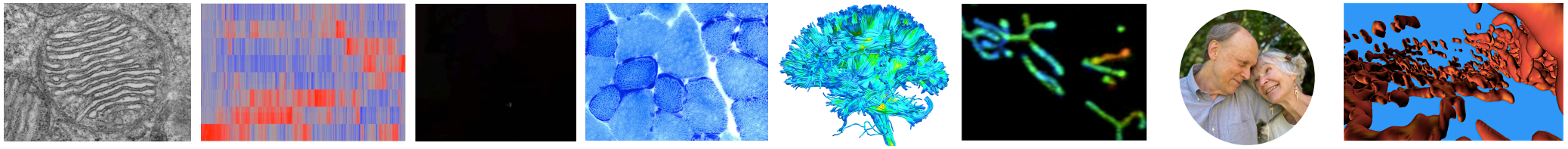
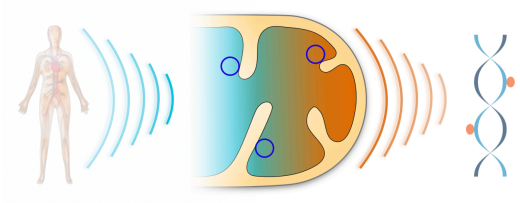


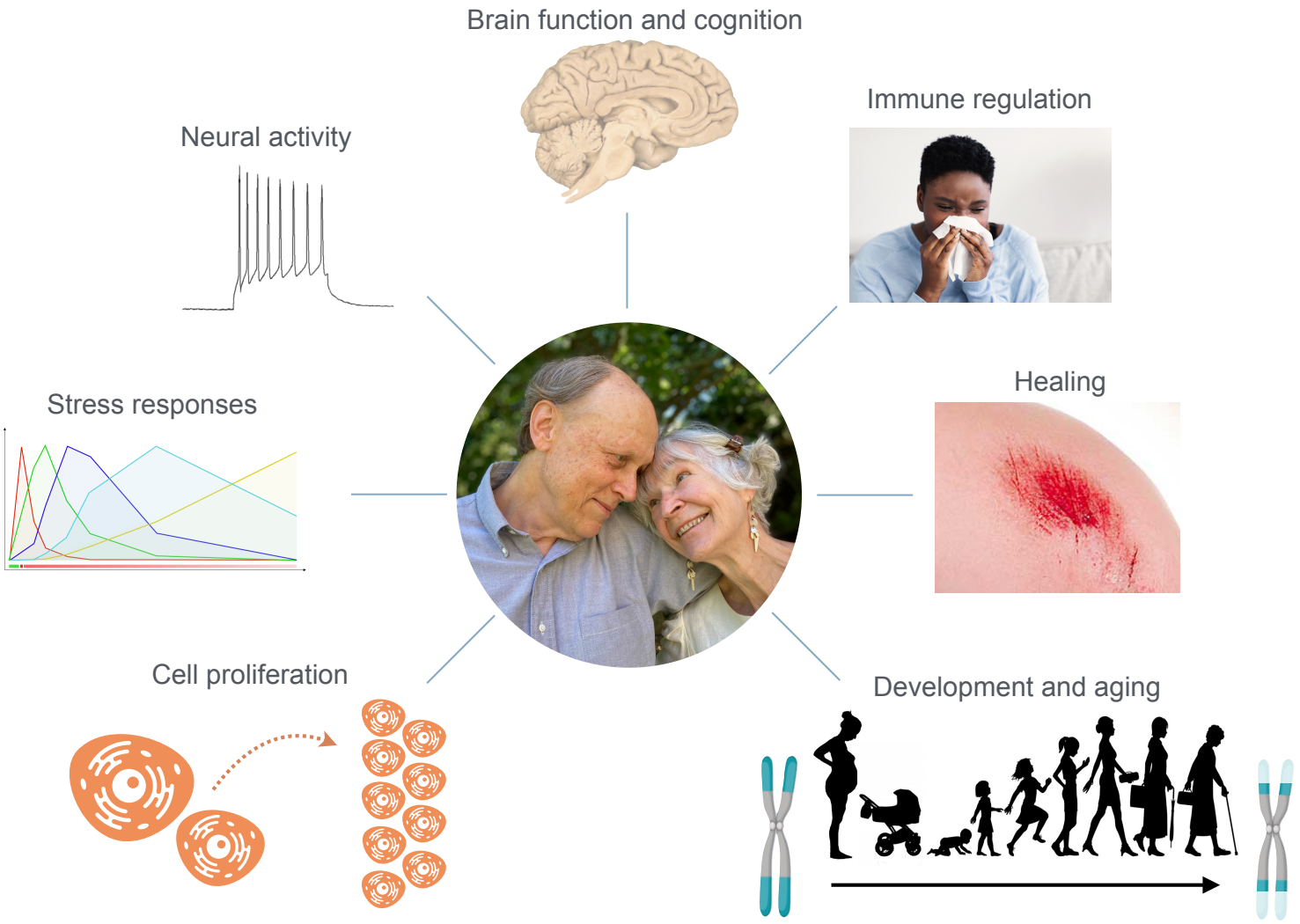
Energetic and Mitochondrial Drivers of Stress responses



Martin Picard, Ph.D.
Department of Psychiatry, Division of Behavioral Medicine
Department of Neurology, H. Houston Merritt Center
Robert N Butler Columbia Aging Center
New York State Psychiatric Institute (NYSPI)

COLUMBIA
COLUMBIA UNIVERSITY
IRVING MEDICAL CENTER

NEW YORK STATE OF OPPORTUNITY. New York State Psychiatric Institute

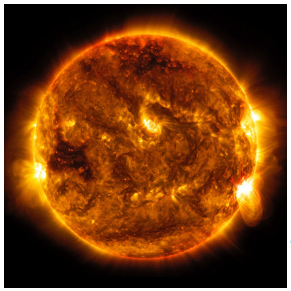


BIOLOGY, PHYSIOLOGY, COGNITION, CONSCIOUSNESS

PSYCHOBIOLOGICAL ALLOSTATIC PROCESSES

RESILIENCE

Biochemistry 2022



Nuclear fusion
Quantum electrodynamics

Photons and heat

Oils and fats, proteins, carbohydrates

CO_2 + H_2O = $C_{17}H_{33}COOH$ + O_2

ENERGY STORED AS CHEMISTRY

Food

O_2

EATING and BREATHING

CO_2 H_2O

'Waste' products

Brain function and cognition

Neural activity

Immune regulation

Stress responses

Healing

Cell proliferation

Development and aging

ENERGY
+ Body heat

Electricity and Chemiosmosis
$\Delta\Psi m + \Delta pH$

Protons (H+)

Electrons

TCA Cycle

Beta Oxidation

Carbon substrates

Electron transport chain

O_2 H_2O

ATP

mtDNA

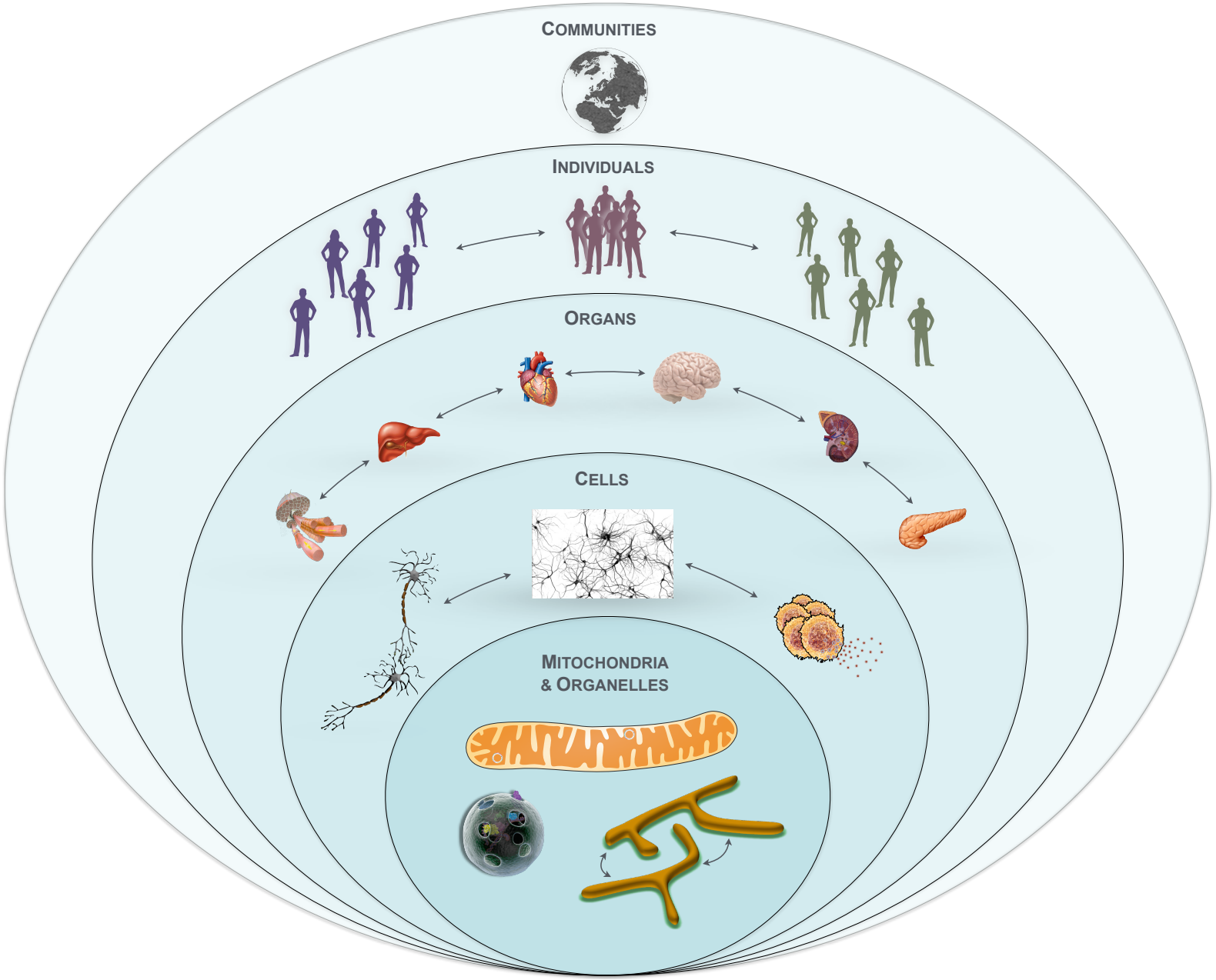
CHEMICAL ENERGY TRANSFORMED INTO ELECTROCHEMICAL FORCE

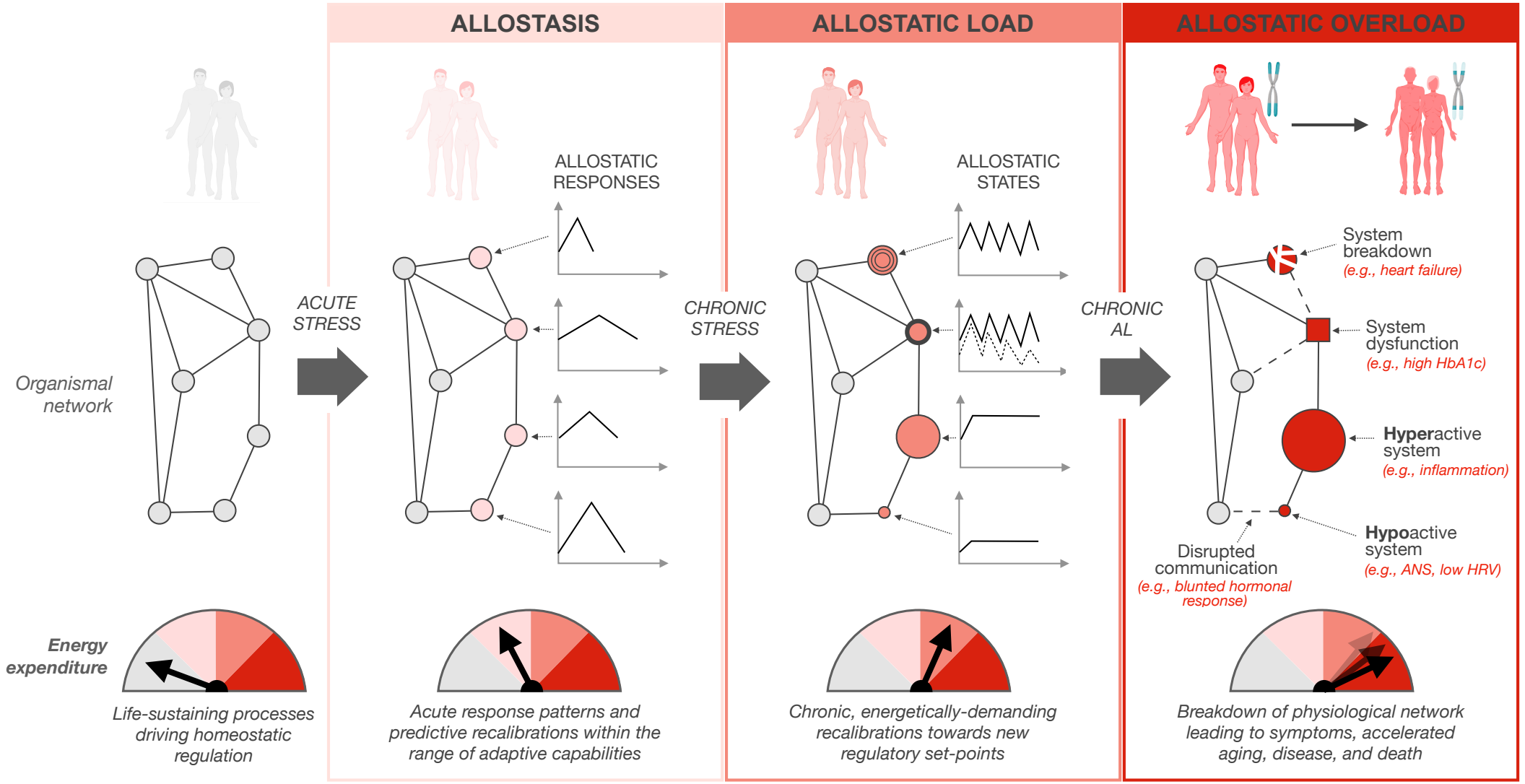
BIOLOGY, PHYSIOLOGY, COGNITION, CONSCIOUSNESS
PSYCHOBIOLOGICAL ALLOSTATIC PROCESSES

RESILIENCE

Biochemistry 2022

How much energy do stress responses cost ?





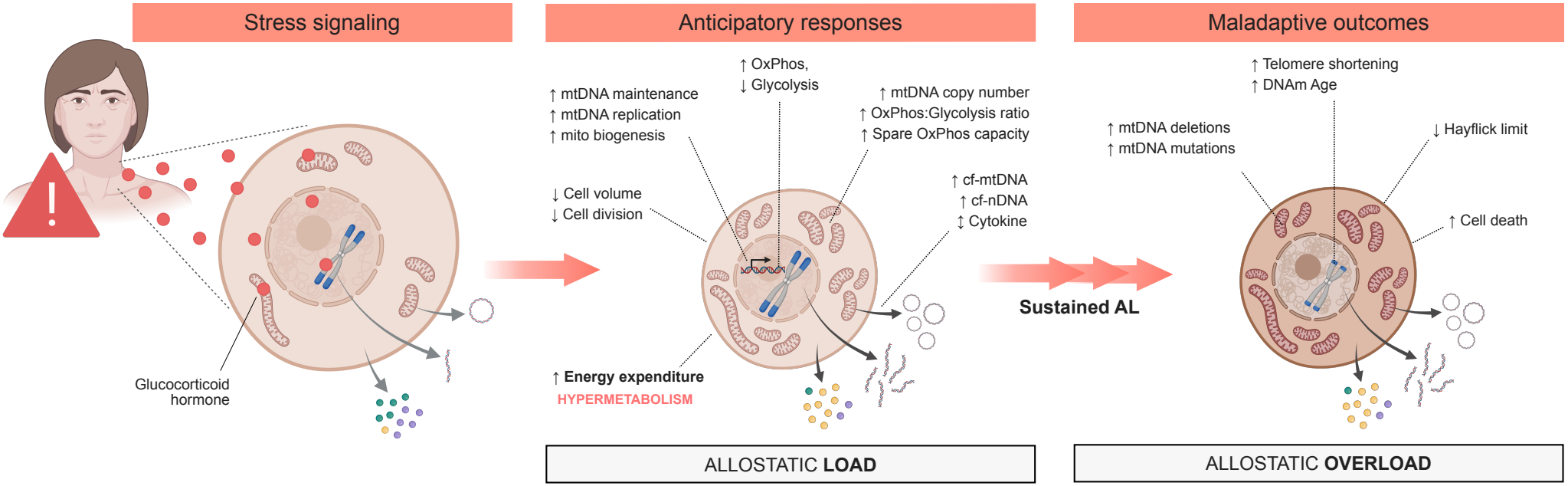
Bobba-Alves, Juster, Picard. *Psychoneuroendocrinol* 2022

Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen

Cellular allostatic load is linked to increased energy expenditure and accelerated biological aging

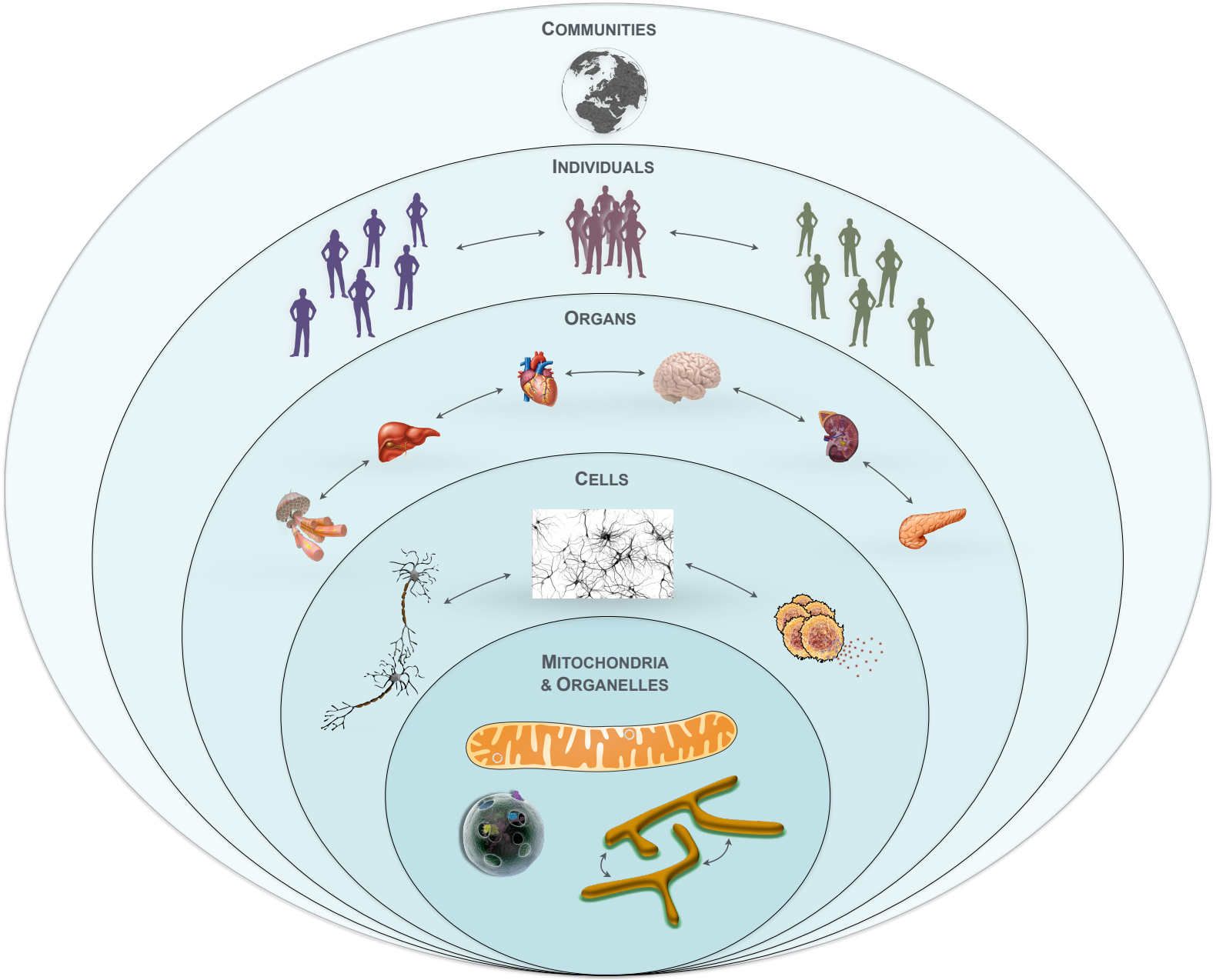


Glucocorticoid signaling increases energy expenditure by **60%**

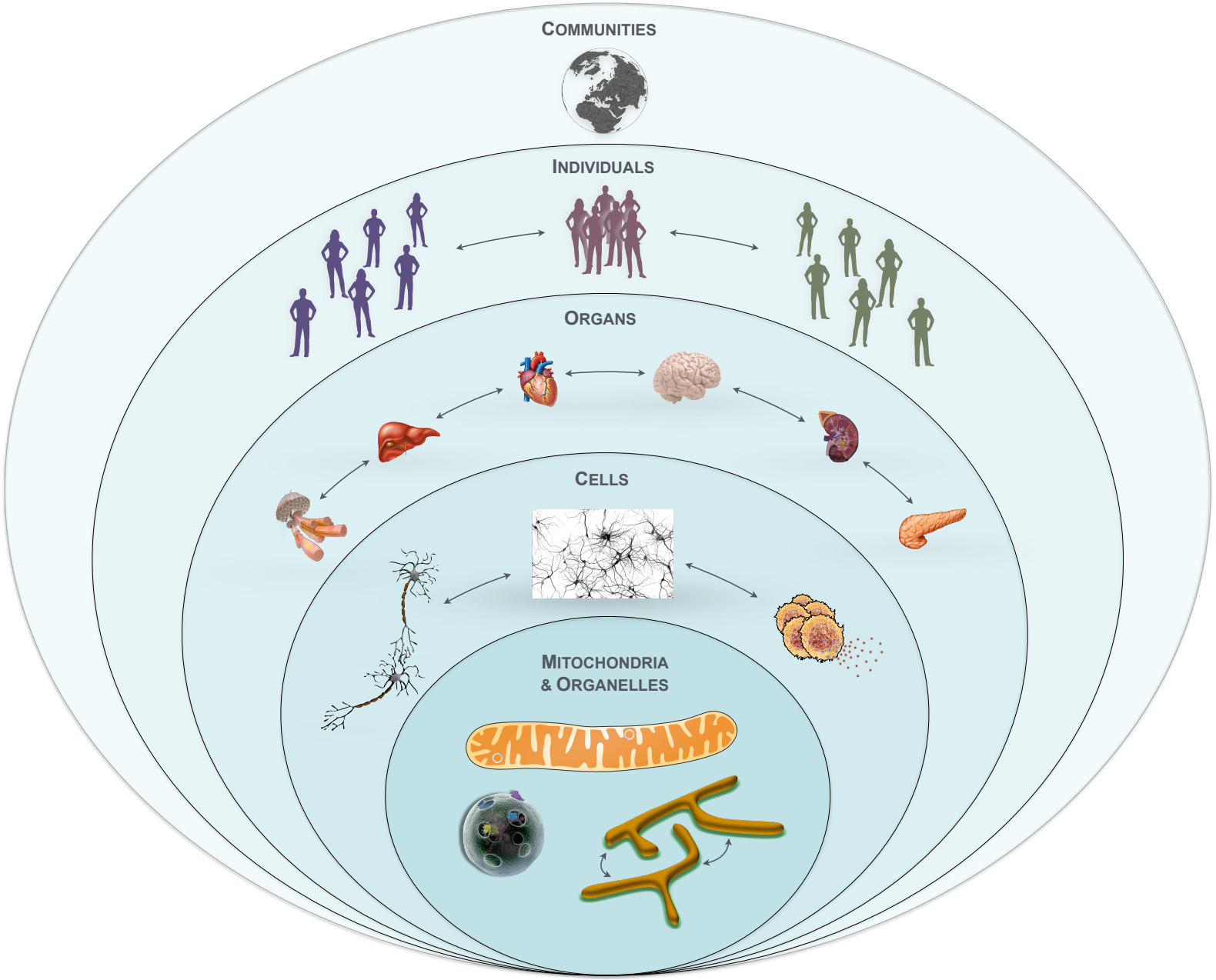
And accelerates cellular aging by **10-40%**

Bobba-Alves et al. *PNEC* 2023

How much energy do stress responses cost ?

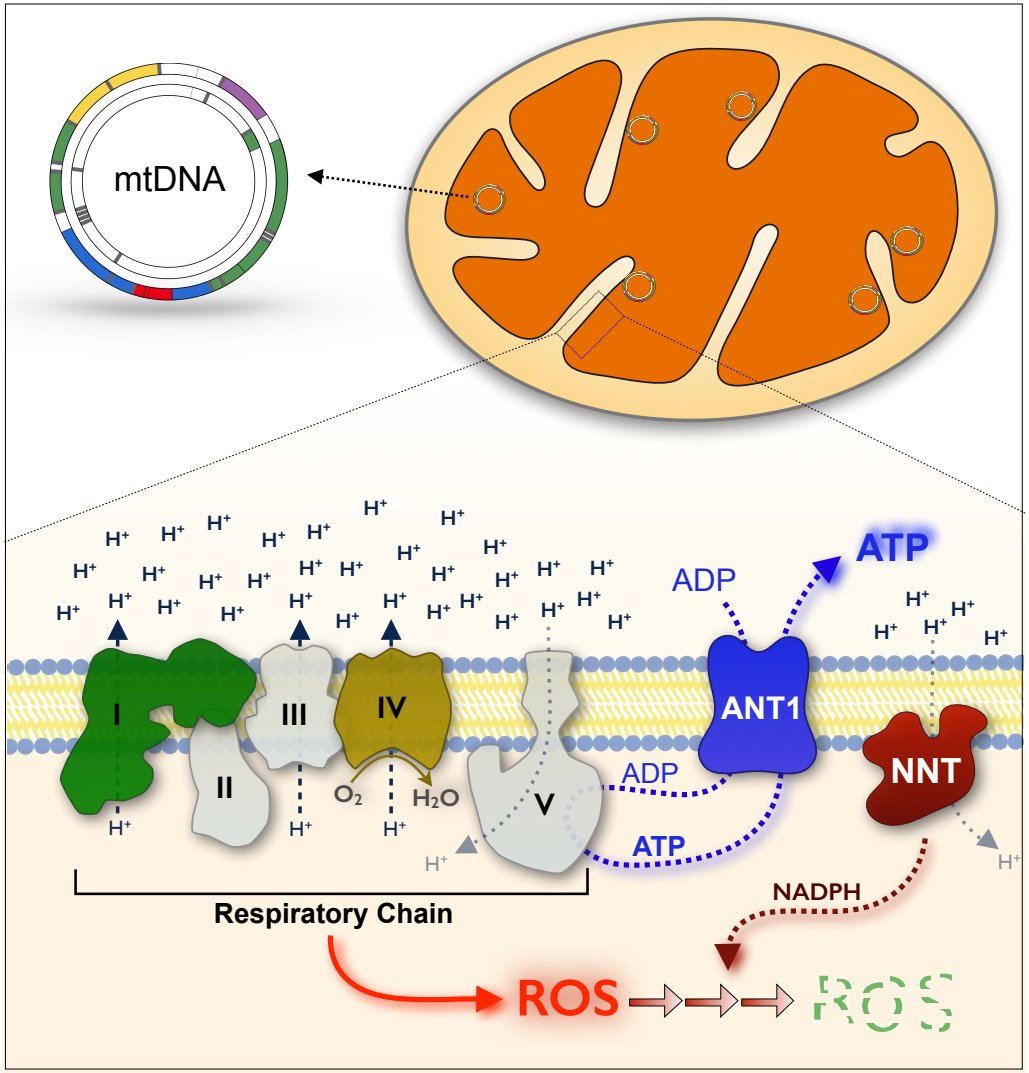


How do energetics and mitochondria influence physiological responses ?



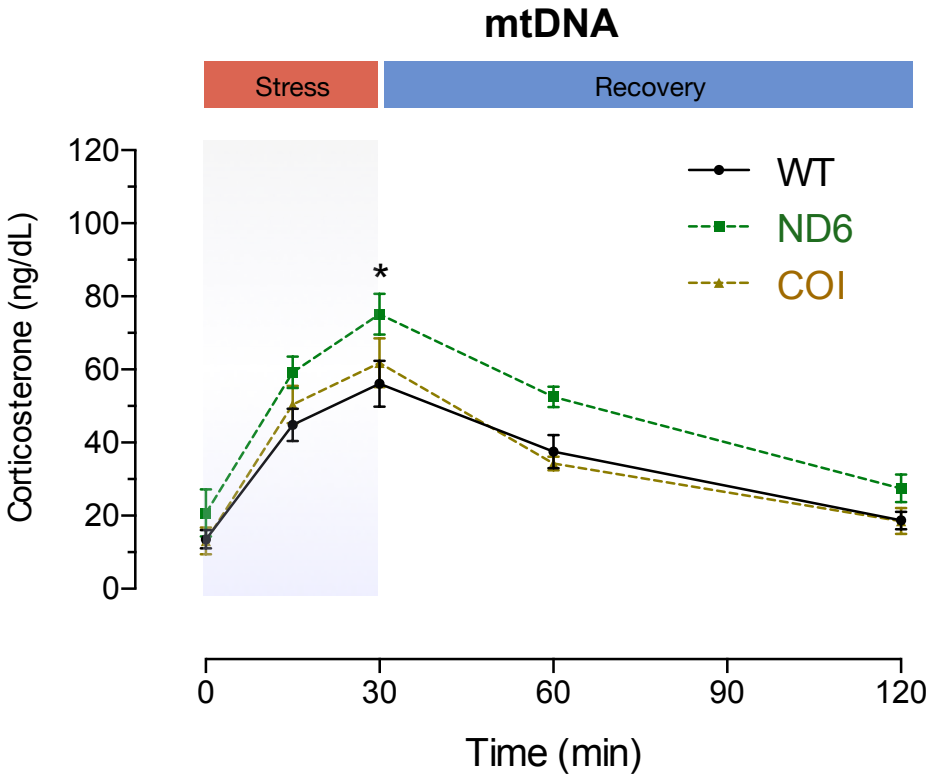
Picard and Sandi. *Neurosci Biobehav Rev* 2021

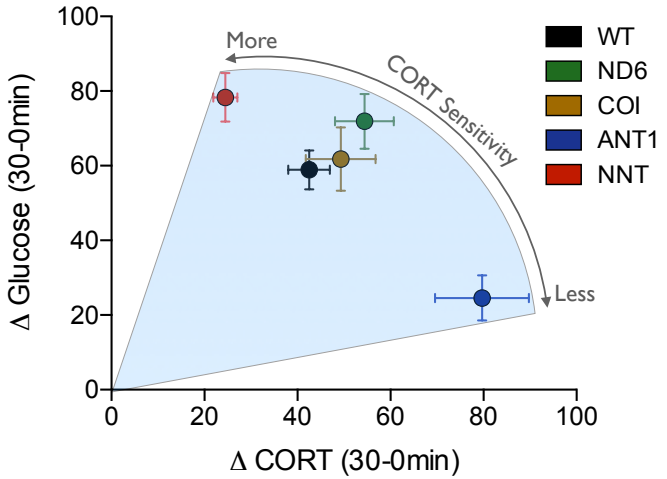
Animal models of impaired mitochondrial OxPhos and redox



Picard et al. *PNAS* 2015

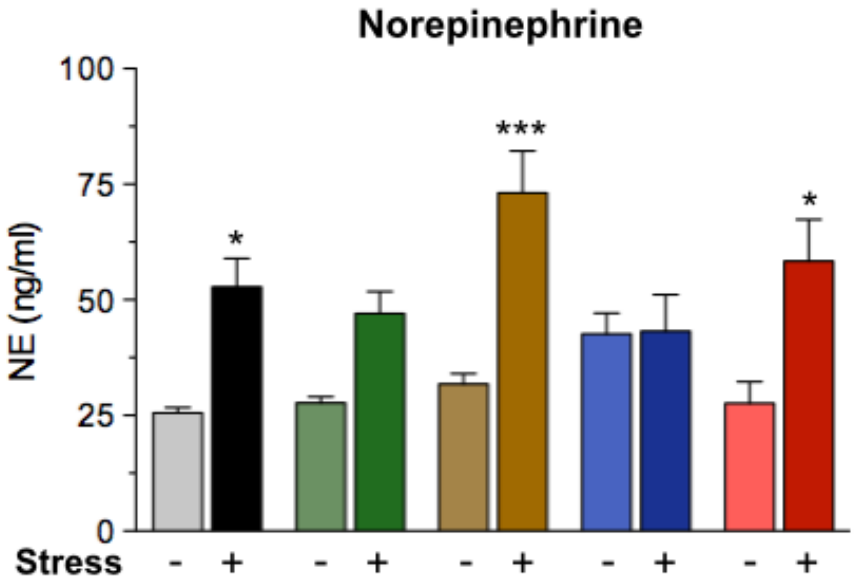
Mitochondrial functions influence stress-induced HPA axis activity

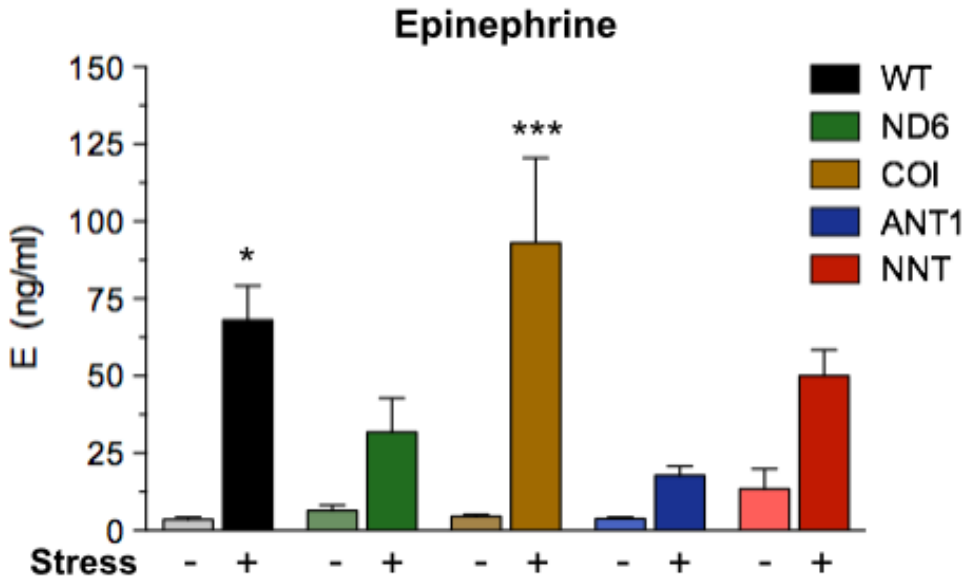




Picard et al. *PNAS* 2015

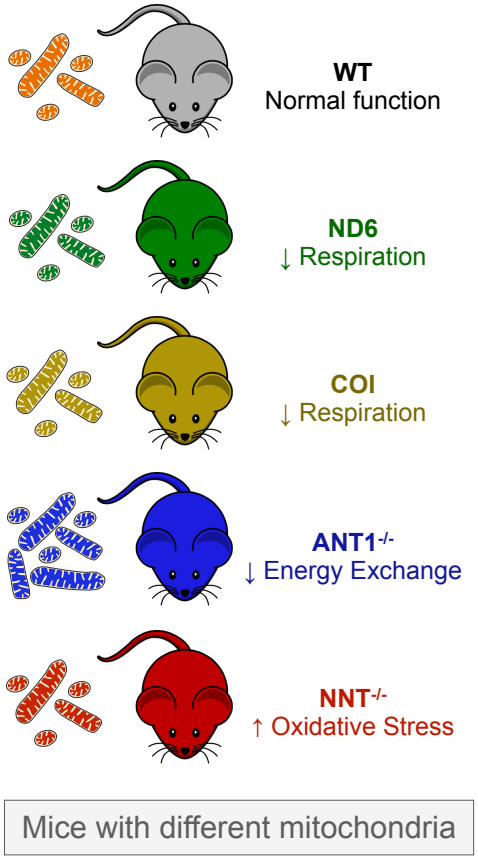
Sympathetic Adrenal-Medullary (SAM) Axis

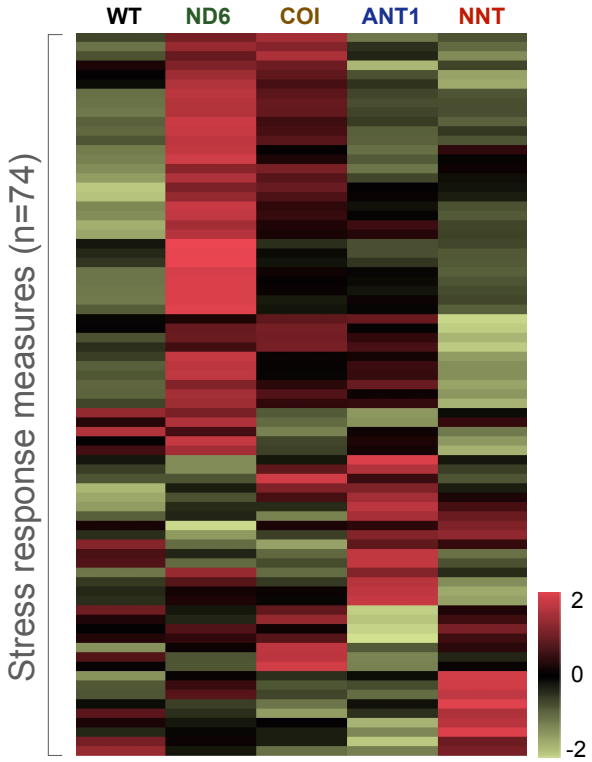


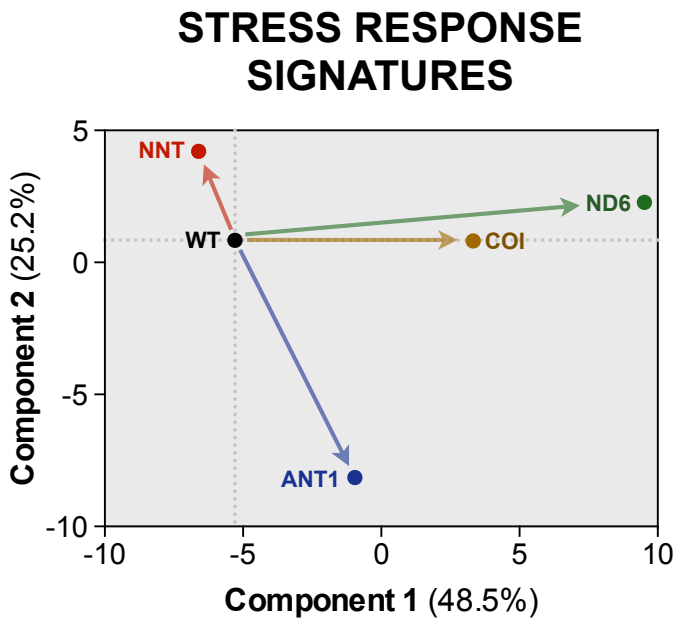


Picard et al. *PNAS* 2015

Mitochondria drive unique stress response “signatures"







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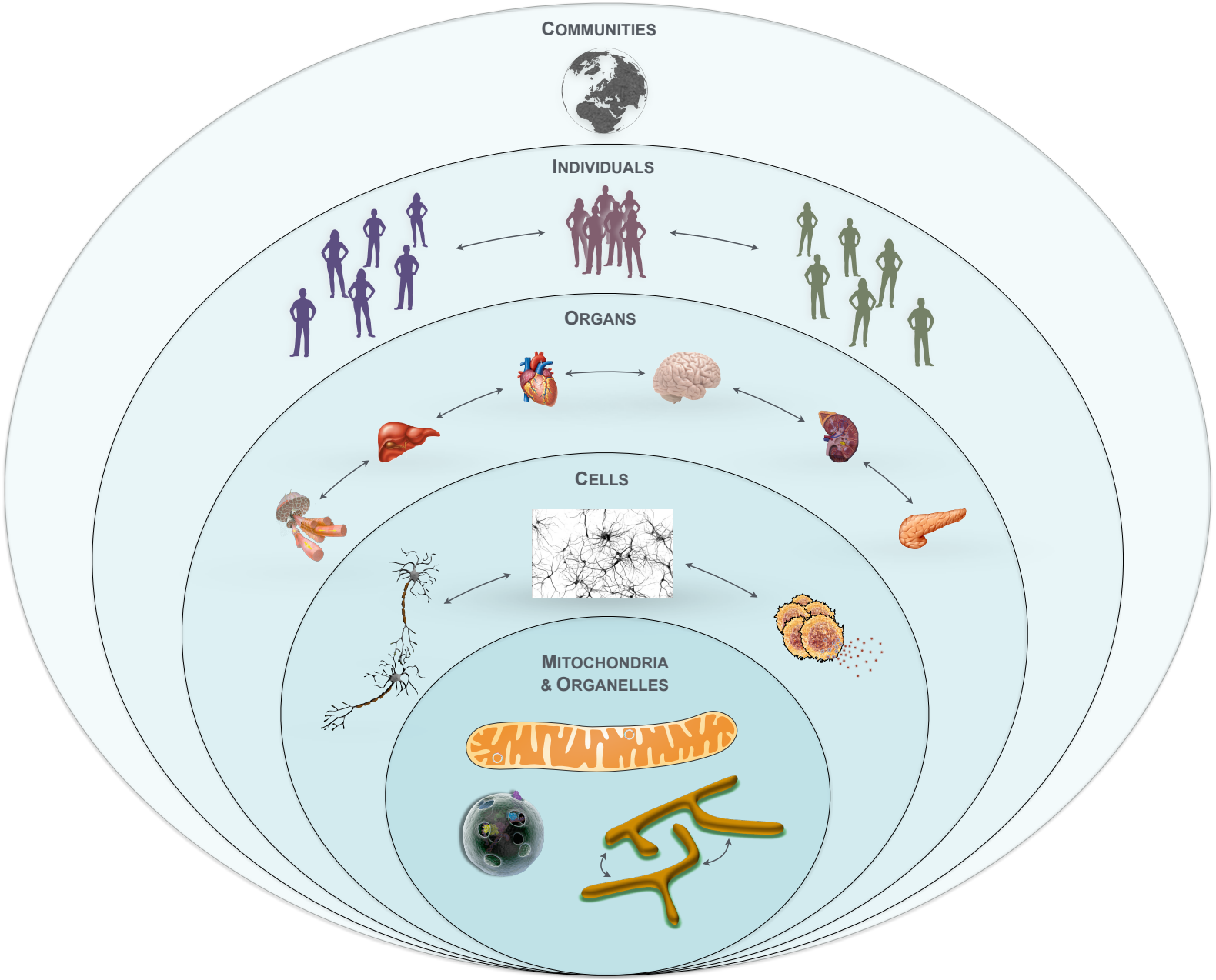
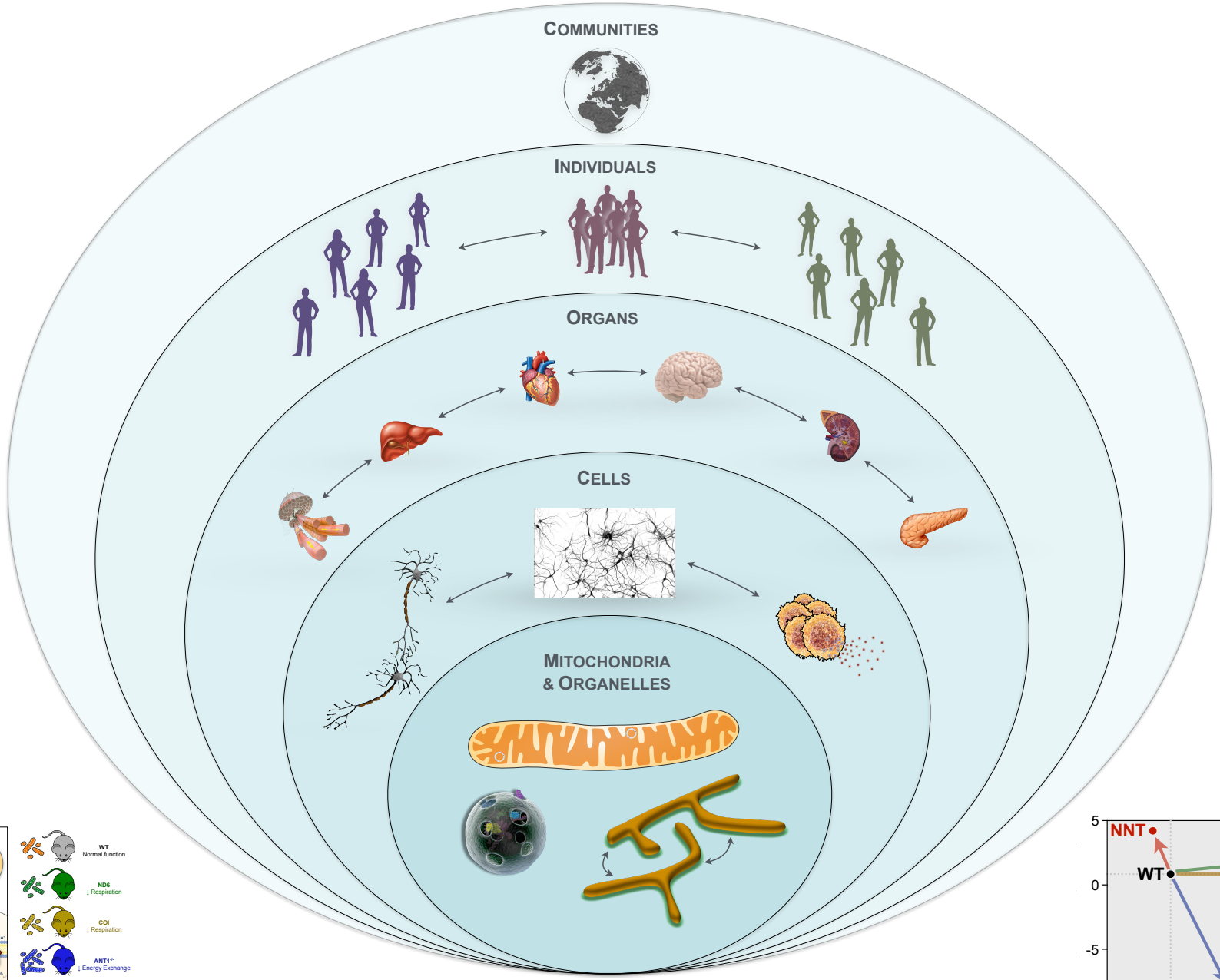
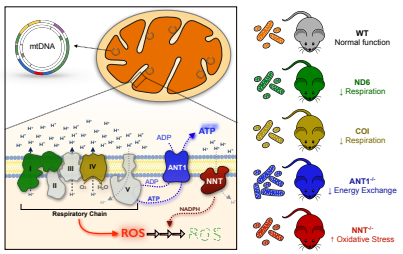
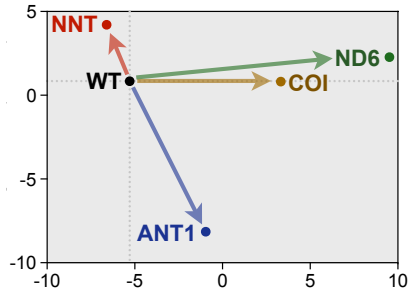


Picard and Sandi. *Neurosci Biobehav Rev* 2021

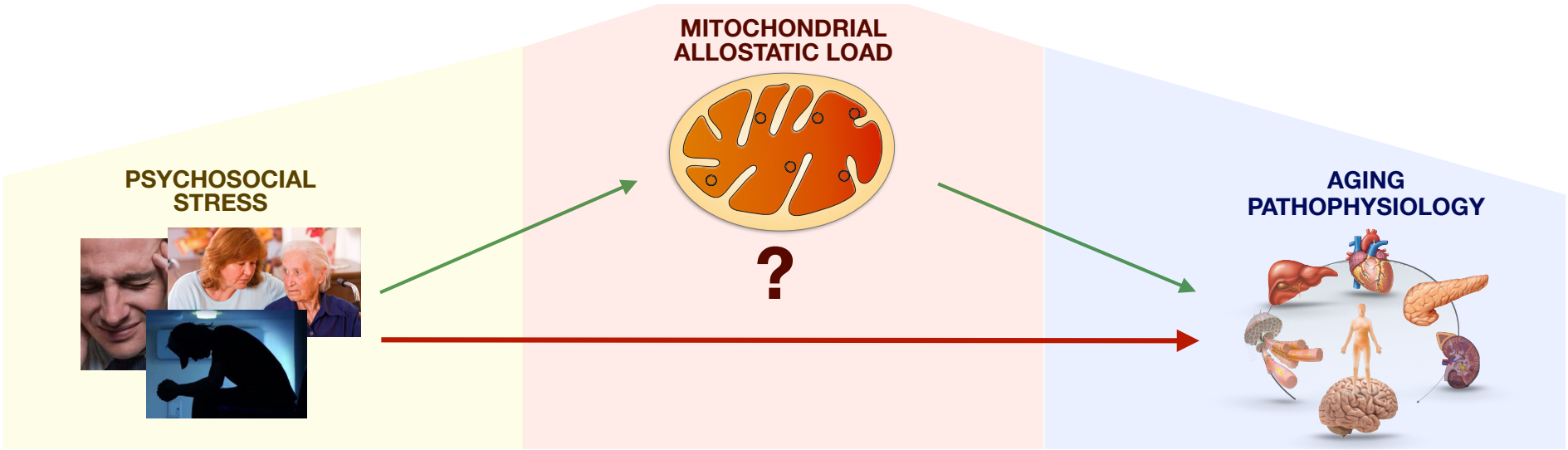
Do mitochondria regulate the stress response in humans?



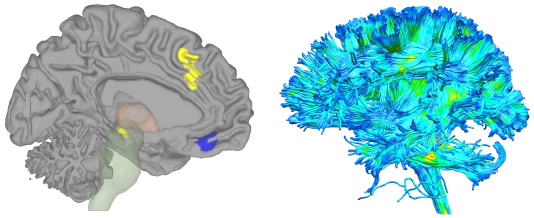




Mitochondrial **S**tress, **B**rain **I**maging, and **E**pigenetics — **MiSBIE**

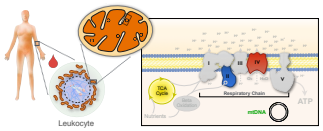


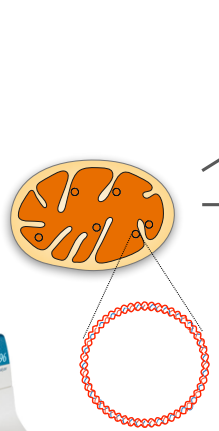
Mitochondrial **S**tress, **B**rain **I**maging, and **E**pigenetics — **MiSBIE**

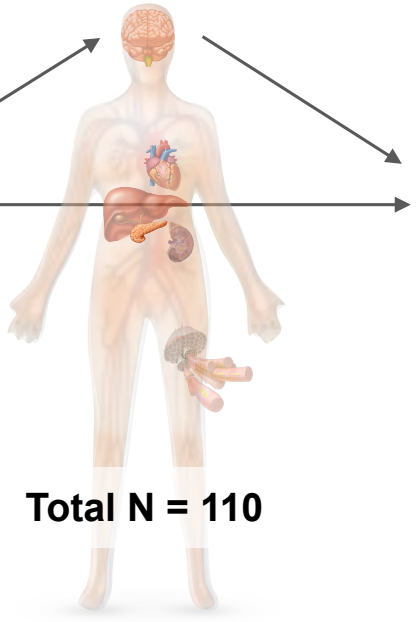


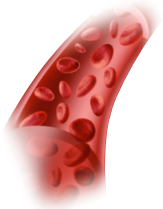
Brain structure and function
Neuropsychological function

mtDNA heteroplasmy
Mitochondrial OxPhos
Lymphocytes, Monocytes,
Neutrophils, Platelets





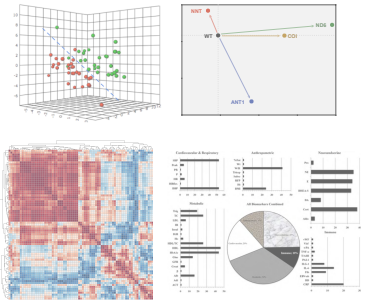




Total N = 110

Disease biomarkers
Stress reactivity
Energy expenditure

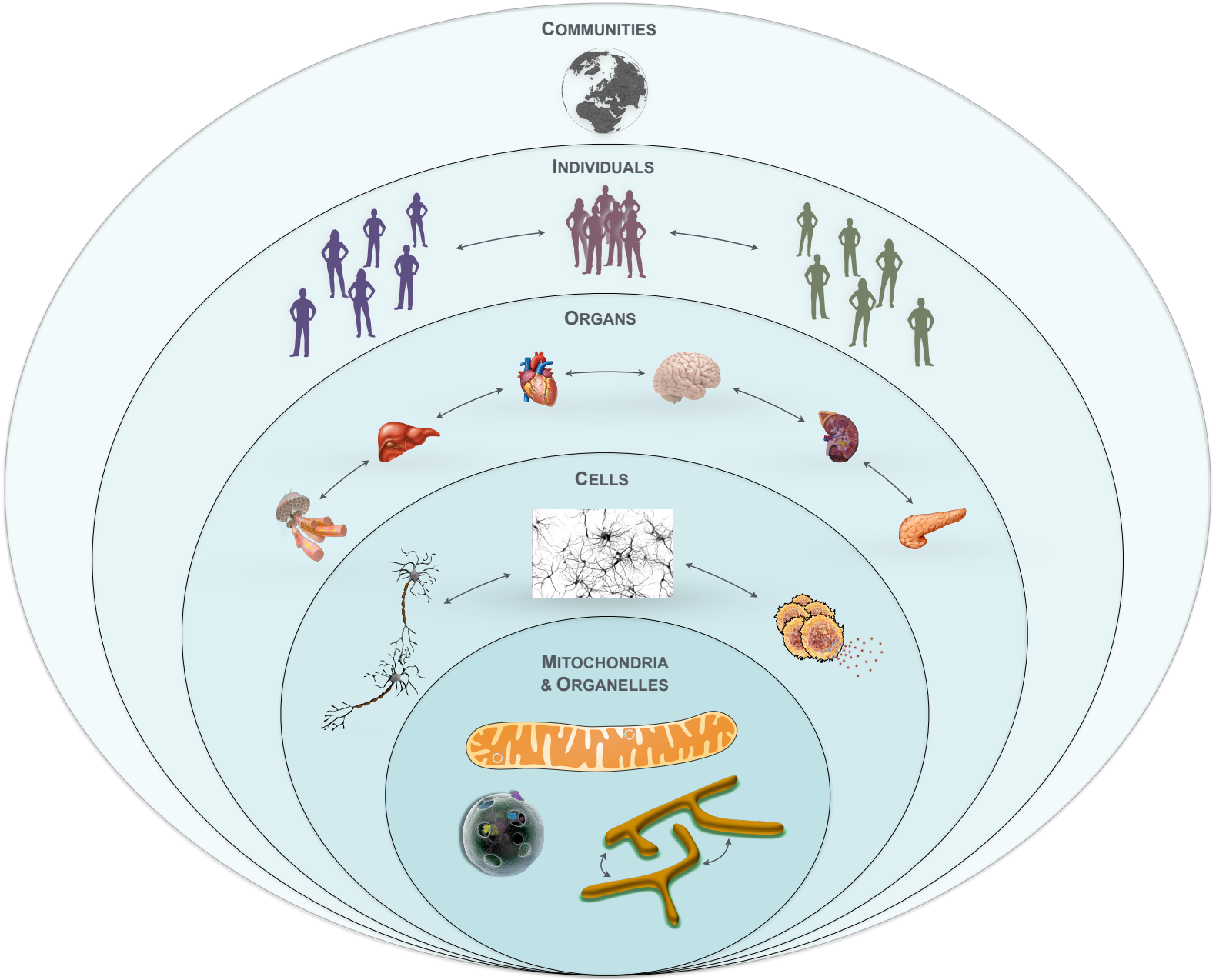
e.g., Cortisol, NE,
GDF15, Lactate, etc.

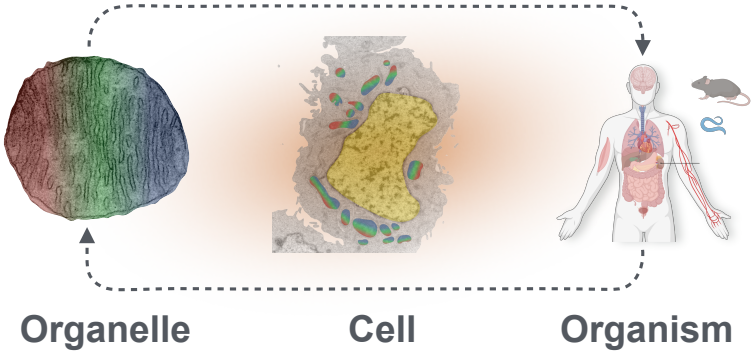


- **Healthy controls** (n = 70)
- **mtDNA defects**
  - **3243A>G (group A)** (n = 20)
  - **3243A>G (group B)** (n = 5)
  - **Single deletion** (n = 15)

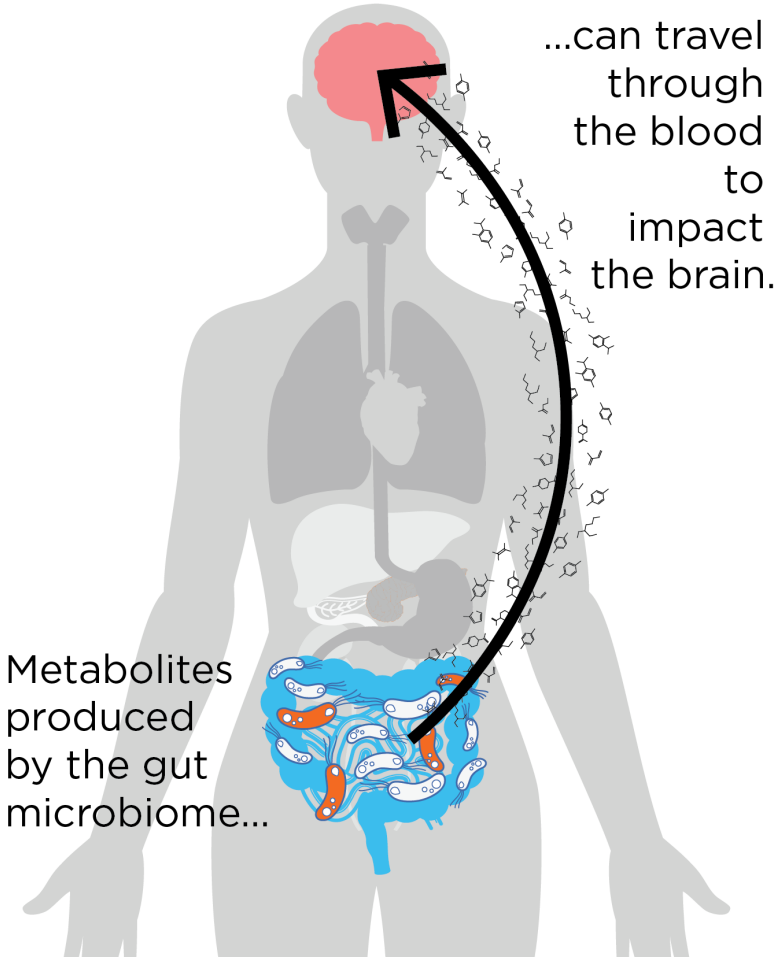
MITOCHONDRIA STRESS BRAIN EPIGENETICS MiSBIE

How do metabolites shape stress responses ?



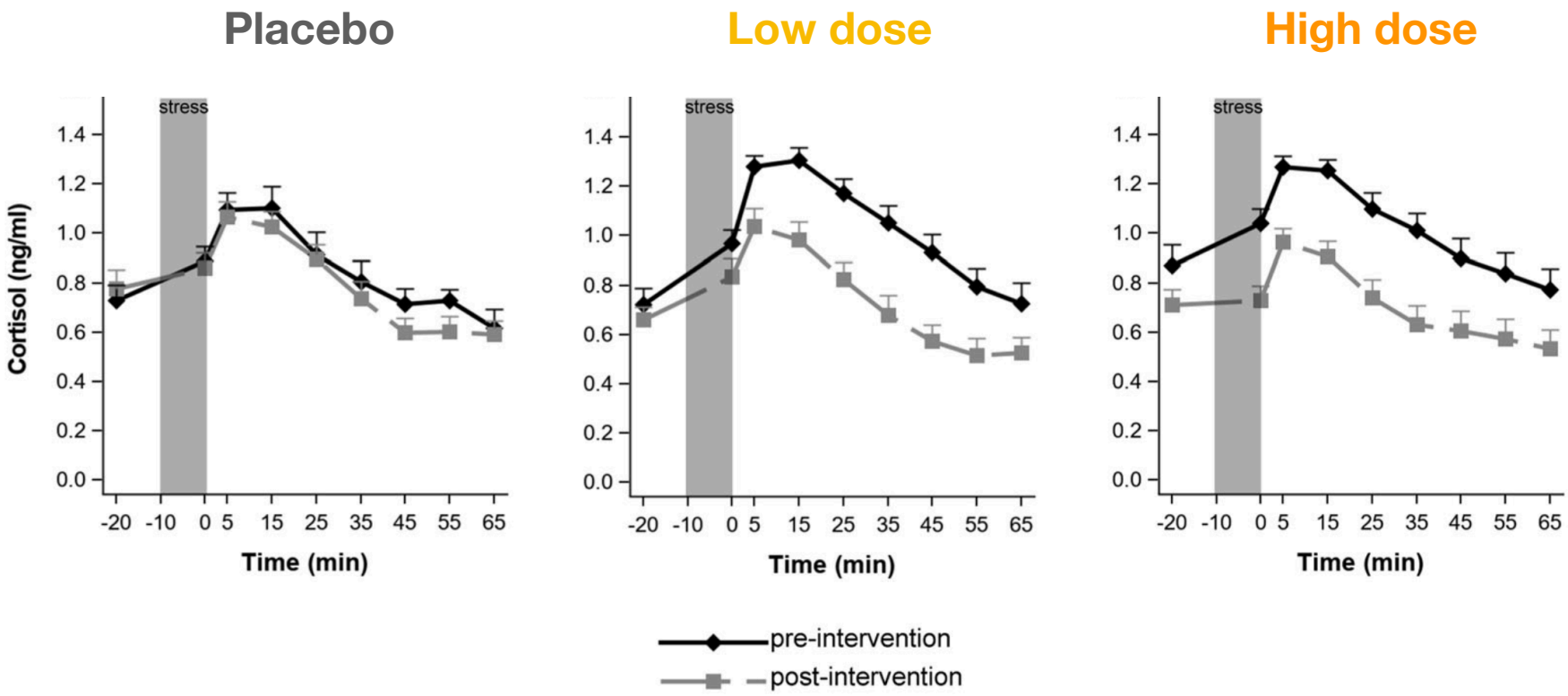


Picard and Shirihai. *Cell Metab* 2022



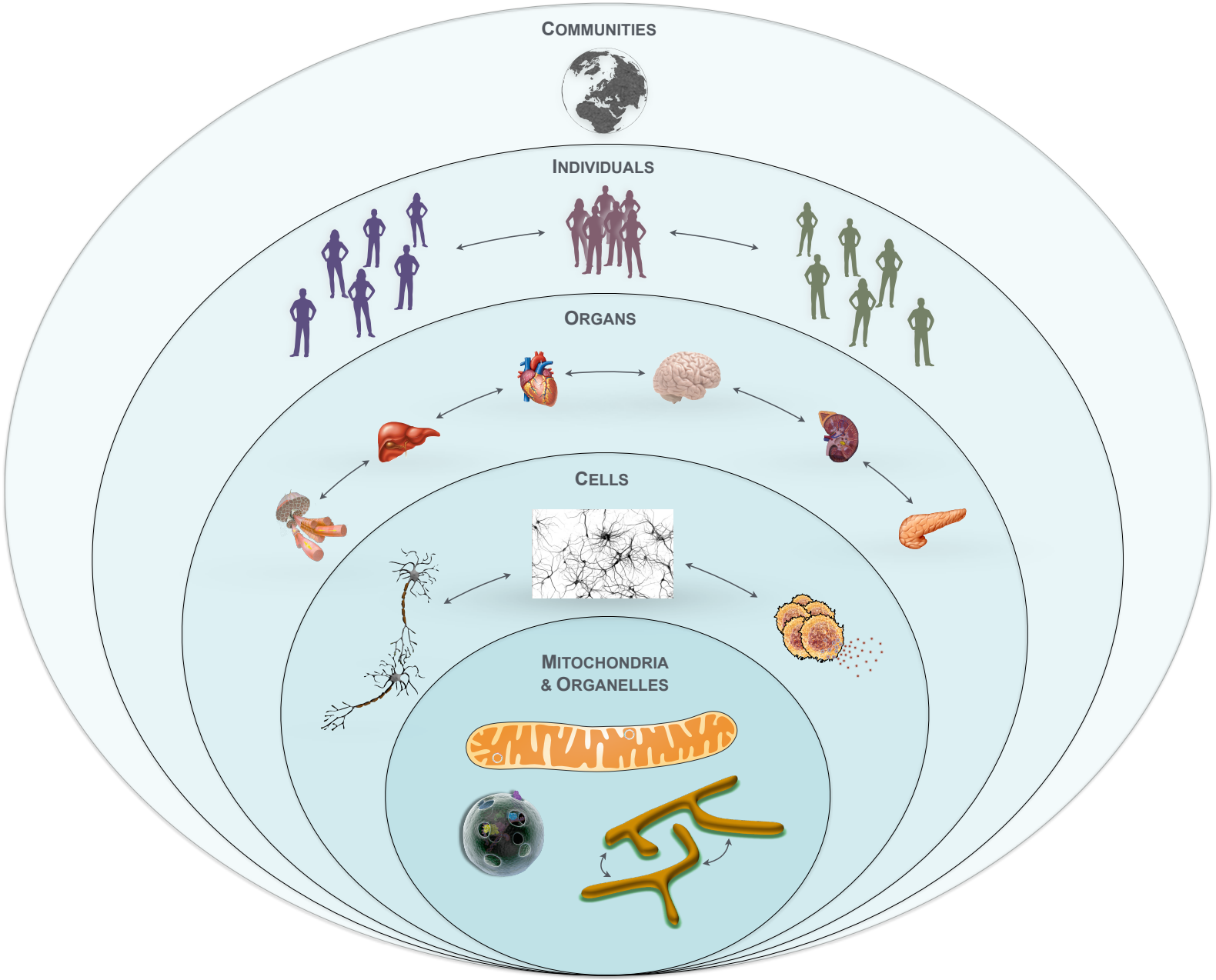
www.owlstonemedical.com

Gut-derived metabolite short-chain fatty acids

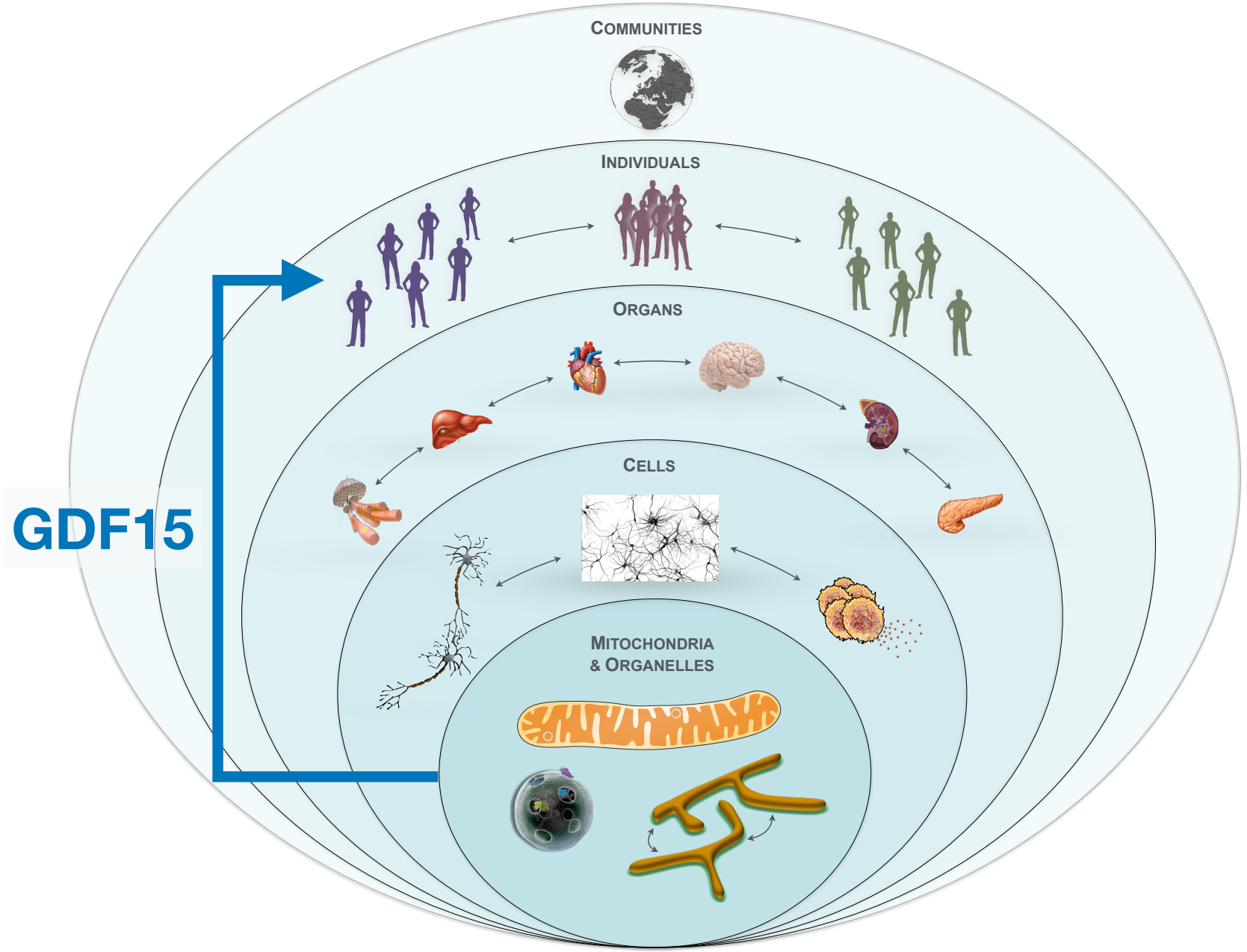


Dalile et al. *Neuropsychopharmacology* 2020
Needham et al. *Nature* 2022

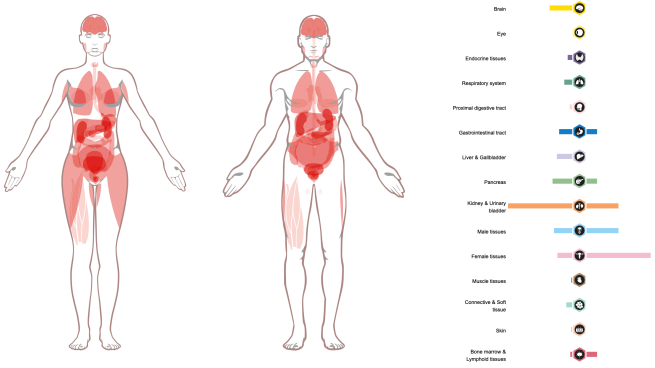
How do metabolites shape stress responses ?



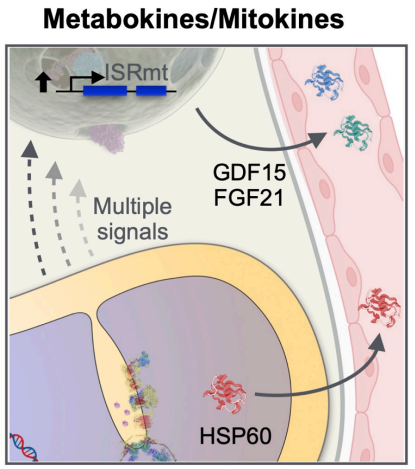
How does information about mitochondrial health reach the brain ?



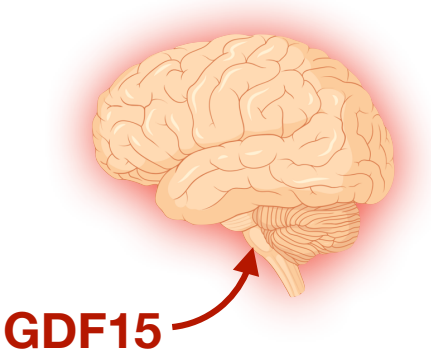
What does GDF15 mean to the organism?



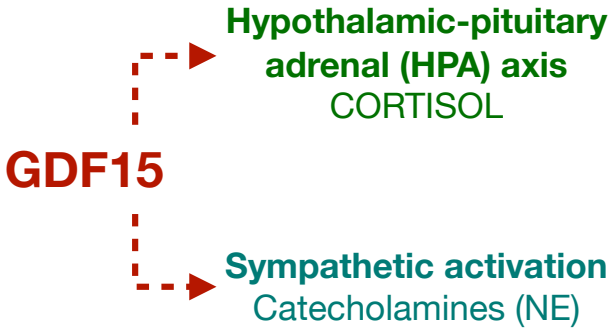
Expressed in >90% of somatic tissues



Triggered by cellular stressors (ISR)



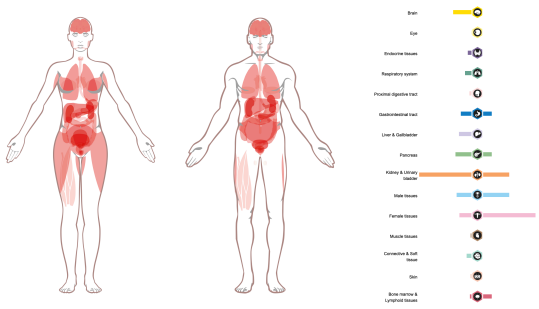
Signals on the brainstem



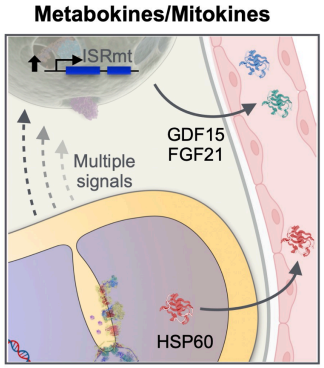
Activates canonical stress axes

Lockhart et al. *Endocr Rev* 2020

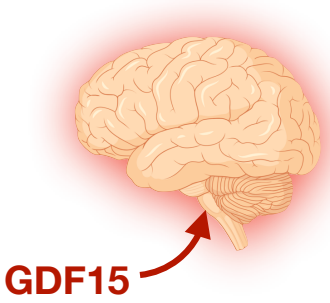
What does GDF15 mean to the organism?



Expressed in >50% somatic tissues



Triggered by cellular stressors (ISR)



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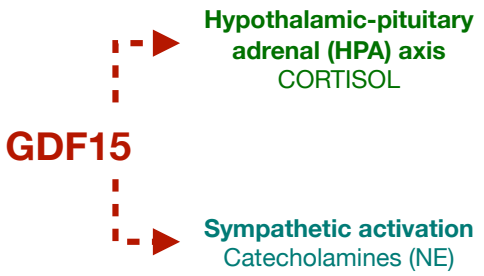
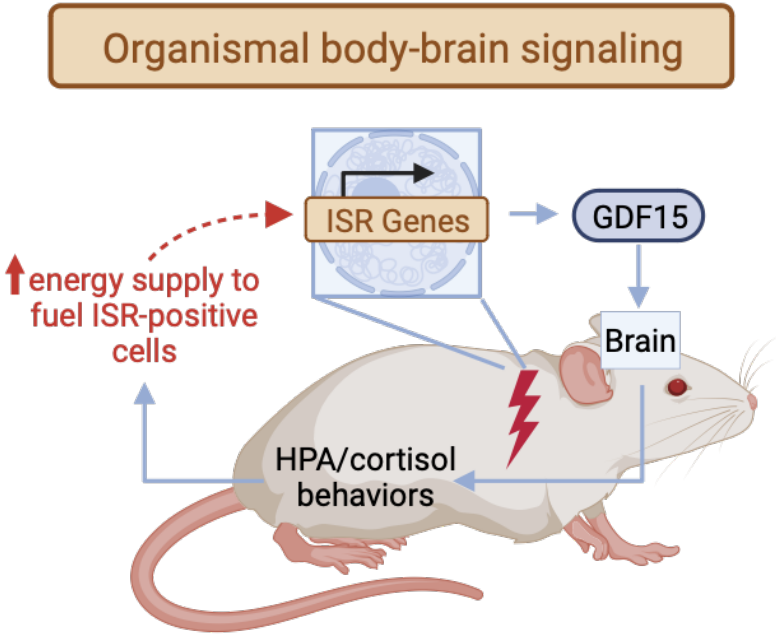
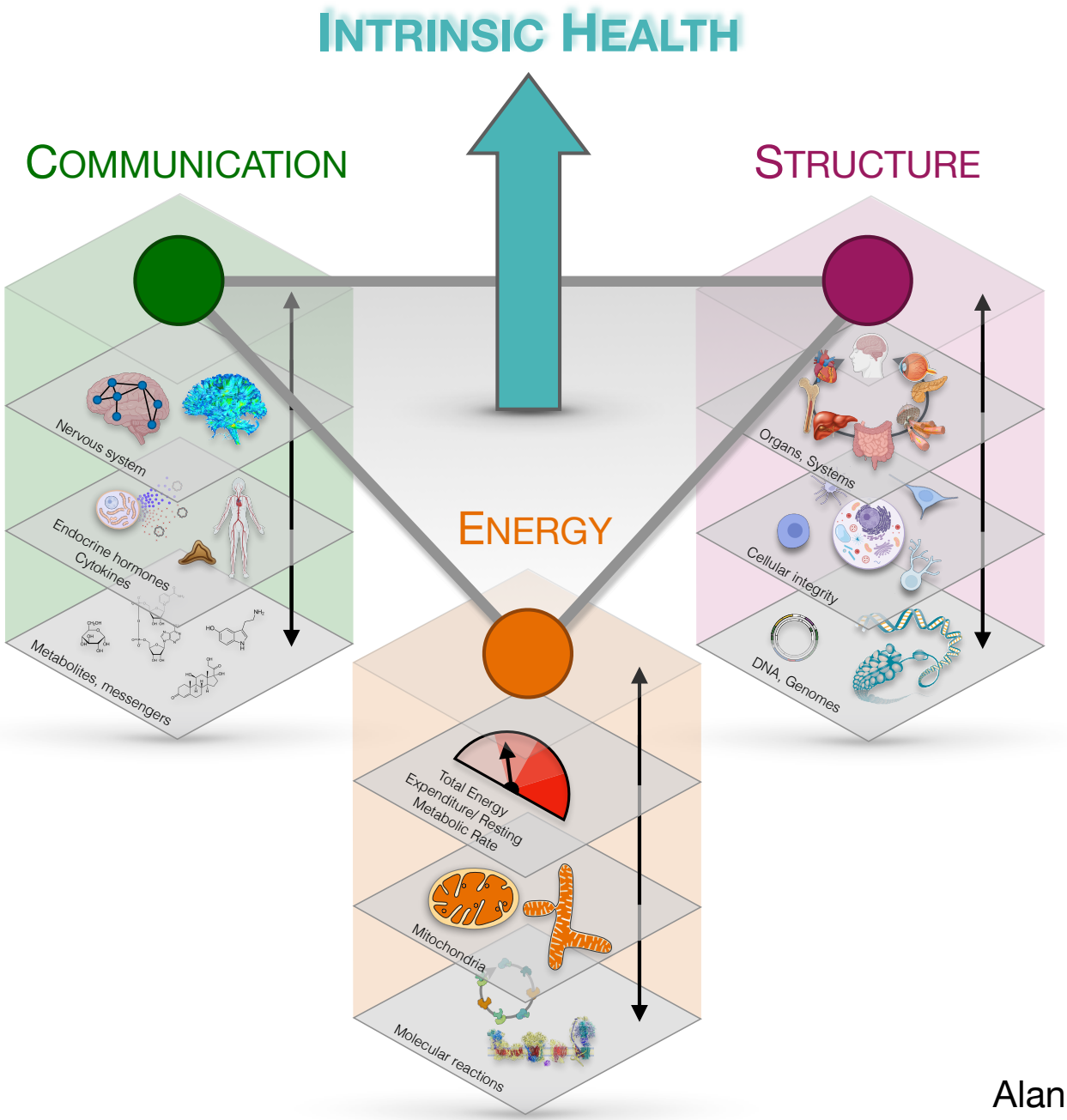


Activates canonical stress axes

Psychological stress transiently increases GDF15 in humans



Monzel et al. *Life Metab* 2024



Alan Cohen, Dan Belsky
Columbia Science of Health Group

Knowledge Gaps

- What proportion of **interindividual differences in the magnitude and nature of stress responses** in humans is driven by interindividual differences in mitochondria? MiSBIE

- **How variable is mitochondrial biology**, within a person, over time? Likely variable

- Can we study mitochondrial stress regulation ***in vitro***, in simple cellular systems? Complexity of stressors, feedback

- Are the **health benefits of interventions** like exercise on physiological systems, mental health, and aging driven by mitochondrial adaptations?

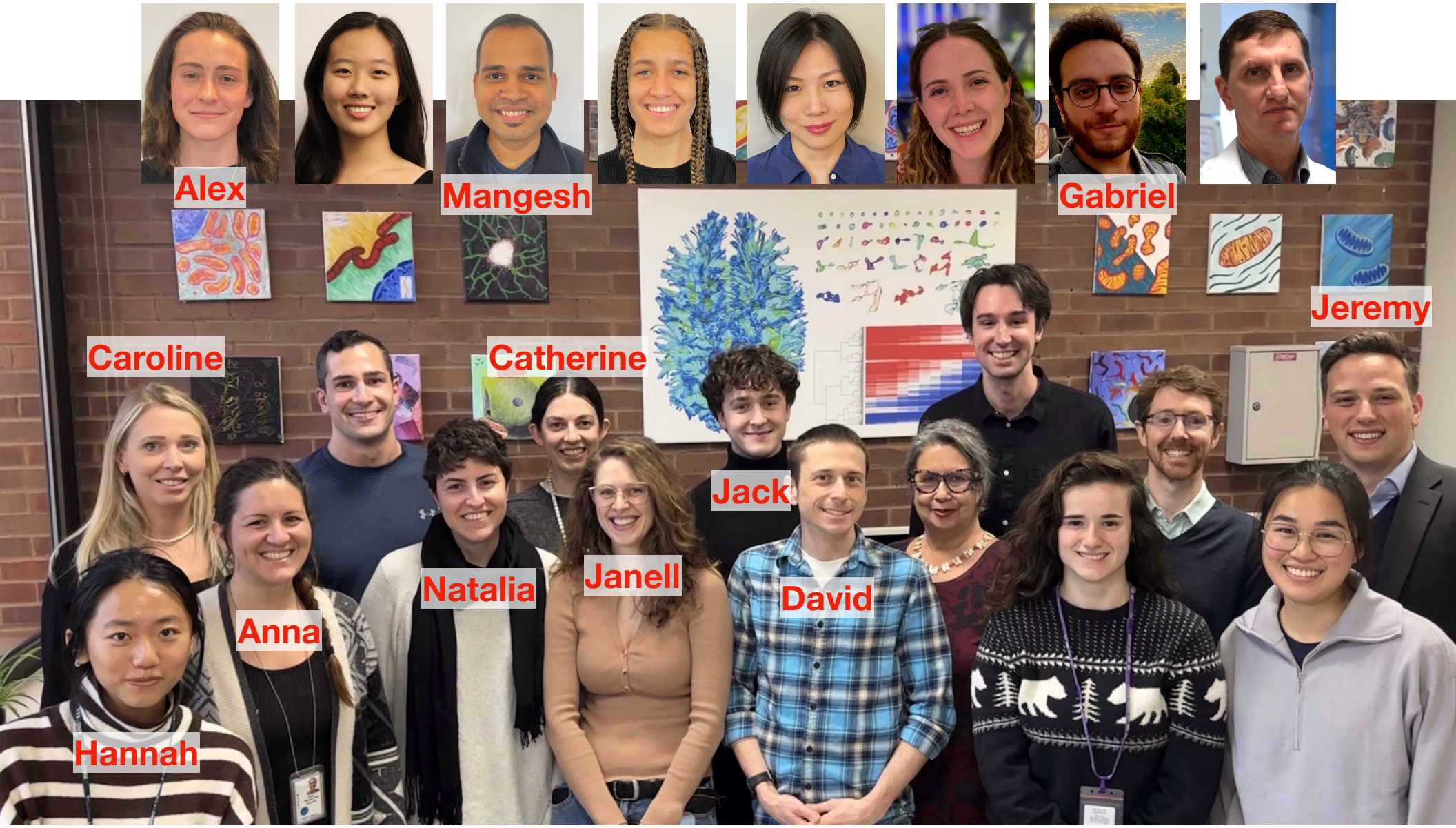
Research Opportunities

- Studies among individuals across a wide spectrum of mitochondrial energy transformation capacity/health (genetic mitochondrial defects — MiSBIE)
- Exogenous metabolite supplementation (SCFAs)
- Understanding the basis of health and resilience, in exceptionally healthy individuals
- Psychobiological studies of resilience beyond biology and physiology

Mitochondrial PsychoBiology Lab

Linking molecular processes within mitochondria with the human experience

OUR RESEARCH



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Jue Lin
Aric Prather
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Eli Puterman
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Luigi Ferrucci
NIA Intramural

NIH National Institute of Mental Health
NIH National Institute of General Medical Sciences
NIH National Institute on Aging

BASZUCKI
BRAIN RESEARCH FUND

The Nathaniel Wharton Fund