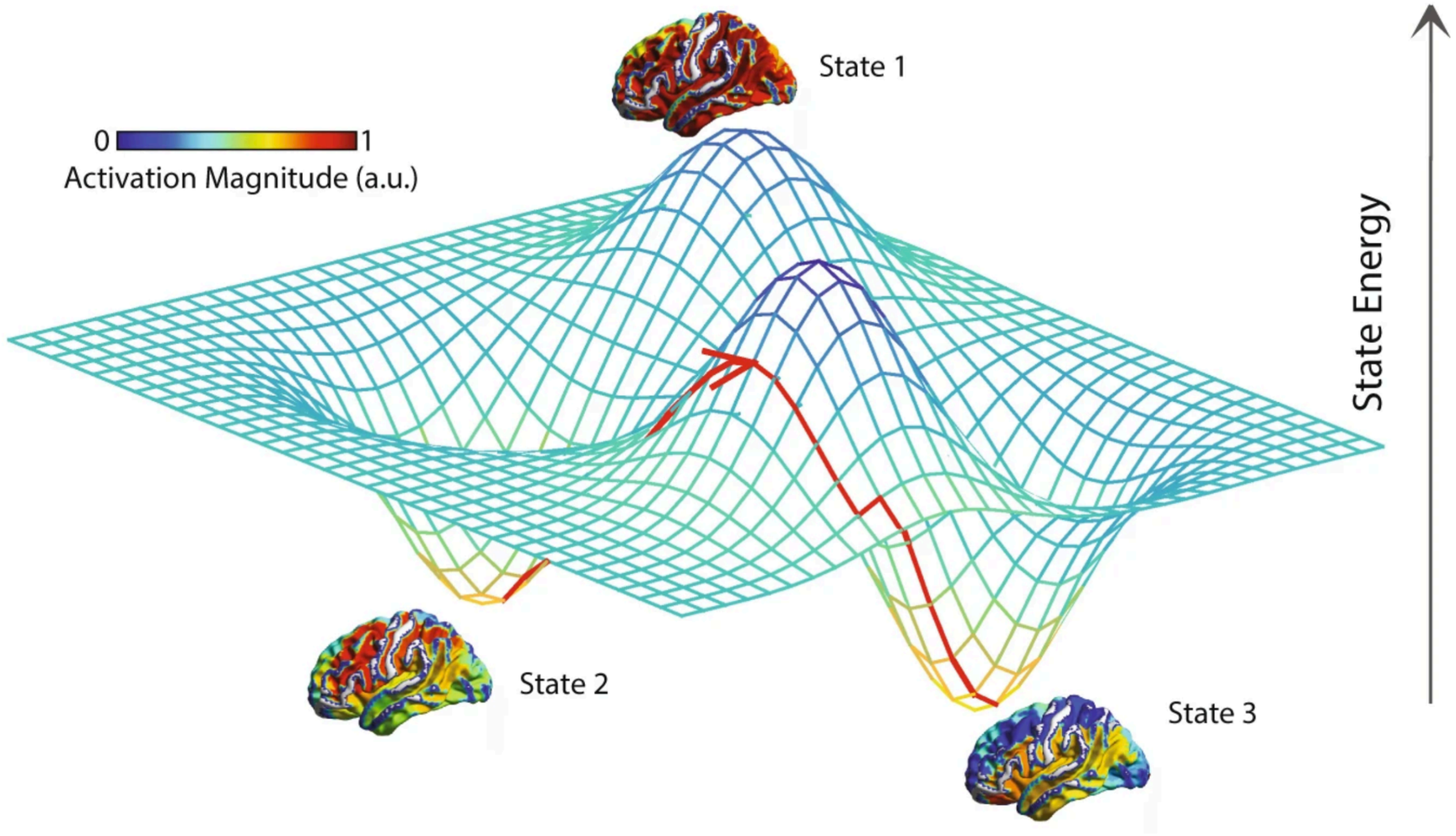
Universal features of **Energy**

1. **Energy is conserved and transformed** (different forms)

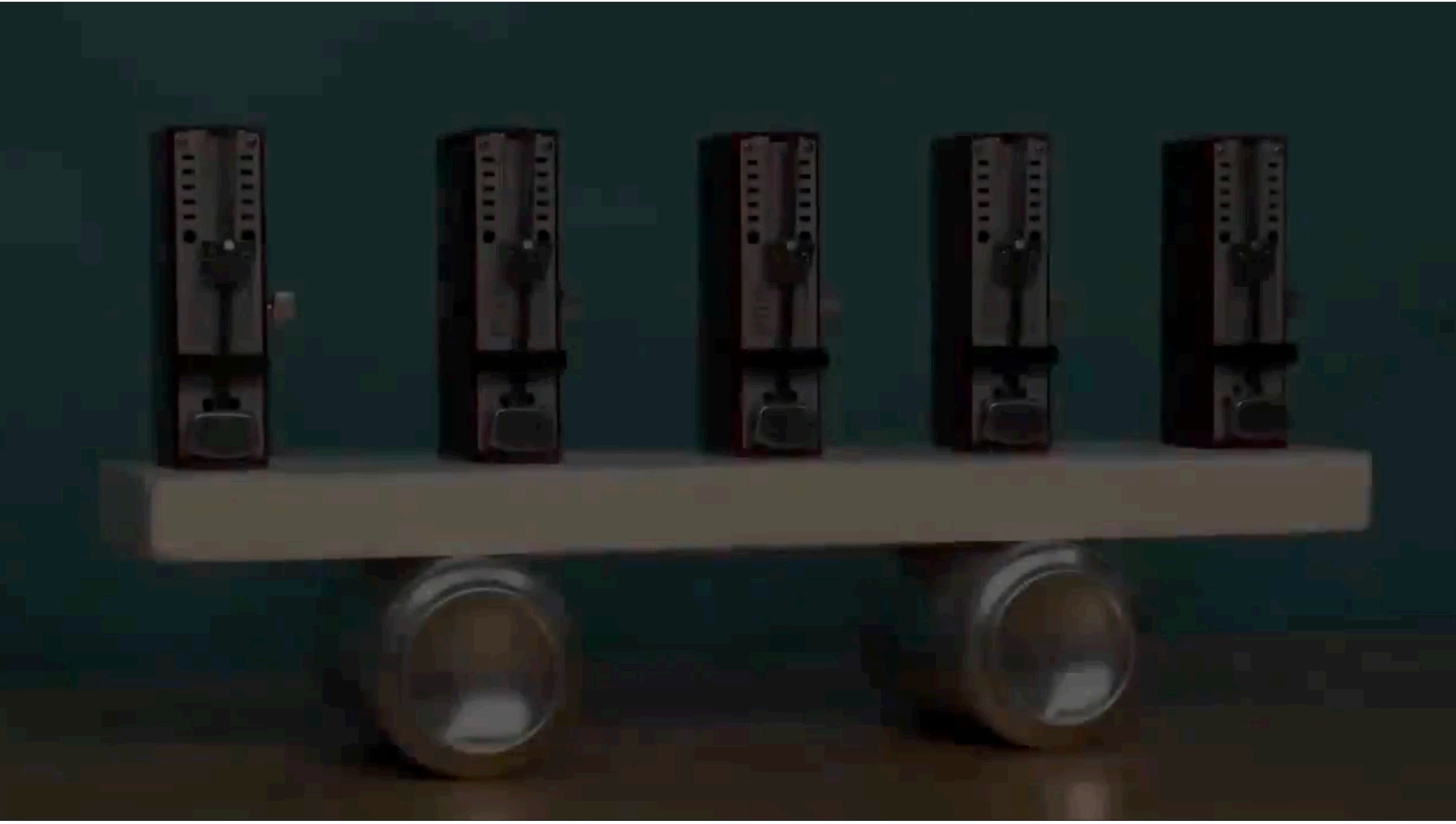
2. **Energy always flows** (entropy)

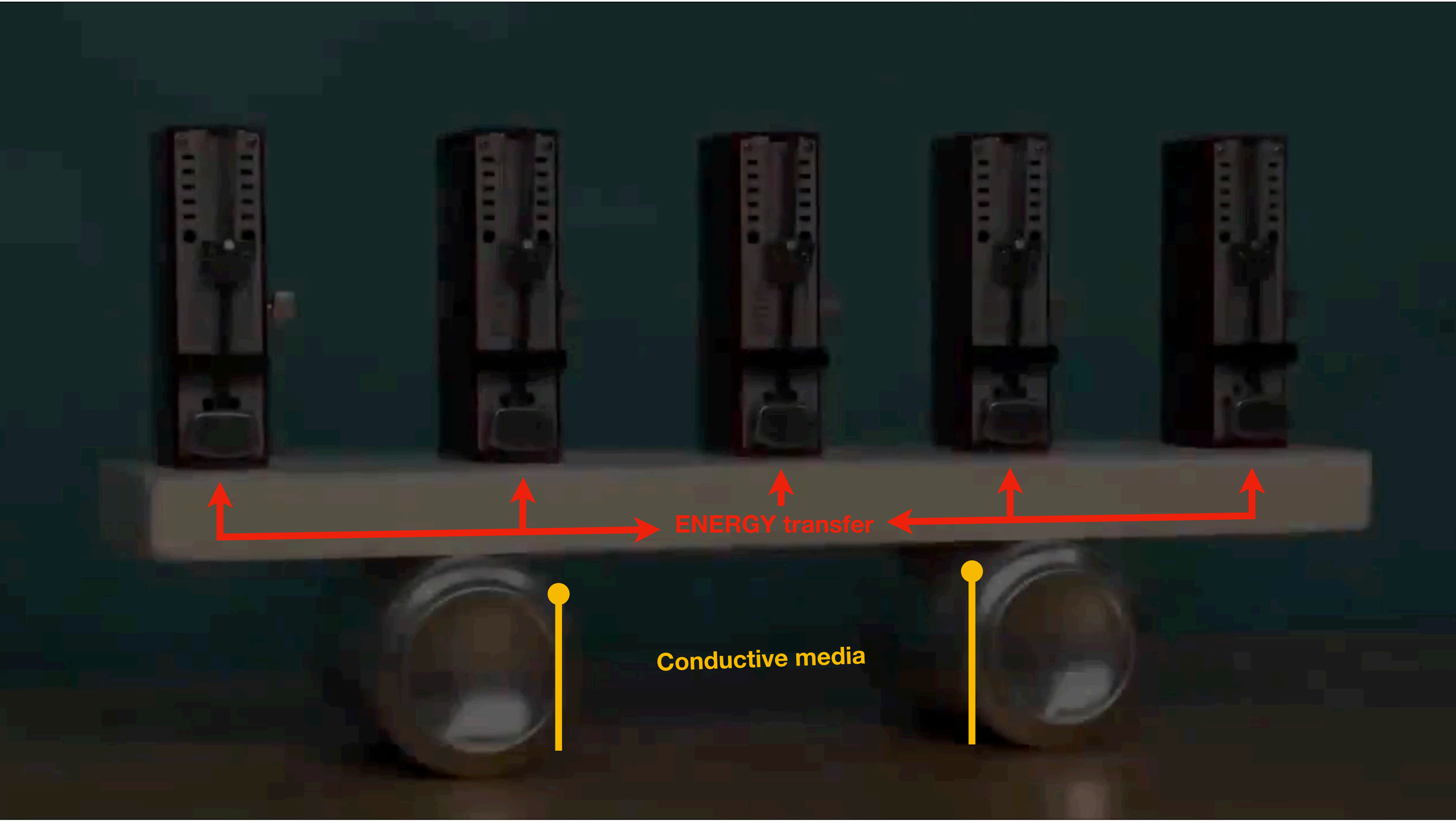
3. **Energy is quantized** (comes in packets)

It costs energy to shift states



Gu et al. *Sci Rep* 2018




ENERGY transfer
Conductive media

The conductive media in animals is

Energy Metabolism

What are the **energetic principles** of human health ?

Three **energetic principles** of human health

1. Total energy transformation **capacity is limited**

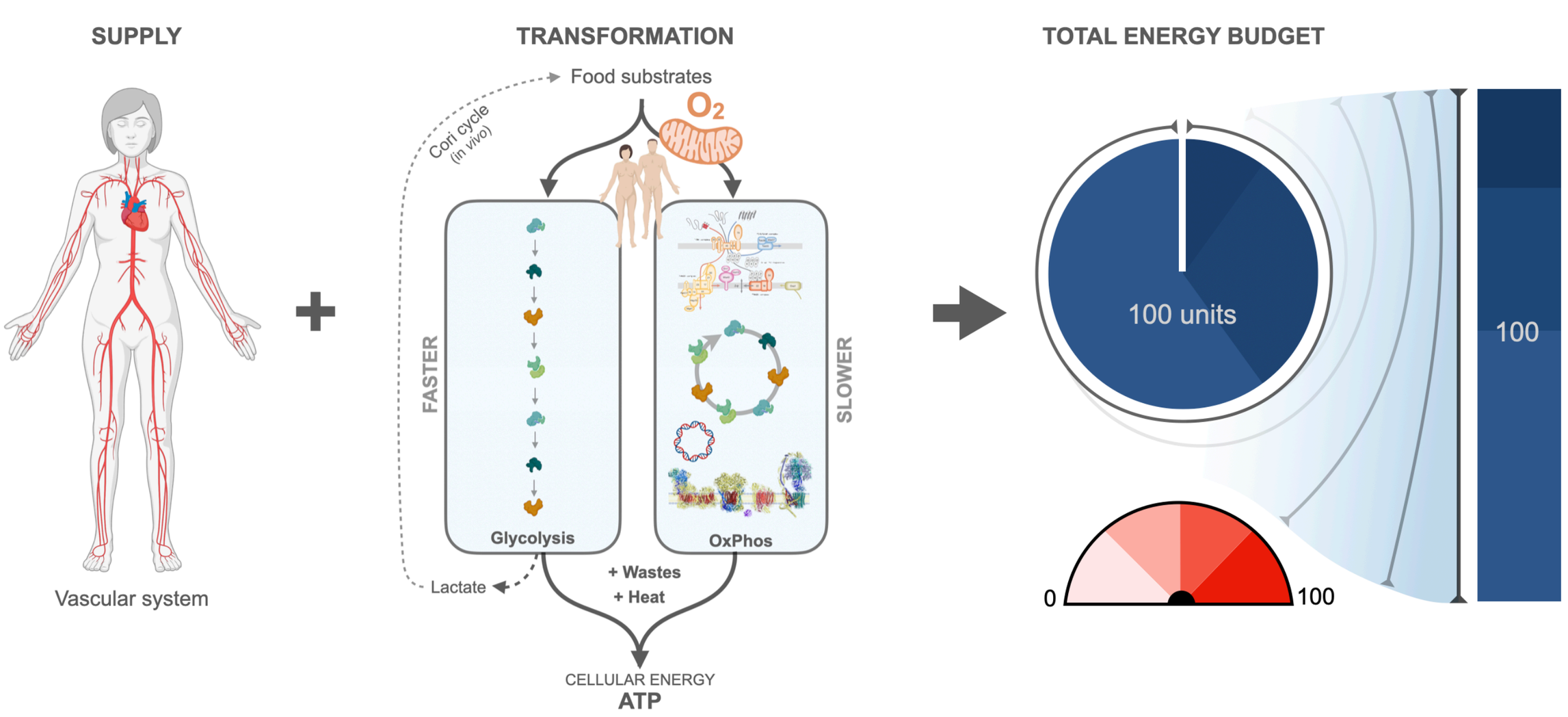
2. Energy allocation follows a **hierarchy of energy needs**

3. The **brain** controls the (re)allocation of energy

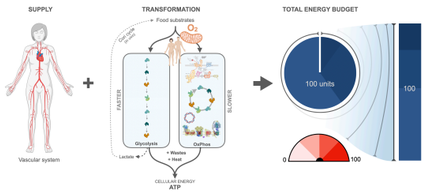
Three **energetic principles** of human health

1. Total energy transformation **capacity is limited**

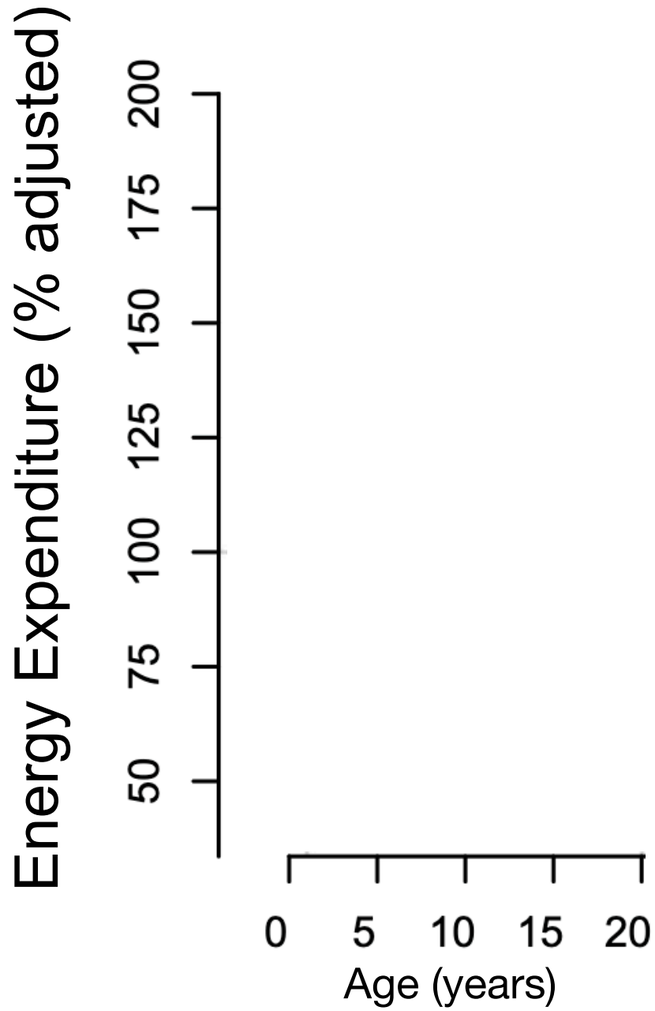
The human energy budget



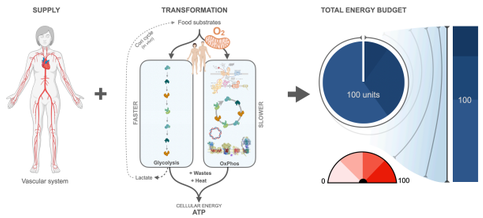
(under review)



The energetic **cost of life** across the human lifespan



Pontzer et al. *Science* 2021



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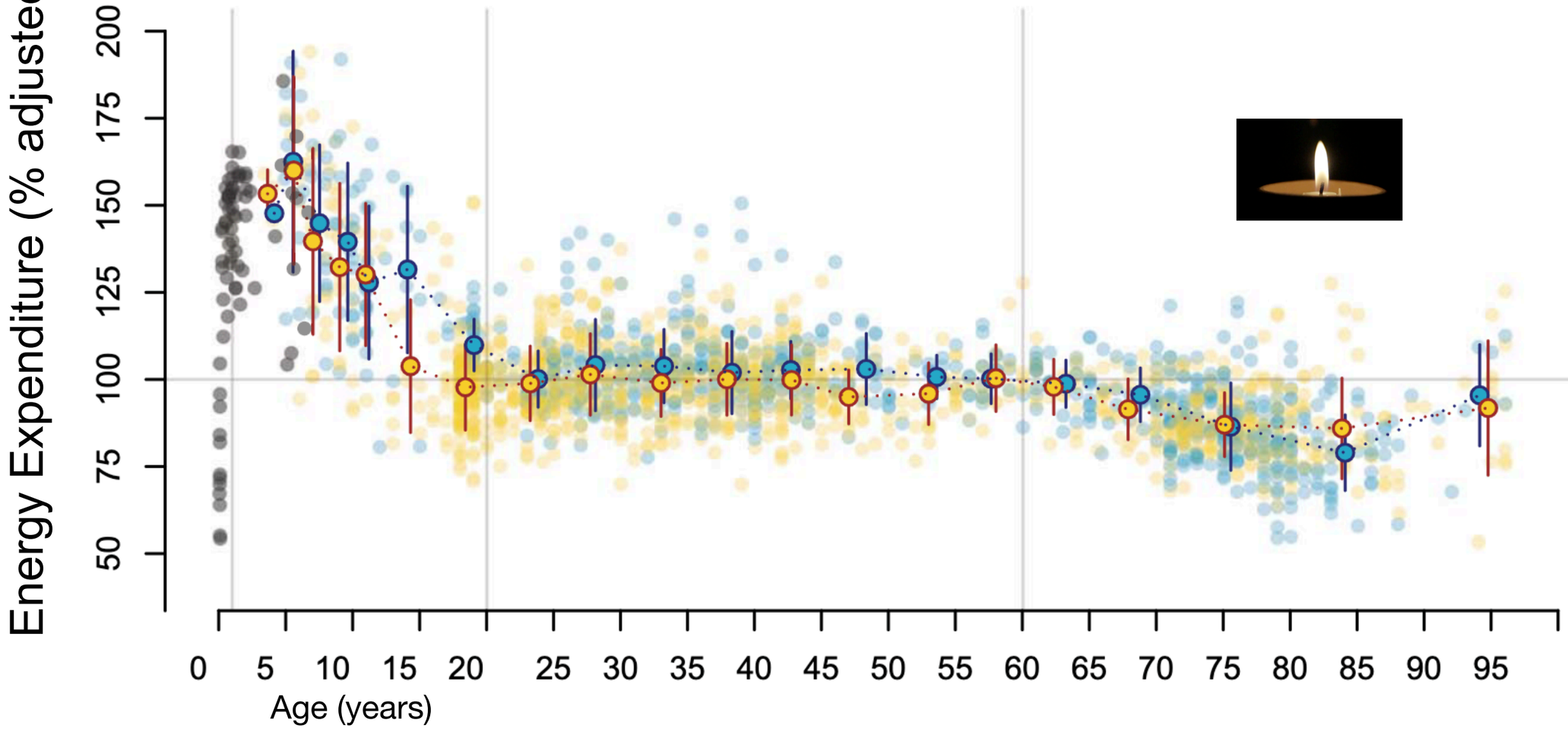
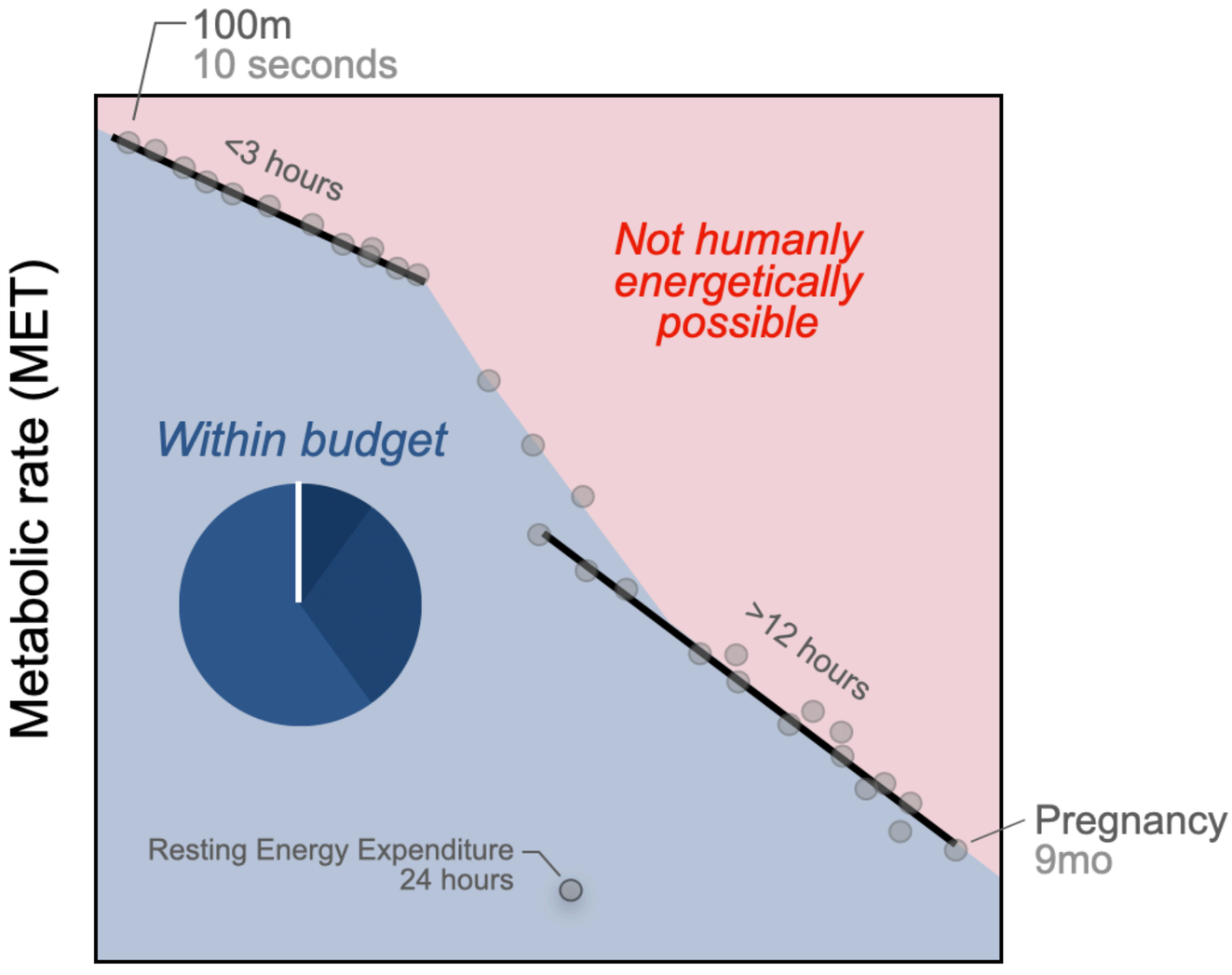
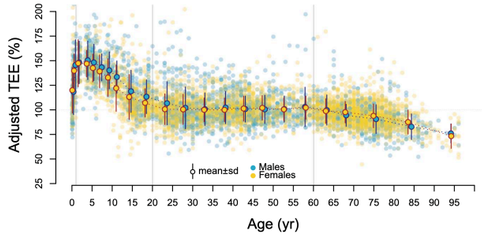


Pontzer et al. *Science* 2021

There is a fixed limit to human energy expenditure





(under review)

Thurber et al. *Sci Adv* 2019

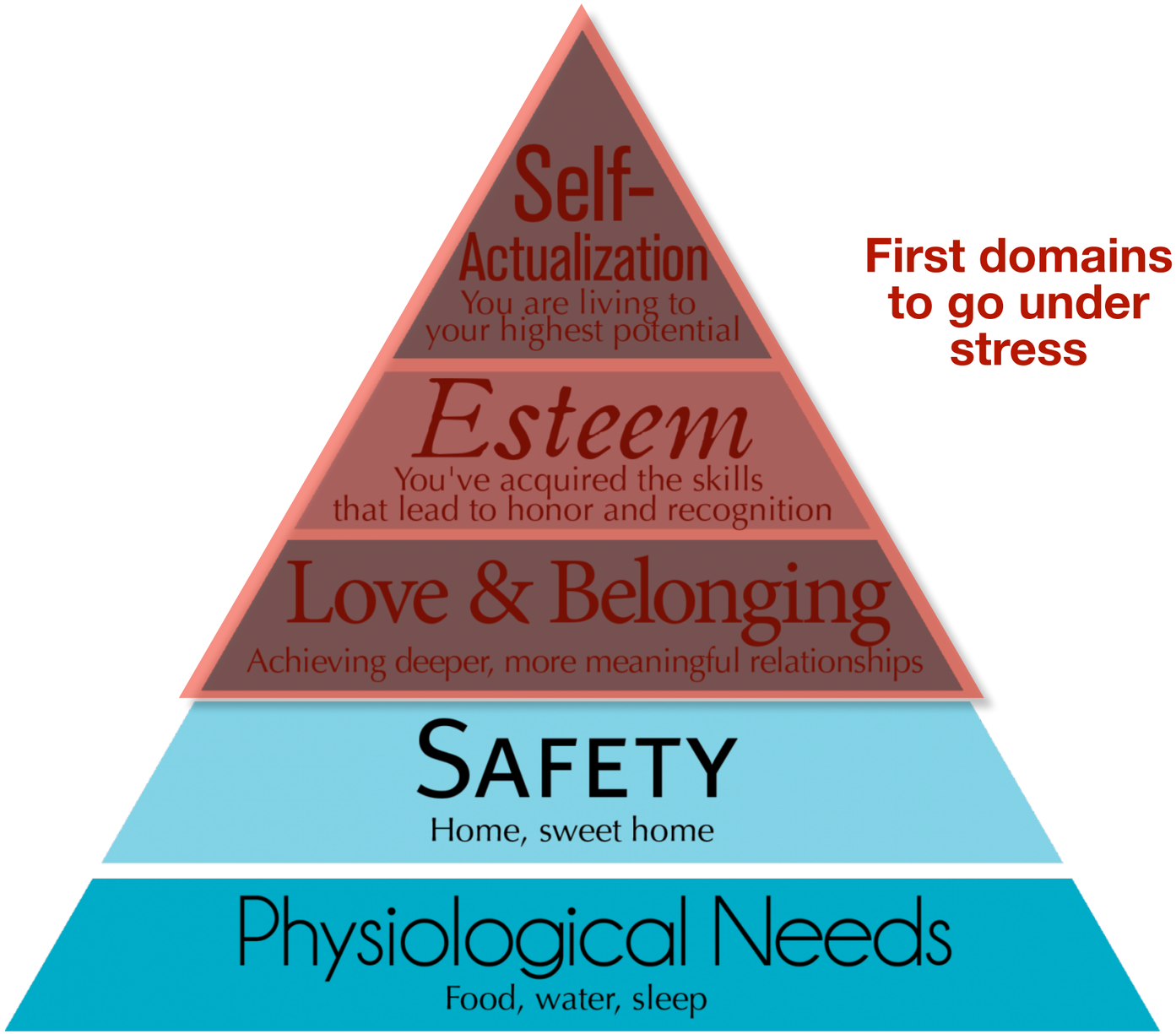
Three **energetic principles** of human health

1. Total energy transformation **capacity is limited**

Three **energetic principles** of human health

2. Energy allocation follows a **hierarchy of energy needs**

Maslow's hierarchy of human needs



First domains to go under stress

HIERARCHY OF ENERGY NEEDS

GMR
Growth
Maintenance
Repair

Most dispensable processes
First functions to be traded off during energy stress/limitations

GMR
Plasticity
Stemness
Epigenome

DNA/RNA synthesis
DNA repair, Telomerase
Antioxidant

STRESS
Protein synthesis
Stress response program (ISR)
Signal transduction

VITAL
MEMBRANE POTENTIAL
Ion exchanges, metabolism

Skills
Vitality
Activity
Motivation
Cognition

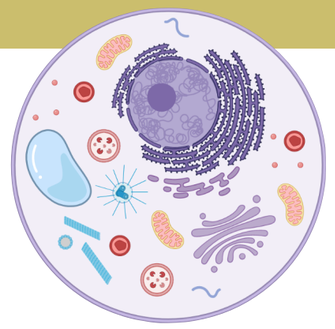
Muscle mass
Energy reserves
Immunity

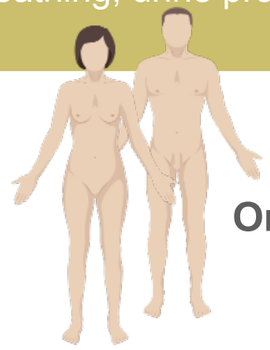
Stress responses
Sympathetic nervous system
Inter-organ coordination, cytokines

VITAL ORGANS & FUNCTIONS
Heart rate, breathing, urine production, brain

Not traded off except in disease or death

Cell level





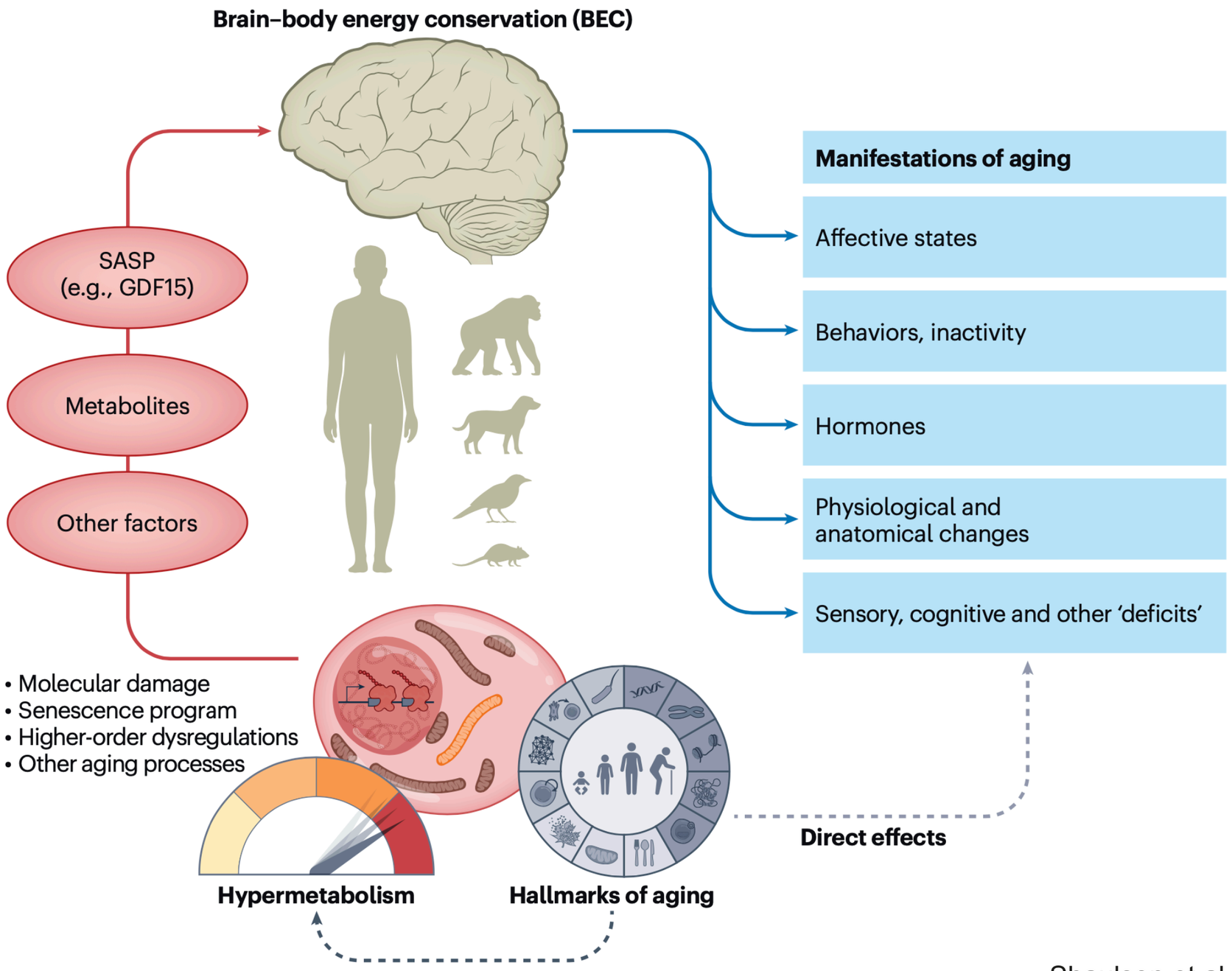
Organism level

Three **energetic principles** of human health

2. Energy allocation follows a **hierarchy of energy needs**

Three **energetic principles** of human health

3. The **brain** controls the (re)allocation of energy



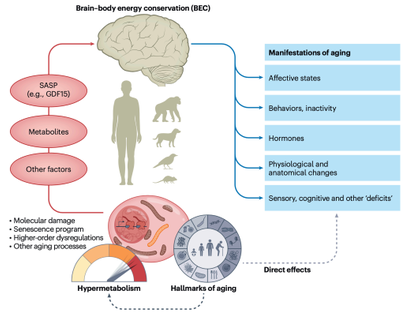
Shaulson et al. *Nat Aging* 2024

nature aging

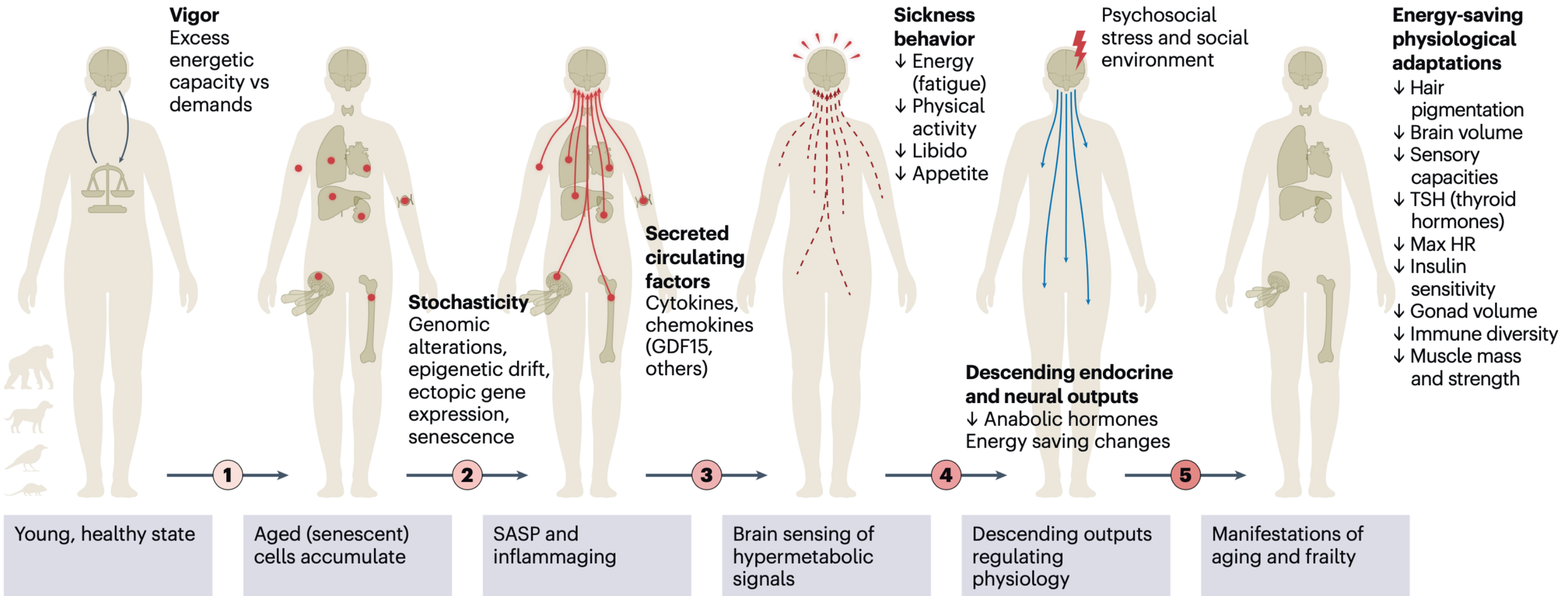
Perspective

https://doi.org/10.1038/s43587-024-00716-x

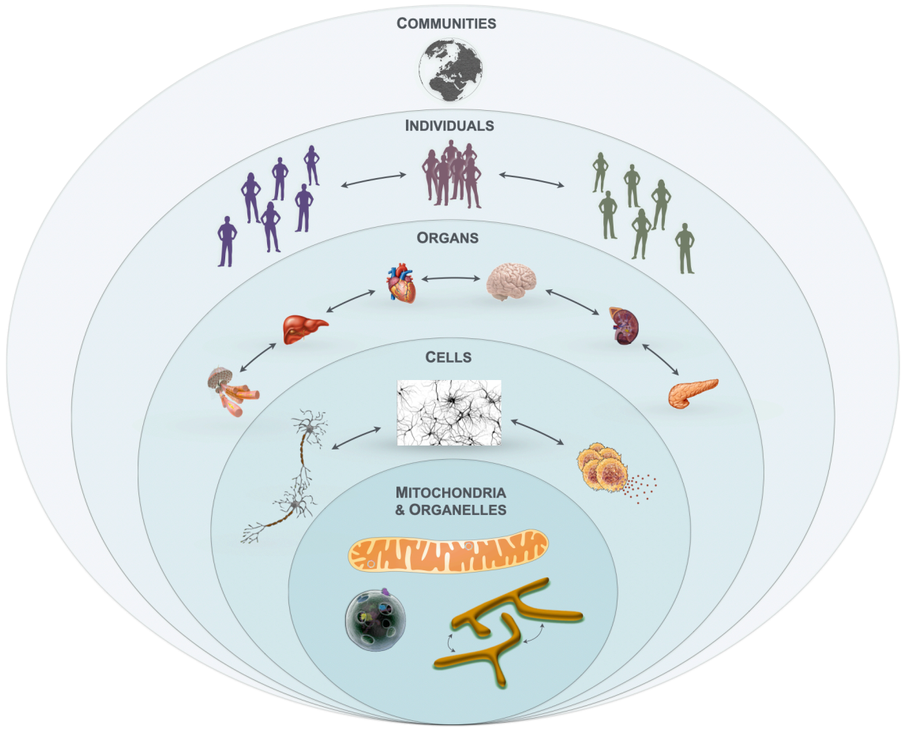
The brain–body energy conservation model of aging

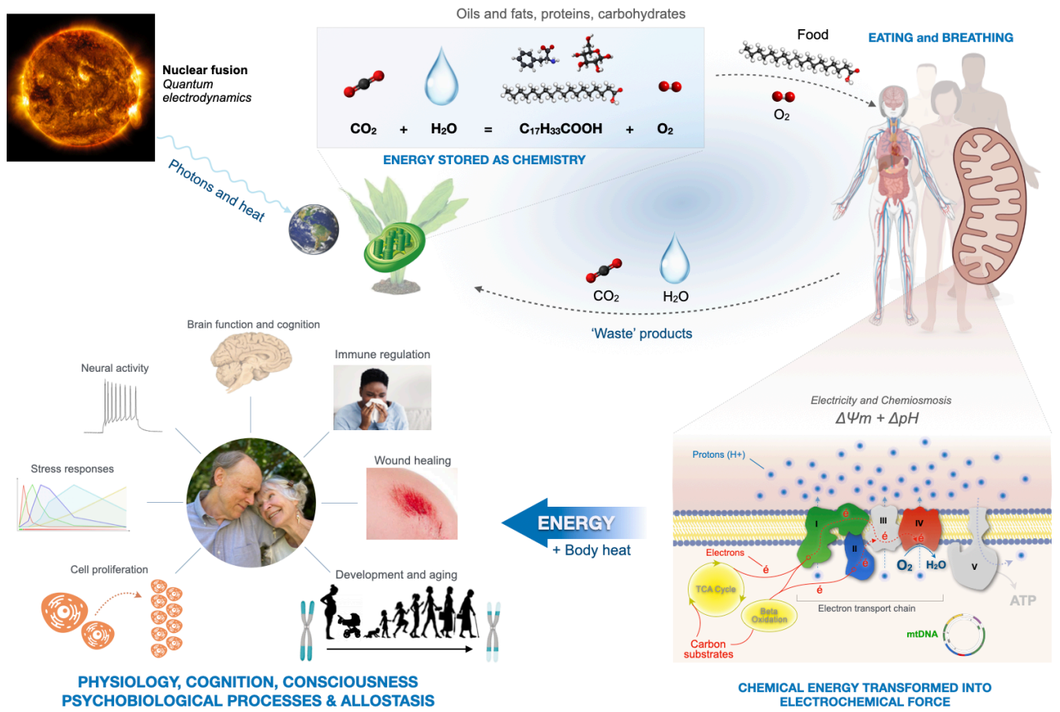


The brain moderates physiological **energy tradeoffs**



Shaulson et al. *Nat Aging* 2024





There are **simple energetic principles** driving the flow and transformation of energy through our biology

A major hub of energy metabolism : **Mitochondria**

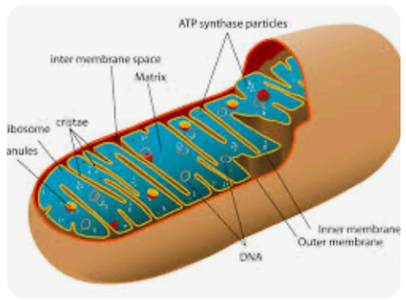
What do **mitochondria** look like?

Google

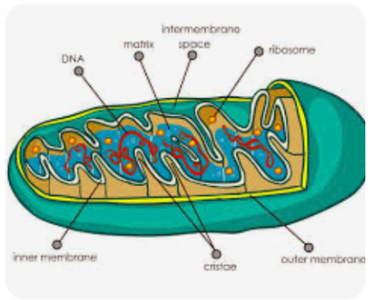
mitochondria

All | Images | Shopping | Videos | News | Short videos | Forums | More | Tools | Saved

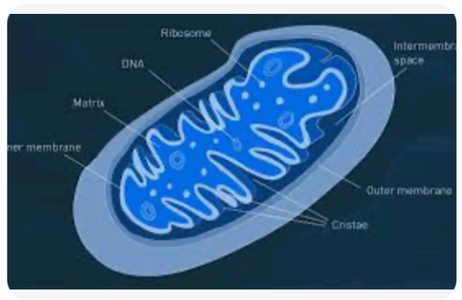
Cell | Diagram | Structure | Drawing | Simple | Labeled | Function | Plant | Real | Chloroplast | Biology



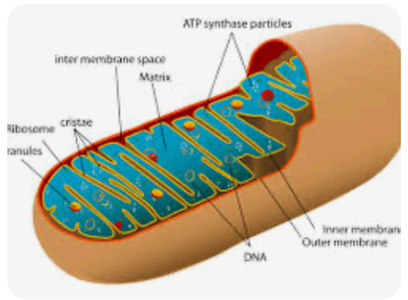
Wikipedia
Mitochondrion - Wikipedia



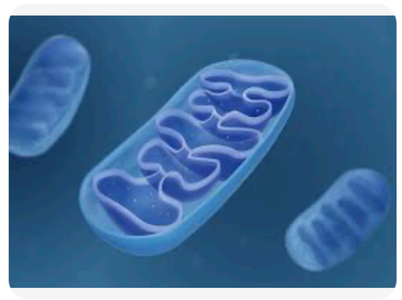
Medical News Today
Mitochondria: Form, function, ...



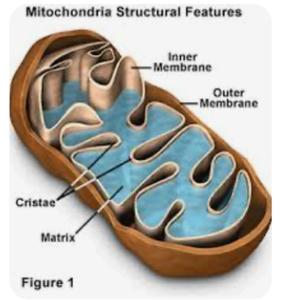
Technology Networks
Roles of Mitochondria in Cells ...



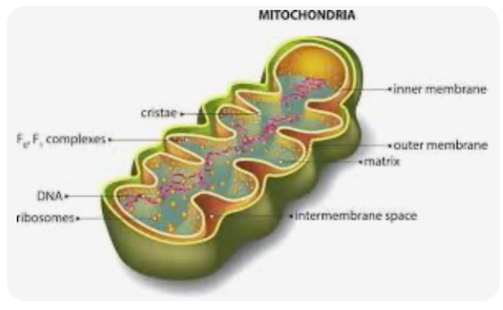
Wikipedia
Mitochondrion - Wikipedia



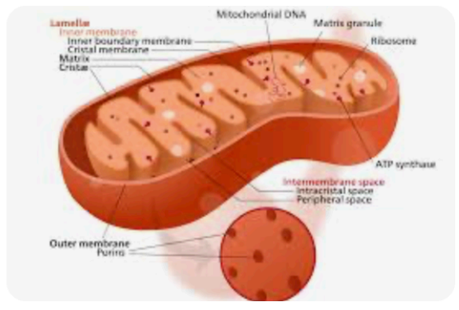
The Scientist
Rebranding Mitochondria | The S...



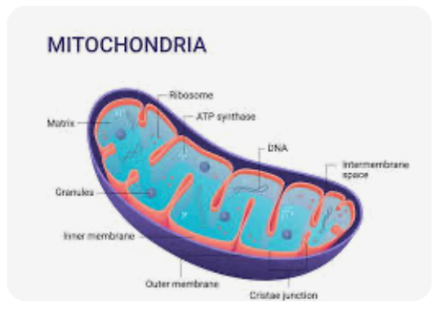
Molecular Expression...
Molecular Expressio...



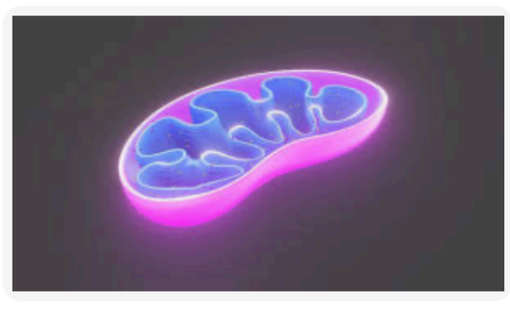
News-Medical.net
What are Mitochondria?



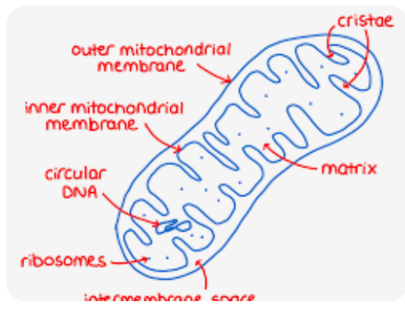
National Ataxia Foundation
National Ataxia Foundation



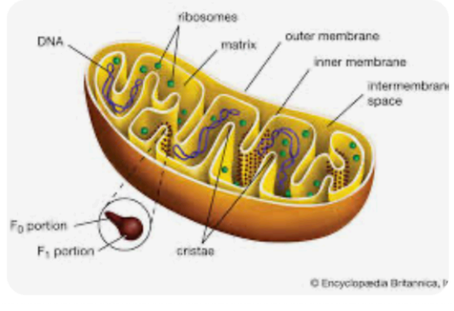
Research Communities by Springer Nat...
Mitochondria and Cellular Signaling ...

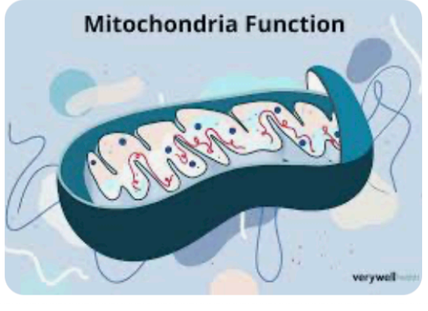


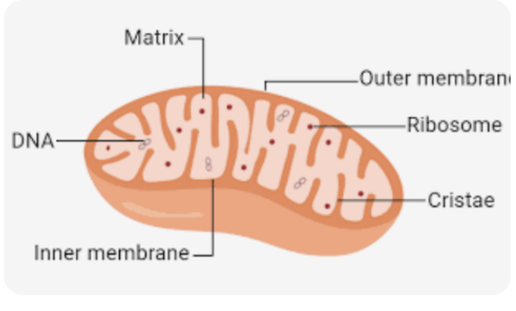
Phys.org
Exploring the mind-mitochondria connection

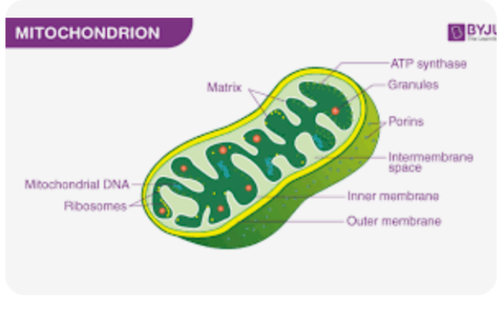


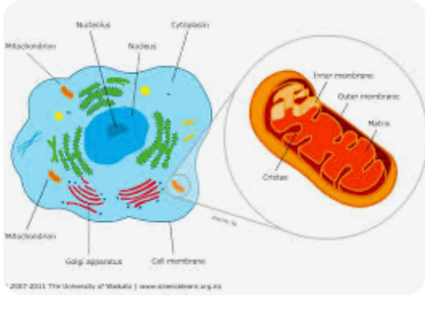
Zoë Huggett Tutorials
The Mitochondria - Cell Organelle...

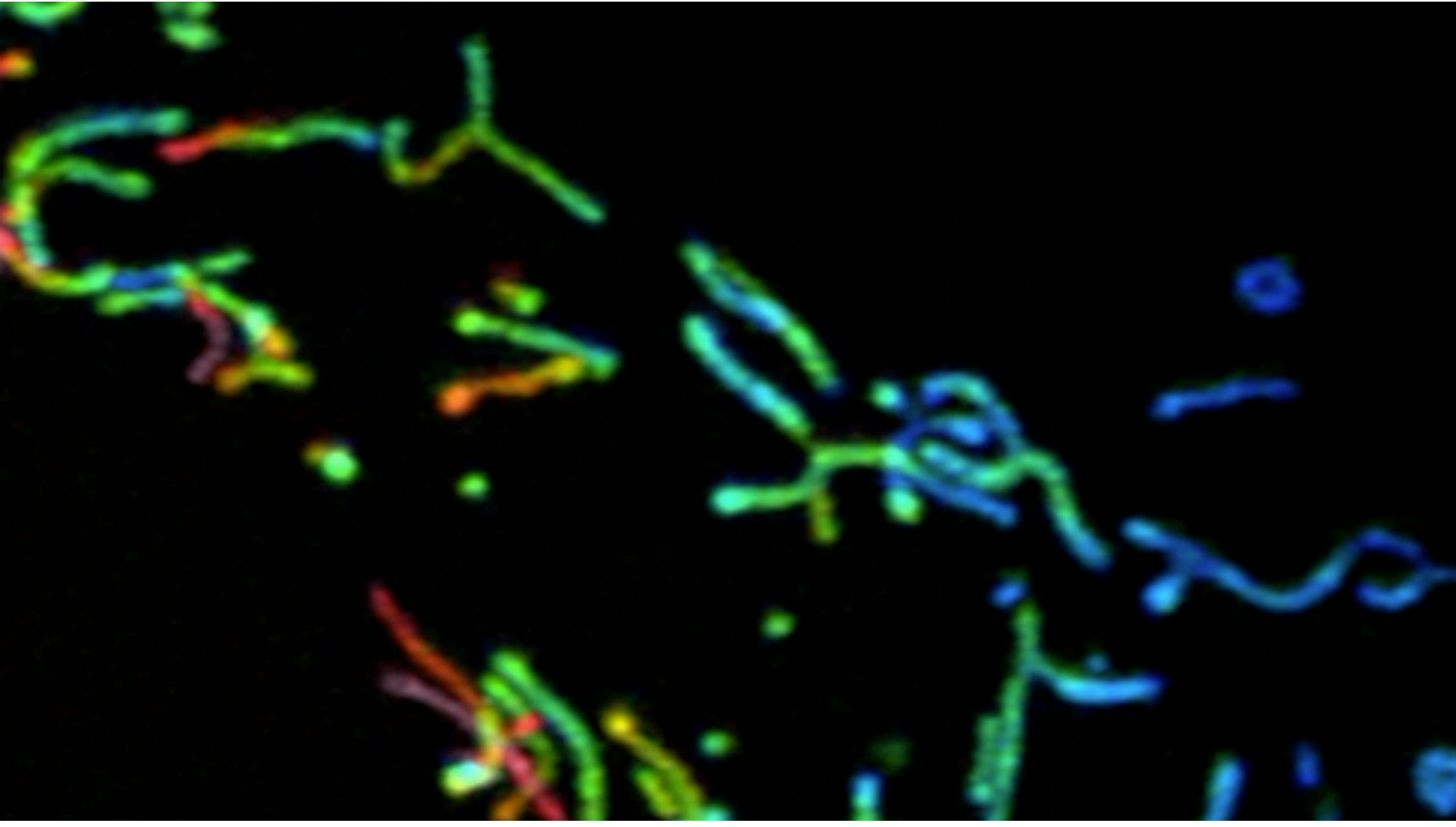


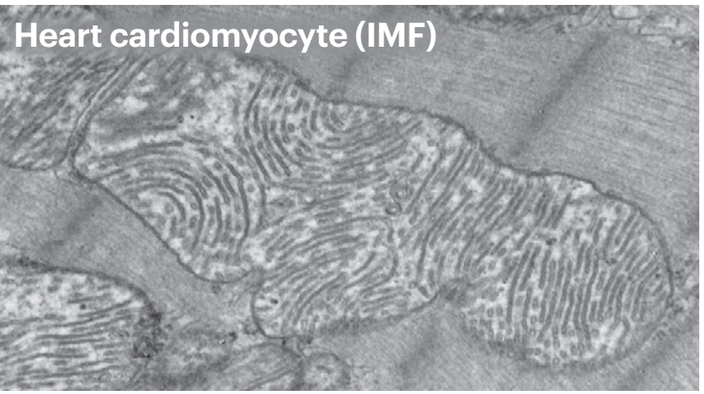


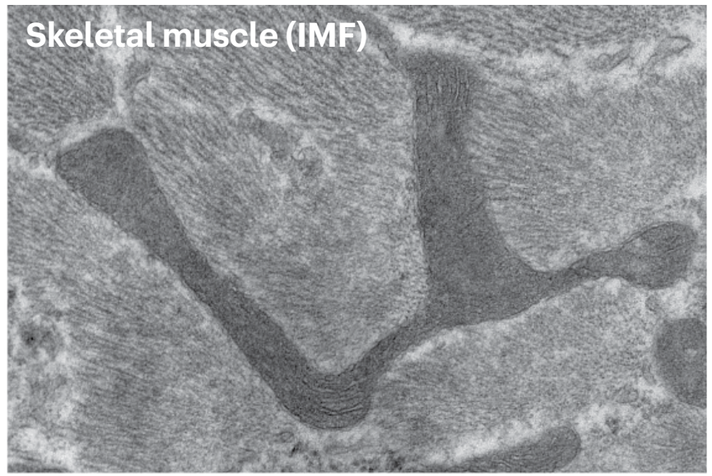


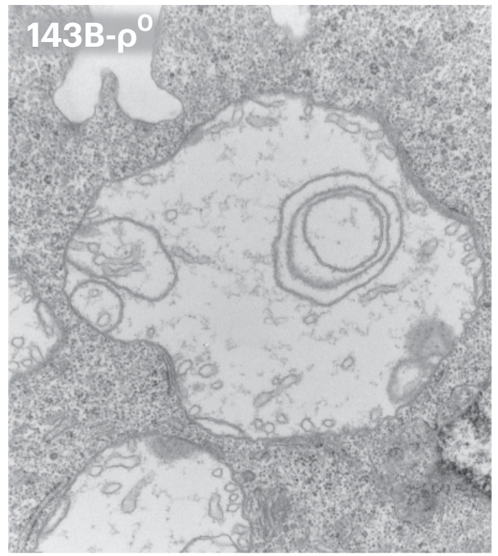


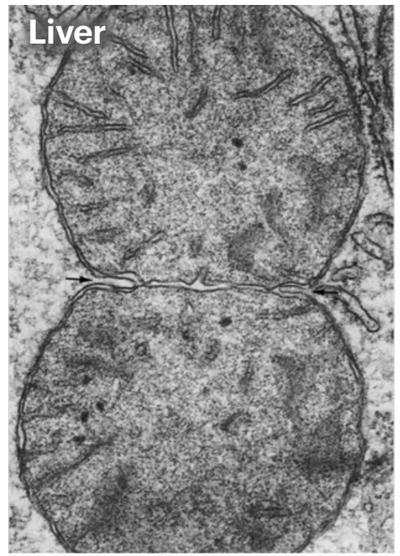


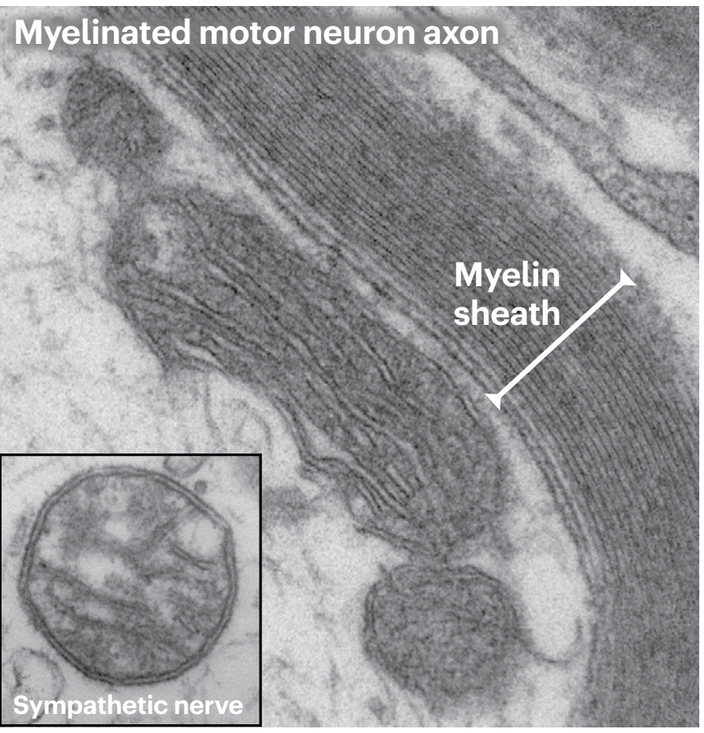


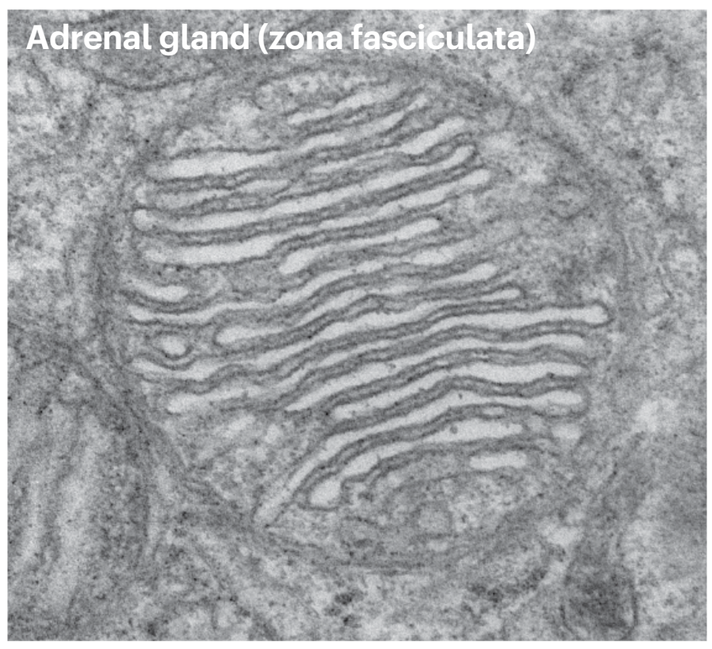


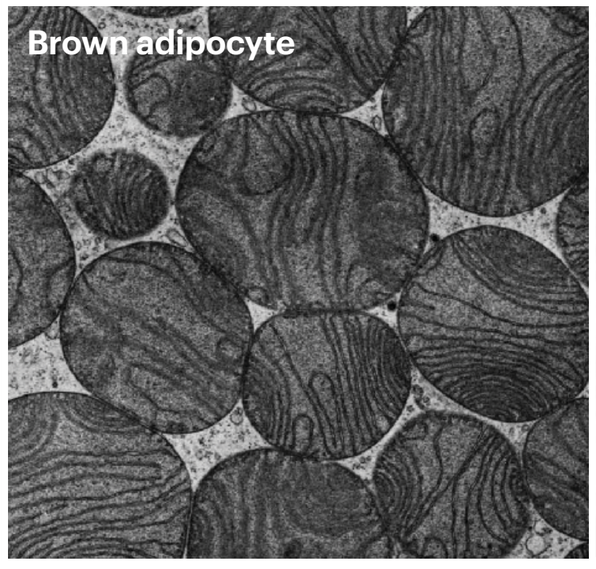


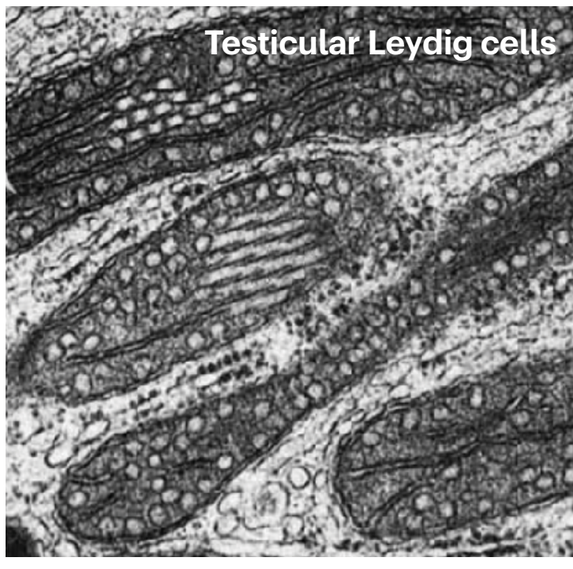








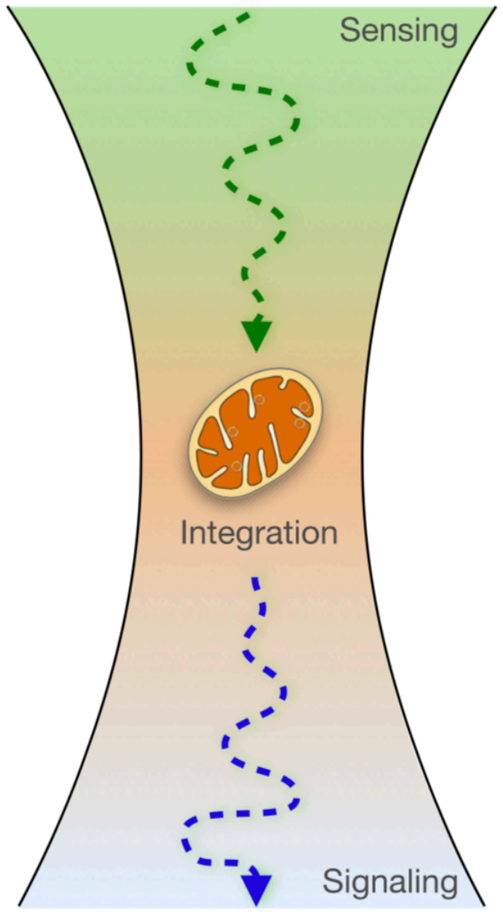




Each organ and cell type has a different **mitotype** / **energy**

Monzel et al. *Nature Metabolism* 2023

STRESSORS



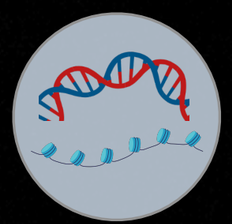
BIOLOGICAL EMBEDDING

Mitochondria as an interface between the energetic states of mind, and the material state of **molecules**

Picard and McEwen. *Psychosom Med* 2018

Exposures / Behaviors
Neuroendocrine factors
States of mind

X



Molecules

Health
Healing
Lifespan

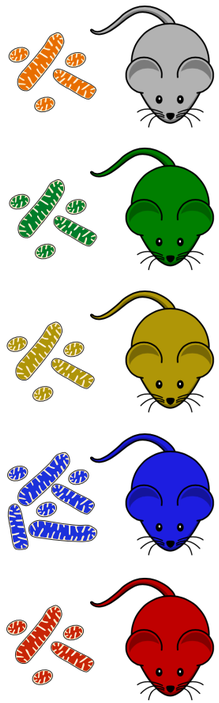
Hypothesis: Mitochondria are the **ENERGETIC INTERFACE**

Is there a Mind ↔ Mitochondria Connection ?

STUDY 1

Mitochondria influence HPA axis function

Mice with different mitochondria



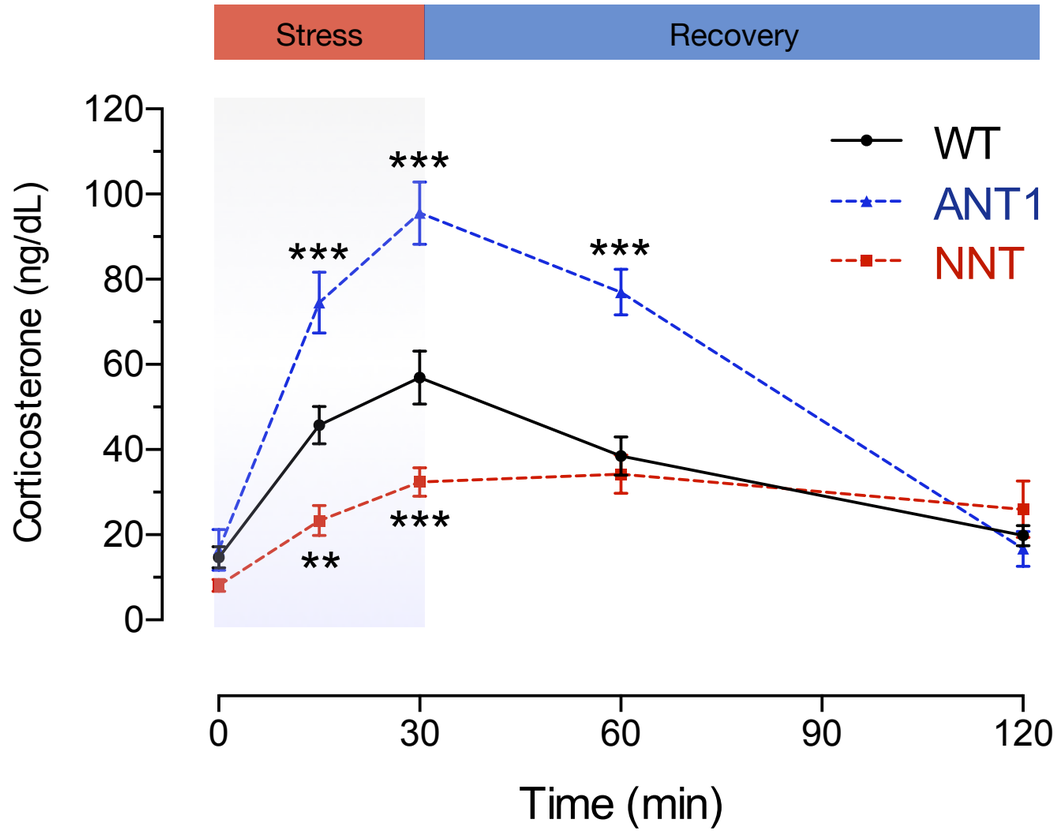
WT
Normal function

ND6
↓ Respiration

COI
↓ Respiration

ANT1$^{-/-}$
↓ Energy Exchange

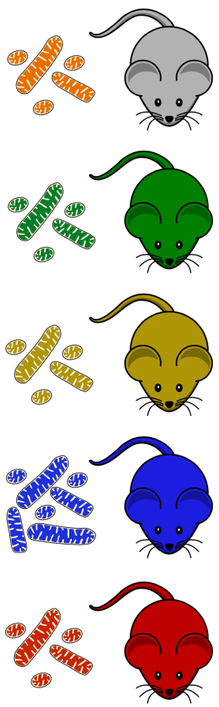
NNT$^{-/-}$
↑ Oxidative Stress



Picard et al. *PNAS* 2015

Mitochondria cause unique stress response “signatures"

Mice with different mitochondria



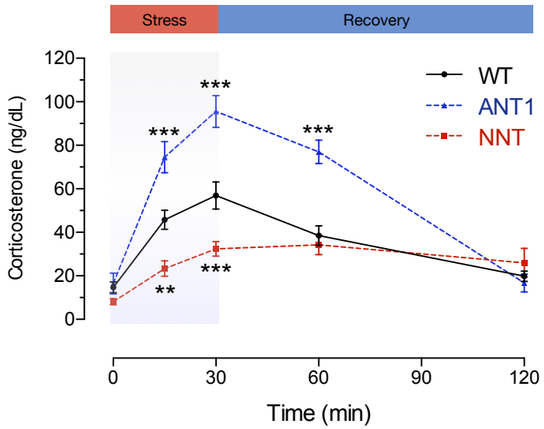
WT
Normal function

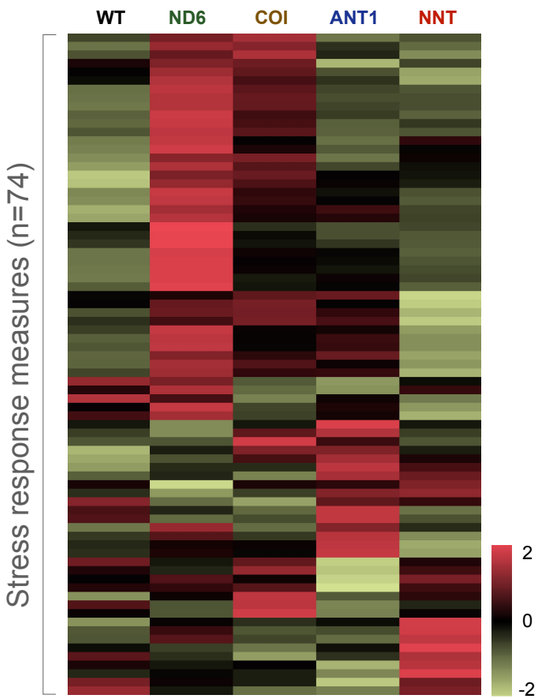
ND6
↓ Respiration

COI
↓ Respiration

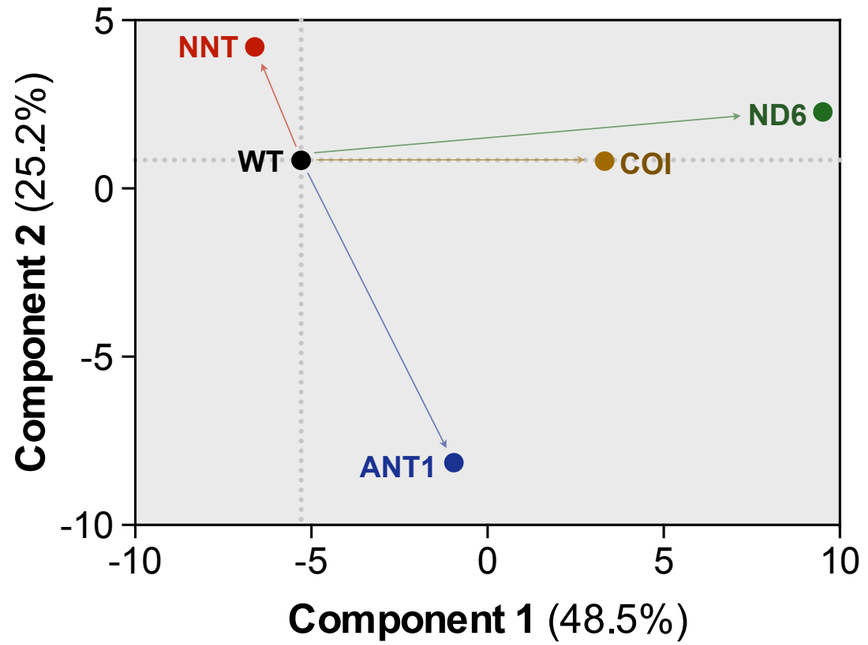
ANT1$^{-/-}$
↓ Energy Exchange

NNT$^{-/-}$
↑ Oxidative Stress





STRESS RESPONSE SIGNATURES



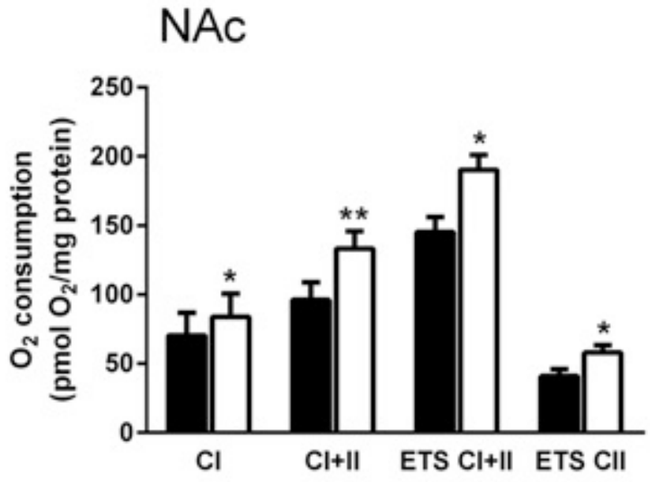
Picard et al. *PNAS* 2015

Is there a Mind ↔ Mitochondria Connection ?

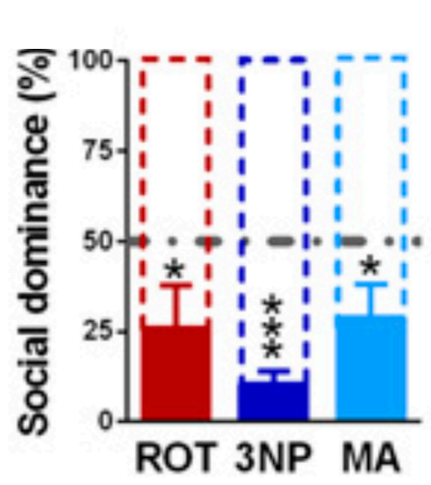
STUDY **2**

Mitochondrial function in the brain links anxiety with social subordination

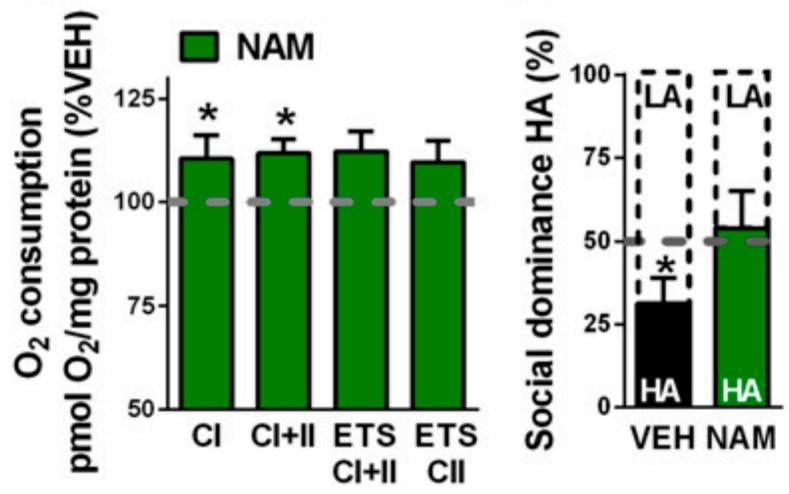
Fiona Hollis[a,1], Michael A. van der Kooij[a,1,2], Olivia Zanoletti[a], Laura Lozano[a], Carles Cantó[b], and Carmen Sandi[a,3]



Mito inhibition decreases social dominance



"Boosting" energy metabolism rescues high-anxious deficit

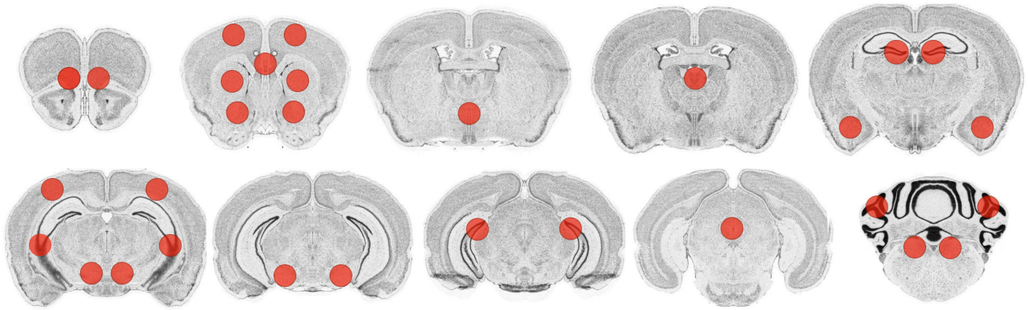


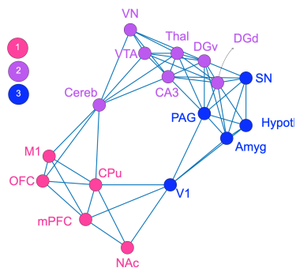
Hollis et al. *PNAS* 2015

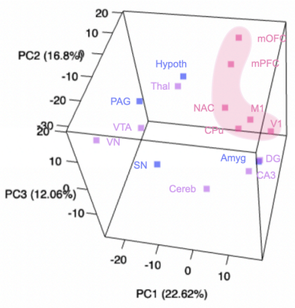
Article

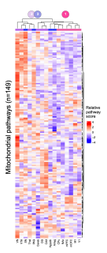
https://doi.org/10.1038/s41467-023-39941-0

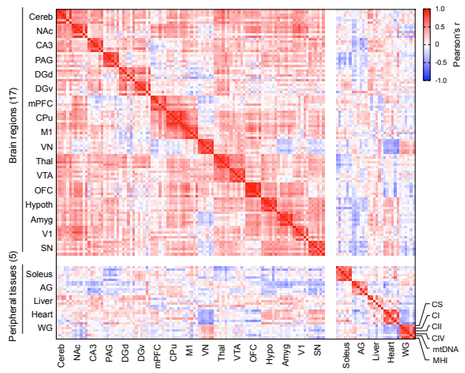
Brain mitochondrial diversity and network organization predict anxiety-like behavior in male mice

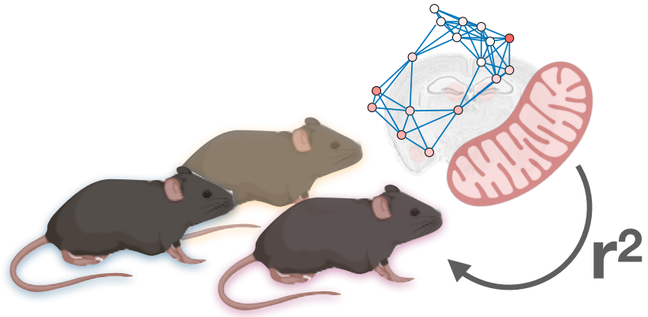


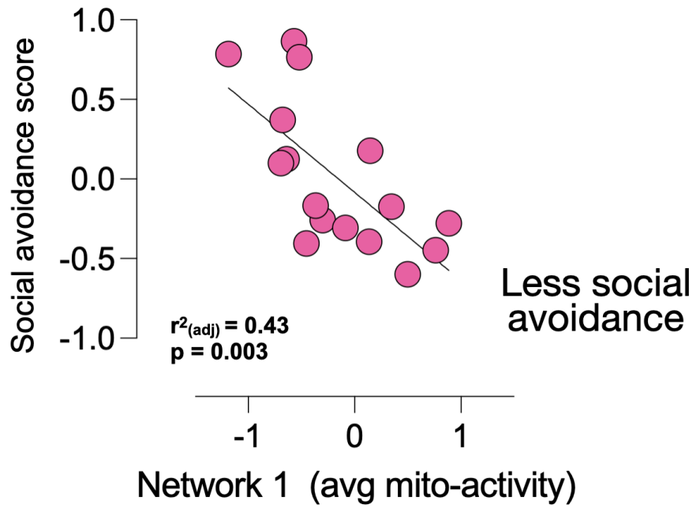












Chris Anacker

Rosenberg et al. *Nat Commun* 2023

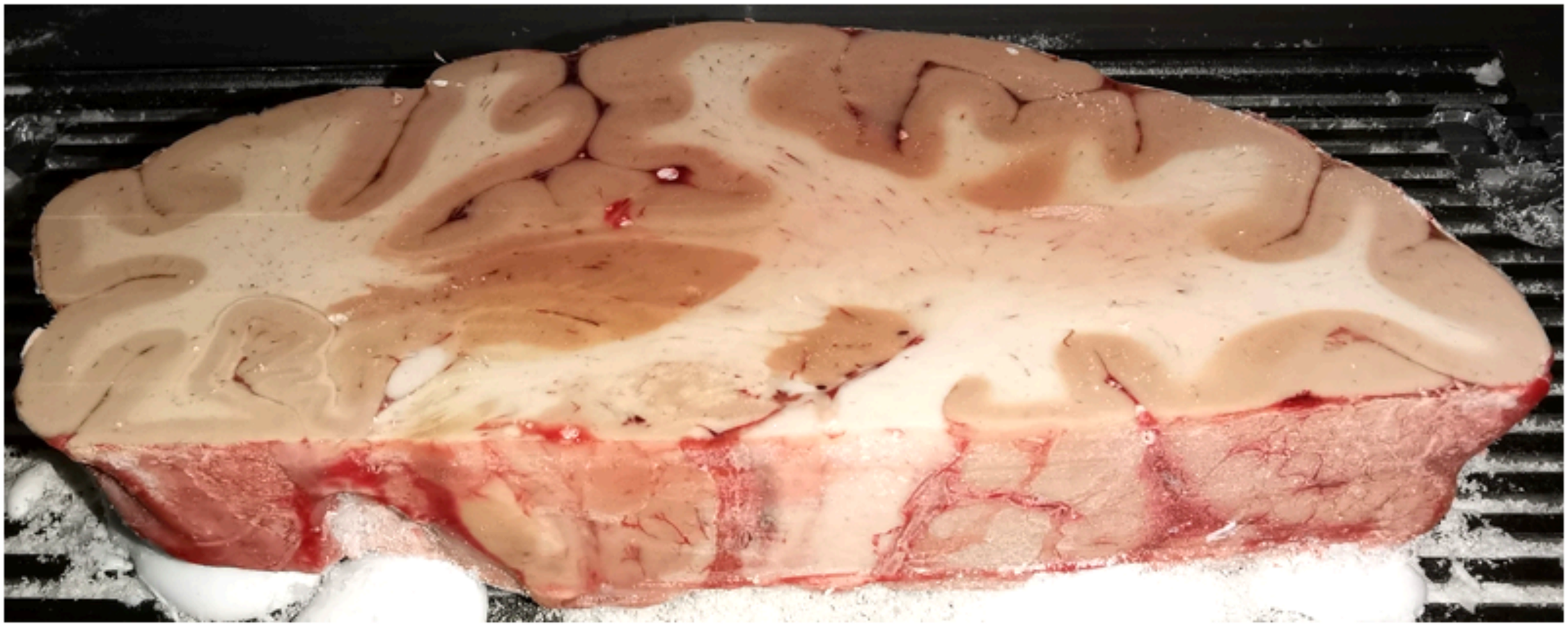
What about **human** brain mitochondria ?

Is there a Mind ↔ Mitochondria Connection ?

STUDY **3**

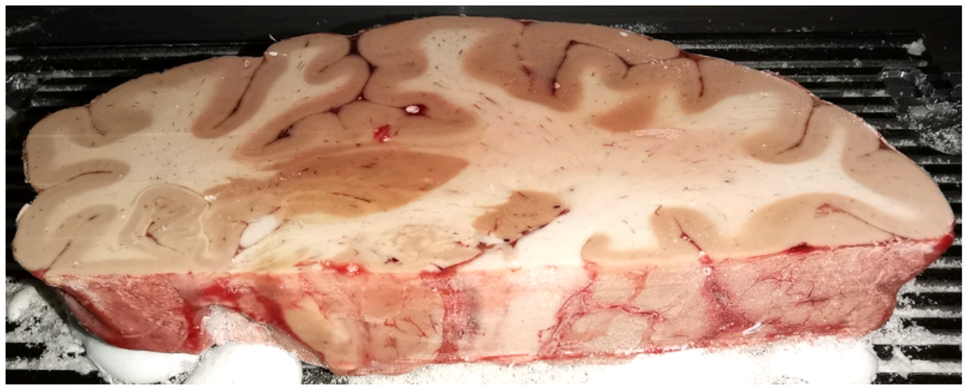
MitoBrainMap v1.0

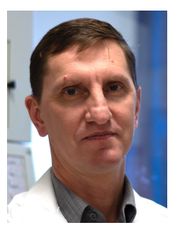
A multi-function mitochondrial atlas of a single human coronal brain section at fMRI resolution



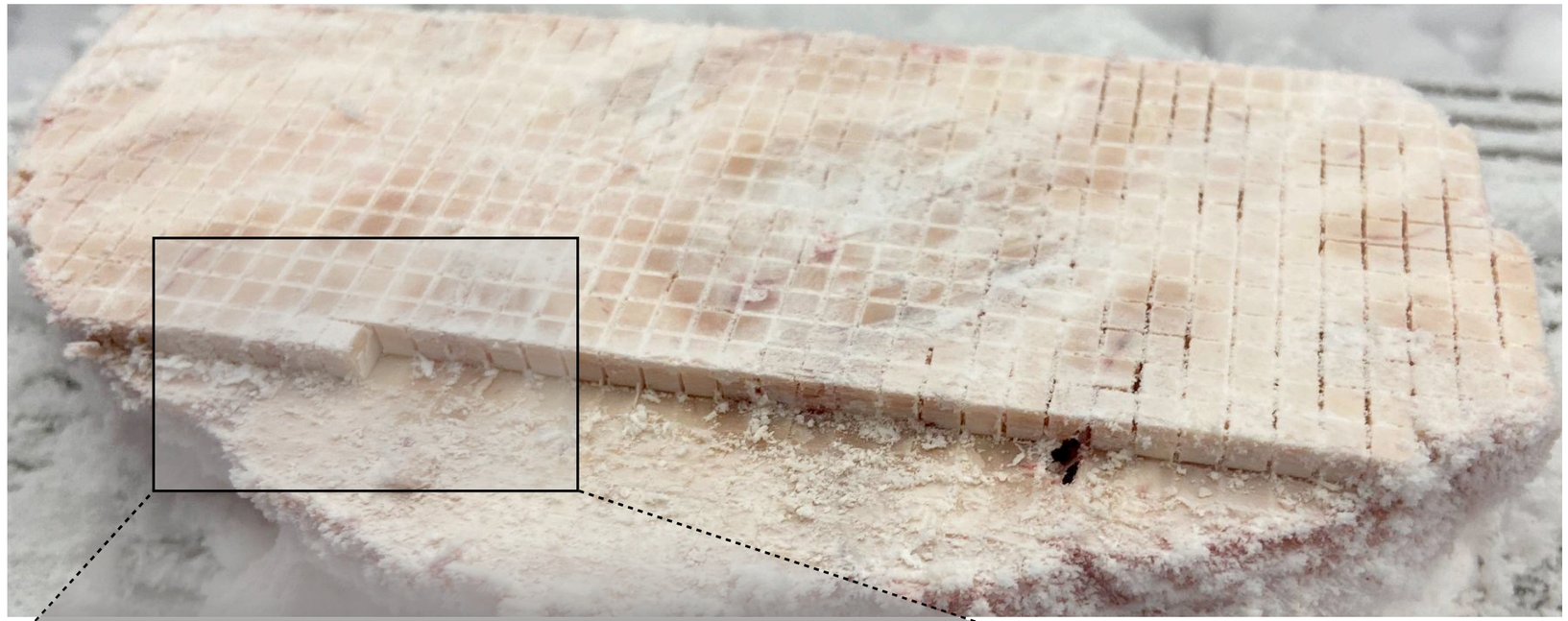
MitoBrainMap v1.0

A multi-function mitochondrial atlas of a single human coronal brain section at fMRI resolution

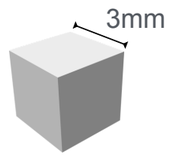




Eugene Mosharov

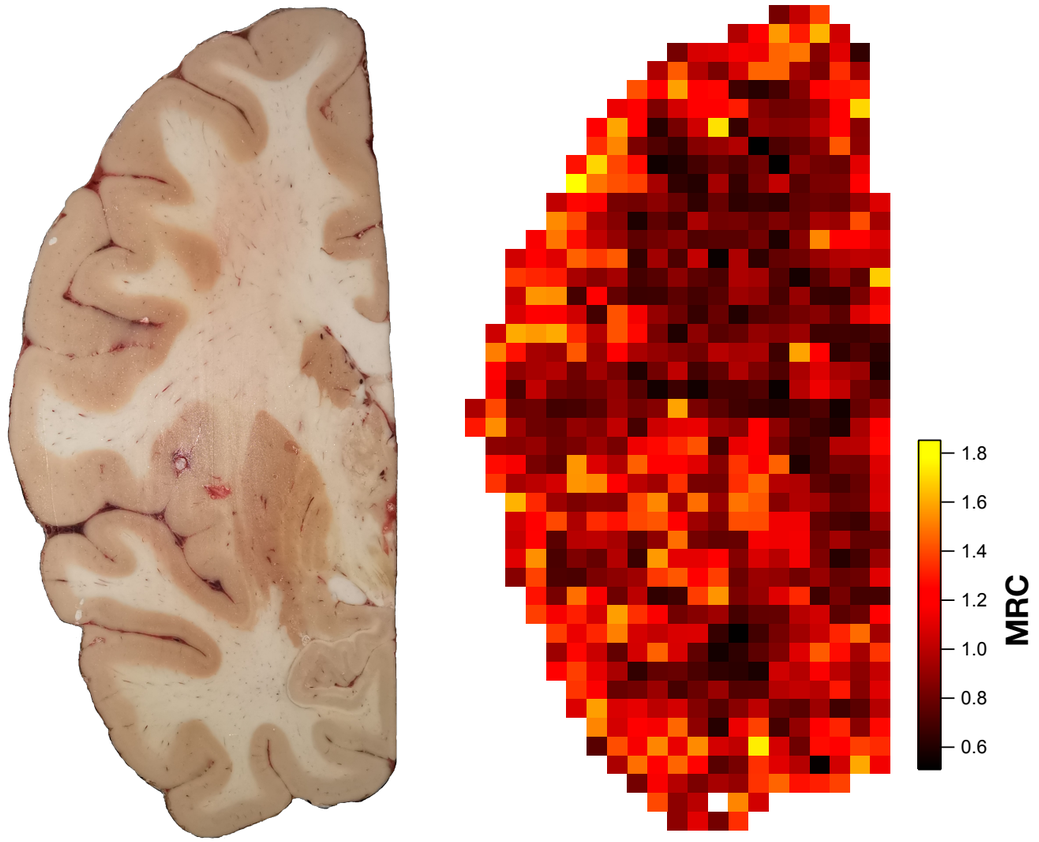


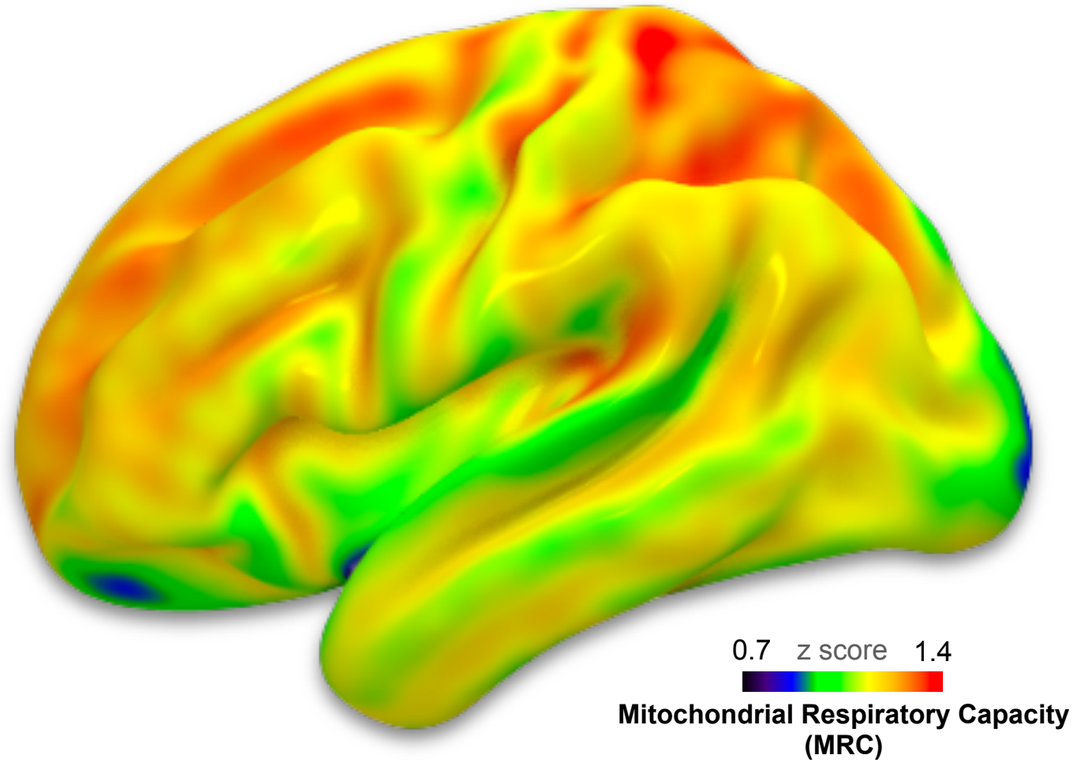
Physical *voxelization*
of the human brain
at fMRI resolution



Article

A human brain map of mitochondrial respiratory capacity and diversity



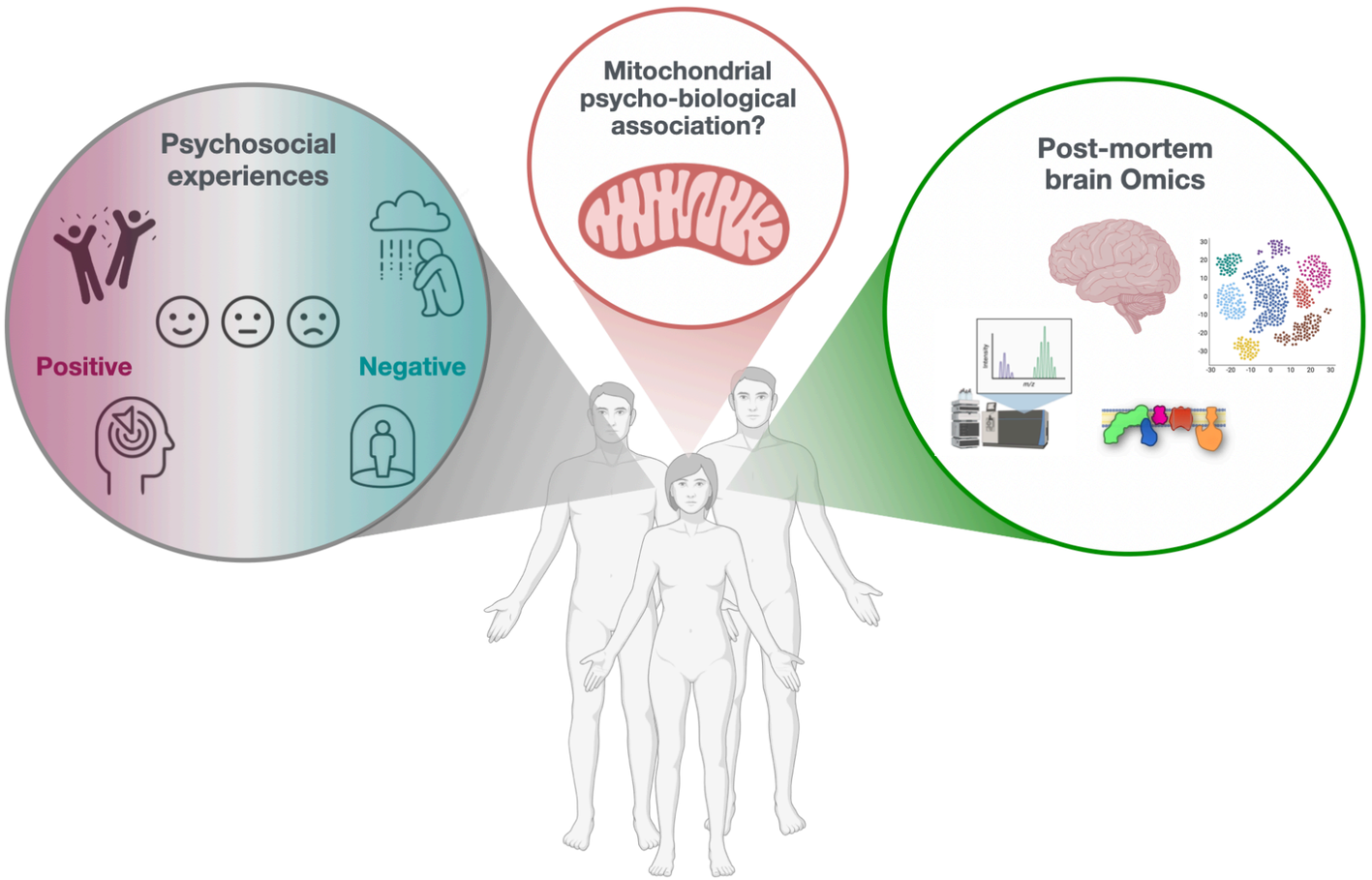


Mosharov et al. *Nature* 2025

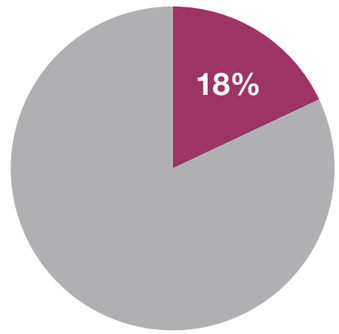
PNAS

RESEARCH ARTICLE | CELL BIOLOGY
PSYCHOLOGICAL AND COGNITIVE SCIENCES

Psychosocial experiences are associated with human brain mitochondrial biology



Variance (r^2) in mitochondrial biology linked to mood



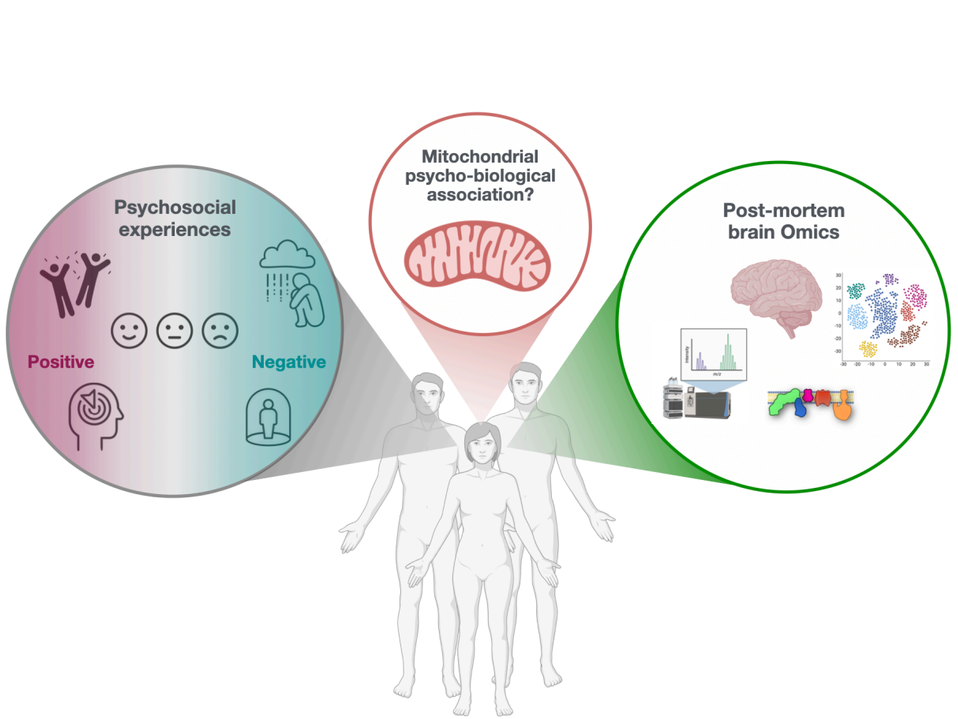
25% in cognitively intact individuals

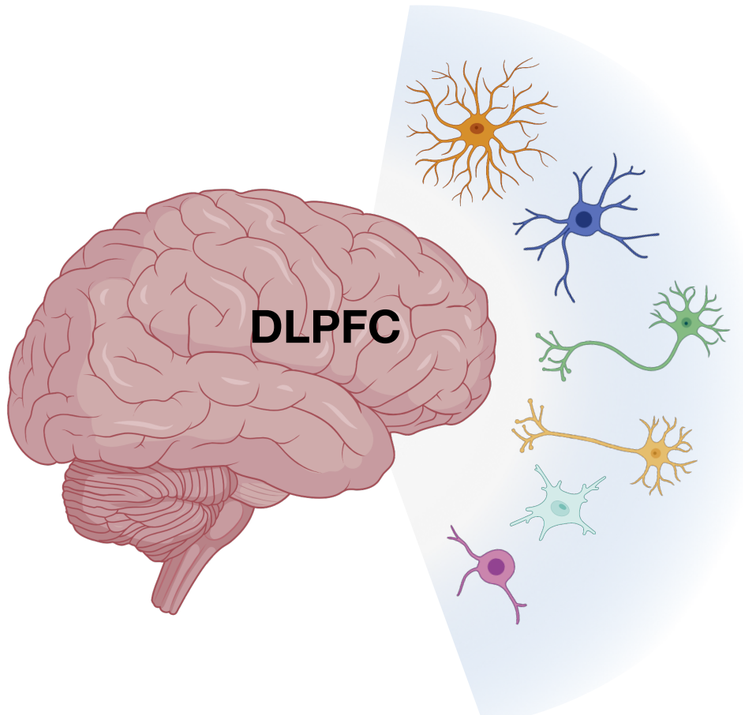
Trumpff et al. *PNAS* 2024

PNAS

RESEARCH ARTICLE | CELL BIOLOGY
PSYCHOLOGICAL AND COGNITIVE SCIENCES

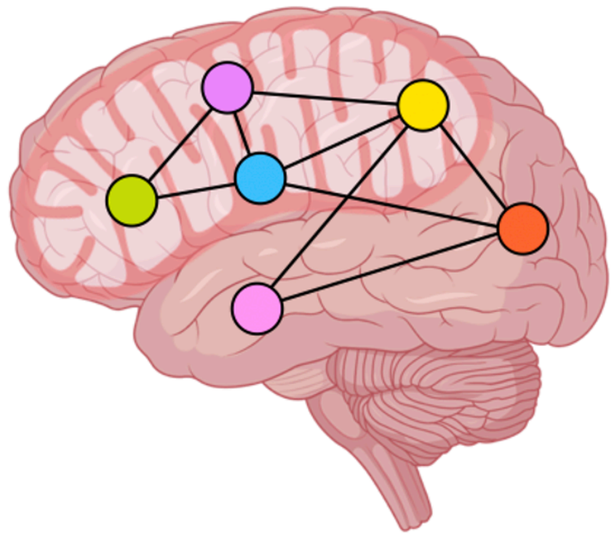
Psychosocial experiences are associated with human brain mitochondrial biology





Glia mitochondria contribute most of the signal

Trumpff et al. *PNAS* 2024

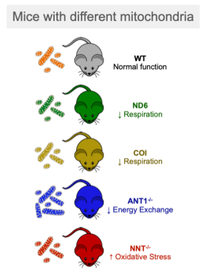


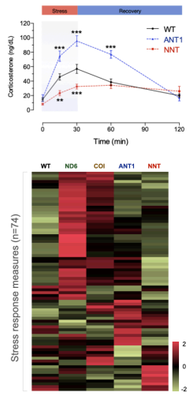
MITO BRAIN

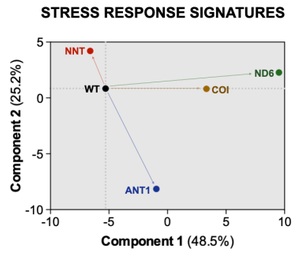
ROSMAP

Cynthia Liu

Is there a Mind ↔ Mitochondria Connection ?



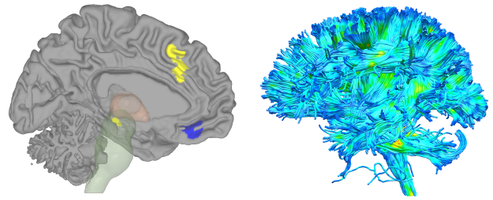




MITOCHONDRIA STRESS BRAIN EPIGENETICS

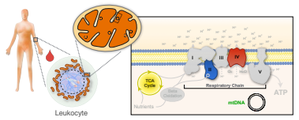
iSBIE

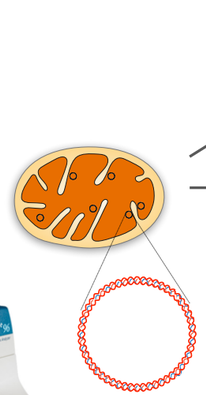
Mitochondrial **S**tress, **B**rain **I**maging, and **E**pigenetics — **MiSBIE**

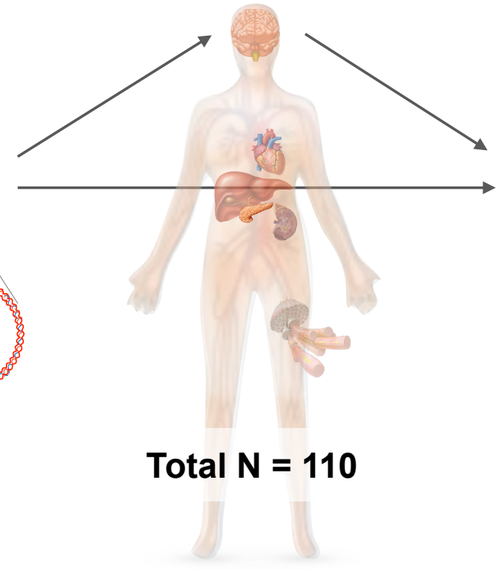


Brain structure and function
Neuropsychological function

mtDNA heteroplasmy
Mitochondrial OxPhos
Lymphocytes, Monocytes,
Neutrophils, Platelets



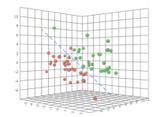


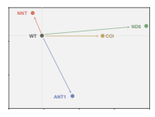


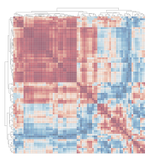
Total N = 110

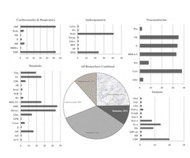
Disease biomarkers
Stress reactivity
Energy expenditure

e.g., Cortisol, NE,
GDF15, Lactate, etc.



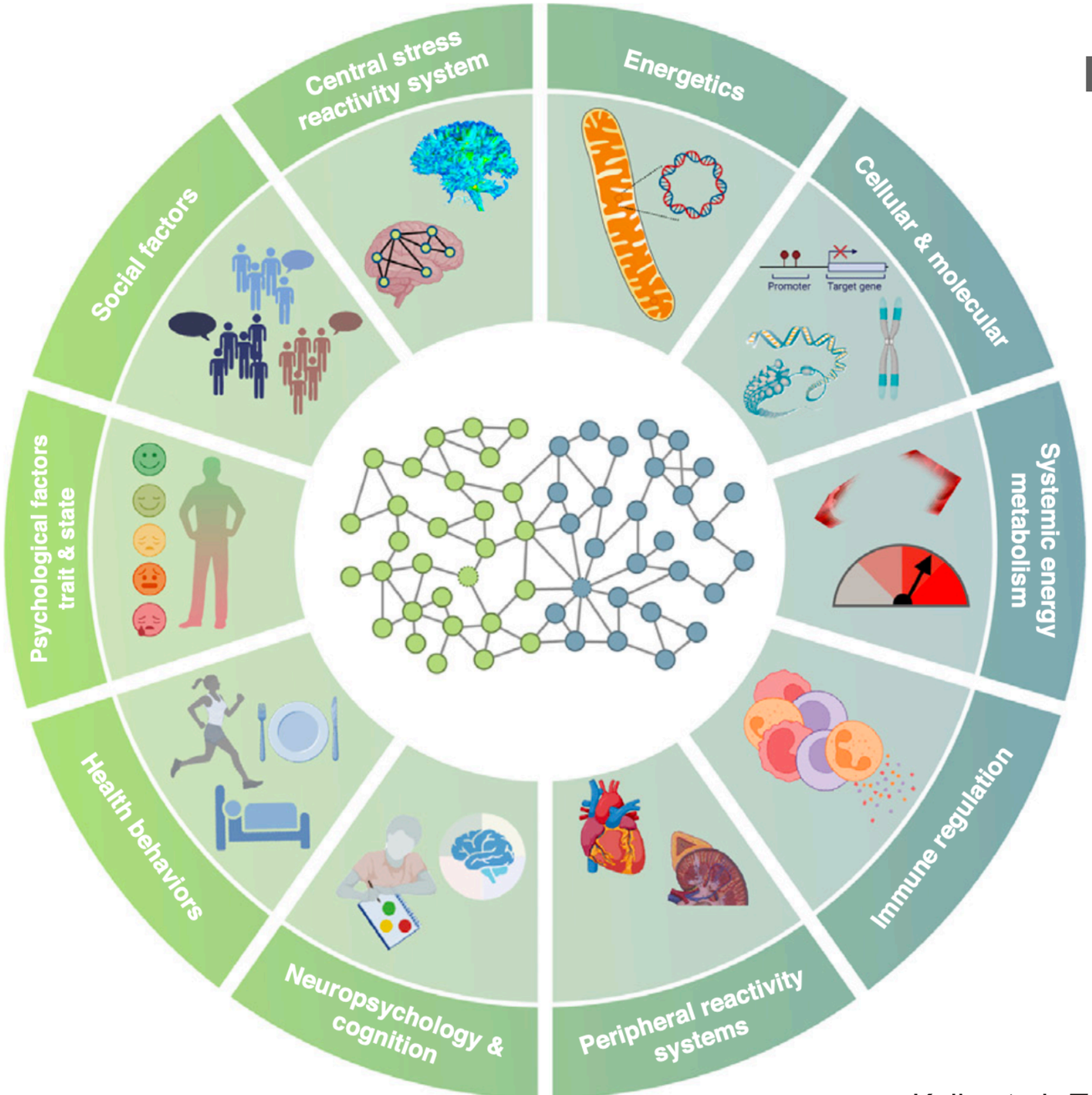




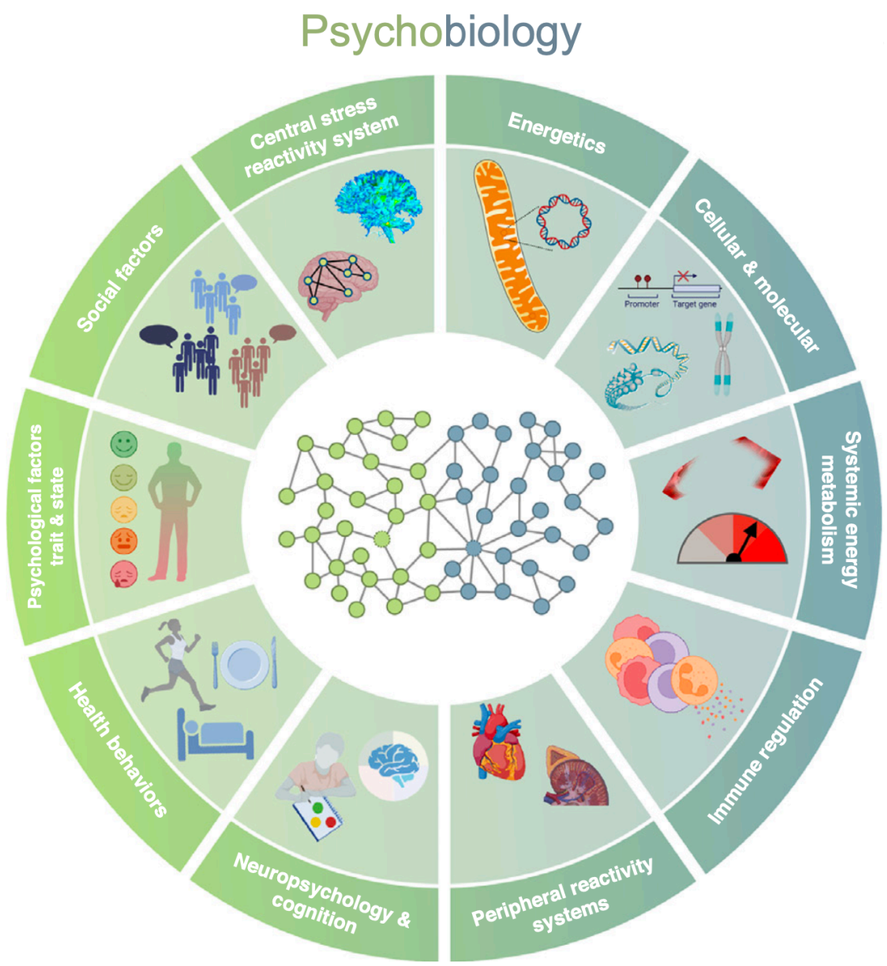


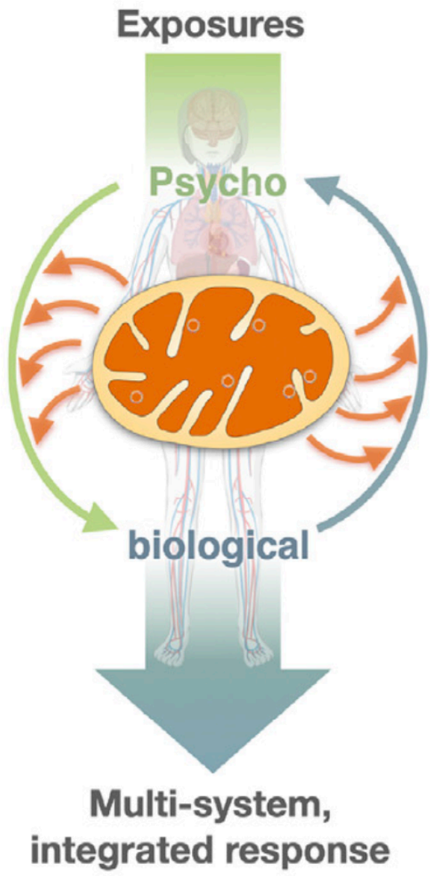
- **Healthy controls** (n = 70)
- **mtDNA defects**
  - **3243A>G (group A)** (n = 20)
  - **3243A>G (group B)** (n = 5)
  - **Single deletion** (n = 15)

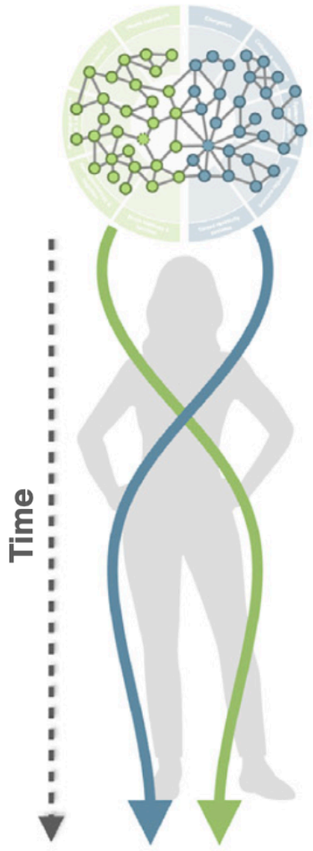
Hallmarks of Psychobiology

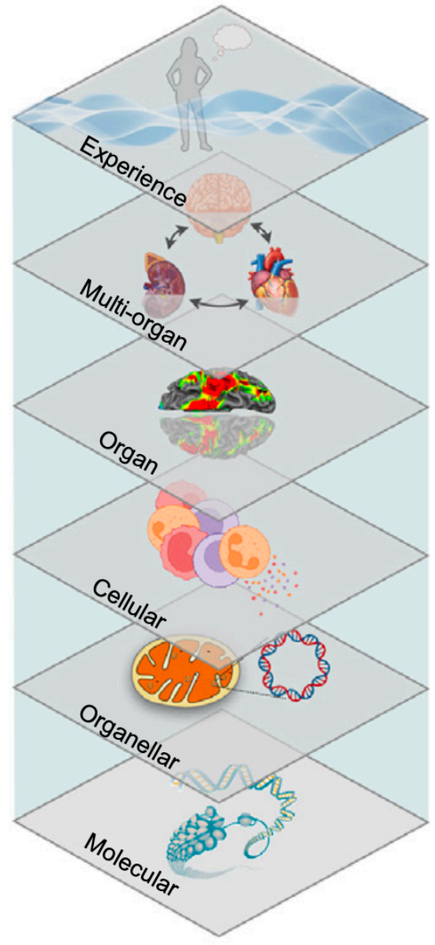


Kelly et al. *Trends Endocrinol Metab* 2024









Kelly et al. *Trends Endocrinol Metab* 2024

How does the brain know that, somewhere in the body, energy is **consumed unsustainably** ?

Nociception

Interoception

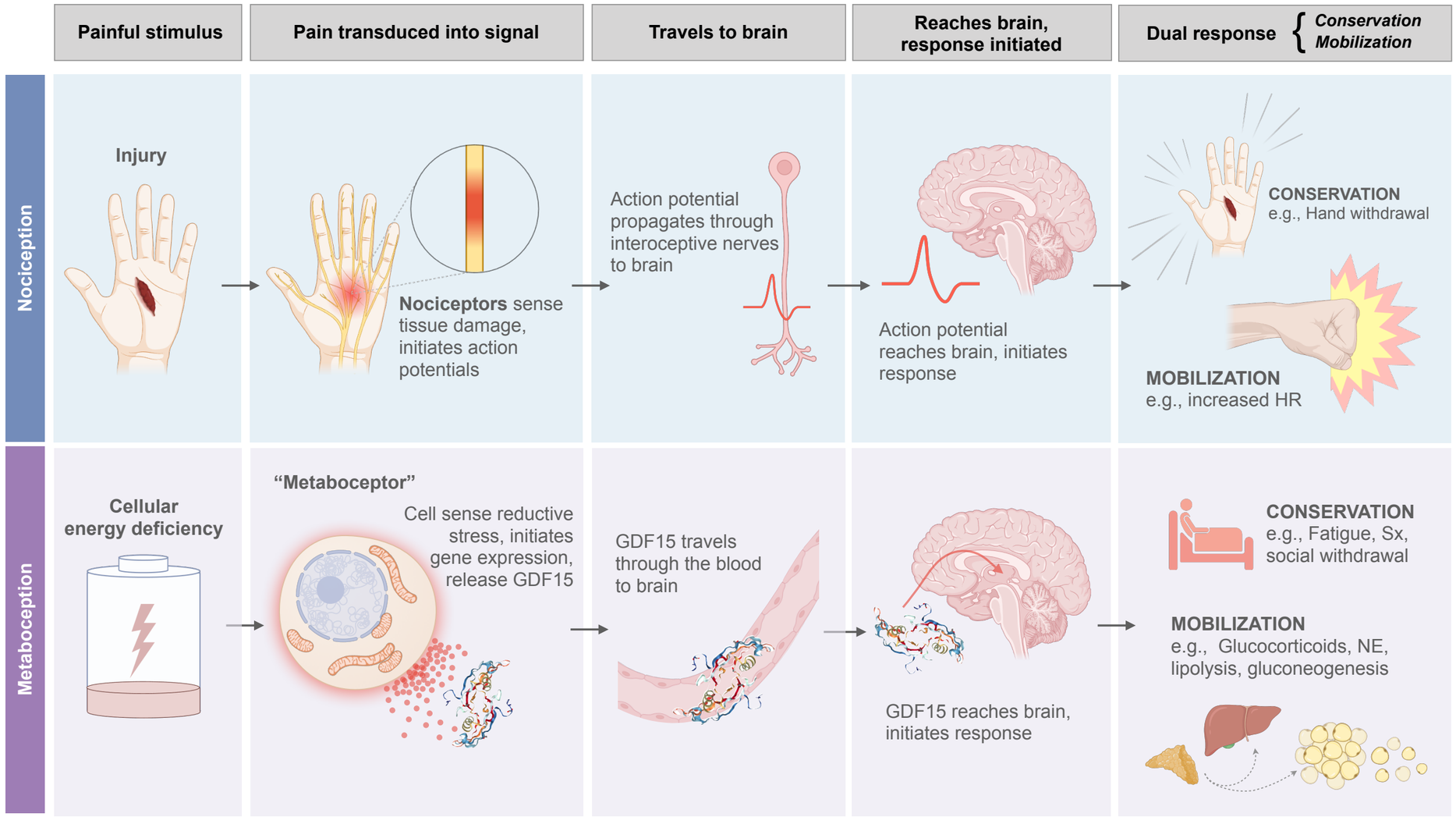
Immunoception (*Neuron* 2022)

Metaboception

The brain's bidirectional monitoring and control of energy metabolism

Liu et al. (under review)

Metaboception: sensing "energetic pain"



Liu et al. (under review)

GDF15 TRIGGERS

Increased energy demand beyond what is sustainable by cellular energy transformation capacity

ISR activation
GDF15 expression and signaling on the brain

Tissue injury

Toxins

Mitochondrial OxPhos defects

Cellular differentiation

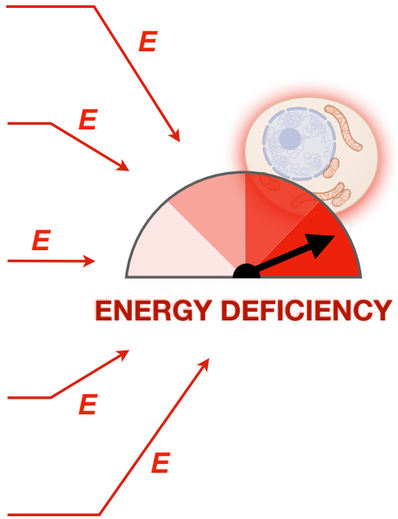
Cellular hyperproliferation (cancer, immune)

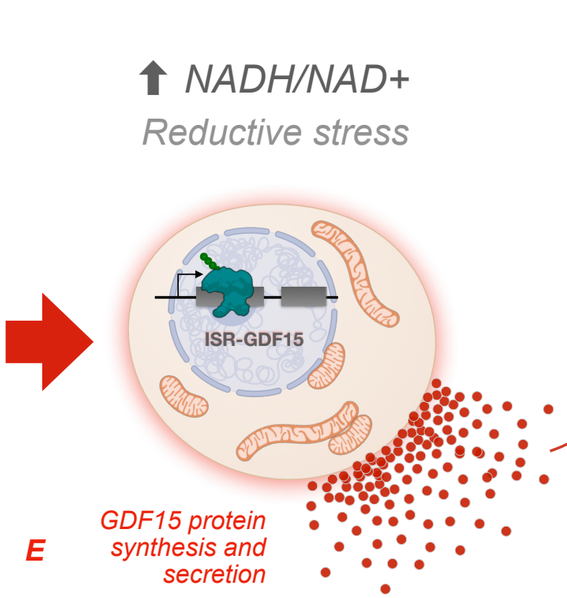
Senescence

Pregnancy

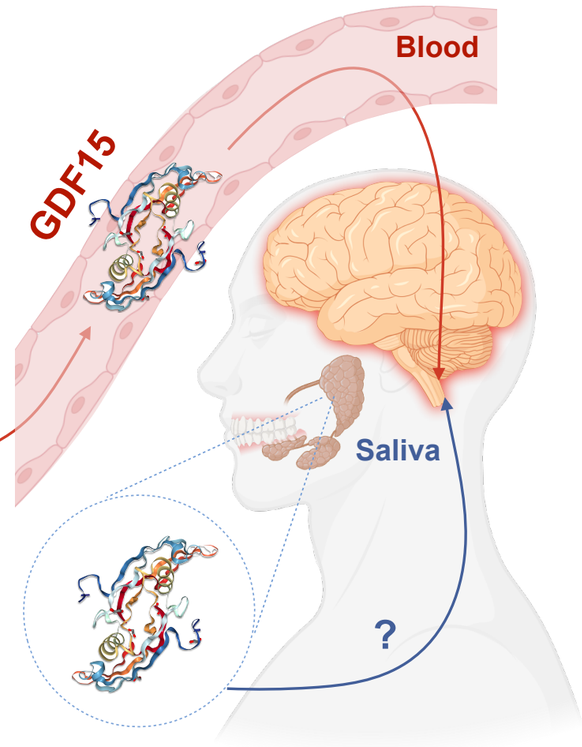
Costly cellular processes:

- Gene expression
- Protein synthesis
- Secretion
- Antioxidant defense
- DNA repair



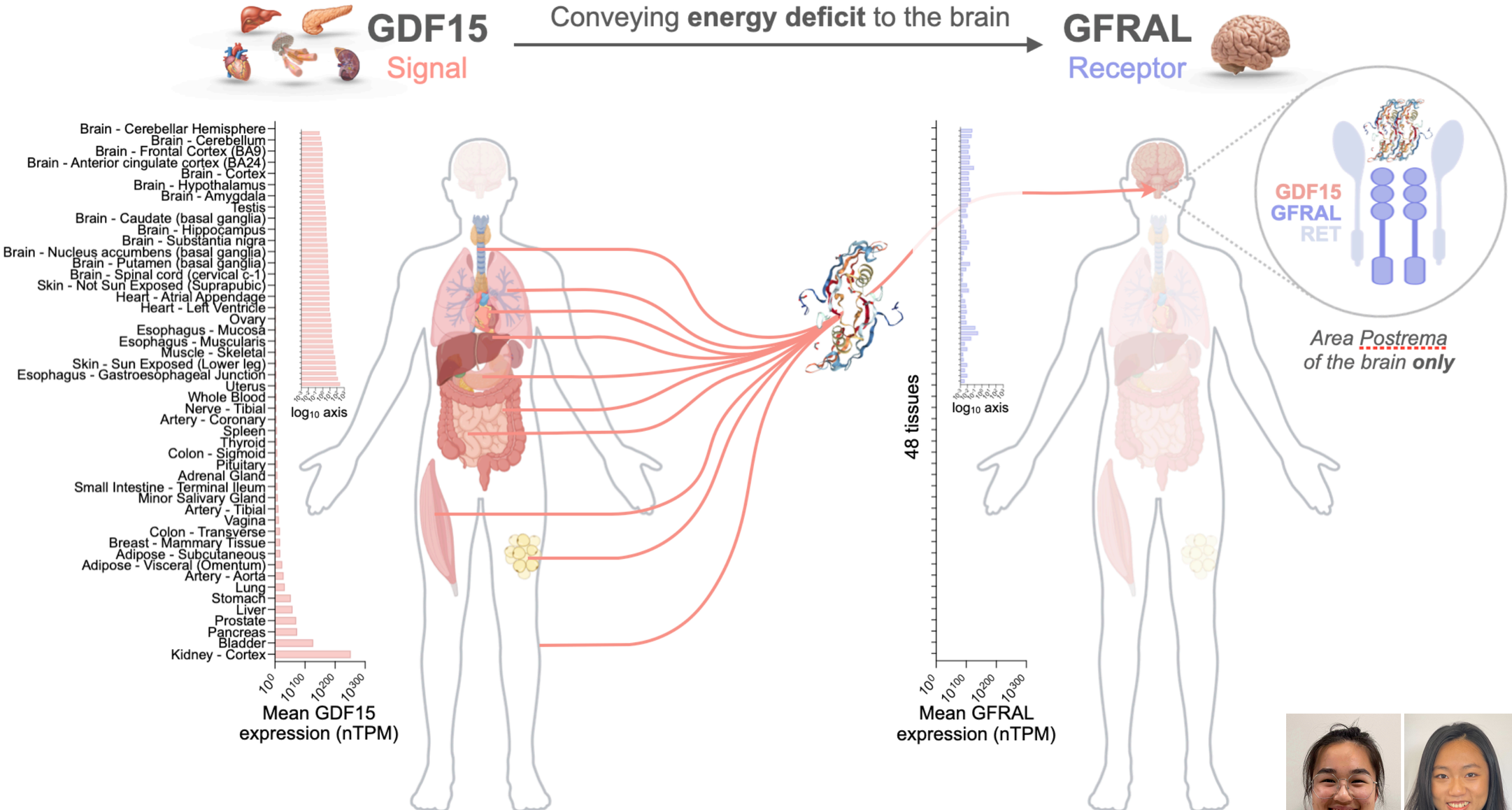


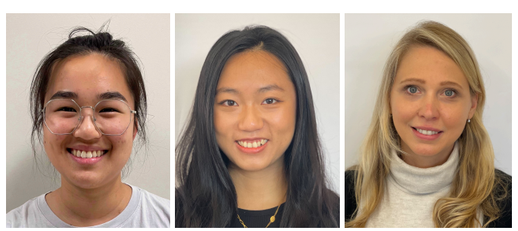
ATF4, ATF5, **DDIT3**
Transcription factors



Other **cytokines**, produced by non-immune tissues, released in response to energetic stress

Liu et al. (under review)



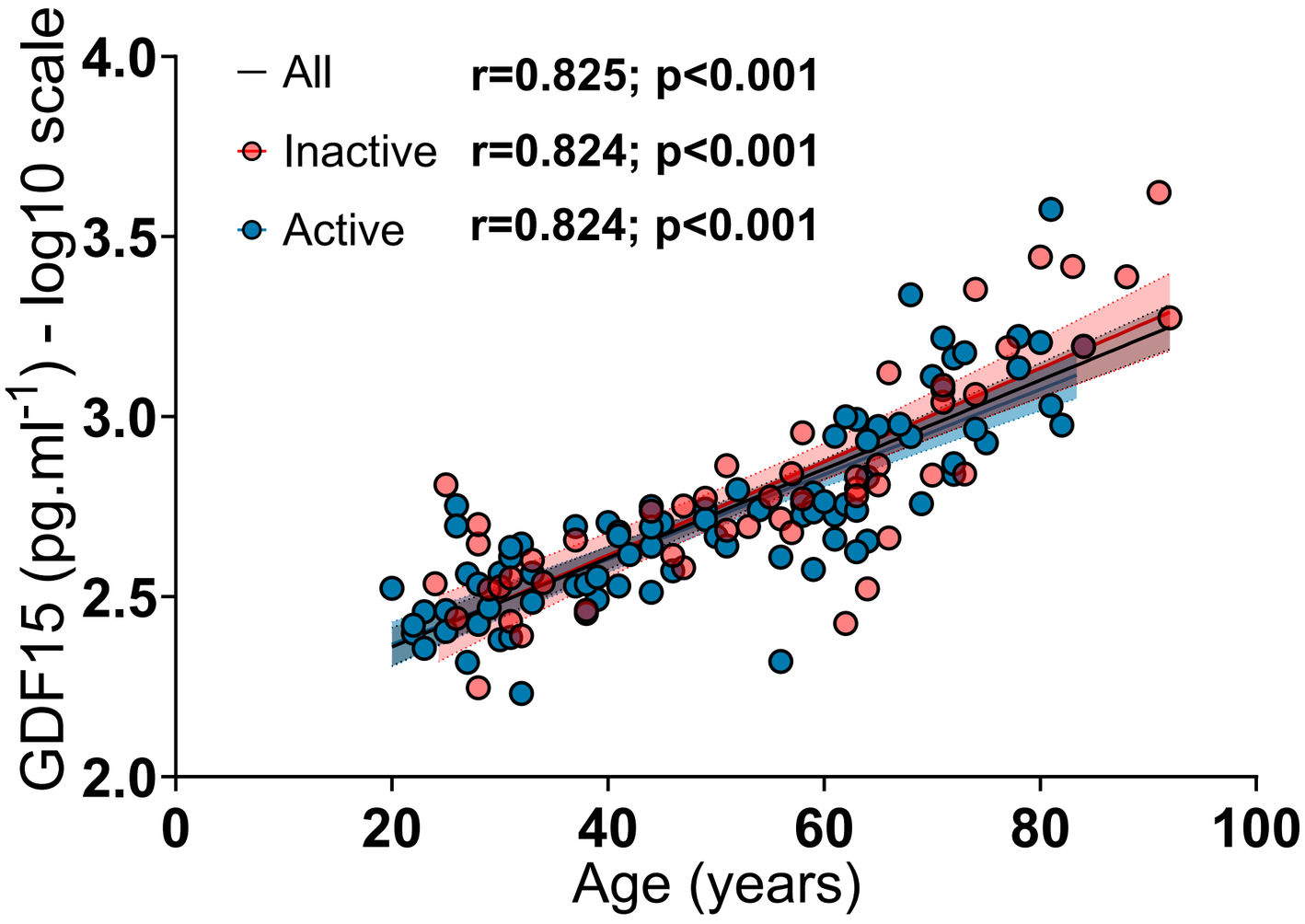


GDF15: Growth differentiation factor 15

Liu, Huang, Trumpff et al. (under review)

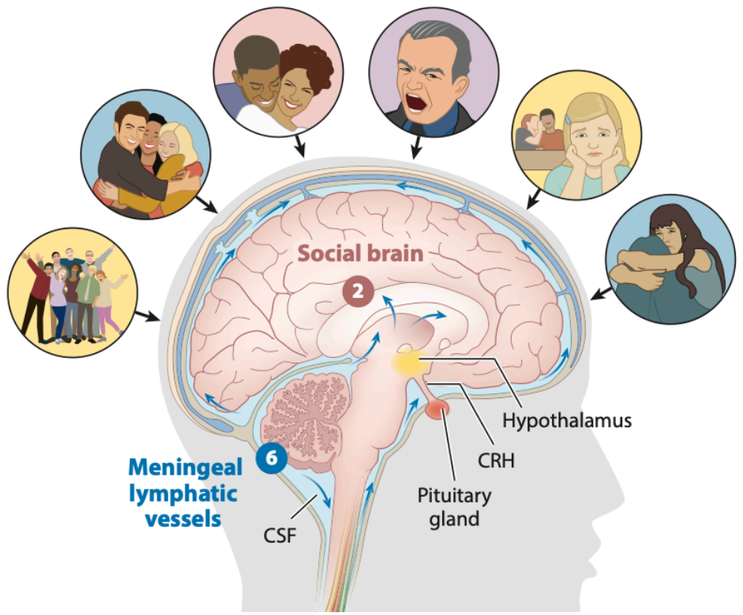
GDF15 across the adult lifespan

“Aging biomarker”



n=139 (51 inactive and 88 active) aged men 20-93

Cefis et al. *Cell Rep Med* 2025



Psychosocial processes influence gene expression (Cole, Slavich)

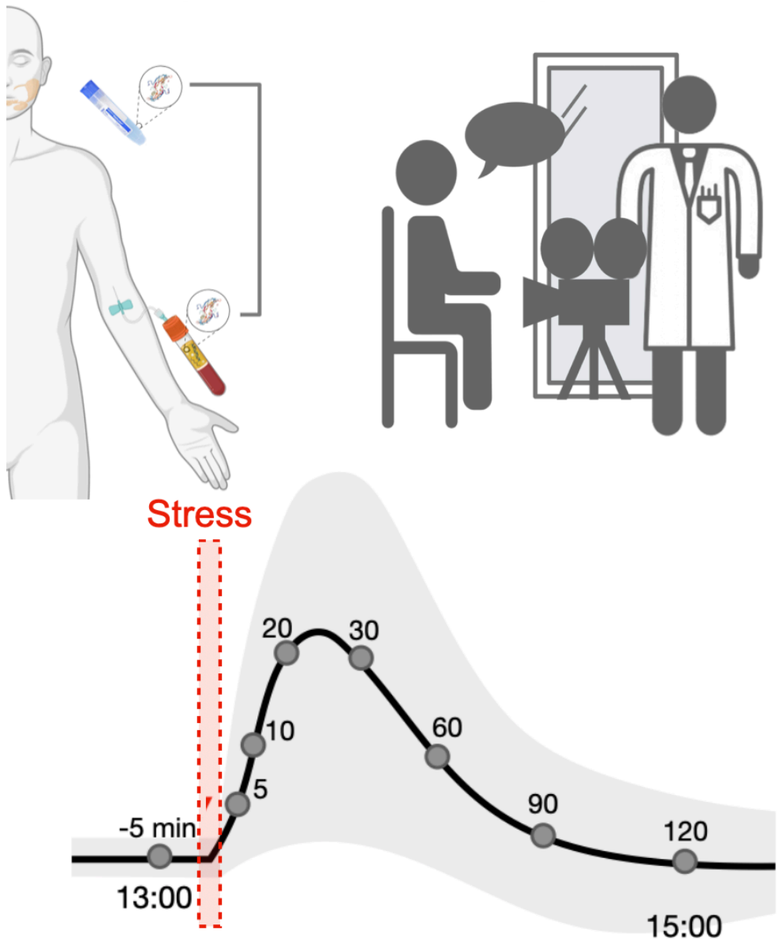
Psychosocial stressors

- ↑ heart rate (E)
- ↑ blood pressure (E)
- ↑ cortisol (E)
- ↑ sweating (E)
- ↑ brain activity (E)
- ↓ digestive activity
- ↑ blood lactate

- **Change in GDF15 ?**

Liu et al. (under review)

Study 1 — one visit
(blood & saliva)



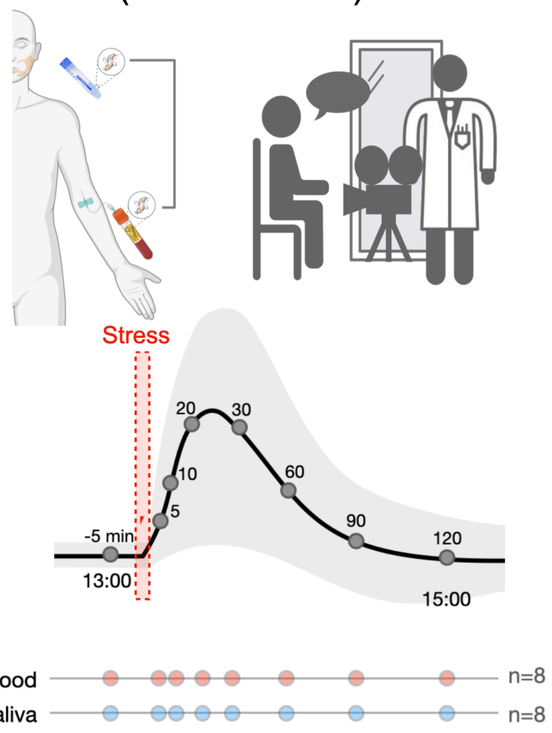
n=70, mean age 38 yo

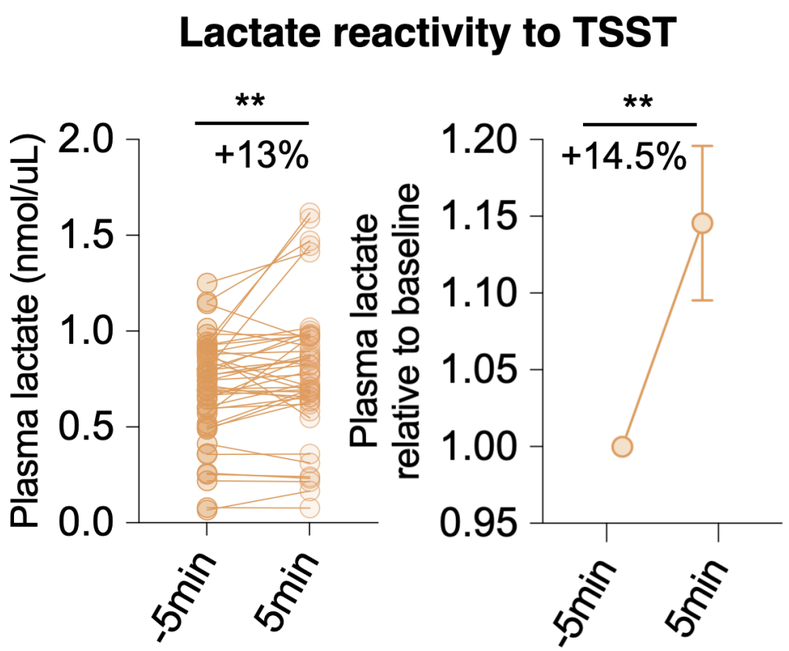
Blood — n=8

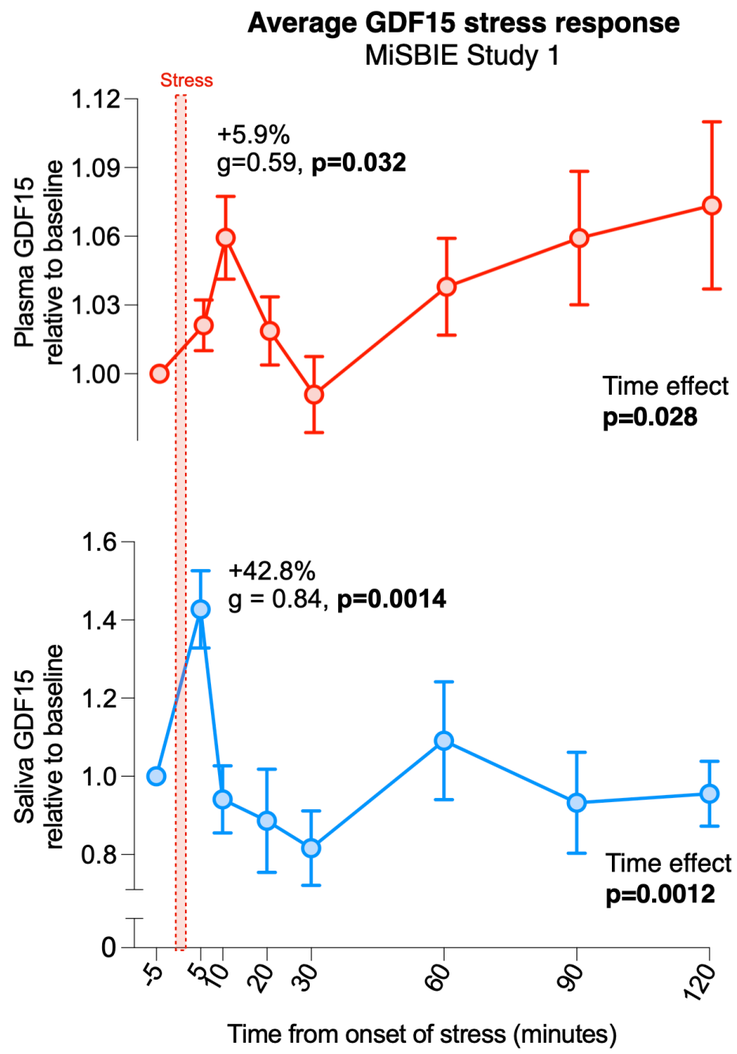
Saliva — n=8

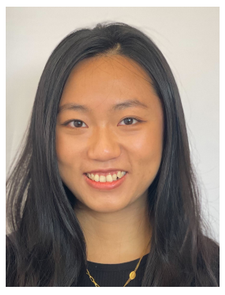
Huang et al. BioRxiv 2024
Liu et al. (under review)

Study 1 — one visit
(blood & saliva)





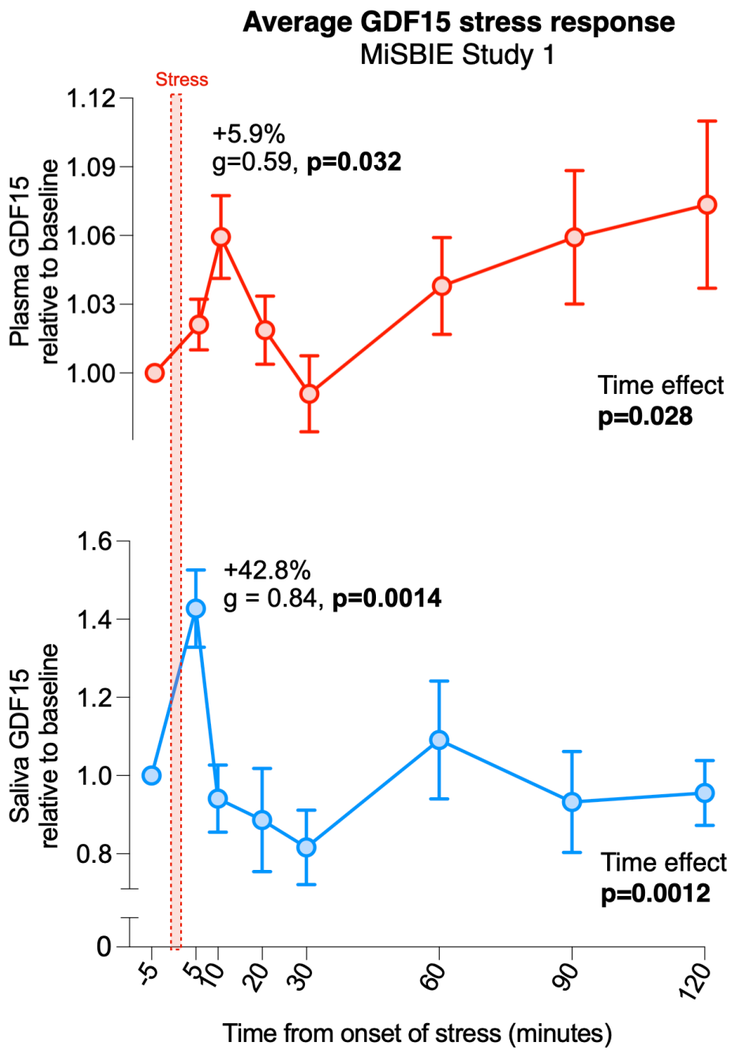


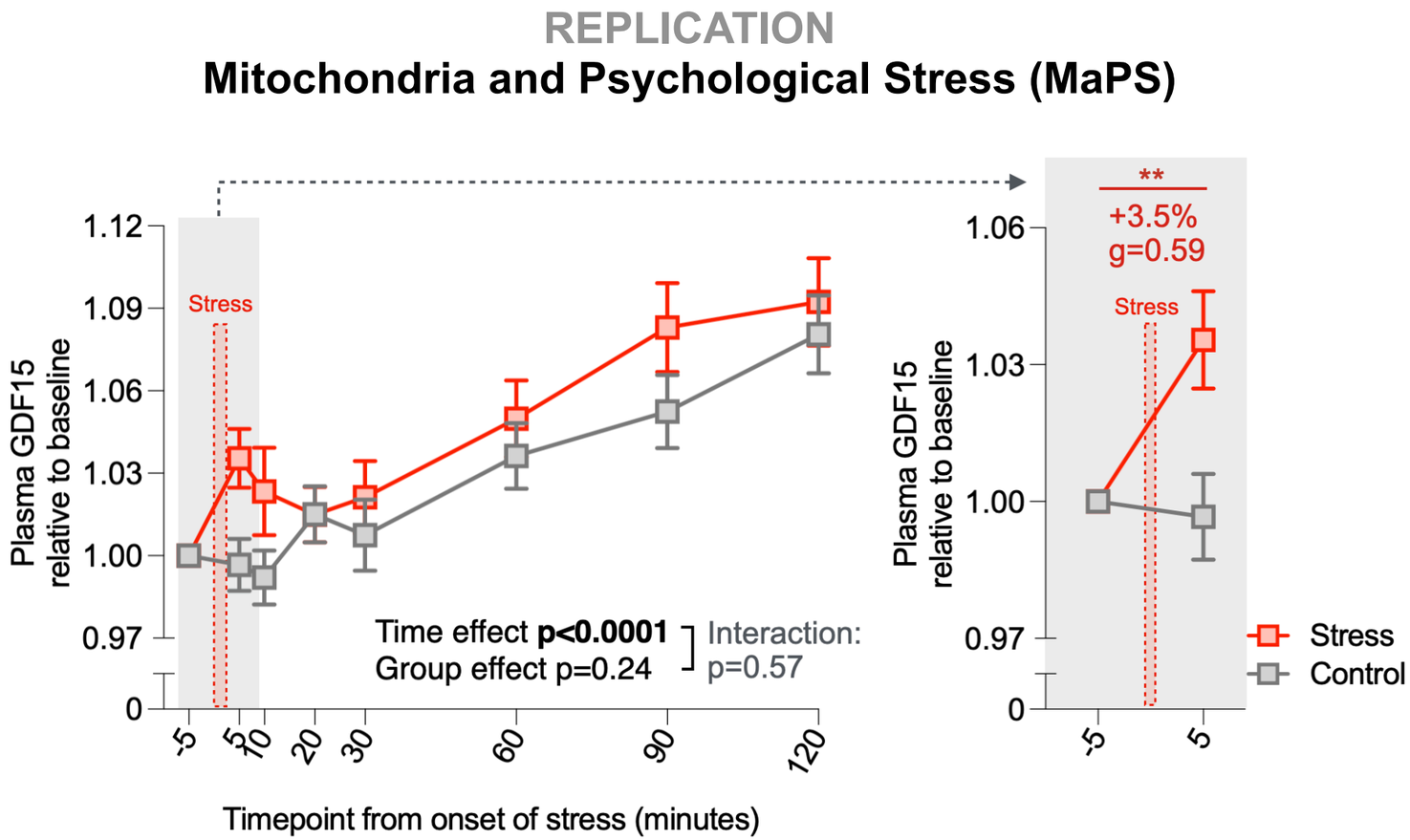


n=70, mean age 38 yo

MITOCHONDRIA STRESS BRAIN EPIGENETICS MiSBIE

Huang et al. BioRxiv 2024
Liu et al. (under review)



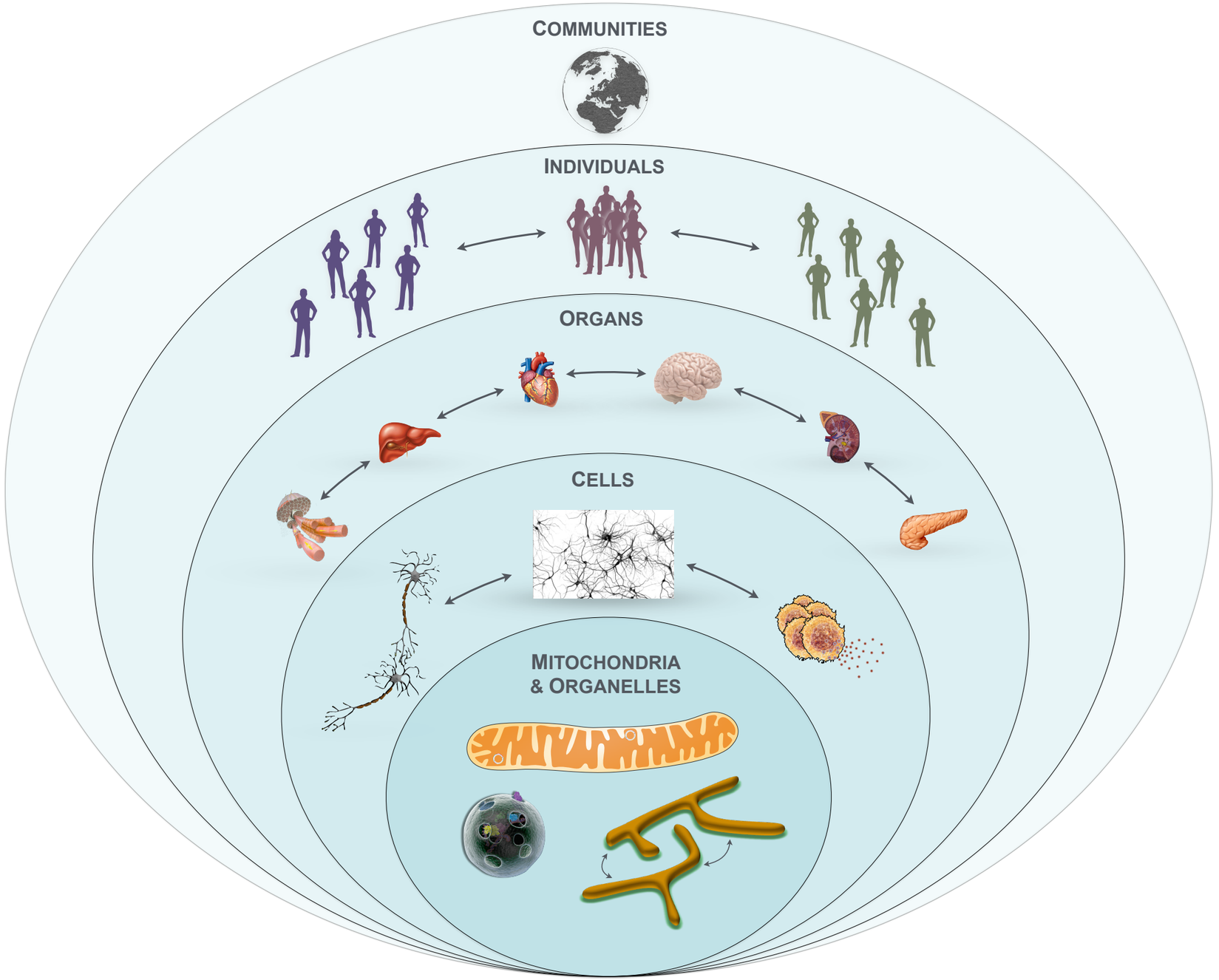


n=70, mean age 38 yo

Acute mental stress acutely increases GDF15

Huang et al. BioRxiv 2024
Liu et al. (under review)

What does **GDF15** mean to the organism?

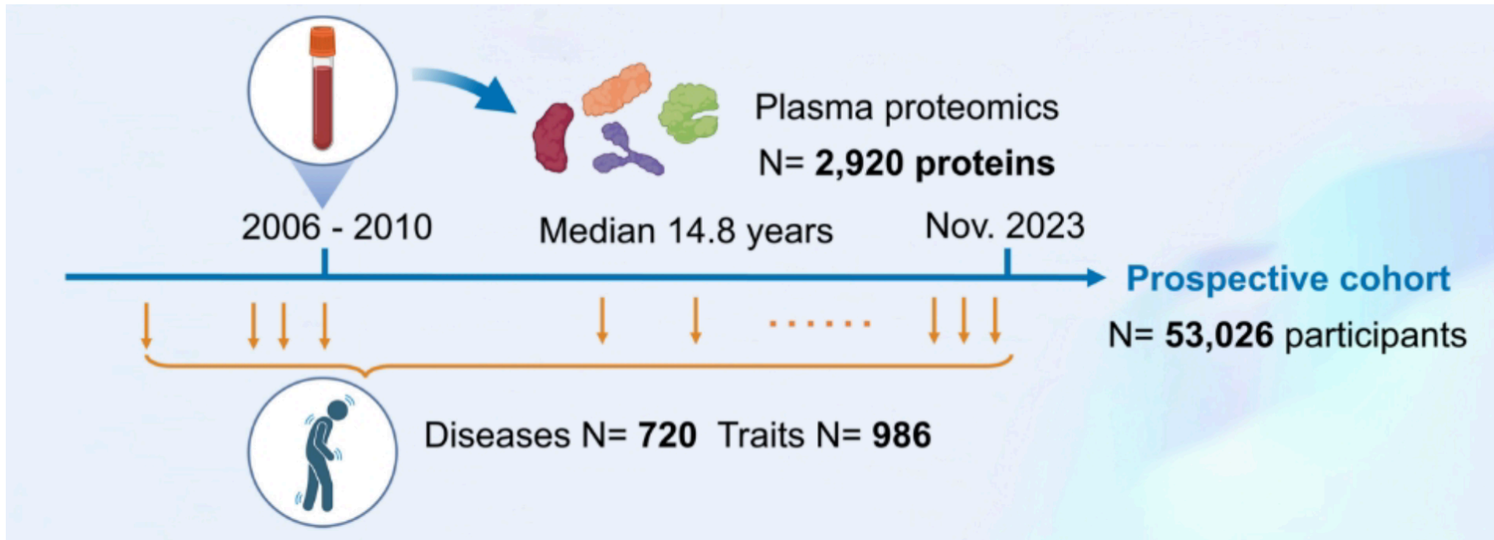

COMMUNITIES
INDIVIDUALS
ORGANS
CELLS
MITOCHONDRIA
& ORGANELLES

What does **Cortisol** mean to the organism?

What does **GDF15** mean to the organism?

What does **GDF15** mean to the organism?

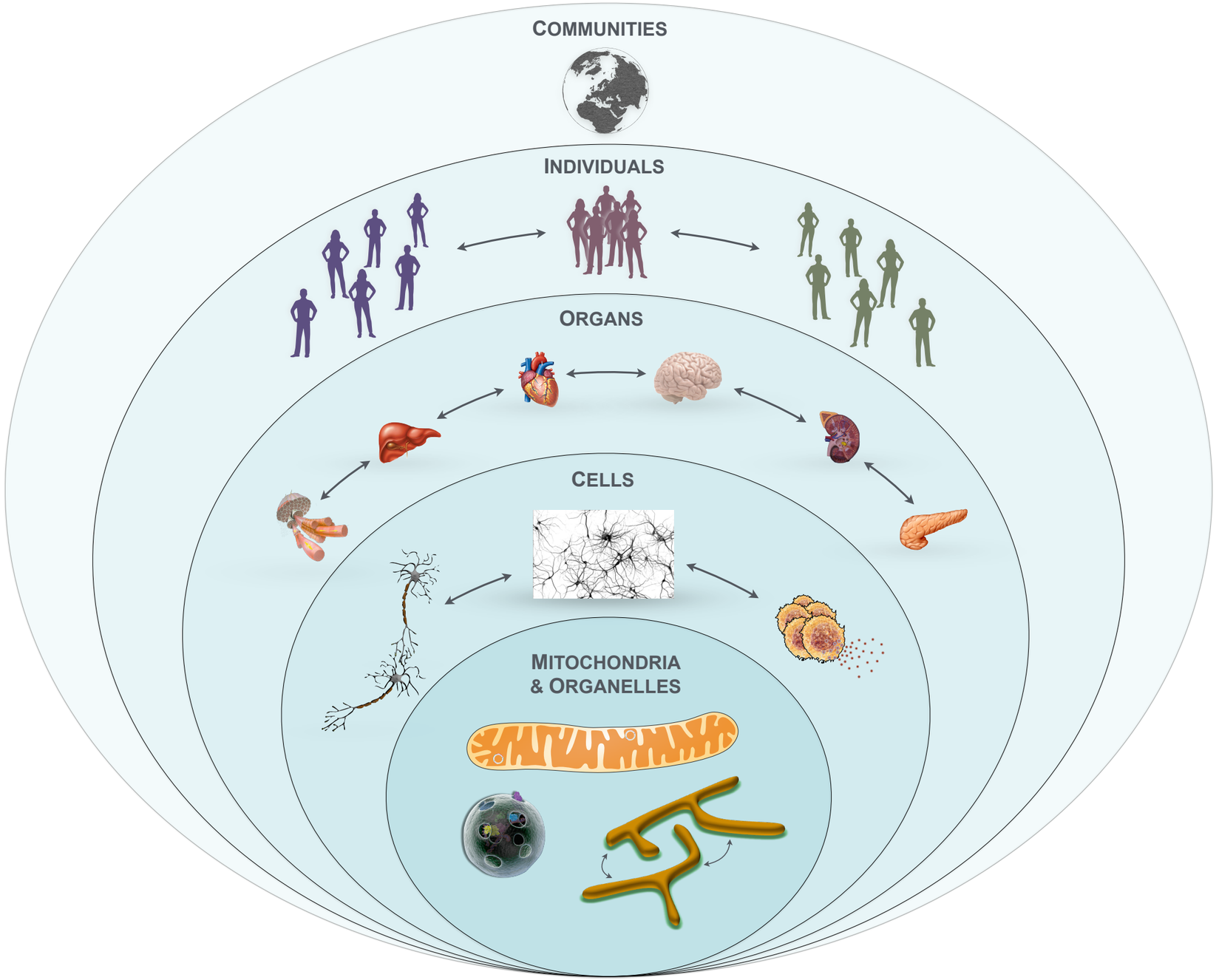
What does it **feel like** to have high GDF15
in your blood ?



GDF15 is associated with …

- Loneliness and social isolation (*Nat Hum Behav* 2025)
- Psychiatric diagnoses (depression, substance abuse)
- Anxiety (*Nat Metab* 2025)
- All-cause mortality
- Not liking to take stairs, or don’t like walking for pleasure
- Fatigue
- Pain
- Other traits consistent with sickness behavior

https://proteome-phenome-atlas.com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Could changing the fuel we feel brain mitochondria change experiences ?

Could changing the fuel we feel brain mitochondria change experiences ?

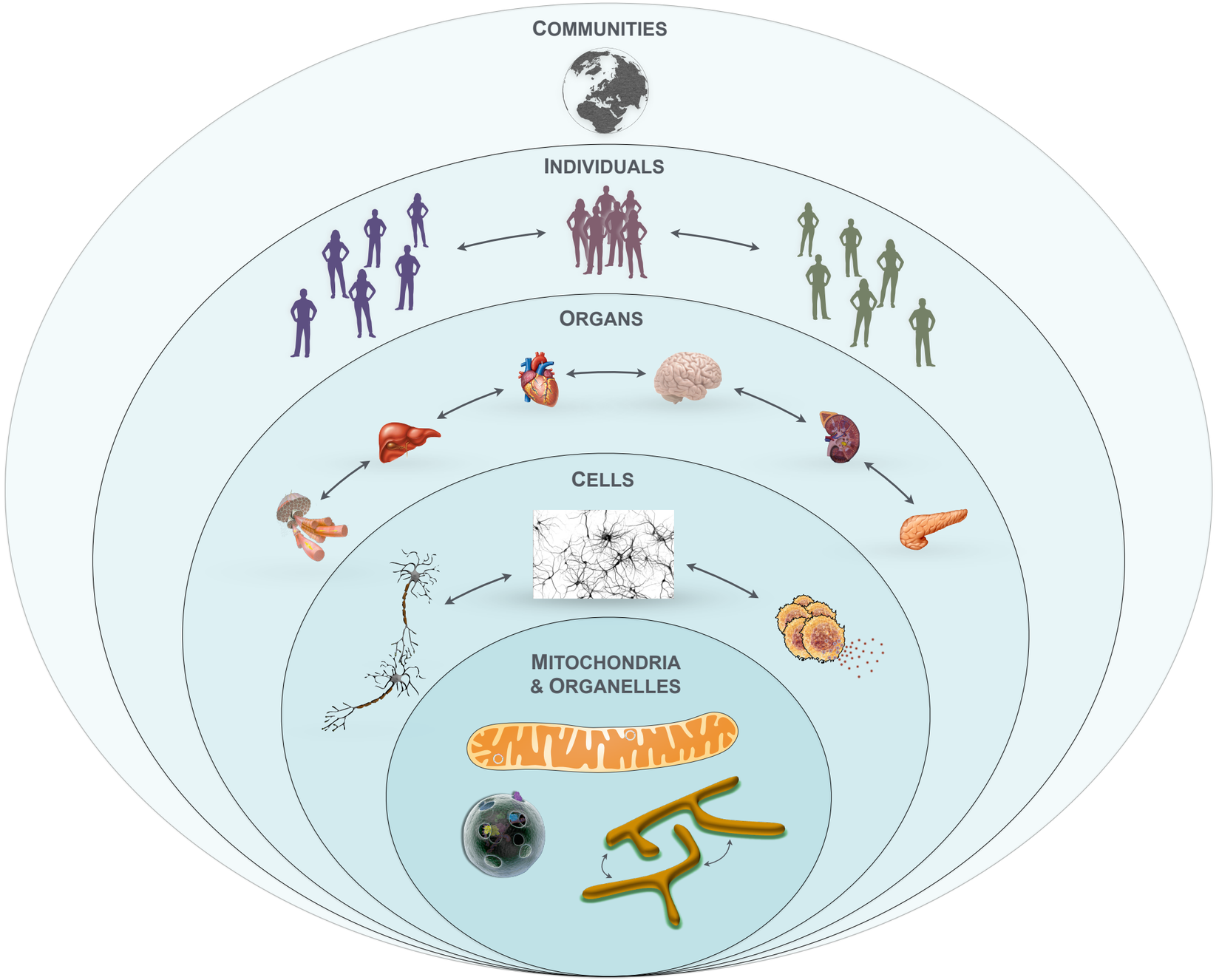
The **ketogenic diet** has been used for 30 years to treat epilepsy

Metabolic Mind + Introduces

THINK + SMART

A Metabolic Framework for Mental Health

Changing Lives with Ketogenic Therapy


COMMUNITIES
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& ORGANELLES

Mitochondrial PsychoBiology Lab

Linking molecular processes within mitochondria with the human experience

OUR RESEARCH

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BASZUCKI BRAIN RESEARCH FUND

The Nathaniel Wharton Fund

NIH National Institute of Mental Health

NIH National Institute of General Medical Sciences

NIH National Institute on Aging