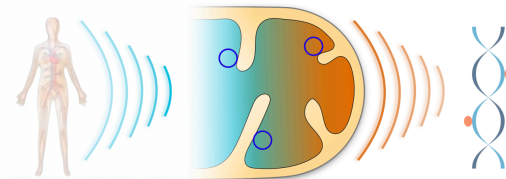


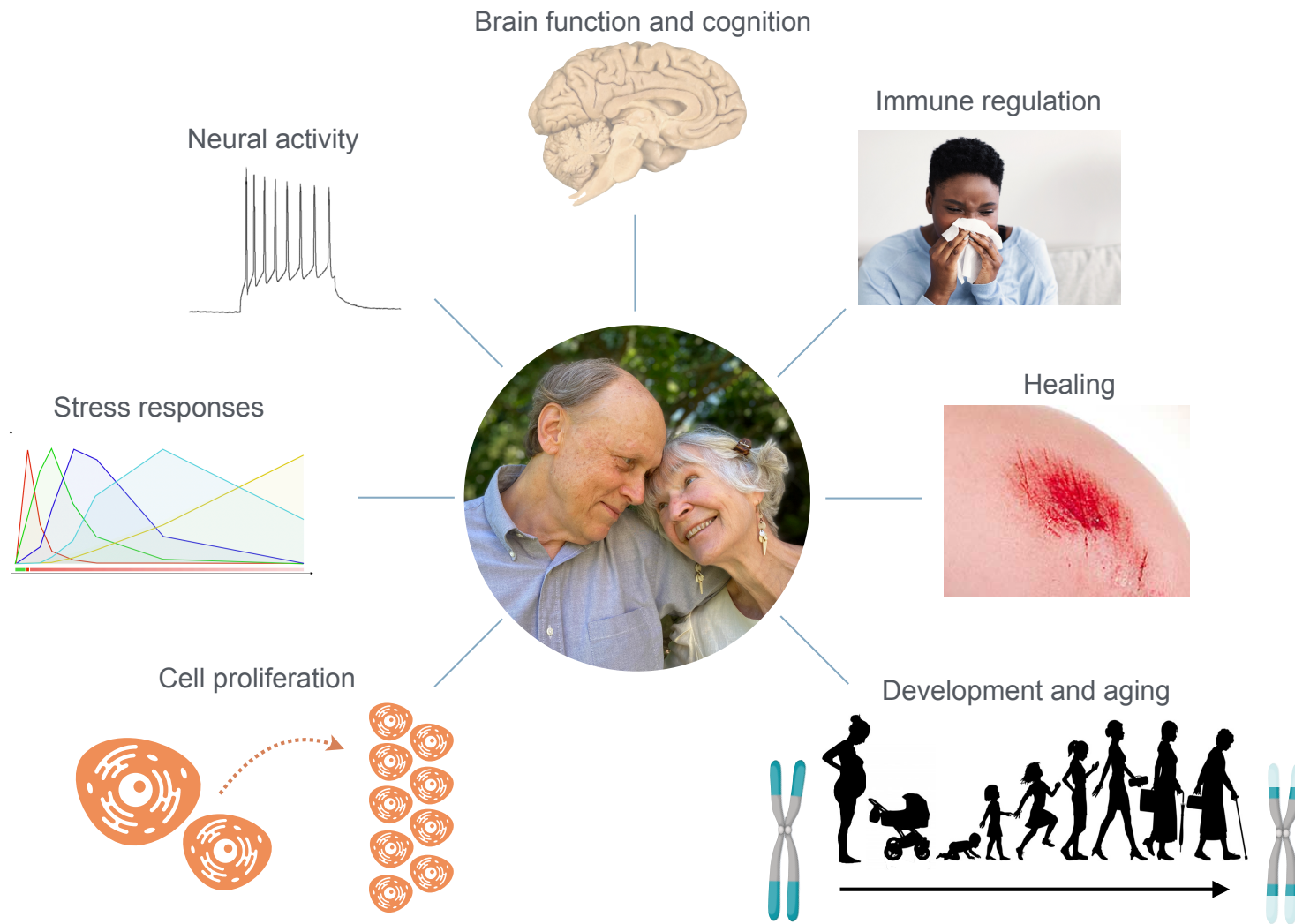
Energetic and Mitochondrial Drivers of Stress responses



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)

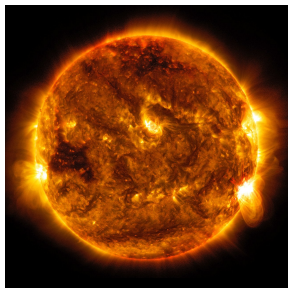
 **COLUMBIA**
COLUMBIA UNIVERSITY
IRVING MEDICAL CENTER

 **New York State
Psychiatric Institute**



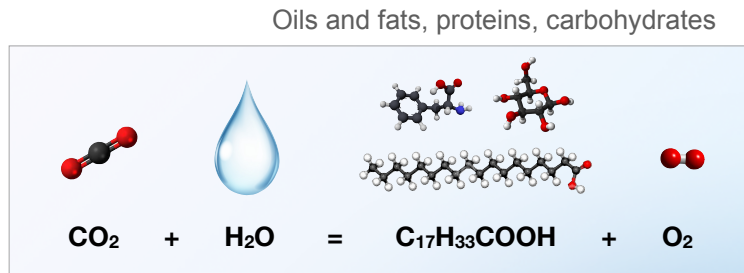
BIOLOGY, PHYSIOLOGY, COGNITION, CONSCIOUSNESS
 PSYCHOBIOLOGICAL ALLOSTATIC PROCESSES

RESILIENCE

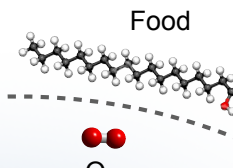
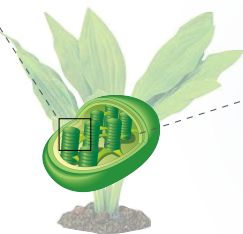


Nuclear fusion
Quantum
electrodynamics

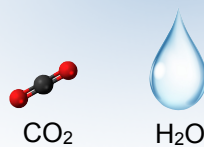
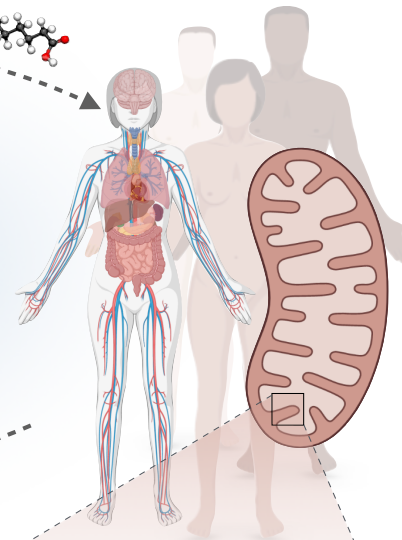
Photons and heat



ENERGY STORED AS CHEMISTRY



EATING and BREATHING



'Waste' products

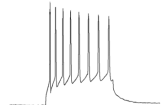
Brain function and cognition



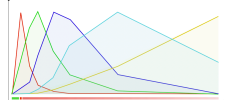
Immune regulation



Neural activity



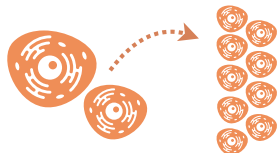
Stress responses



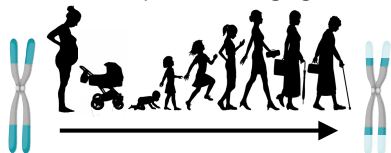
Healing



Cell proliferation

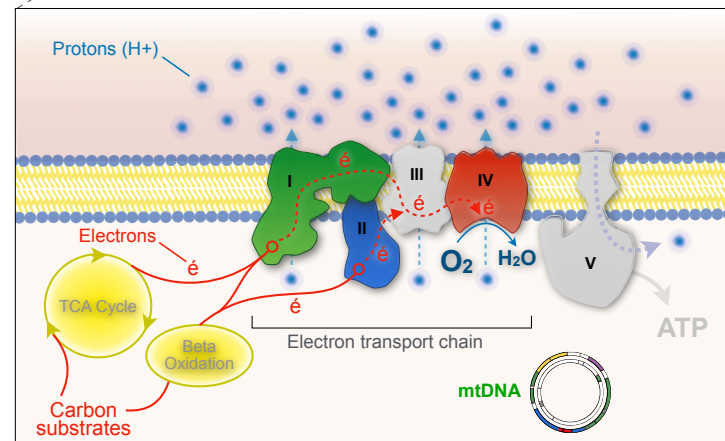


Development and aging



ENERGY
+ Body heat

Electricity and Chemiosmosis
 $\Delta\Psi_m + \Delta pH$

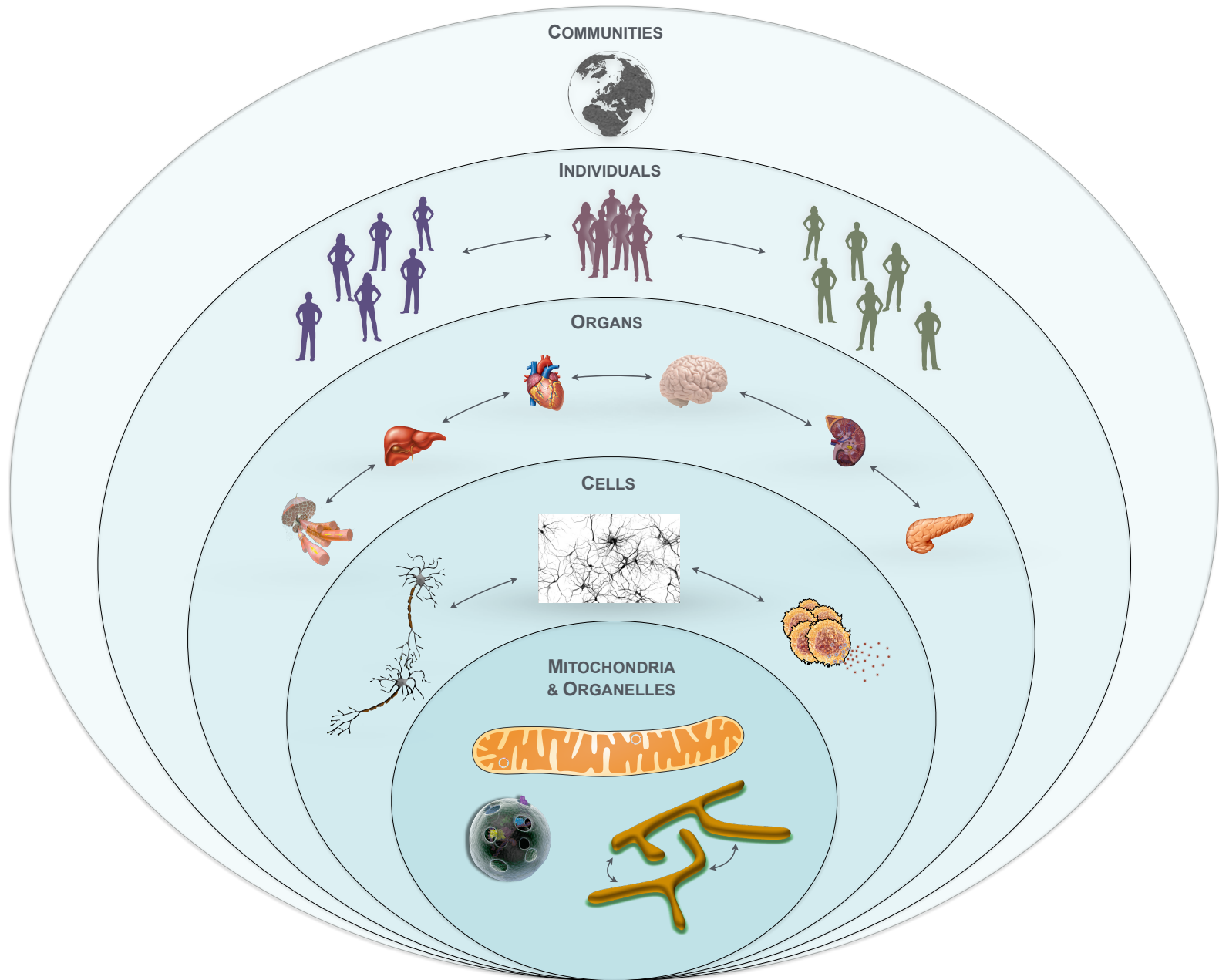


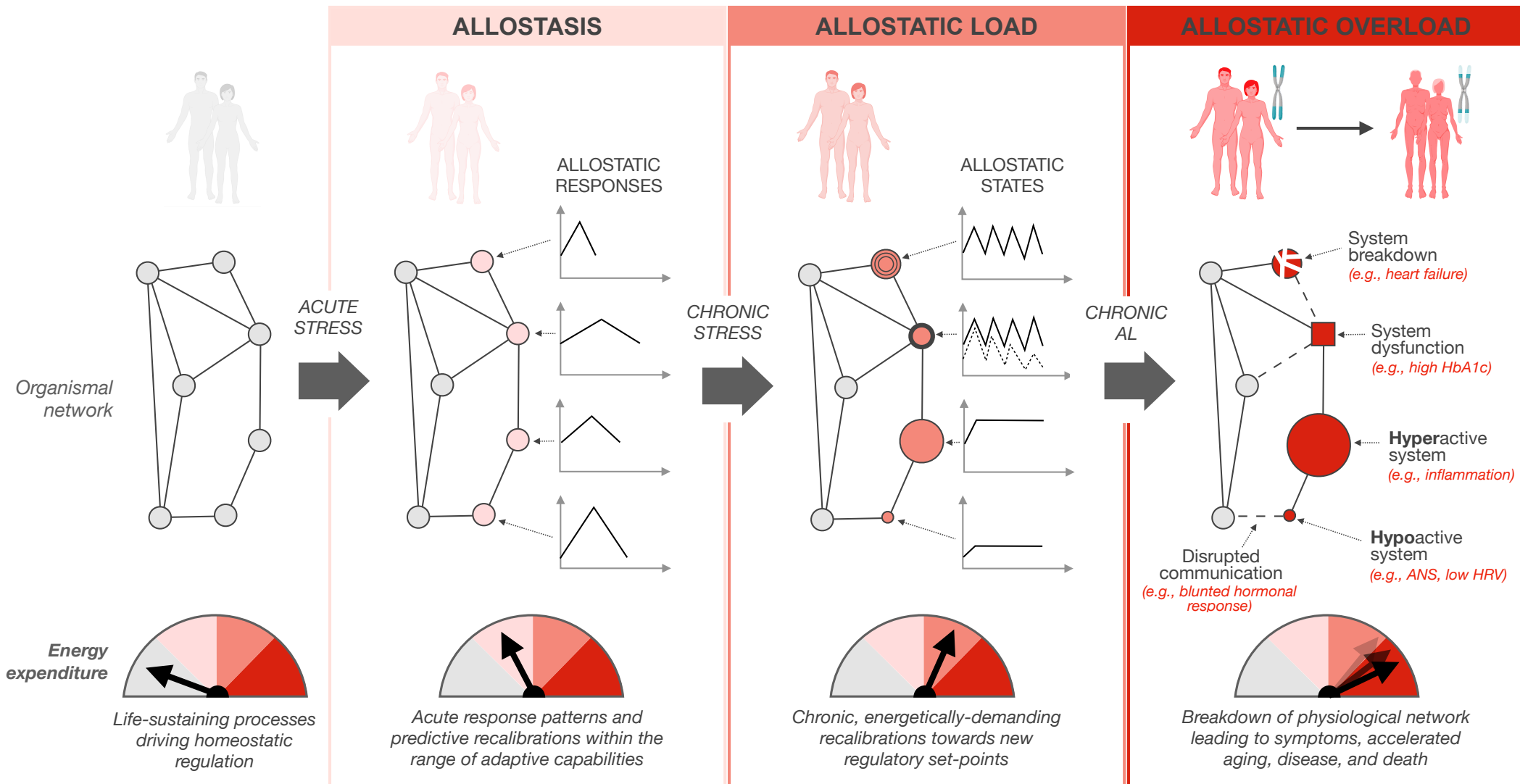
**CHEMICAL ENERGY TRANSFORMED INTO
ELECTROCHEMICAL FORCE**

BIOLOGY, PHYSIOLOGY, COGNITION, CONSCIOUSNESS
PSYCHOBIOLOGICAL ALLOSTATIC PROCESSES

RESILIENCE

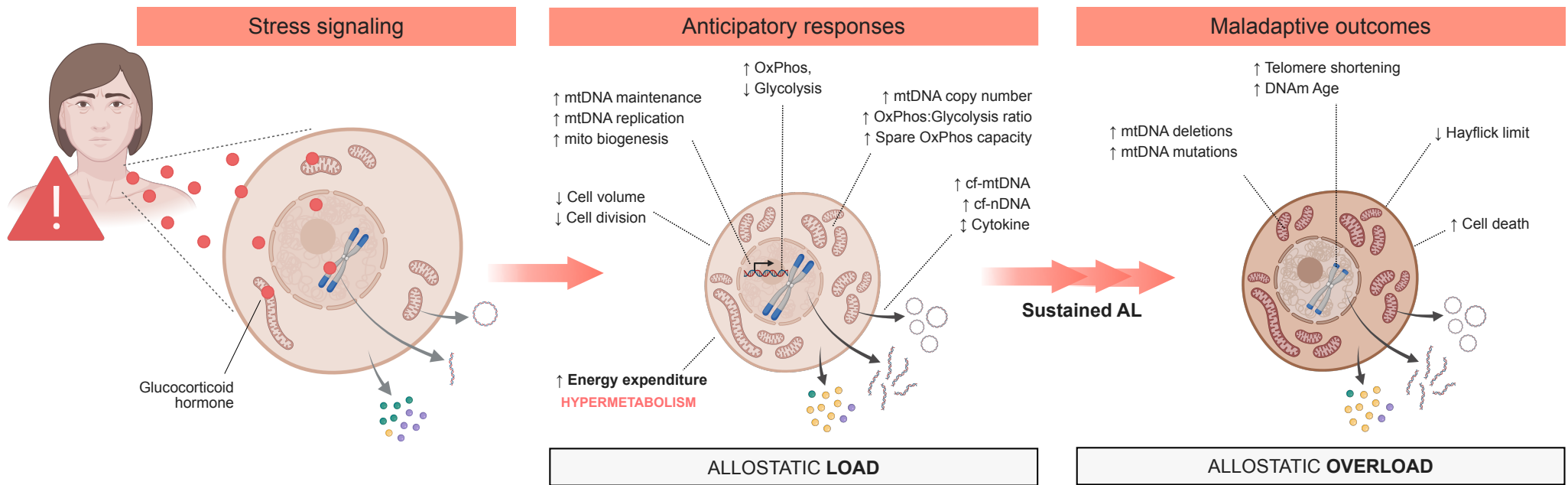
How much energy do stress responses cost ?







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

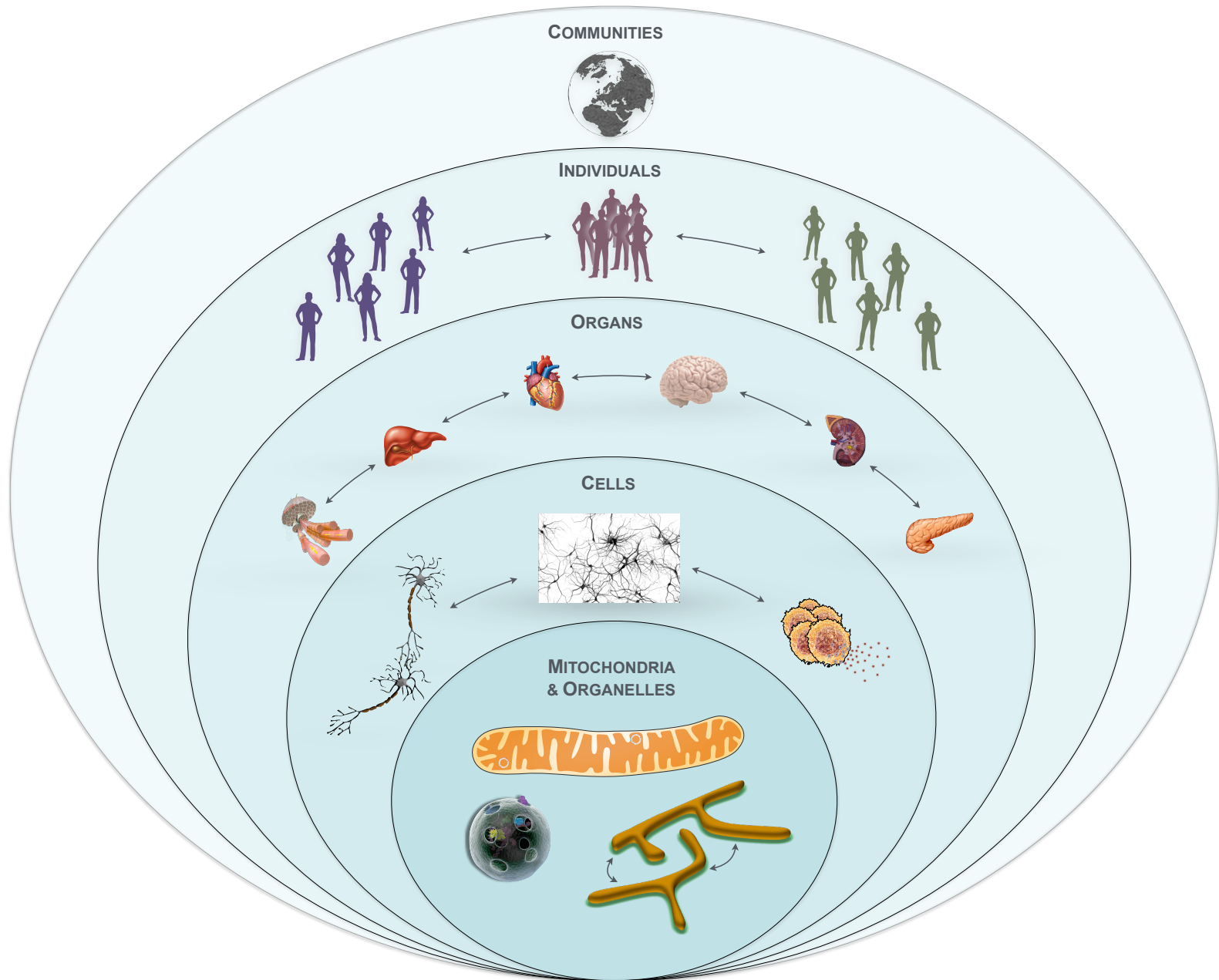


Glucocorticoid signaling increases energy expenditure by **60%**

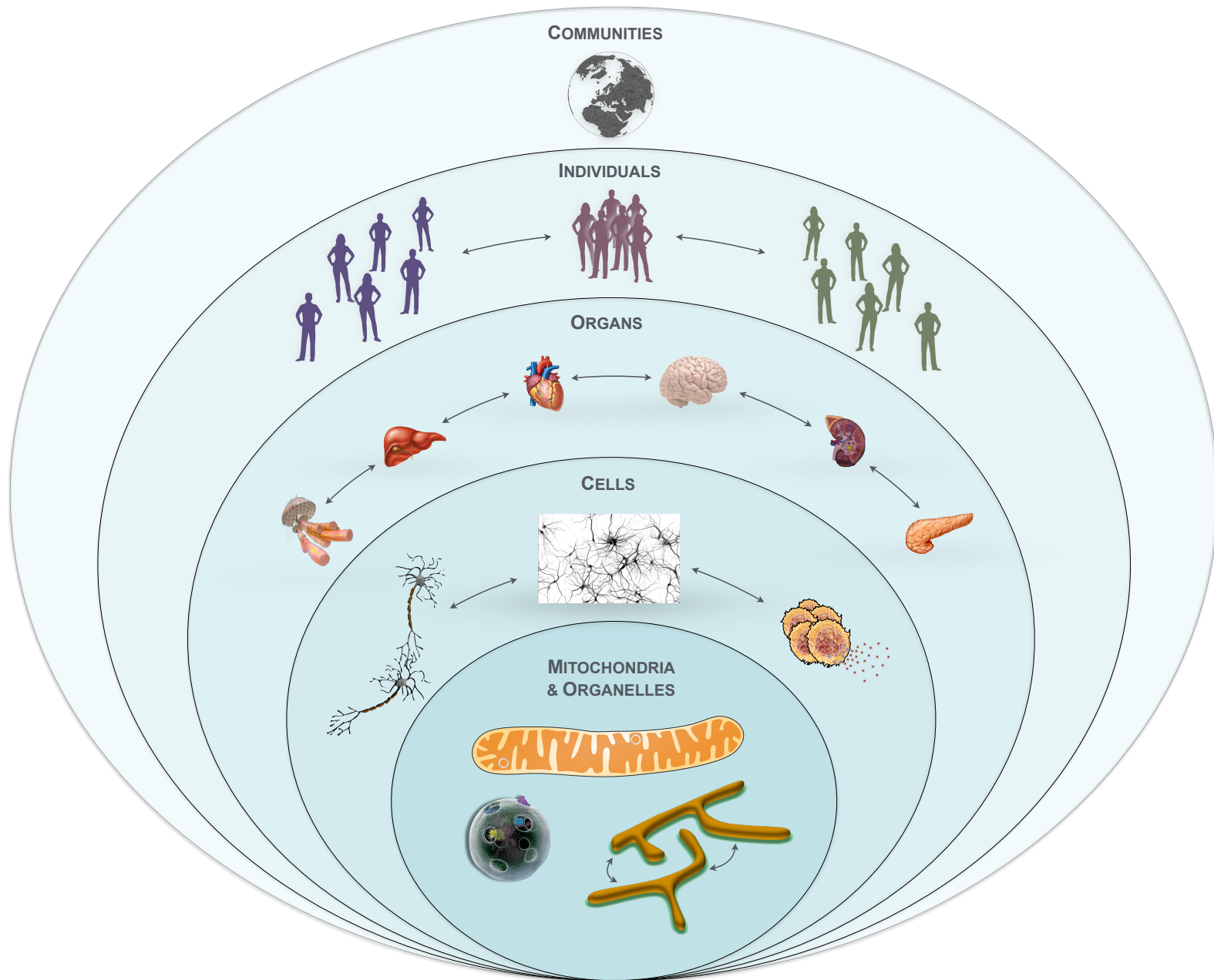
And accelerates cellular aging by **10-40%**



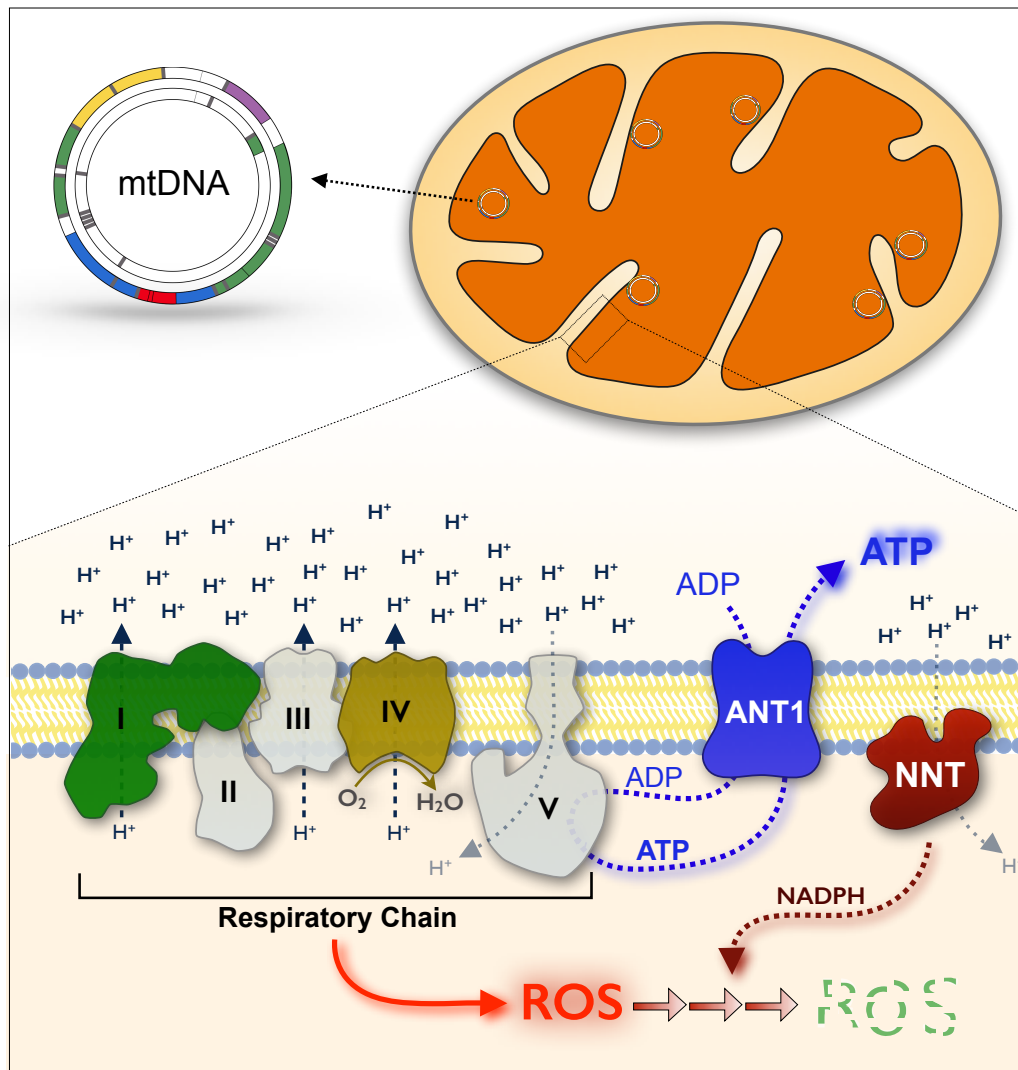
How much energy do stress responses cost ?



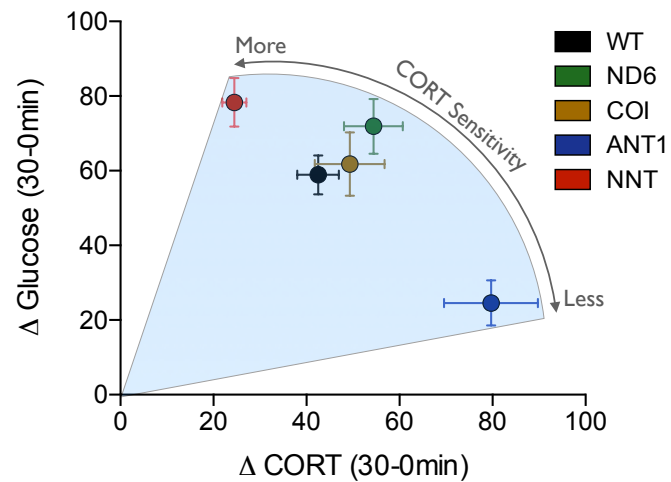
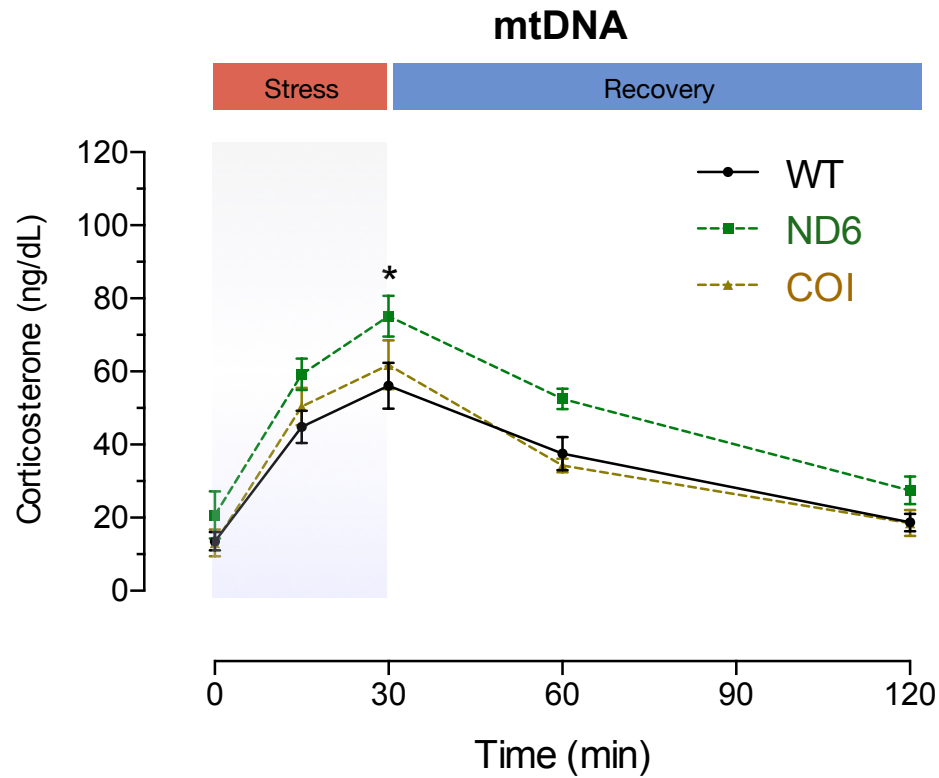
How do energetics and mitochondria influence physiological responses ?



Animal models of impaired mitochondrial OxPhos and redox

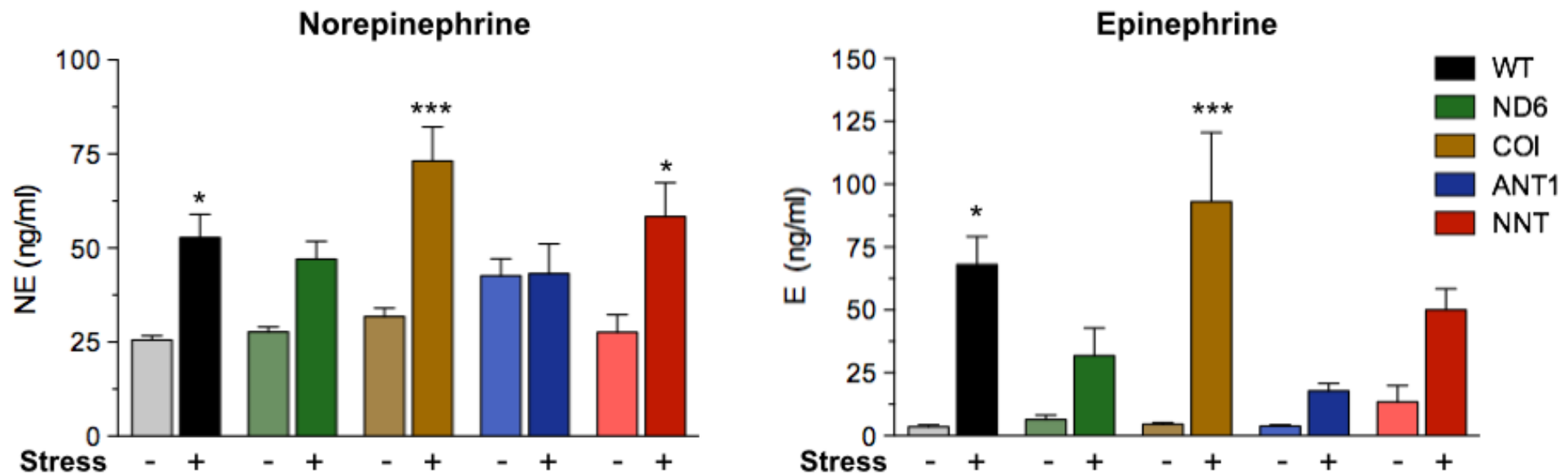


Mitochondrial functions influence stress-induced HPA axis activity

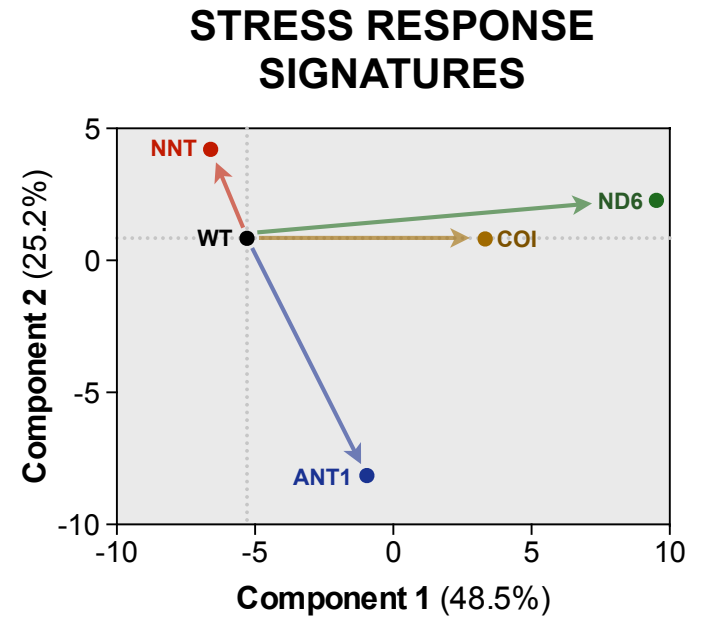
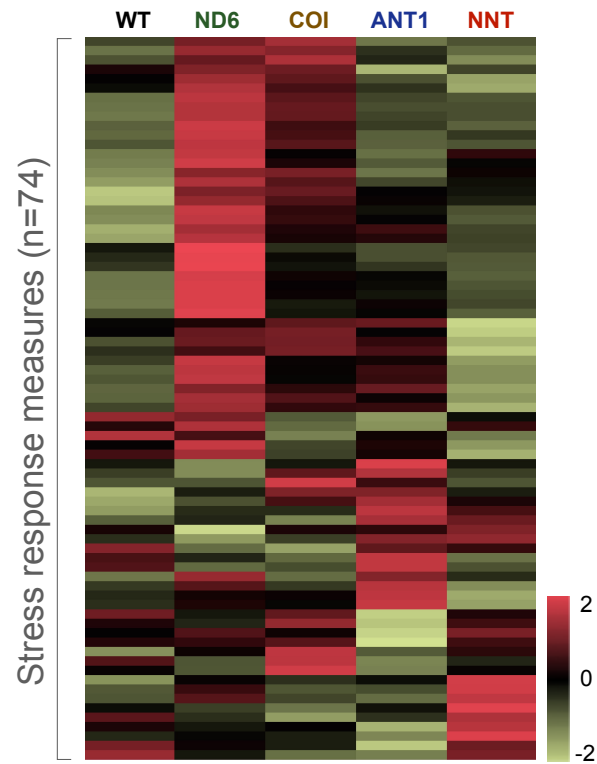
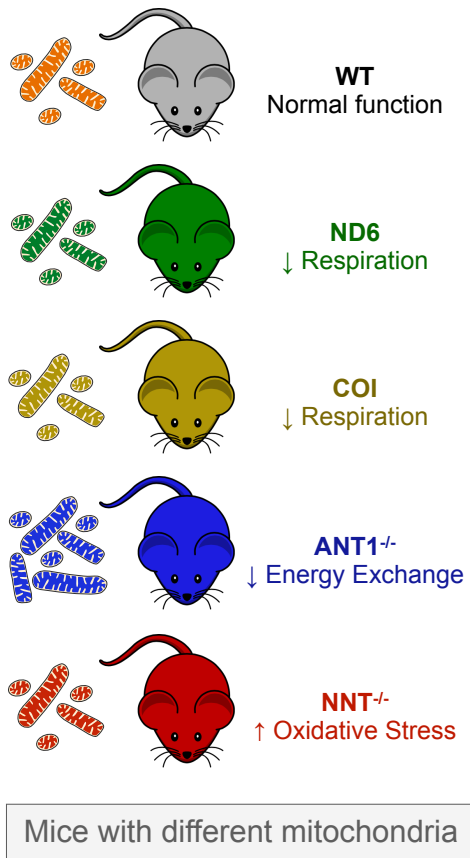




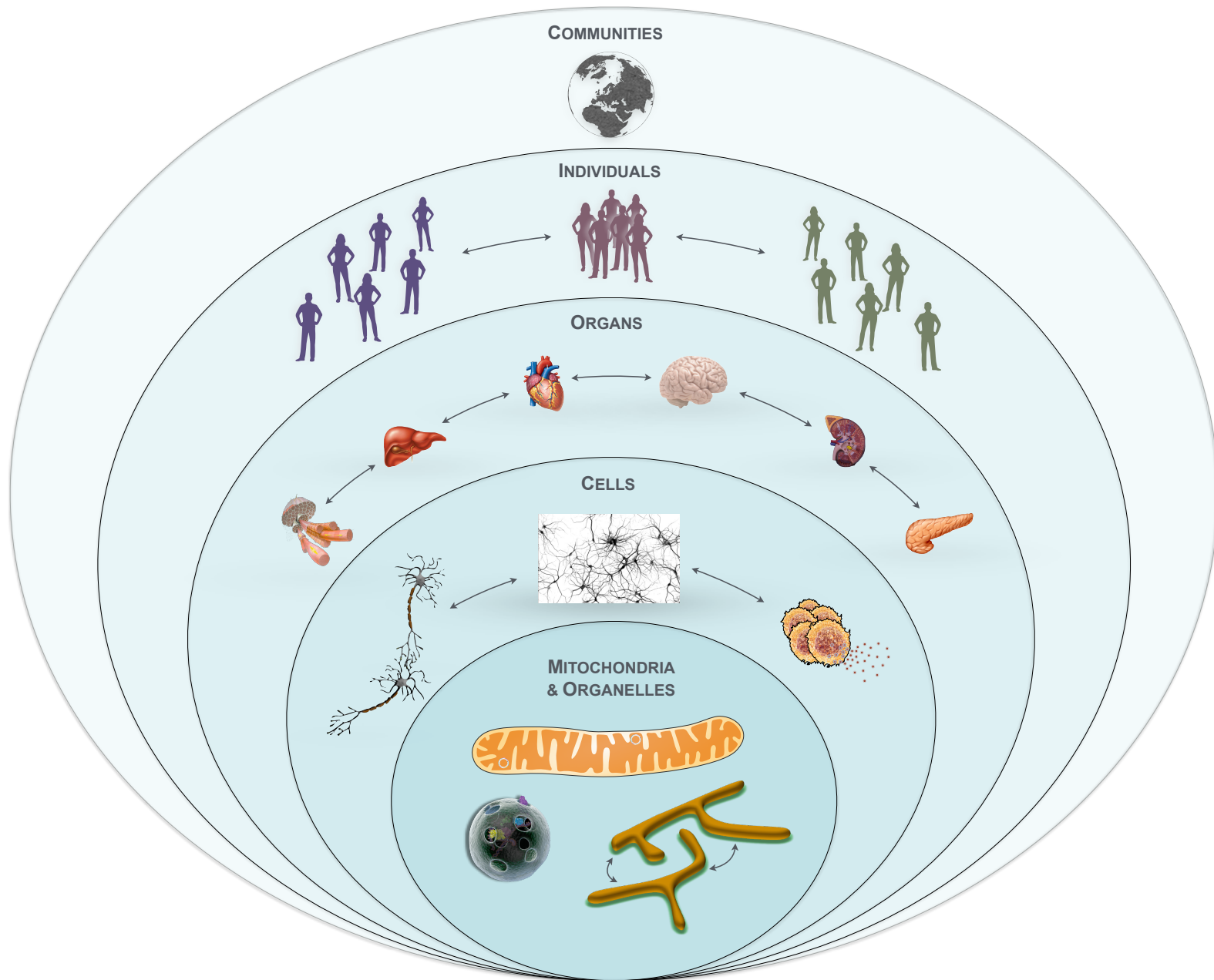
Sympathetic Adrenal-Medullary (SAM) Axis



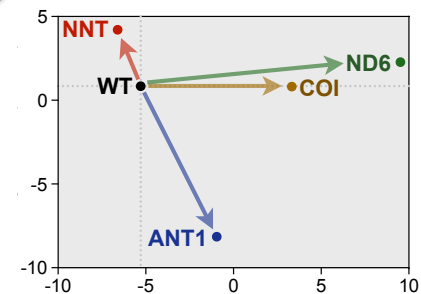
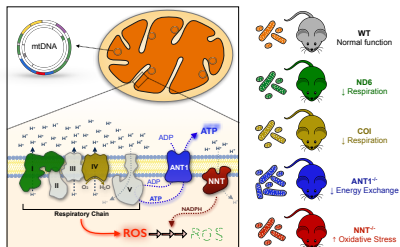
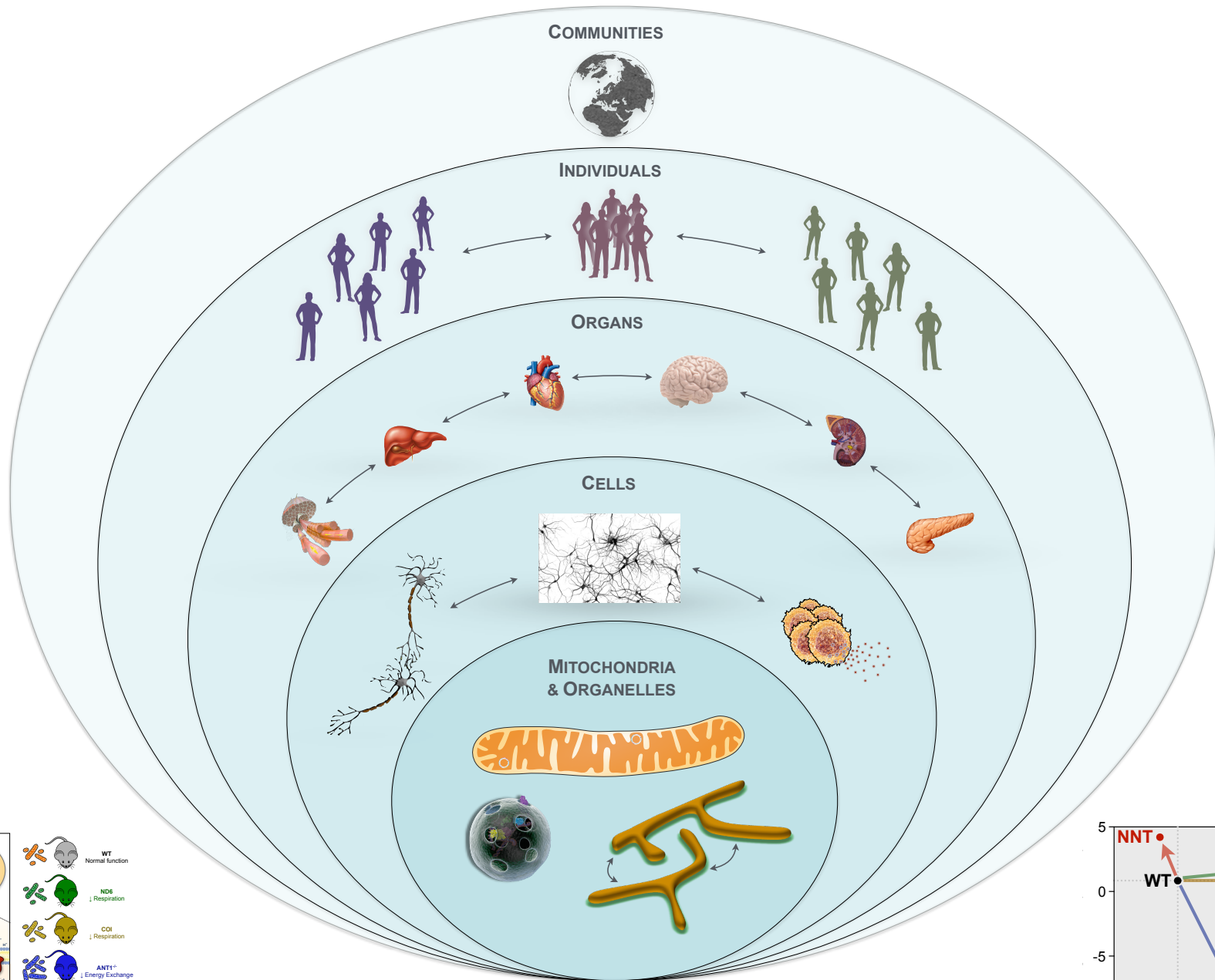
Mitochondria drive unique stress response “signatures”



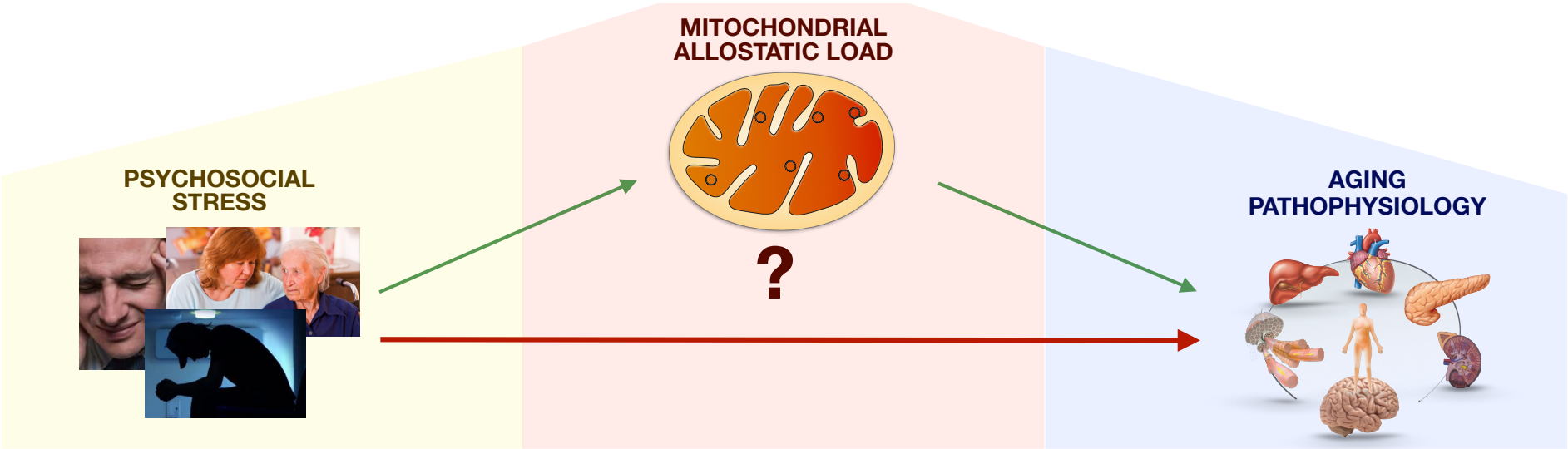
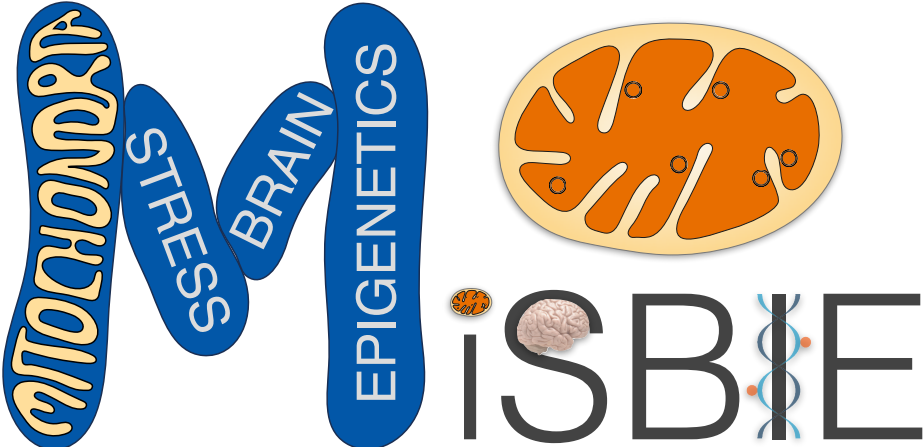
How do energetics and mitochondria influence physiological responses ?



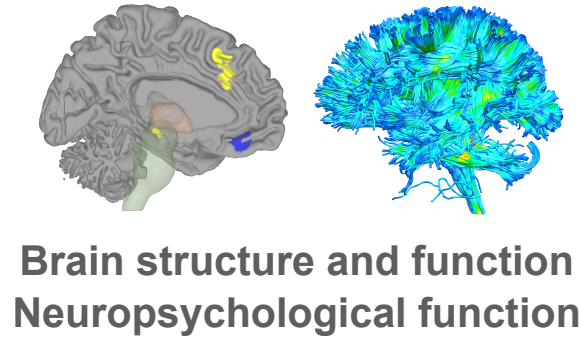
Do mitochondria regulate the stress response in humans?



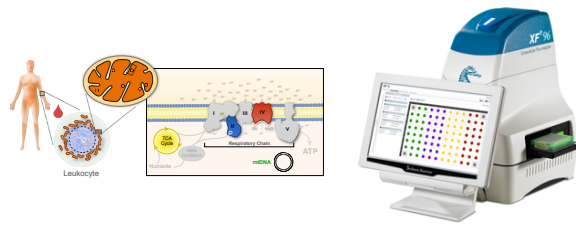
Mitochondrial Stress, Brain Imaging, and Epigenetics — MiSBIE



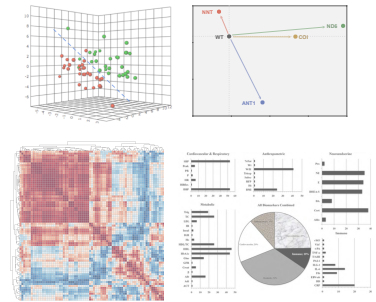
Mitochondrial Stress, Brain Imaging, and Epigenetics — MiSBIE



mtDNA heteroplasmy
Mitochondrial OxPhos
Lymphocytes, Monocytes,
Neutrophils, Platelets

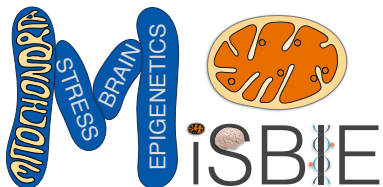


Disease biomarkers
Stress reactivity
Energy expenditure
e.g., Cortisol, NE,
GDF15, Lactate, etc.

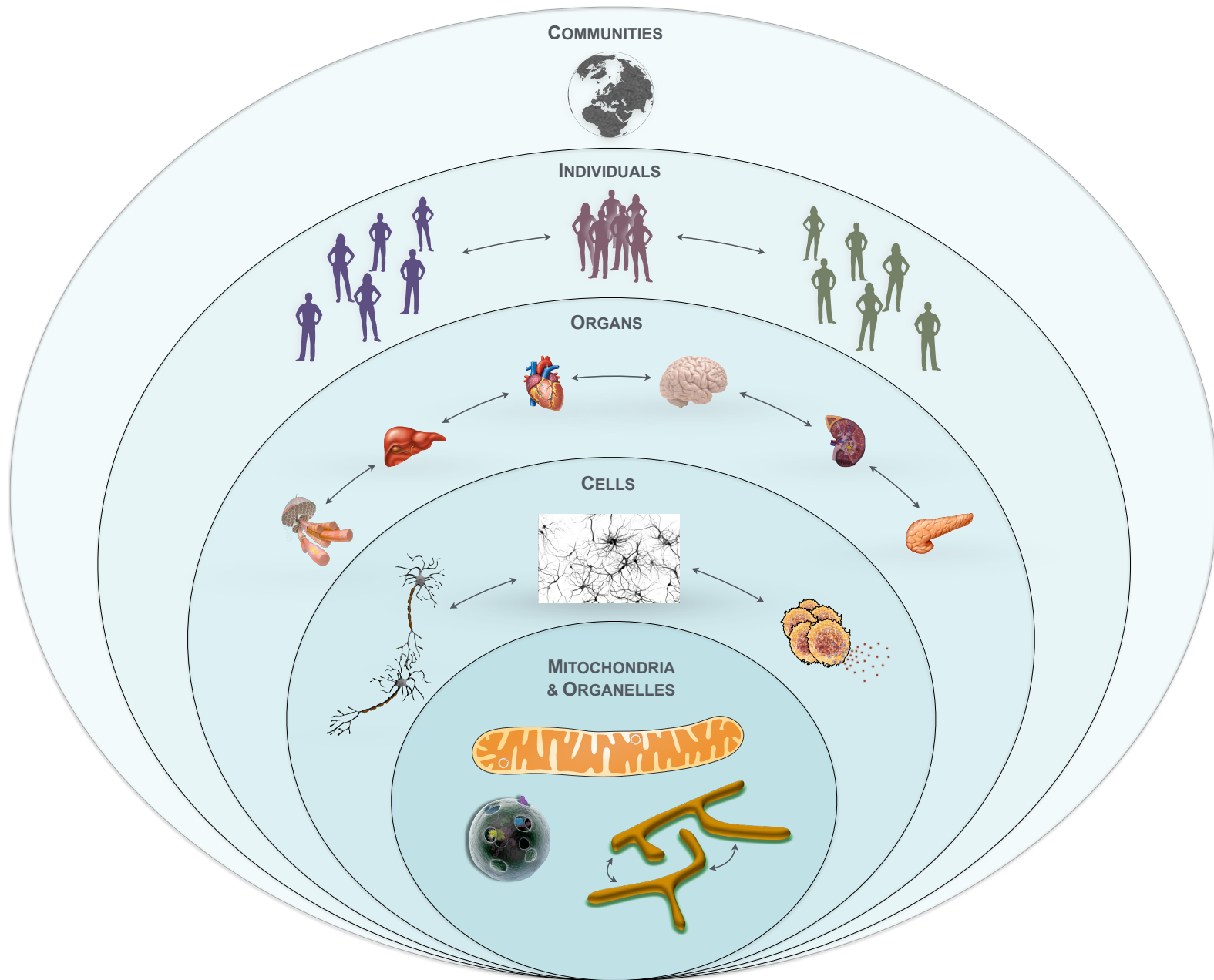


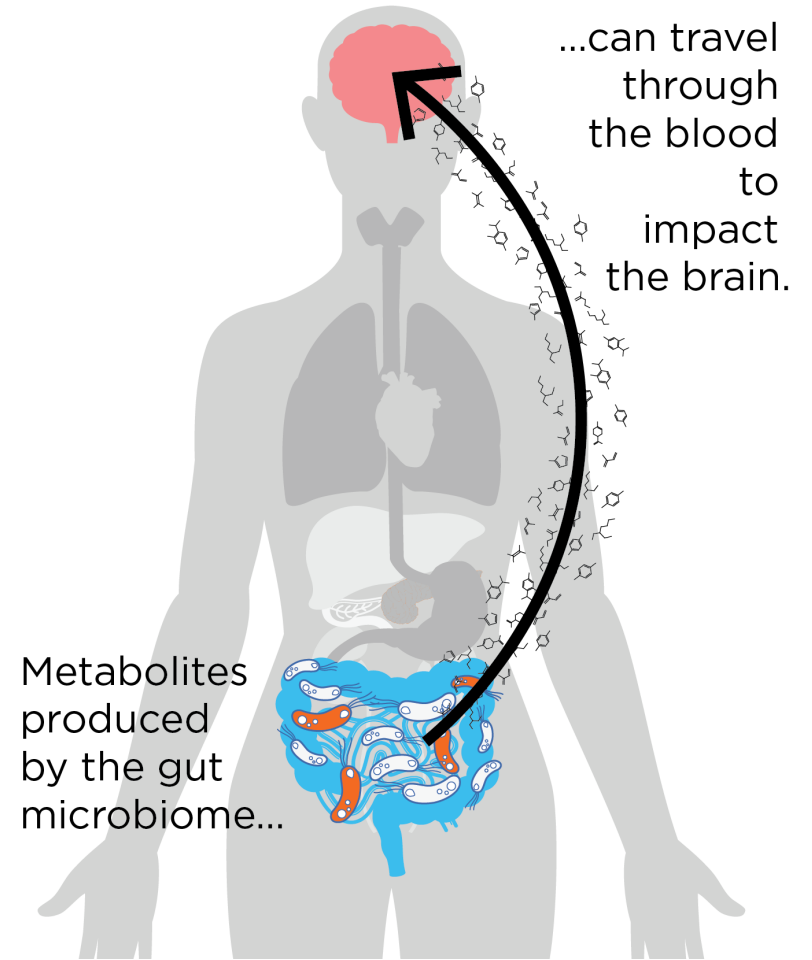
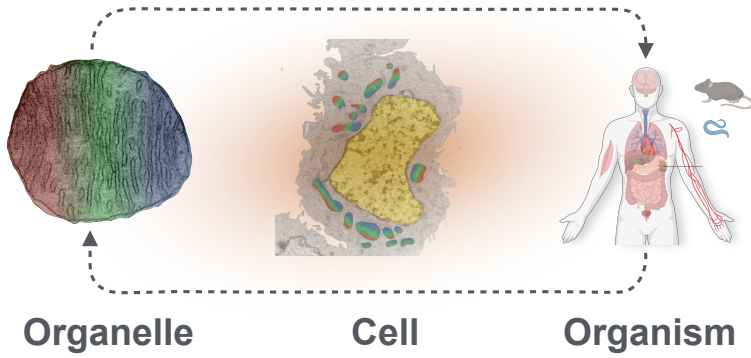
Total N = 110

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



How do metabolites shape stress responses ?

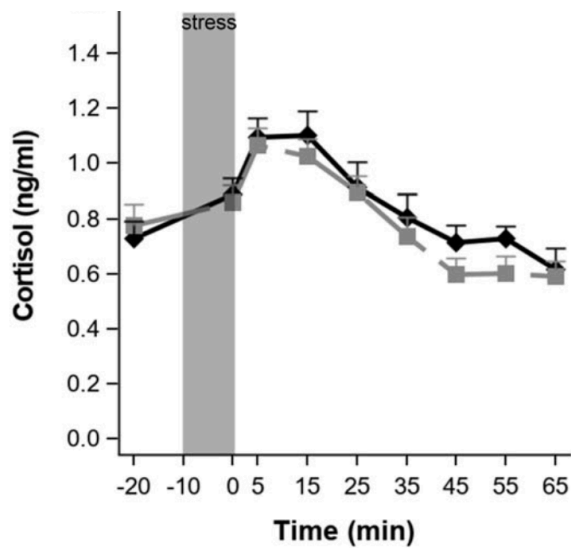




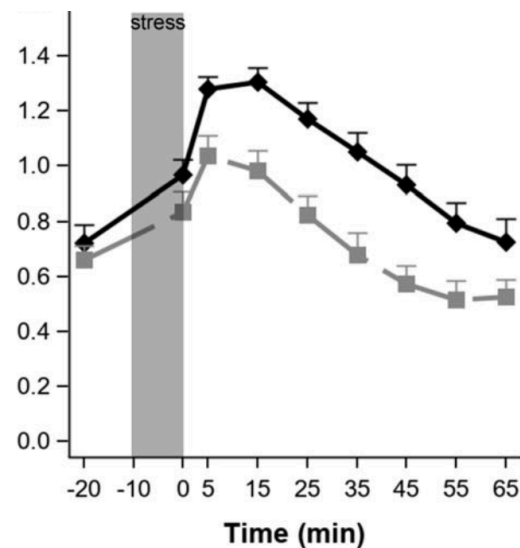
www.owlstonemedical.com

Gut-derived metabolite short-chain fatty acids

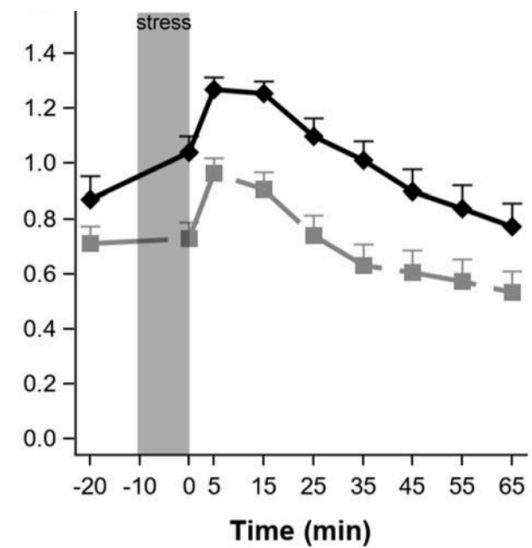
Placebo



Low dose

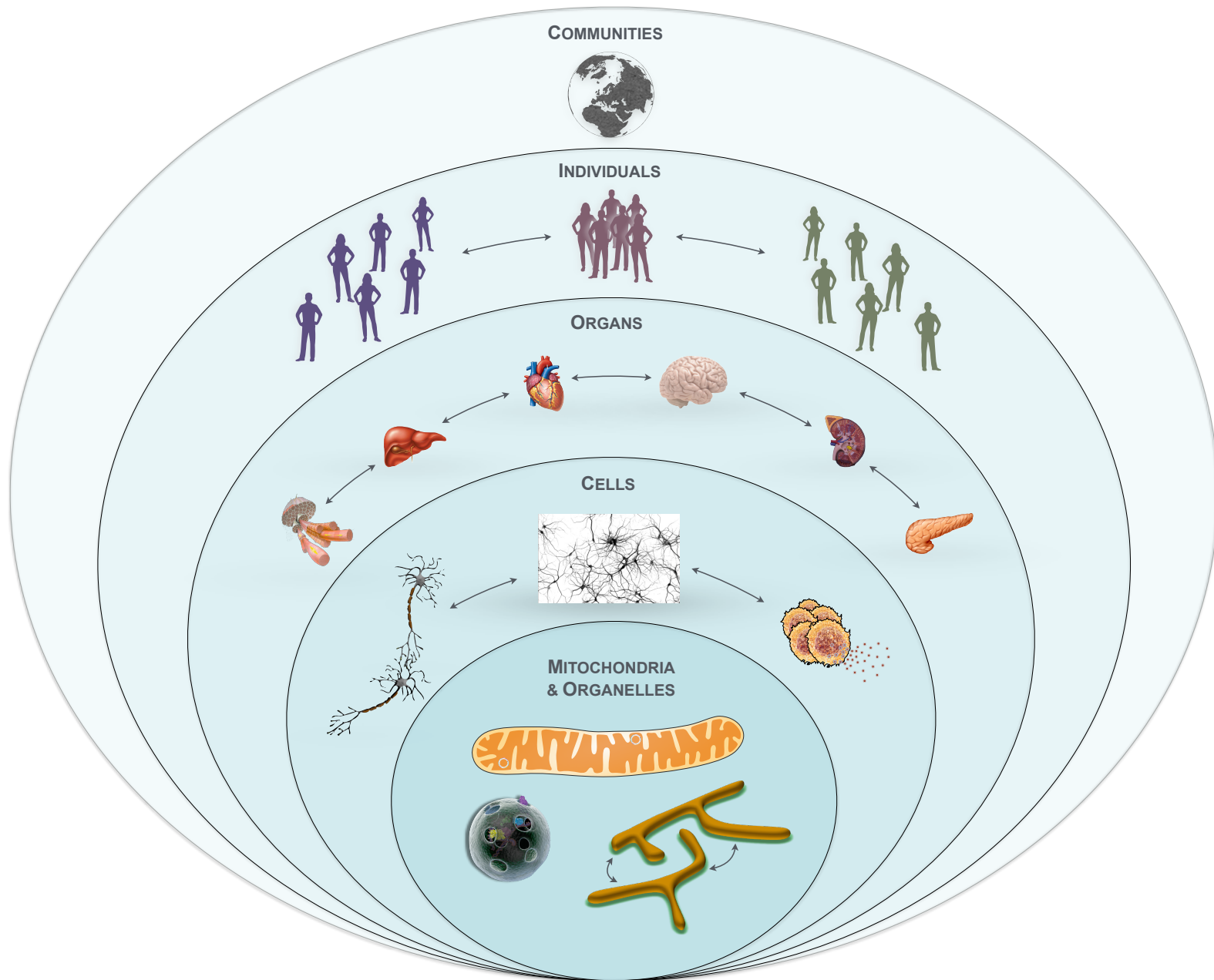


High dose

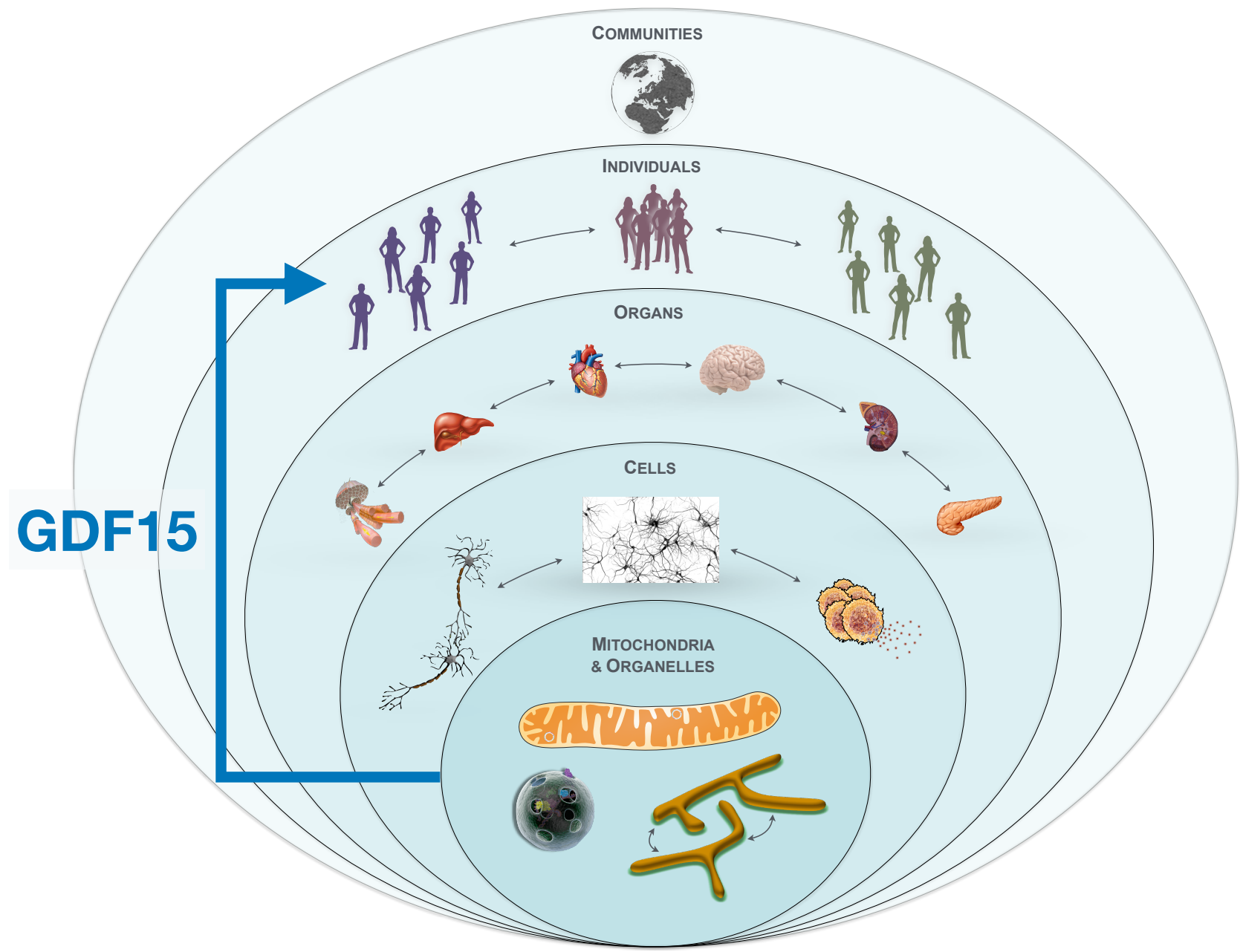


—◆— pre-intervention
—■— post-intervention

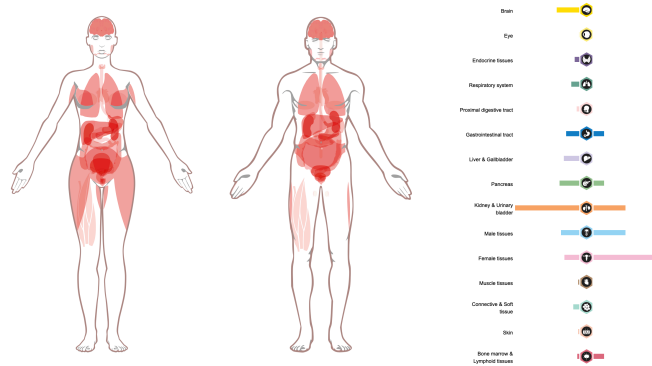
How do metabolites shape stress responses ?



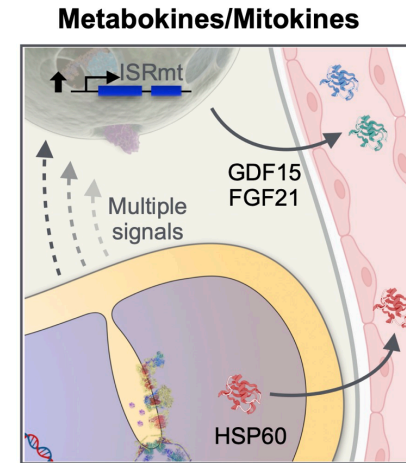
How does information about mitochondrial health reach the brain ?



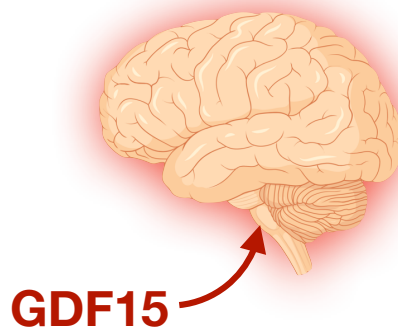
What does GDF15 mean to the organism?



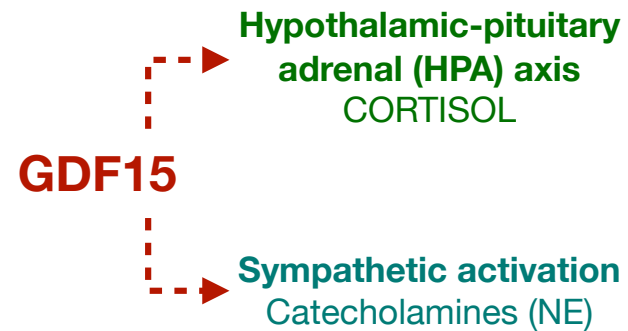
Expressed in >90% of somatic tissues



Triggered by cellular stressors (ISR)

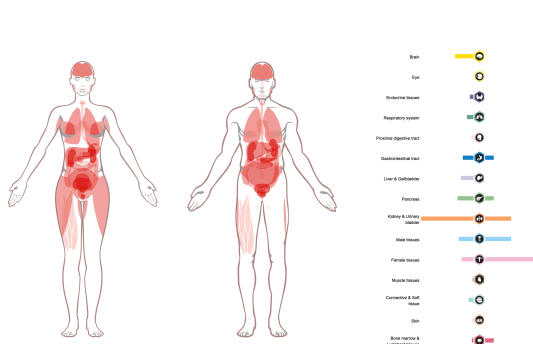


Signals on the brainstem

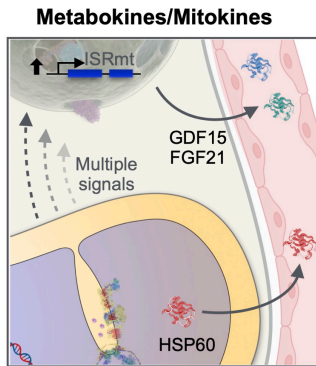


Activates canonical stress axes

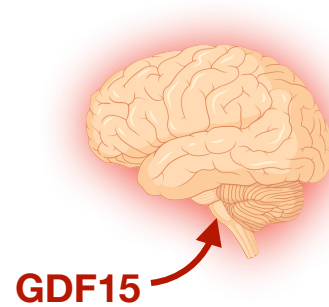
What does GDF15 mean to the organism?



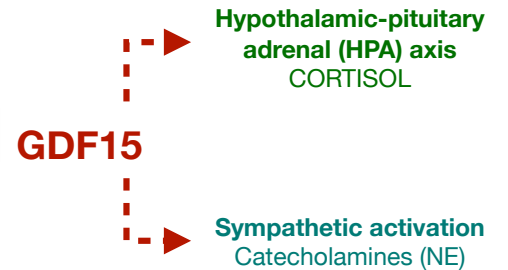
Expressed in >50% somatic tissues



Triggered by cellular stressors (ISR)

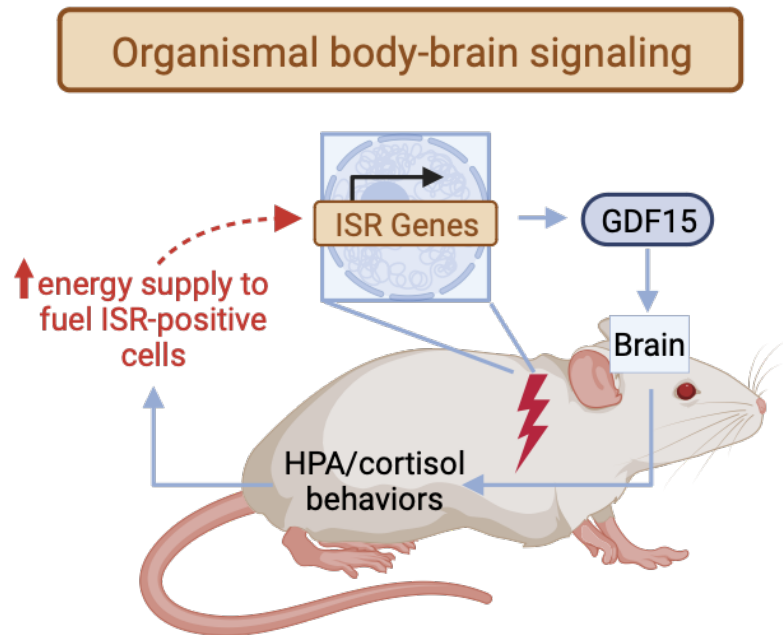


Signals on the brainstem

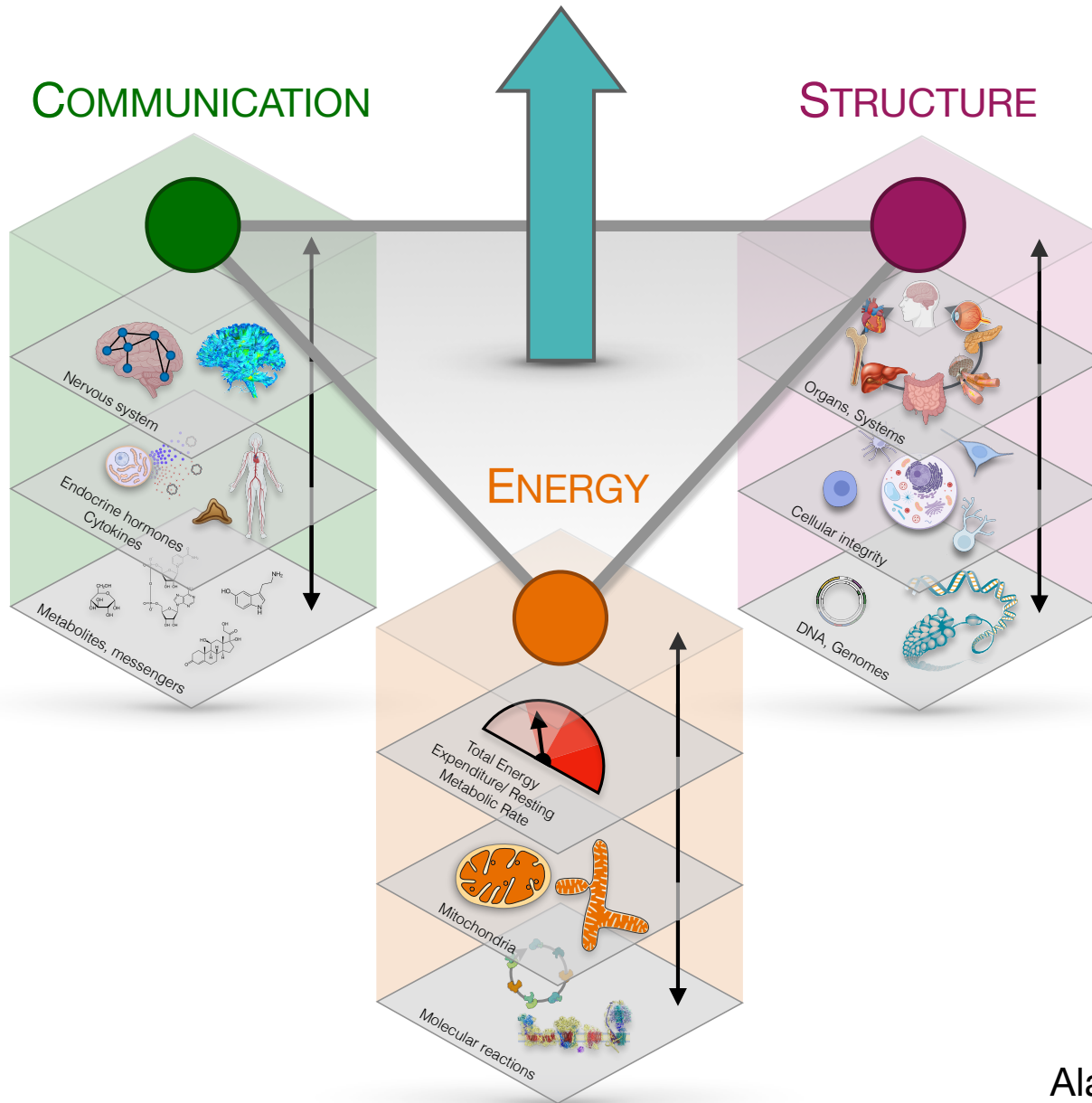


Activates canonical stress axes

Psychological stress transiently increases GDF15 in humans



INTRINSIC HEALTH



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

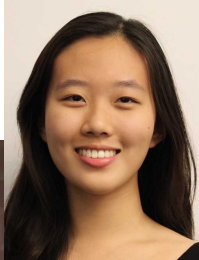
Mitochondrial PsychoBiology Lab

Linking molecular processes within mitochondria with the human experience

OUR RESEARCH



Alex



Mangesh



Catherine



Jack



David



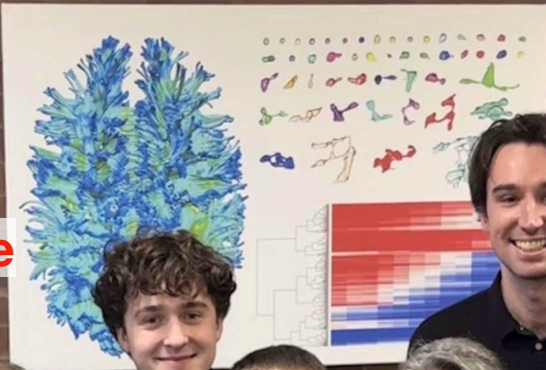
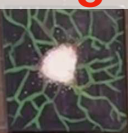
Anna



Gabriel



Jeremy



Caroline



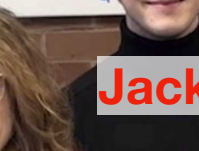
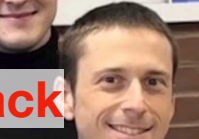
Janell



Hannah



Natalia



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Pittsburgh University

Gyuri Hajnóczy
Erin Seifert
Thomas Jefferson University

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Mike Irwin
UCLA

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CNIC Madrid

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Rohit Sharma
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University of Michigan

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Jon Brestoff
Wash U

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University of Luxembourg

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EPFL

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Julie Herbstman
Linda Fried
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Nour Makarem
Sen Pei
Dan Malinsky
Ying Wei
Mailman & Columbia Aging Center

Luigi Ferrucci
NIA Intramural

 National Institute of Mental Health

 National Institute of General Medical Sciences

 National Institute on Aging

BASZUCKI

BRAIN RESEARCH FUND

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