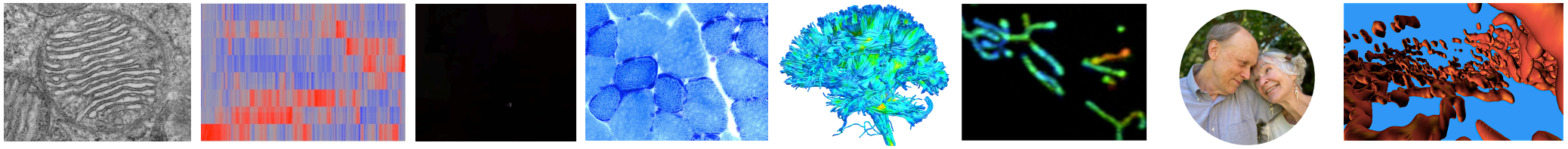
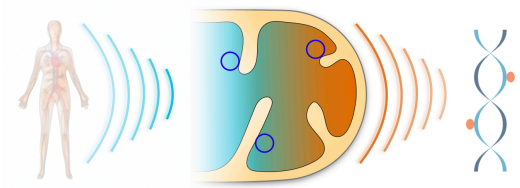


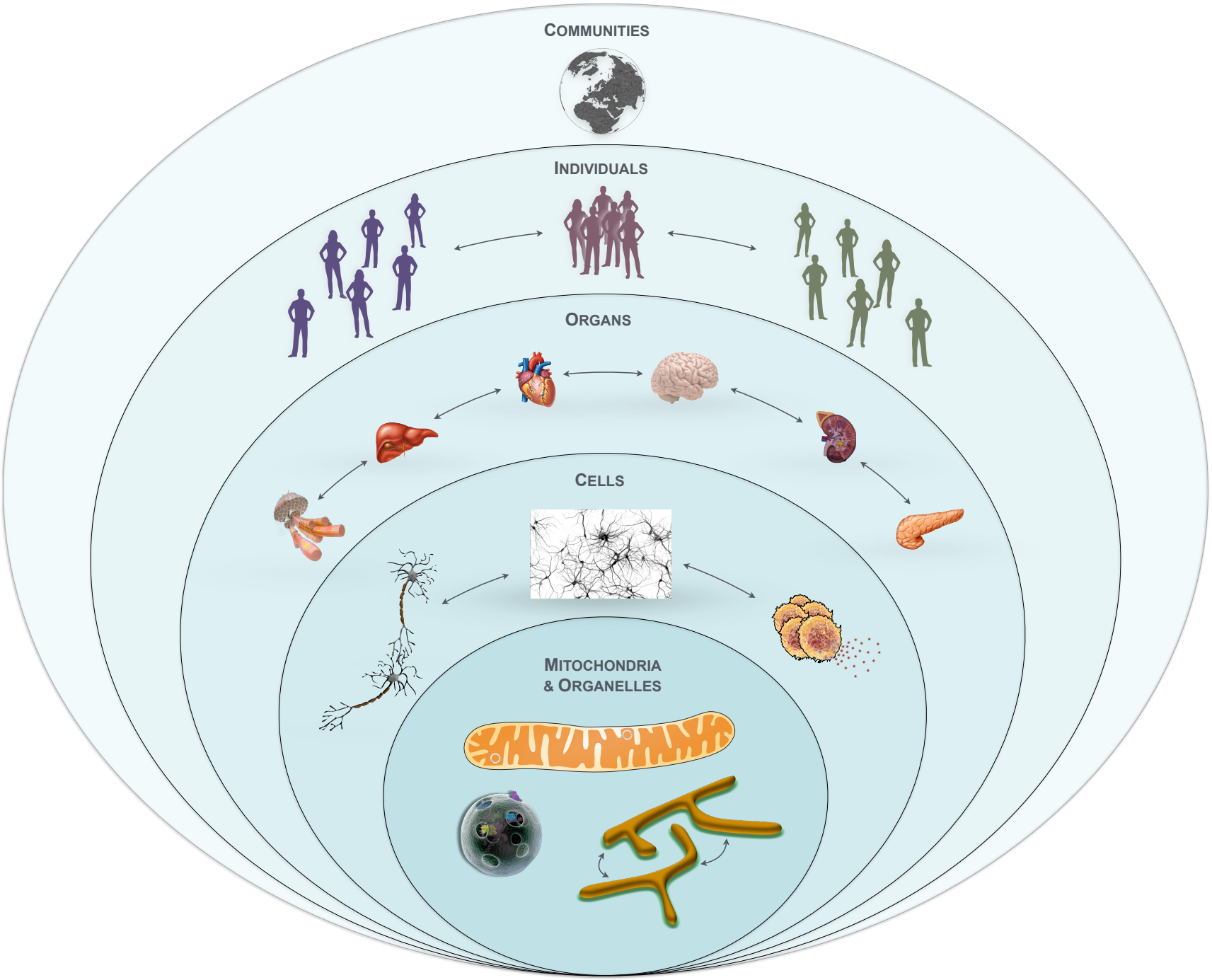
Mitochondrial psychobiology in immune and brain cells



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

COLUMBIA
COLUMBIA UNIVERSITY
IRVING MEDICAL CENTER

NEW YORK STATE OF OPPORTUNITY.
New York State Psychiatric Institute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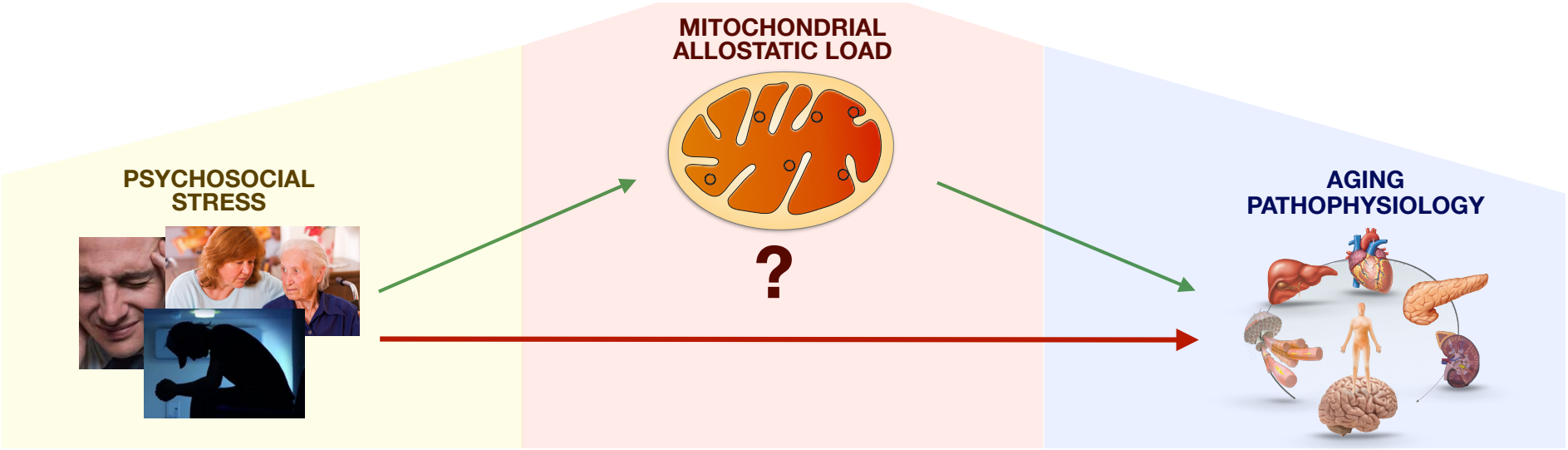
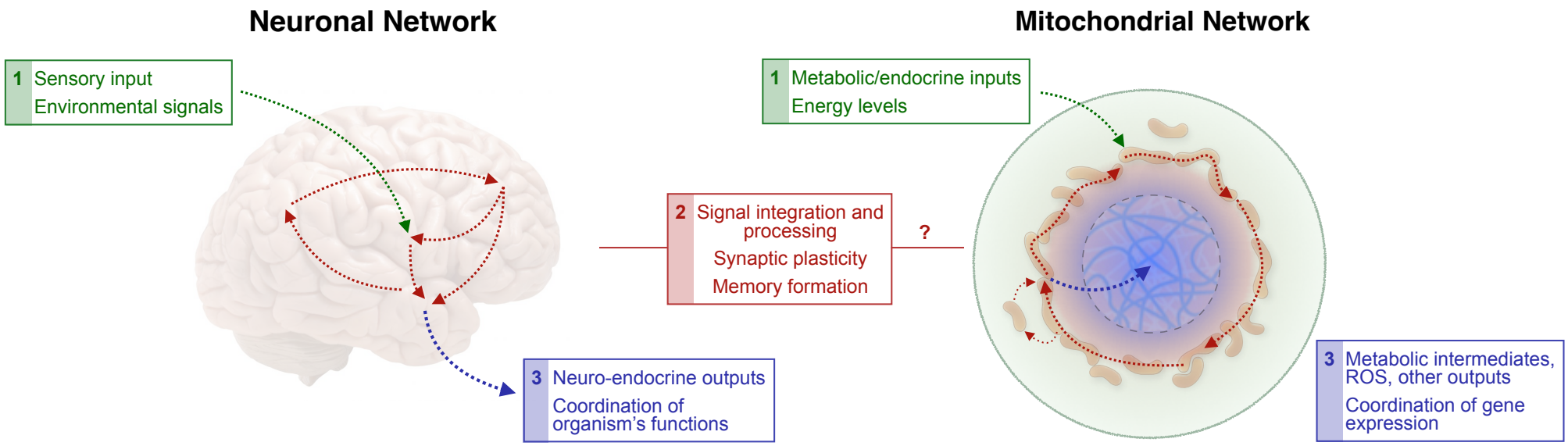


MITOCHONDRIAL PSYCHOBIOLOGY

Mitochondrial psychobiology examines the interactions between **psychological states** and the **molecular and energetic processes** within mitochondria

Curr Opin Behav Sci (2019)

Mitochondria are signal-processing units

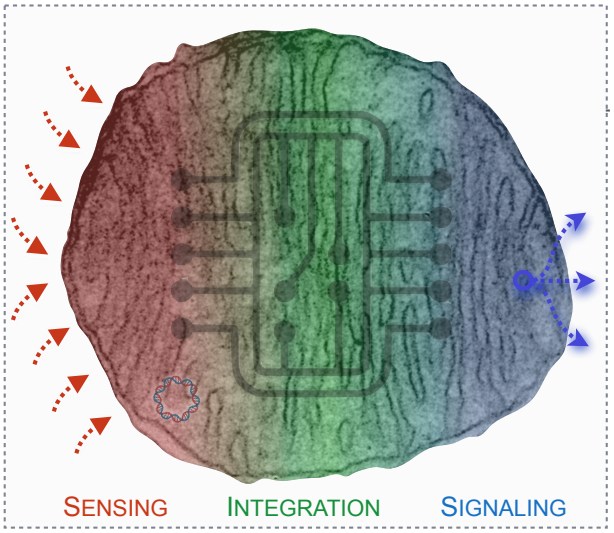


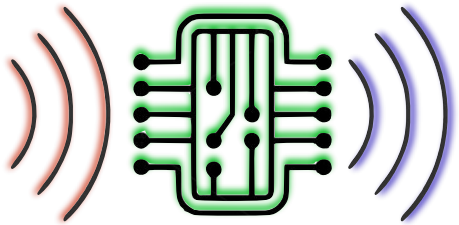
"The organism is integrated into a larger system of information exchange […]. The brain and the rest of the organism are not qualitatively different in their ability to compute information, but show only qualitative differences in their purposiveness." — *Herbert Weiner,* **Perturbing the Organism** *(1992)*

Trends Neurosci 2015

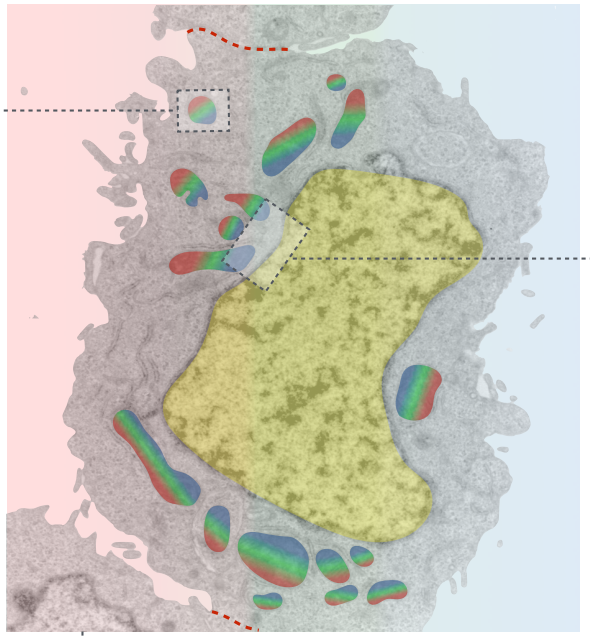
Mitochondrial **I**nformation **P**rocessing **S**ystem — **MIPS**

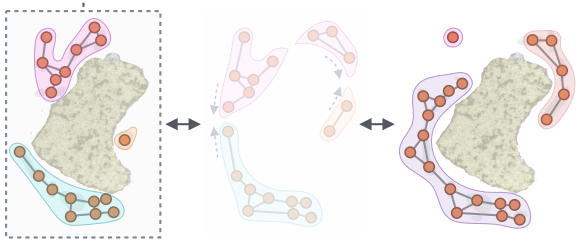
Signal transducing mitochondrion



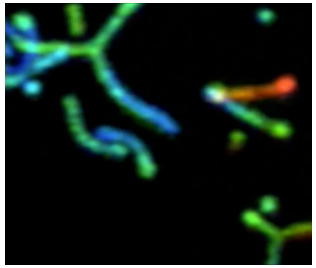


"Mitochondria are the processor of the cell"

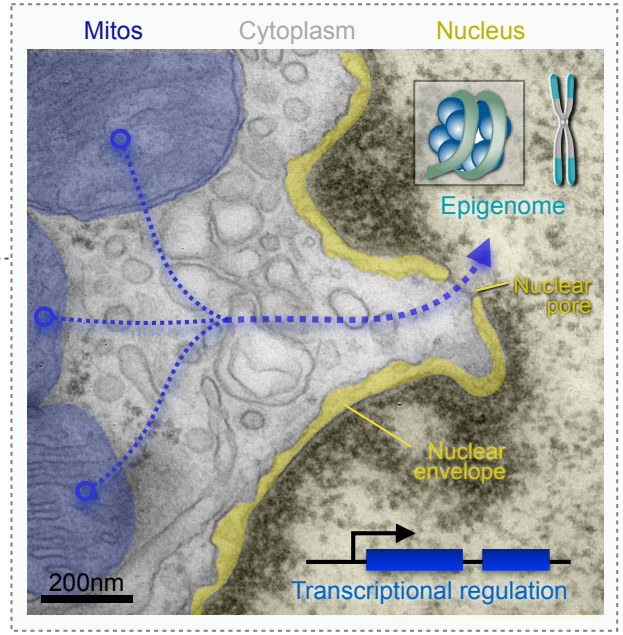


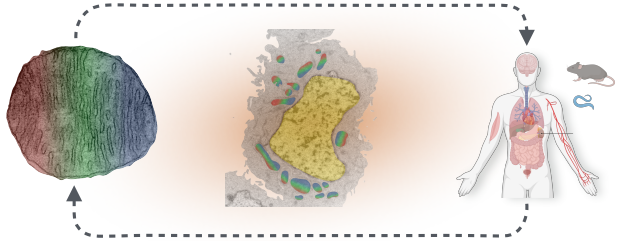


Dynamic remodeling of mito networks



Mito-nuclear unit

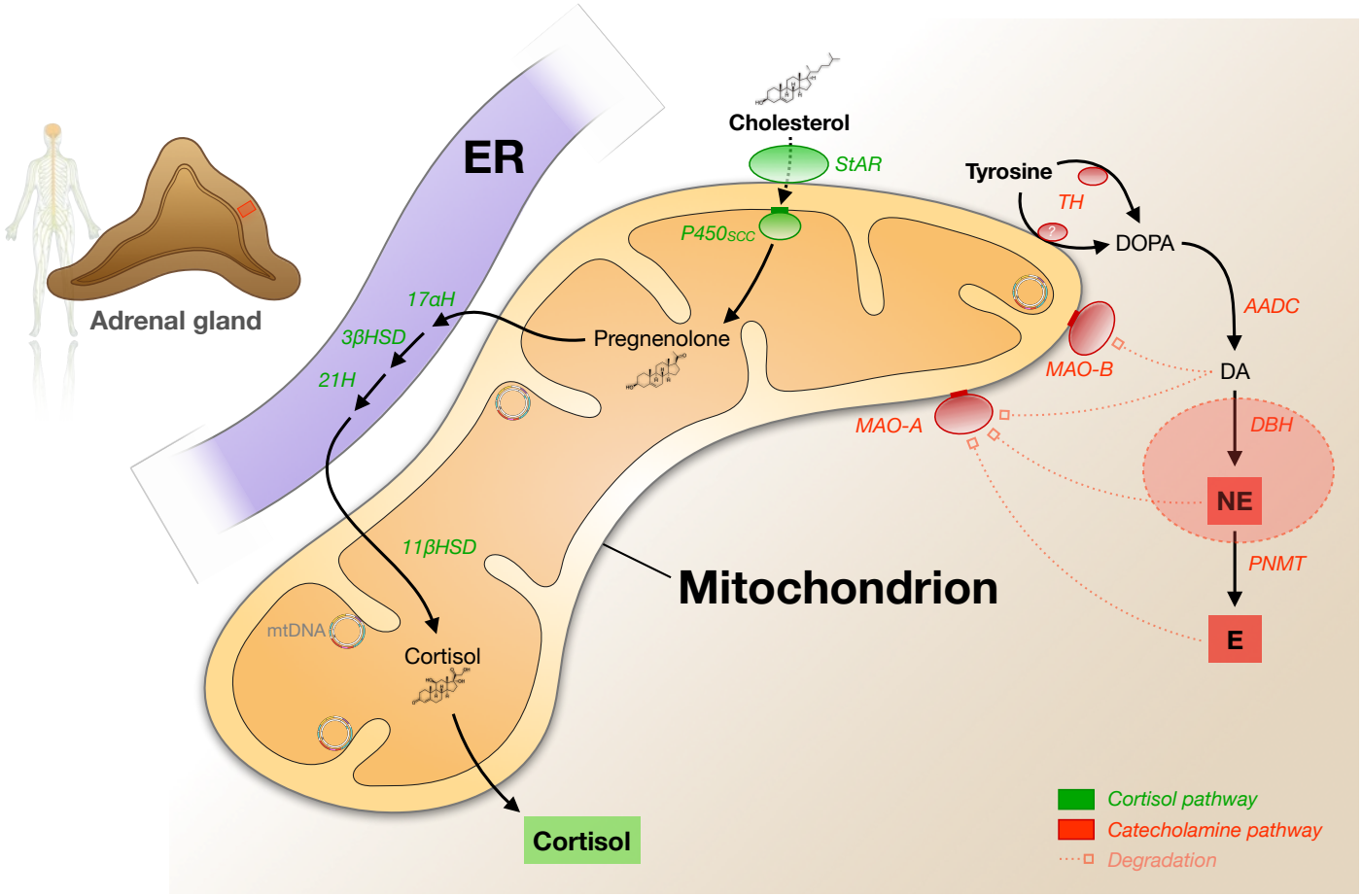


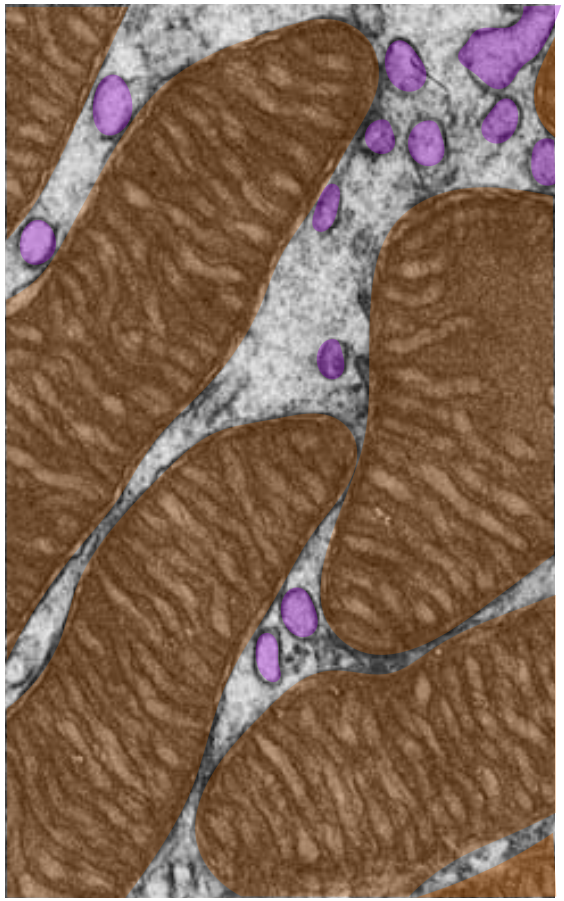


Picard and Shirihai. *Cell Metab* 2022

Mitochondria and hormones?

Mitochondria synthesize glucocorticoid and sex hormones

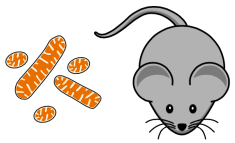




Picard, McEwen, Epel, Sandi. *Front Neuroendocrinol* 2018

Mitochondria cause unique stress response signatures

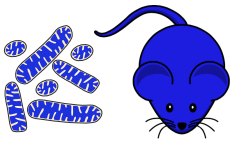
Mice with different mitochondria



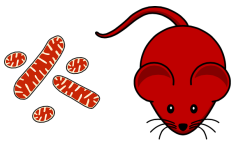
WT
Normal function

ND6
↓ Respiration

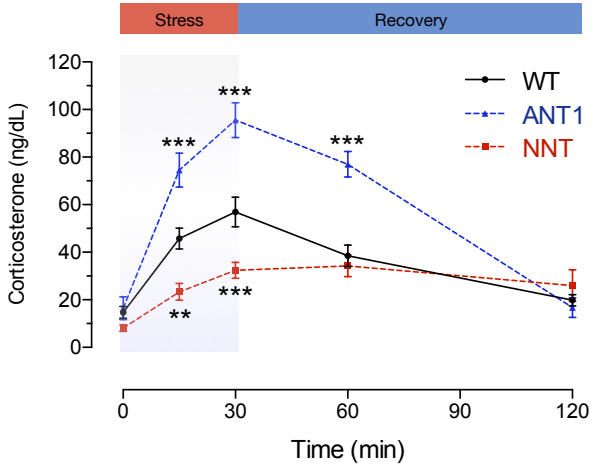
COI
↓ Respiration

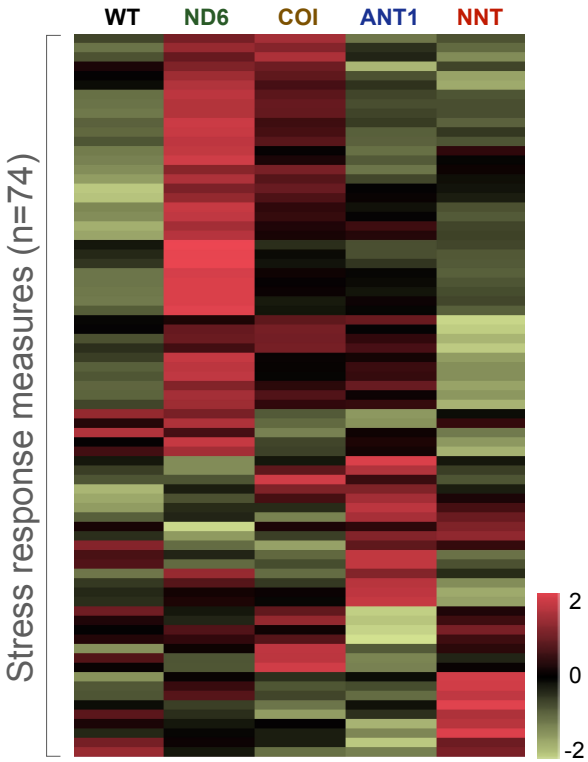


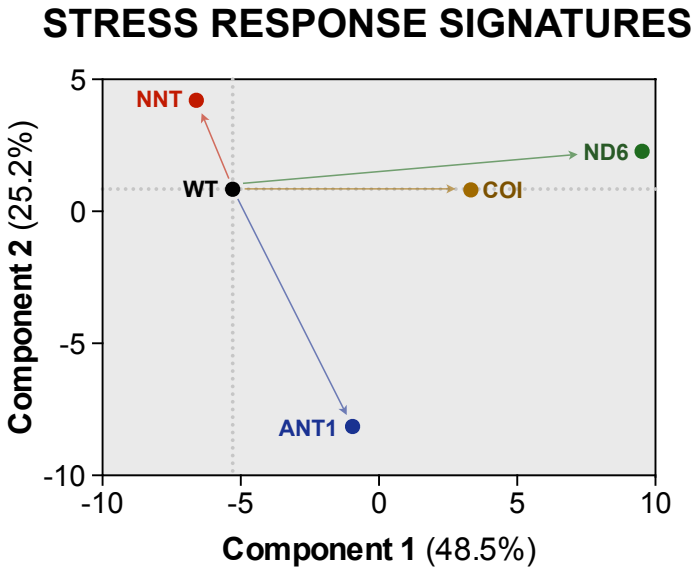
ANT1$^{-/-}$
↓ Energy Exchange



NNT$^{-/-}$
↑ Oxidative Stress

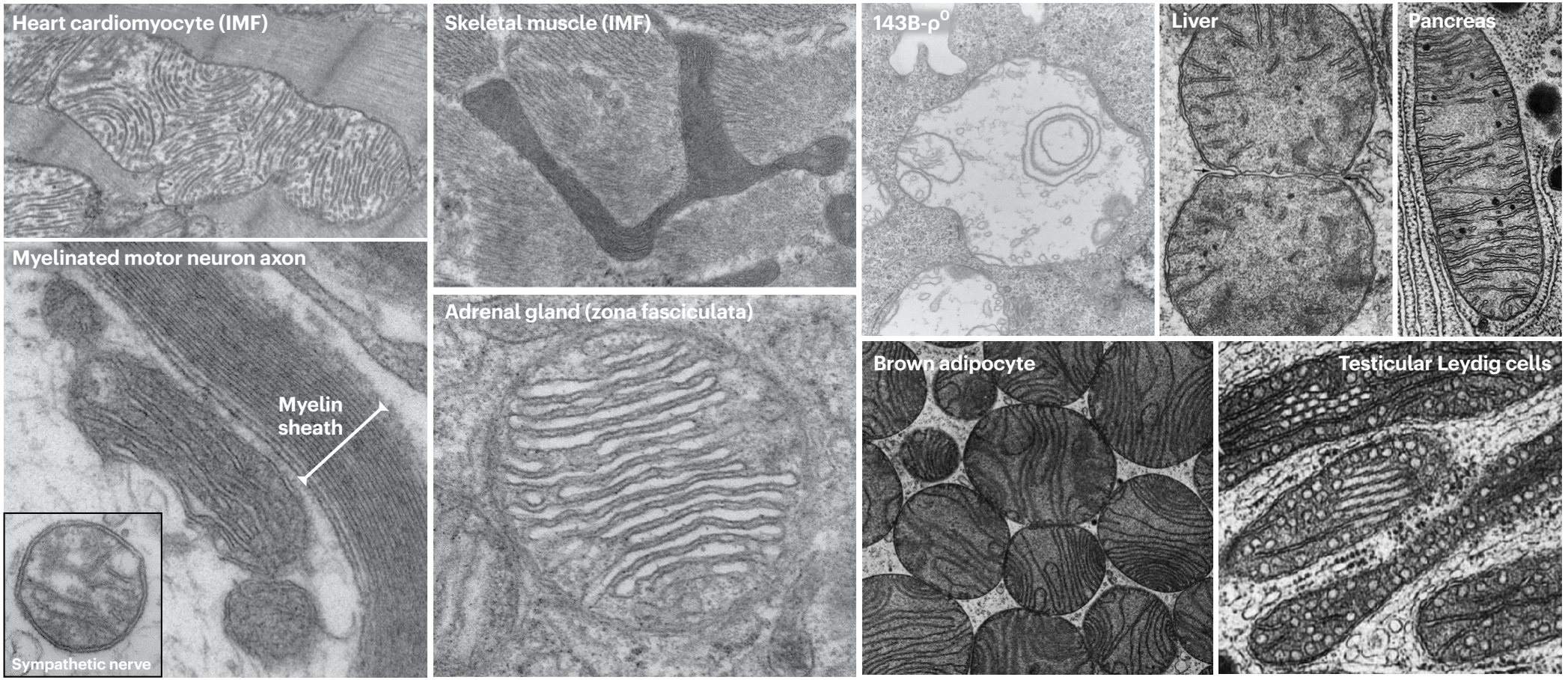


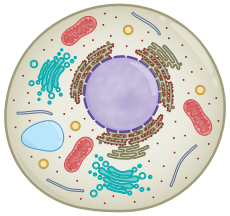




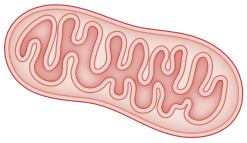
Picard et al. *PNAS* 2015

Different mitochondria types (mitotypes)



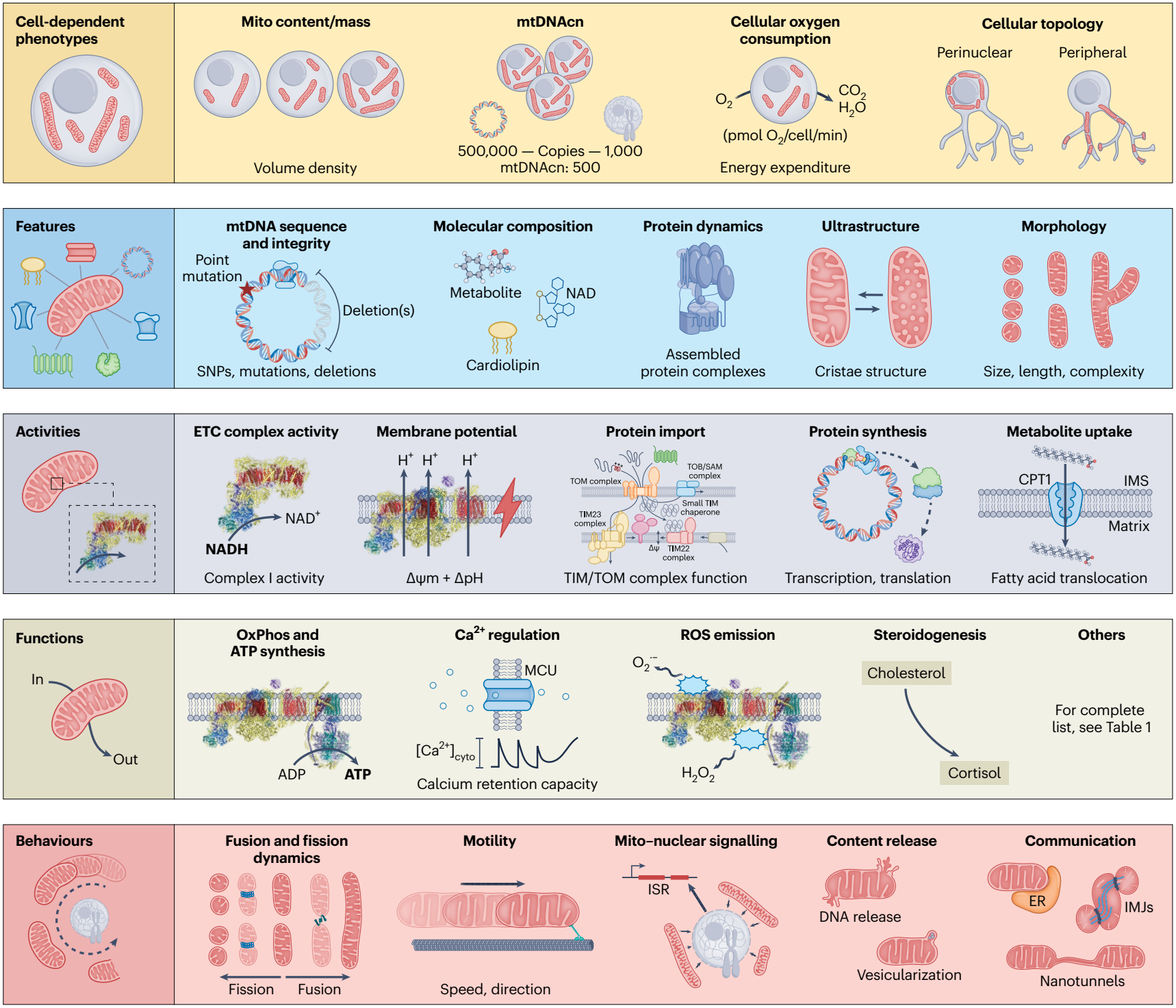


Cell types and subtypes



Mitochondrial phenotypes

Monzel et al.
Nat Metab 2023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Mito content/mass
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500,000 — Copies — 1,000
mtDNAcn: 500
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O2
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Energy expenditure
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Perinuclear
Peripheral
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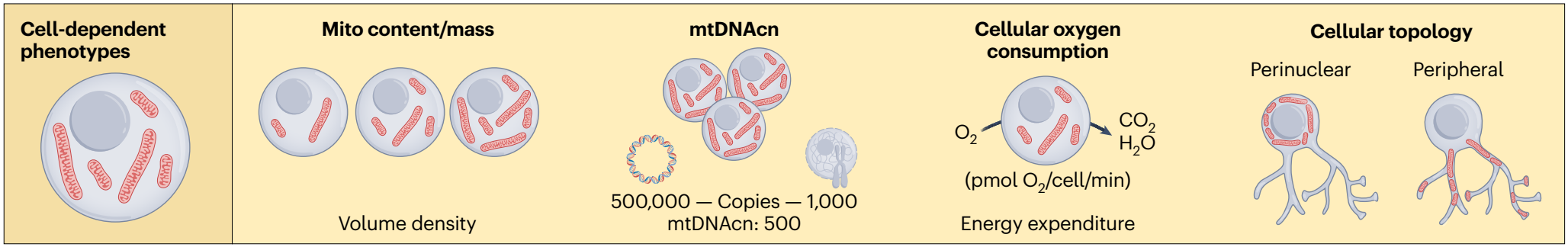
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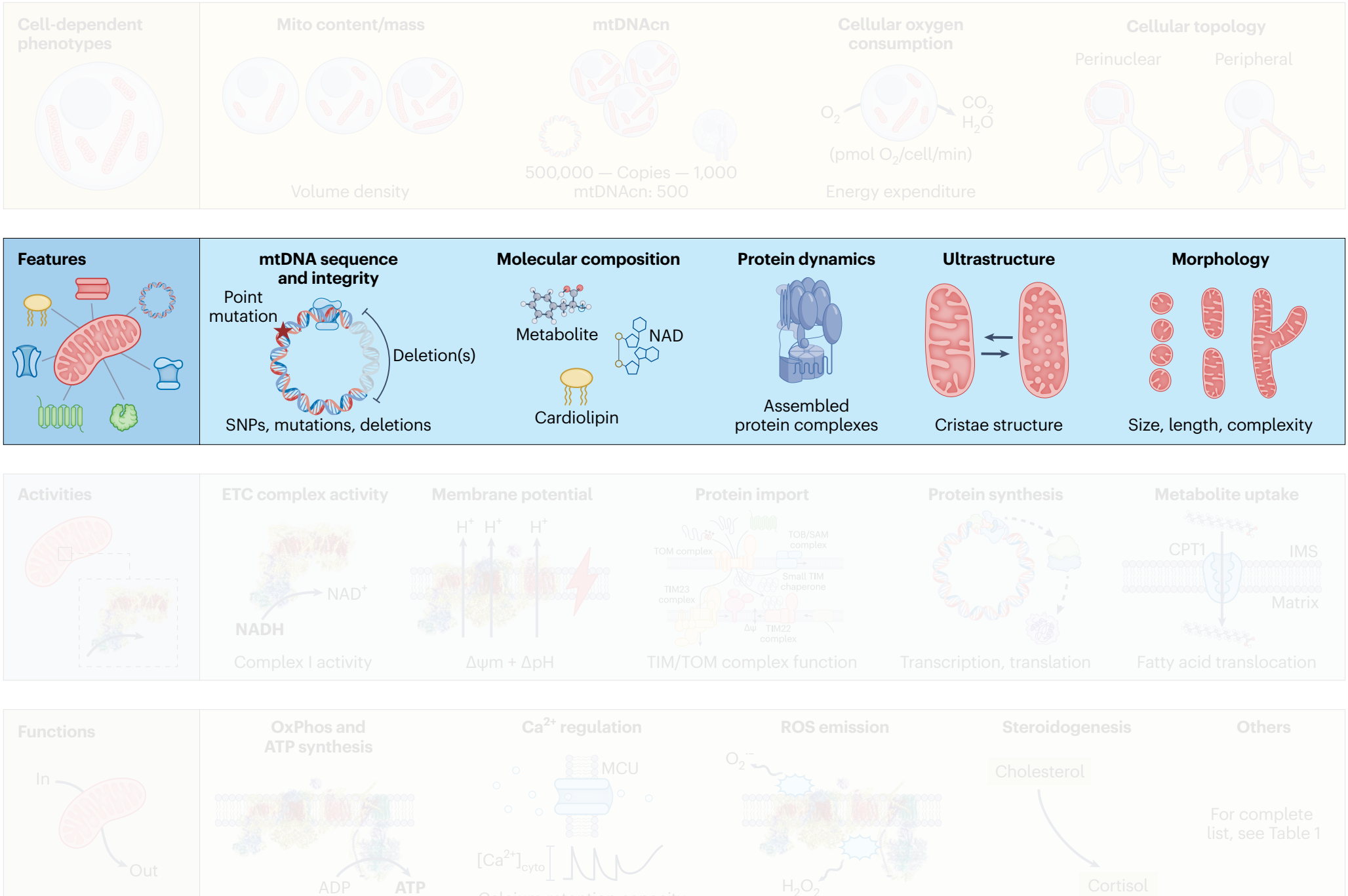
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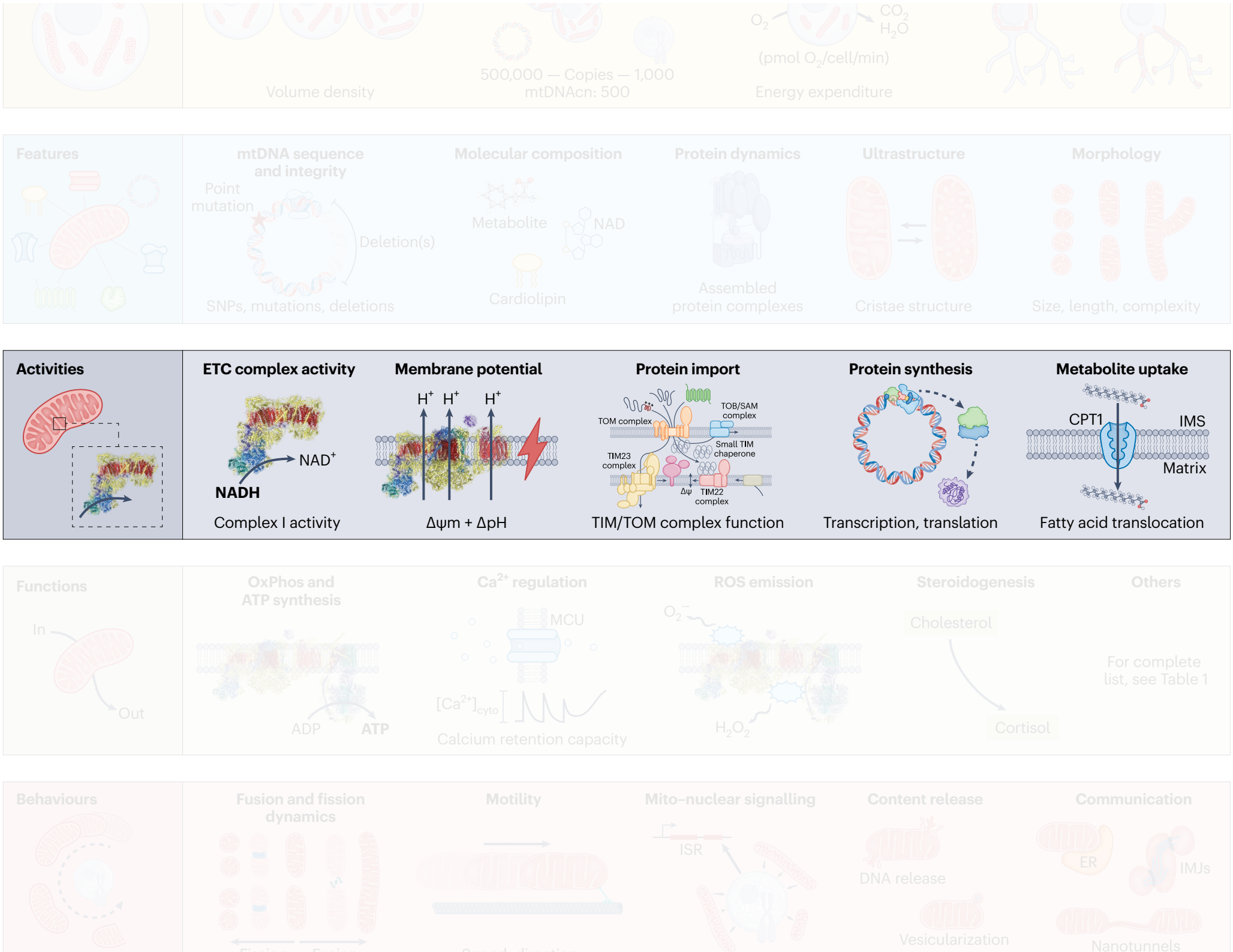
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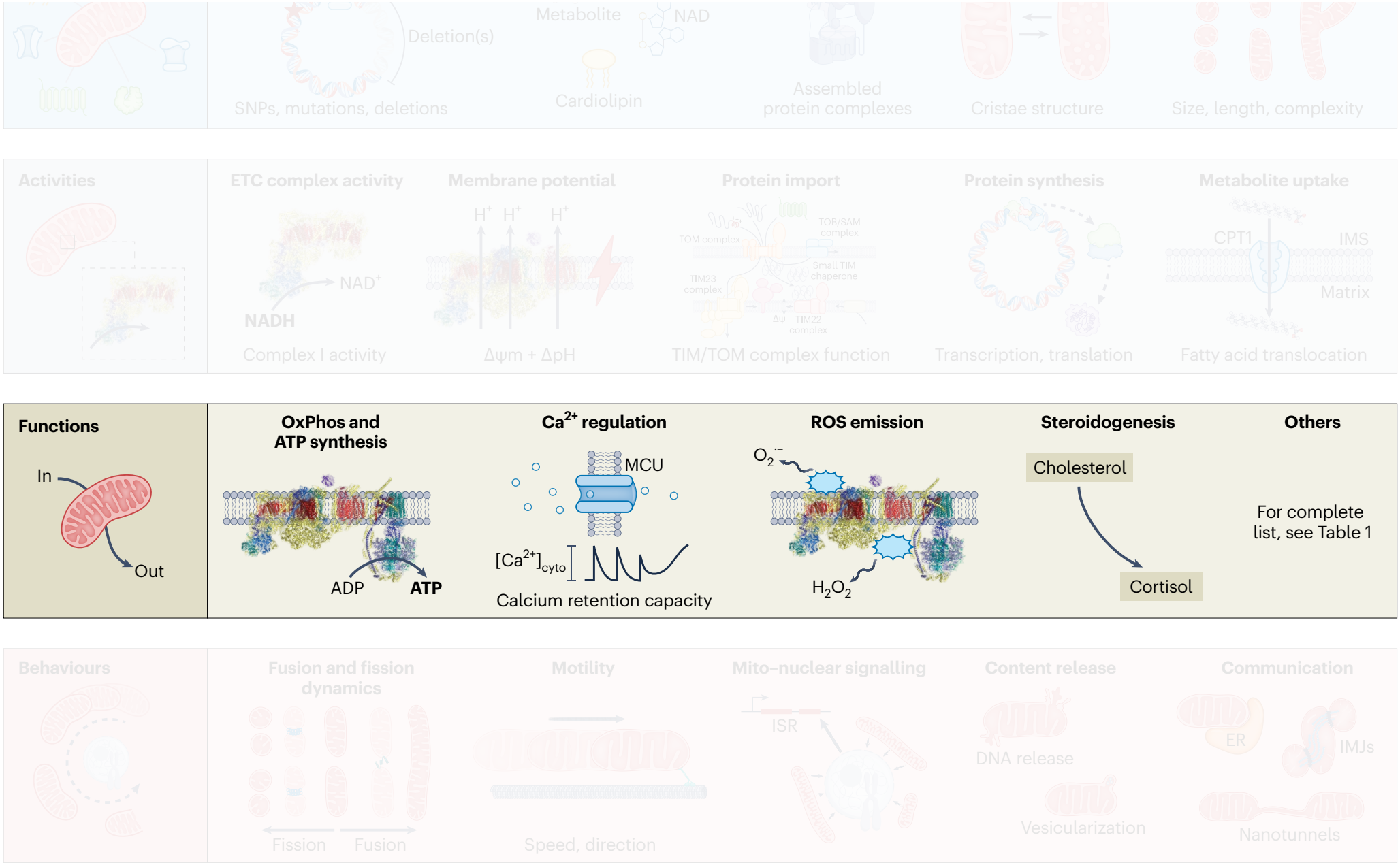
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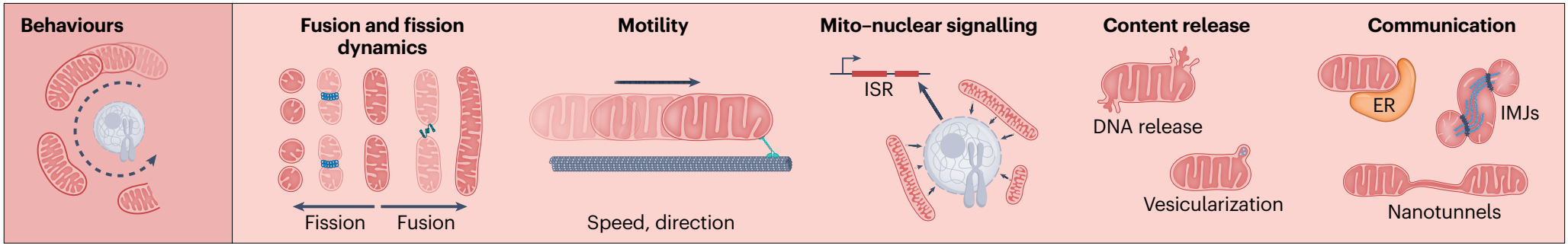
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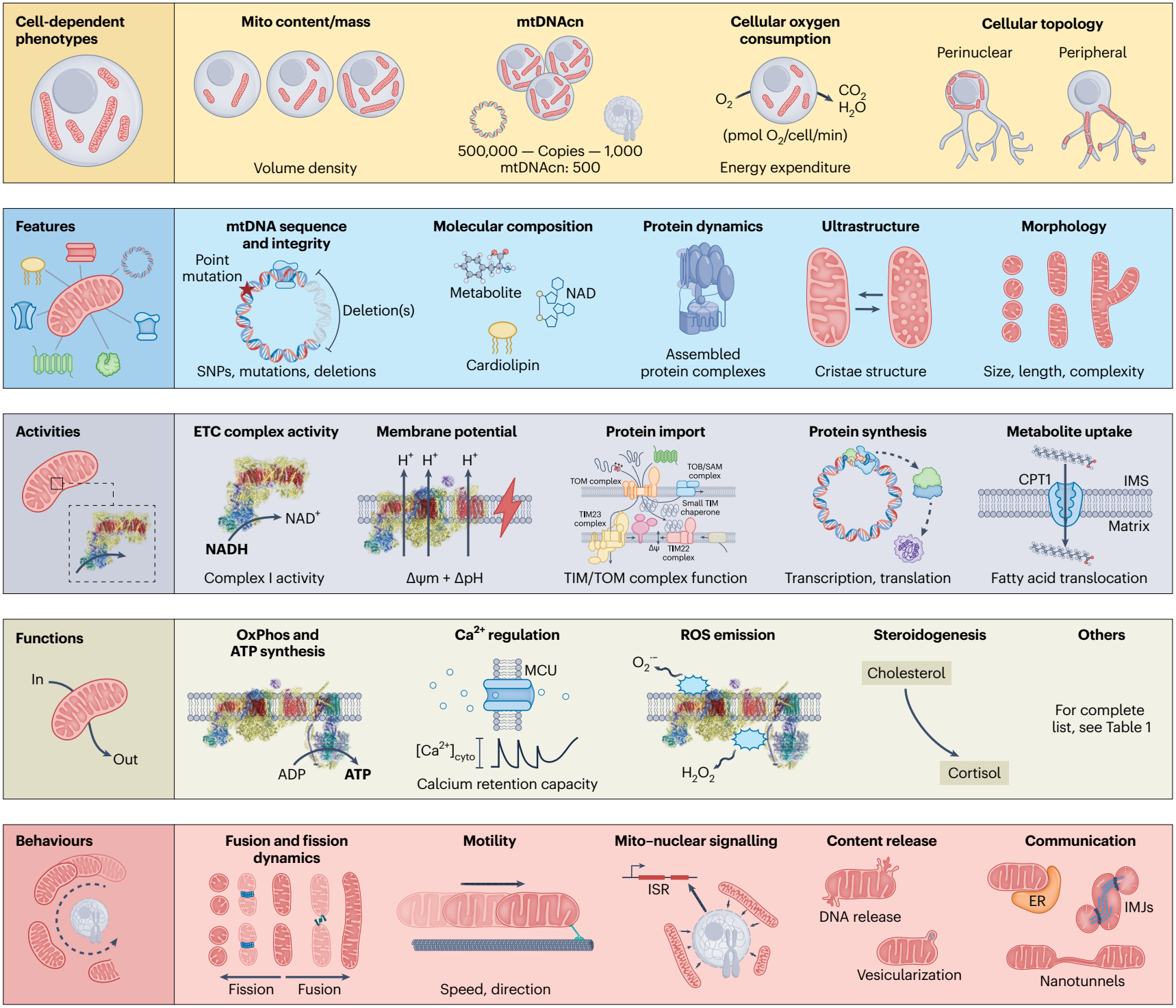
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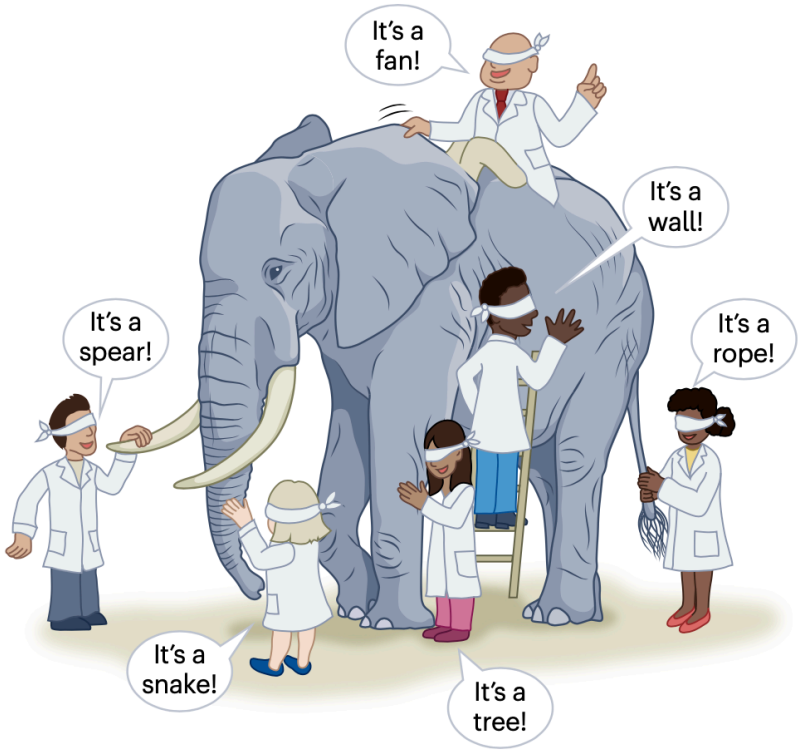
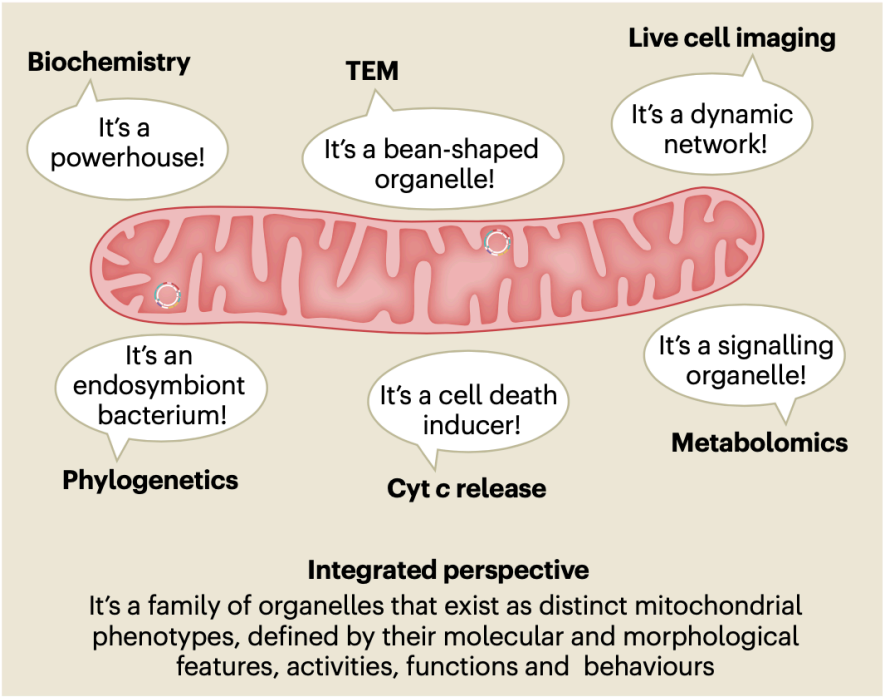
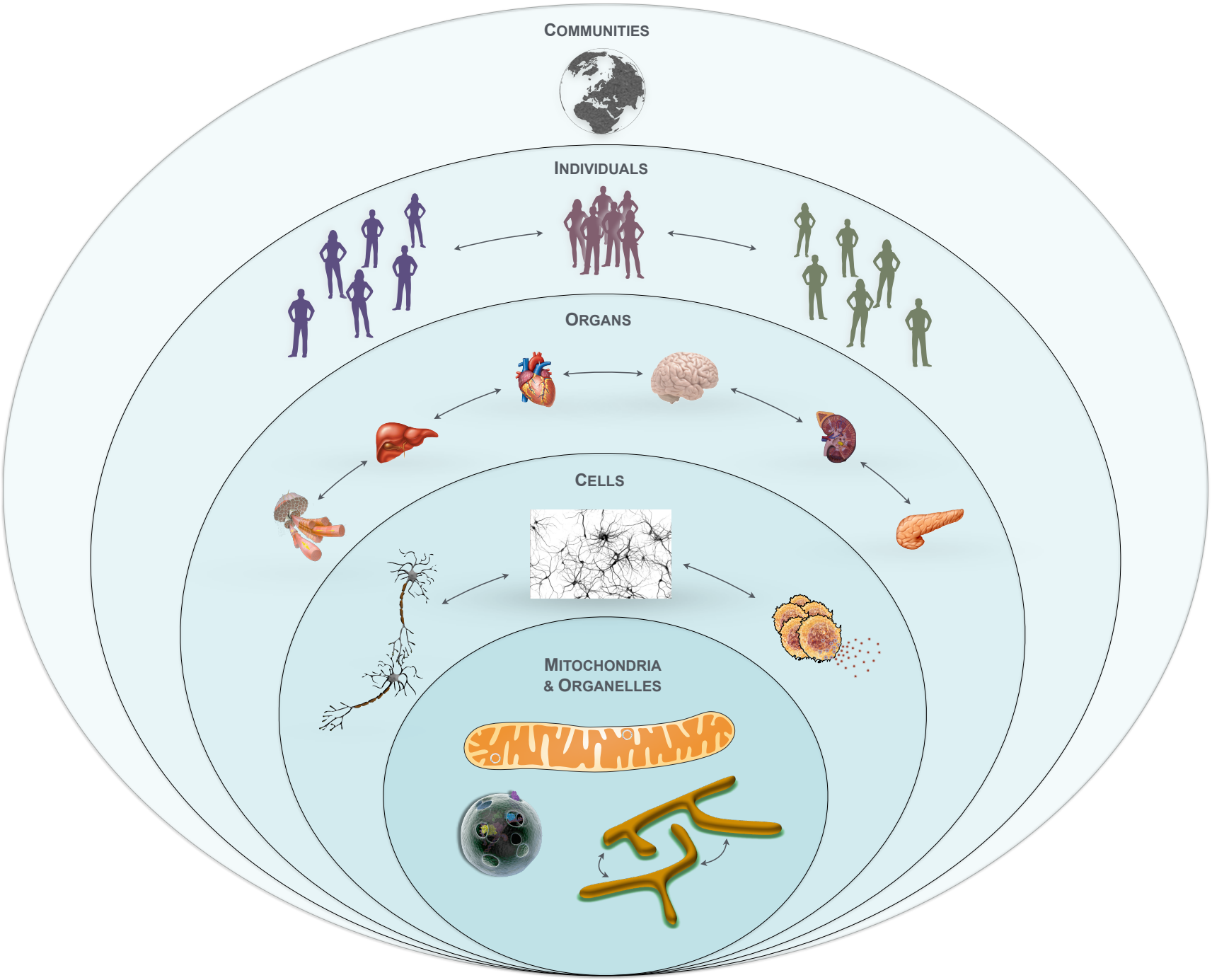
Perspective https://doi.org/10.1038/s42255-023-00783-1

Multifaceted mitochondria: moving mitochondrial science beyond function and dysfunction





Monzel, Enriques, Picard. *Nat Metab* 2023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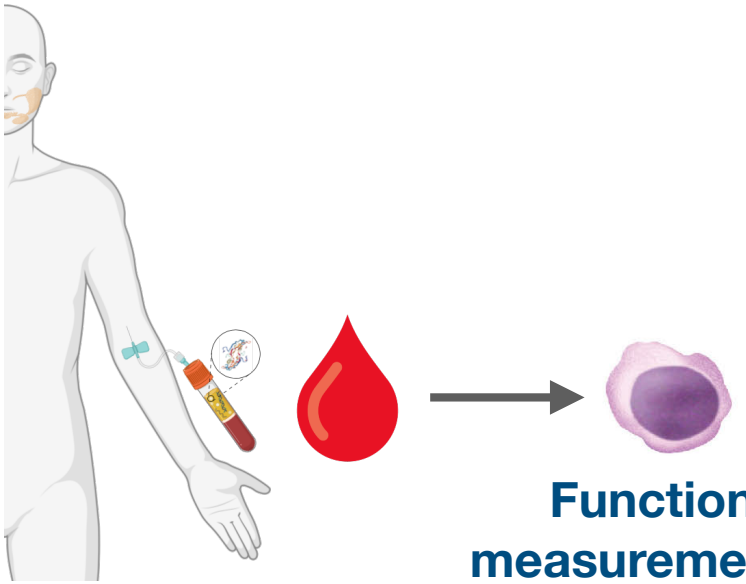
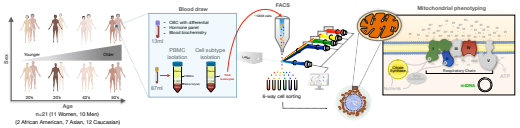
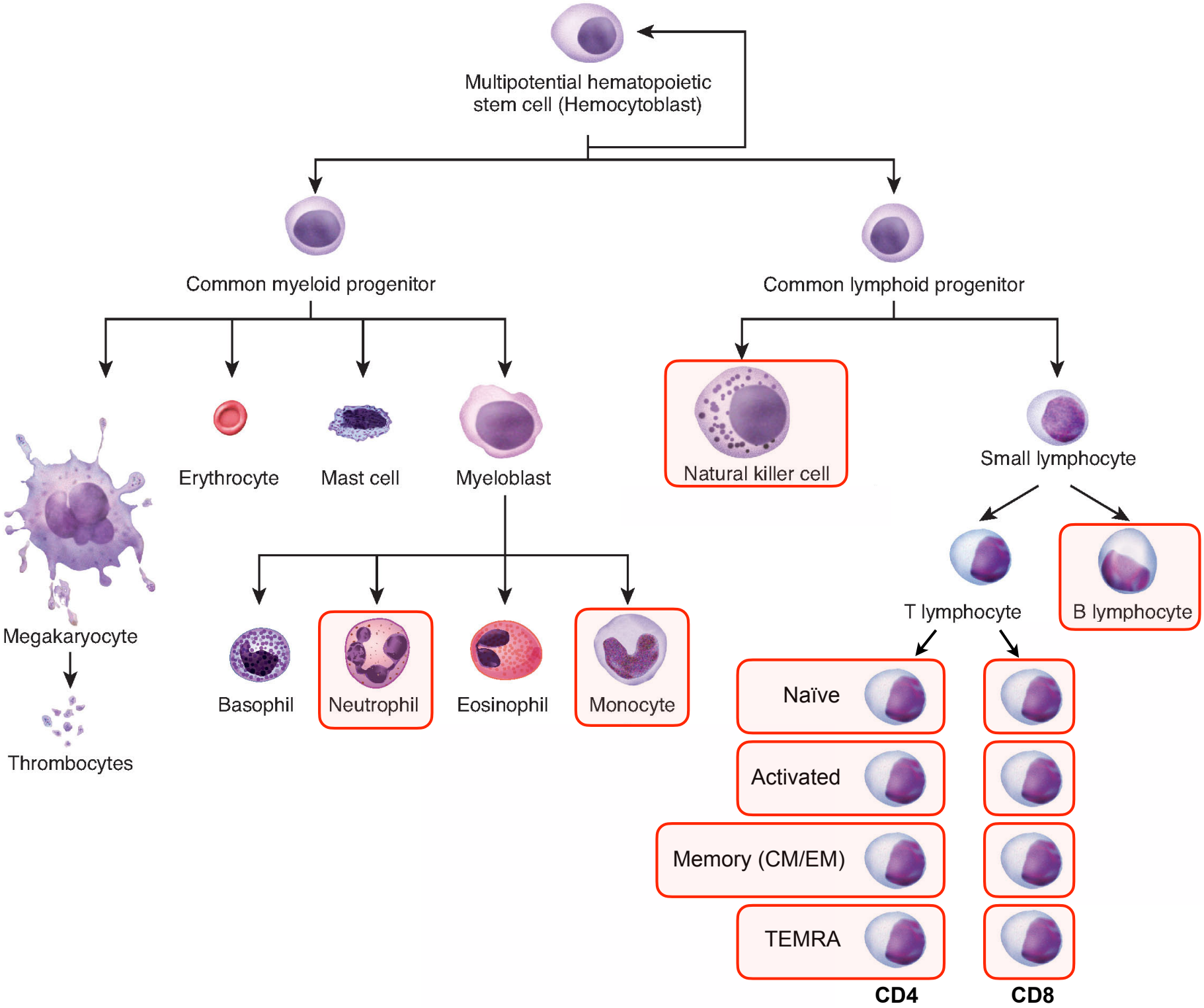
How can we capture mitochondrial diversity and signaling in relation to psychosocial states?

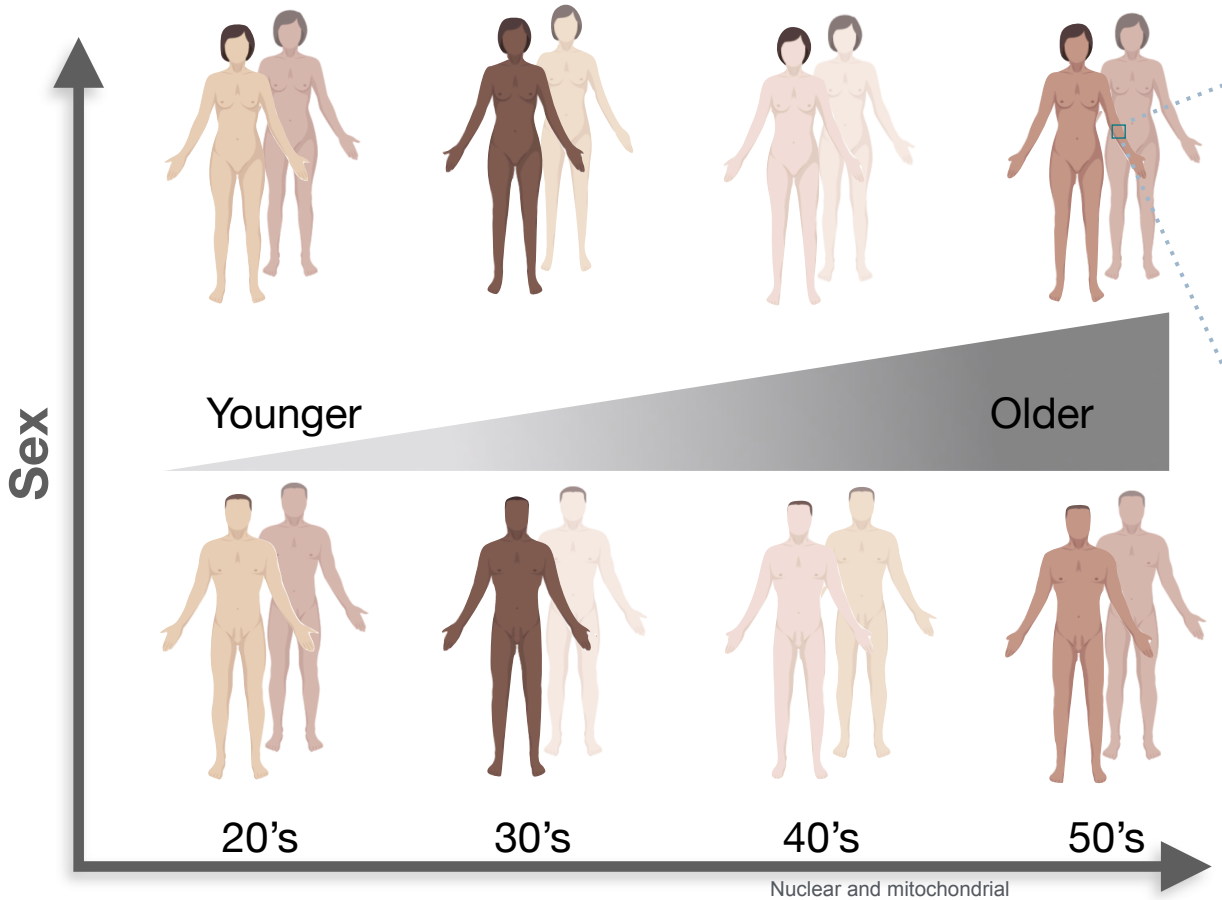


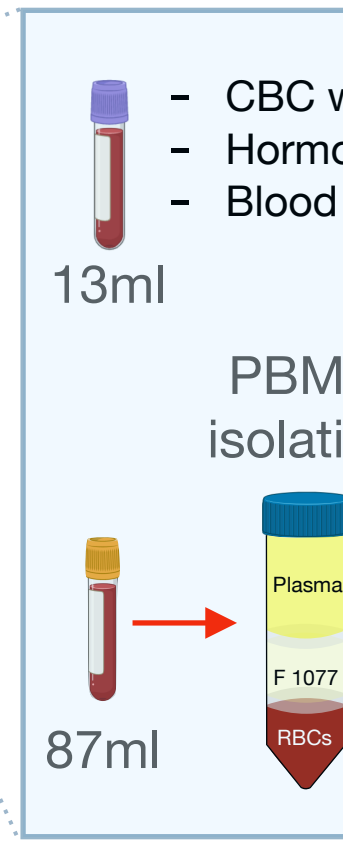
Functional measurements in white blood cells

1



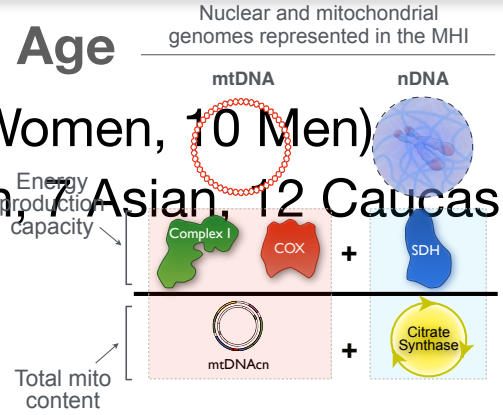

Multipotential hematopoietic stem cell (Hemocytoblast)
Common myeloid progenitor
Common lymphoid progenitor
Erythrocyte
Mast cell
Myeloblast
Natural killer cell
Small lymphocyte
Megakaryocyte
Thrombocytes
Basophil
Neutrophil
Eosinophil
Monocyte
T lymphocyte
B lymphocyte
Naïve
Activated
Memory (CM/EM)
TEMRA
CD4
CD8



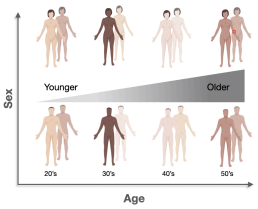


n=21 (11 Women, 10 Men)

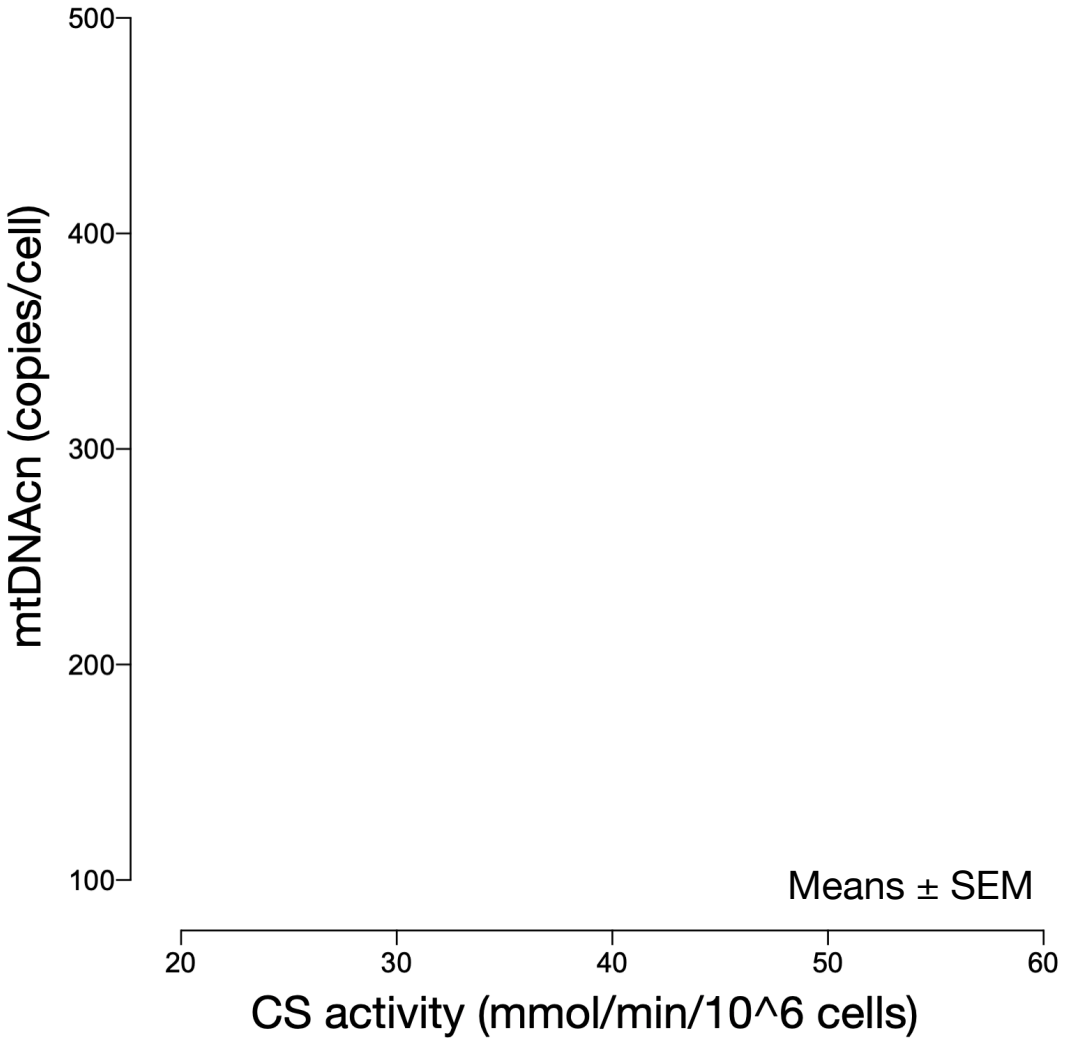
(2 African American, 7 Asian, 12 Caucasian)



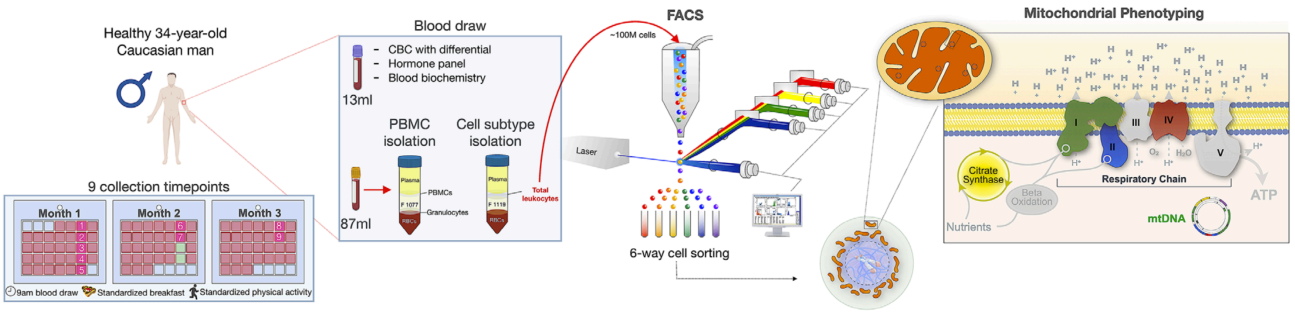
Rausser et al. *eLife* 2021

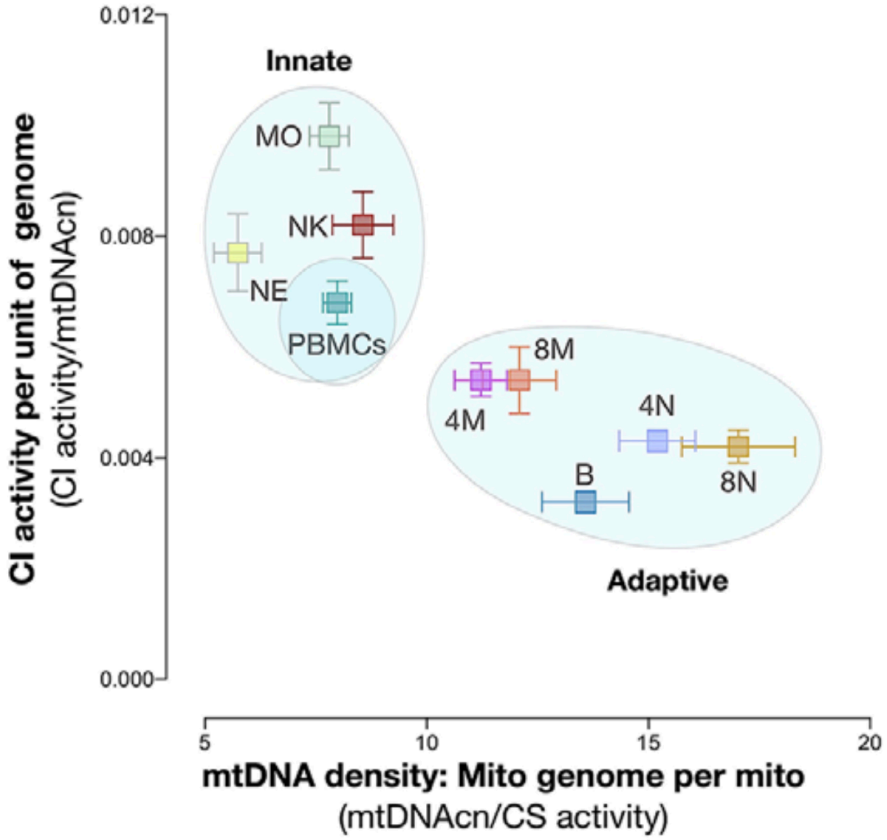


Mitochondrial phenotypes (mitotypes)



Rausser et al. *eLife* 2021



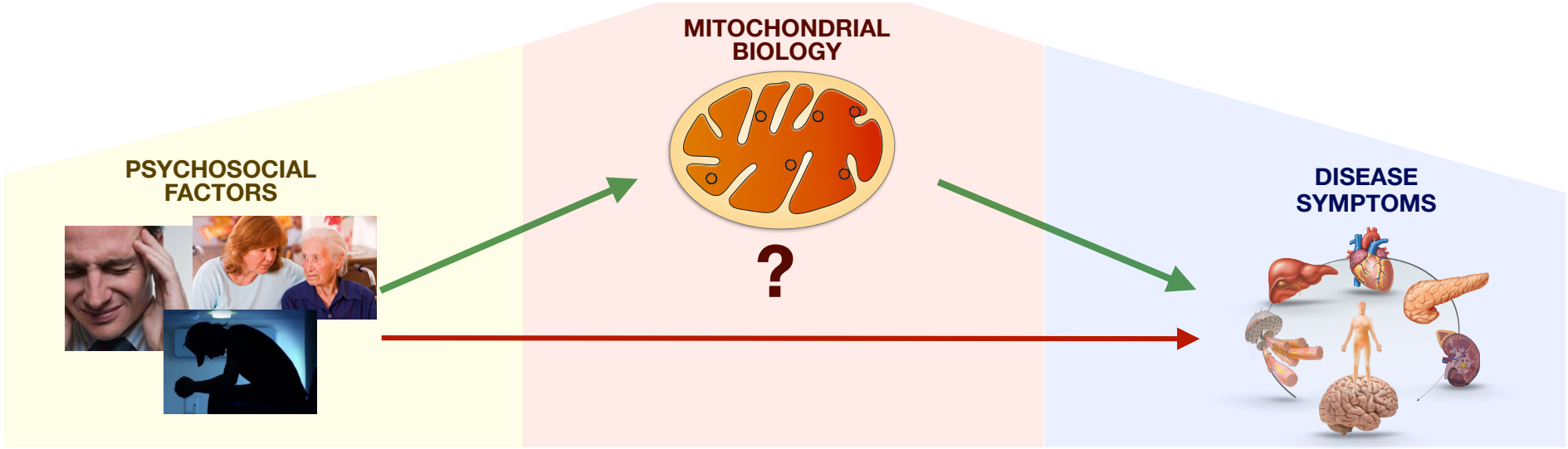


Cell type-specific estimates of effect sizes, dynamics, sex & age, biomarkers

Foundational data *to design human mitochondrial studies*

Rausser et al. *eLife* 2021

Why do patients believe that “stress” exaggerates or cause their symptoms?



Stress → Mitochondria → Disease

Well being → Mitochondria → Health ?

Picard et al. *Nat Rev Endocrinol* 2014
Kelly et al. *BioRxiv* 2024

Is mitochondrial energy transformation capacity related to psychological states?

Psychological stress and disease

Psychological Stress and Disease

Sheldon Cohen, PhD
Denise Janicki-Deverts, PhD
Gregory E. Miller, PhD

DESPITE WIDESPREAD PUBLIC BELIEF THAT PSYCHOlogical stress leads to disease, the biomedical community remains skeptical of this conclusion. In this Commentary, we discuss the plausibility of the belief that stress contributes to a variety of disease processes and summarize the role of stress in 4 major diseases: clinical depression, cardiovascular disease (CVD), human immunodeficiency virus (HIV)/AIDS, and cancer.

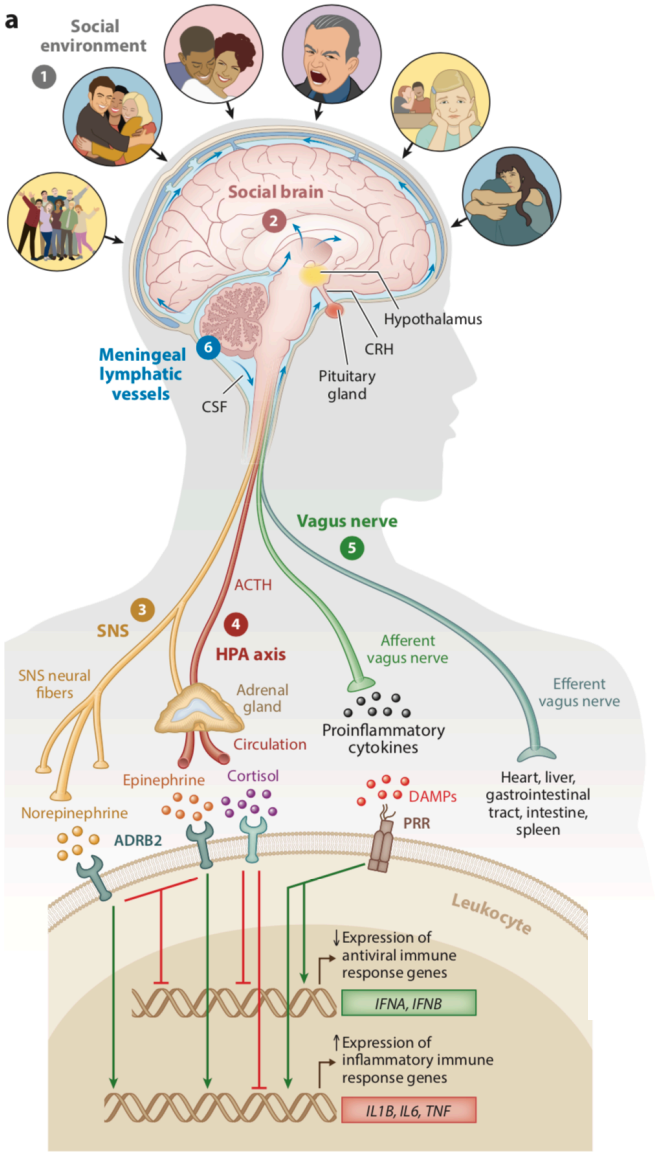
Cohen et al. *JAMA* 2007

Brain on stress: How the social environment gets under the skin

Bruce S. McEwen[1]

Laboratory of Neuroendocrinology, The Rockefeller University, New York, NY 10065

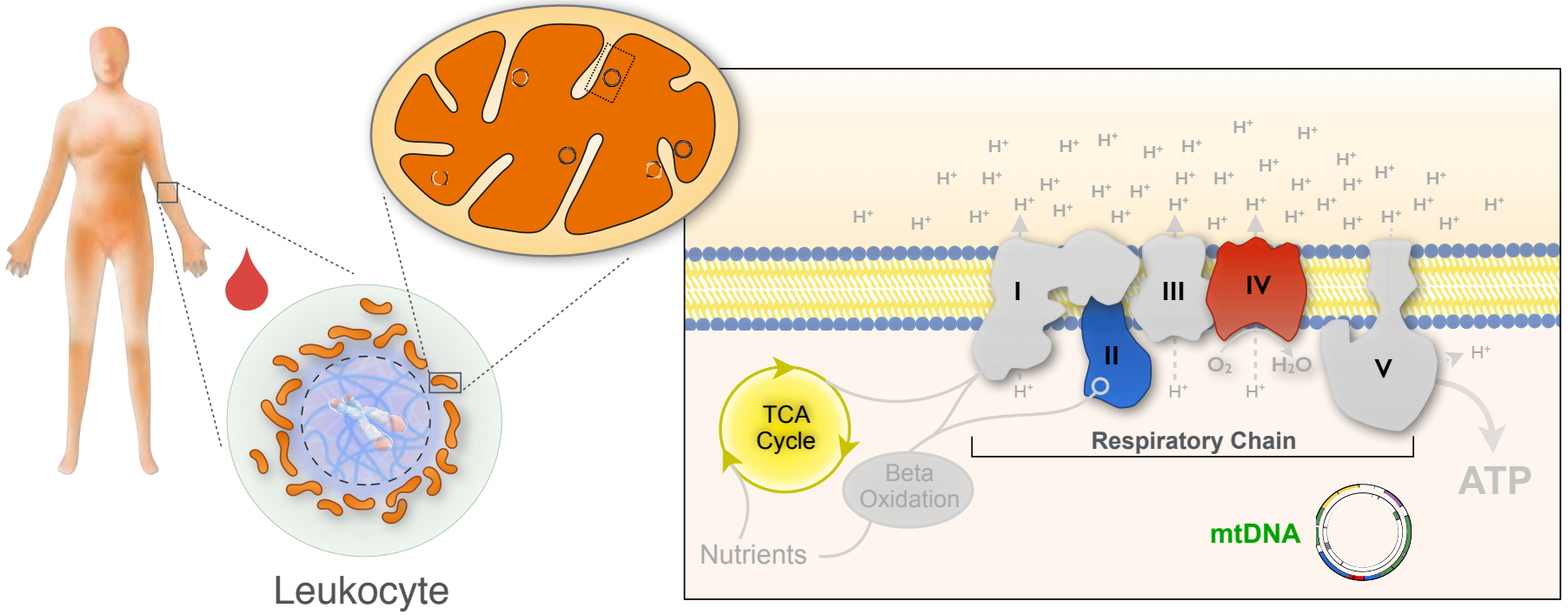
McEwen et al. *PNAS* 2012

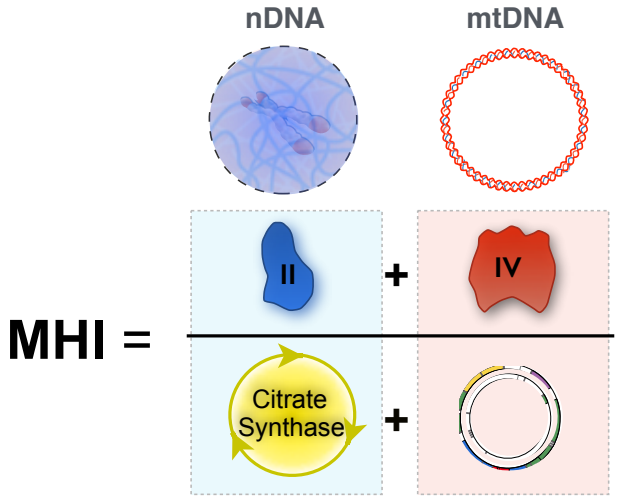


G Slavich. *Annu Rev Clin Psychol* 2020

Placebos in RCTs?

1. Measuring mitochondrial respiratory capacity in blood leukocytes





Elissa Epel (*UCSF*)
Yan Burelle (*University of Ottawa*)

2. Measuring psychological states (mood)

For each of the emotions listed below, please tell us how much you have felt that emotion this evening.

Not at all	A little bit	Moderately	Quite a bit	Extremely
0	1	2	3	4

___ 1. What is the most **amused, fun-loving**, or **silly** you felt?

___ 2. What is the most **angry, irritated**, or **annoyed** you felt?

___ 3. What is the most **ashamed, humiliated**, or **disgraced** you felt?

___ 4. What is the most **awe, wonder,** or **amazement** you felt?

___ 5. What is the most **contemptuous, scornful**, or **disdainful** you felt?

___ 6. What is the most **disgust, distaste**, or **revulsion** you felt?

___ 7. What is the most **embarrassed, self-conscious**, or **blushing** you felt?

___ 8. What is the most **grateful, appreciative,** or **thankful** you felt?

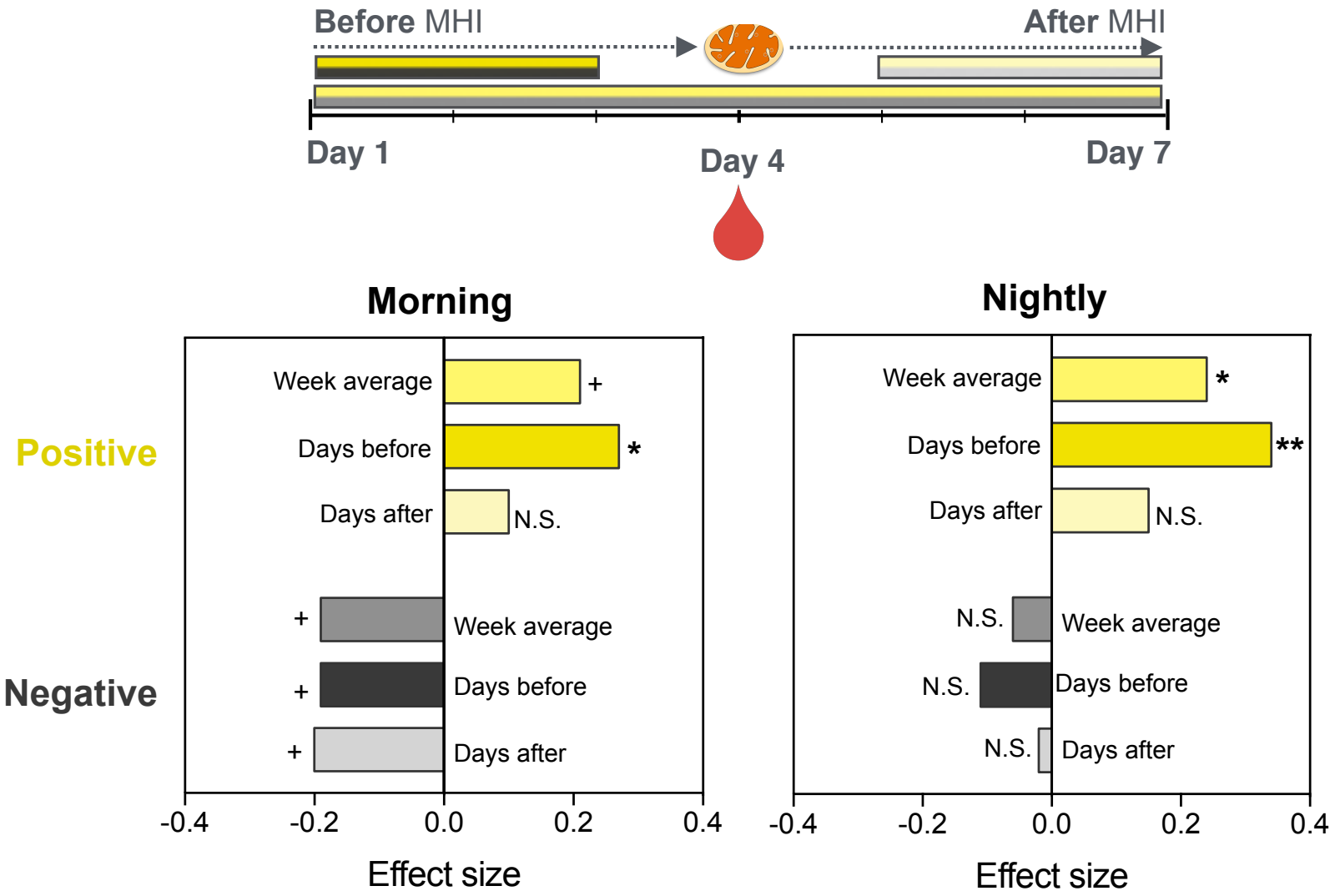
___ 9. What is the most **guilty, repentant**, or **blameworthy** you felt?

___ 10. What is the most **hate, distrust**, or **suspicion** you felt?

Modified Differential Emotional Scale (mDES)

Coll. Elissa Epel, Eli Puterman, Aric Prather - SAGE study

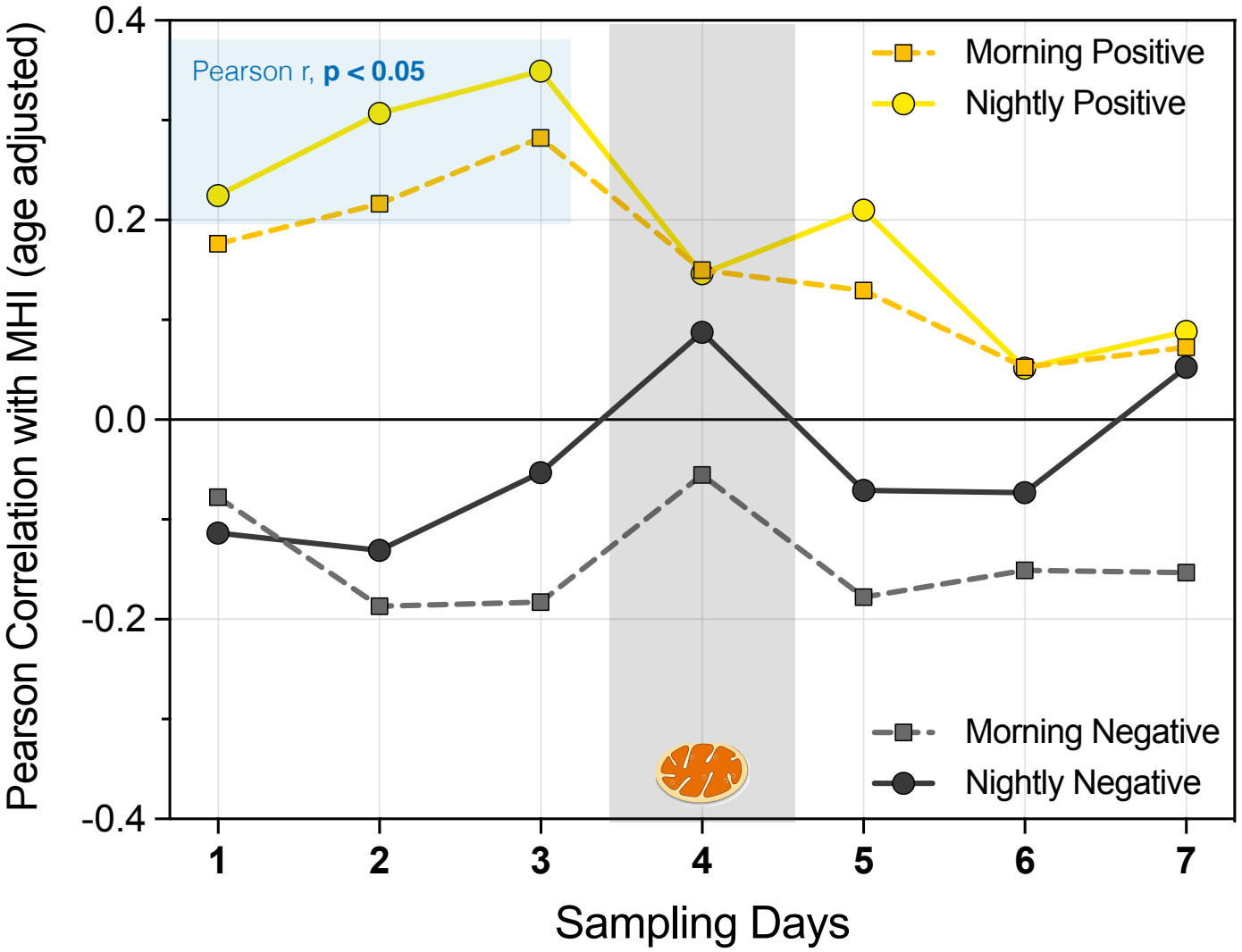
Is mitochondrial respiratory capacity in PBMCs linked to mood?



Modified Differential Emotional Scale (mDES)
n = 86-89 women. + P<0.10, * P<0.05, ** P<0.01

Picard et al. *Biol Psychiatr* 2018
Elissa Epel

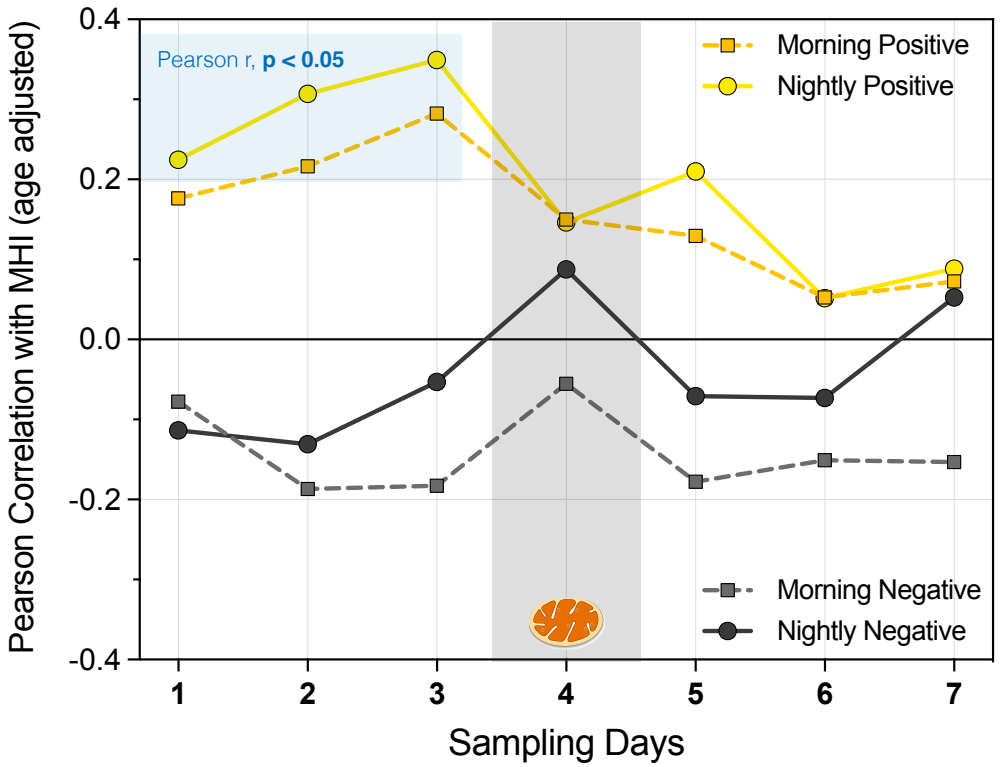
Mood on days *preceding* blood draw correlate with MHI

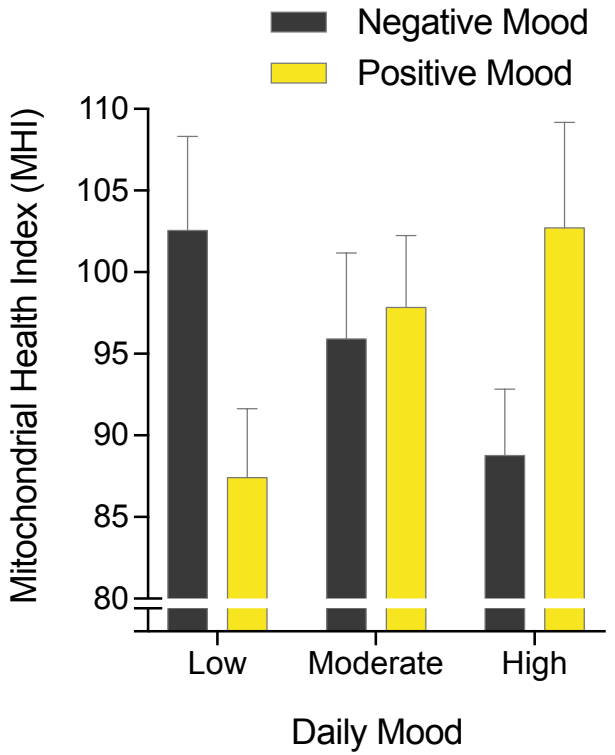


Picard et al. *Biol Psychiatr* 2018

Elissa Epel

Mood on days *preceding* blood draw correlate with MHI





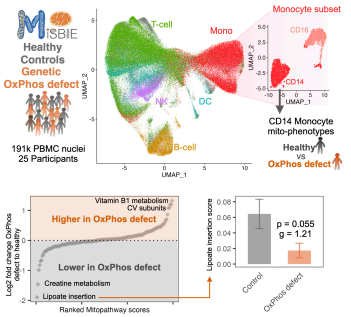
Previous day mood accounts for **10-15%** of the variance in MHI

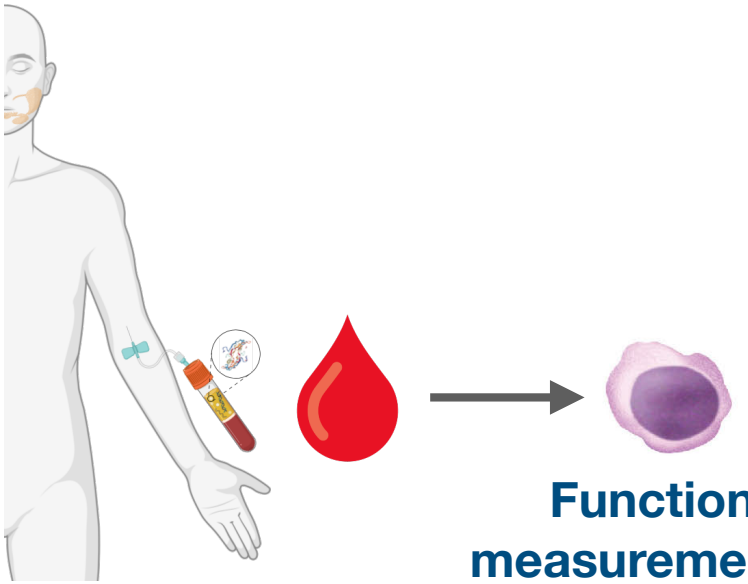
Picard et al. *Biol Psychiatr* 2018

How can we capture mitochondrial diversity and signaling in relation to psychosocial states?

2

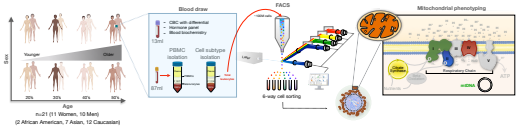
Bulk gene-expression based mitotyping

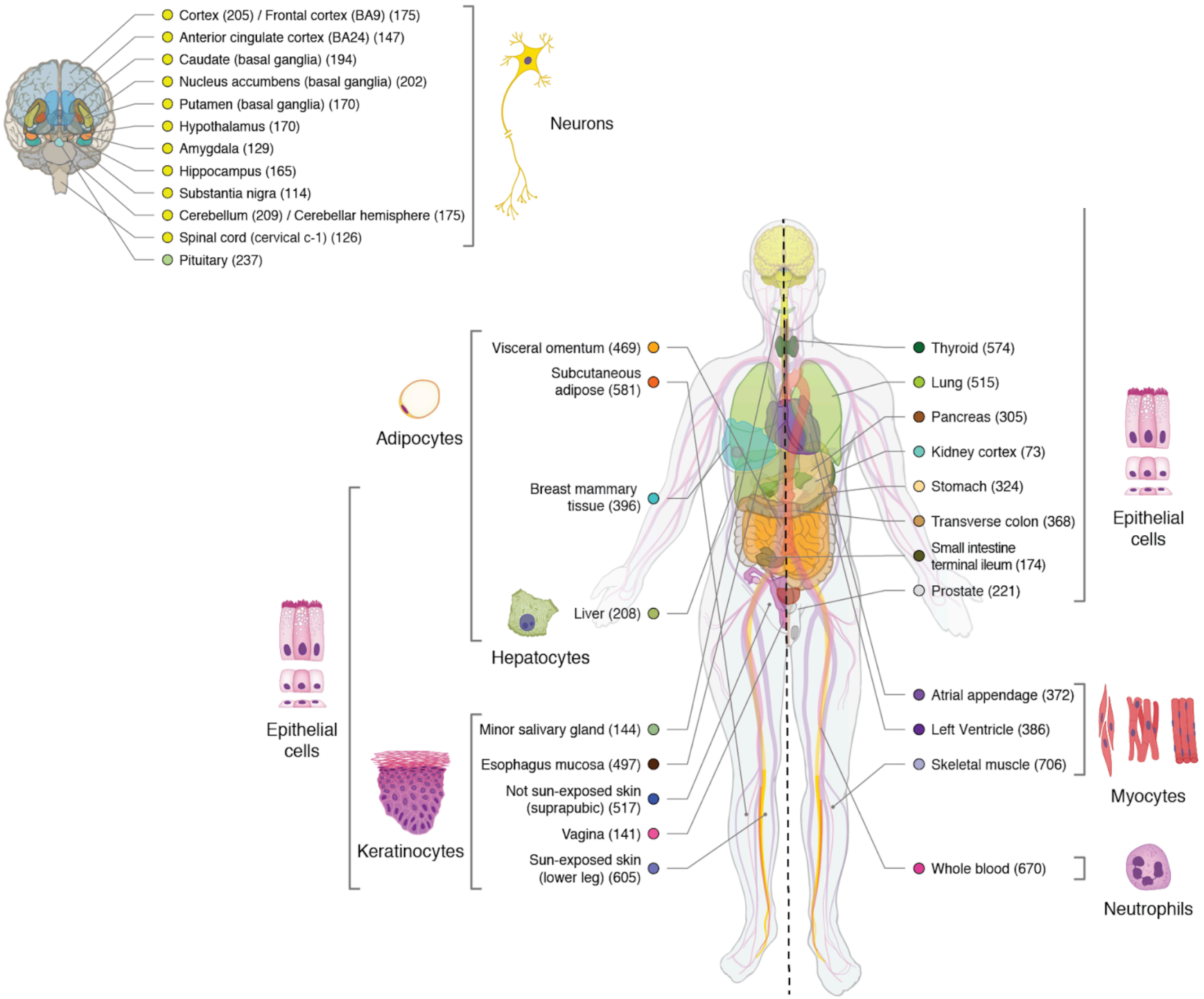




Functional measurements in white blood cells

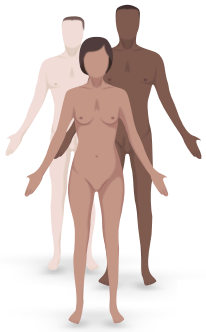
1



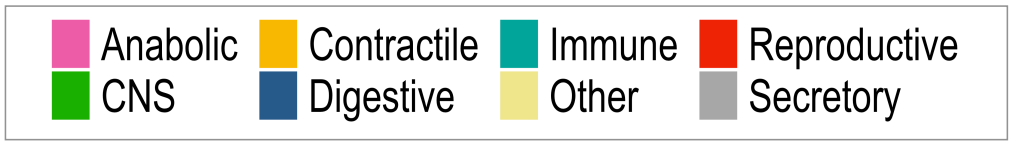


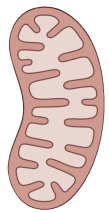
Kim-Hellmuth et al. *Science* 2020

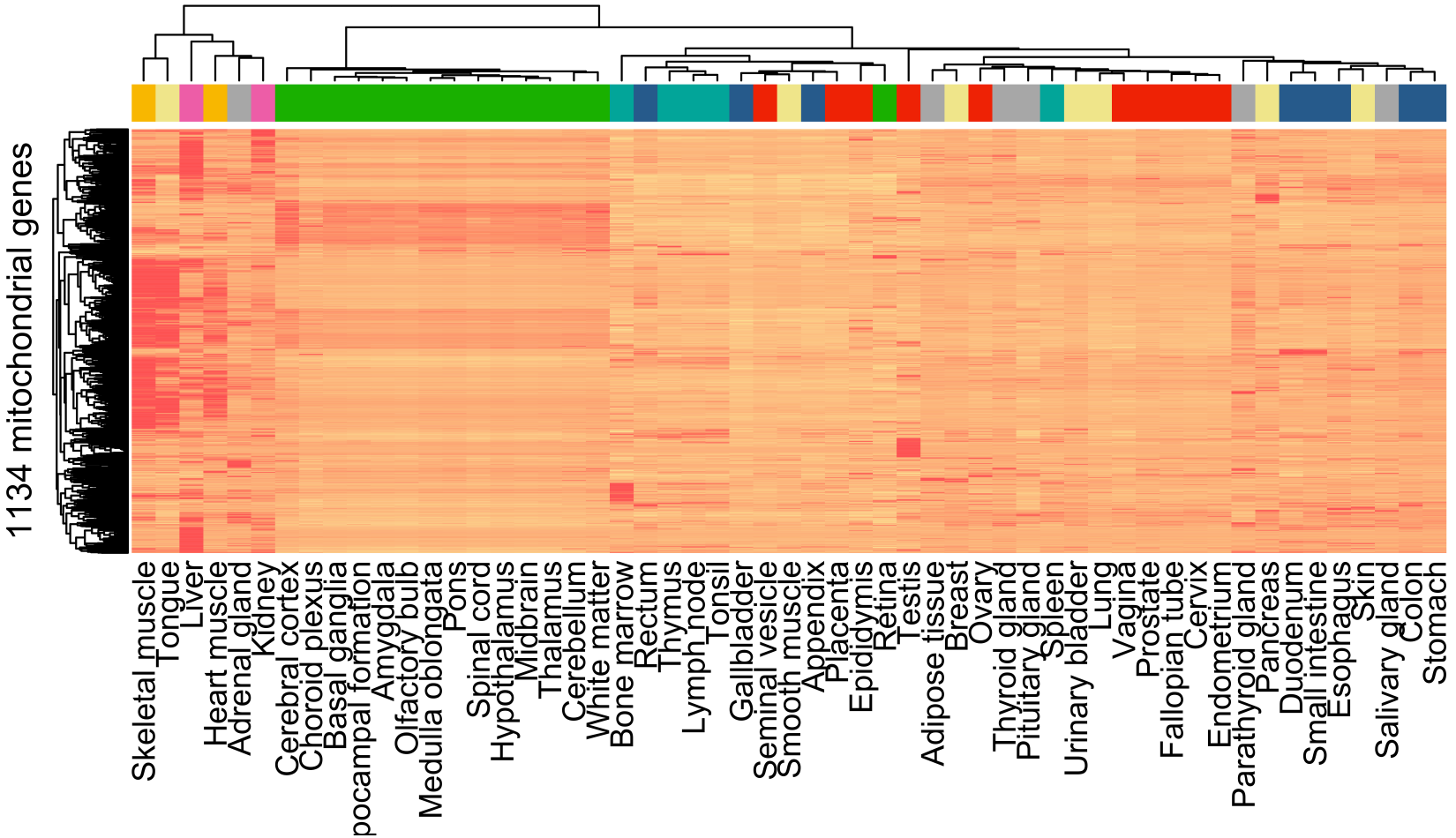
Molecular mitochondrial phenotyping across tissues



50 tissues

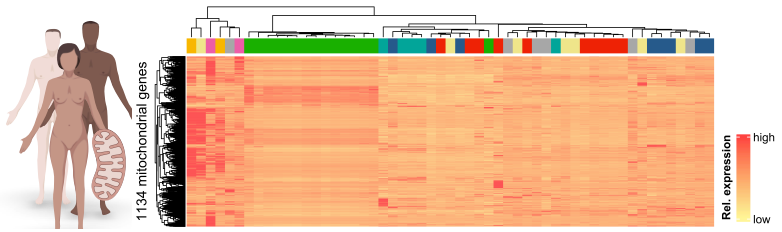


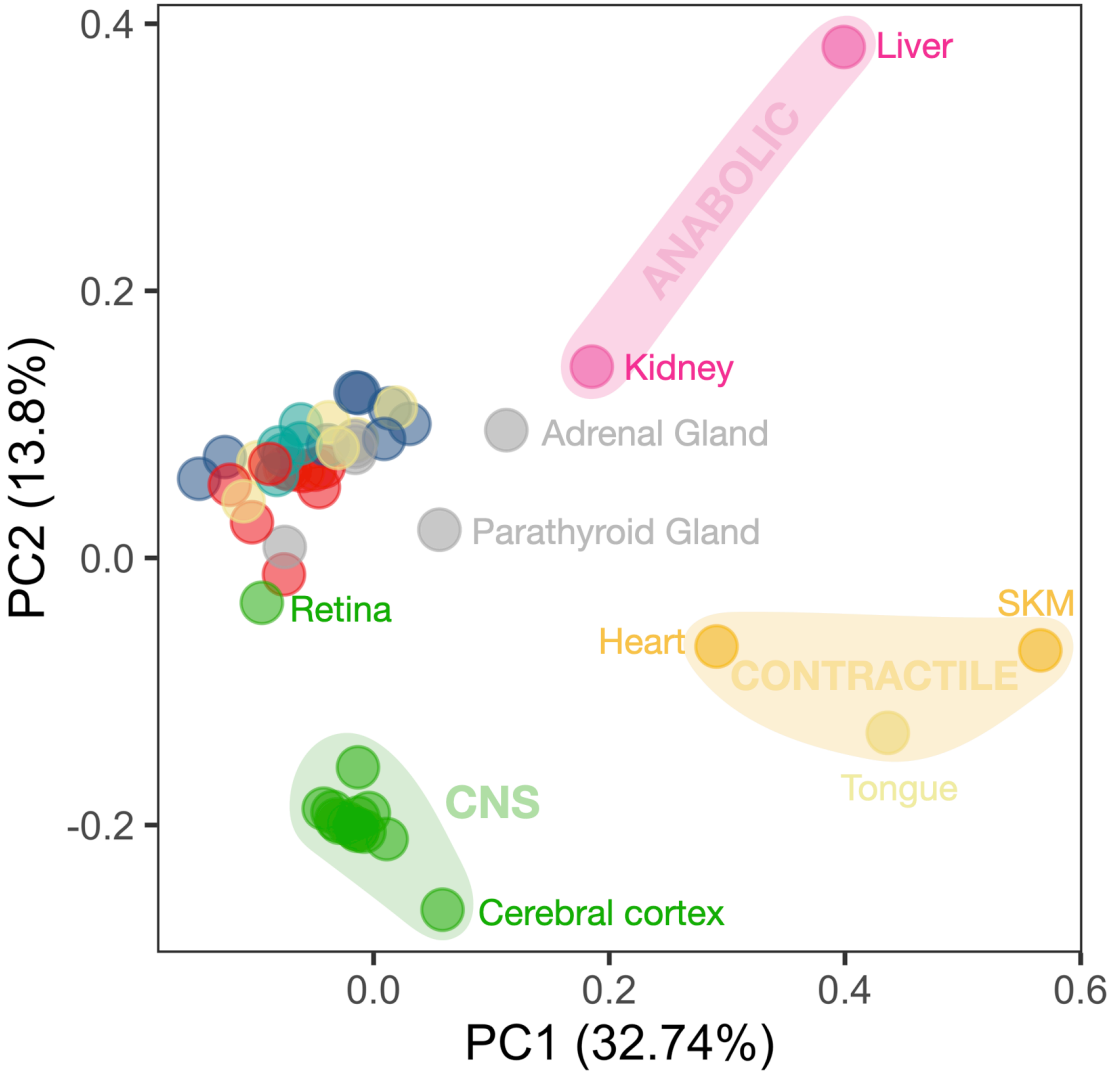




Anna Monzel

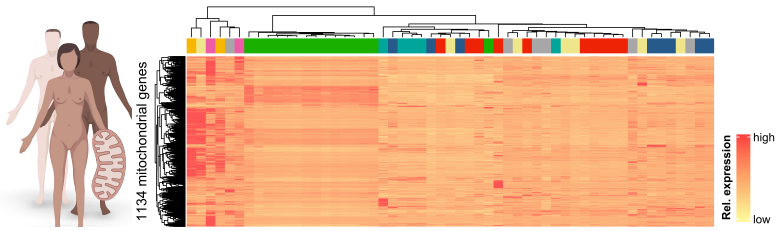
There are different mitochondria types — Mitotypes

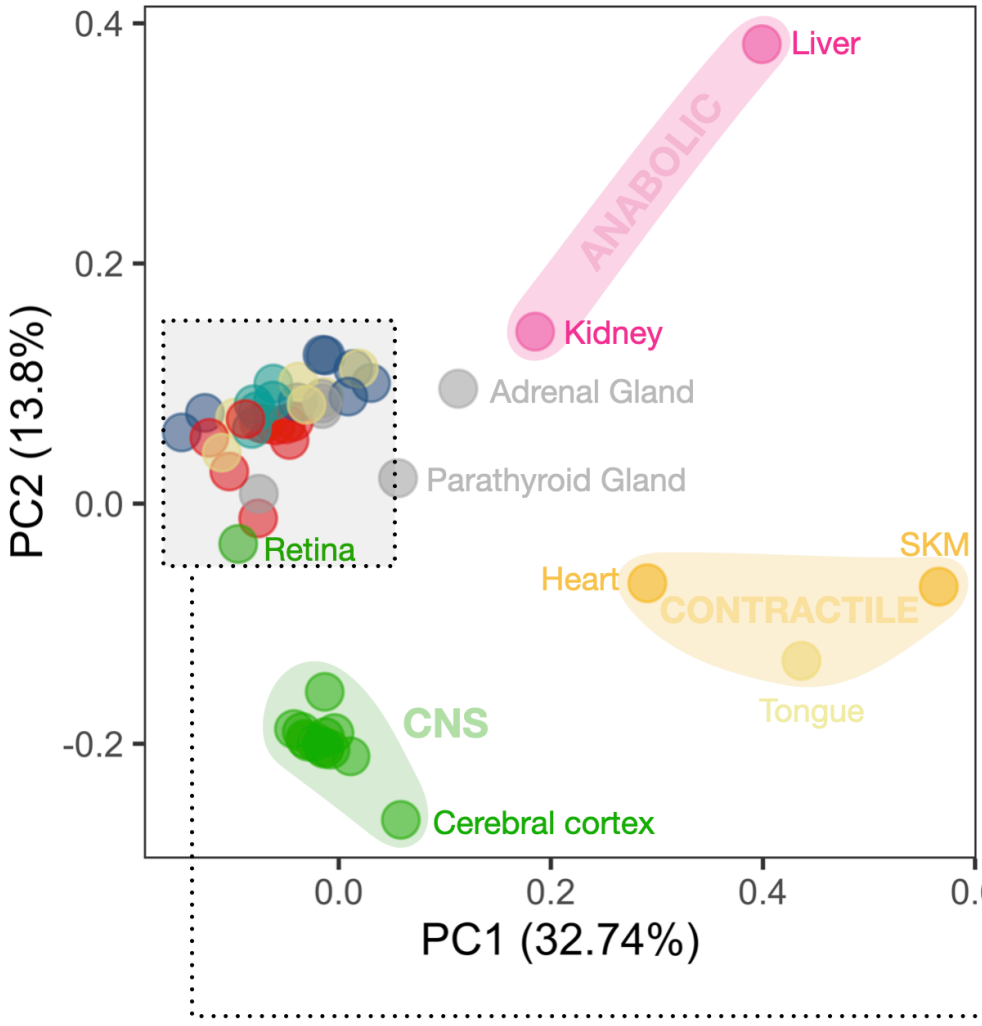


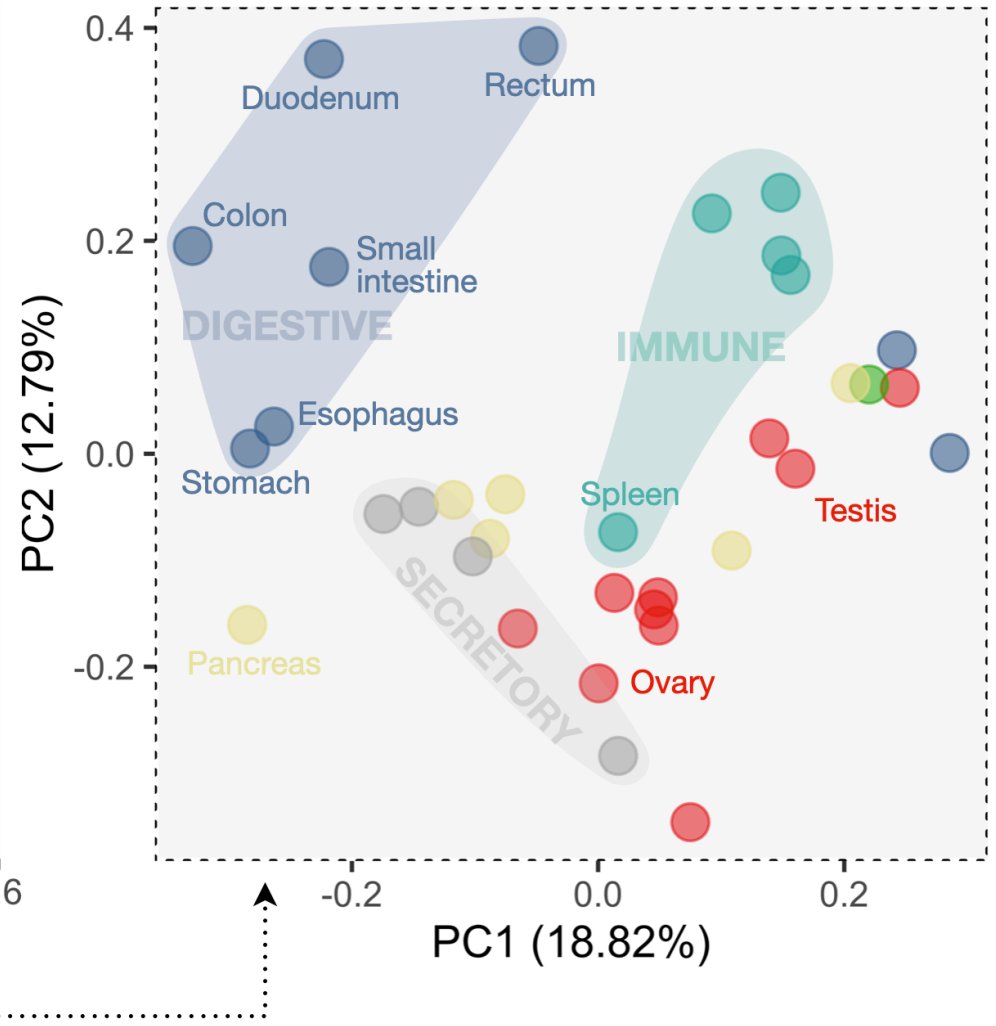


Mitochondrial genes alone

There are different mitochondria types — Mitotypes



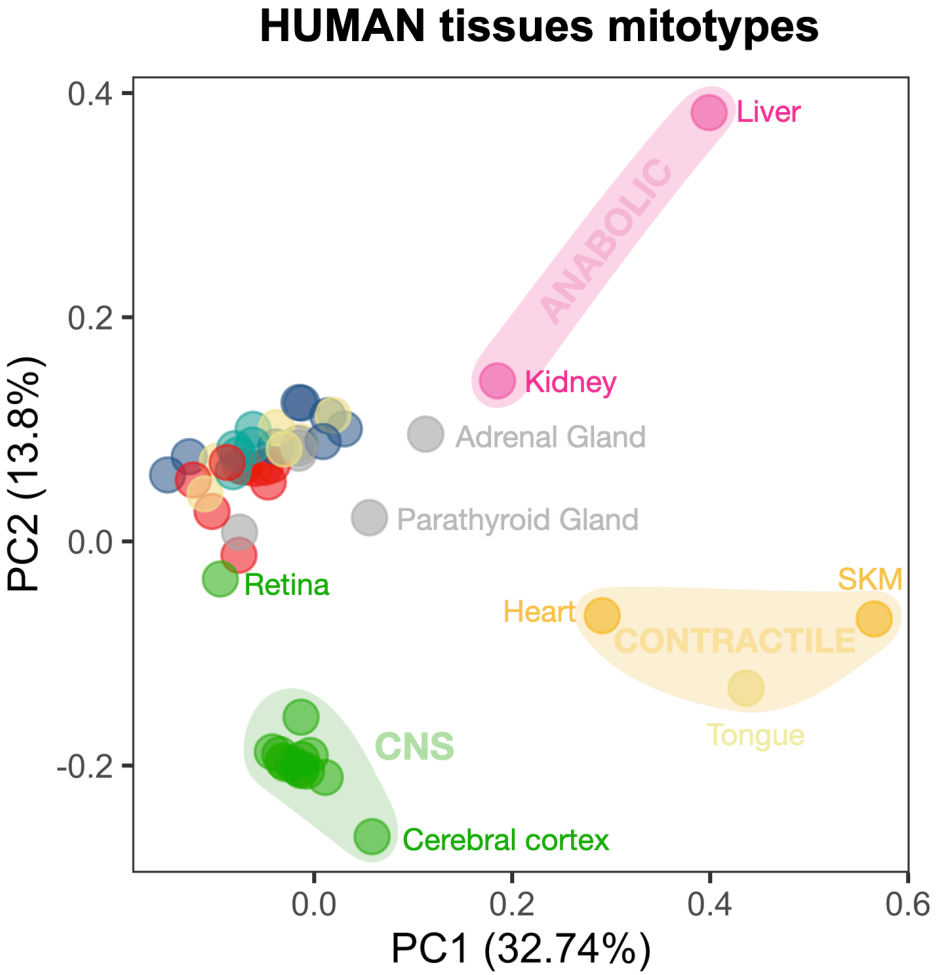


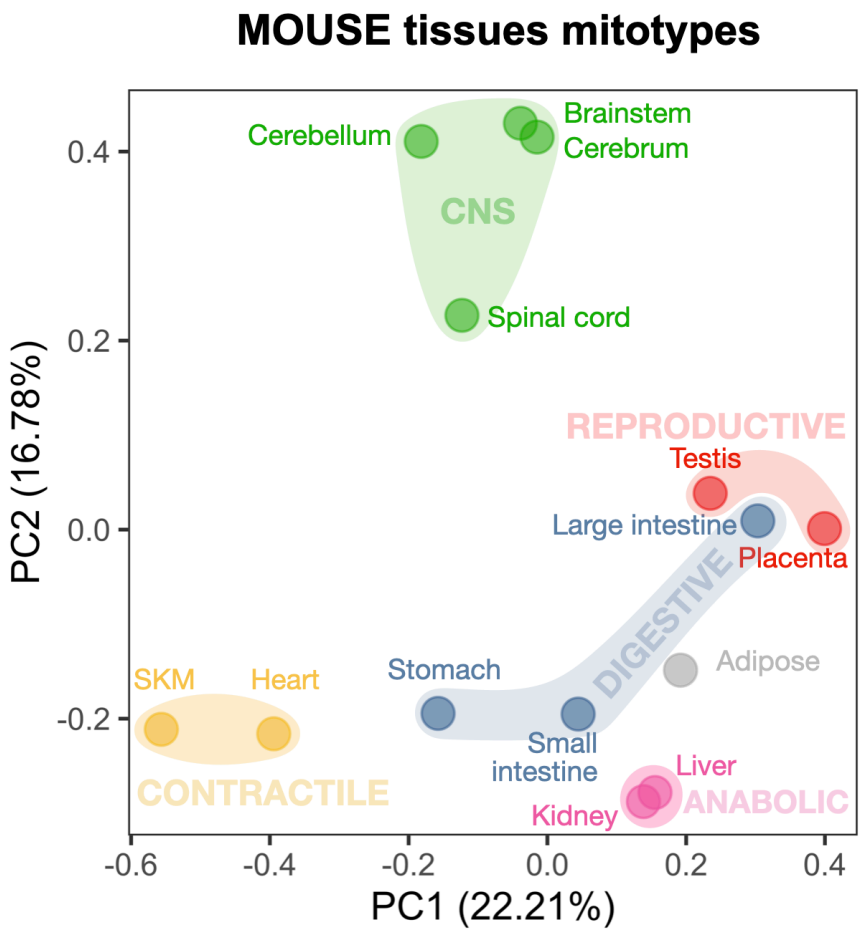


New PCA with tissue subset

Monzel et al. *Nat Metab* 2023
Monzel et al. (in preparation)

Conserved mitotype signatures in human and mouse tissues

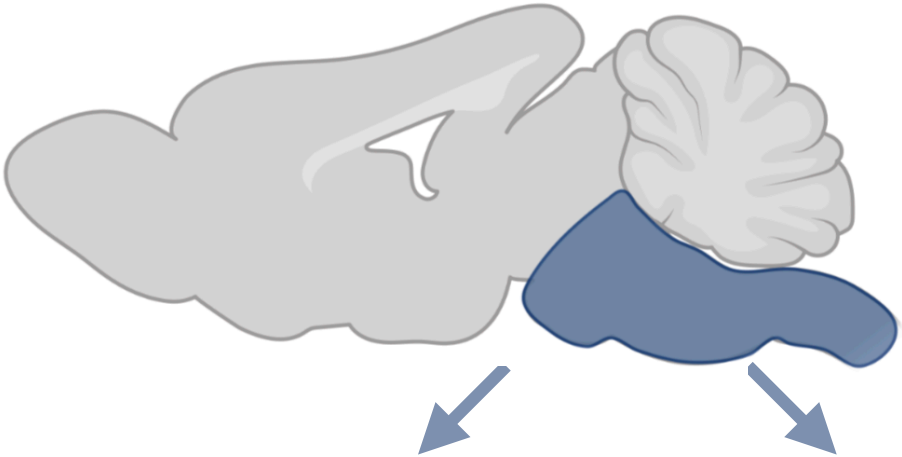




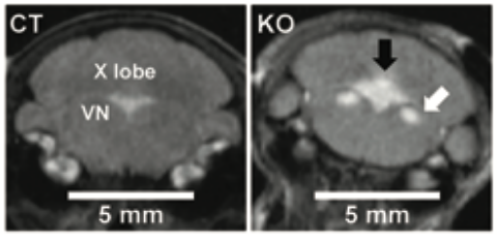
Monzel et al. *Nat Metab* 2023
Monzel et al. (in preparation)

Can we use mitotyping to understand disease risk or vulnerability?

Selective neurodegeneration and neuroinflammation in the brain stem in Ndufs4 KO mice

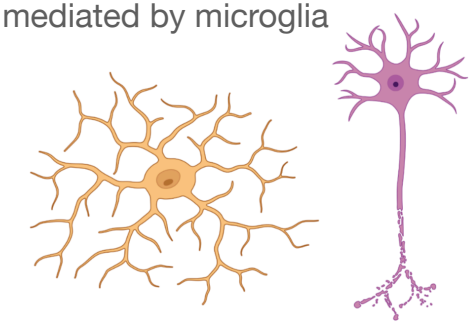


Selective degeneration in the vestibular nuclei area of the brain stem



Quintana et al., JCI 2012

Neuronal degeneration is mediated by microglia



Aguilar et al., Glia 2022

Anna Monzel

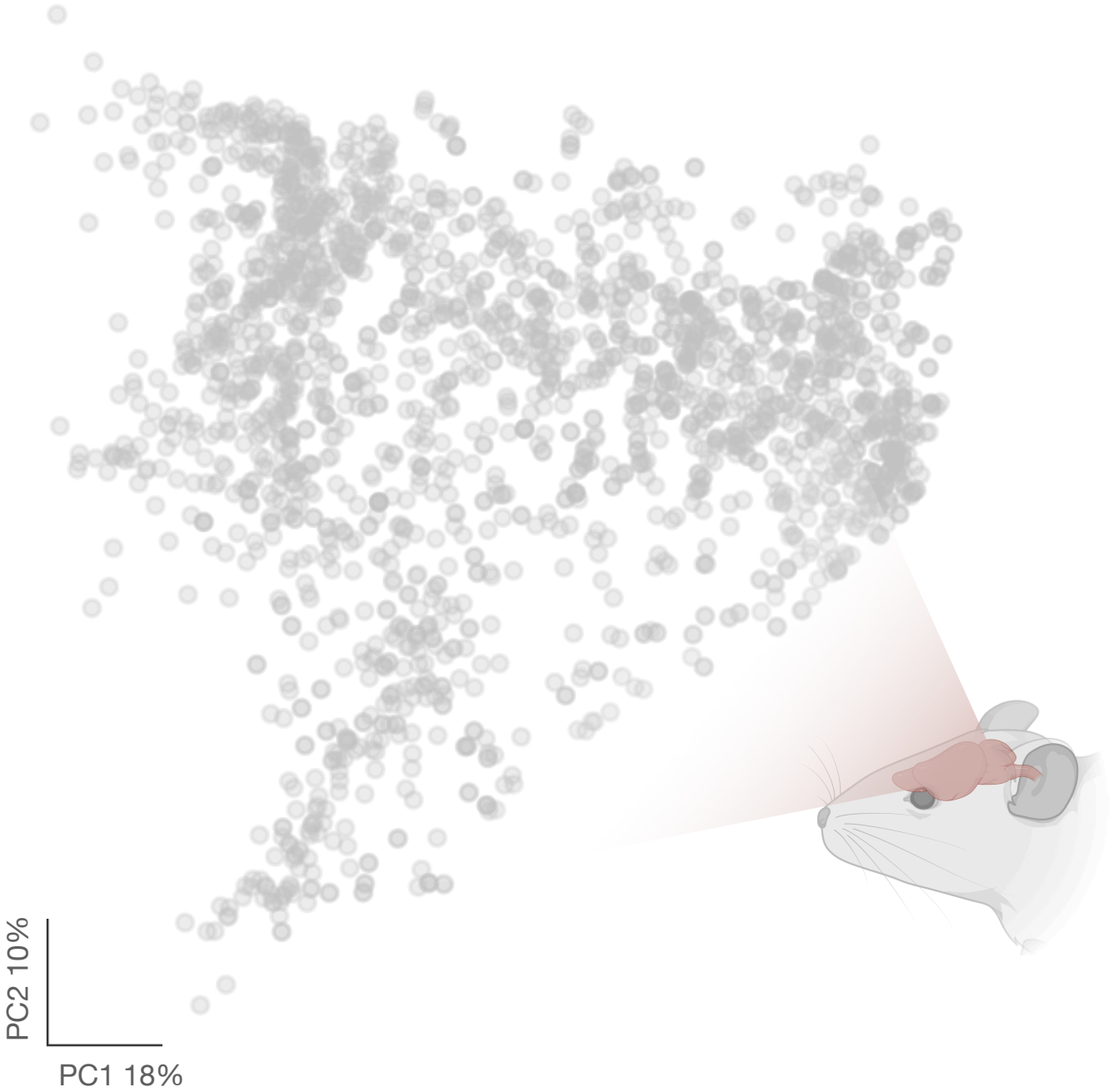
Mitotyping the mouse brain

Allen mouse brain atlas

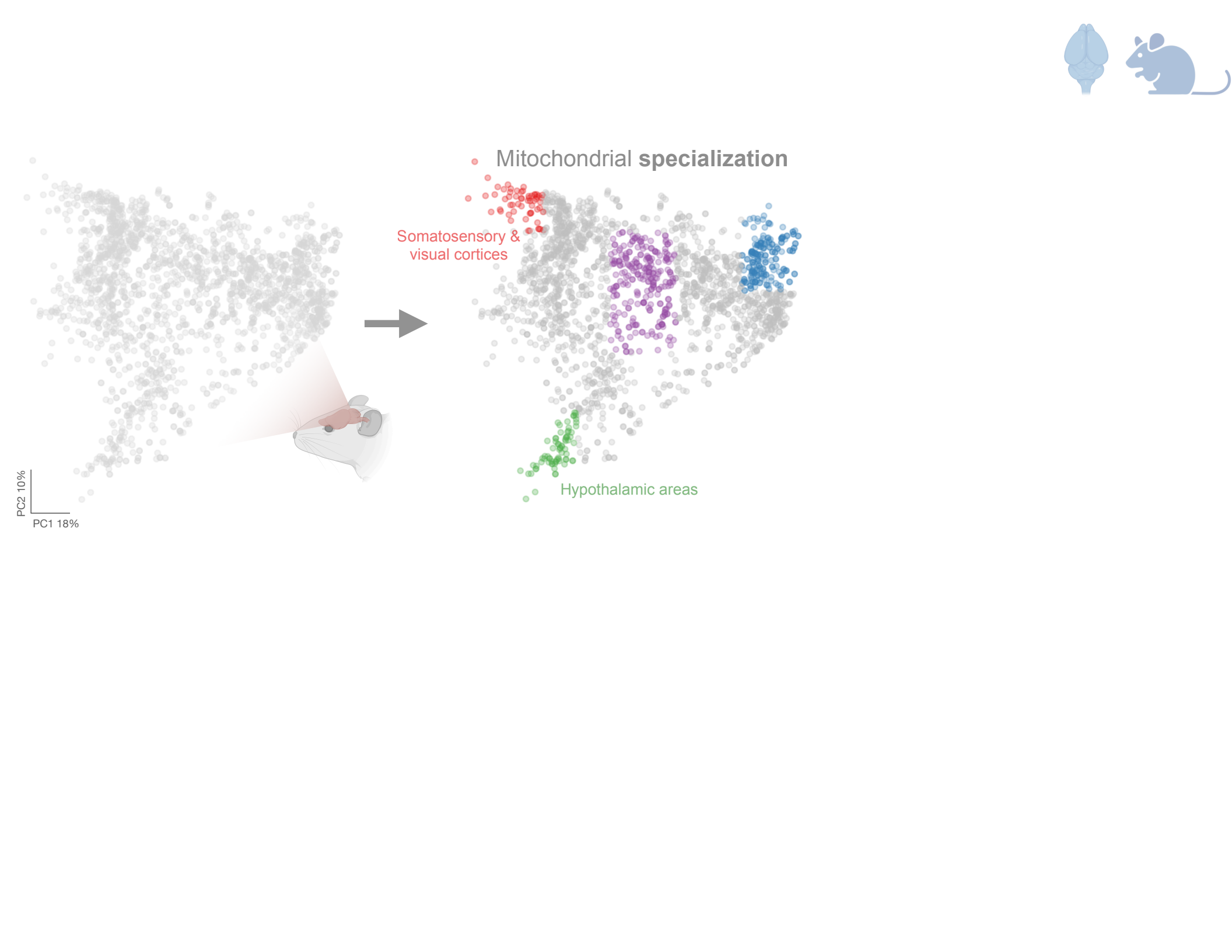
In situ hybridization

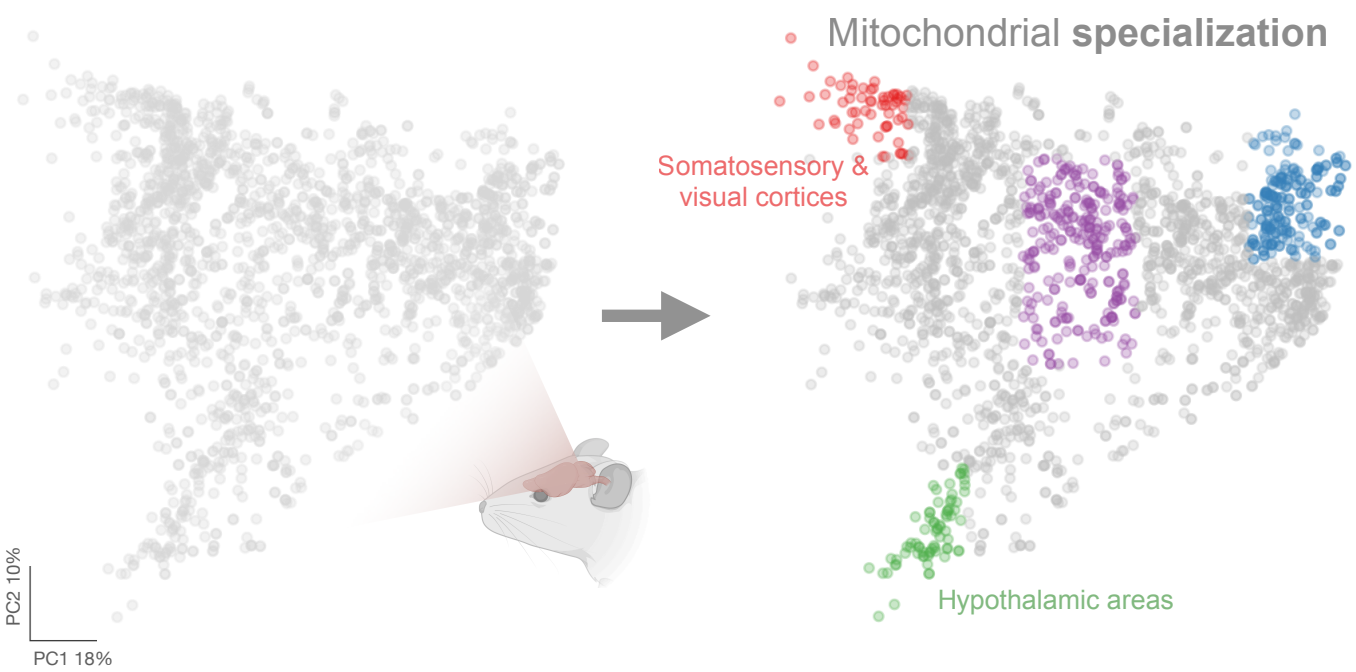
2232 brain regions

948 mitochondrial genes



Anna Monzel


Mitochondrial **specialization**
Somatosensory &
visual cortices
Hypothalamic areas
PC2 10%
PC1 18%


Mitochondrial specialization
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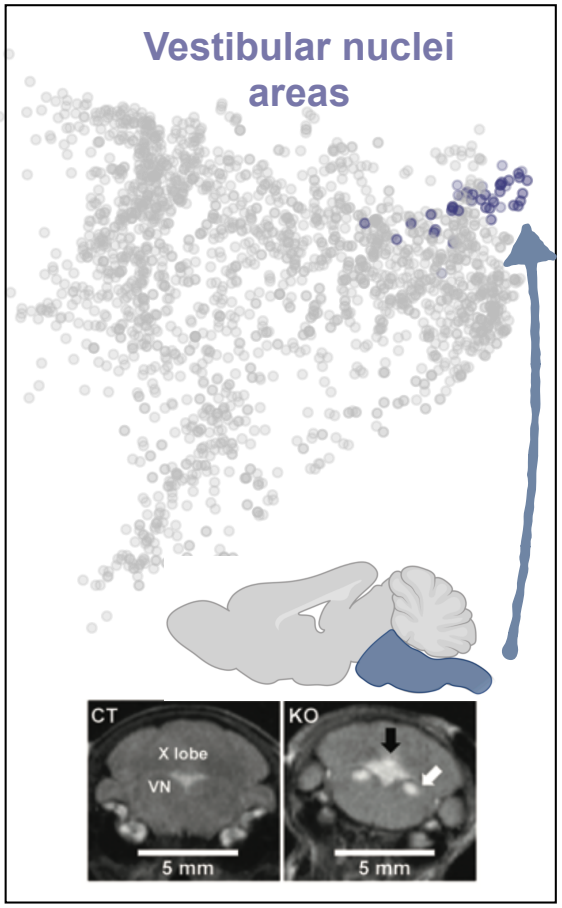
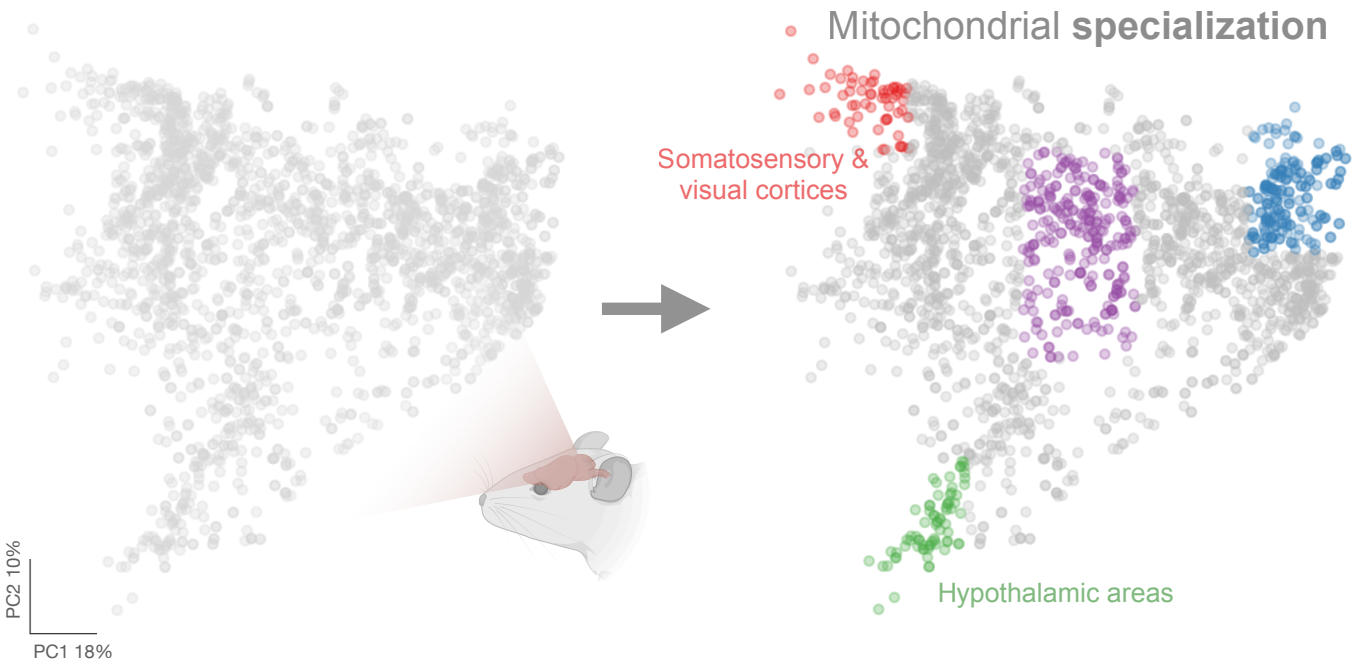

Vestibular nuclei
areas
CT
X lobe
VN
5 mm
KO
5 mm


Mitochondrial specialization
Somatosensory & visual cortices
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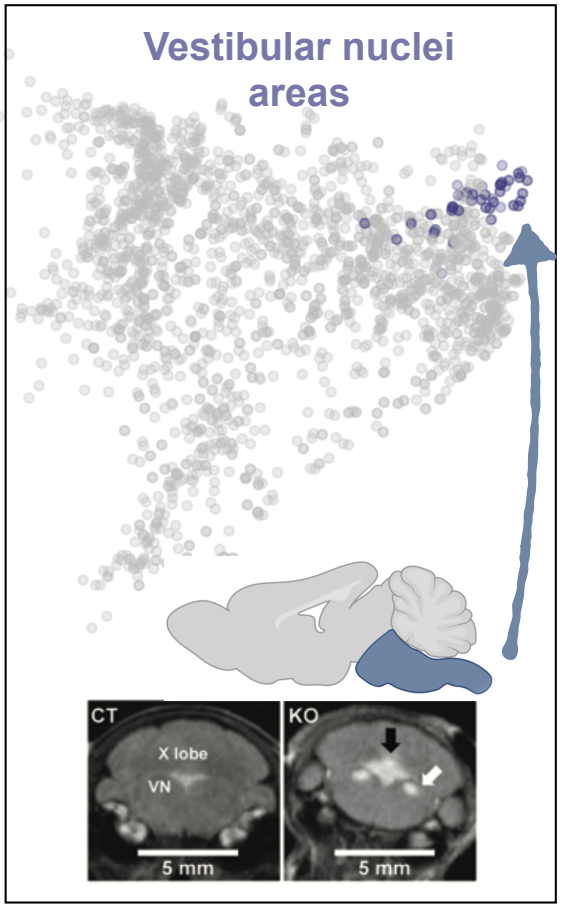
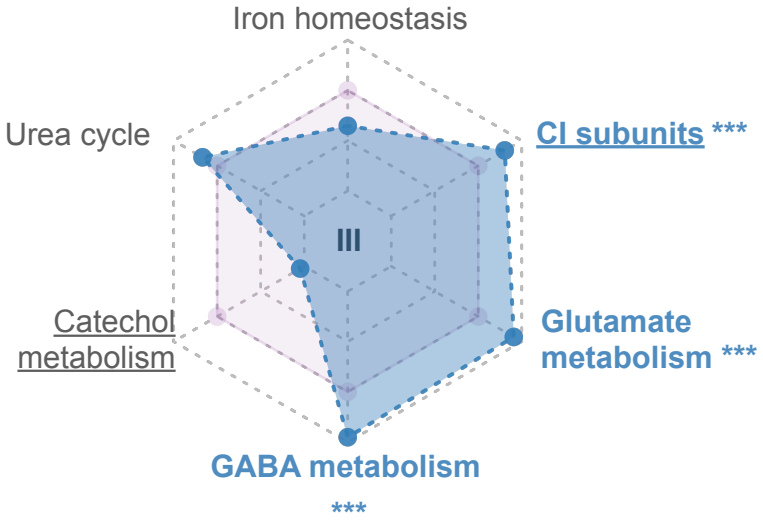
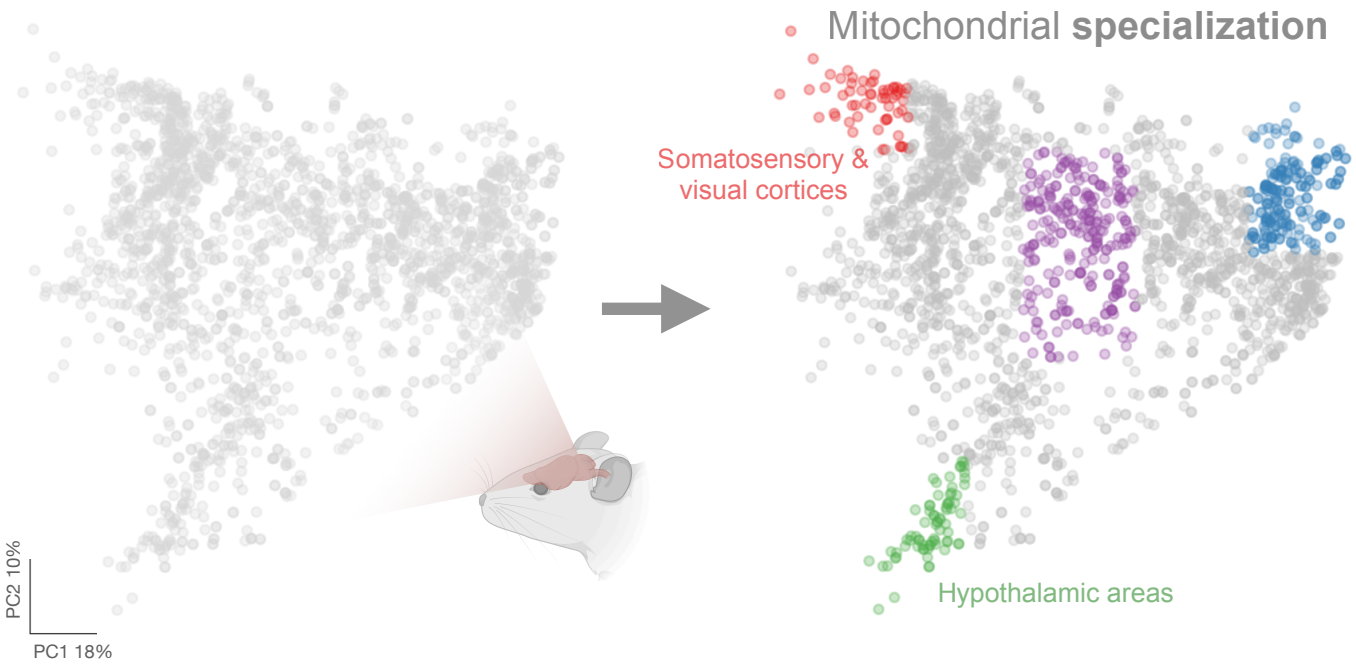

Vestibular nuclei areas
CT
X lobe
VN
5 mm
KO
5 mm


Iron homeostasis
Urea cycle
CI subunits ***
III
Catechol metabolism
Glutamate metabolism ***
GABA metabolism
***


Mitochondrial specialization
Somatosensory & visual cortices
Hypothalamic areas
PC2 10%
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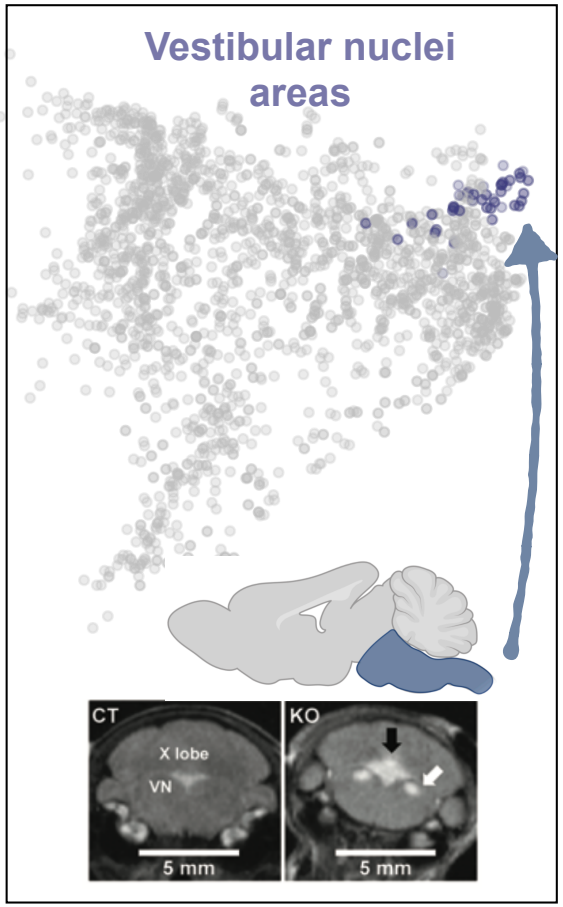
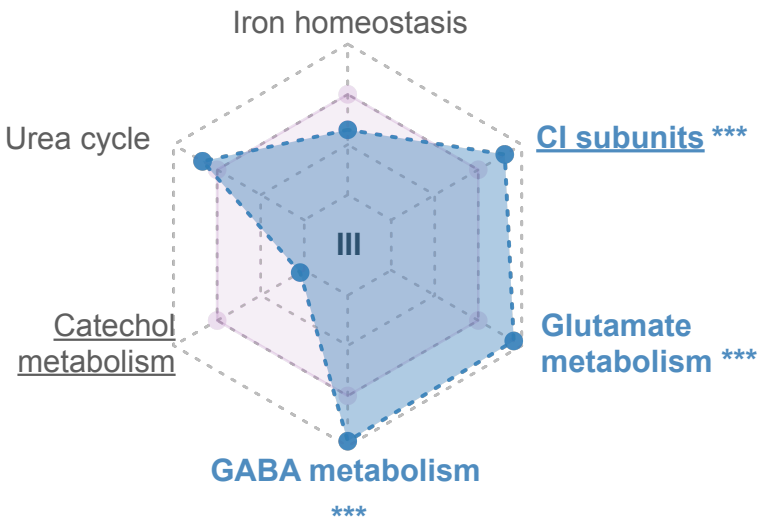
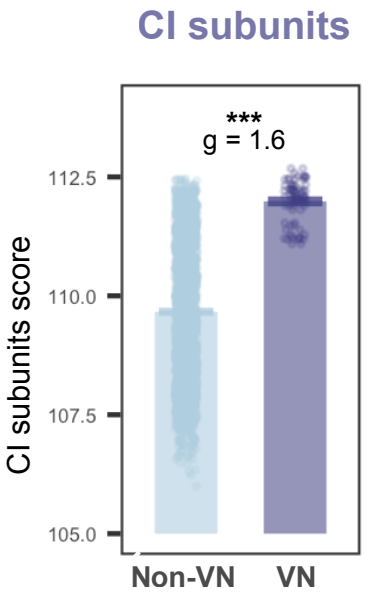
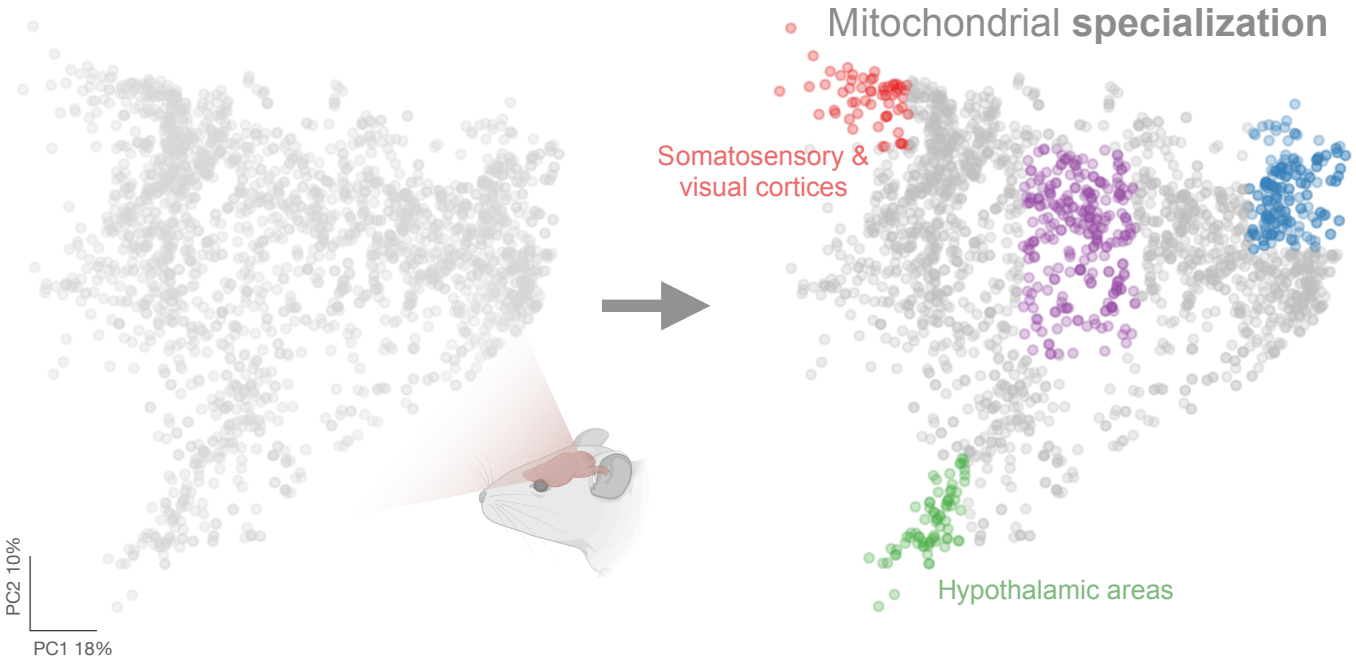
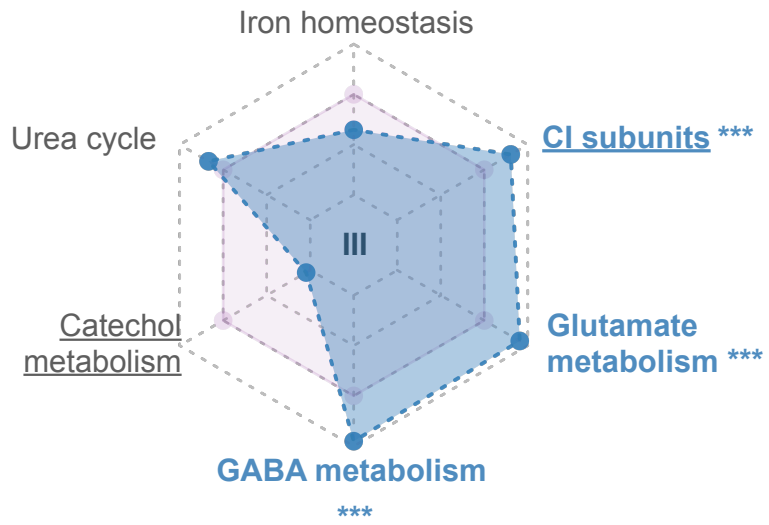
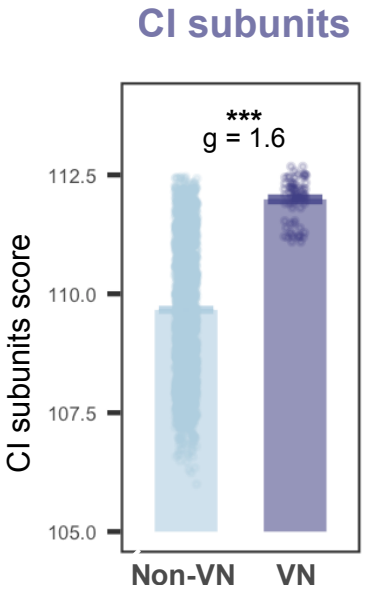

Vestibular nuclei areas
CT
X lobe
VN
5 mm
KO
5 mm

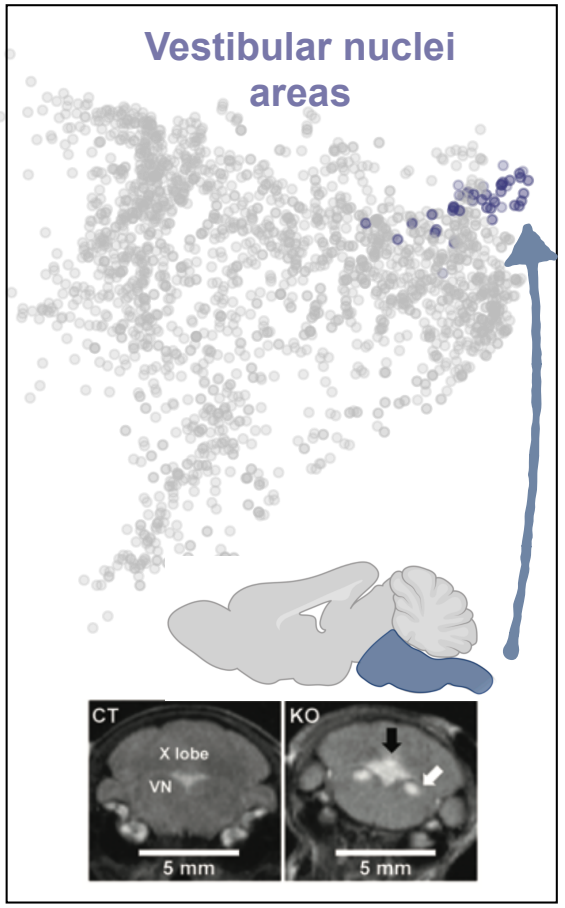

Iron homeostasis
Urea cycle
CI subunits ***
III
Catechol metabolism
Glutamate metabolism ***
GABA metabolism
***


CI subunits
***
g = 1.6
CI subunits score
112.5
110.0
107.5
105.0
Non-VN
VN







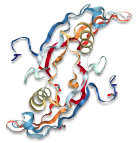


➤ Mitochondria in the vestibular nucleus are **enriched in complex I-related pathways**

How can we capture mitochondrial diversity and signaling in relation to psychosocial states?

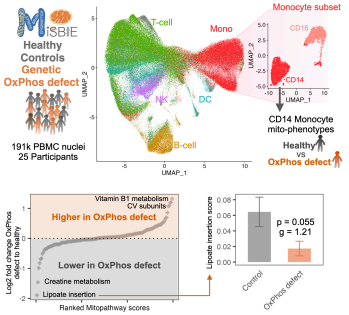
3

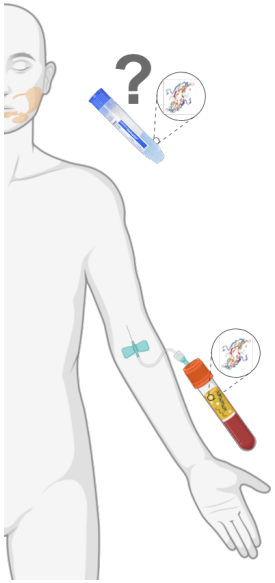
Dynamic blood and saliva biomarkers

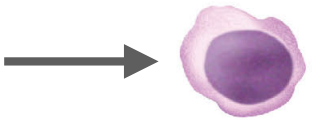


2

Bulk gene-expression based mitotyping

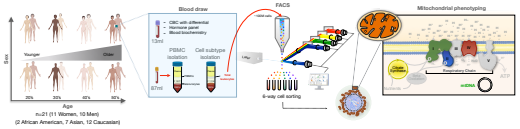




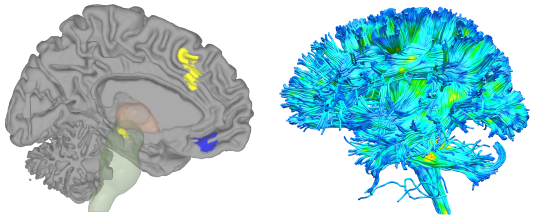


1

Functional measurements in white blood cells

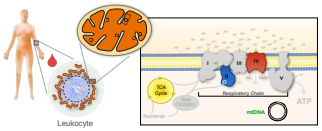


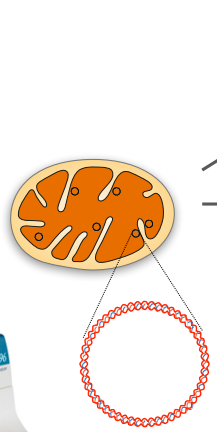
The Mitochondrial Stress, Brain Imaging, and Epigenetics (MiSBIE) Study

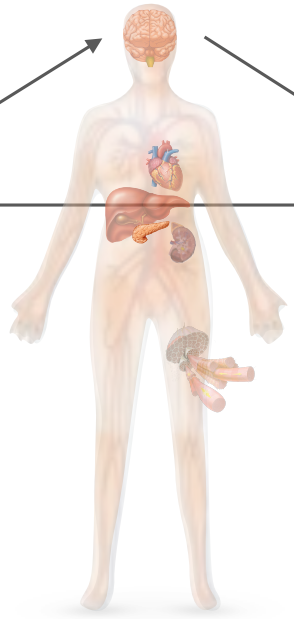


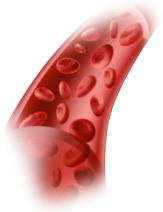
Brain structure and function
Mental health

Mitochondrial health
MHI / MRC

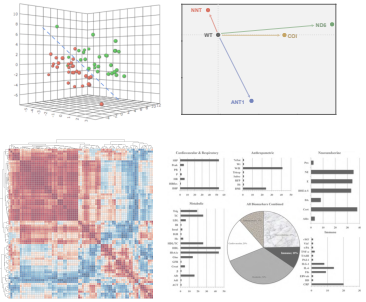








Allostatic load
Stress reactivity
Disease biomarkers



n=110, 4 groups including mtDNA defects

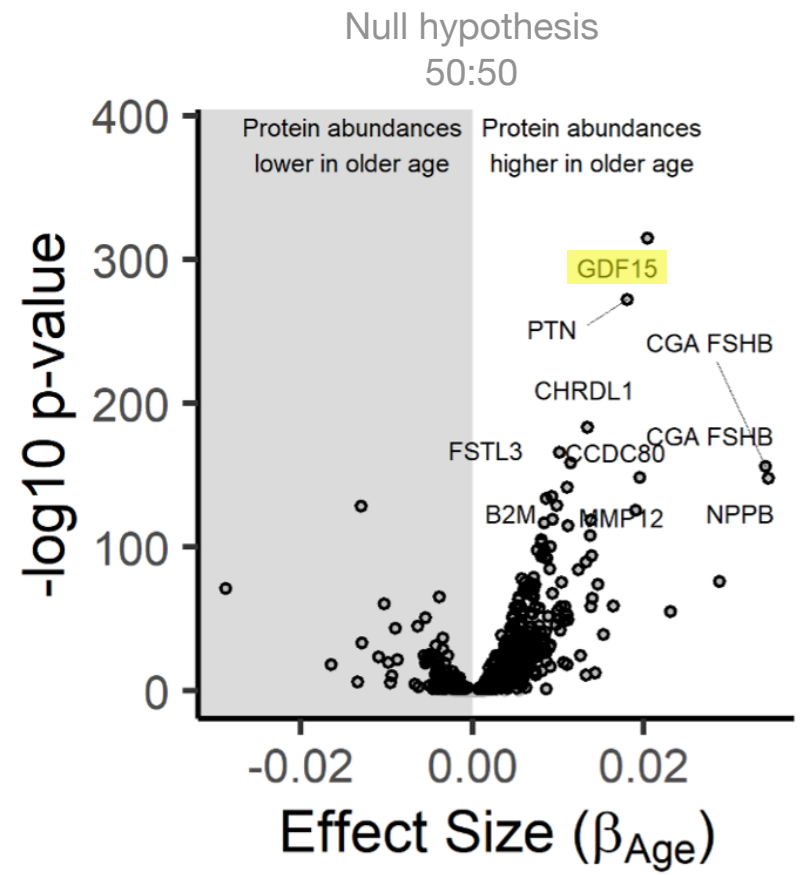
National Institute of Mental Health

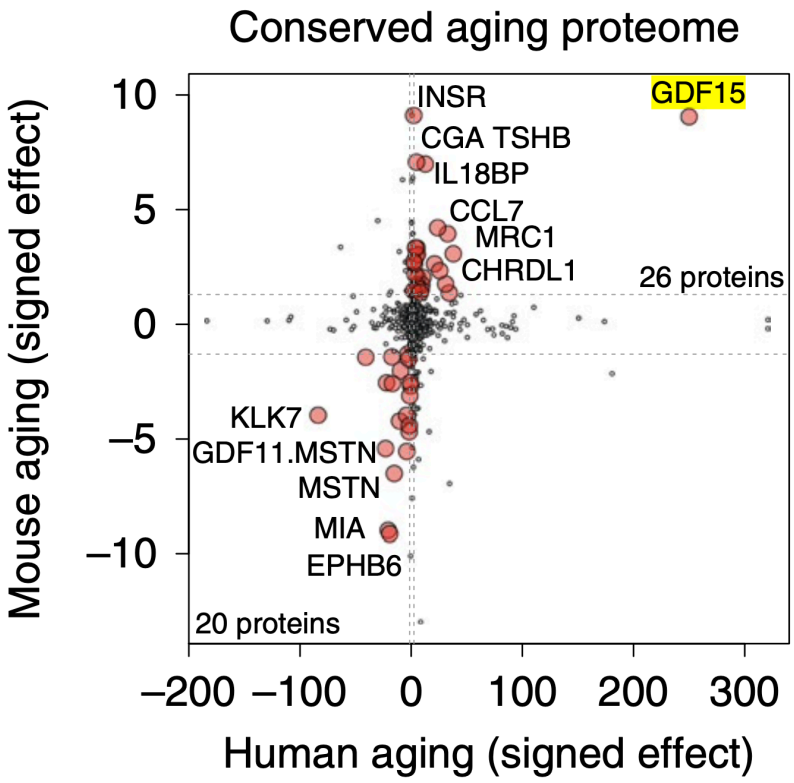
BASZUCKI BRAIN RESEARCH FUND

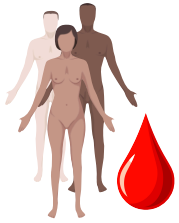
Growth differentiation factor 15

GDF15

GDF15 is the most significantly upregulated protein in human aging



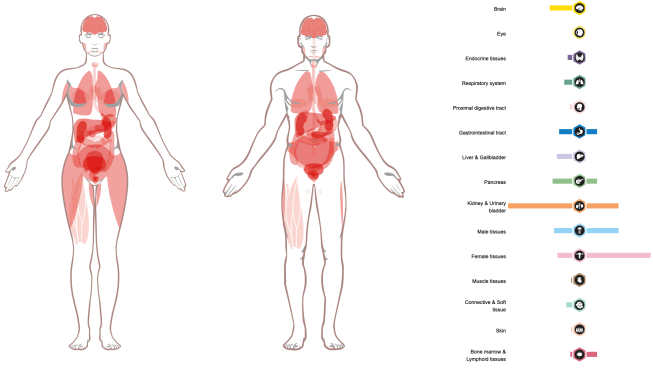




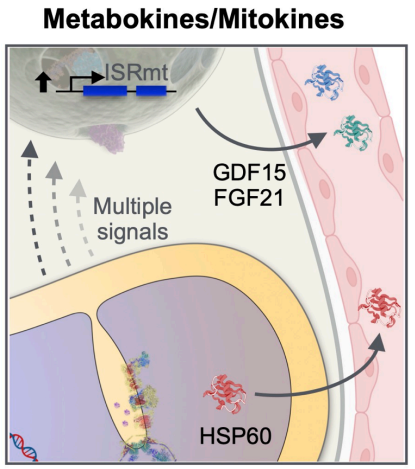
Tanaka et al. *Aging Cell* 2020

Lehallier et al. *Nature* 2019

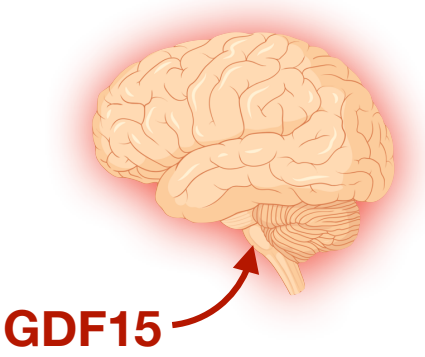
What does GDF15 mean to the organism?



Expressed in >90% of somatic tissues



Triggered by mito OxPhos defects (ISR)



Signals on the brainstem, energy conservation

Hypothalamic-pituitary adrenal (HPA) axis
CORTISOL

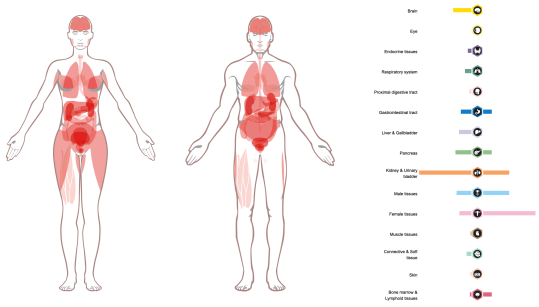
GDF15

Sympathetic activation
Catecholamines (NE)

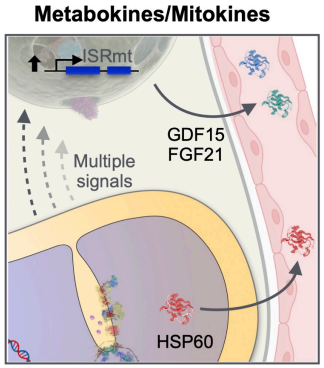
Activates canonical stress axes

Lockhart et al. *Endocr Rev* 2020

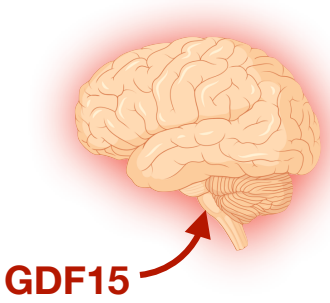
What does GDF15 mean to the organism?



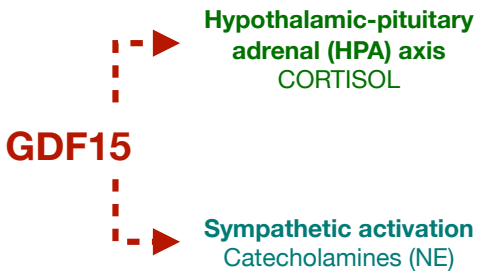
Expressed in >50% somatic tissues



Triggered by cellular stressors (ISR)

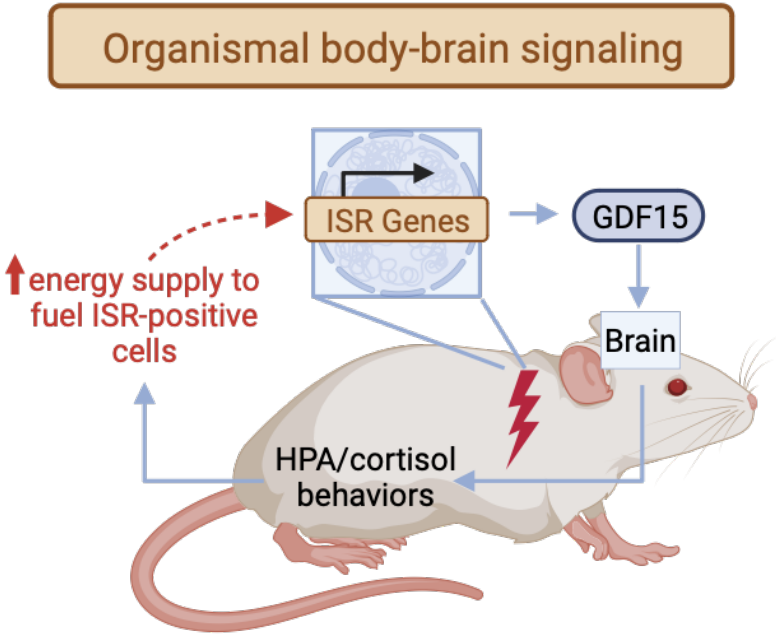


Signals on the brainstem, energy conservation



Activates canonical stress axes

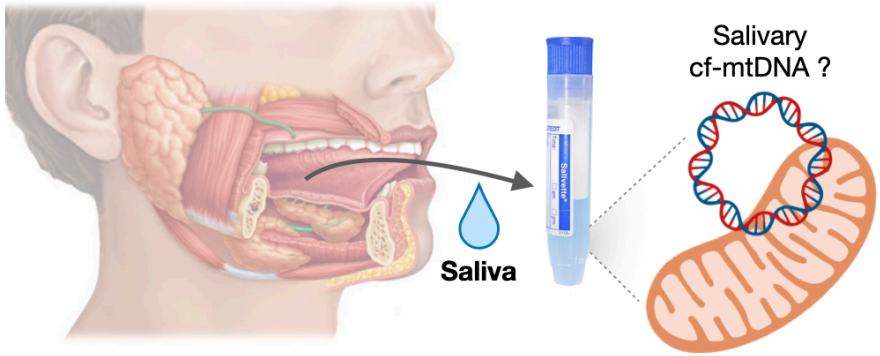
Psychological stress transiently increases GDF15 in humans



Monzel et al. *Life Metab* 2024

Stress hormones & metabolites are detectable in saliva

Can we quantify cf-mtDNA and other "mitokines" in human saliva?

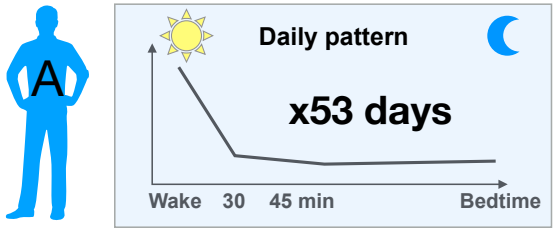


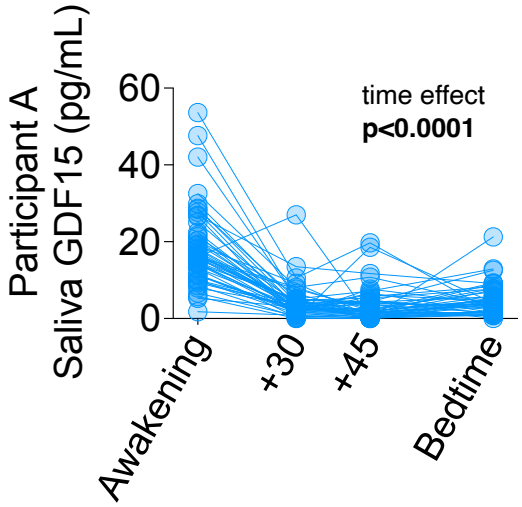
If so: this would make possible epidemiological and high-temporal resolution timecourse studies of GDF15

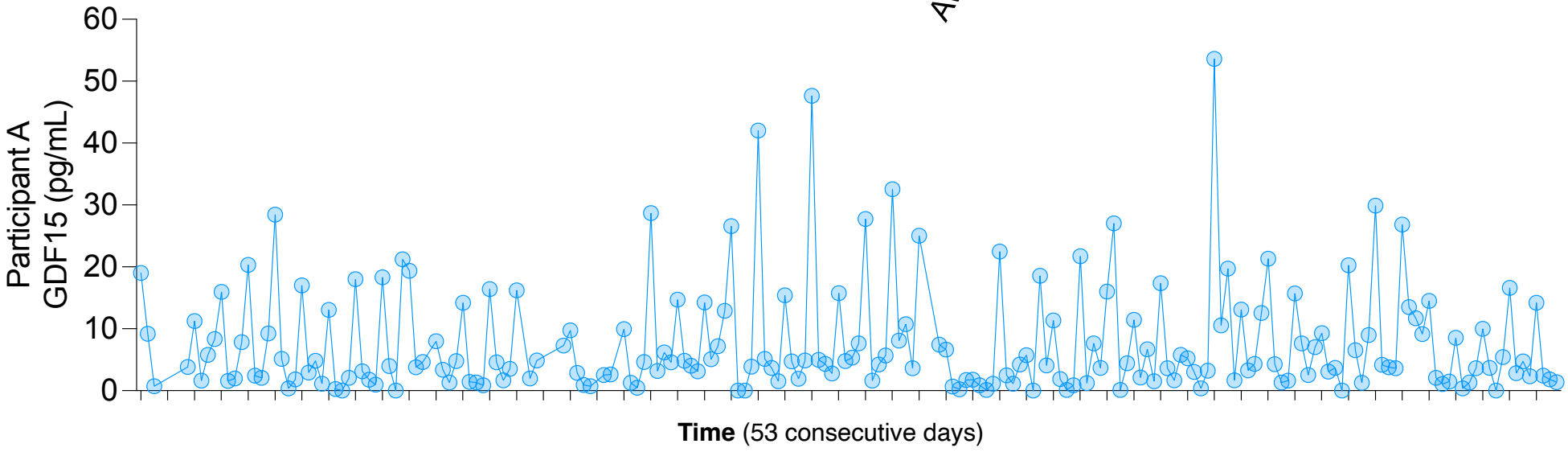
Shannon Rausser

Caroline Trumpff

Saliva GDF15 dynamics

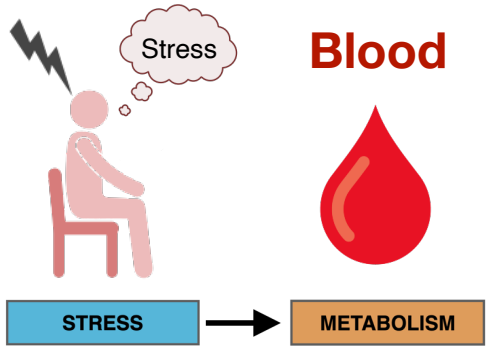


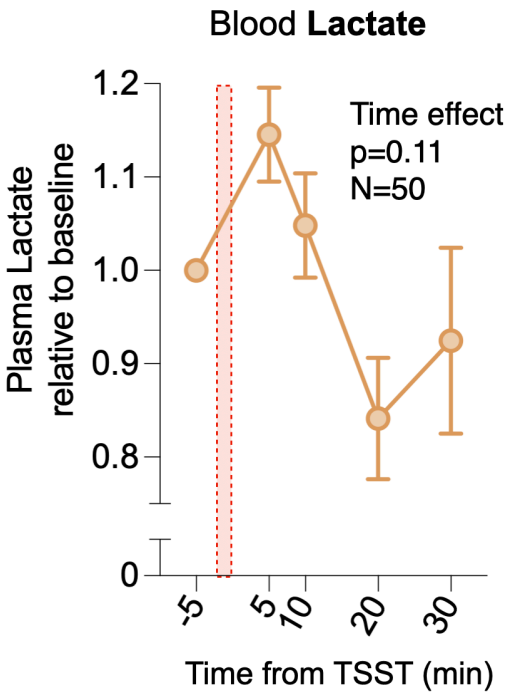


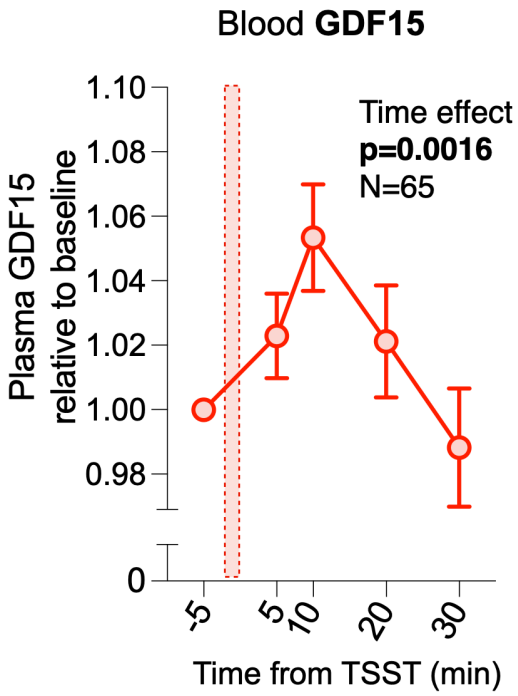


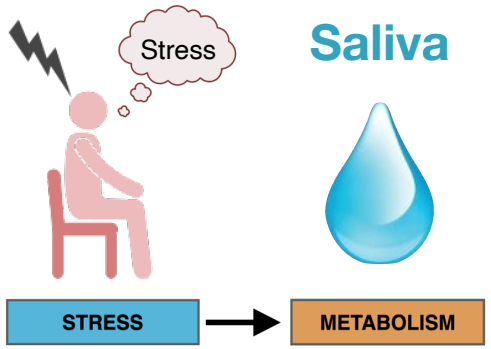
n=1, male participant, 53 days
From Trumpff et al. *PNEC* 2019

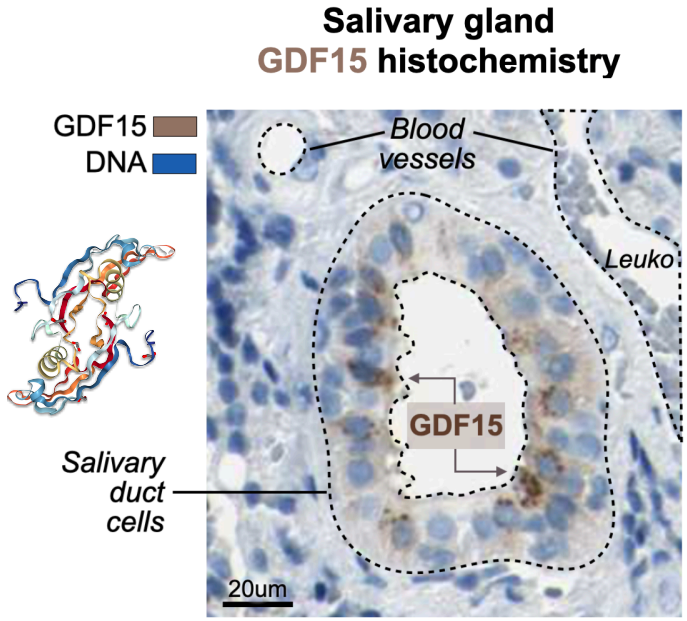
Rachel Haahr
Shannon Rausser
Hannah Huang
Caroline Trumpff

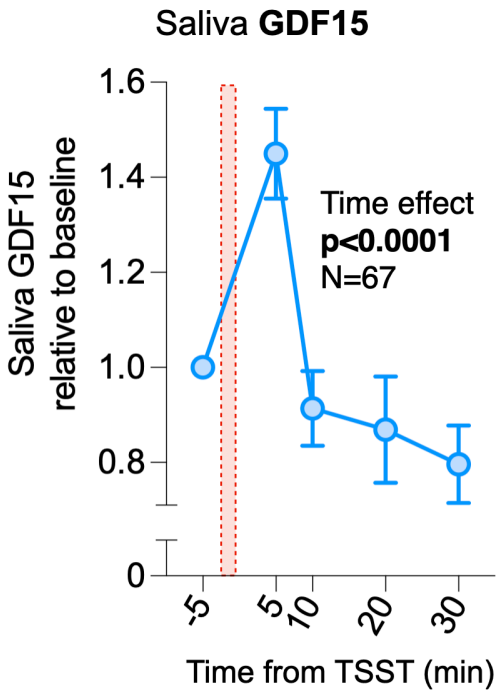

Stress
Blood
STRESS
METABOLISM


Blood Lactate
Plasma Lactate relative to baseline
1.2
1.1
1.0
0.9
0.8
0
Time effect
p=0.11
N=50
-5
5
10
20
30
Time from TSST (min)

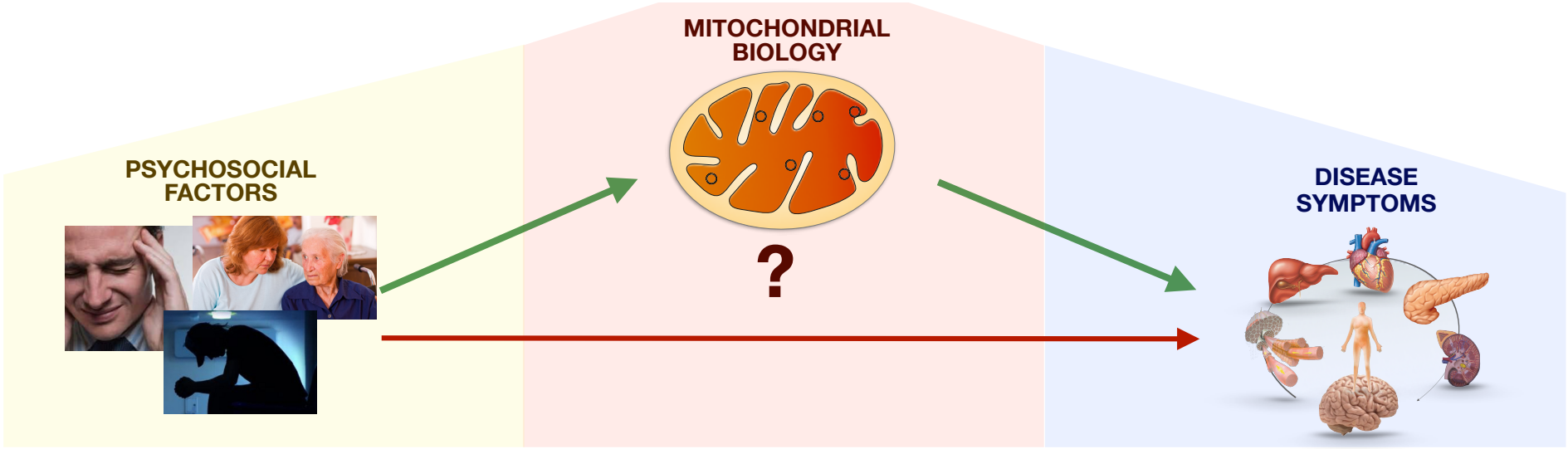

Blood GDF15
Plasma GDF15 relative to baseline
1.10
1.08
1.06
1.04
1.02
1.00
0.98
0
Time effect
p=0.0016
N=65
-5
5
10
20
30
Time from TSST (min)


Stress
Saliva
STRESS
METABOLISM


Salivary gland
GDF15 histochemistry
GDF15
DNA
Blood vessels
Leuko
GDF15
Salivary duct cells
20um


Saliva GDF15
Saliva GDF15 relative to baseline
1.6
1.4
1.2
1.0
0.8
0
Time effect
p<0.0001
N=67
-5
5
10
20
30
Time from TSST (min)

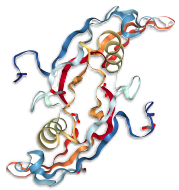
Why do patients believe that “stress” exaggerates or cause their symptoms?



Stress

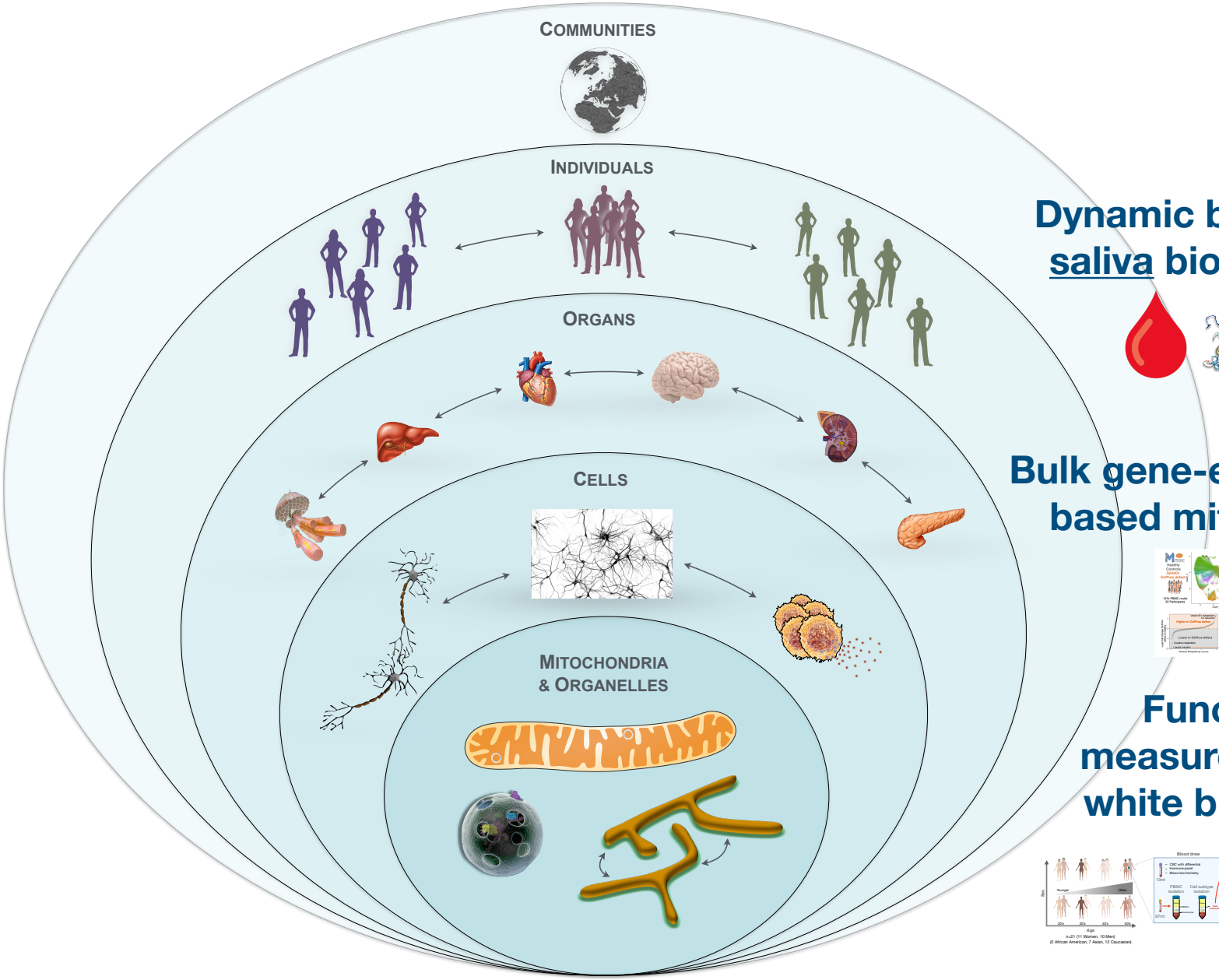
OxPhos defects

Shared biology (GDF15)

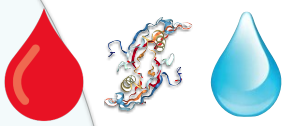


Disease onset & progression

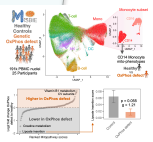
Huang, Trumpff et al. (BioRxiv 2024)



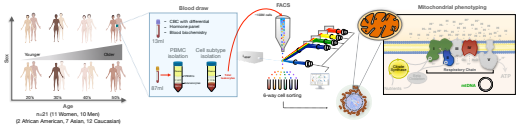
Dynamic blood and saliva biomarkers 3



Bulk gene-expression based mitotyping 2

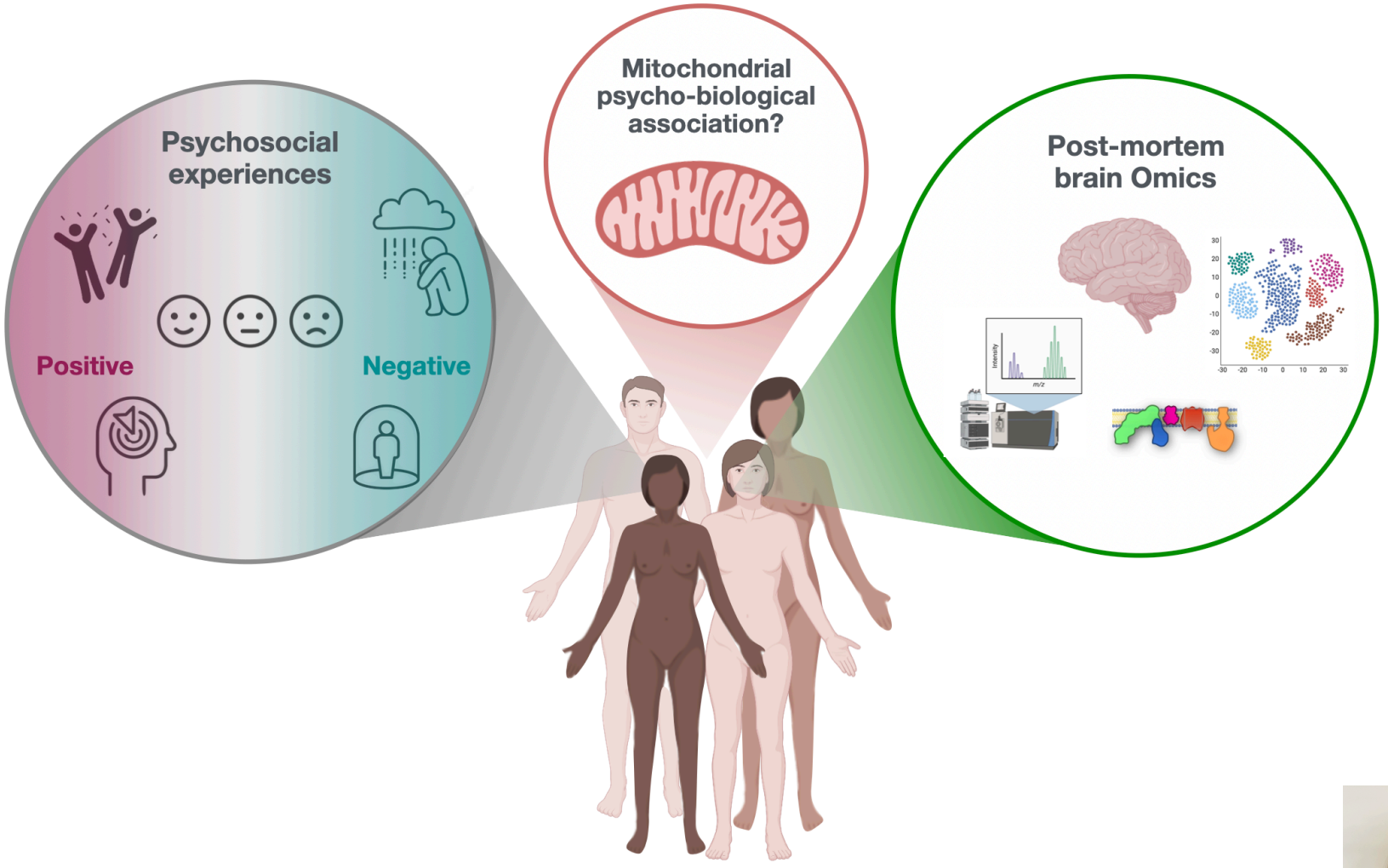


Functional measurements in white blood cells 1

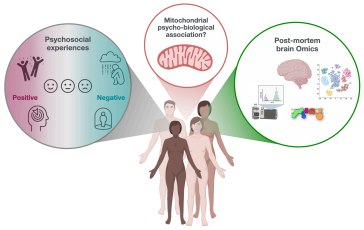


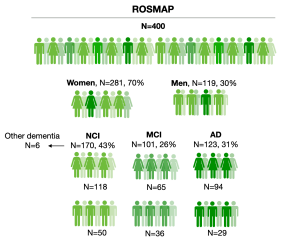
Picard and Sandi. *Neurosci Biobehav Rev* (2021)

Are brain mitochondrial phenotypes linked to psychosocial exposures & experiences in humans?

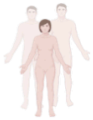


Caroline Trumpff





ROSMAP



Ante-mortem
<1 year

Post-mortem

Up to 20 years — *Length of follow up (yearly)*

Positive Experiences

Social network size,
Late life social activity,
Purpose in life,
Satisfaction with life,
Time horizon,
Well-being

Negative Experiences

Adverse childhood experiences*,
Negative life events,
Social isolation,
Depressive symptoms,
Negative mood,
Perceived stress

1 year

TMT Proteomics

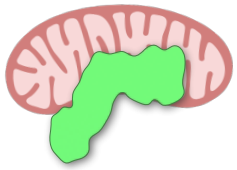
SRM Proteomics

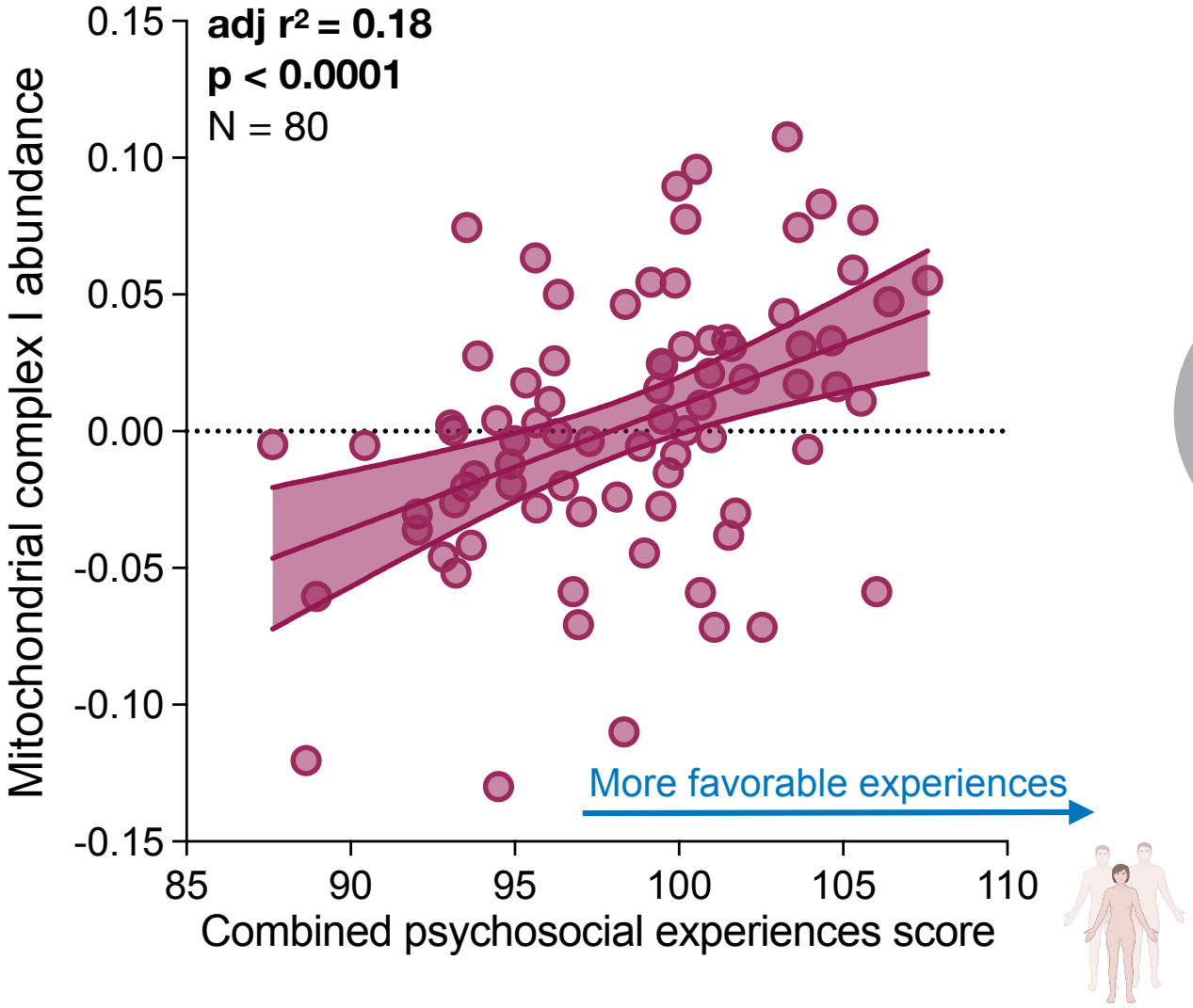
Bulk RNA-seq

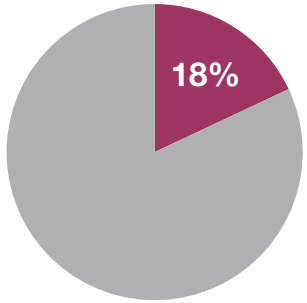
Single-nucleus RNA-seq

Caroline Trumpff

Psychobiological associations in human brain mitochondria

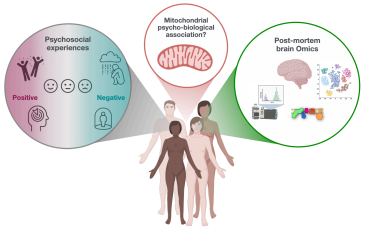


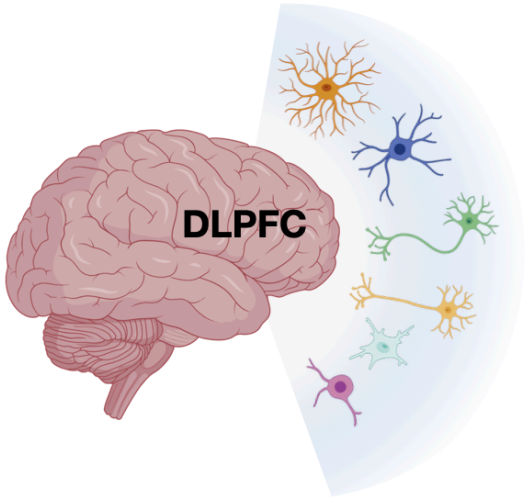




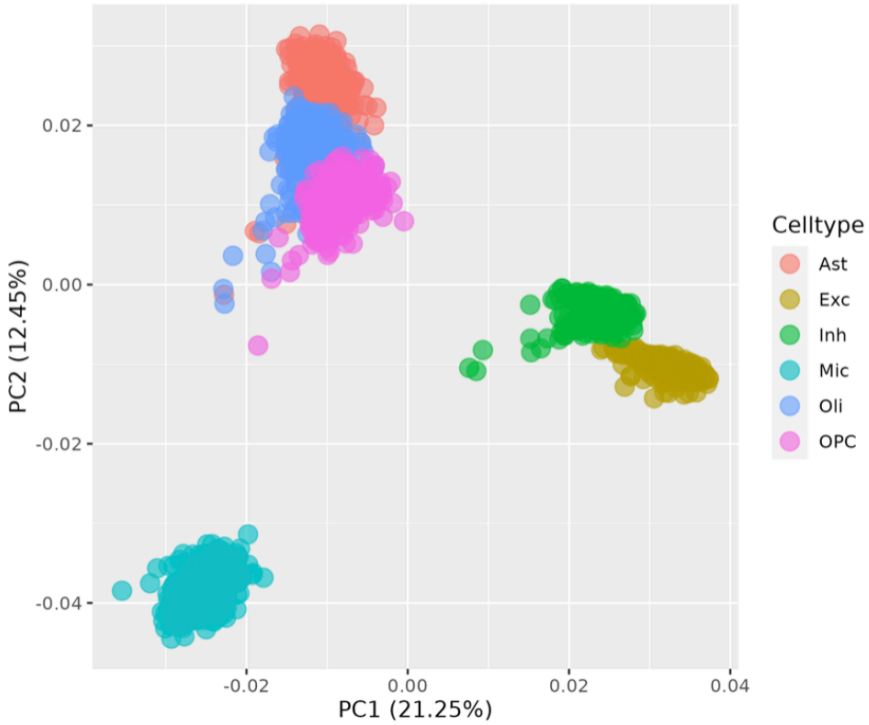
Multiple linear regression adjusted for sex and cognitive status; cell type abundances

Trumpff et al. *BioRxiv* 2023





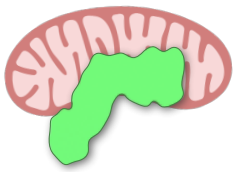
single-nucleus
RNA-seq pseudobulk data

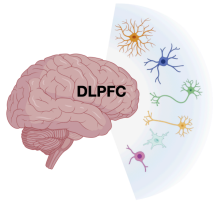


Phil de Jager

Anna Monzel

Trumpff et al. *BioRxiv* 2023





single-nucleus
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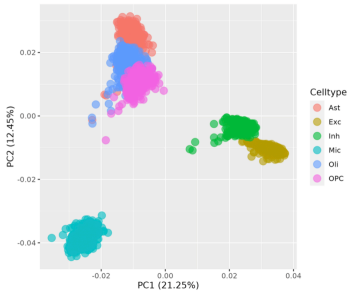
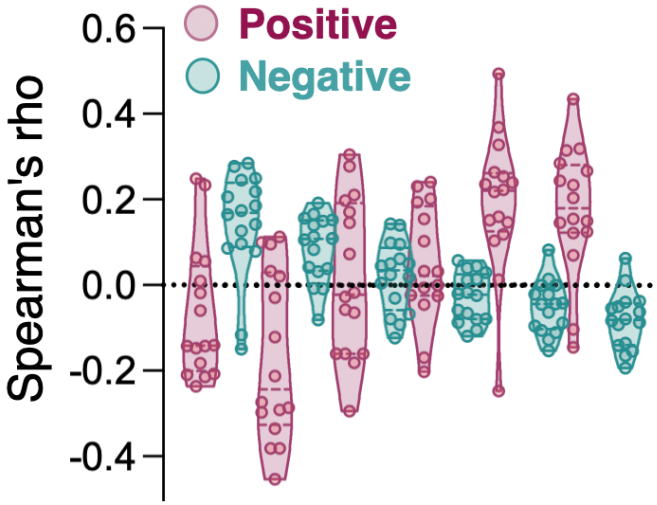
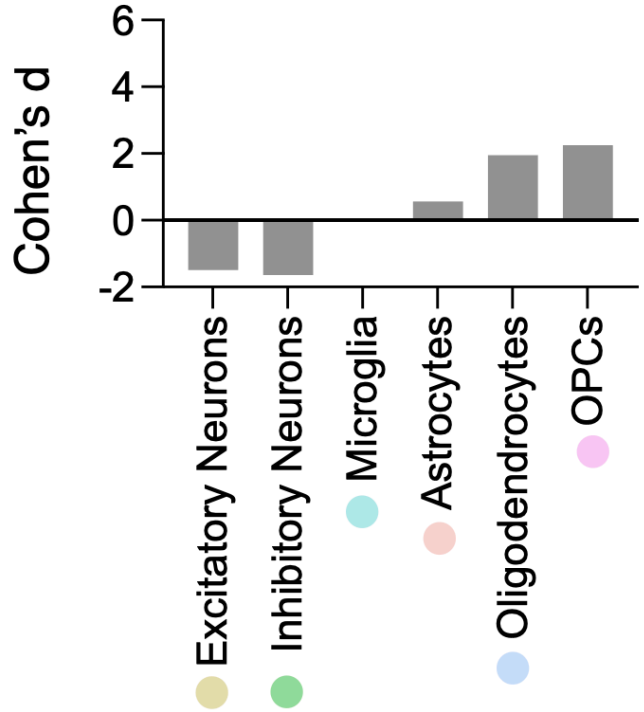
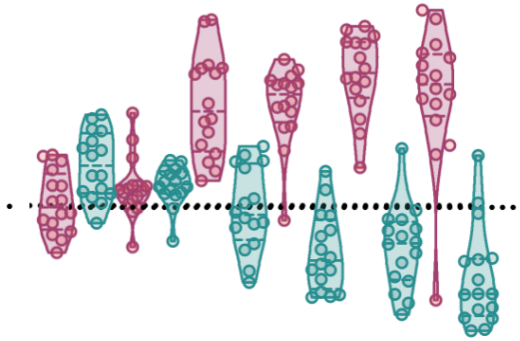


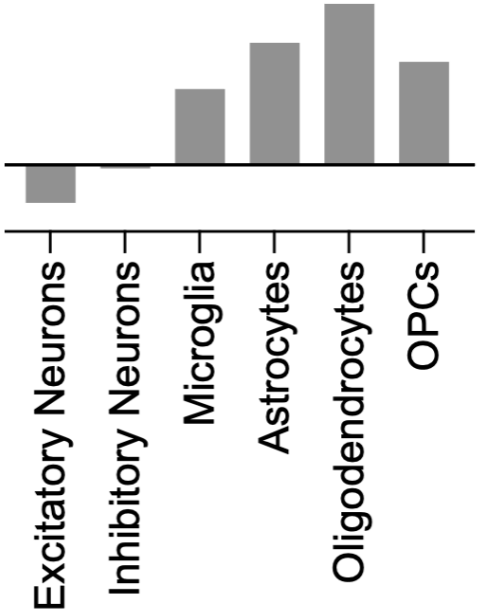
Summary scores





Well-being & Negative life events





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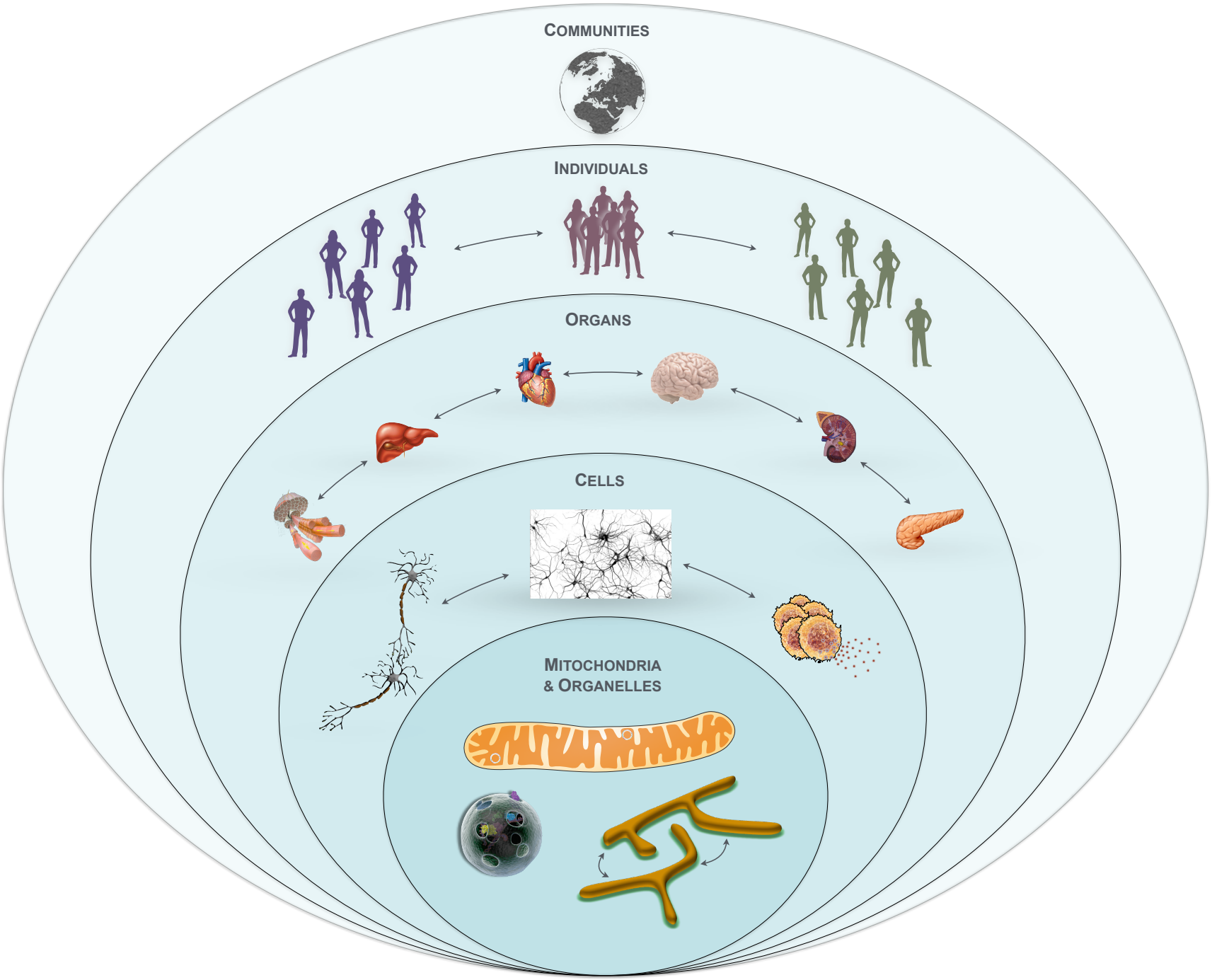
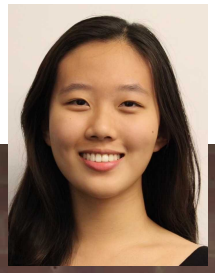
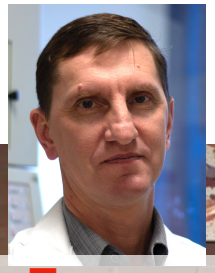

COMMUNITIES
INDIVIDUALS
ORGANS
CELLS
MITOCHONDRIA
& ORGANELLES

Mitochondrial PsychoBiology Lab

Linking molecular processes within mitochondria with the human experience

OUR RESEARCH





Ayelet

Eugene Mosharov
Sulzer Lab

Caroline

Anna

Hannah

Cynthia

Collaborators

Mitochondrial Biology & Medicine

Michio Hirano
Catarina Quinzii
CUIMC Neurology

Brett Kaufman
Pittsburgh University

Gyuri Hajnóczy
Erin Seifert
Thomas Jefferson University

Orian Shirihai
Mike Irwin
UCLA

Vamsi Mootha
Rohit Sharma
Harvard & MGH

Edward Owusu-Ansah
CUIMC Physiology & Biophysics

Ryan Mills
University of Michigan

Gilles Gouspillou
UQAM

Tonio Enriques
Madrid

MiSBIE & MDEE Teams

Kris Engelstad
Catherine Kelly
Shufang Li
Anna Monzel
Mangesh Kurade

Psychosocial Sciences

Robert-Paul Juster
Université de Montréal

Elissa Epel
Jue Lin
Aric Prather
Ashley Mason
UCSF

Eli Puterman
UBC

Clemens Kirshbaum
Dresden University

Anna Marsland
Rebecca Reed
Pittsburgh University

Suzanne Segerstrom
University of Kentucky

David Almeida
Penn State University

Energy expenditure & metabolism

Marie-Pierre St-Onge
Dympna Gallagher
Michael Rosenbaum
CUIMC Medicine

Chris Kempes
Santa Fe Institute

Herman Pontzer
Duke

Sam Urlacher
Baylor

Brain Neurobiology & Neuroimaging

Phil De Jager
Hans Klein
Vilas Menon
Stephanie Assuras
CUIMC Neurology

Eugene Mosharov
Dave Sulzer
John Mann
Maura Boldrini
Mark Underwood
Gorazd Rosoklija
Andrew Dwork
Chris Anacker
Dani Dumitriu
Catherine Monk
Vincenzo Lauriola
Richard Sloan
Caroline Trumpff
CUIMC Psychiatry

Tor Wager
Dartmouth

Michel Thiebaut de Schotten
CNRS Bordeaux

Manish Saggar
Stanford

Anne Grunewald
University of Luxembourg

Carmen Sandi
EPFL

Efrat Levy
Pasquale D'acunzo
NYU

Biological Aging

Steve Horvath
Morgan Levine
Altos

Albert Higgins-Chen
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Marie-Abèle Bind
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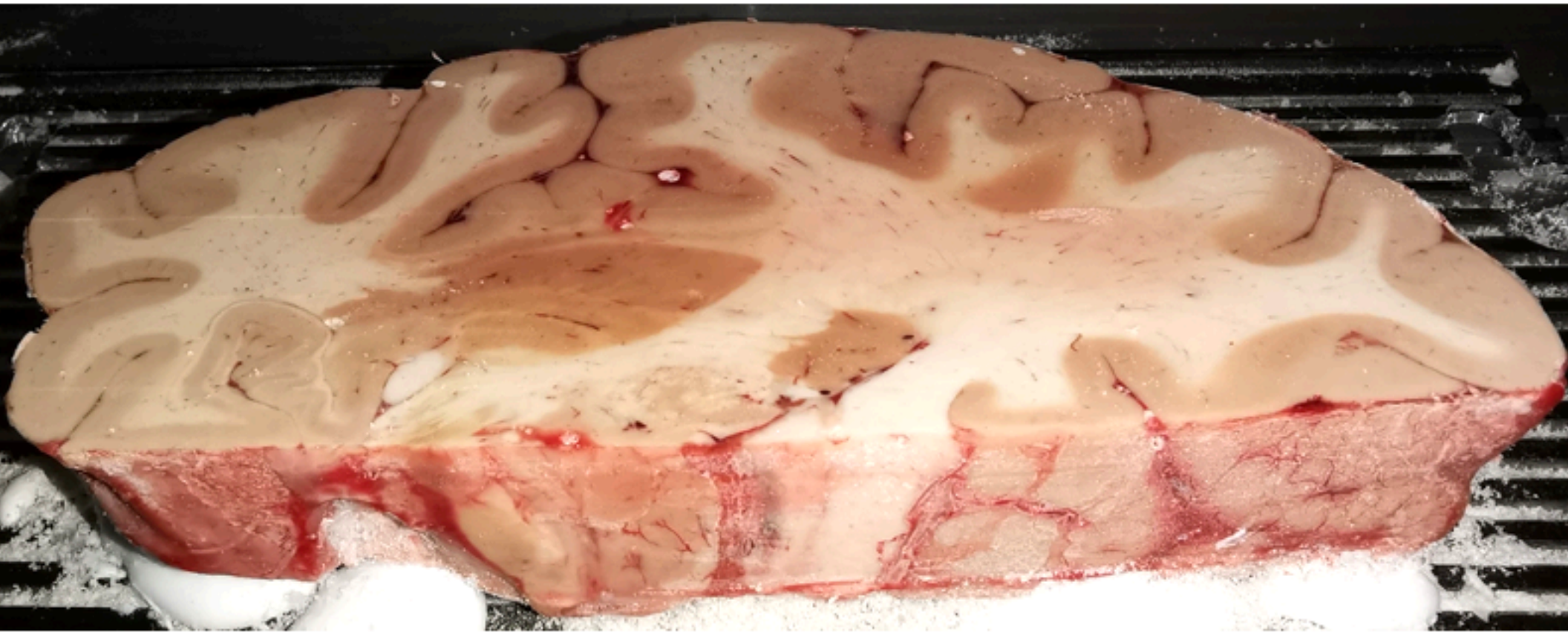
MITOCHONDRIAL
PSYCHOBIOLOGY LAB

MITOCHONDRIA STRESS BRAIN EPIGENETICS
iSBIE

How are mitochondria distributed, and do they specialize across the human brain?

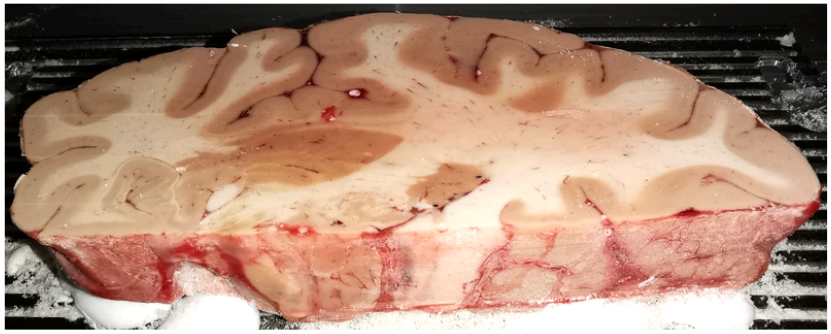
MitoBrainMap v1.0

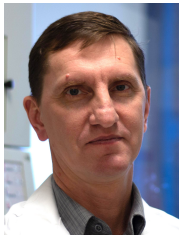
A multi-function mitochondrial atlas of a single human coronal brain section at fMRI resolution



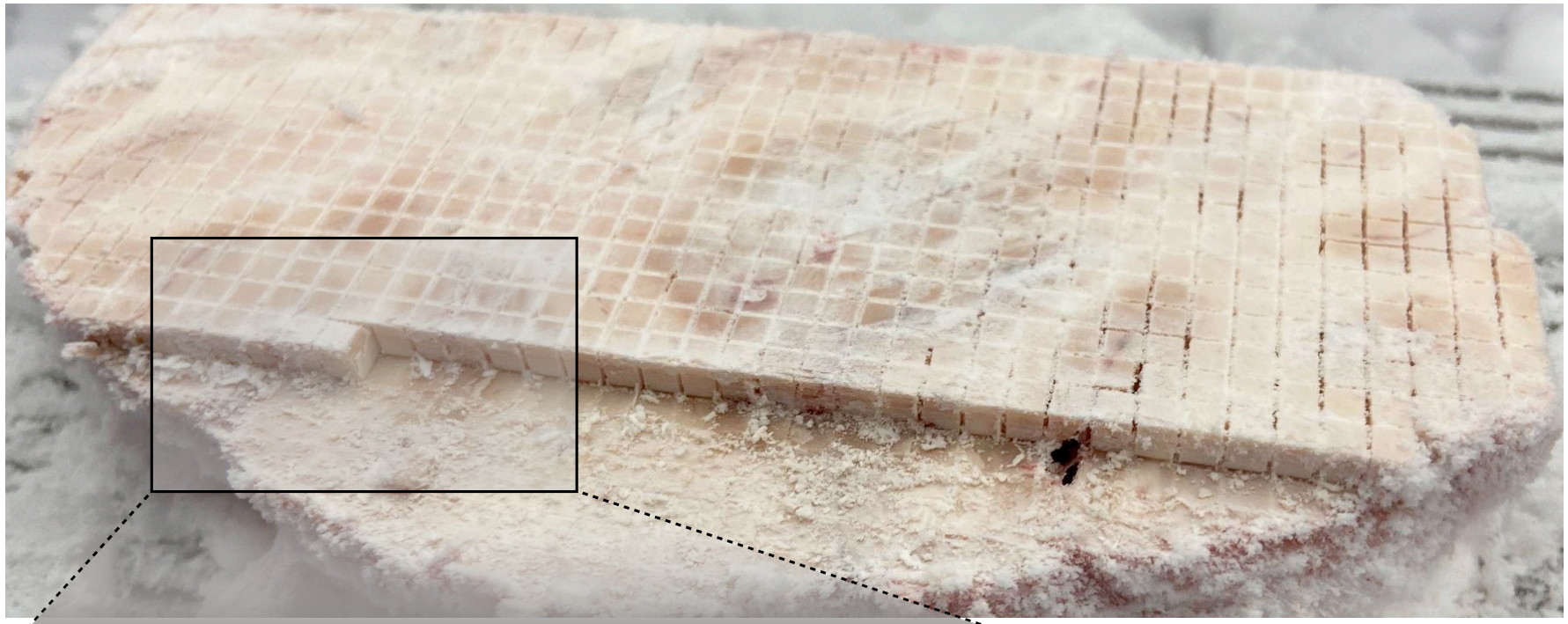
MitoBrainMap v1.0

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

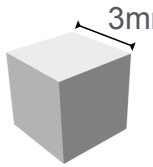




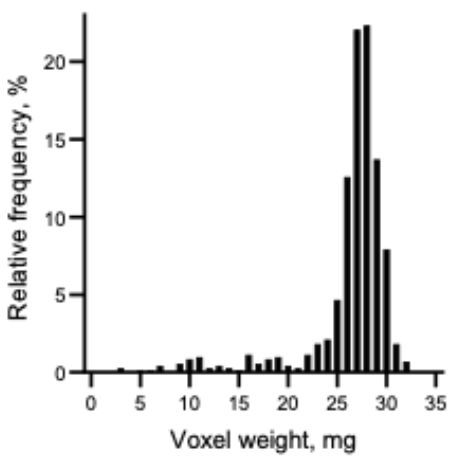
Eugene Mosharov

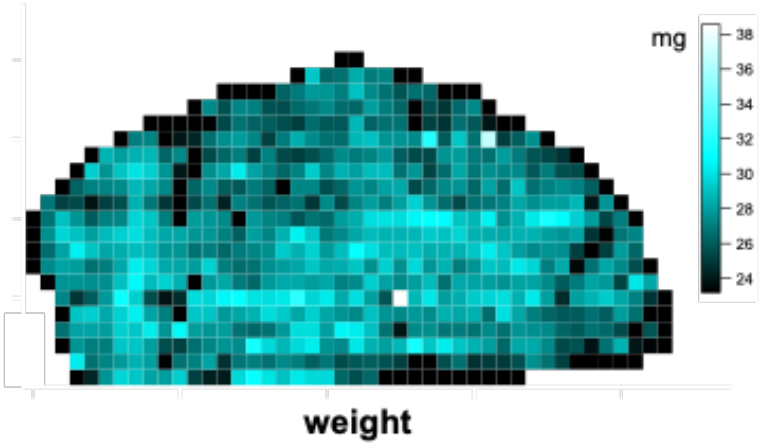


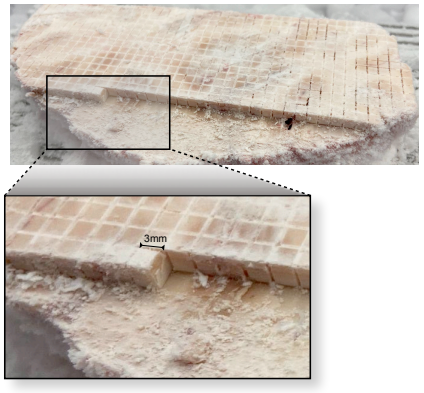
Physical *voxelization*
of the human brain
*a*t fMRI resolution

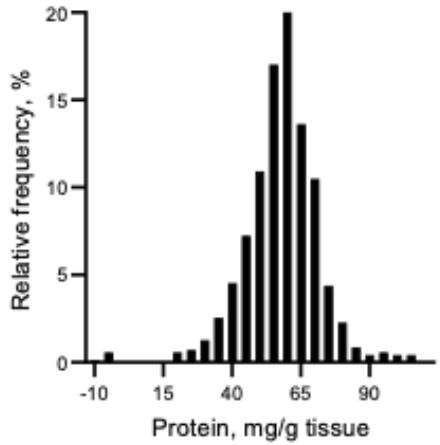


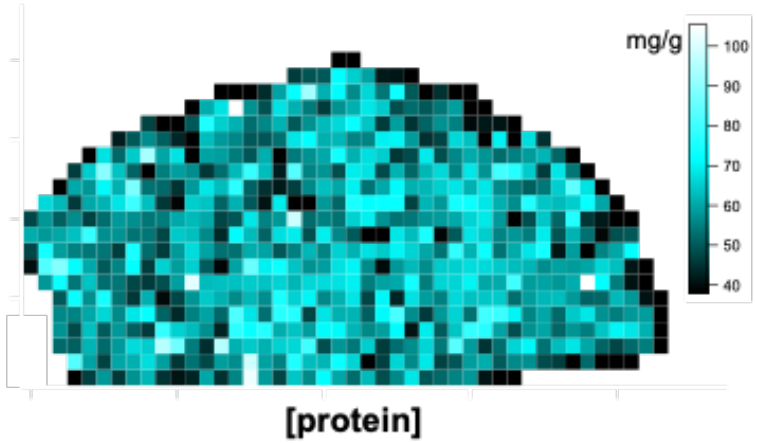
Quality control on 702 human brain voxels

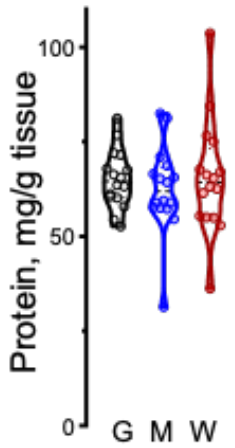












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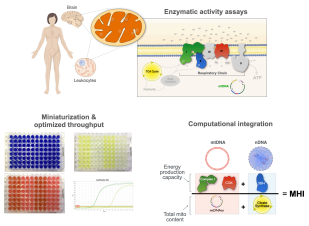
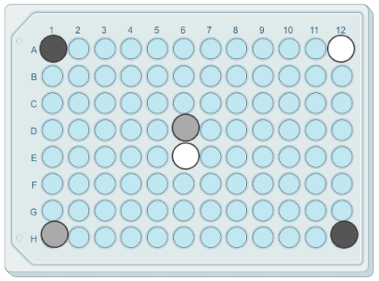


OxPhos and mtDNA profiling

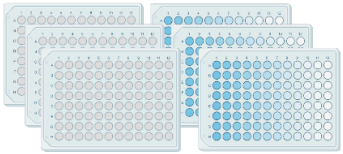
Assay plate layout



Controls

- Grey matter
- White matter
- Mixed tissue

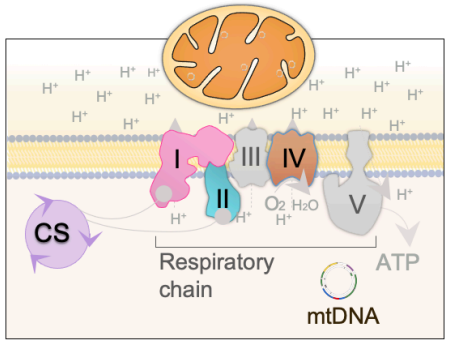
90 unique voxels per plate
8 plates total

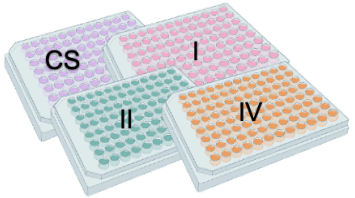


3x triplicate negative control plates

3x triplicate plates

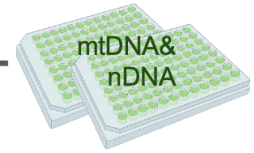
Mitochondrial colorimetric assays





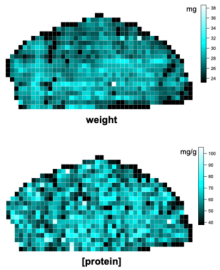
Enzymatic activities measured by spectrophotometric assays

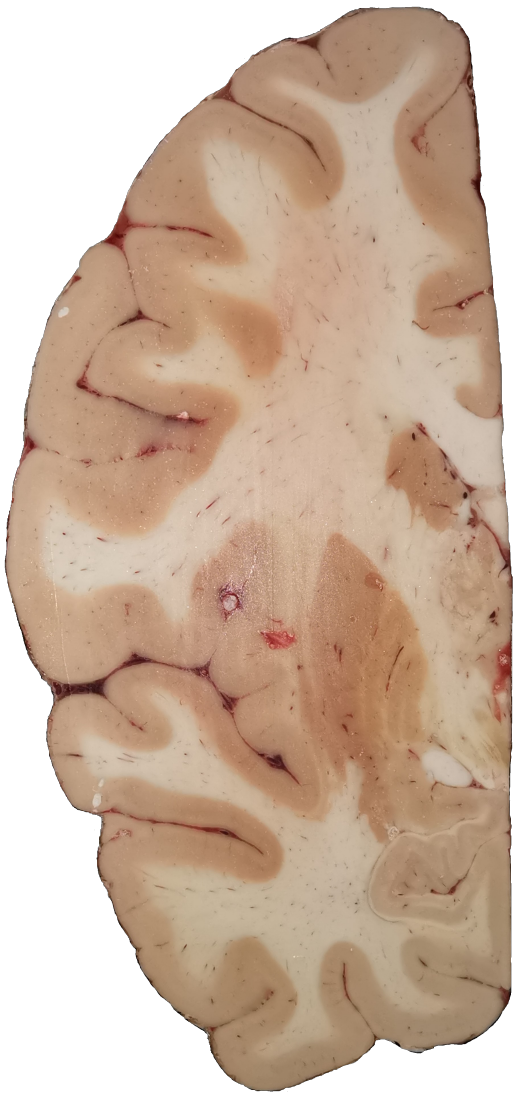
+

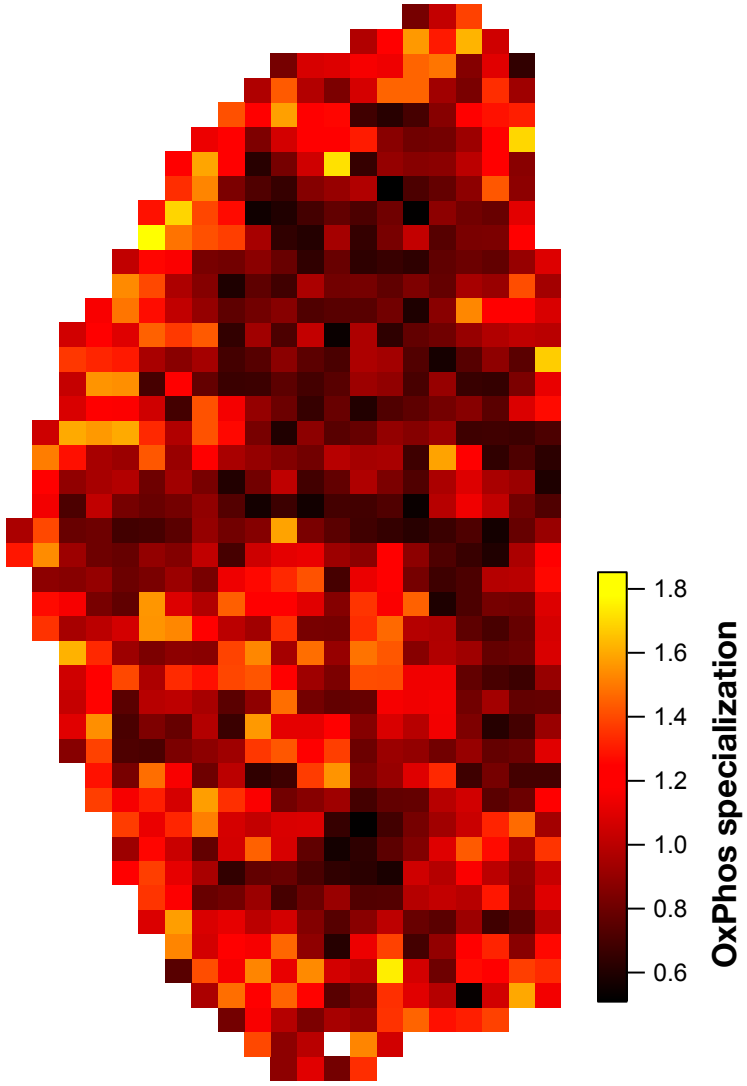


Mitochondrial DNA measured by qPCR, measured in duplicate plates

Corey Osto, Linsey Stiles, Orian Shirihai
Ayelet Rosenberg

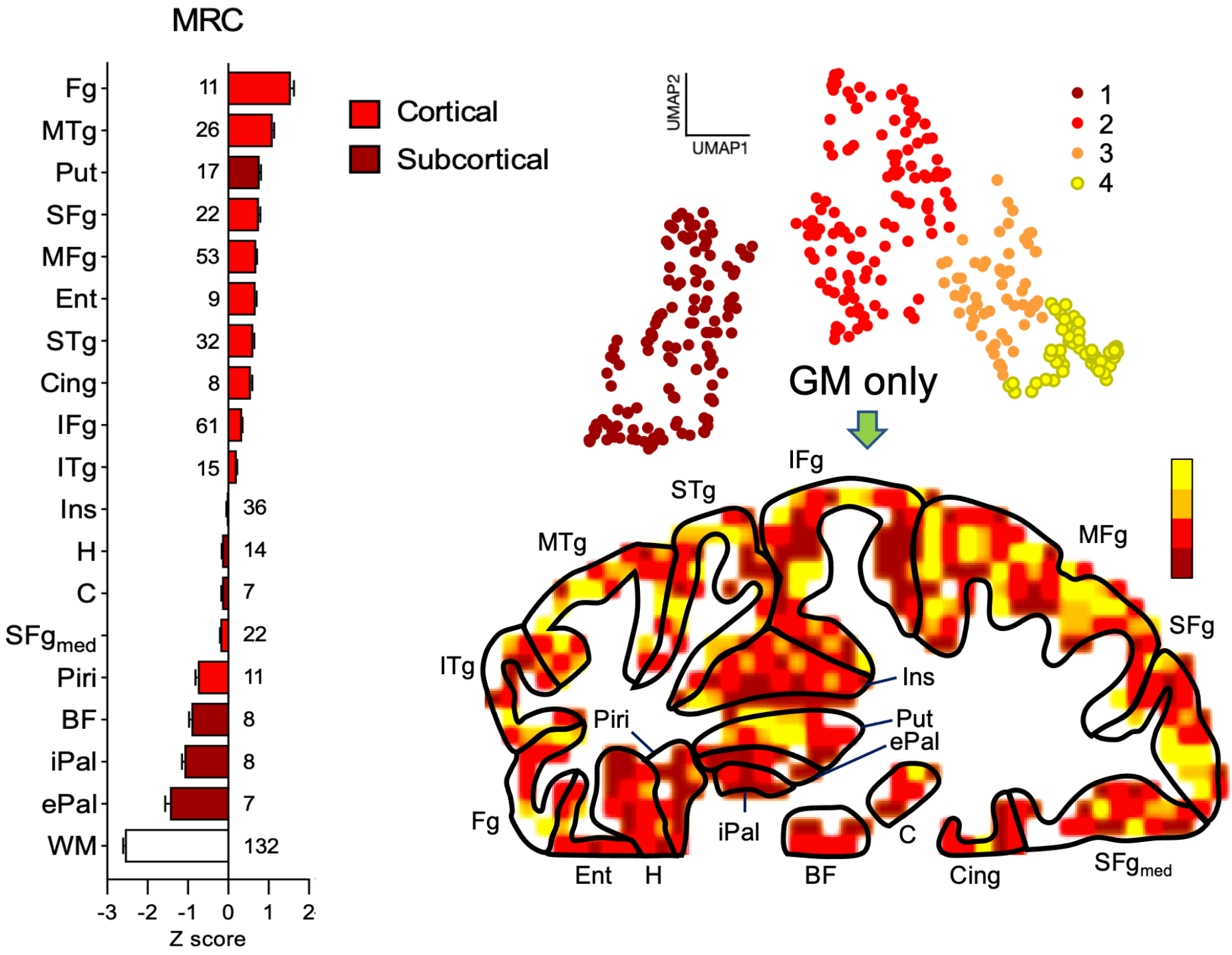






Mitochondrial profiling of 703 physical brain voxels at fMRI resolution

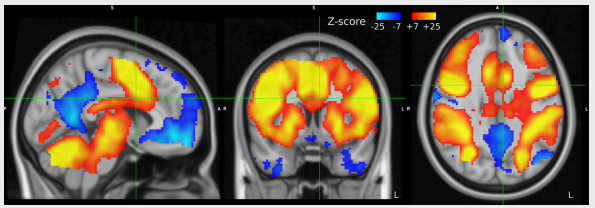
Eugene Mosharov
Ayelet Rosenberg
Michel Thiebaut de Schotten



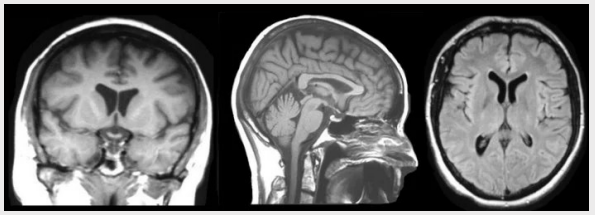
Mosharov et al. (under review)

Building a predictive model of brain mitochondria

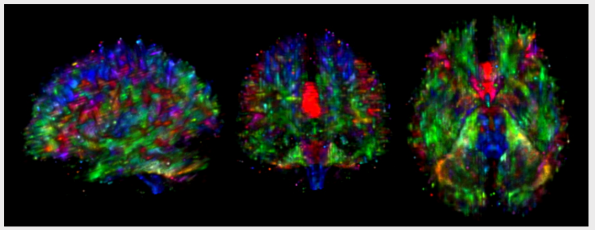
fMRI-BOLD

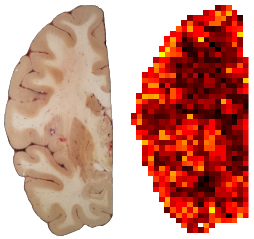


T1/T2 structural

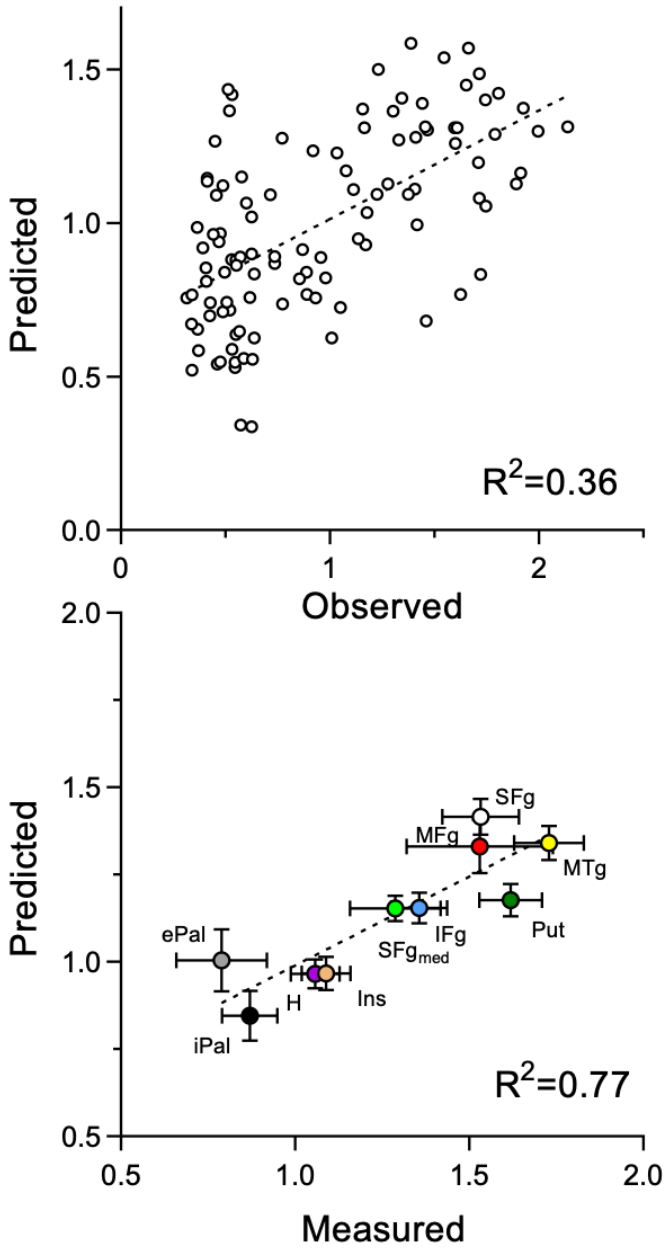


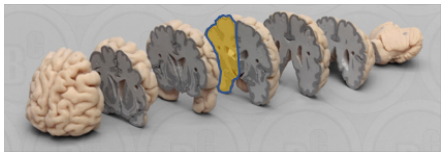
Diffusion imaging

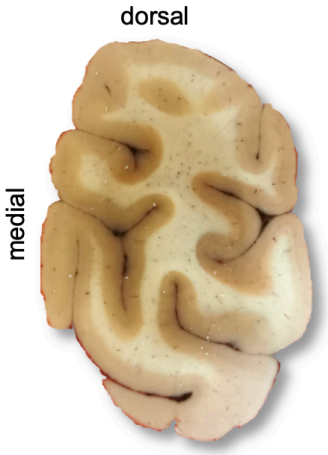




Training: 80%
Test: 20%







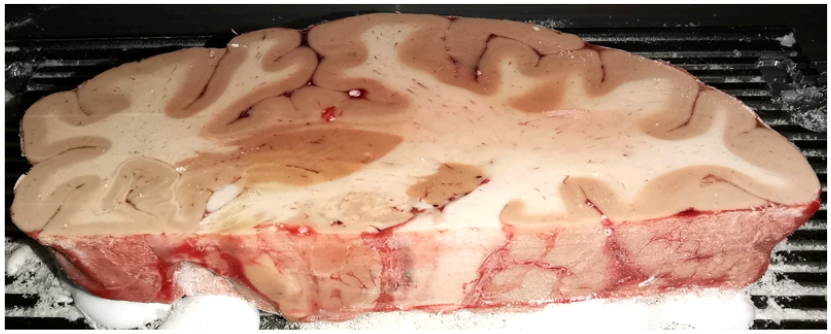
Occipital lobe (mean±S.D.)

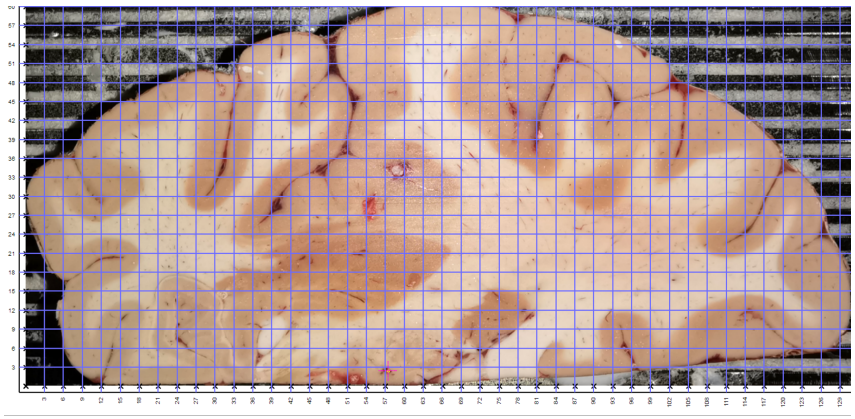
Feature	Observed	Predicted
CI	1.43±0.27	1.41±0.26
CII	1.25±0.16	1.35±0.14
CIV	1.44±0.17	1.31±0.24
MitoD	1.17±0.02	1.15±0.07
TRC	1.39±0.15	1.32±0.18
MRC	1.22±0.13	1.23±0.12

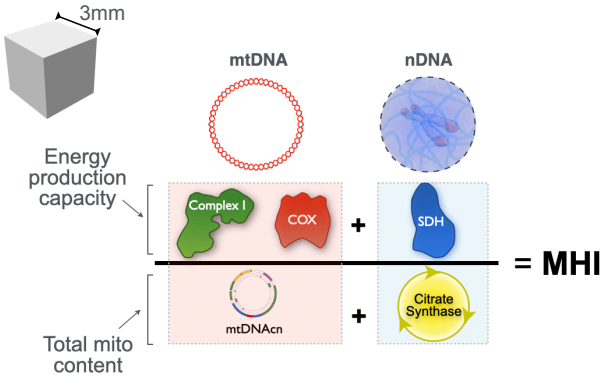
r = 0.75

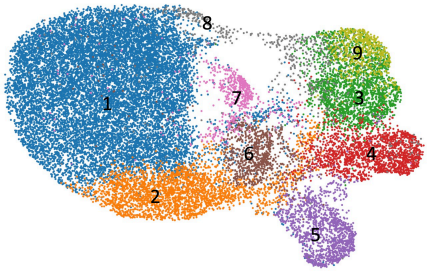
MitoBrainMap v1.0

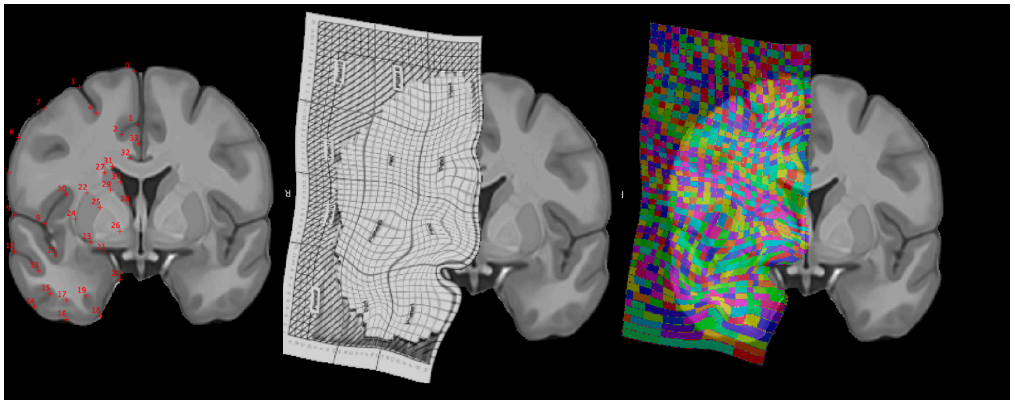
A multi-function mitochondrial atlas of a single human coronal brain section at fMRI resolution





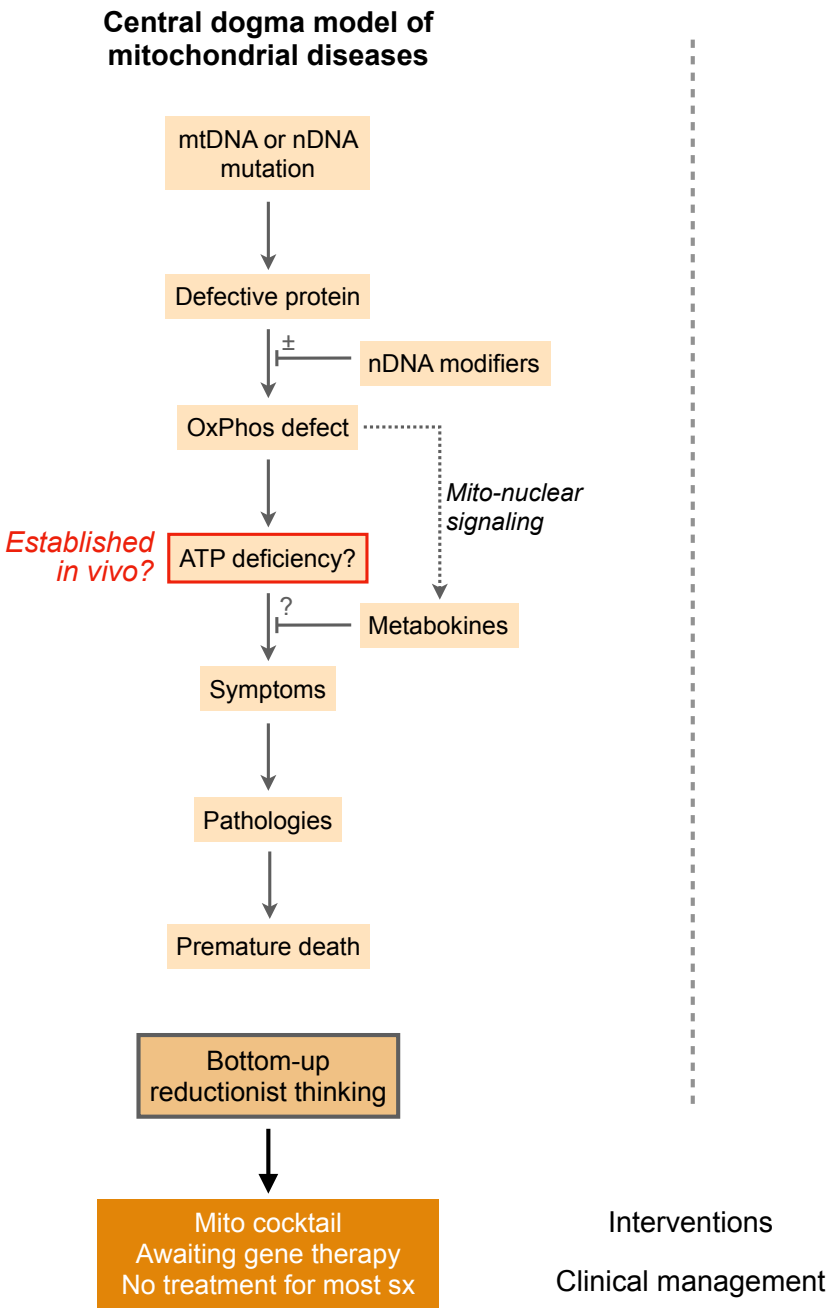






Closing the gap between organellar bioenergetic profiling and whole-brain neuroimaging modalities (fMRI, PET, CBV, DWI, etc)

Eugene Mosharov



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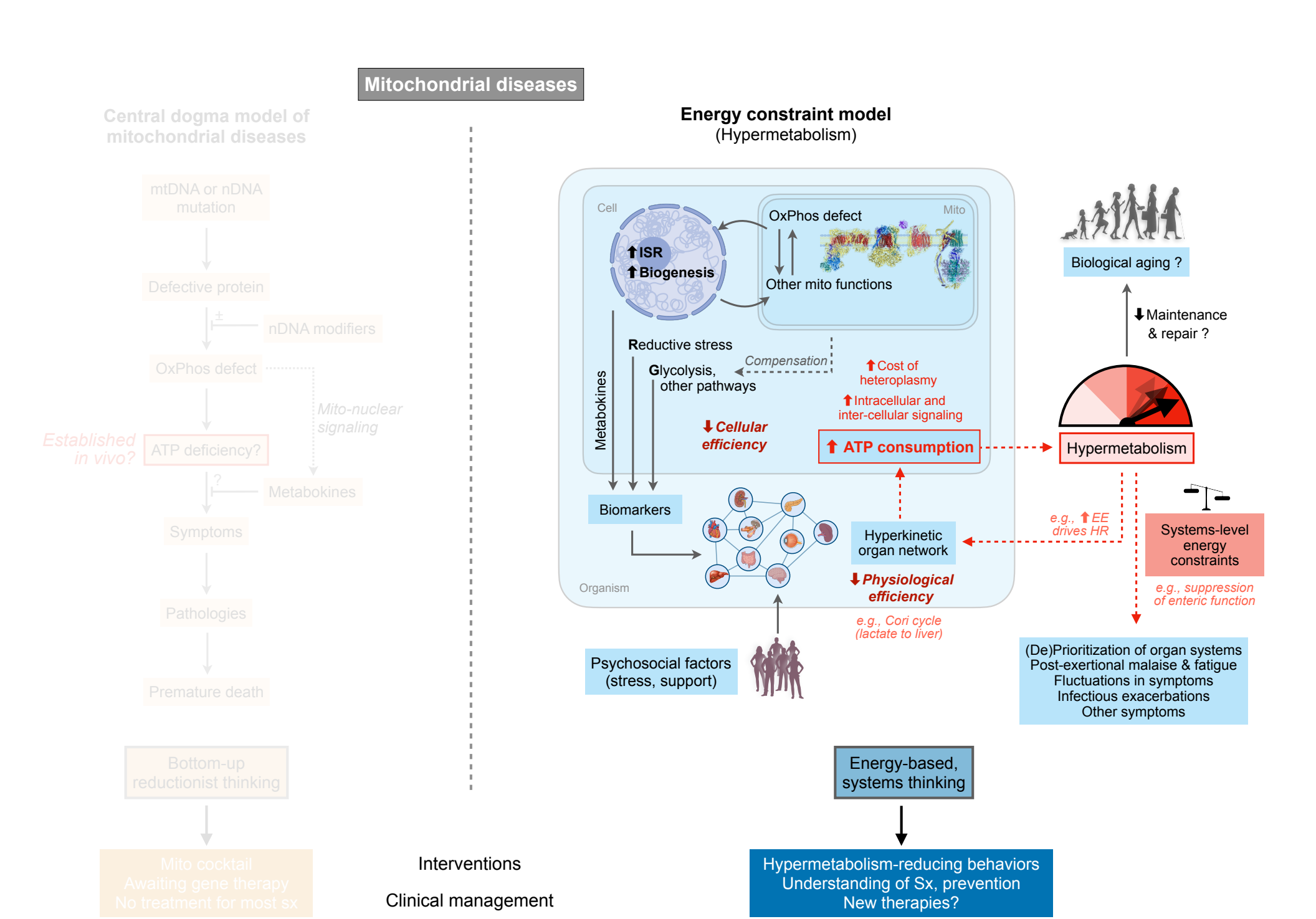

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