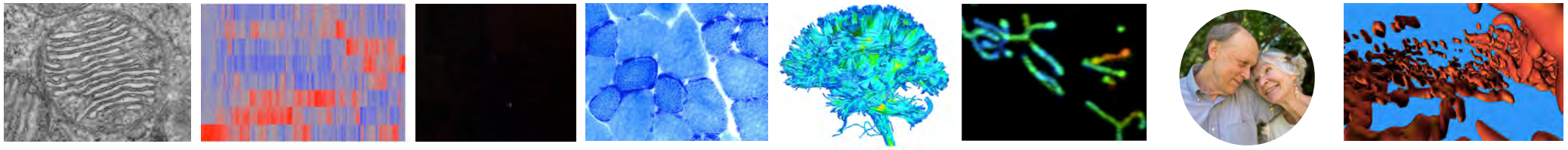
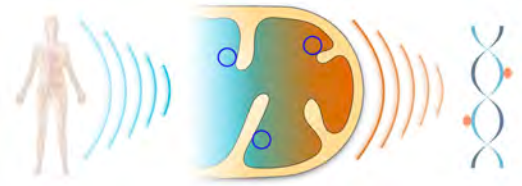


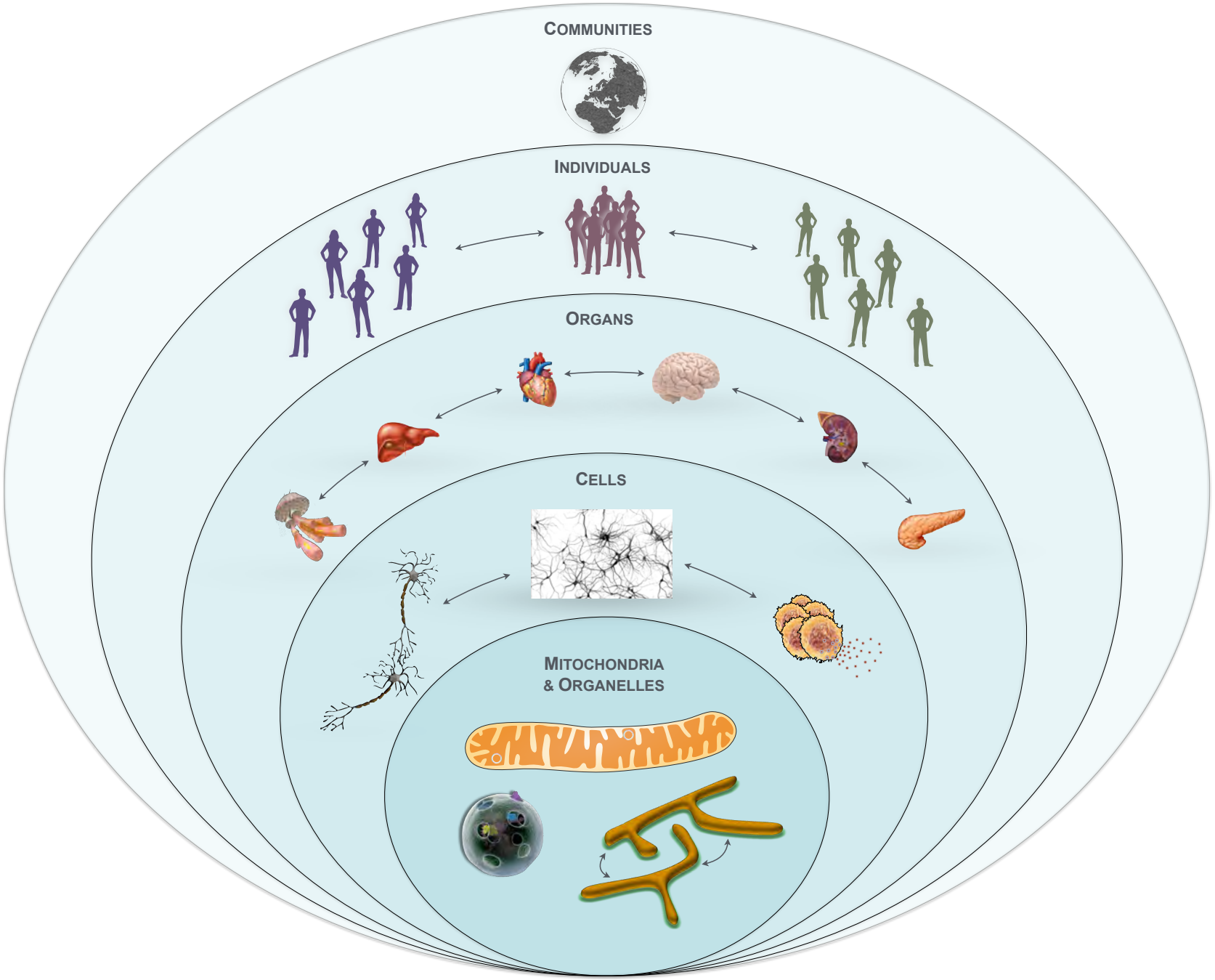
Mitochondrial diversity in mouse and human brains



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

COLUMBIA
COLUMBIA UNIVERSITY
IRVING MEDICAL CENTER

NEW YORK STATE OF OPPORTUNITY. New York State Psychiatric Institute

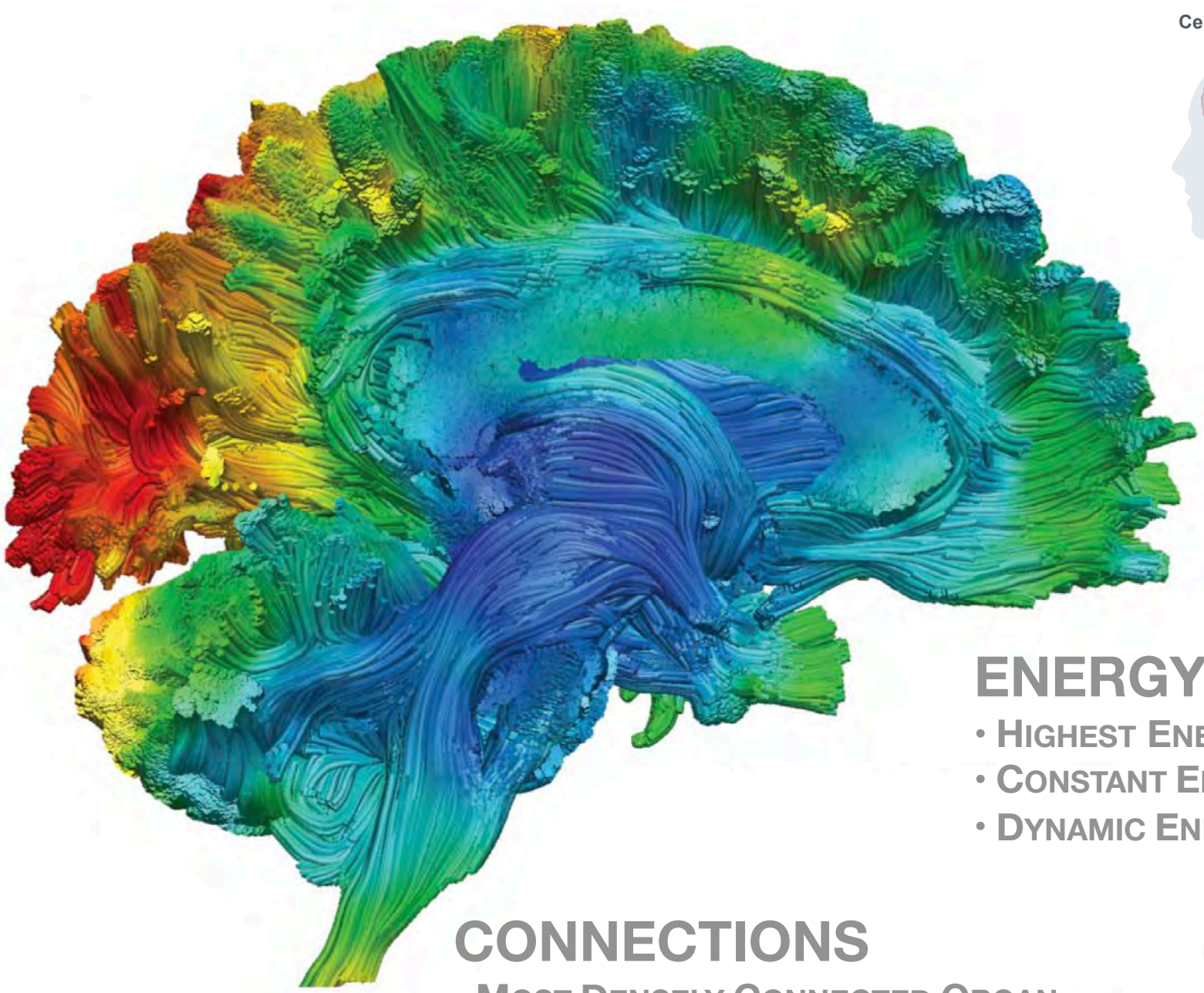


Picard and Sandi. *Neurosci Biobehav Rev* (2021)

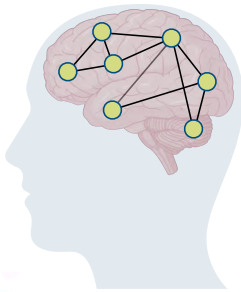
Life is a regulated **energetic cascade** sustained by

information transfer across

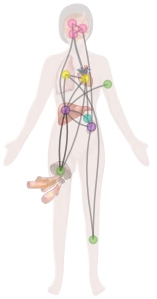
interconnected biological systems



Cell network (brain)



Organ network



ENERGY

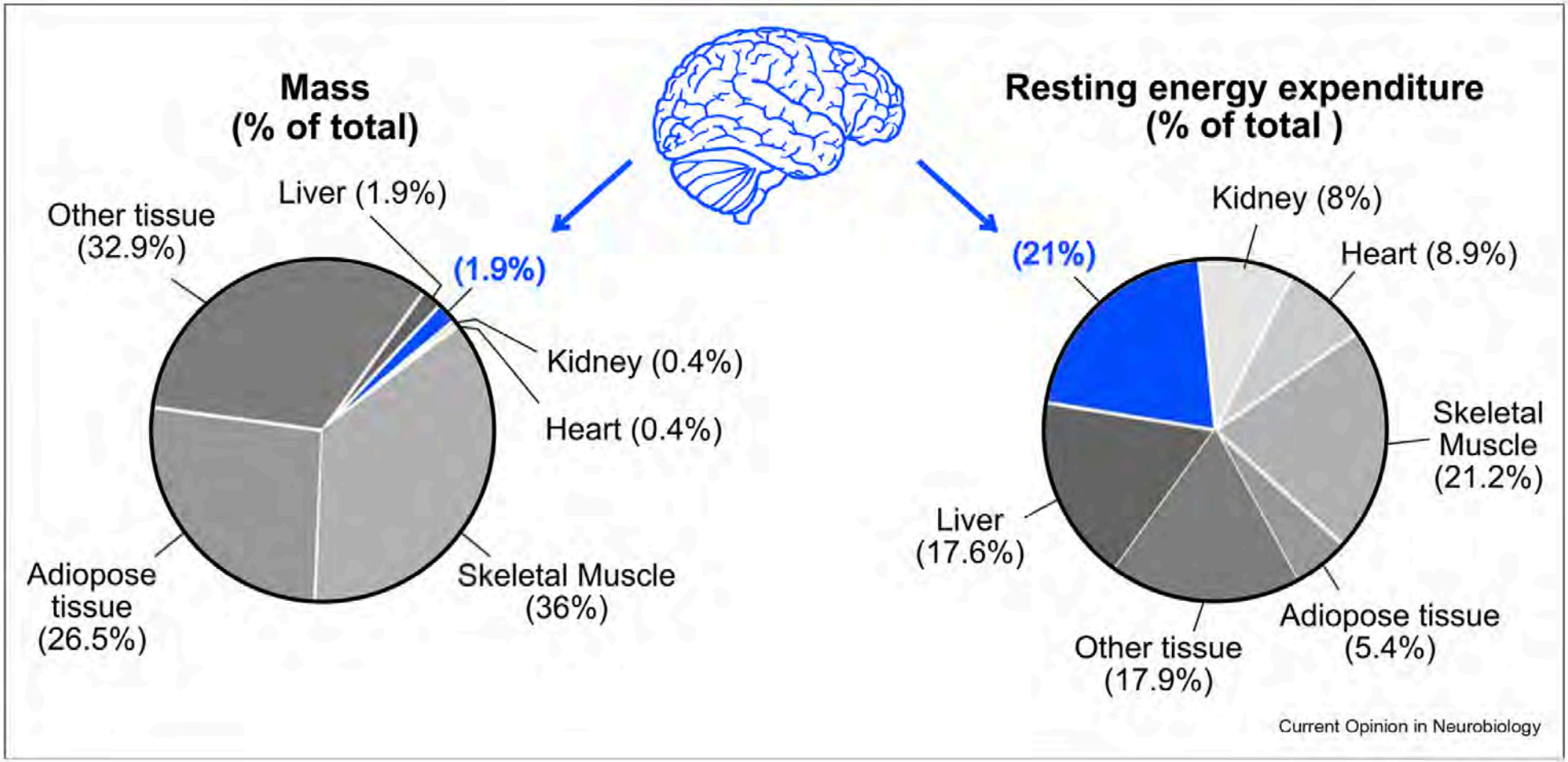
- HIGHEST ENERGY CONSUMPTION
- CONSTANT ENERGY FLUX
- DYNAMIC ENERGY PATTERNS

CONNECTIONS

- MOST DENSELY CONNECTED ORGAN
- LONG-RANGE CONNECTIONS
- PLASTICITY

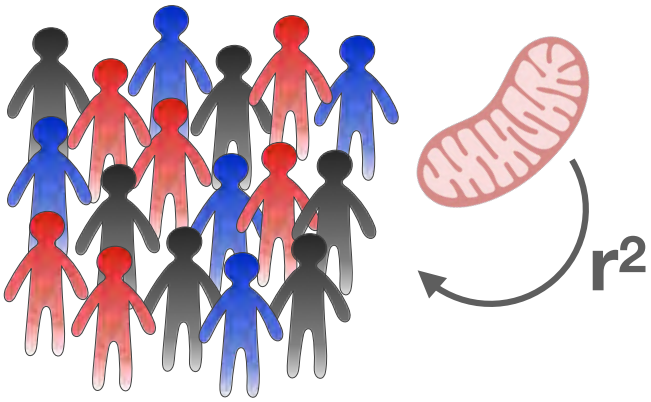
Thiebaut de Schotten and Forkel. *Science* 2022

The brain's enormous, constant energy demand



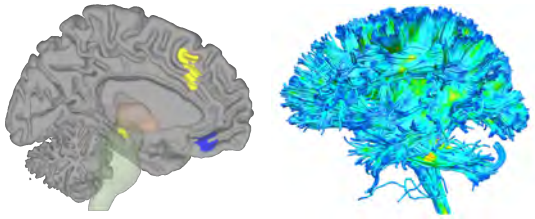
Variations from rest to activity is ~5%

Padamsey and Rochefort. *Curt Opin Neurobiol* 2023



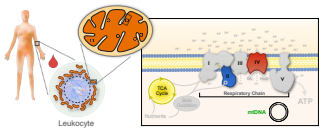
How much of inter-individual differences in **behaviors** are driven by **mitochondria**?

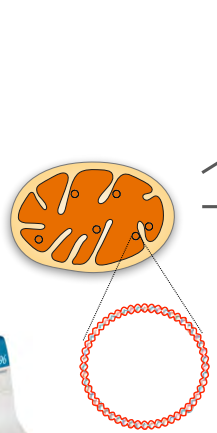
Mitochondrial **S**tress, **B**rain **I**maging, and **E**pigenetics — **MiSBIE**

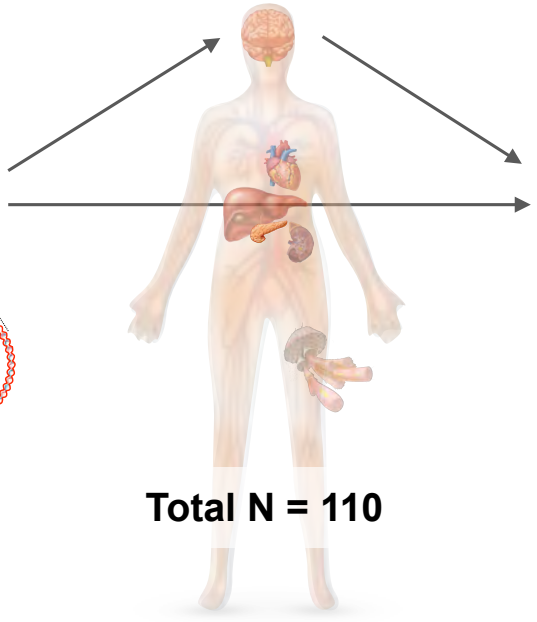


Brain structure and function
Neuropsychological function

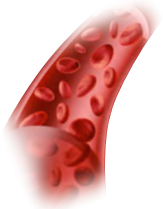
mtDNA heteroplasmy
Mitochondrial OxPhos
Lymphocytes, Monocytes,
Neutrophils, Platelets





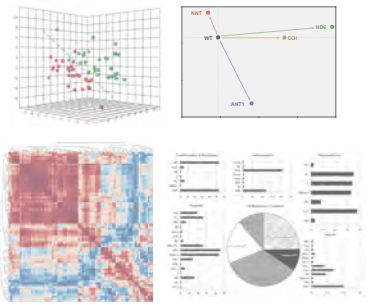


Total N = 110

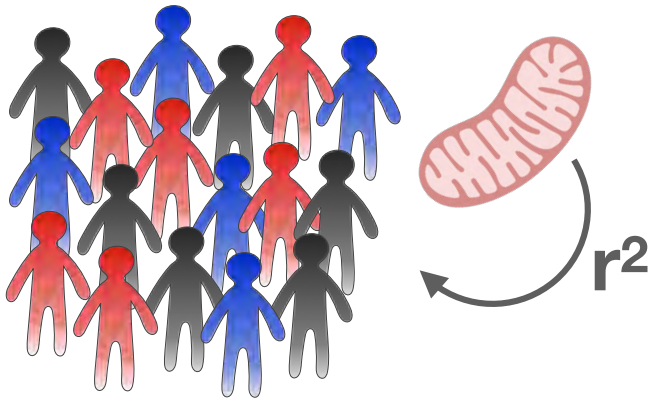


Disease biomarkers
Stress reactivity
Energy expenditure

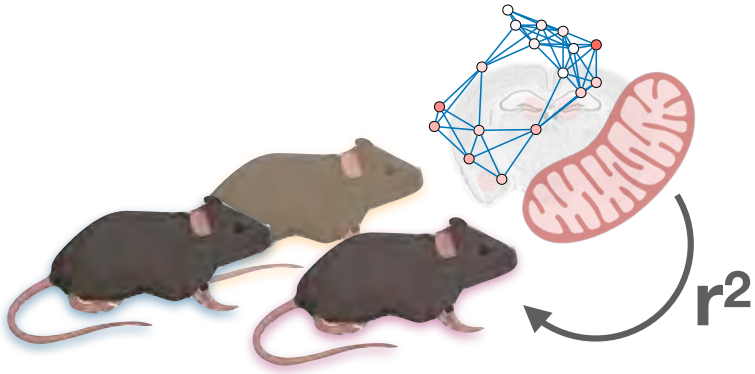
e.g., GDF15, Lactate,
Pyruvate, Alanine, etc.



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

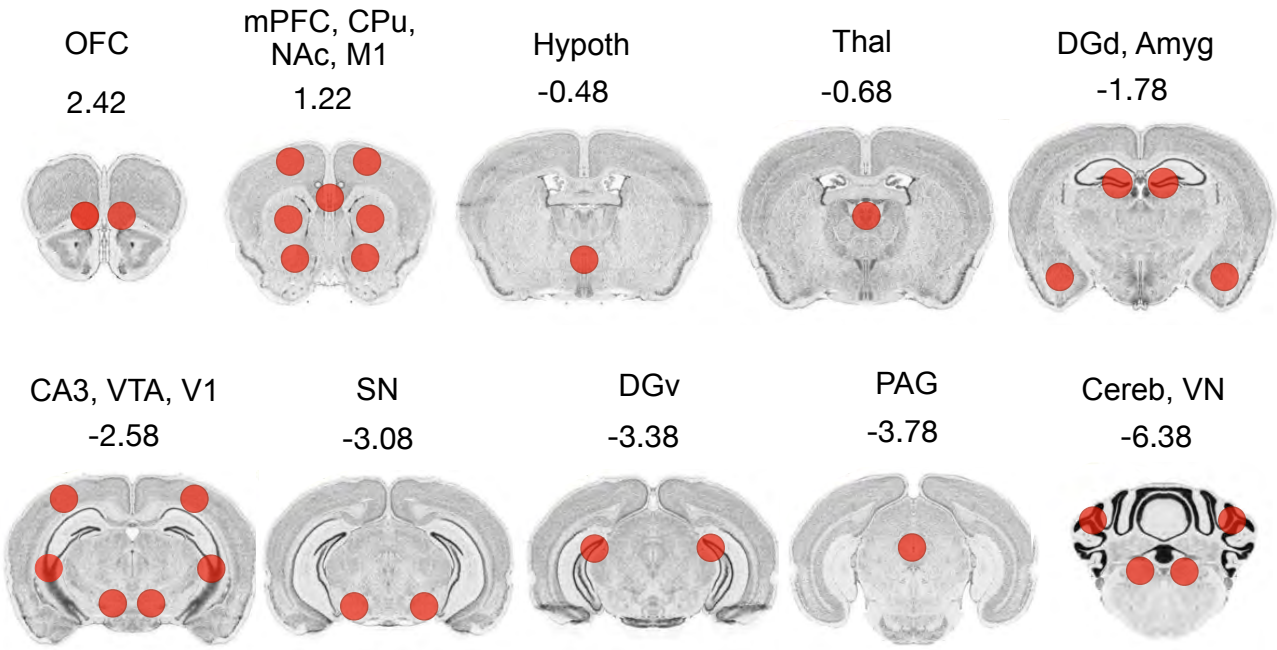


How much of inter-individual differences in **behaviors** are driven by **mitochondria**?



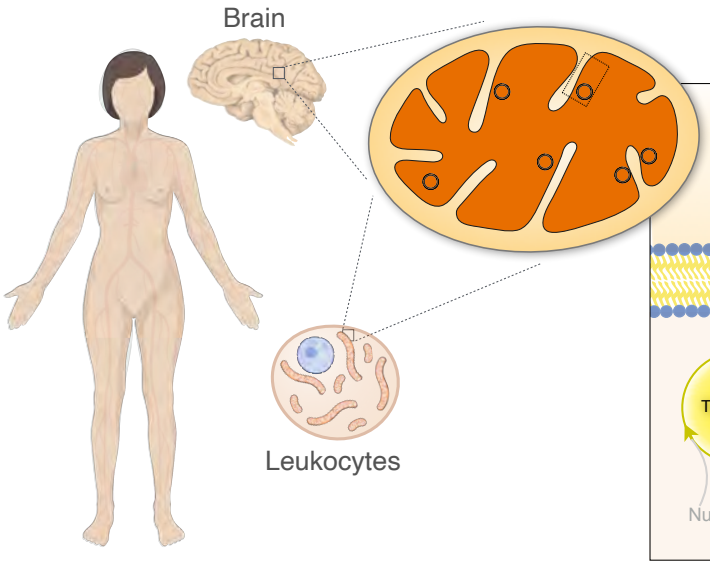
Mitochondrial functional profiling in the mouse brain

1mm punches
(n=17)

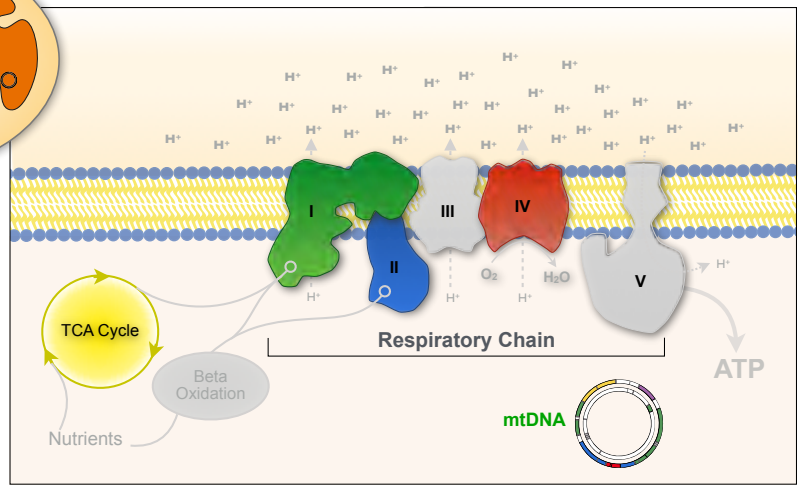


Each punch is <1mg
n > 500 samples

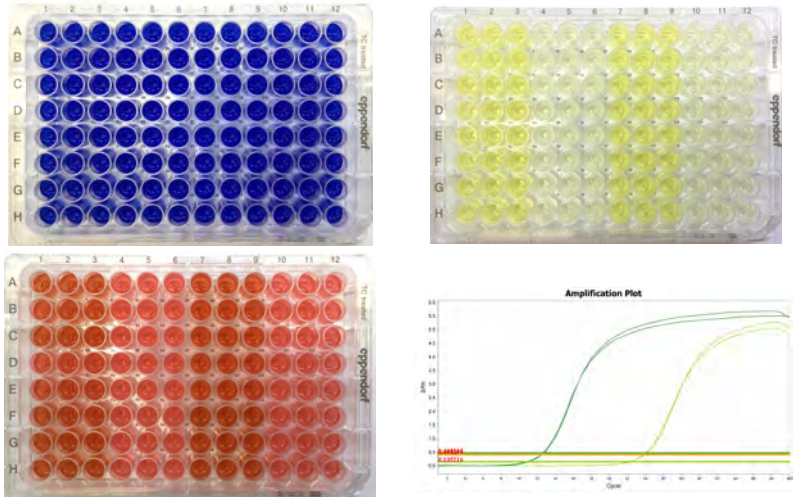
Rosenberg et al. *Nat Commun* 2023



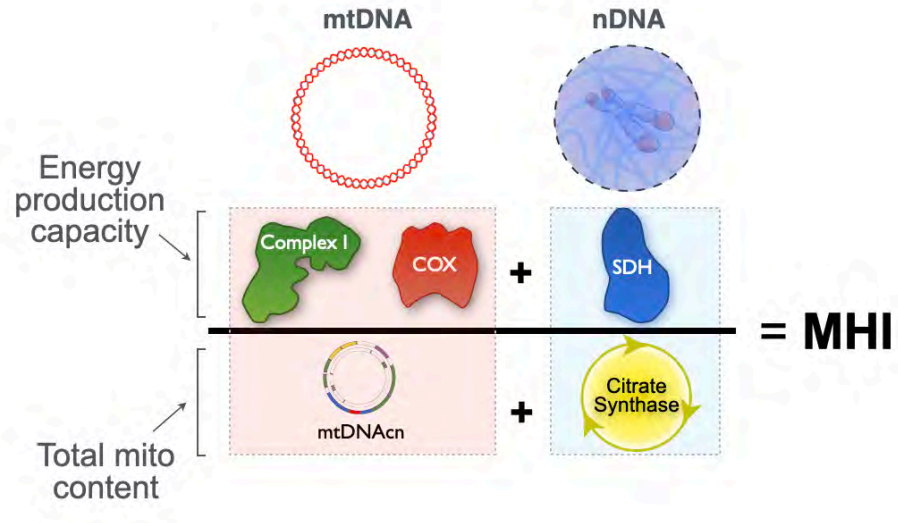
Enzymatic activity assays

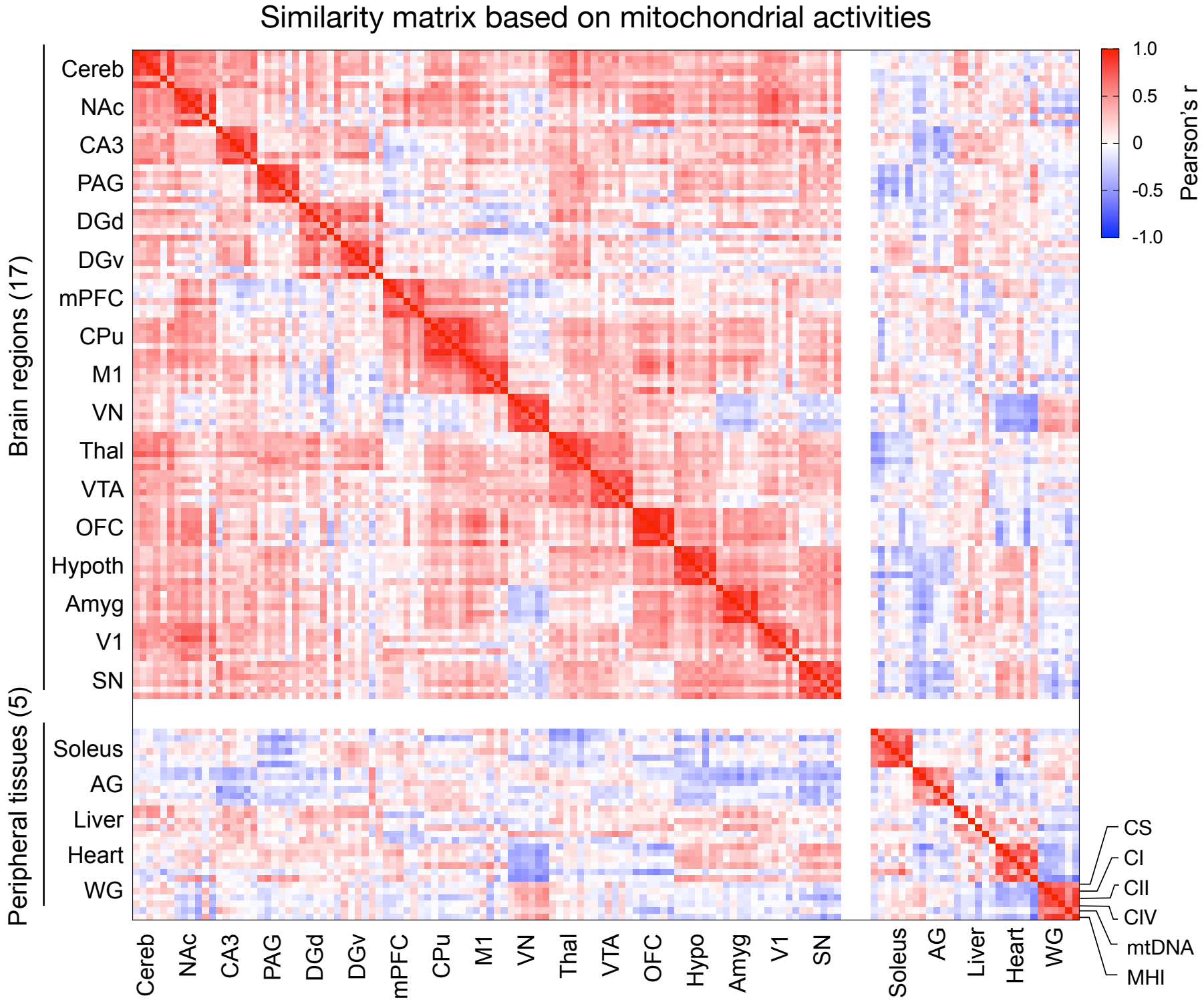


Miniaturization & optimized throughput

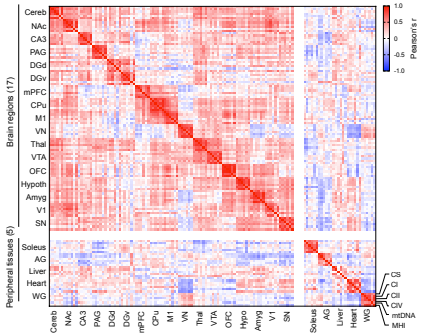


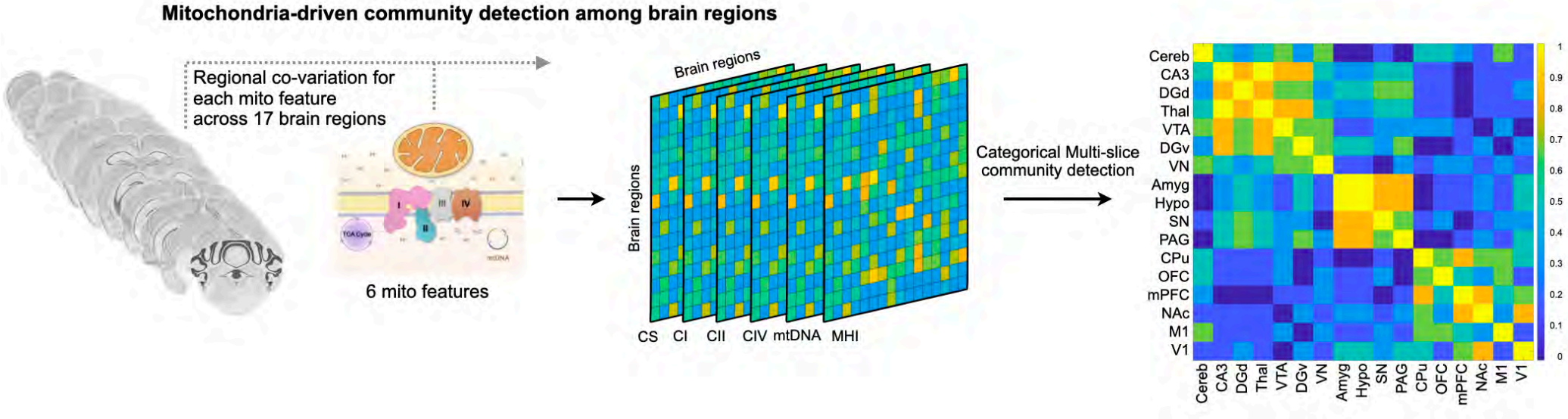
Computational integration




Similarity matrix based on mitochondrial activities
Brain regions (17)
Peripheral tissues (5)
Cereb
NAc
CA3
PAG
DGd
DGv
mPFC
CPu
M1
VN
Thal
VTA
OFC
Hypoth
Amyg
V1
SN
Soleus
AG
Liver
Heart
WG
Hypo
1.0
0.5
0
-0.5
-1.0
Pearson's r
CS
CI
CII
CIV
mtDNA
MHI

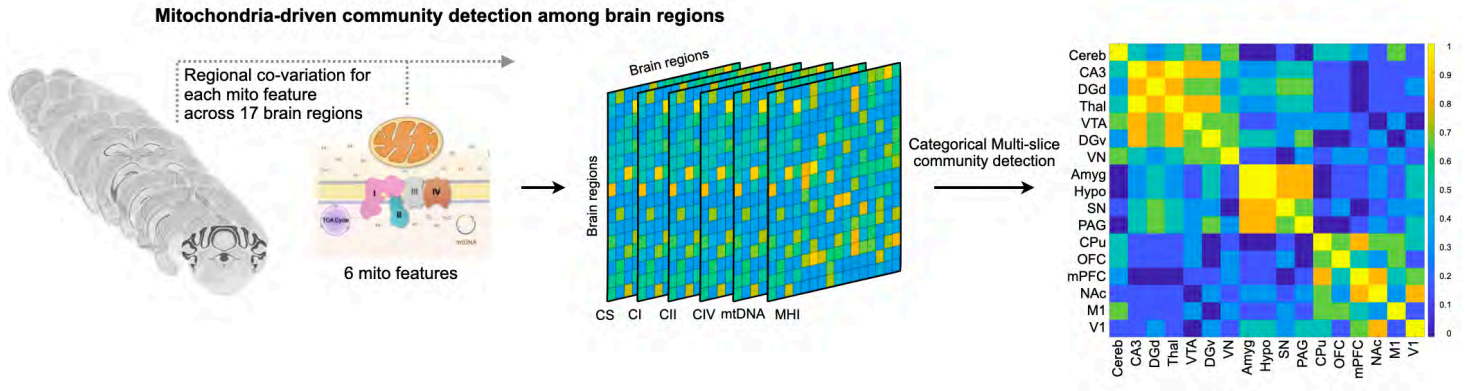
Are there brain networks with shared mitochondrial phenotypes?

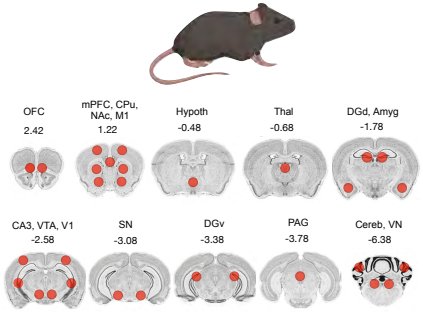


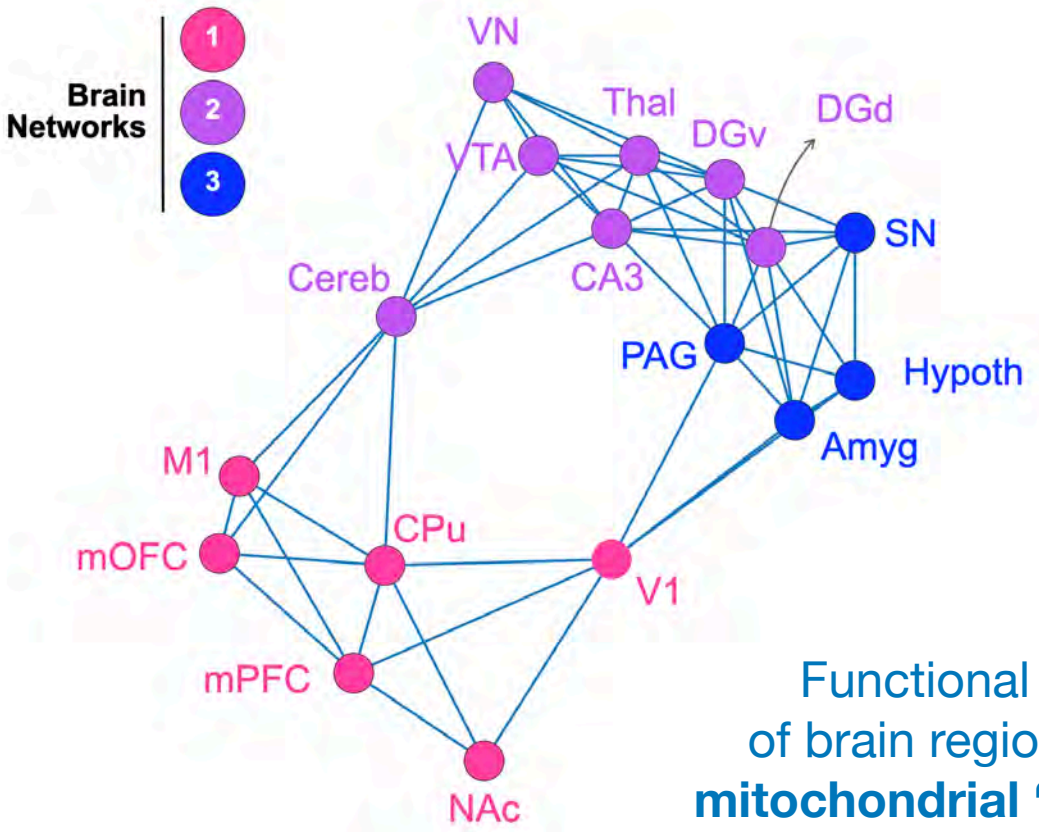


Manish Saggar

Rosenberg et al. *Nat Commun* 2023





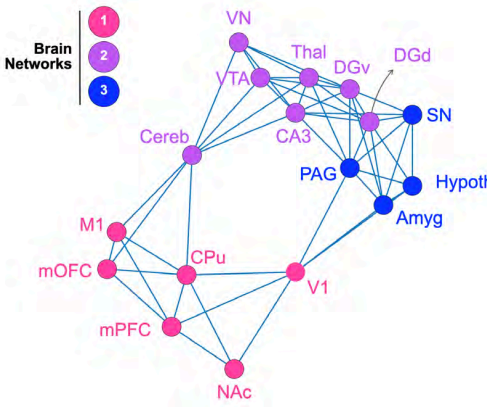


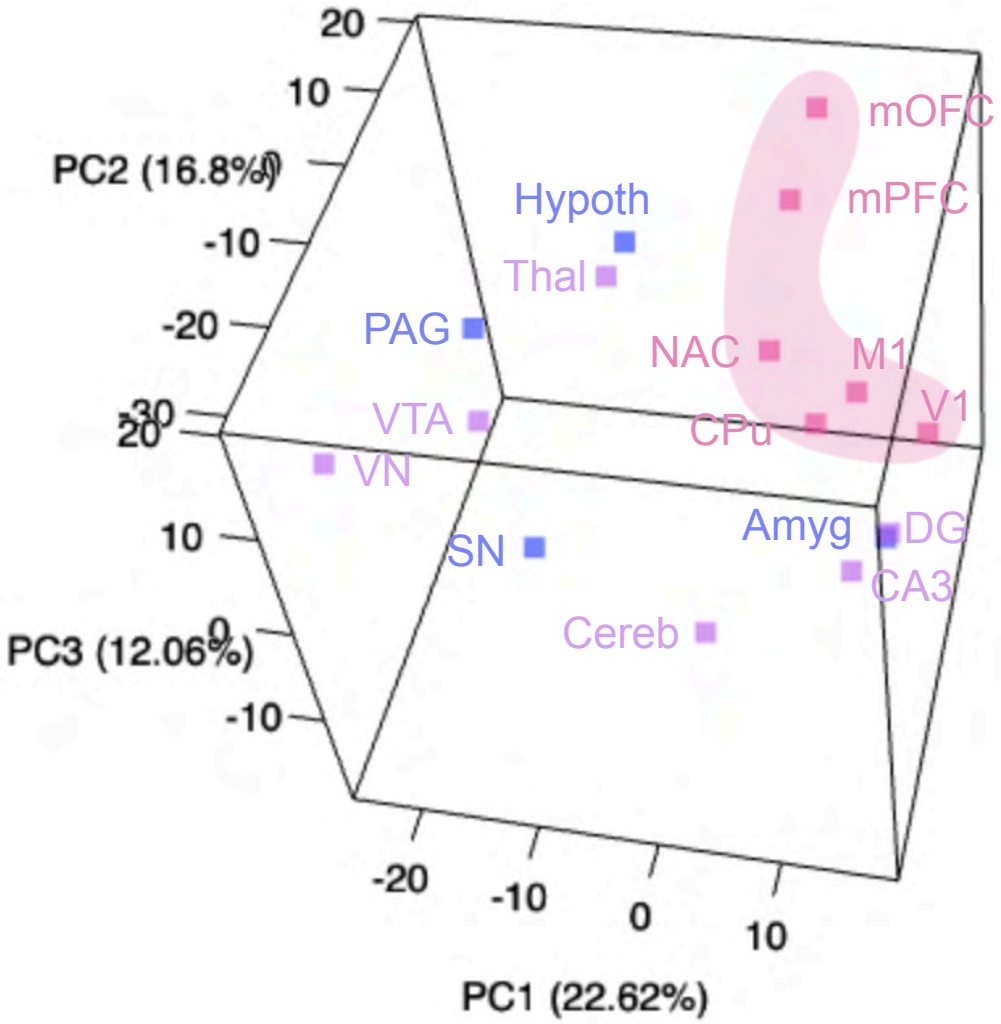
Functional clustering of brain regions based on **mitochondrial "connectivity"**

Manish Saggar

946 mitochondrial **genes**

PCA: Shared mitochondrial **gene signature**





Jack Devine

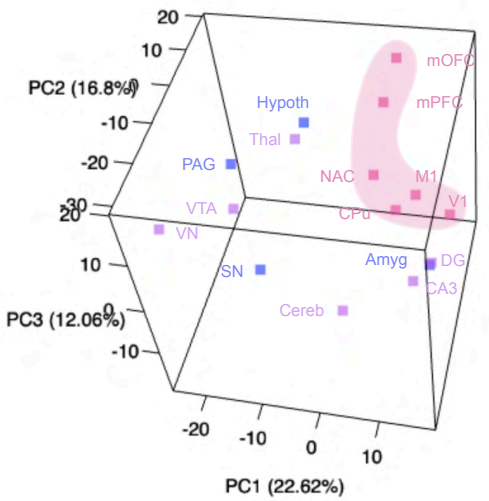
Anna Monzel

Enrichment of *mitochondrial* genes and pathways

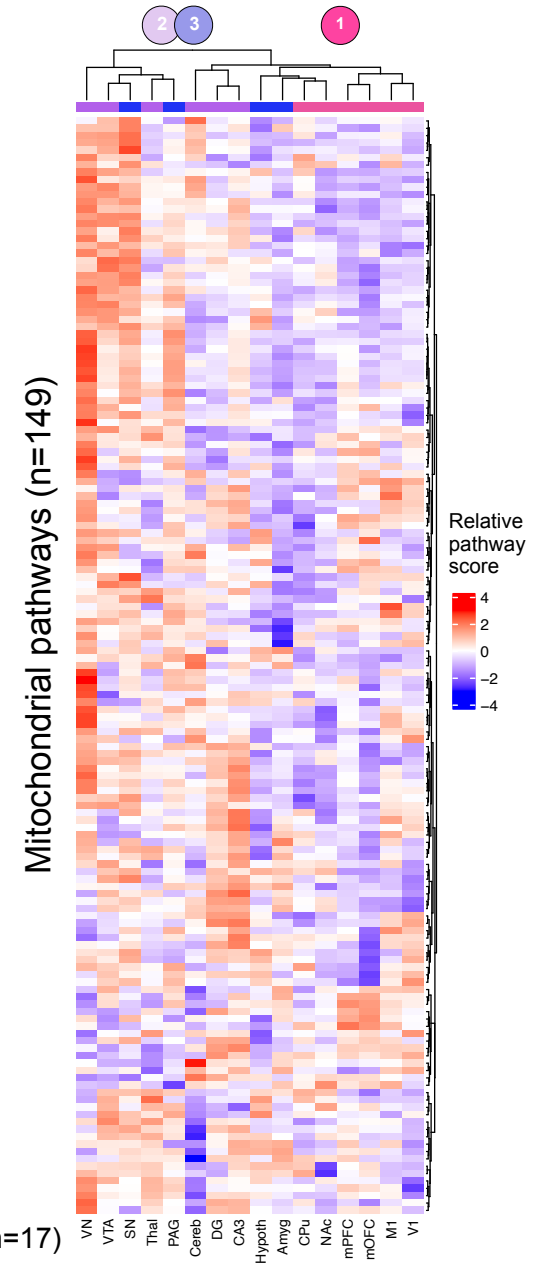
946 mitochondrial **genes**

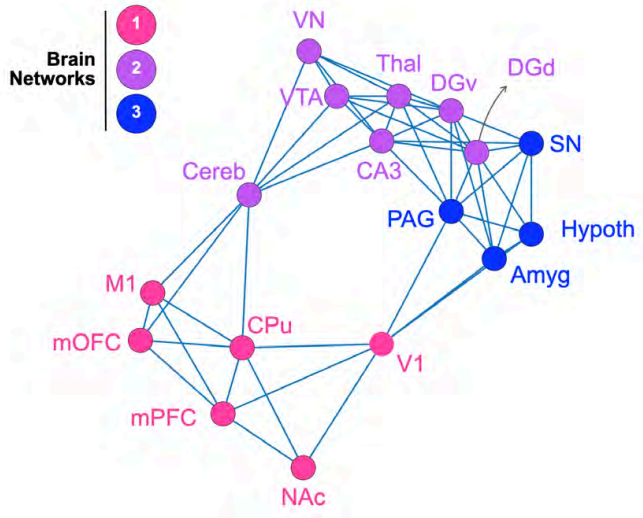
149 mitochondrial **pathways**

PCA: Shared mitochondrial **gene signature**



Hierarchical clustering: Shared mitochondrial **pathway signature**

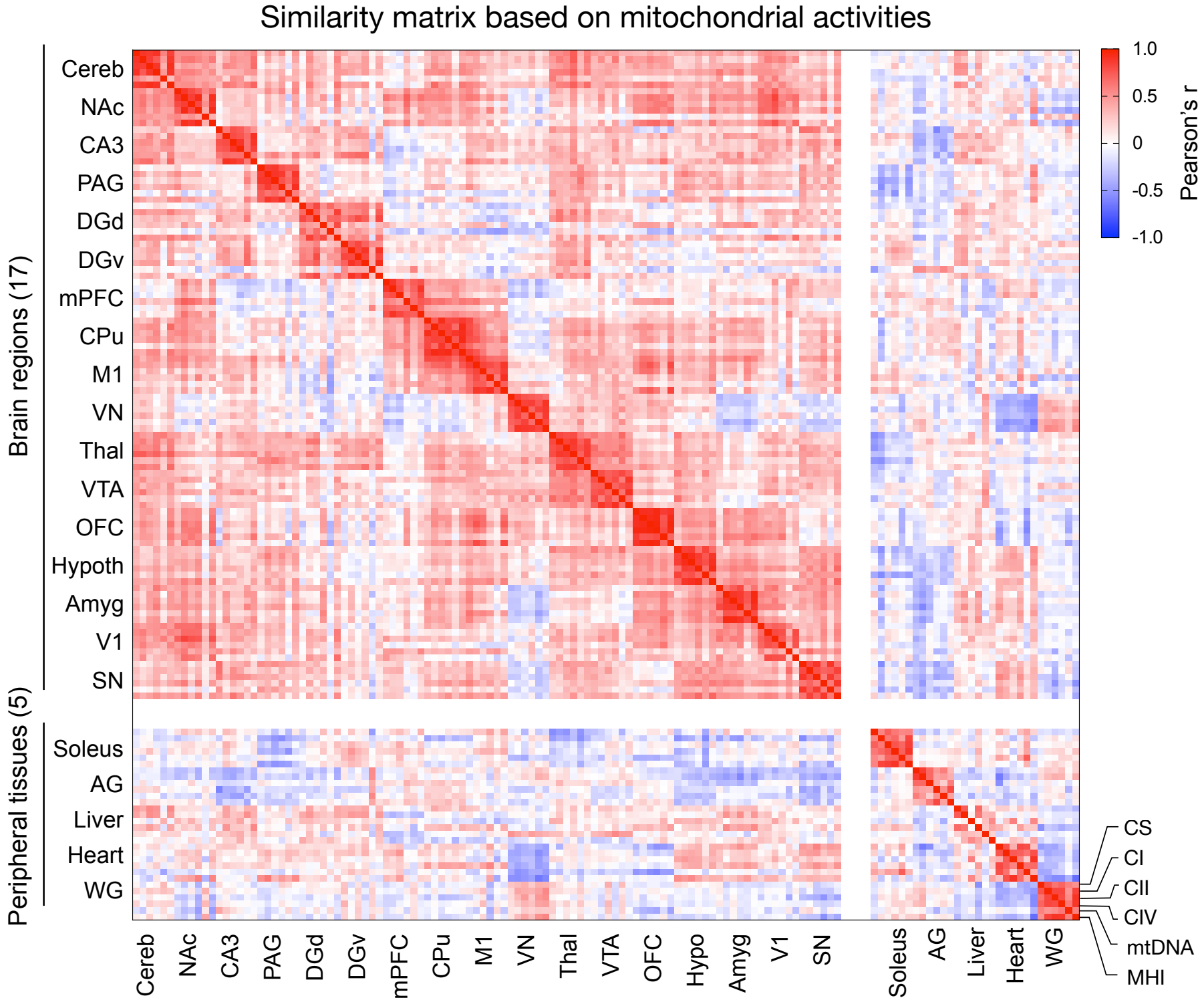




Data from *Allen Mouse Brain Atlas*
Mitopathways from *MitoCarta 3.0*

Jack Devine

Anna Monzel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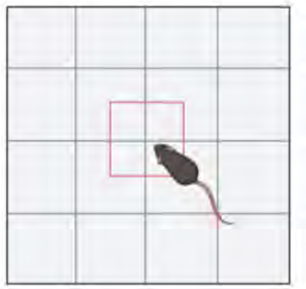
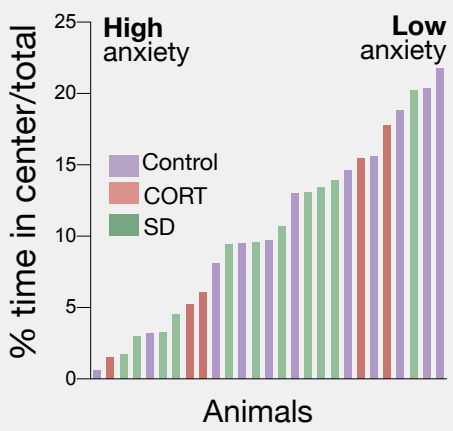
V1
SN
Soleus
AG
Liver
Heart
WG
Hypo
1.0
0.5
0
-0.5
-1.0
Pearson's r
CS
CI
CII
CIV
mtDNA
MHI

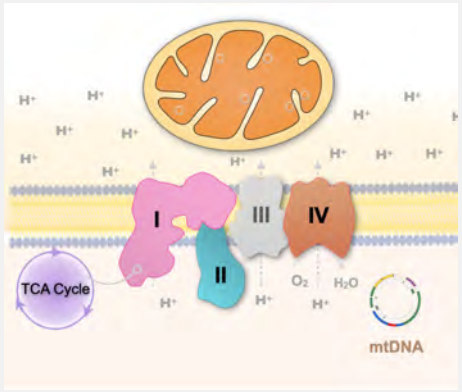
Mitochondria-behavior correlations



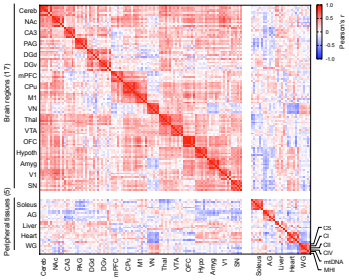
Open Field Test



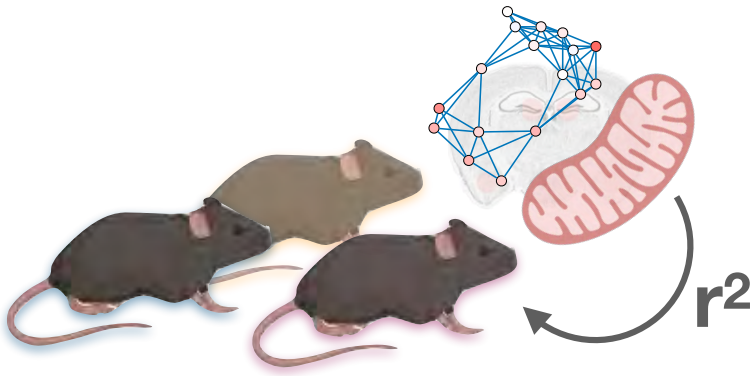
4 anxiety-related behavioral tests



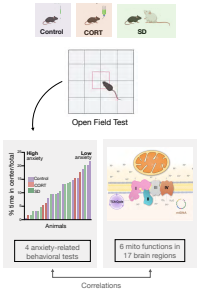
6 mito functions in 17 brain regions

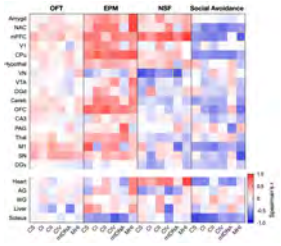


Correlations

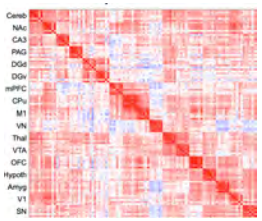


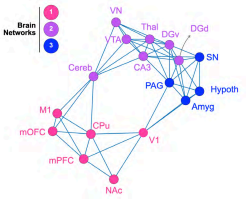
Rosenberg et al. *Nat Commun* 2023



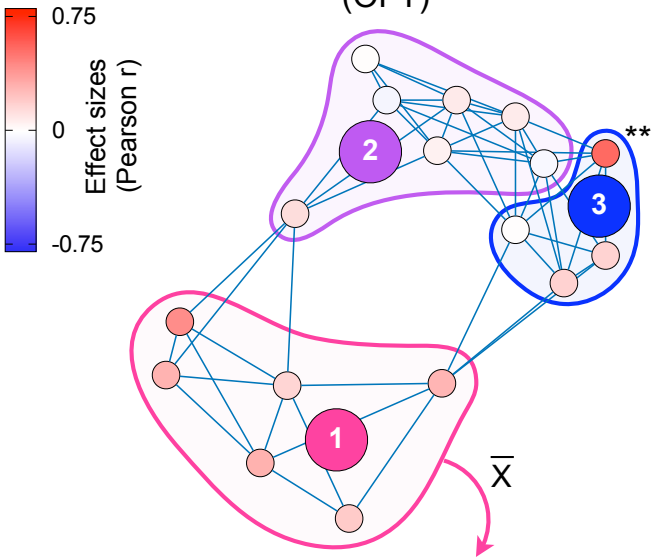


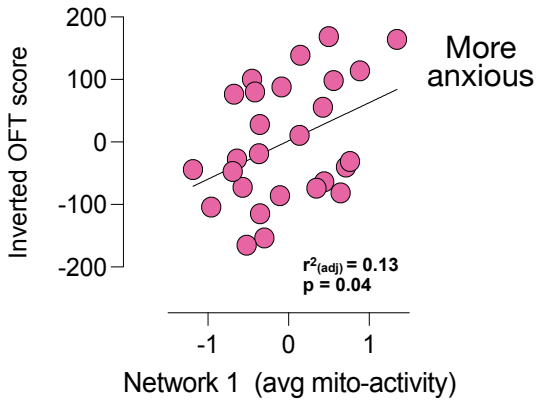
Network-based mito-behavior correlations



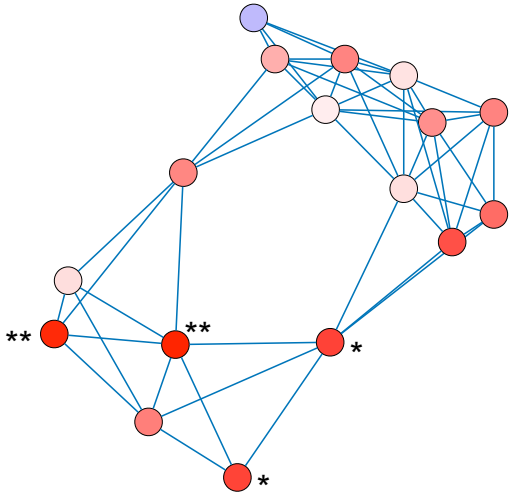


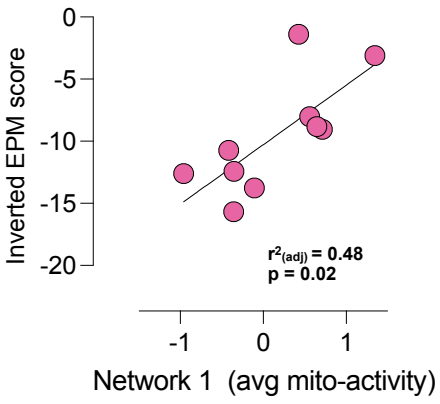
Open field test correlations (OFT)



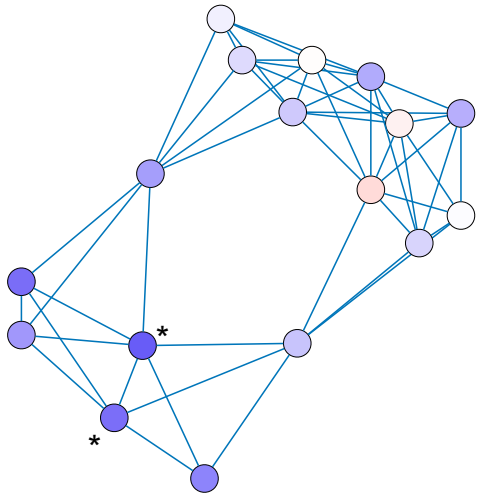


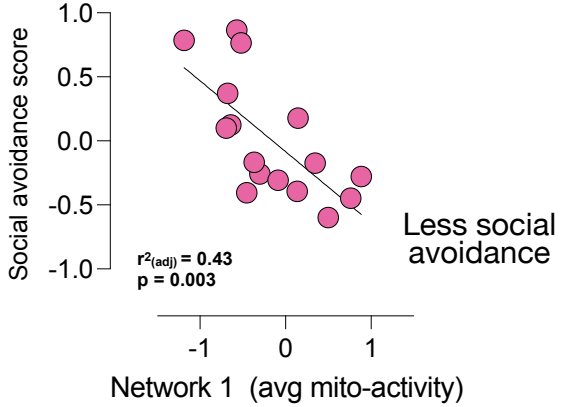
Elevated plus maze correlations (EPM)

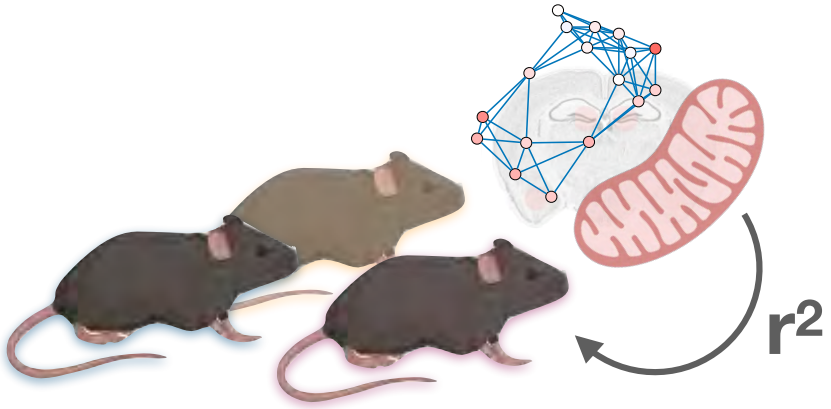




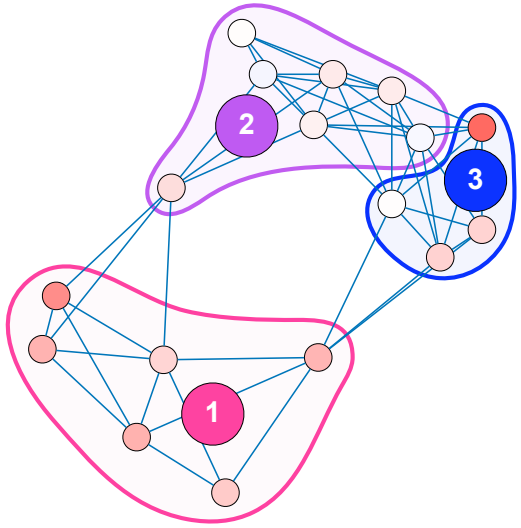
Social interaction correlations (SI)

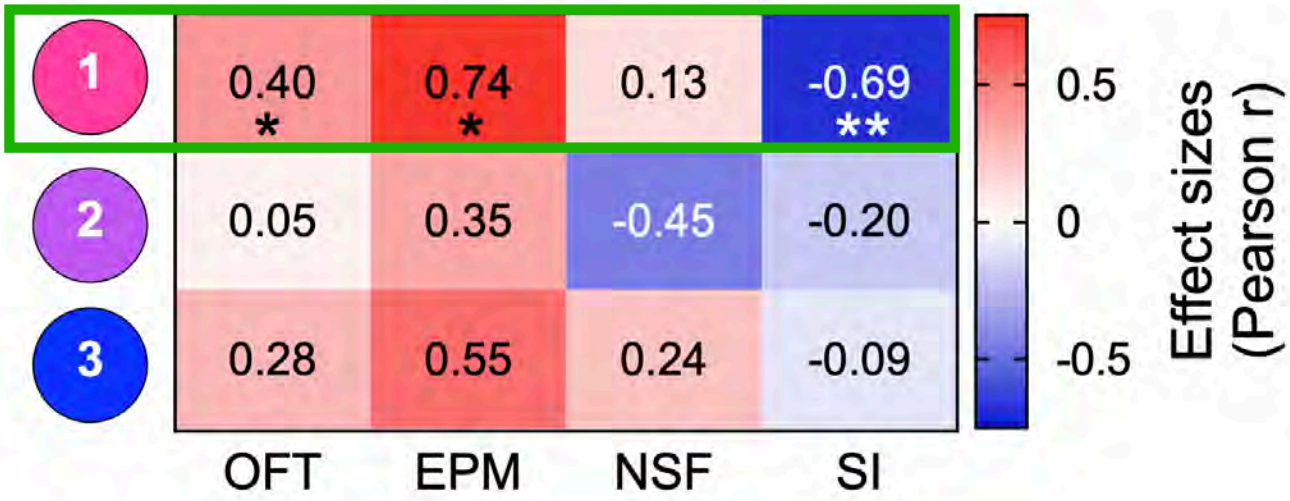






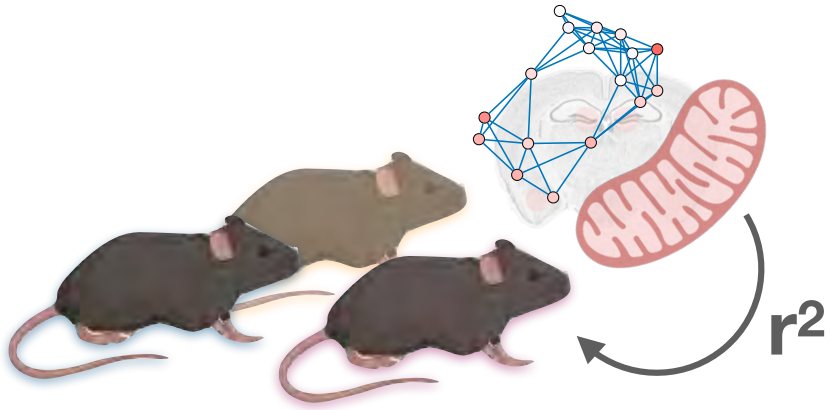
Network-based mito-behavior correlations



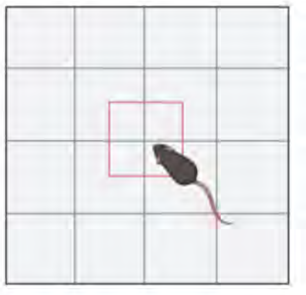


Brain mitochondria account for **up to ~20-45%** of the explainable variance in behaviors between animals

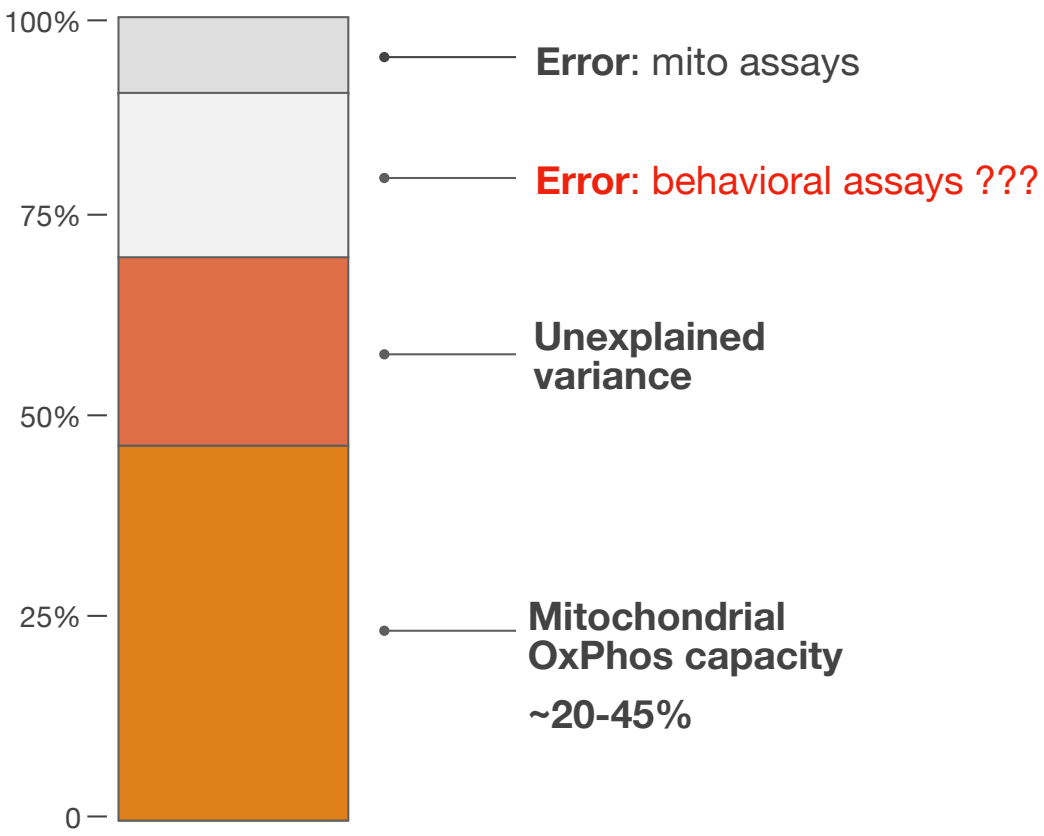
Rosenberg et al. *Nat Commun* 2023



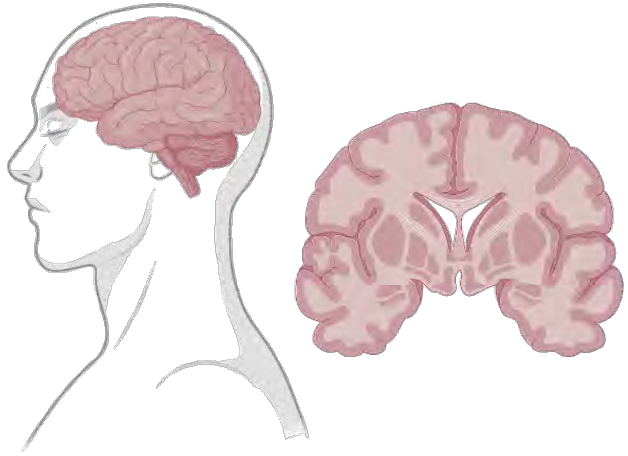
TOTAL OBSERVED VARIANCE IN ANIMAL BEHAVIORS



Open Field Test

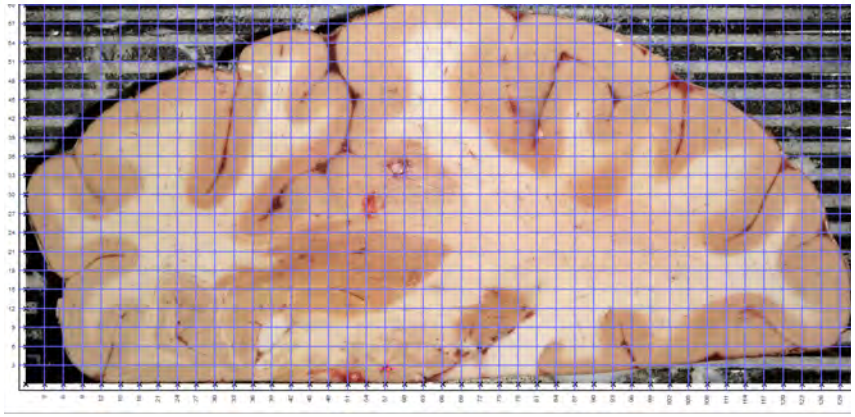


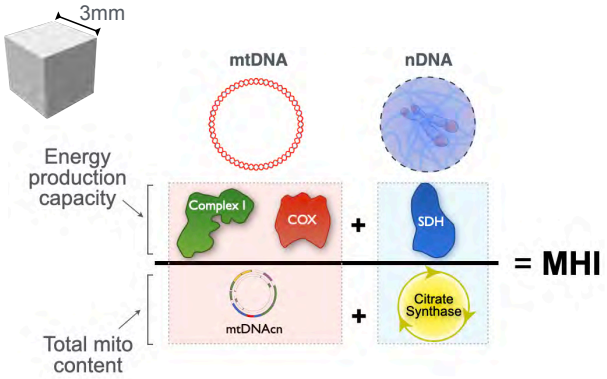
How are mitochondria distributed, and do they specialize across the *human* brain?

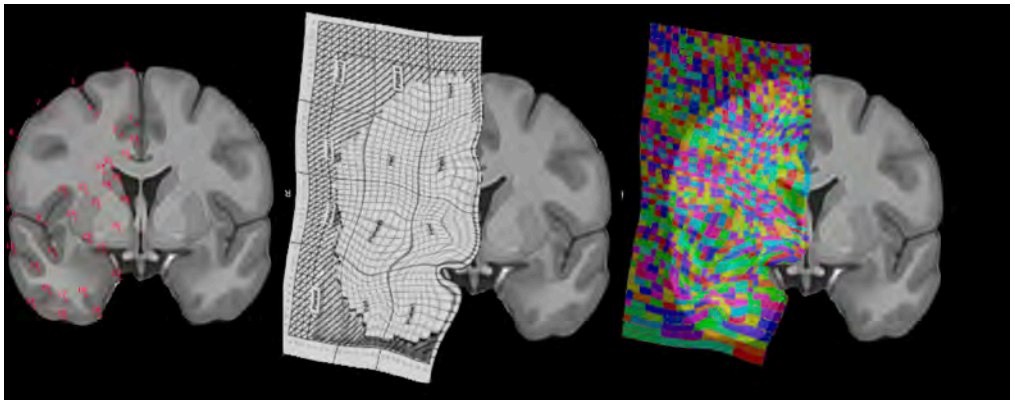


MitoBrainMap v1.0

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

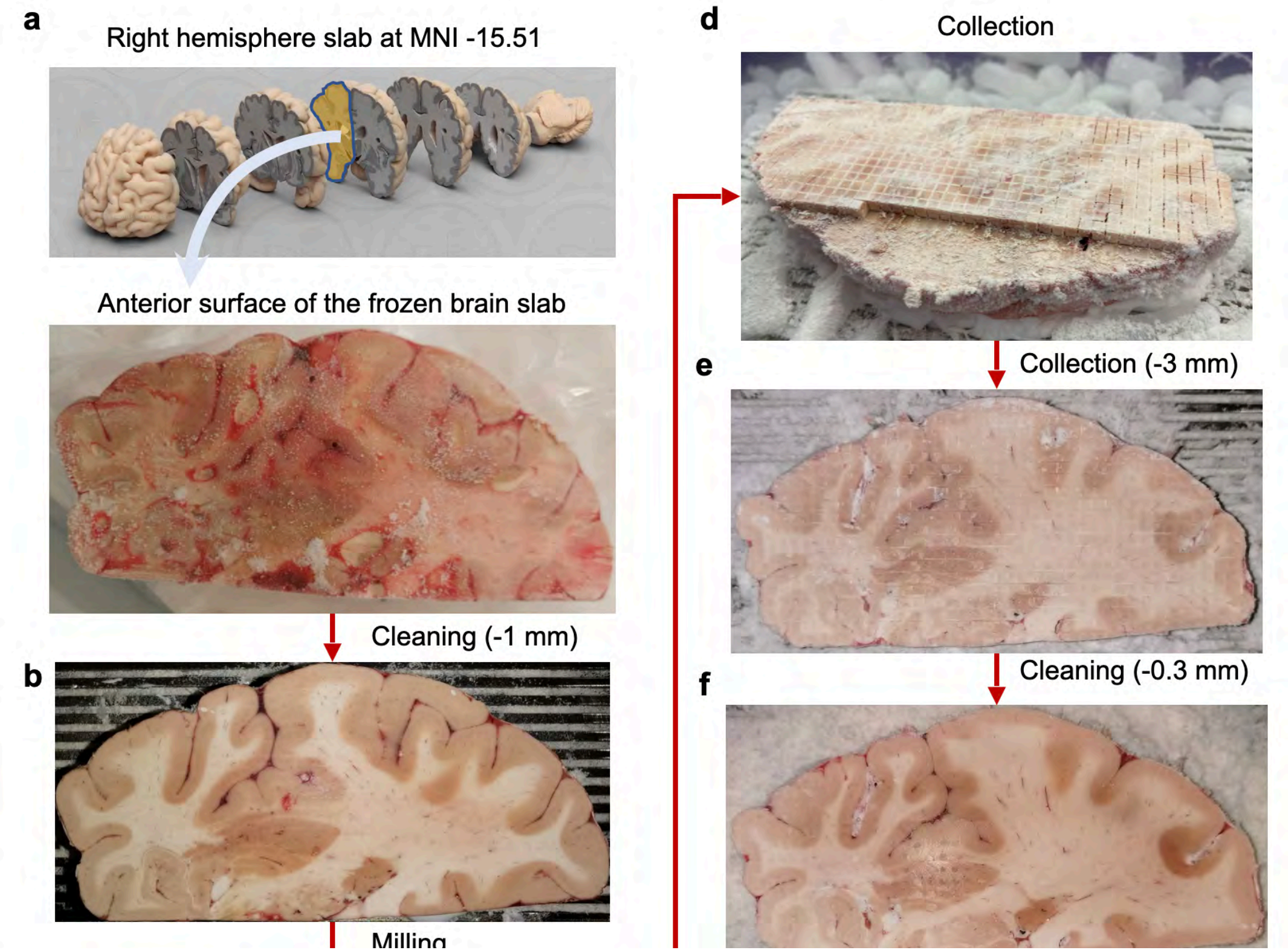






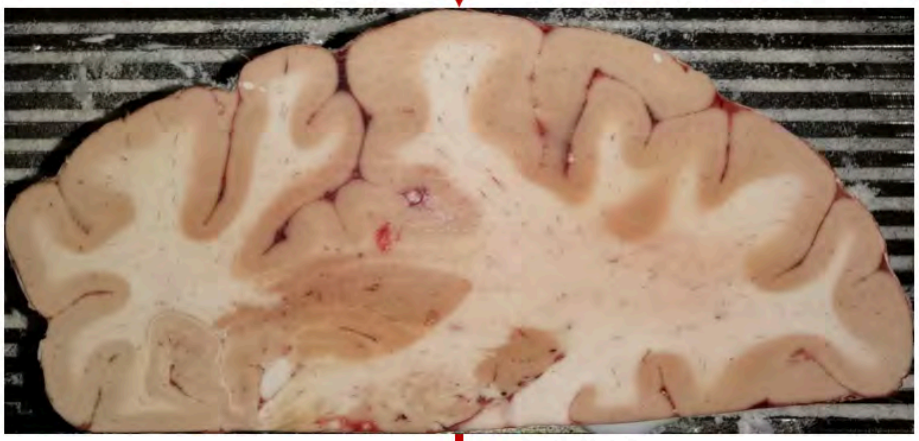
Closing the gap between organellar bioenergetic profiling and whole-brain neuroimaging modalities (fMRI, PET, CBV, DWI, etc)

Eugene Mosharov


a
Right hemisphere slab at MNI -15.51
Anterior surface of the frozen brain slab
Cleaning (-1 mm)
b
Milling
d
Collection
e
Collection (-3 mm)
Cleaning (-0.3 mm)
f

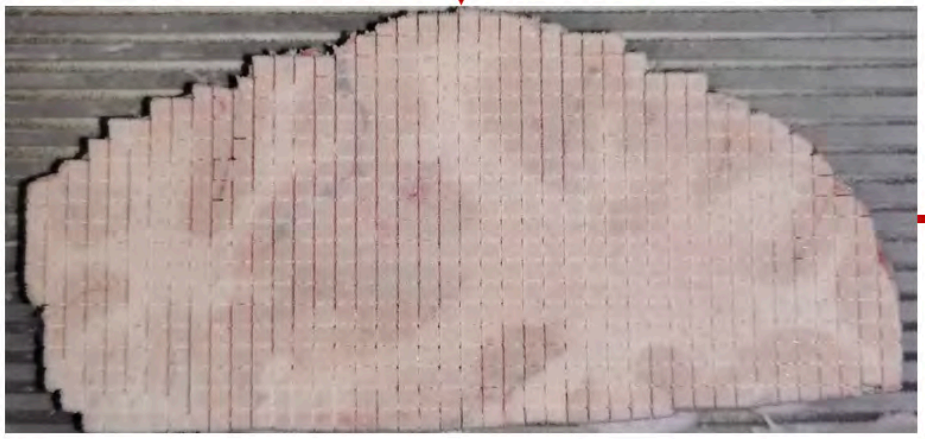
Cleaning (-1 mm)

b



Milling

c



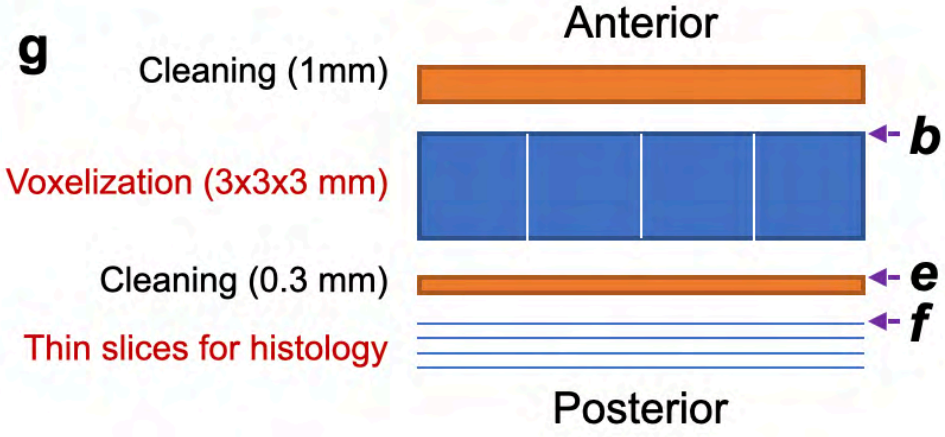
e

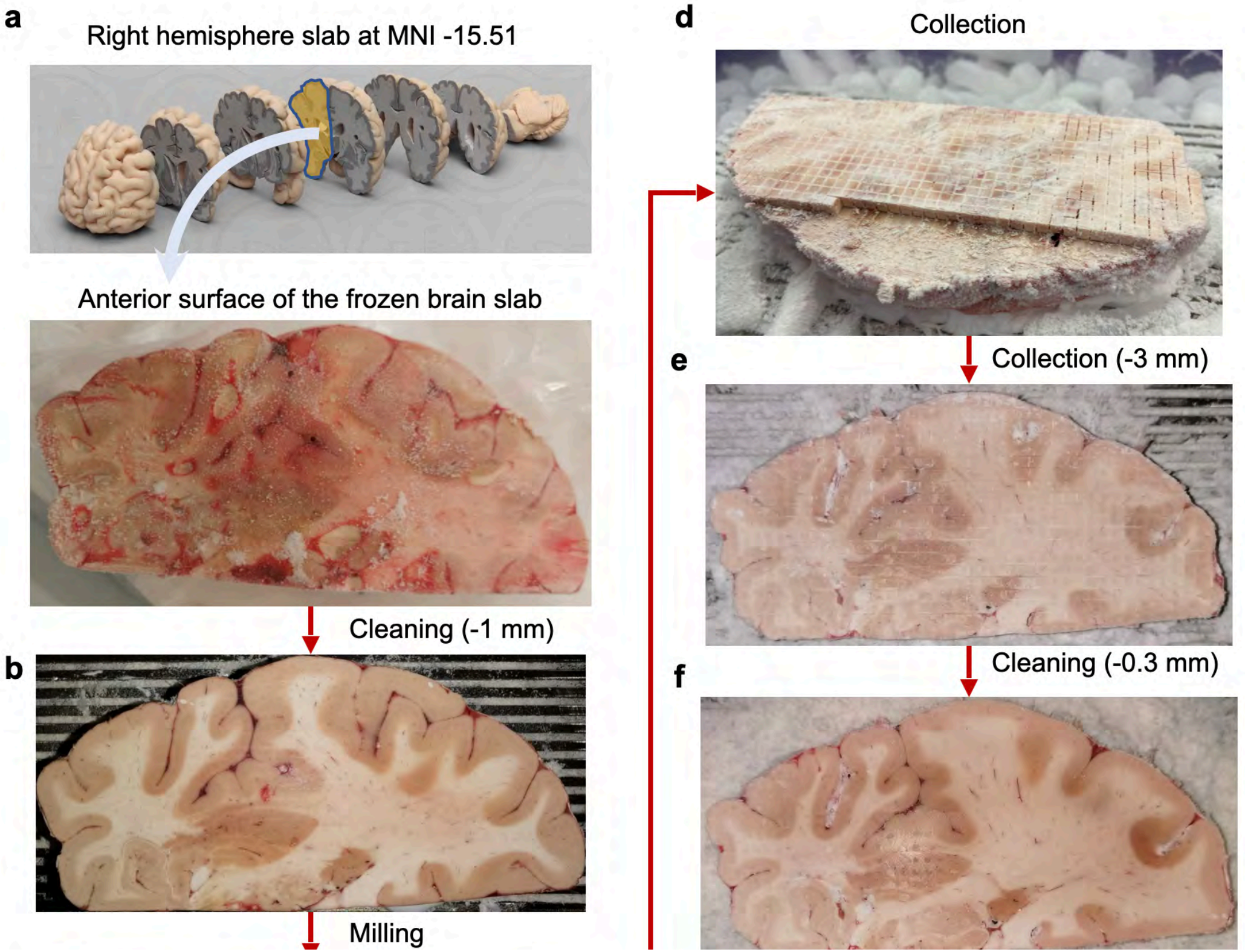
Collection (-3 mm)

Cleaning (-0.3 mm)

f

g




a
Right hemisphere slab at MNI -15.51
Anterior surface of the frozen brain slab
Cleaning (-1 mm)
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Milling
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Collection
Collection (-3 mm)
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Cleaning (-0.3 mm)
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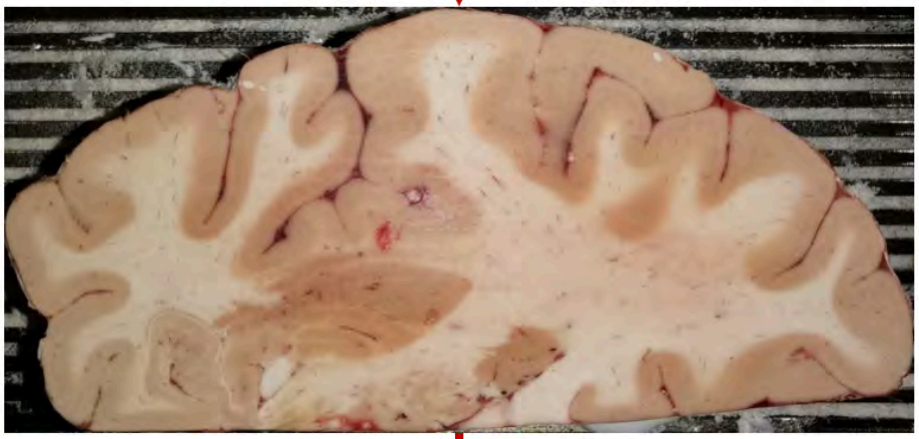
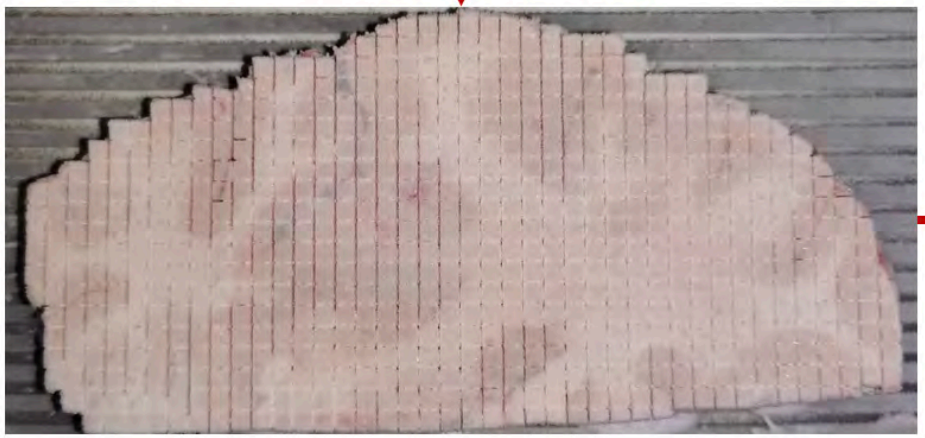
Cleaning (-1 mm)

b



Milling

c



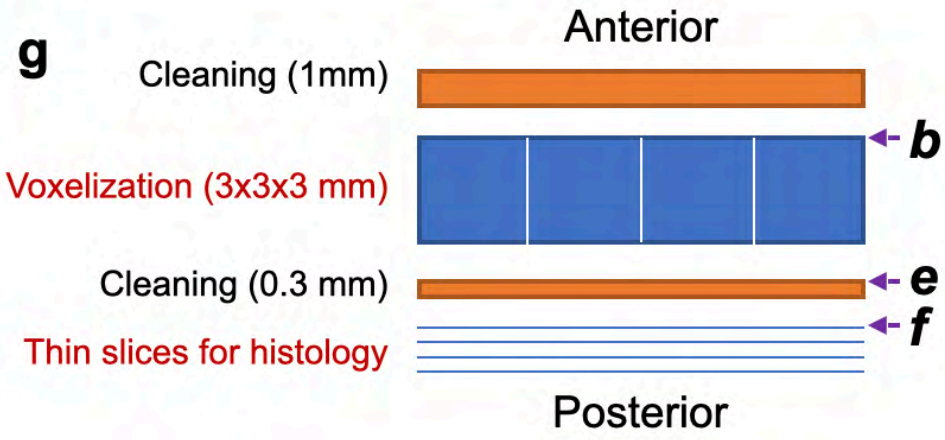
e

Collection (-3 mm)

f

Cleaning (-0.3 mm)

g



MitoBrainMap v1.0

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

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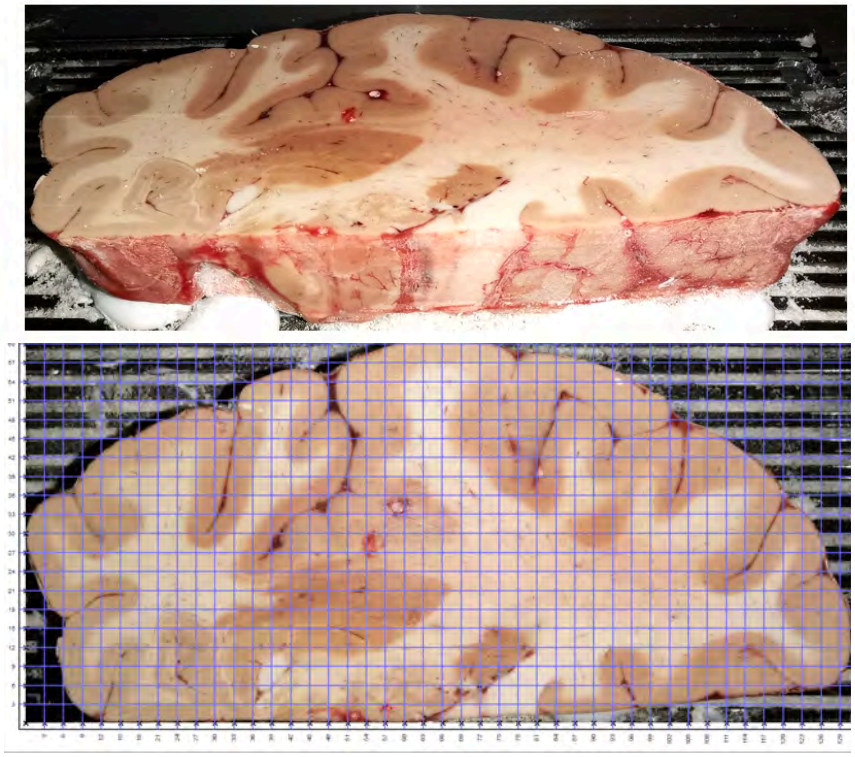
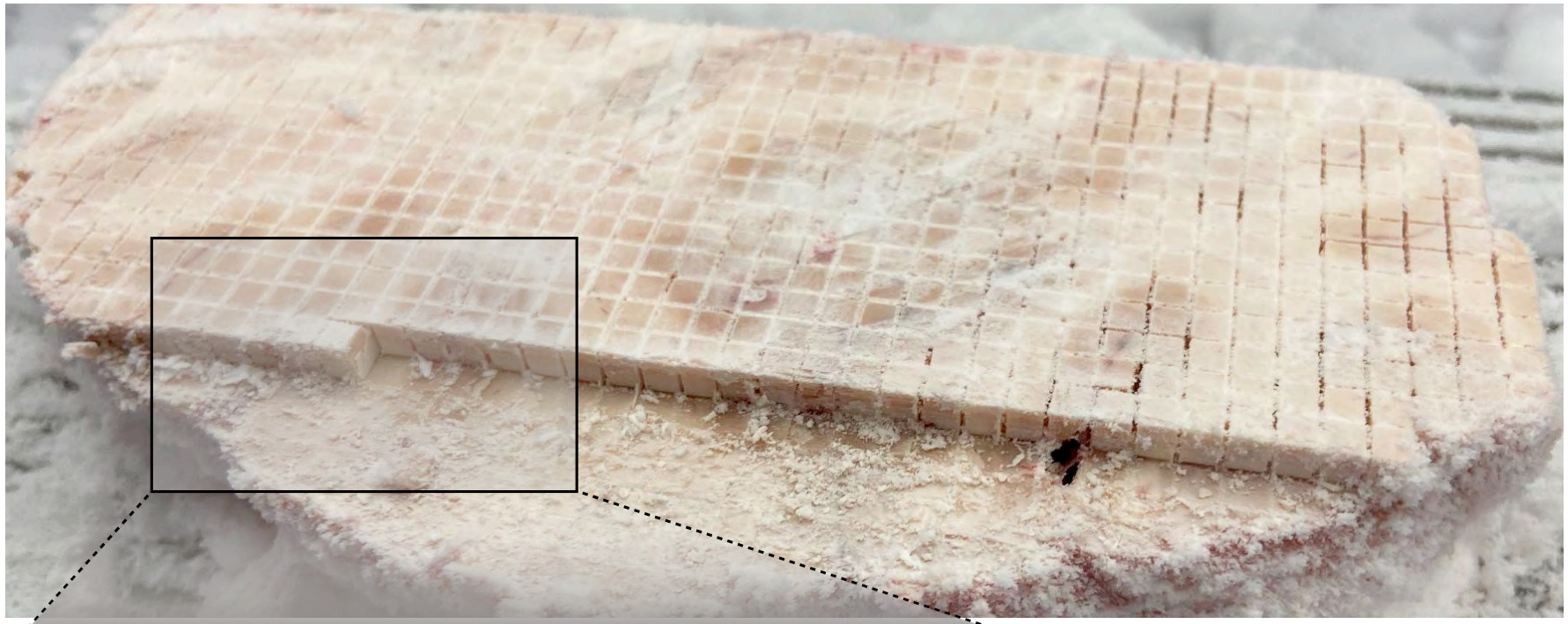
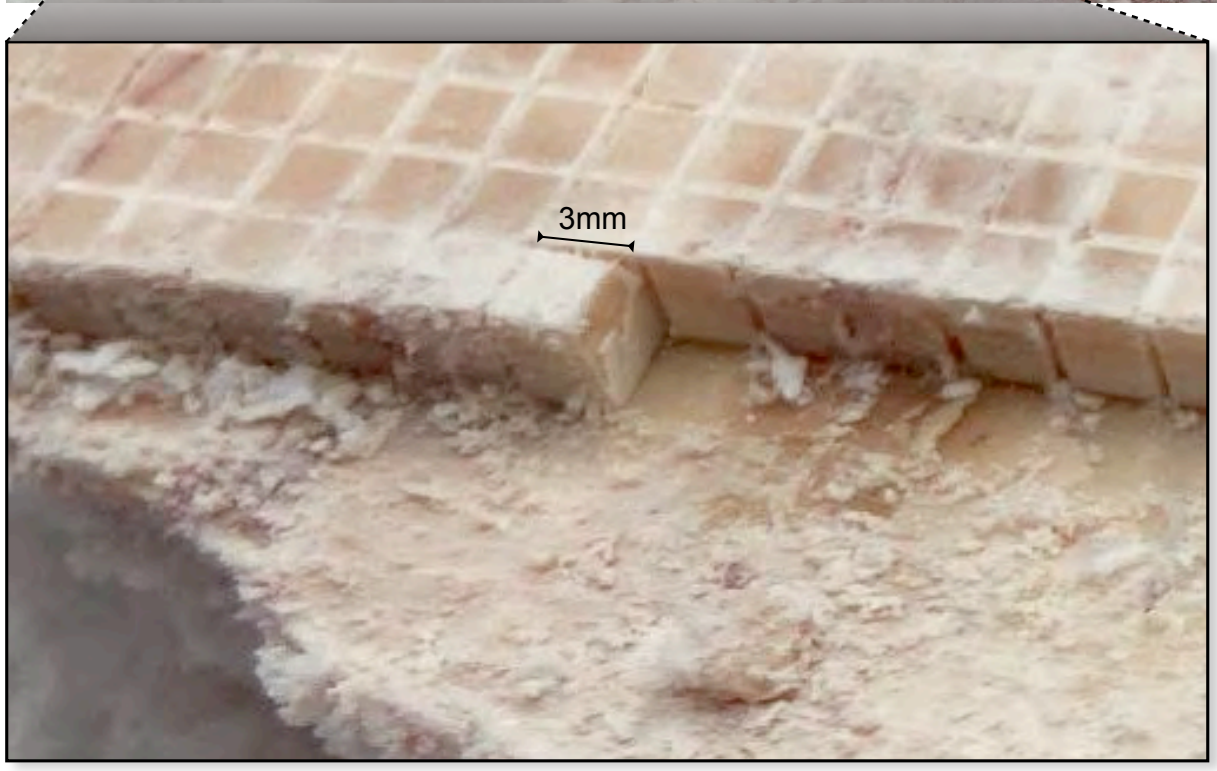


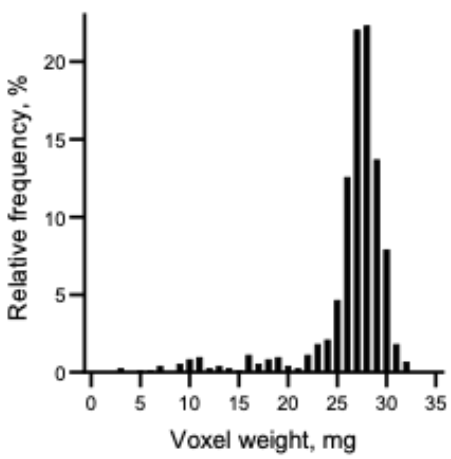
Eugene Mosharov

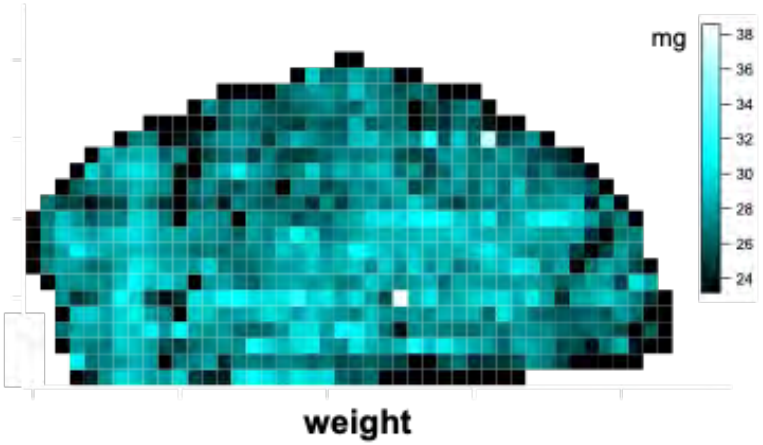


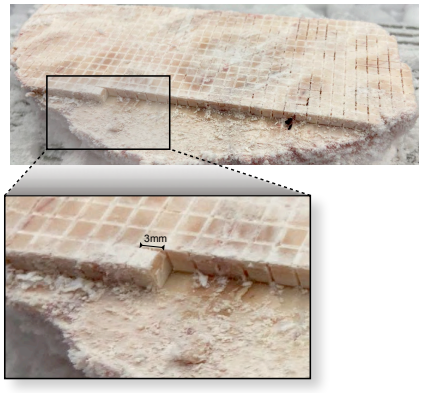


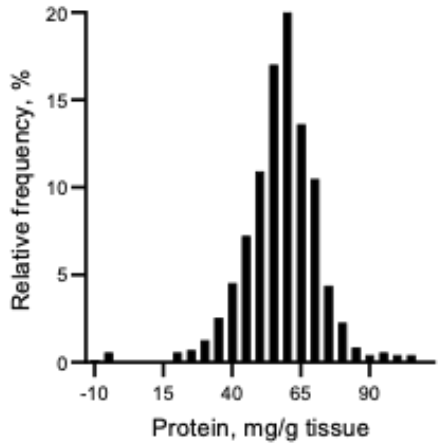
Physical *voxelization*
of the human brain
*a*t fMRI resolution

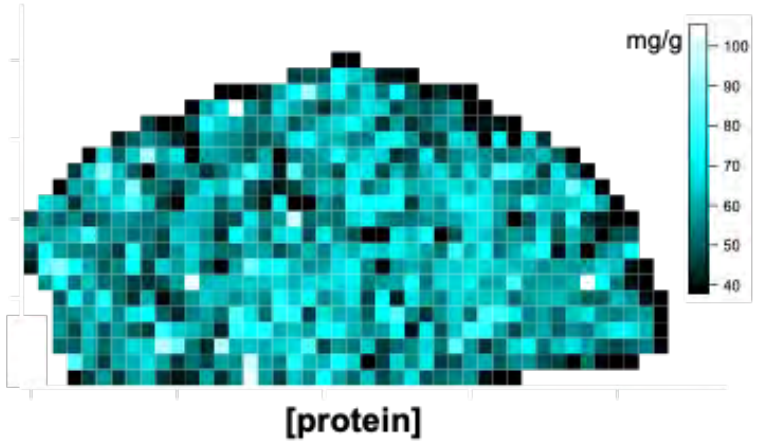
Quality control on 702 human brain voxels

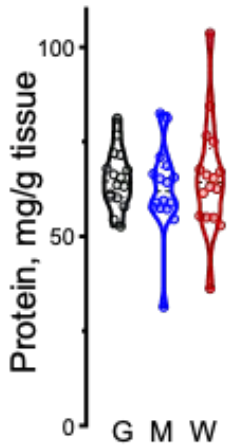




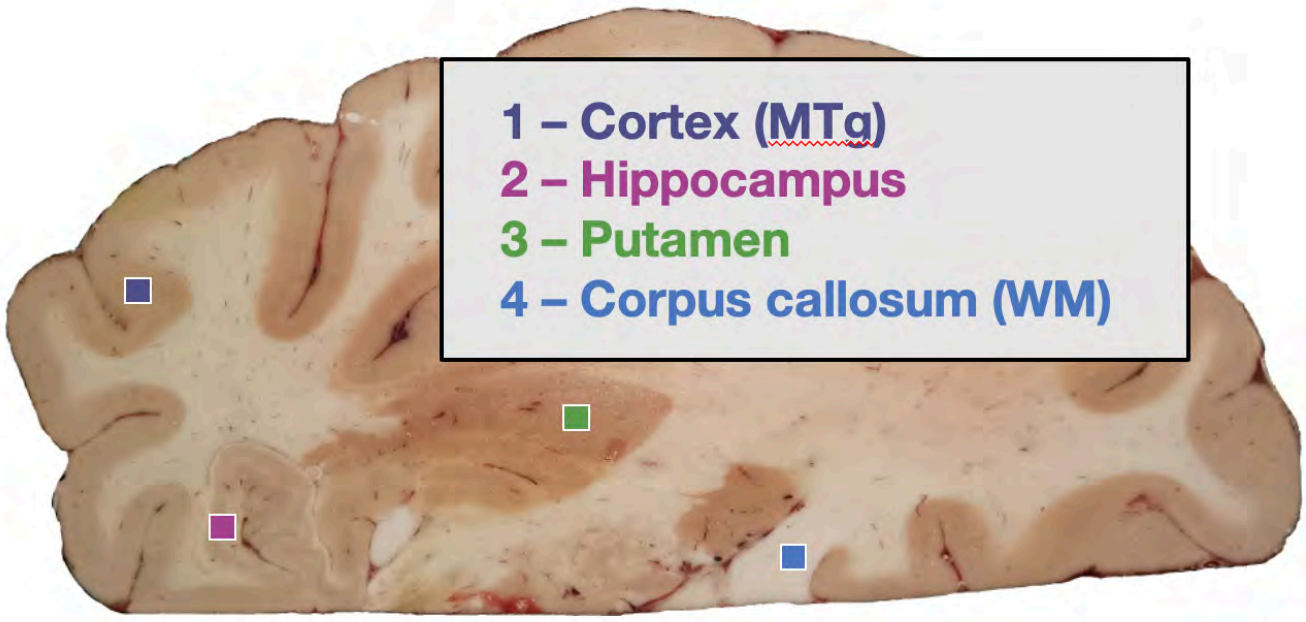


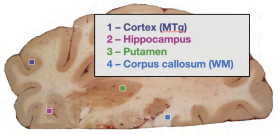






Eugene Mosharov


1 – Cortex (MTg)
2 – Hippocampus
3 – Putamen
4 – Corpus callosum (WM)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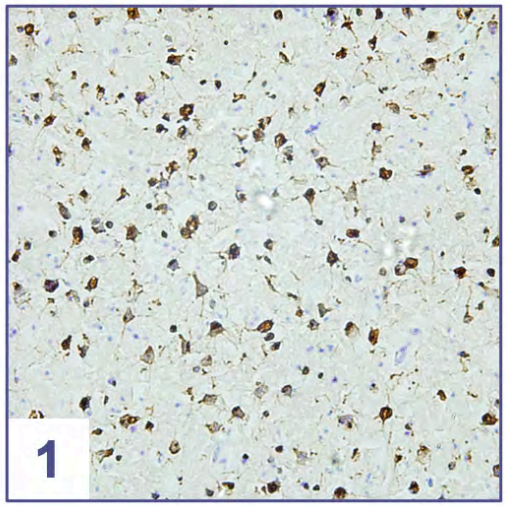
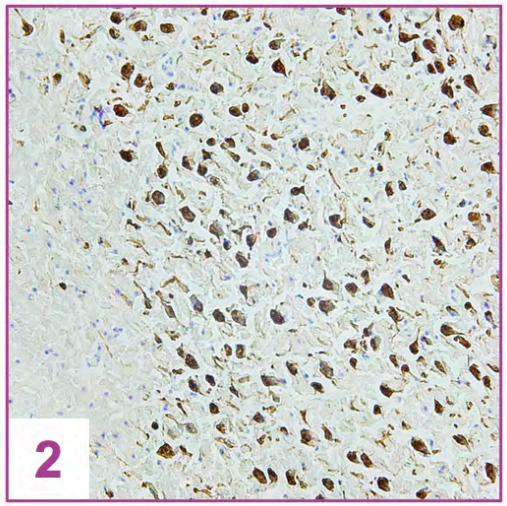

1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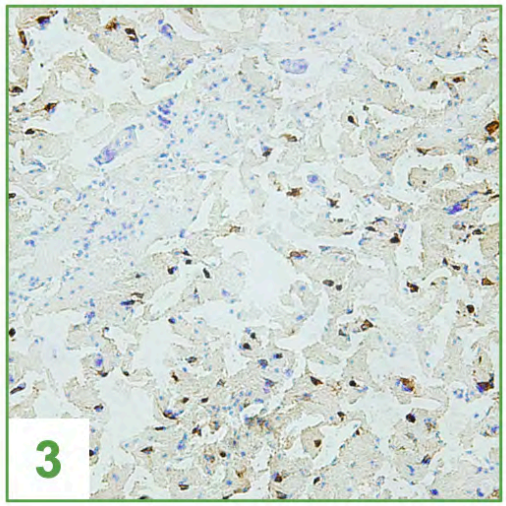
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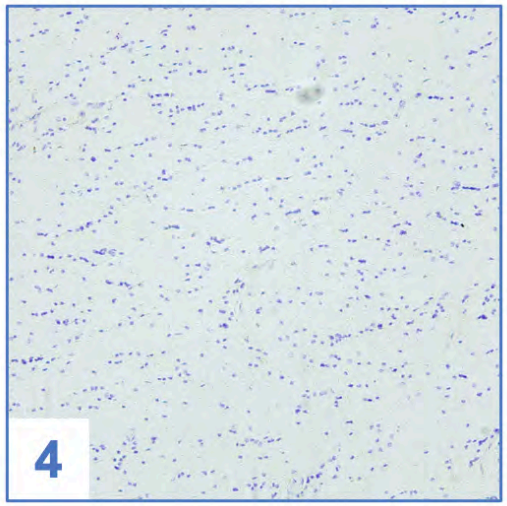
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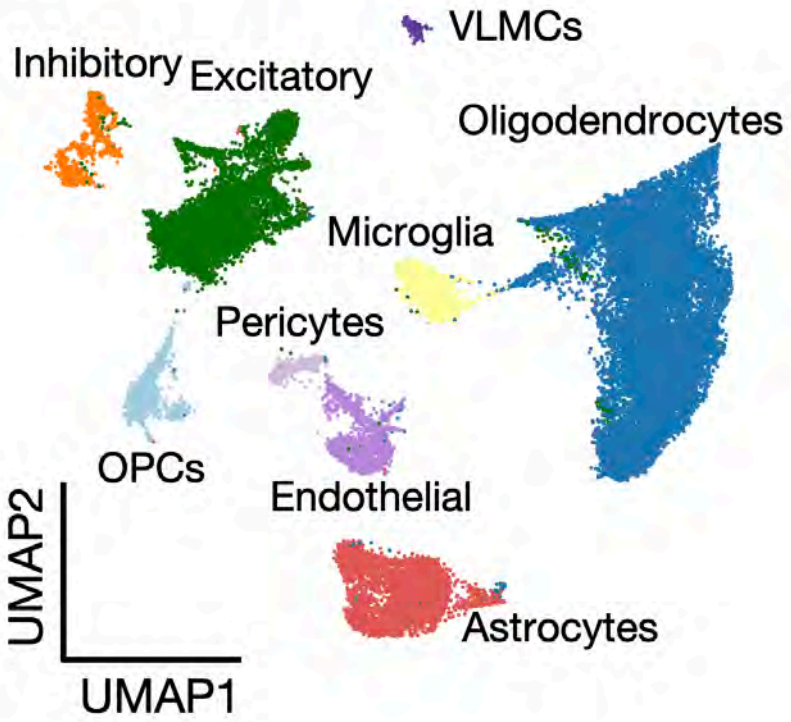
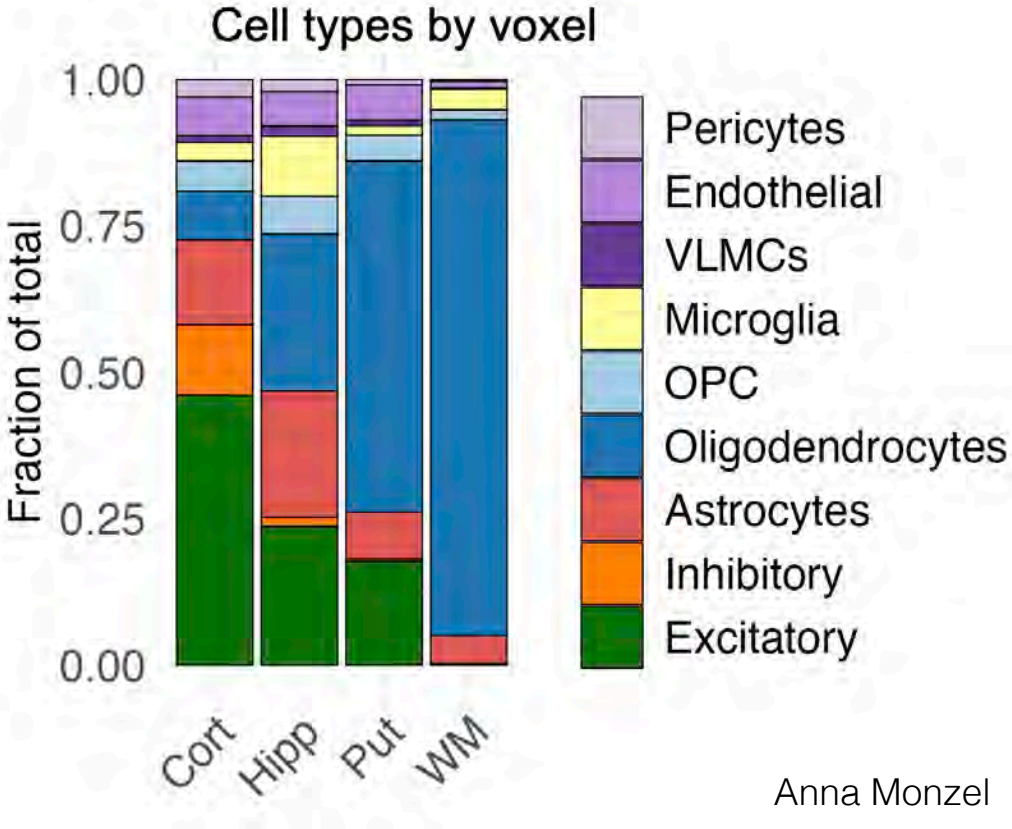
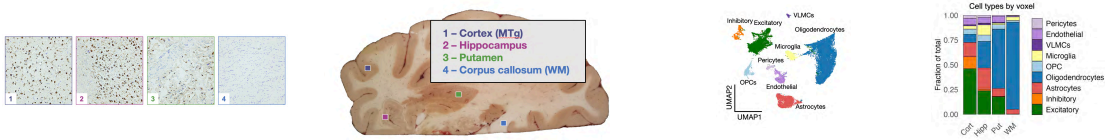

VLMCs
Inhibitory
Excitatory
Oligodendrocytes
Microglia
Pericytes
OPCs
Endothelial
Astrocytes
UMAP2
UMAP1


Cell types by voxel
Fraction of total
1.00
0.75
0.50
0.25
0.00
Cort
Hipp
Put
WM
Pericytes
Endothelial
VLMCs
Microglia
OPC
Oligodendrocytes
Astrocytes
Inhibitory
Excitatory

Anna Monzel


1 – Cortex (MTg)
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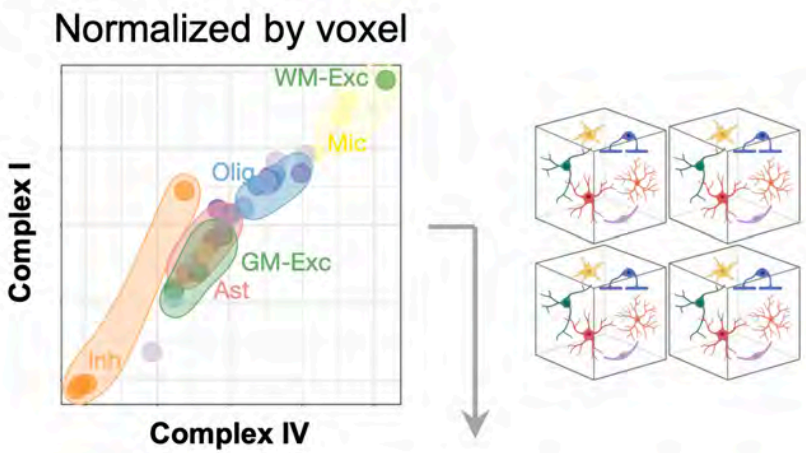
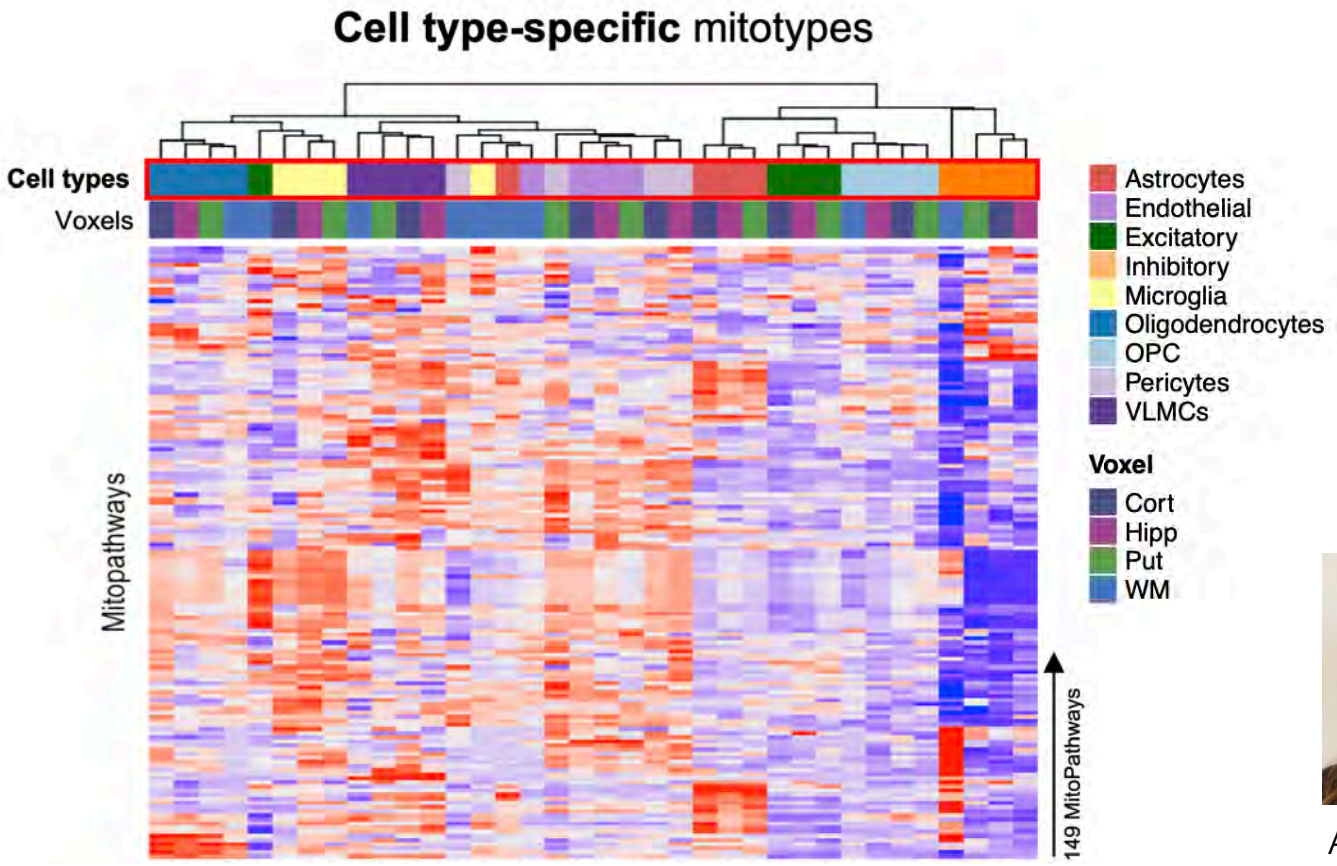
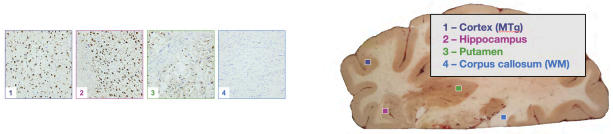
4 – Corpus callosum (WM)
Cell types by voxel
Fraction of total
Cort
Hipp
Put
WM
Pericytes
Endothelial
VLMCs
Microglia
OPC
Oligodendrocytes
Astrocytes
Inhibitory
Excitatory
UMAP1
UMAP2

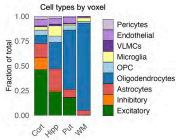

Normalized by voxel
WM-Exc
Mic
Olig
GM-Exc
Ast
Inh
Complex I
Complex IV

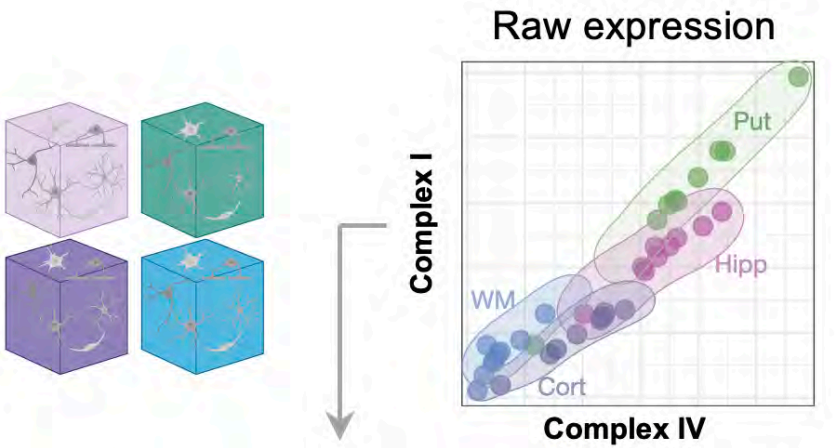

Cell type-specific mitotypes
Cell types
Voxels
Mitopathways
149 MitoPathways
Astrocytes
Endothelial
Excitatory
Inhibitory
Microglia
Oligodendrocytes
OPC
Pericytes
VLMCs
Voxel
Cort
Hipp
Put
WM

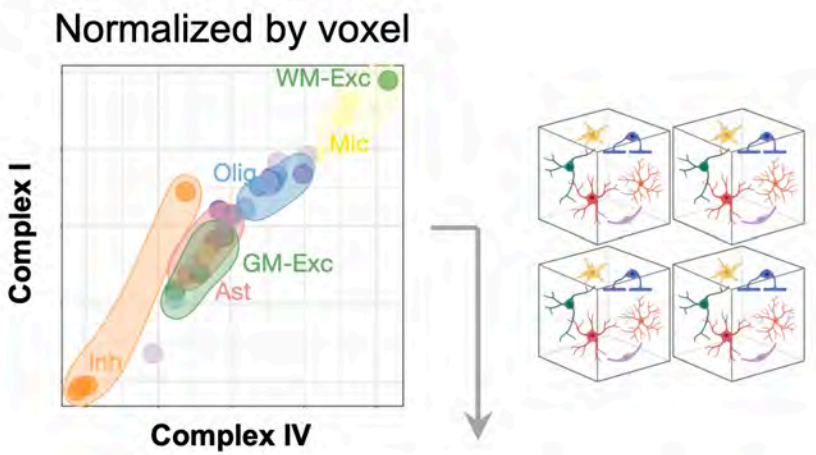
Anna Monzel

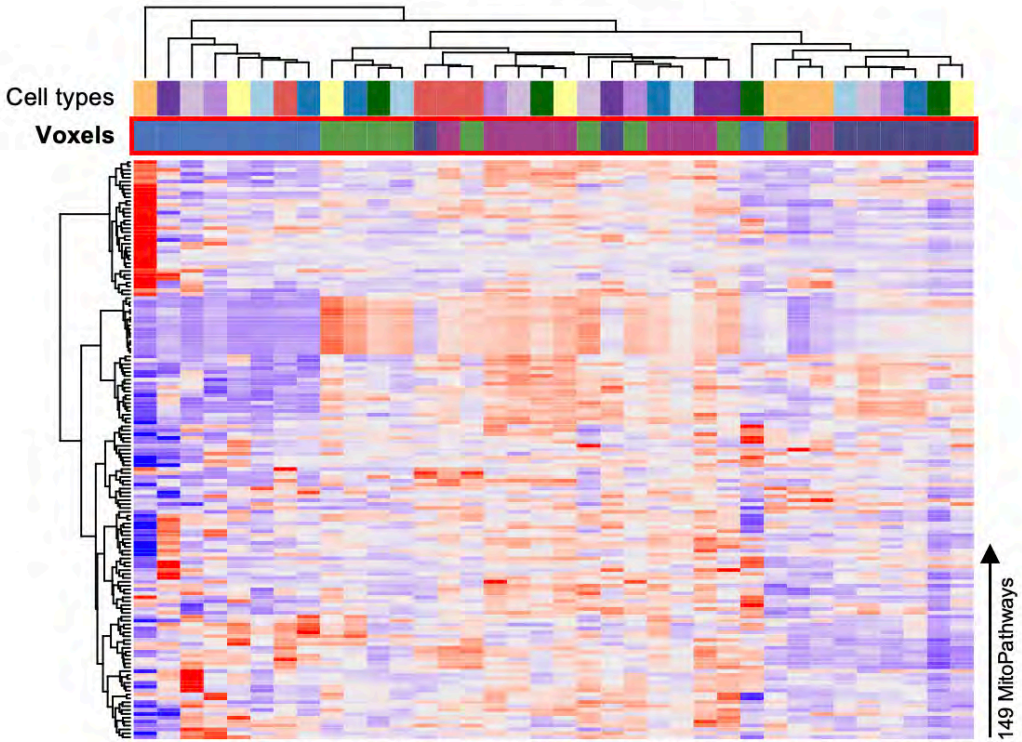

1 – Cortex (MTg)
2 – Hippocampus
3 – Putamen
4 – Corpus callosum (WM)

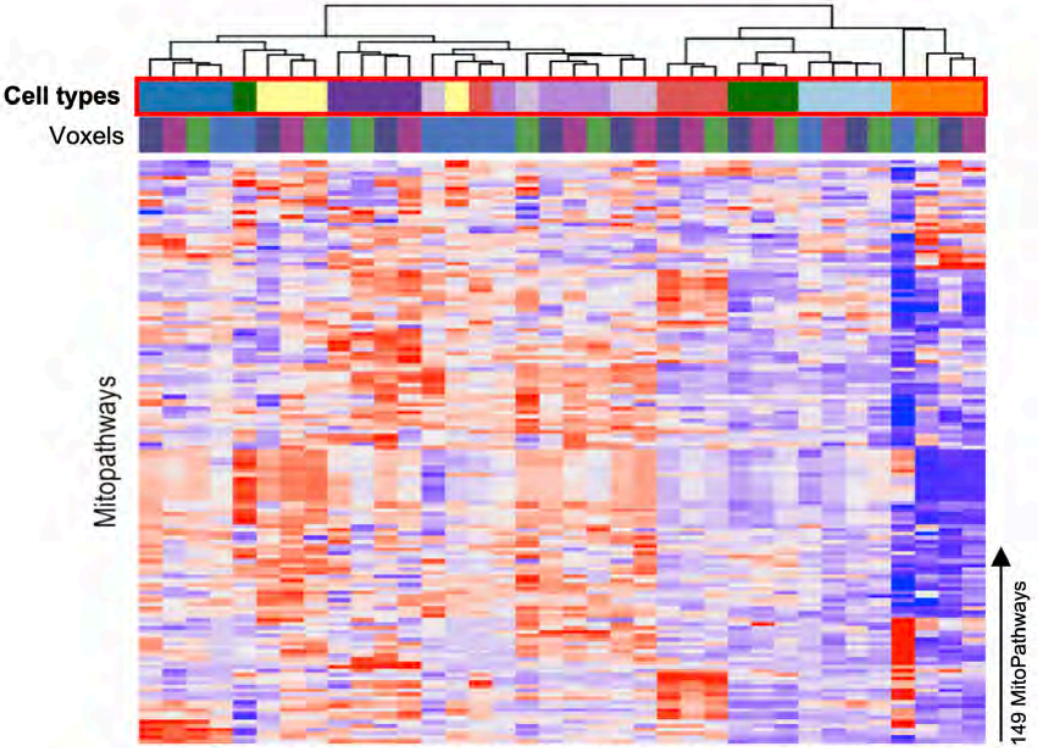

Inhibitory
Excitatory
VLMCs
Oligodendrocytes
Microglia
Pericytes
OPCs
Endothelial
Astrocytes
UMAP2
UMAP1


Cell types by voxel
Fraction of total
Cort
Hipp
Put
WM
Pericytes
Endothelial
VLMCs
Microglia
OPC
Oligodendrocytes
Astrocytes
Inhibitory
Excitatory

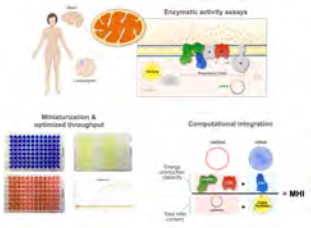

Raw expression
Complex I
Complex IV
Put
Hipp
WM
Cort


Normalized by voxel
Complex I
Complex IV
WM-Exc
Mic
Olig
GM-Exc
Ast
Inh


Voxels-specific mitotypes
Cell types
Voxels
149 MitoPathways

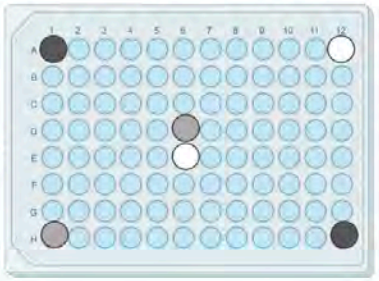

Cell type-specific mitotypes
Cell types
Voxels
Mitopathways
149 MitoPathways

Human brain mitochondrial specialization is driven by both REGIONS & CELL TYPES



OxPhos and mtDNA profiling

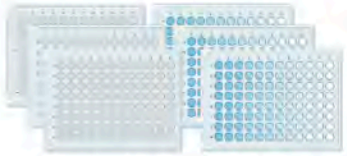
Assay plate layout



Controls

- Grey matter
- White matter
- Mixed tissue

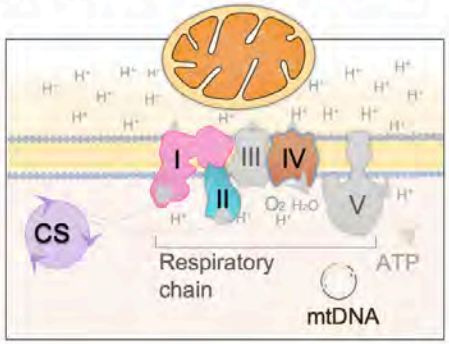
90 unique voxels per plate
8 plates total



3x triplicate negative control plates

3x triplicate plates

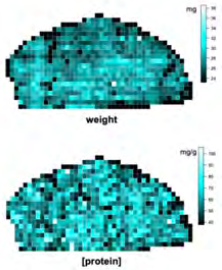
Mitochondrial colorimetric assays

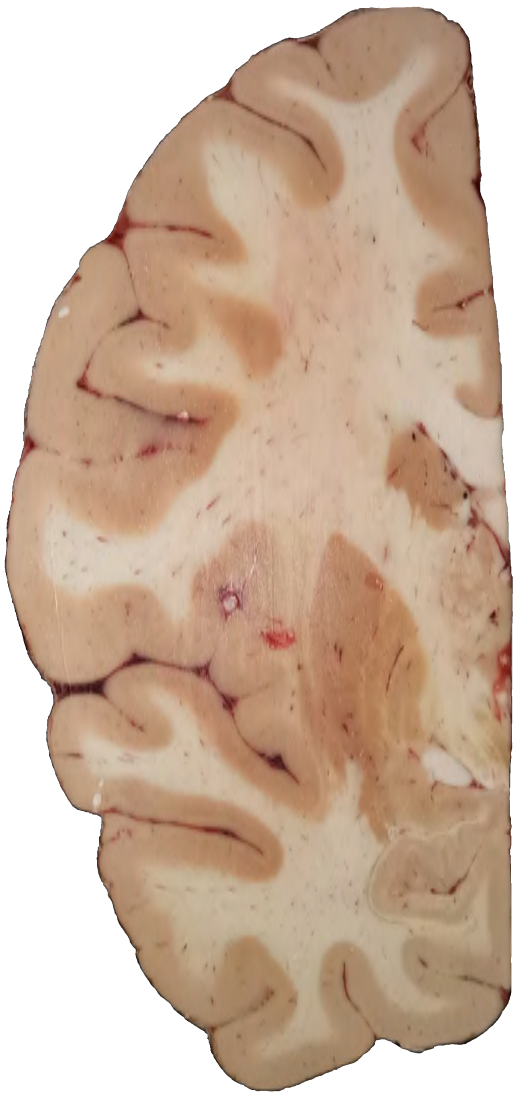


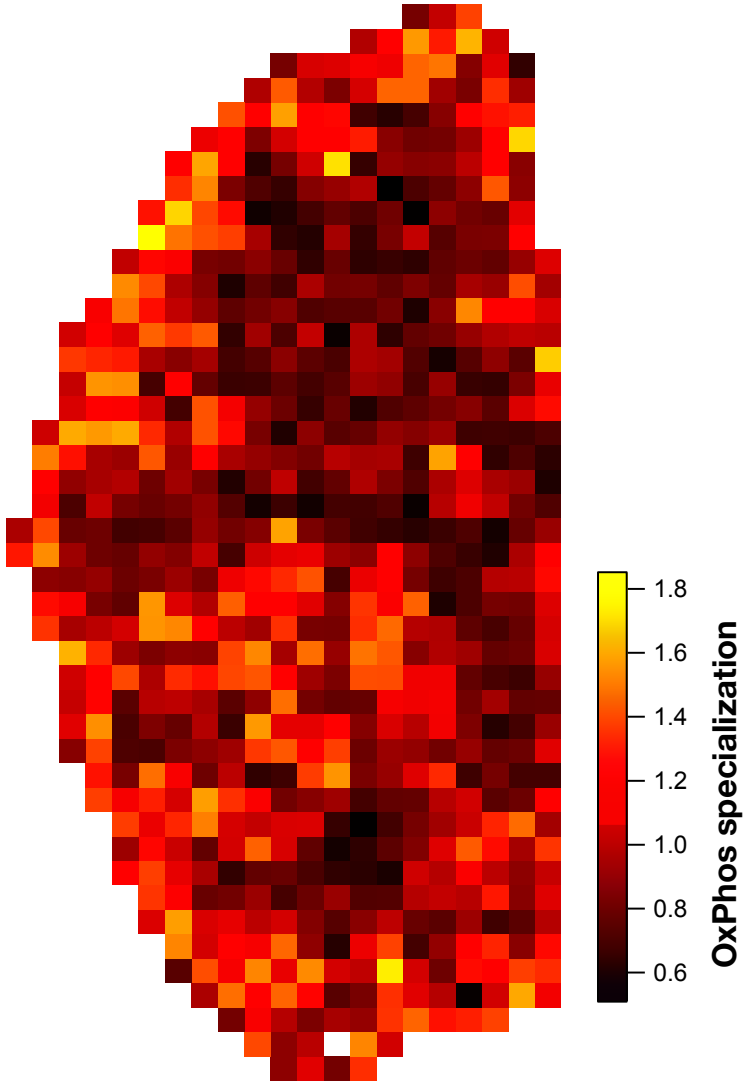
Enzymatic activities measured by spectrophotometric assays

Mitochondrial DNA measured by qPCR, measured in duplicate plates

Corey Osto, Linsey Stiles, Orian Shirihai
Ayelet Rosenberg

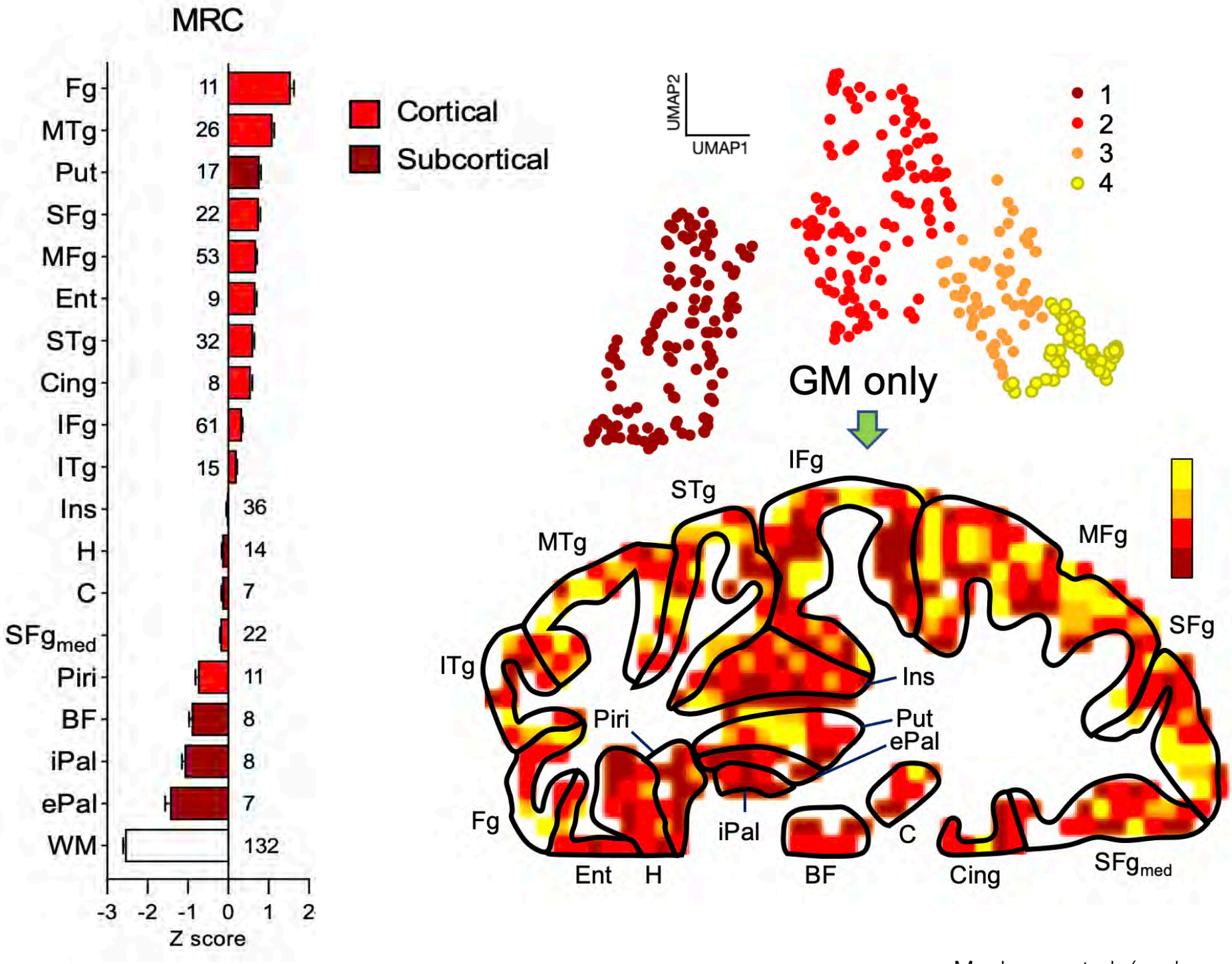






Mitochondrial profiling of 703 physical brain voxels at fMRI resolution

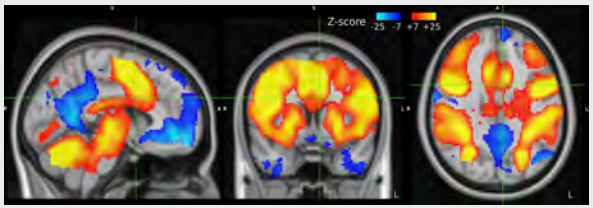
Eugene Mosharov
Ayelet Rosenberg
Michel Thiebaut de Schotten



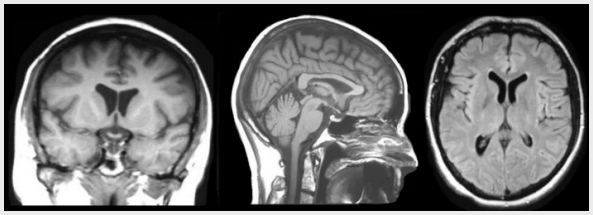
Mosharov et al. (under review)

Building a predictive model of brain mitochondria

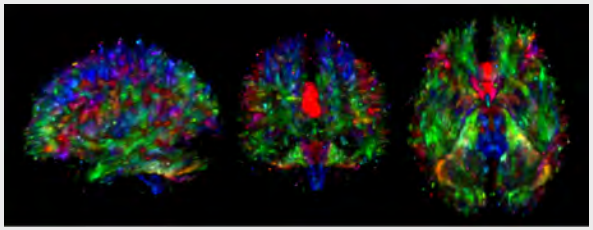
fMRI-BOLD

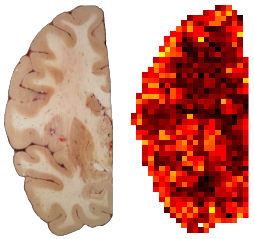


T1/T2 structural

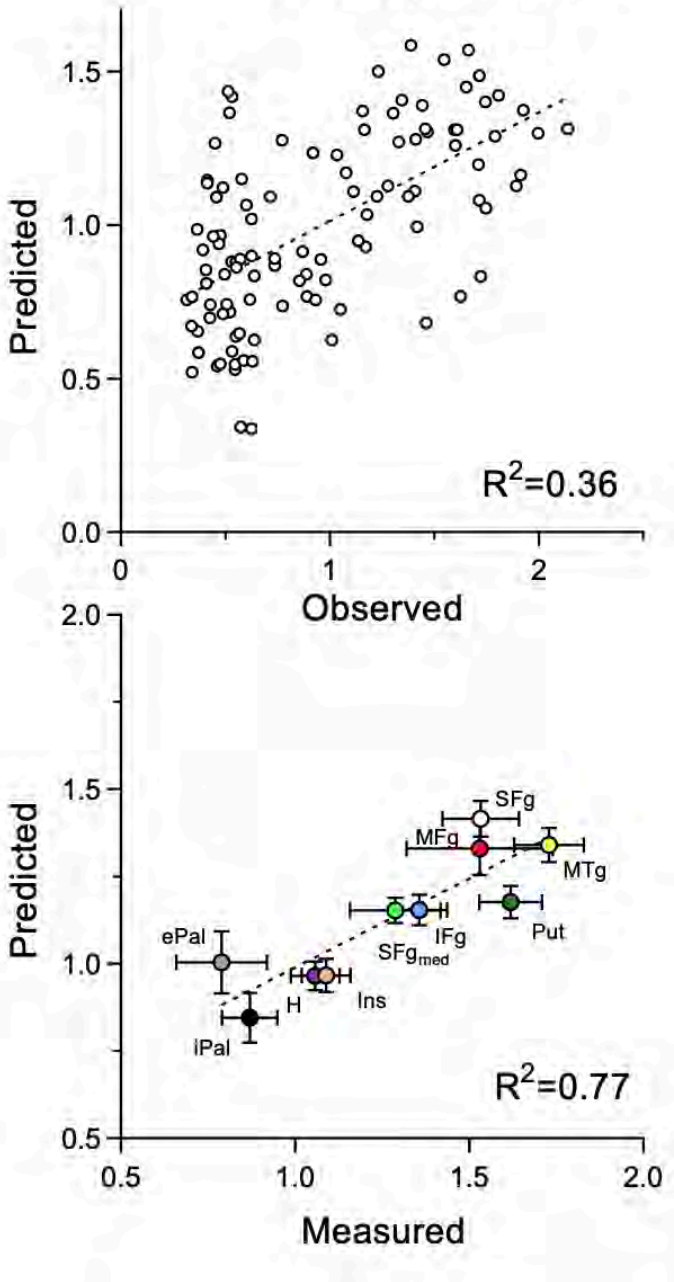


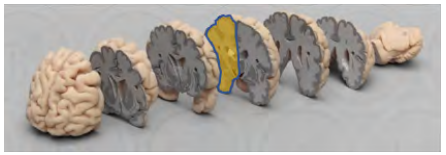
Diffusion imaging

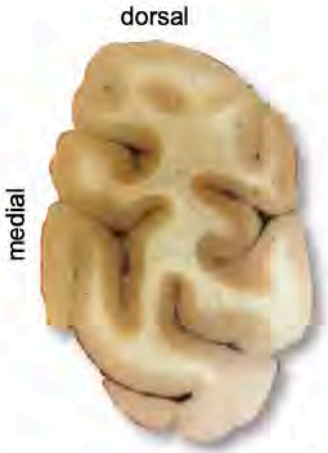




Training: 80%
Test: 20%



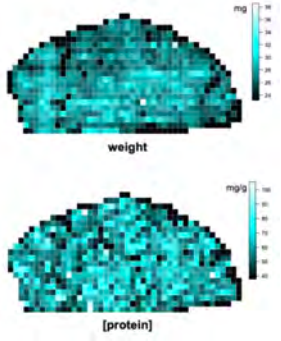


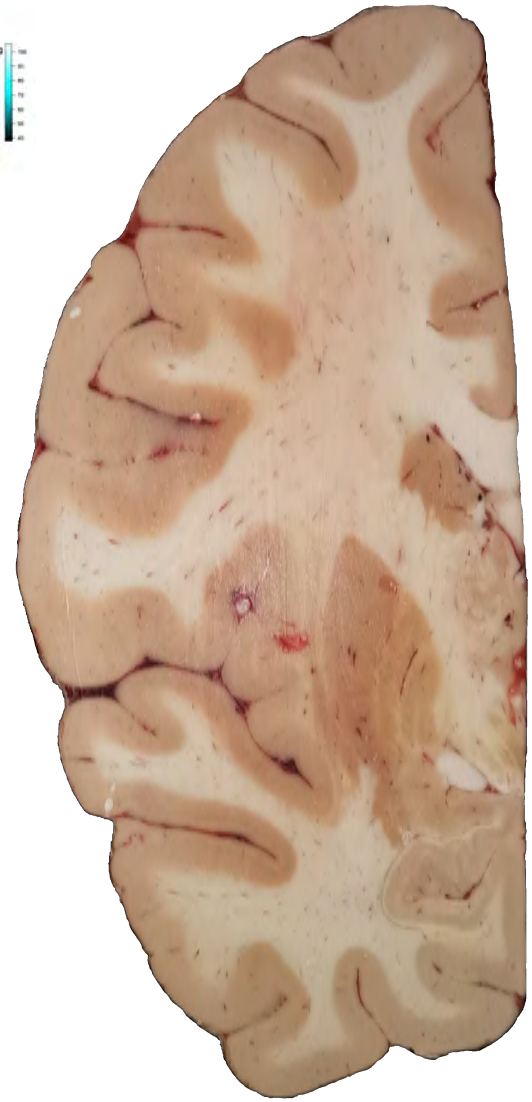


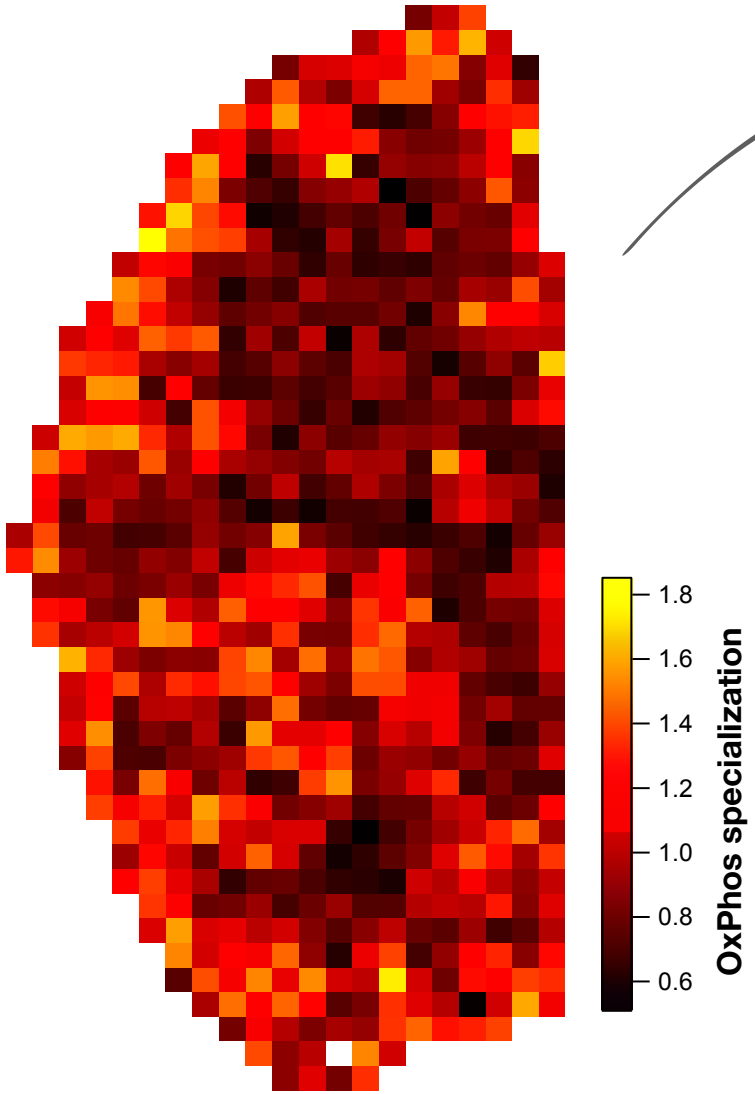
Occipital lobe (mean±S.D.)

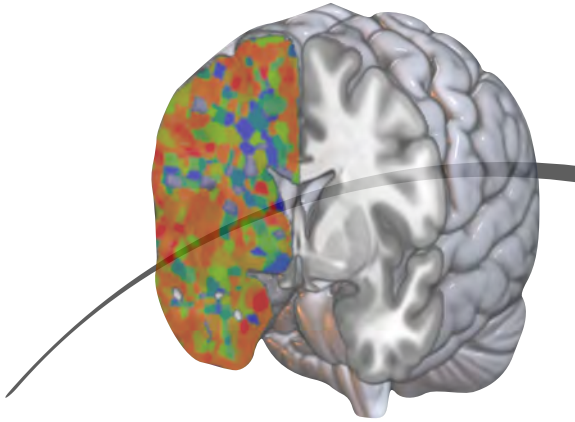
Feature	Observed	Predicted
CI	1.43±0.27	1.41±0.26
CII	1.25±0.16	1.35±0.14
CIV	1.44±0.17	1.31±0.24
MitoD	1.17±0.02	1.15±0.07
TRC	1.39±0.15	1.32±0.18
MRC	1.22±0.13	1.23±0.12

r = 0.75



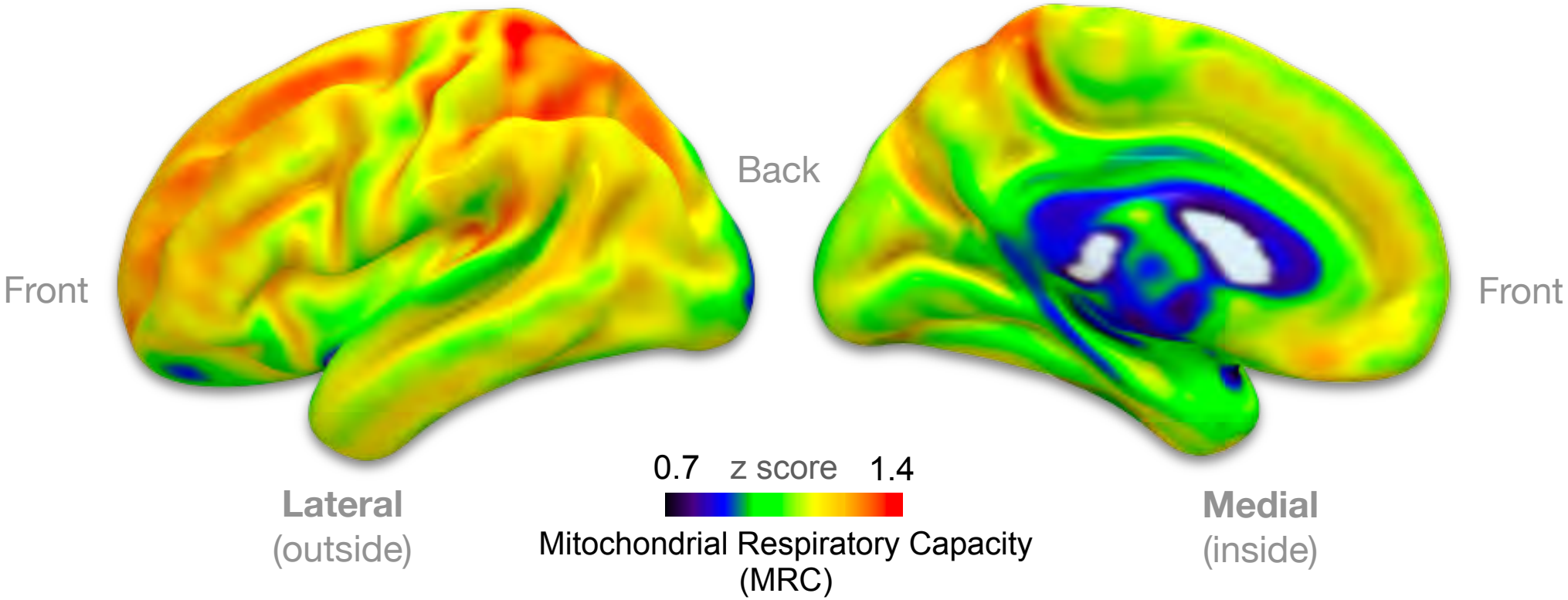




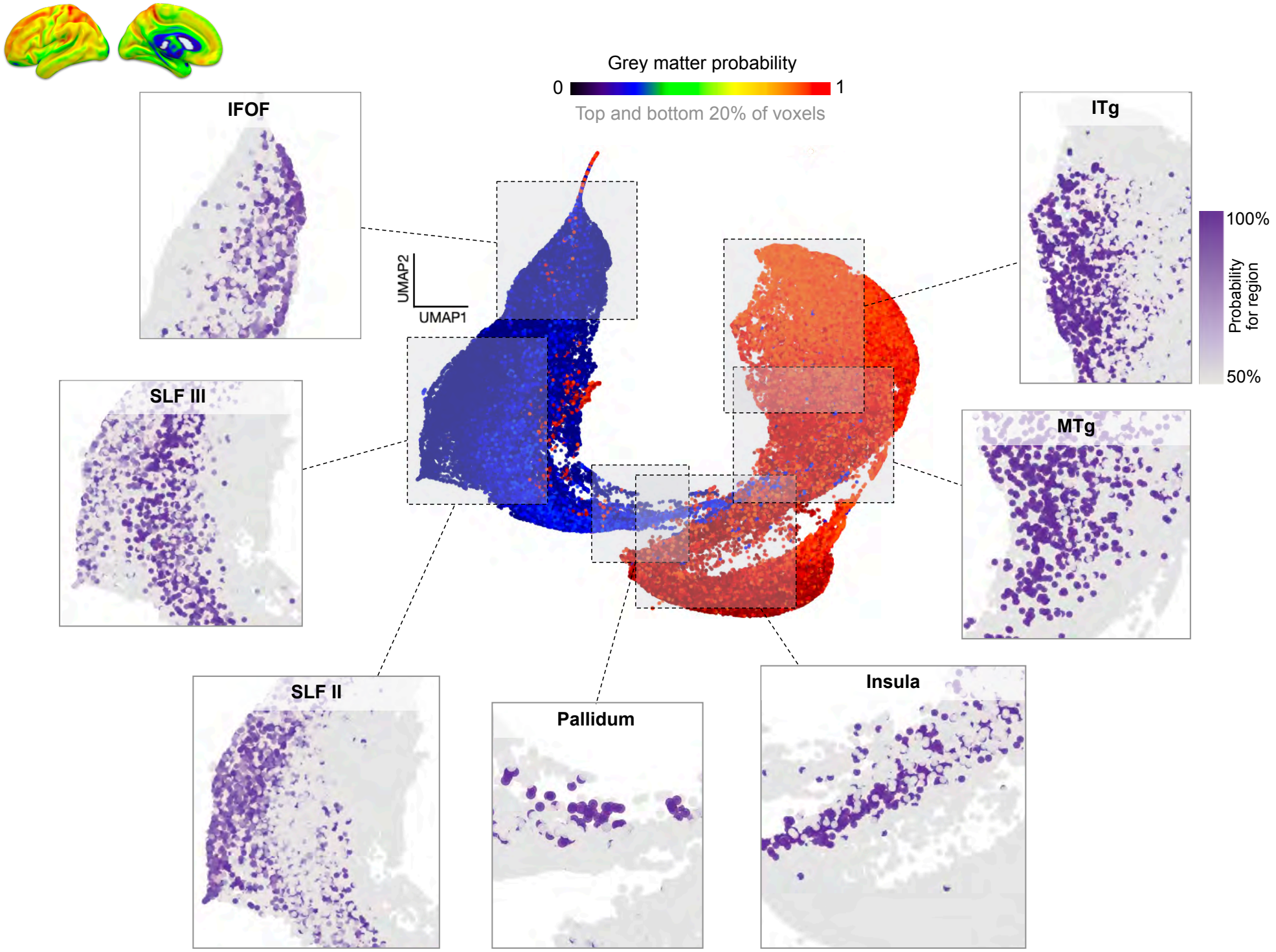


Mitochondrial profiling of 703 physical brain voxels at fMRI resolution

Back-projected onto 20 structural and functional neuroimaging modalities to create a probabilistic mitochondrial map across the whole brain (1.8M voxels)



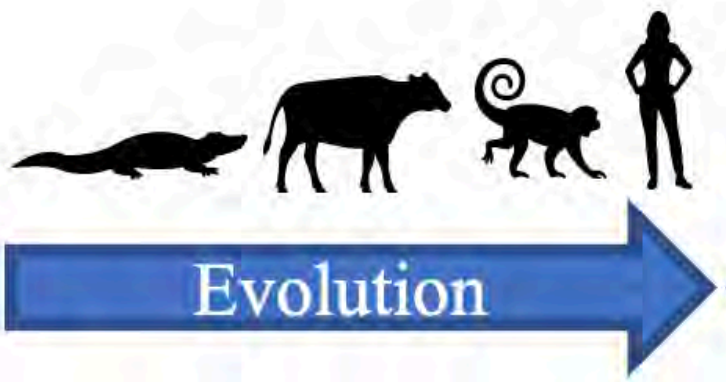
Mosharov et al. (in preparation)

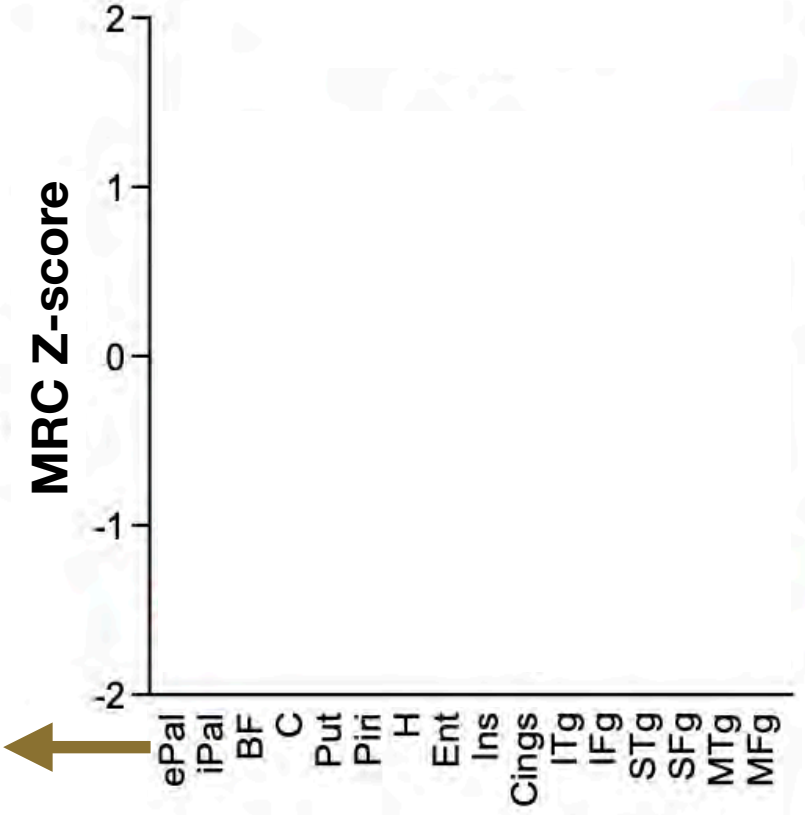


Michel Thiebaut de Shotten

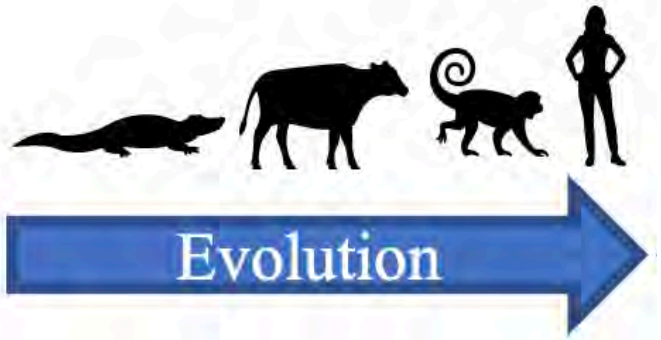
Why are there different types of mitochondria across the brain?

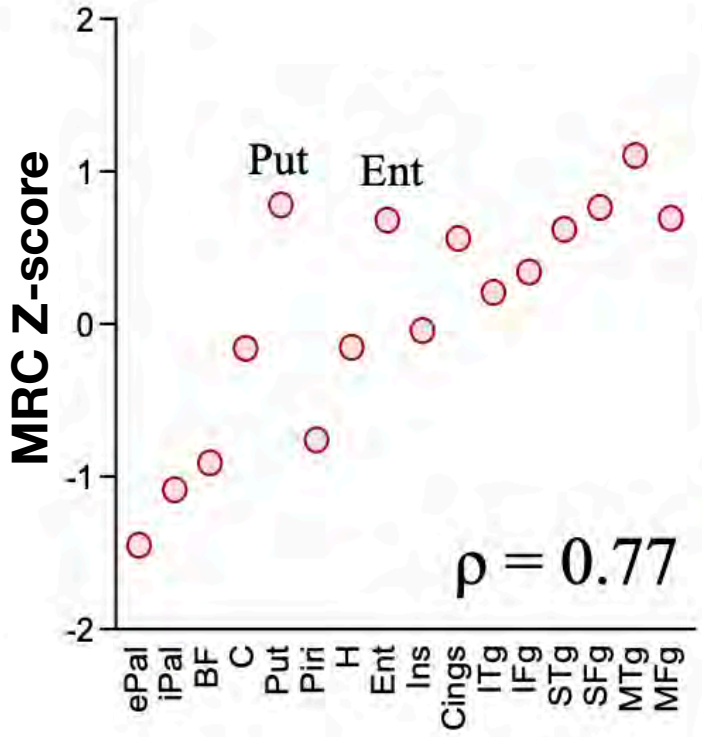
Evolutionary correlate of mitochondrial OxPhos specialization

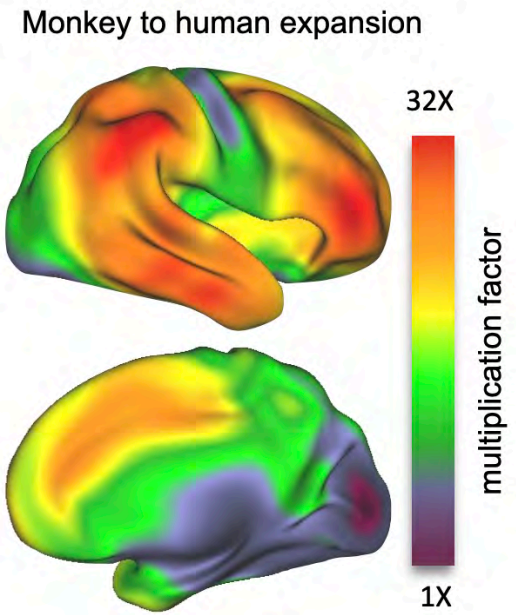


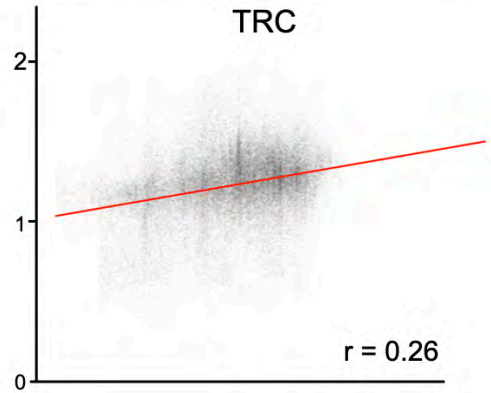


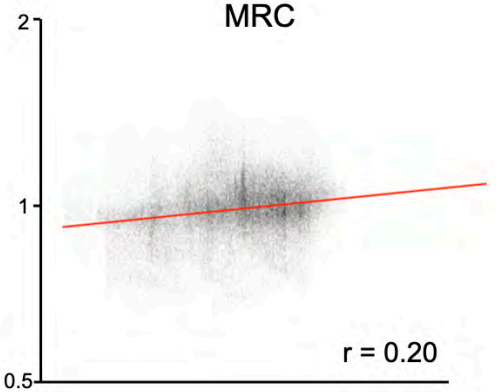
Most **"ancient"** ← → Most **"recent"**











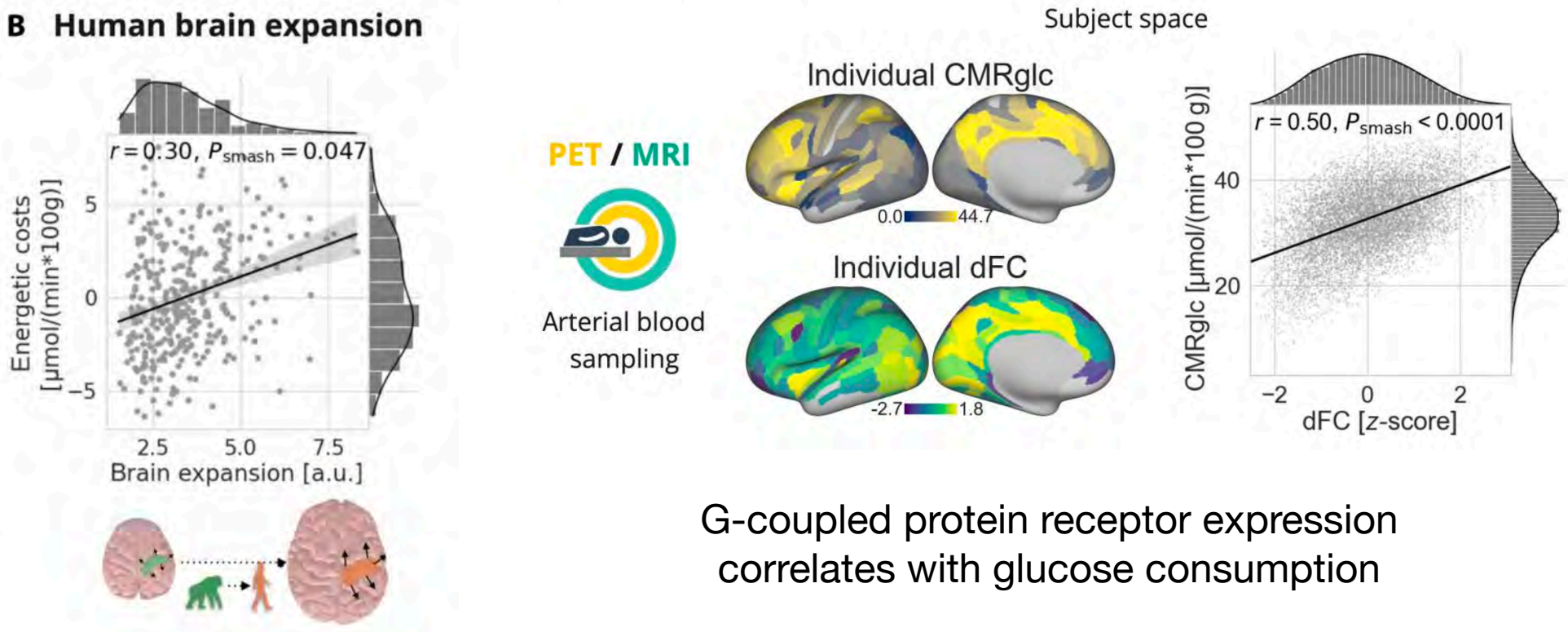
Eugene Mosharov
Michel Thiebaut de Shotten

SCIENCE ADVANCES | RESEARCH ARTICLE

NEUROSCIENCE

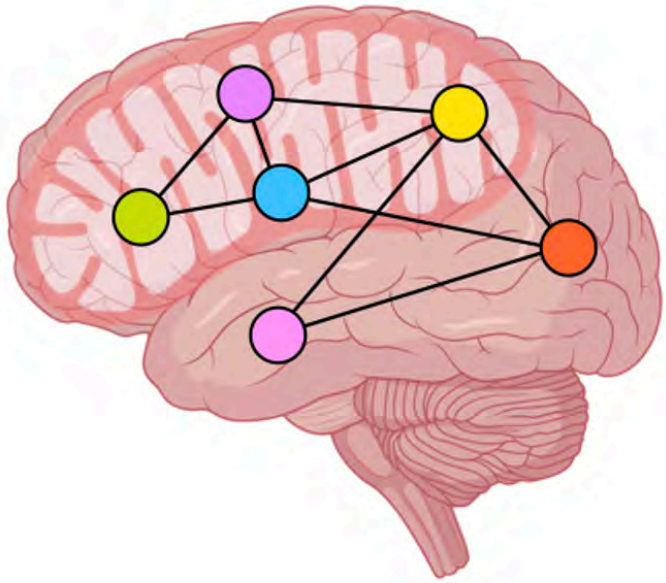
An energy costly architecture of neuromodulators for human brain evolution and cognition

Gabriel Castrillon[1,2,3], Samira Epp[1,4], Antonia Bose[1,4], Laura Fraticelli[1,4], André Hechler[1,4], Roman Belenya[1,4], Andreas Ranft[5], Igor Yakushev[6], Lukas Utz[1], Lalith Sundar[7], Josef P Rauschecker[8,9], Christine Preibisch[1,10], Katarzyna Kurcyus[1], Valentin Riedl[1,3]*



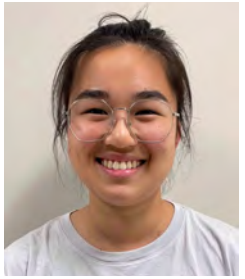
G-coupled protein receptor expression correlates with glucose consumption

Castrillon et al. *Sci Adv* 2023

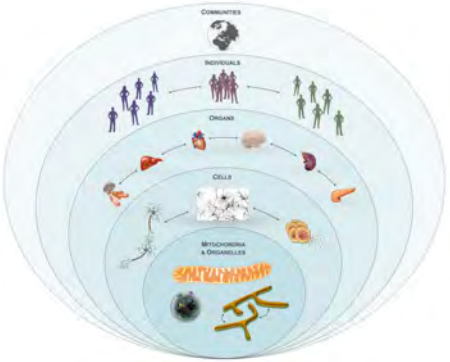


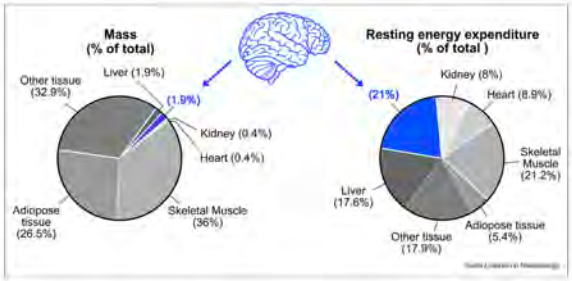
MITO BRAIN

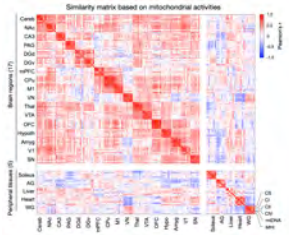
ROSMAP

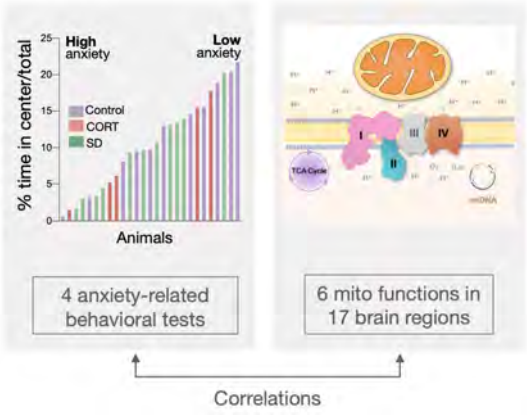


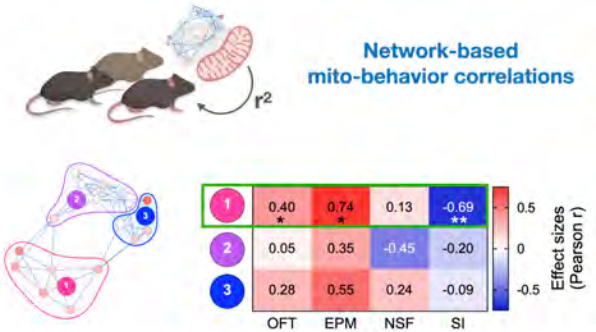
Cynthia Liu

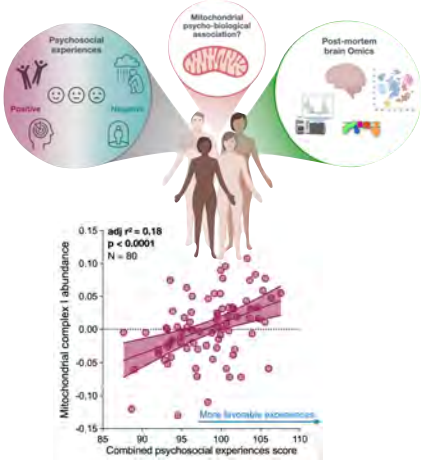

COMMUNITIES
INDIVIDUALS
ORGANS
CELLS
MITOCHONDRIA & ORGANELLES

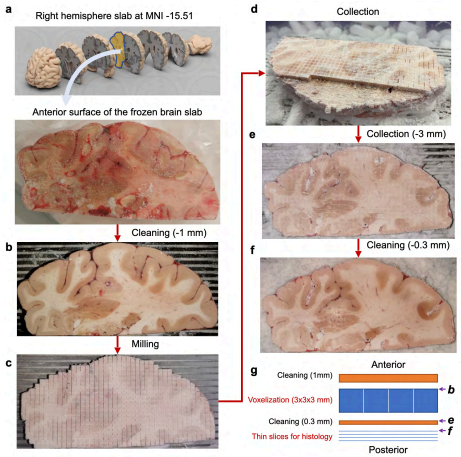

Mass
(% of total)
Liver (1.9%)
(1.9%)
Other tissue
(32.9%)
Kidney (0.4%)
Heart (0.4%)
Adicipose
tissue
(26.5%)
Skeletal Muscle
(36%)
Resting energy expenditure
(% of total)
Kidney (8%)
Heart (8.9%)
(21%)
Skeletal
Muscle
(21.2%)
Liver
(17.6%)
Other tissue
(17.9%)
Adiopose tissue
(5.4%)

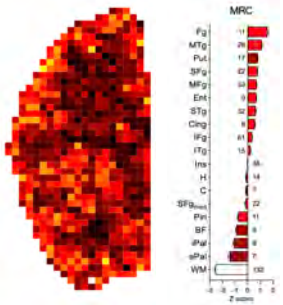

Similarity matrix based on mitochondrial activities

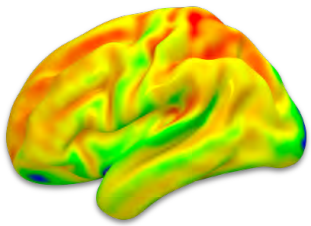

High
anxiety
Low
anxiety
Control
CORT
SD
% time in center/total
Animals
4 anxiety-related
behavioral tests
6 mito functions in
17 brain regions
Correlations

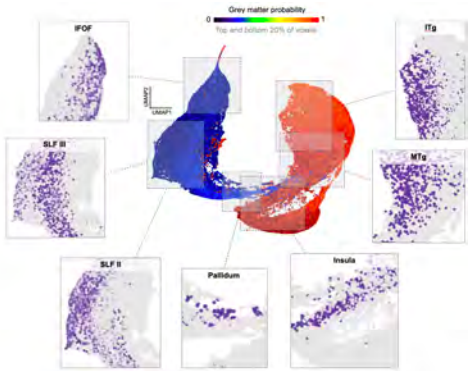

r2
Network-based
mito-behavior correlations
0.40
0.74
0.13
-0.69
0.05
0.35
-0.45
-0.20
0.28
0.55
0.24
-0.09
OFT
EPM
NSF
SI
Effect sizes
(Pearson r)

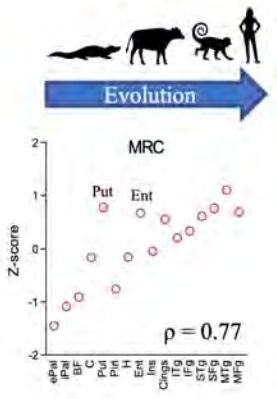

Psychosocial
experiences
Positive
Negative
Mitochondrial
psycho-biological
association?
Post-mortem
brain Omics
adj r² = 0.18
p < 0.0001
N = 80
Mitochondrial complex I abundance
More favorable experiences
Combined psychosocial experiences score

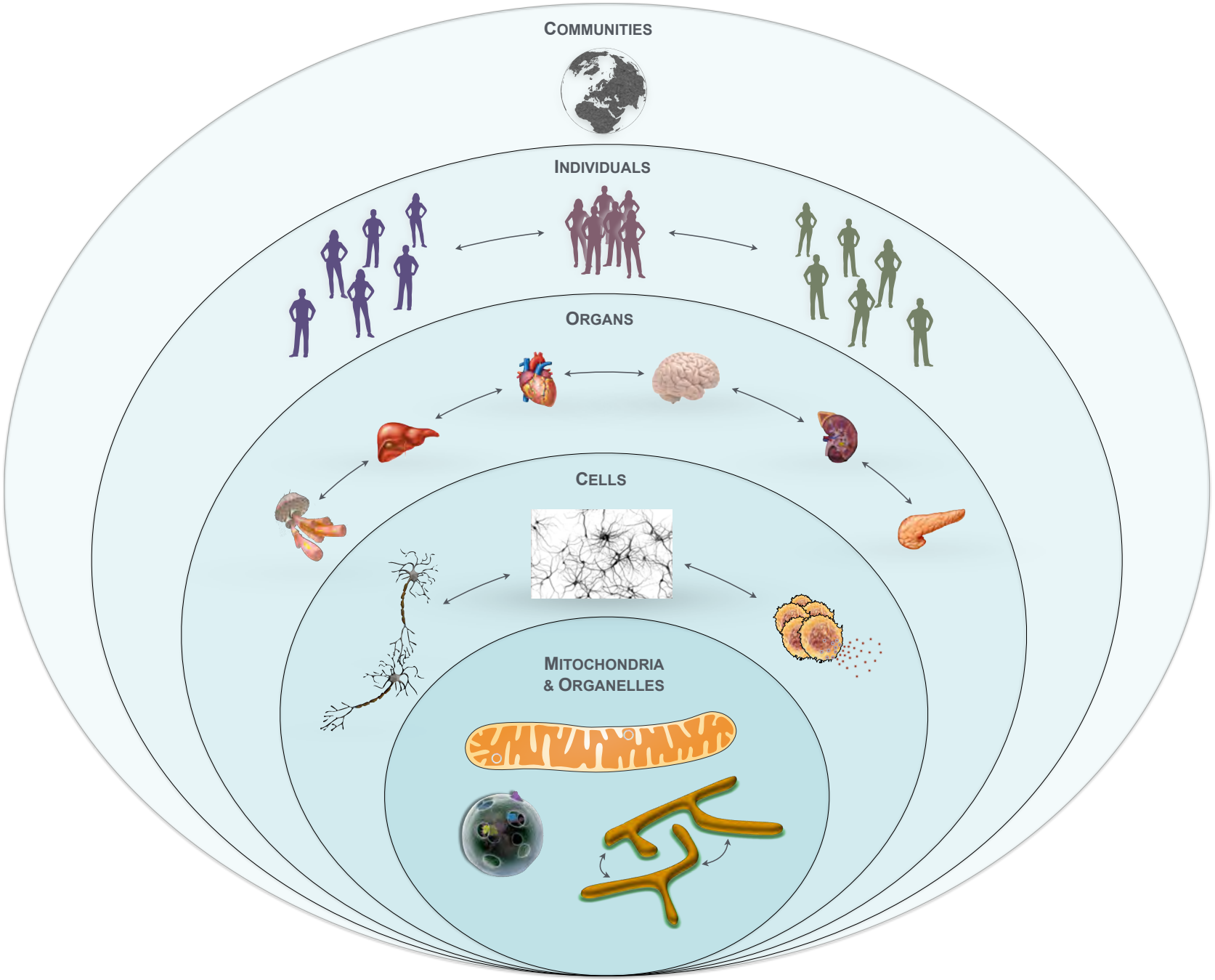

a
Right hemisphere slab at MNI -15.51
Anterior surface of the frozen brain slab
Cleaning (-1 mm)
b
Milling
c
d
Collection
Collection (-3 mm)
e
Cleaning (-0.3 mm)
f
Anterior
g
Cleaning (1mm)
Voxelization (3x3x3 mm)
Cleaning (0.3 mm)
Thin slices for histology
Posterior


MRC
Fg
MTg
Put
SFg
MFg
Ent
STg
Cing
IFg
ITg
Ins
H
C
SFg
Pin
BF
ePal
iPal
WM
Z scores




Grey matter probability
IFOF
ITg
SLF III
MTg
SLF II
Pallidum
Insula


Evolution
MRC
Put
Ent
Z-score
ρ = 0.77
ePal
iPal
BF
C
Put
Pin
H
Ent
Ins
Cings
ITg
IFg
STg
SFg
MTg
MFg



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

Mitochondrial PsychoBiology Lab

Linking molecular processes within mitochondria with the human experience

OUR RESEARCH

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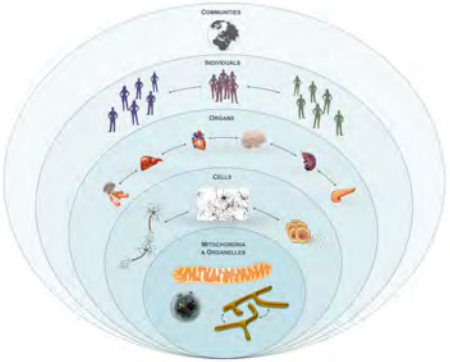
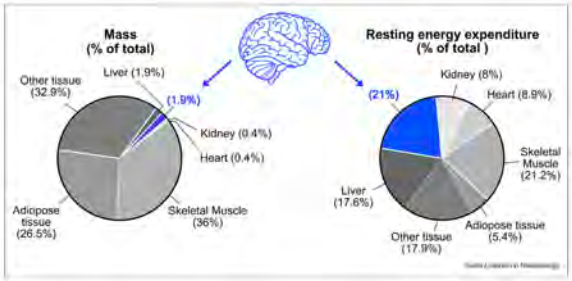
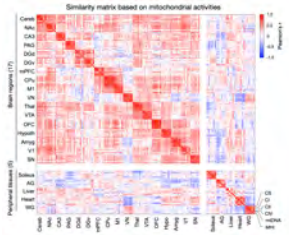
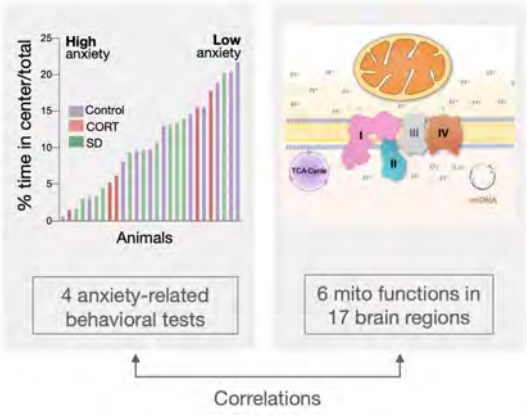
MITOCHONDRIAL PSYCHOBIOLOGY LAB

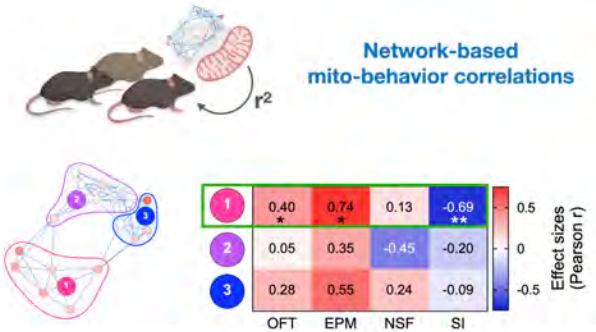
MITOCHONDRIA STRESS BRAIN EPIGENETICS iSBIE

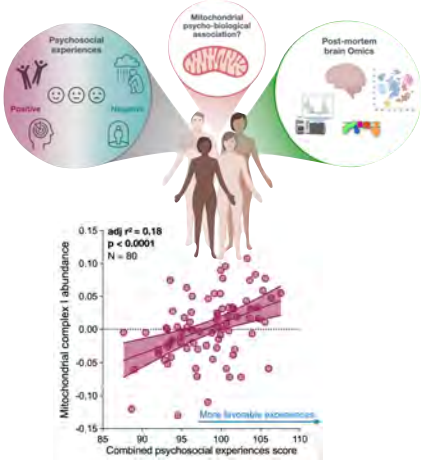

COMMUNITIES
INDIVIDUALS
ORGANS
CELLS
MITOCHONDRIA & ORGANELLES

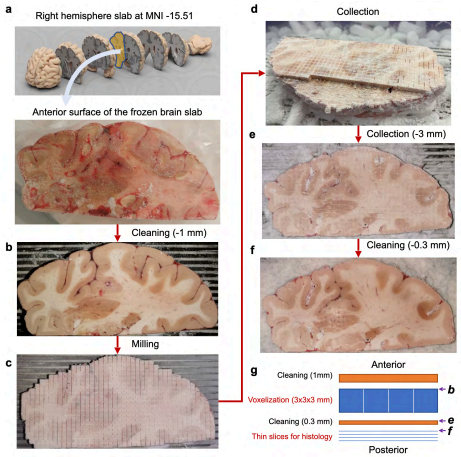

Mass
(% of total)
Liver (1.9%)
(1.9%)
Other tissue
(32.9%)
Kidney (0.4%)
Heart (0.4%)
Adicipose
tissue
(26.5%)
Skeletal Muscle
(36%)
Resting energy expenditure
(% of total)
Kidney (8%)
Heart (8.9%)
(21%)
Skeletal
Muscle
(21.2%)
Liver
(17.6%)
Other tissue
(17.9%)
Adiopose tissue
(5.4%)

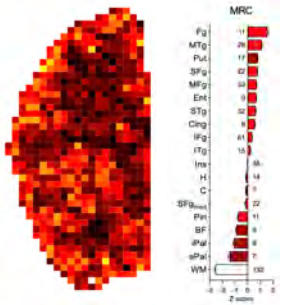

Similarity matrix based on mitochondrial activities

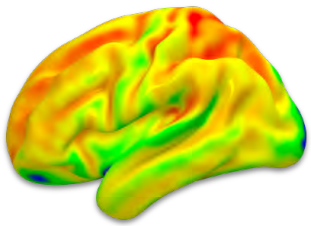

High
anxiety
Low
anxiety
Control
CORT
SD
% time in center/total
Animals
4 anxiety-related
behavioral tests
6 mito functions in
17 brain regions
Correlations

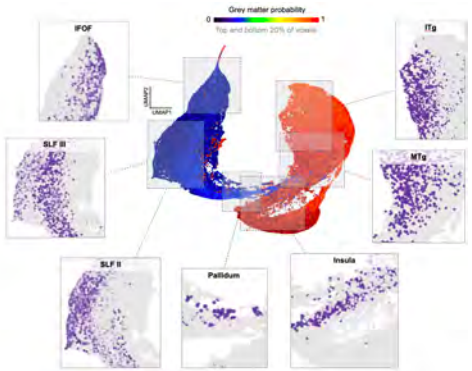

r2
Network-based
mito-behavior correlations
0.40
0.74
0.13
-0.69
0.05
0.35
-0.45
-0.20
0.28
0.55
0.24
-0.09
OFT
EPM
NSF
SI
Effect sizes
(Pearson r)

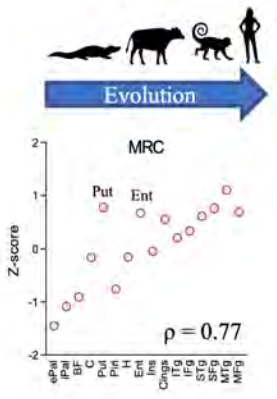

Psychosocial
experiences
Positive
Negative
Mitochondrial
psycho-biological
association?
Post-mortem
brain Omics
adj r² = 0.18
p < 0.0001
N = 80
Mitochondrial complex I abundance
More favorable experiences
Combined psychosocial experiences score


a
Right hemisphere slab at MNI -15.51
Anterior surface of the frozen brain slab
Cleaning (-1 mm)
b
Milling
c
d
Collection
Collection (-3 mm)
e
Cleaning (-0.3 mm)
f
Anterior
g
Cleaning (1mm)
Voxelization (3x3x3 mm)
Cleaning (0.3 mm)
Thin slices for histology
Posterior


MRC
Fg
MTg
Put
SFg
MFg
Ent
STg
Cing
IFg
ITg
Ins
H
C
SFg
Pin
BF
ePal
iPal
WM
Z scores




Grey matter probability
IFOF
ITg
SLF III
MTg
SLF II
Pallidum
Insula


Evolution
MRC
Put
Ent
Z-score
ρ = 0.77
ePal
iPal
BF
C
Put
Pin
H
Ent
Ins
Cings
ITg
IFg
STg
SFg
MTg
MFg

Extended Data Table 1 | List of neuroimaging metrics and their standardized beta coefficient relationship with the mitochondrial features.

	Abbreviation	MRI metric	CI	CII	CIV	MitoD	TRC	MRC
Diffusion MRI	AD	axial water diffusivity		.242			.246	
	FA	white matter density			.681	.820		
	RD	radial water diffusivity	-.365		.439	.632		-.175
	StreDensity	streamlines density		-.184				
	ICVF	intra-cellular volume fraction	-.371					
	ISOCF	extra-cellular volume fraction		-.158	-.438	-.445	-.330	
	MD	mean water diffusivity						
	OD	orientation dispersion index (neurite complexity)	.363	.323	.628	.499	.481	.334
Structural MRI	T1W	T1w imaging						
	T2W	T2w imaging	-.245	-.304	-.458	-.410	-.330	-.244
	T1w/T2w	T1w/T2w ratio	-.656	-.580	-.723	-.622	-.617	-.593
	FLAIR	imaging approach to see the anatomy of the brain		-.221		-.339		
	CT	cortical thickness						
	inner_CSA	local surface for inner cortical ribbon						
	plial_CSA	local surface for outer cortical ribbon						
	GM	probability of gray matter	-1.038		-1.382		-1.177	-.939
	WM	probability of white matter	-1.082		-1.263	-.312	-1.040	-.906
Functional MRI	Max_activity	maximum bold derived from fMRI			.380		.333	.501
	Reho	regional homogeneity		.145		.135		
	Entropy	synaptic complexity derived from fMRI			-.386		-.365	-.560
	ALFF	amplitude of Low-Frequency Fluctuation						
	fALFF	ratio between low and and high frequency fluctuations						