MiSBIE Transition Meeting

Mitochondrial Stress, Brain Imaging, and Epigenetics

A summary, update, and forward-looking discussion among MiSBIE Team members, collaborators, and partners

April 5, 2024

Columbia University Irving Medical Center and Zoom

April 5, 2024

Welcome to this MiSBIE Study celebration!

2016 - present

The MiSBIE Team (Clinical and Laboratory)


Catherine Kelly


Kris Engelstad


Shufang Li


Grace Liu


Kathleen McIntyre


Lea Gregorio


Mangesh Kurade

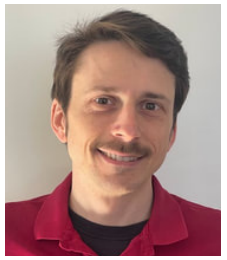

Anna Monzel


Jeremy Michelson

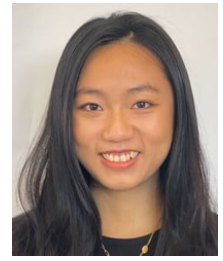

Natalia Bobba-Alves


Janell Smith


Cynthia Liu


David Shire


Darshana Kapri


Hannah Huang


Alex Junker


Jack Baker


Sophia Tepler
(Sloan Lab)


Sophie Basarrate


Soah Grace Franklin


Ke Bo
(Wager group)


Gabriel Sturm


Alex Behnke

Past members: Marlon McGill, Ellie Yan, Marissa Cross, Veronica Taleon

The MiSBIE Team (Primary investigators, co-investigators)

Frances Champagne
UT Austin

Stephanie Assuras
Columbia

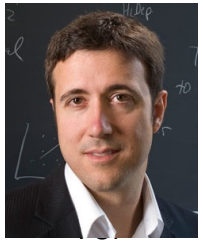
Caroline Trumpff
Columbia

Richard Sloan
Columbia

Vincenzo Lauriola
Columbia

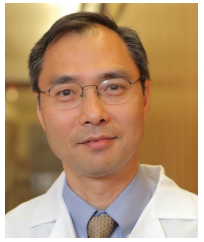
Bruce McEwen
Rockefeller

Robert-Paul Juster
U Montreal



Wager
Dartmouth

Michel Thiebaut de Schotten
Bordeaux



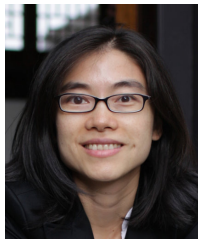
Michio Hirano
Columbia

Martin Picard
Columbia

Aric Prather
UCSF

Elissa Epel
UCSF

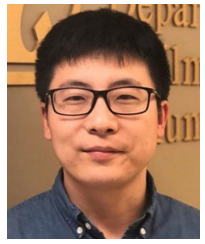
Clemens Kirschbaum
Dresden



Shuang Wang
Columbia

Alan Cohen
Columbia

Molei Liu
Columbia



Sen Pei
Columbia

Jue Lin
UCSF

Dan Belsky
Columbia

And others

Past contributors: Jennifer Manly, Marisa Spann, Julie Spicer

Funding partners

The Nathaniel Wharton Fund

Irving Institute for clinical and translational research

NIH National Institute of Mental Health

R21MH113011, PO: Meinecke
R01MH122706-5, PO: Meinecke

BASZUCKI BRAIN RESEARCH FUND

NIH National Institute of General Medical Sciences

NIH National Institute on Aging

MiSBIE Transition Meeting
April 5, 2024

Scientific Program

Todd Auditorium, P&S 16th Fl, Room 405, Columbia University Irving Medical Center

Part I – MiSBIE Study status, rationale, and protocol (45 min)

2:00	Zoom setup https://columbiacuimc.zoom.us/j/5779841445
2:05	**Welcome** – Martin Picard MiSBIE Team, Collaborators, Partners Agenda for today's *MiSBIE Transition meeting*
2:10	**MiSBIE Study overview** – Martin Picard Rationale, primary hypotheses, scientific opportunities The stress-disease cascade hypothesis Study timeline, recruitment, and completion
2:15	**Mitochondrial diseases** – Michio Hirano Which clinical population does MiSBIE include? MELAS, CPEO, multi-system disease Markers of disease severity: neurological, functional capacity, autonomic, fatigue, etc
2:20	**MiSBIE protocol –** Catherine Kelly What did participants experienced during a MiSBIE visit? Protocol overview
2:30	**Psychosocial assessments and questionnaires** – Caroline Trumpff Constructs & instruments *PRELIMINARY RESULTS: Psychophenotypes and mental health variables*
2:35 10 min	**Questions**

Part II – Procedures, preliminary data, and results – short vignettes (50 min)

2:45 3 min	**RedCap Database** – Grace Liu Dimensionality and properties of MiSBIE database
3 min	**Stress psychophysiology session** – Vincenzo Lauriola Continuous measures of heart rate, blood pressure, respiration, skin conductance *PRELIMINARY RESULTS: Psychophysiological stress reactivity at different resolution*
3 min	**Biospecimen processing and MiSBIE Biobank** – Mangesh Kurade From participant to lab to cryostorage: What samples are available? *PRELIMINARY RESULTS: Success rates and sample availability*
3 min	**Steroid hormones in saliva and hair** – Natalia Bobba-Alves / Clemens Kirschbaum Cortisol, corticosterone, DHEA-s, testosterone, others *PRELIMINARY RESULTS: Cortisol stress reactivity and awakening response*
3 min	**Immune cell bioenergetics** – Anna Monzel Seahorse in leukocytes, JATP calculations, sn/scRNAseq, and MHI *PRELIMINARY RESULTS: Seahorse cell type differences, monocyte gene expression*
3 min	**Neuropsychological assessment** – Stephanie Assuras / Catherine Kelly Instruments, domains of cognition assessed *PRELIMINARY RESULTS: Cognitive domains affected in mitochondrial diseases*
3 min	**Clinical biochemistry and allostatic load** – Alex Junker / Robert-Paul Juster Standard blood chemistry, biomarkers, allostatic load indices *PRELIMINARY RESULTS: Clinical biochemistry and multisystem dysregulation in MitoD*
3 min	**Neuroimaging** – Ke Bo / Tor Wager / Michel Thiebaut de Schotten MRI protocol: structural, fMRI-BOLD rest and tasks, DWI *Preliminary results*: Brain activation maps, pain signature, hemodynamic responses
3 min	**Cell-free mitochondrial DNA** – David Shire Socioevaluative speech task-induced cf-mtDNA in saliva, serum, plasma *PRELIMINARY RESULTS: cf-mtDNA stress reactivity across biofluids*
3 min	**Home-based assessments** – Aric Prather MiSBIE App, surveys, actigraphy *PRELIMINARY RESULTS: Sample data from actigraphy-based sleep monitoring*
3 min	**Saliva proteomics** – Molei Liu, Alan Cohen Saliva awakening response proteome, dynamics statistical models *PRELIMINARY RESULTS: Saliva awakening proteome dynamic signature of MitoD*
3 min	**Age-related and mitochondrial disease biomarker dynamics** – Hannah Huang GDF15 in blood and saliva, stress reactivity, also FGF21 (Mangesh Kurade) *PRELIMINARY RESULTS: Elevated saliva GDF15 in MitoD, and is a stress hormone*
3 min	**Single cell transcriptomics –** Anna Monzel PBMC cryopreservation, 10x genomics, immune-disease connection and integration *PRELIMINARY RESULTS: Mitochondrial molecular phenotyping in single immune cells*
3:25 10 min	**Questions**

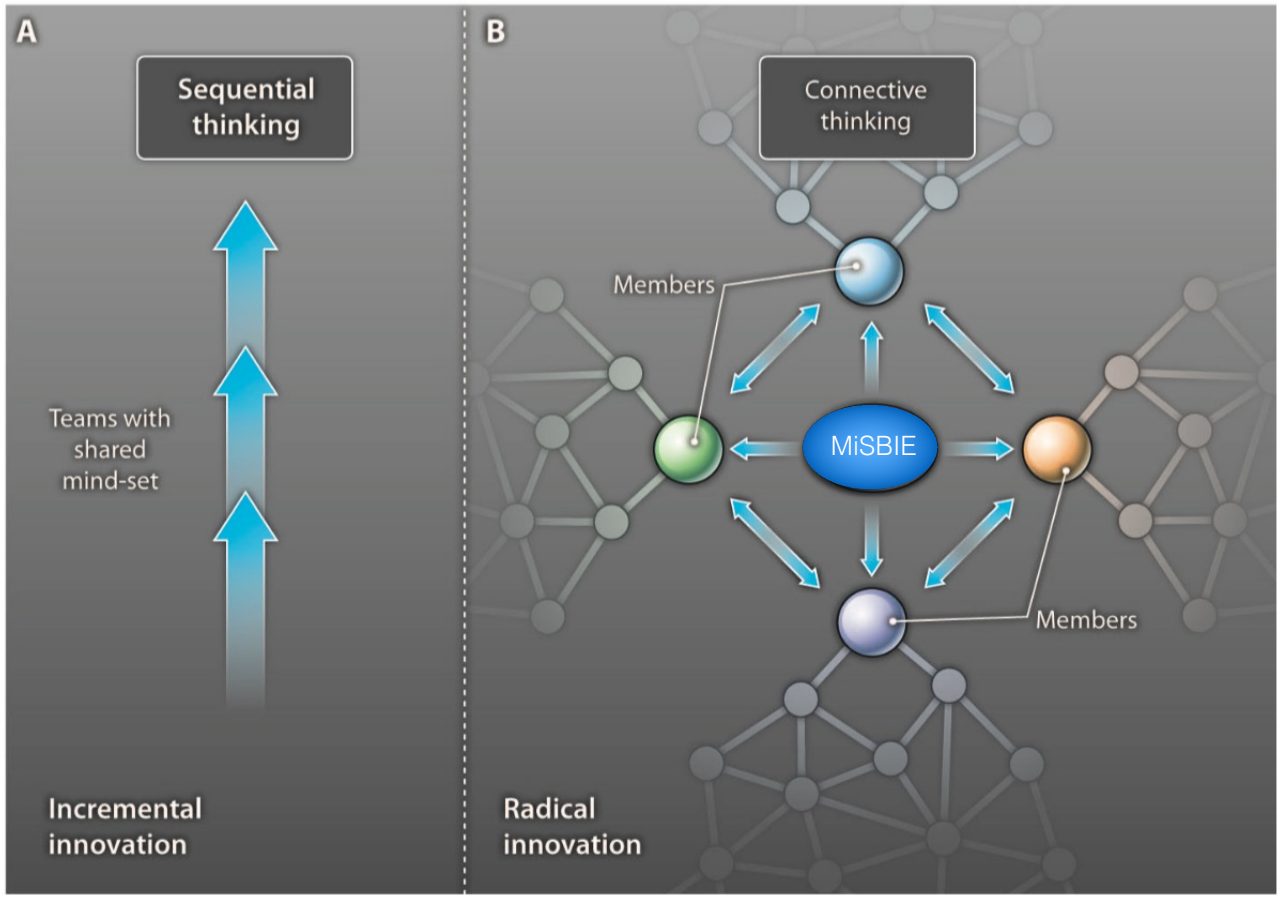
PART III – Future plans and discussion (25 min)

3:35	**Future plans for MiSBIE** – Martin Congratulations to the MiSBIE Team Key scientific questions, planned biomarker analyses, opportunities Pending and planned NIH grants MiSBIE mother paper – inviting "*MiSBIE Group Collaborators*"
3:40	**Using MiSBIE data and samples** – Martin R01 data in NIMH Data Archive (NDA), Omics on GEO, Requesting other data Annual MISBIE symposium *Coordinator: Vanessa Giardino* *Data Manager: Grace Liu*
3:45 15 min	**Questions and Discussion**

4:00	**MiSBIE Wine & Cheese** Behavioral Medicine Conference room – Presbyterian Hospital 15th floor (PH1505)

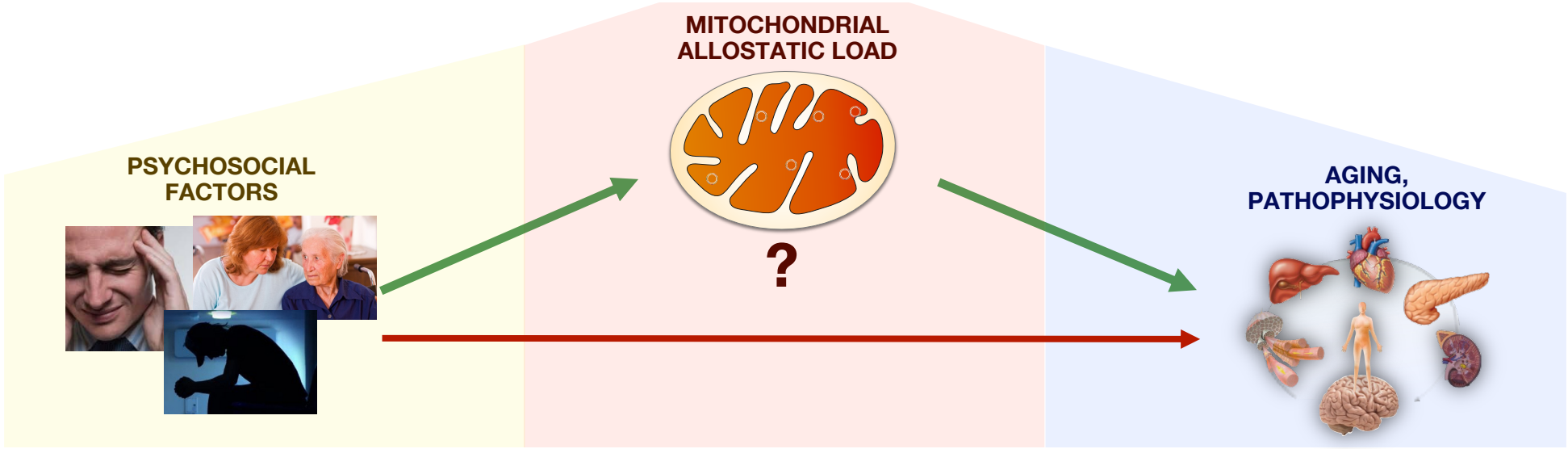
MiSBIE Study Overview

Transdisciplinary science — MiSBIE

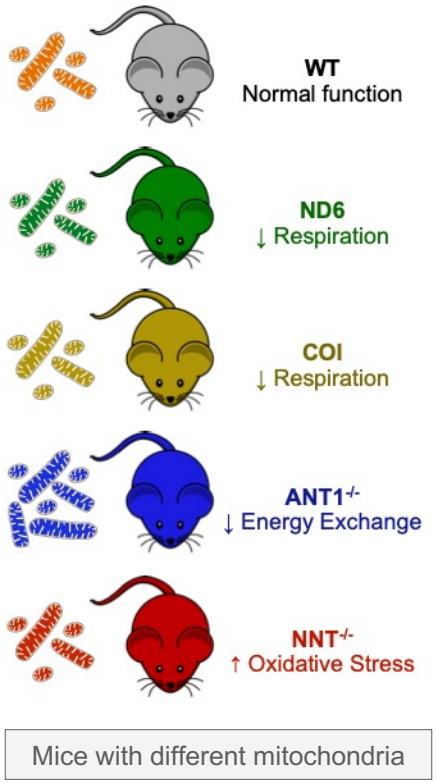


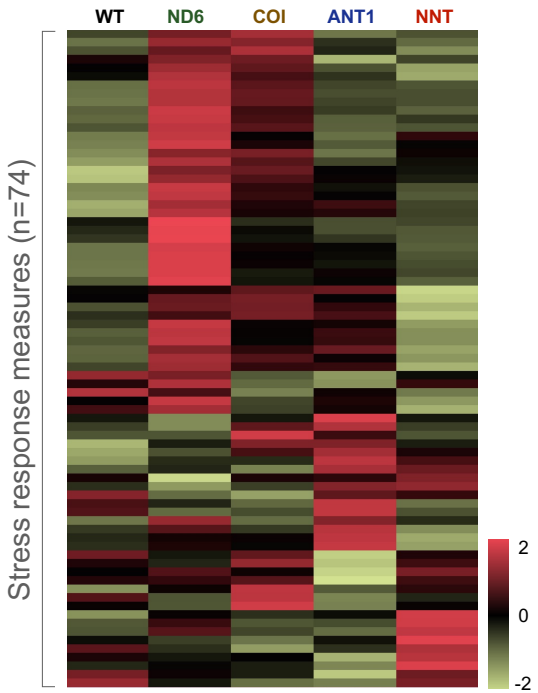
Disis and Slattery. *Science Transl Med* (2010)

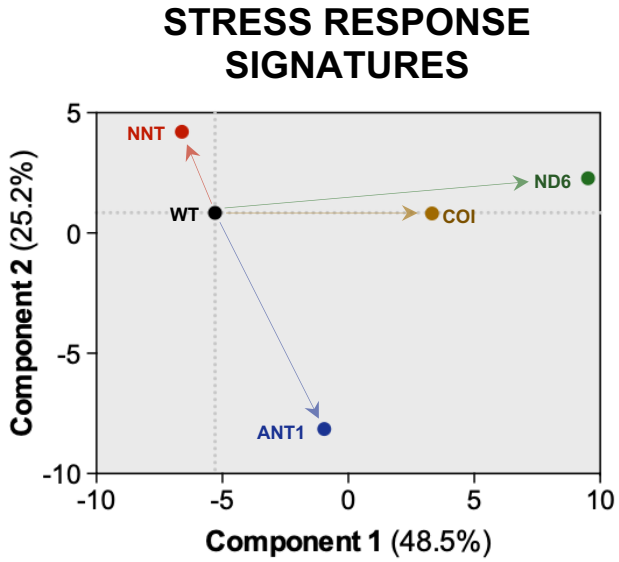
How does **energy** and **mitochondrial biology** influence human psychobiological processes, aging, and the expression of mitochondrial diseases?



Preclinical studies motivating MiSBIE

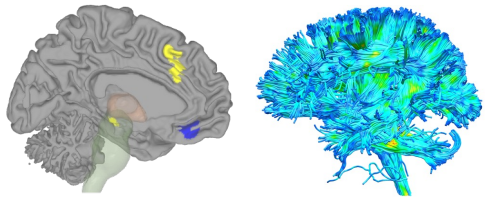






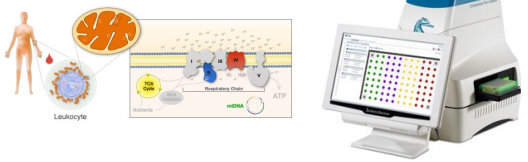
Picard et al. *PNAS* (2015)

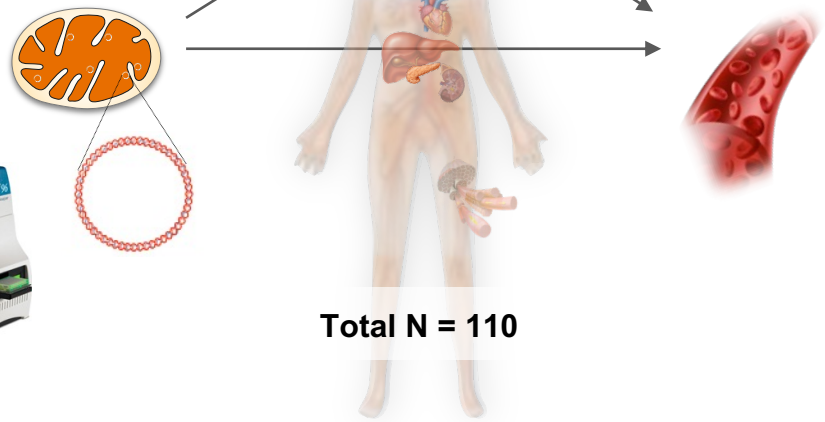
Central MiSBIE hypothesis



Brain structure and function
Neuropsychological function

mtDNA heteroplasmy
Mitochondrial OxPhos
Lymphocytes, Monocytes,
Neutrophils, Platelets

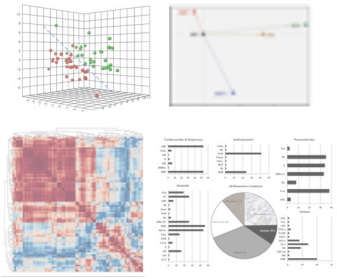




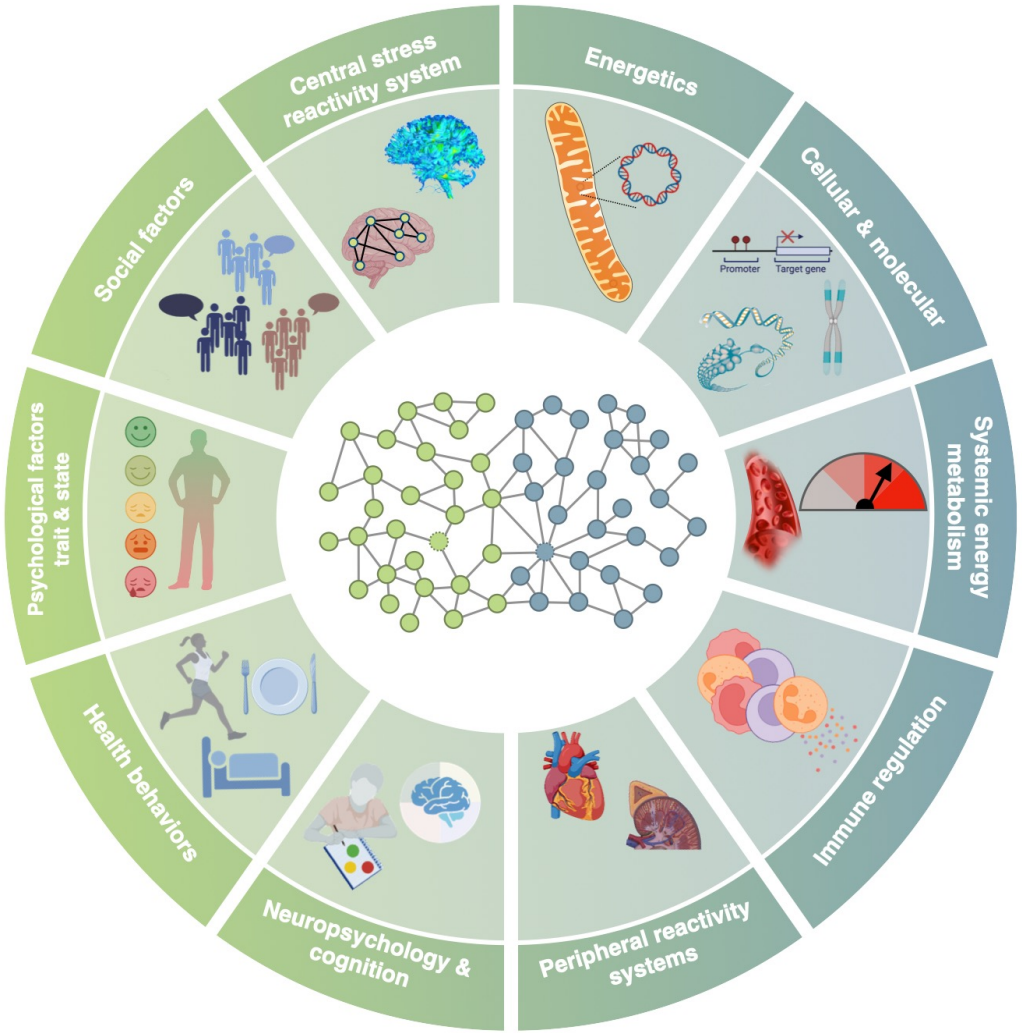
Total N = 110

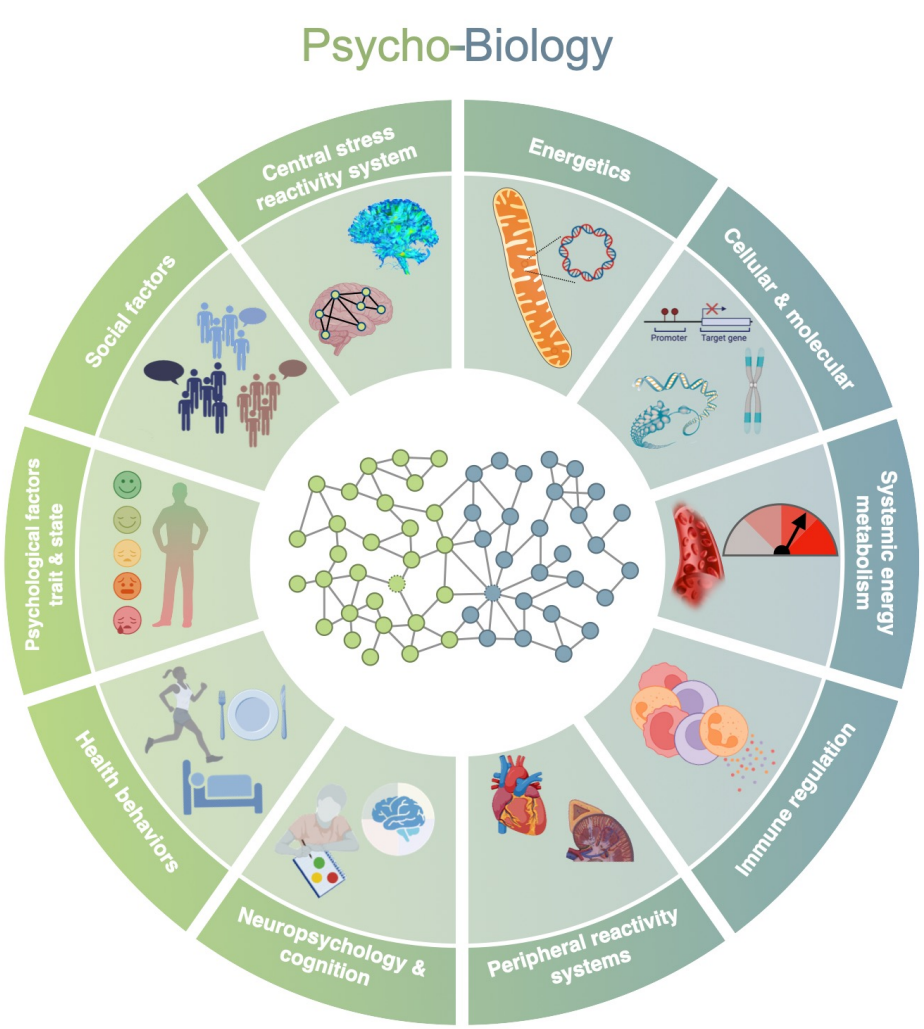
Disease biomarkers
Stress reactivity

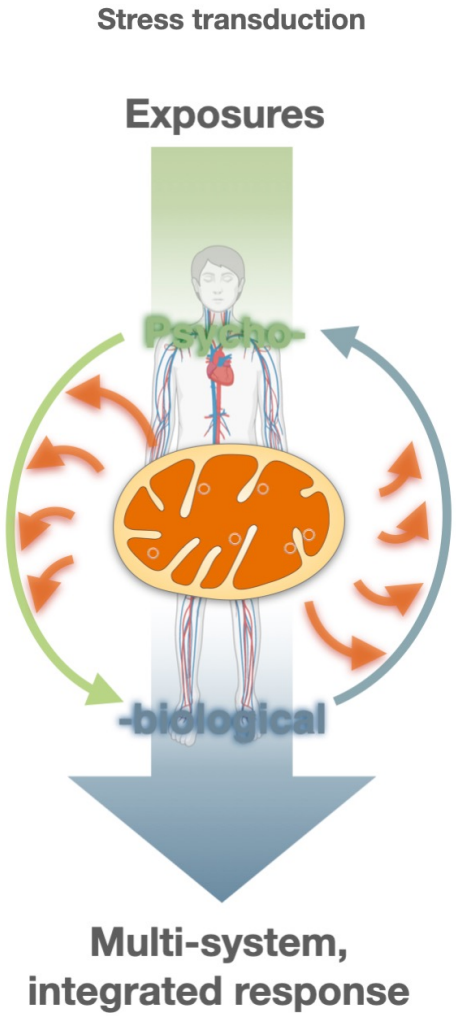
Energy expenditure
e.g., GDF15, FGF21, Lactate,
Alanine, Cytokines, CBC, etc.

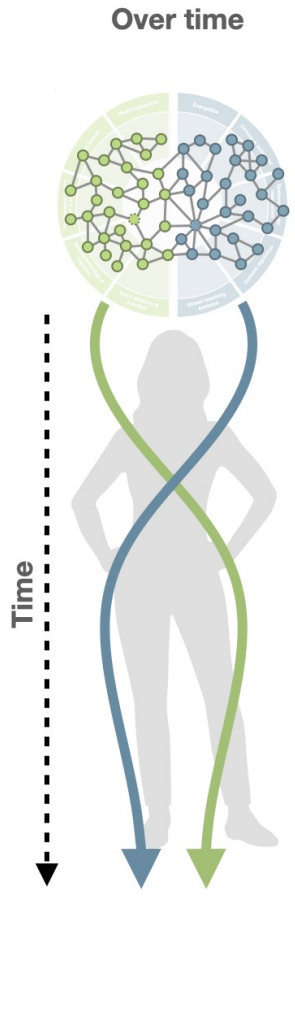


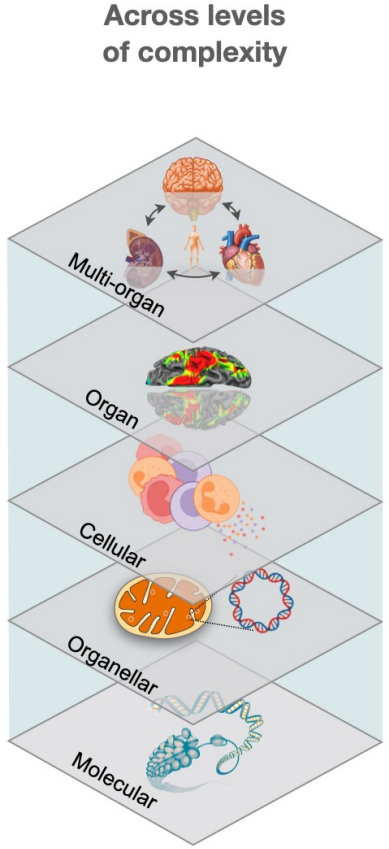
Psycho-Biology

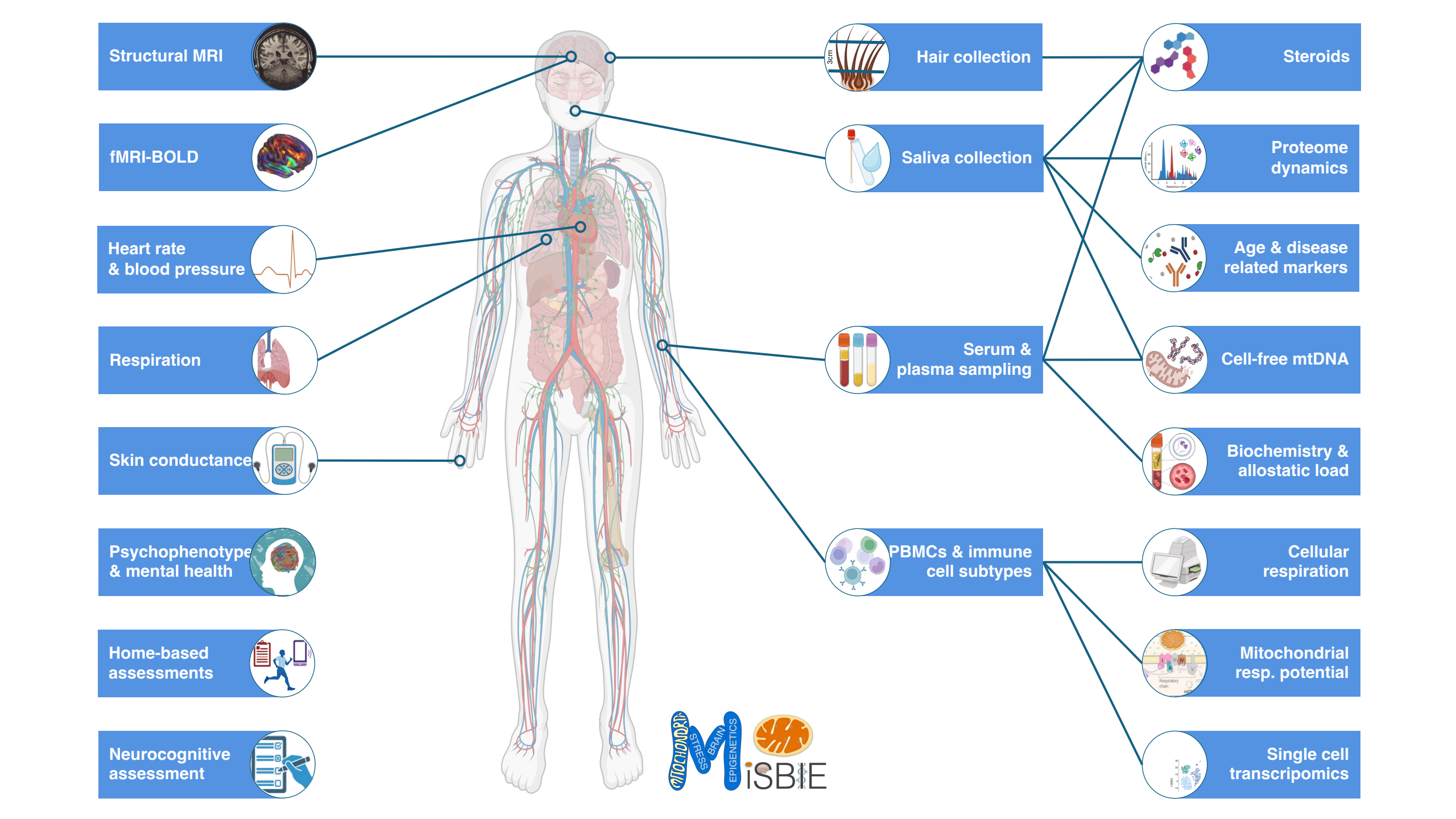



Psycho-Biology
Central stress reactivity system
Energetics
Cellular & molecular
Systemic energy metabolism
Immune regulation
Peripheral reactivity systems
Neuropsychology & cognition
Health behaviors
Psychological factors trait & state
Social factors
Promoter
Target gene


Stress transduction
Exposures
Psycho-
-biological
Multi-system, integrated response


Over time
Time


Across levels of complexity
Multi-organ
Organ
Cellular
Organellar
Molecular


Structural MRI
fMRI-BOLD
Heart rate & blood pressure
Respiration
Skin conductance
Psychophenotype & mental health
Home-based assessments
Neurocognitive assessment
Hair collection
3cm
Saliva collection
Serum & plasma sampling
PBMCs & immune cell subtypes
Steroids
Proteome dynamics
Age & disease related markers
Cell-free mtDNA
Biochemistry & allostatic load
Cellular respiration
Mitochondrial resp. potential
Single cell transcripomics
MITOCHONDRIA
STRESS
BRAIN
EPIGENETICS
iSBSE

Core MiSBIE study design elements

1. Capture **multiple dimensions**, across scales

2. Use **stress + repeated measures** to perturb the system and reveal regulation

3. Precise **mtDNA lesion** *(as in brain lesion for neuroscience)*

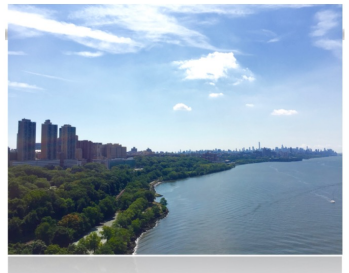
4. **Laboratory** *(precise)* **+ home** *(ecologically valid)*

MiSBIE brochure

The MiSBIE Study

Mitochondrial **S**tress **B**rain **I**maging and **E**pigenetics

Investigating the link between the mind and the body



COLUMBIA UNIVERSITY
IN THE CITY OF NEW YORK

MiSBIE

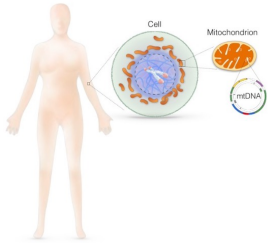
Understanding Mitochondrial Disease

Researchers are just starting to understand the factors that influence aging and the progression of various diseases. Life stress can change the function of the body and influence the development of certain age-related diseases, such as cardiovascular disease and neurodegeneration.

The goal of the MiSBIE study is to understand how an individual's life experience and emotions affect physical health, psychological functioning, and disease risk.

Each cell of the body contains hundreds of mitochondria, which have their own DNA: mitochondrial DNA (mtDNA). Mitochondria produce energy and signals enabling cells to function normally. The MiSBIE study investigates the link between mitochondria, brain function, and different organs to understand their interaction, and *the person as a whole*.

This study also aims to understand the behavior of genes, whether they are turned "on" or "off". This is called "epigenetics" and is measured in DNA from different cells.



Columbia University Medical Center

The MiSBIE study is a research study taking place at the College of Physicians and Surgeons at the **Columbia University Medical Center (CUMC)**, a leading medical institution of care and research.

The partnering Department of Neurology and Department of Psychiatry have a long history of clinical care and research in studying the effects of stress on the body and in mitochondrial disease.

CUMC is located at 168th Street and Broadway in Upper Manhattan, by the Hudson River in New York City, NY.

COLUMBIA UNIVERSITY MEDICAL CENTER

The MiSBIE Study

A two-day visit

This research includes two visits of about 8 hours each. Participants stay overnight at a nearby hotel.

Breakfast and lunch are provided.

Transport

Would you need to travel to NYC? If so, the MiSBIE Team will arrange your travel and reimburse your expenses associated with the study.

Study tests

On Day 1, participants undergo a laboratory evaluation. Saliva and blood samples, and a small clip of hair are collected. Heart rate and blood pressure are monitored. Participants also complete a medical exam with a doctor.

On Day 2, magnetic resonance imaging (MRI, *picture above*) is used to safely measure brain activity, participants complete questionnaires on an iPad, and meet with a neuropsychologist.

Participants also collect saliva at home.

Confidentiality

All results and biological samples are kept **strictly confidential**.

Compensation

Participants who complete the study receive a compensation of $599.

Eligibility

You are eligible if you are a woman or man between the ages of 18 and 60, and willing to visit Columbia University Medical Center (CUMC) for a two-day visit.

We are recruiting individuals with the following mtDNA mutations:

- m.3243A>G (MELAS)
- Single, large scale deletion (CPEO)

The MiSBIE Team

The MiSBIE team is a group of caring clinicians and researchers from academic disciplines including mitochondrial medicine, physiology, neuroscience, epigenetics, and psychology.

For more information about the study, please contact the clinical coordinator (see contact information on the back).

Sponsors

NIH National Institutes of Health

IRVING INSTITUTE FOR clinical and translational research

Contact Information

Questions about the study? Interested to participate?

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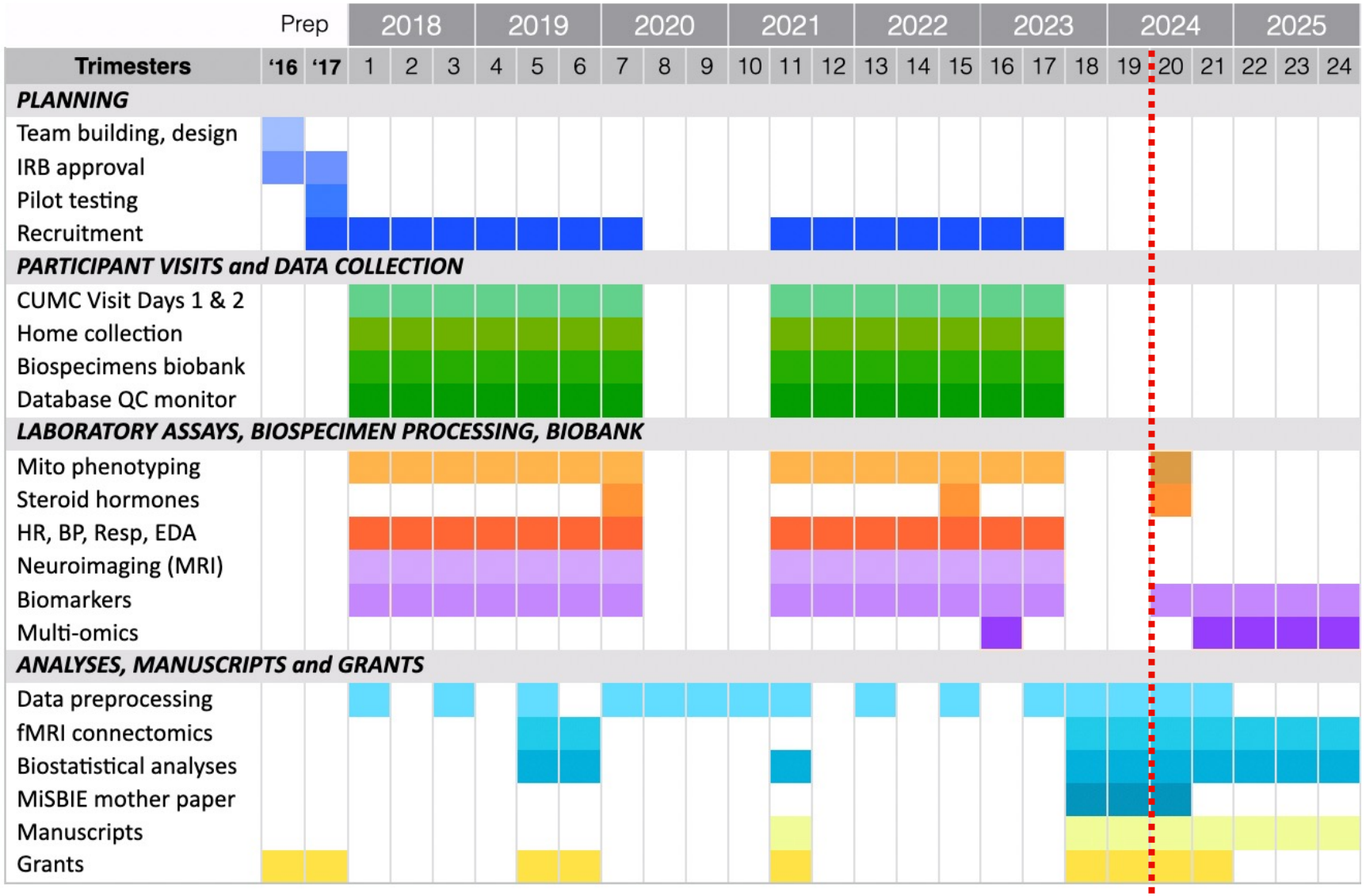
212-342-5767

MiSBIE



CTSA Irving Institute

MiSBIE R21

R01MH113011
PO: Meinecke

MiSBIE parent R01

R01MH122706
PO: Meinecke

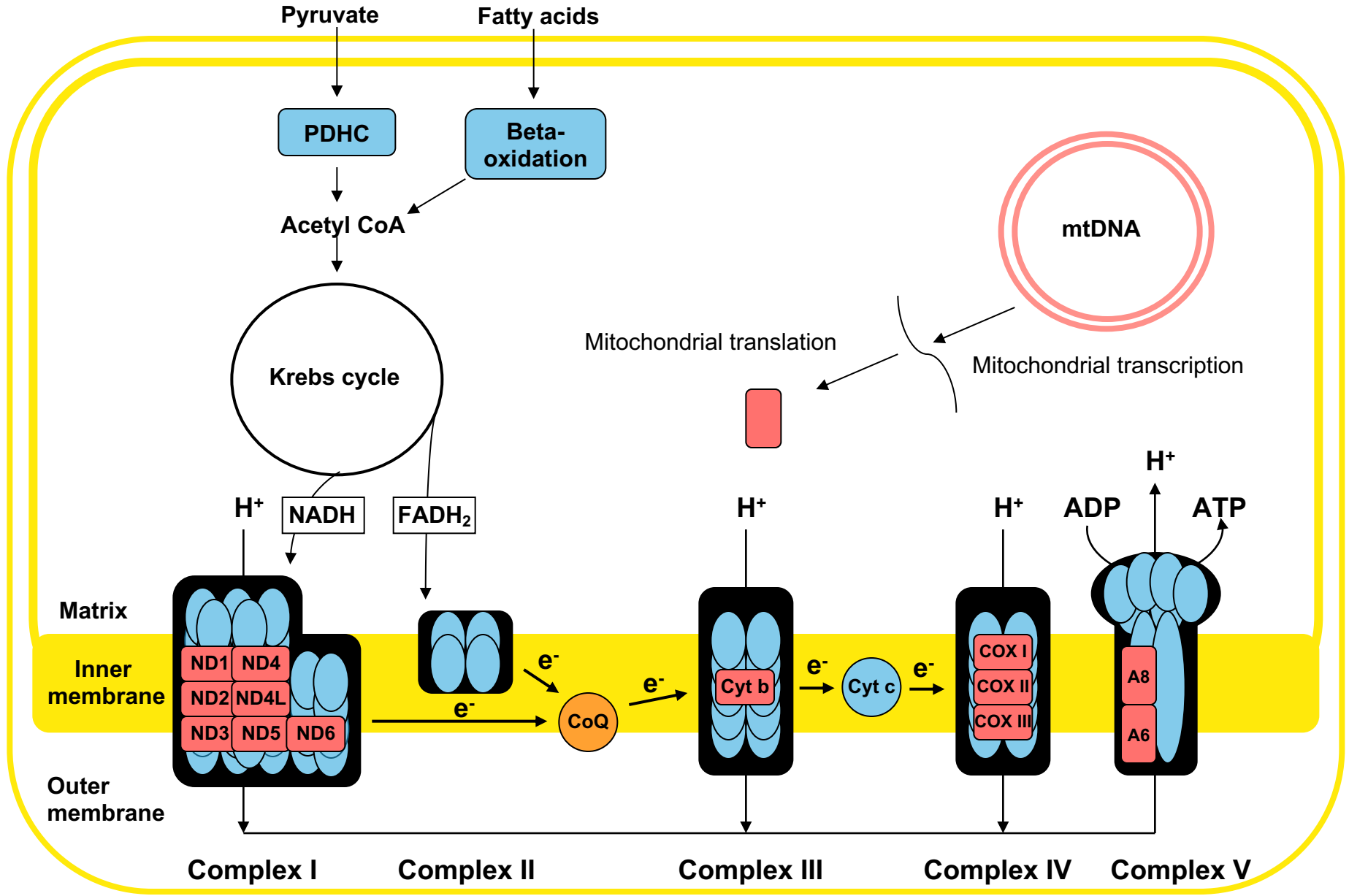
MitoBrain RF1

RF1AG076821
PO: Max Guo

Mitochondrial Diseases

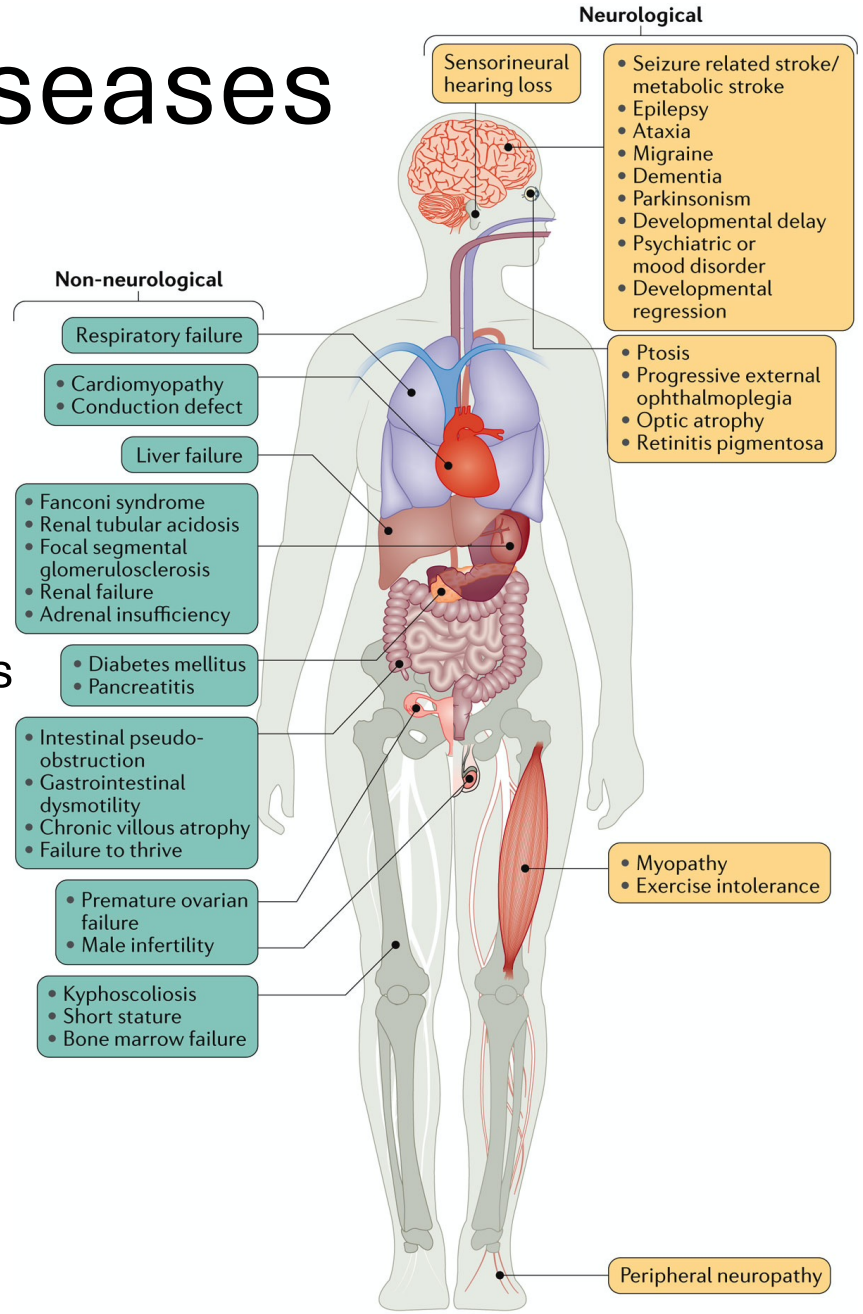
Michio Hirano, MD

Department of Neurology – CUIMC



	Complex I	Complex II	Complex III	Complex IV	Complex V
mtDNA-encoded	7	0	1	3	2
nDNA-encoded	38	4	10	10	12

Mitochondrial Diseases



28% migraines

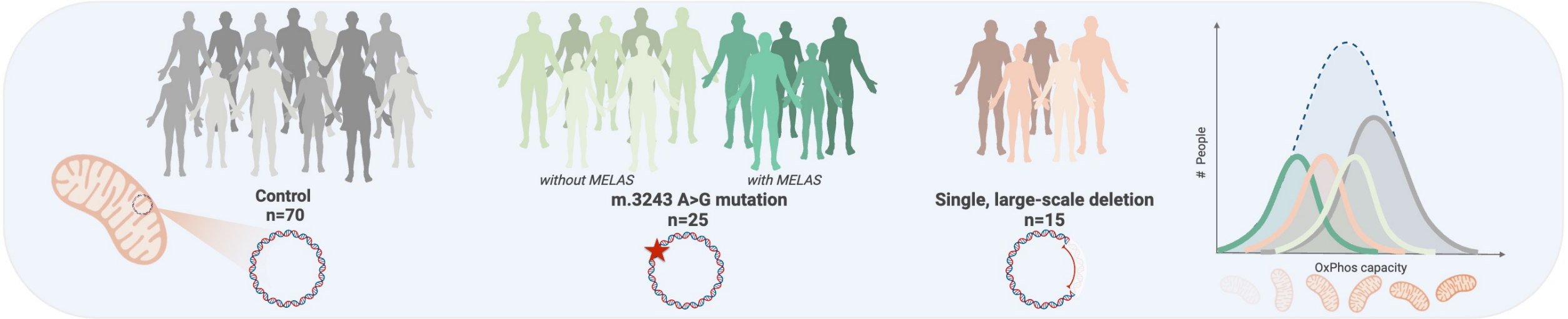
28% psychiatric symptoms

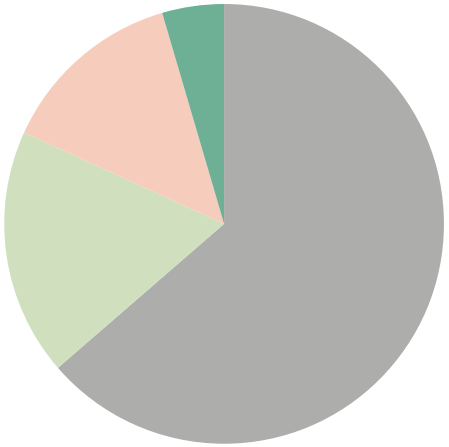
40% ptosis

23% diabetes

Gorman, Chinnery, DiMauro, Hirano, *et al. Nat Rev Dis Primers* 2016

MiSBIE Groups





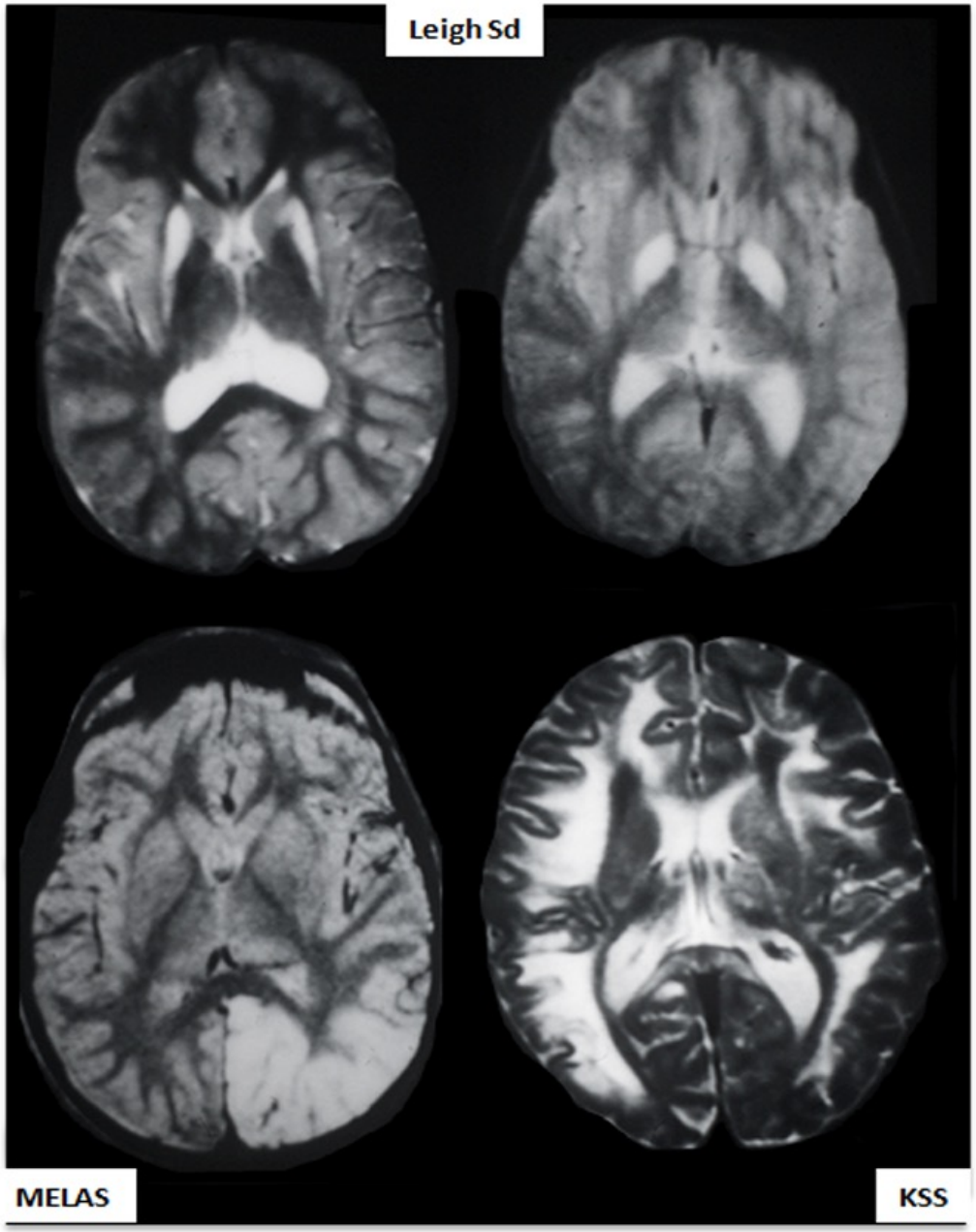
MELAS: mitochondrial encephalomyopathy with stroke-like episodes

CPEO: chronic progressive external ophthalmoplegia

Multisystem disease: ≥3 organs affected, typically brain and skeletal muscle (encephalomyopathy)

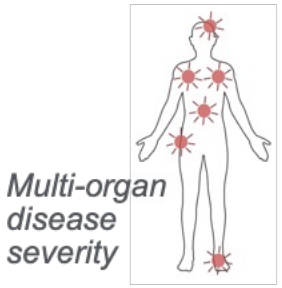
Total n=110, mean age: 38 years, 69% female

Brain MRIs of patients with Leigh syndrome, MELAS, and Kearns-Sayre syndrome

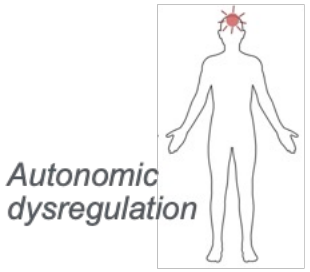


DiMauro, Barca, Hirano
Mitochondrial Encephalomyopathies
Merritt's Textbook of Neurology 2022

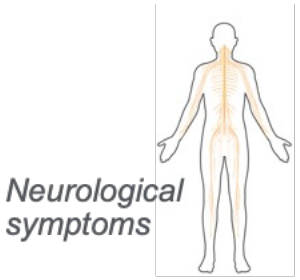
Medical Assessment and Preliminary Data



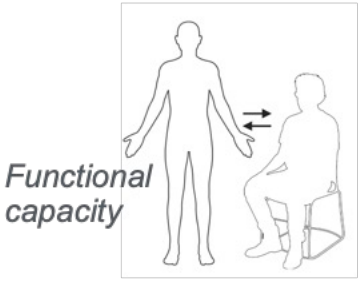
NMDAS Score



COMPASS Score



CNS Score

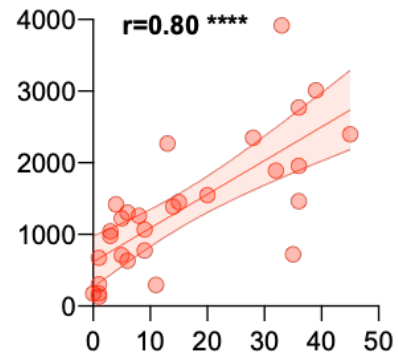


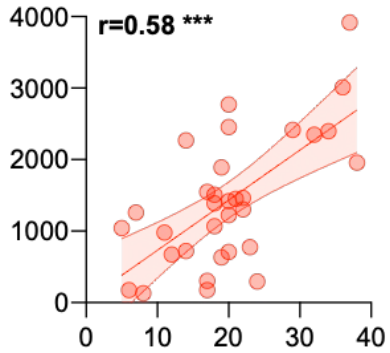
Number of sit-stand in 30s

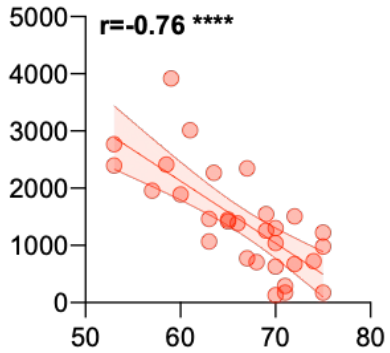
Total Fatigue Score

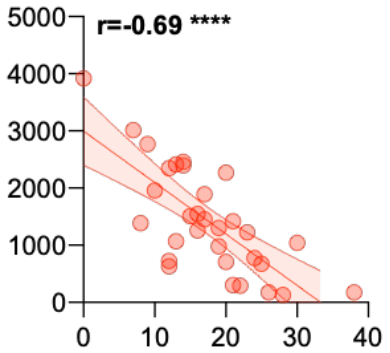
Plasma

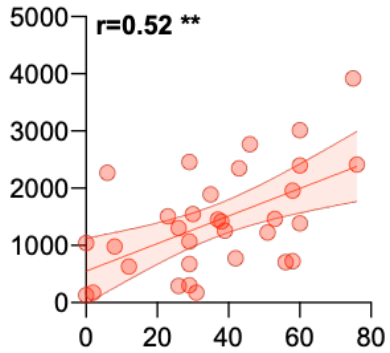
GDF15 (pg/ml)











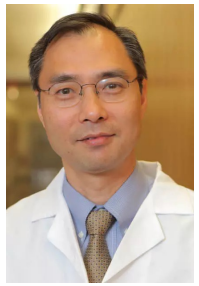
MiSBIE Protocol

Catherine Kelly

Columbia University / Mitochondrial Psychobiology Group

Participant Experience

Recruitment → Participant Arrival



- 32 participants traveled from out of state for their 2-day MiSBIE visit
- 100% of participants stayed in a nearby hotel for a minimum of 2 nights to ensure consistency between visits and ease

NAMDC
North American Mitochondrial Disease Consortium

The Champ Foundation
Fighting against Pearson Syndrome

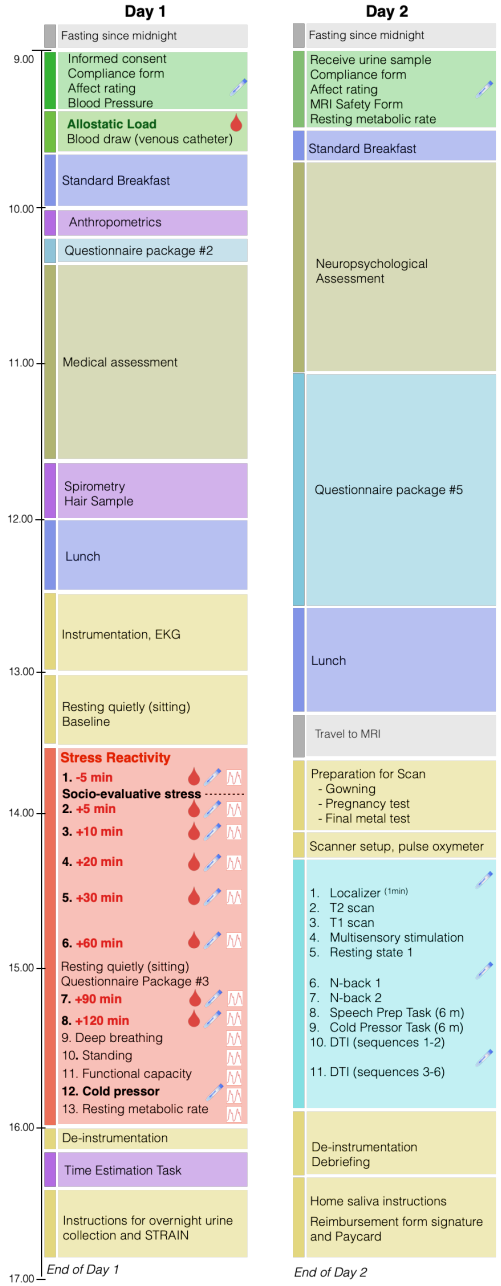
UNITED MITOCHONDRIAL DISEASE FOUNDATION®

Children's Hospital of Philadelphia

COLUMBIA|RecruitMe

MiSBIE

MiSBIE Protocol



Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday

Day 1

Fasting since midnight

9.00

Informed consent
Compliance form
Affect rating
Blood Pressure

Allostatic Load
Blood draw (venous catheter)

Standard Breakfast

10.00

Anthropometrics

Questionnaire package #2

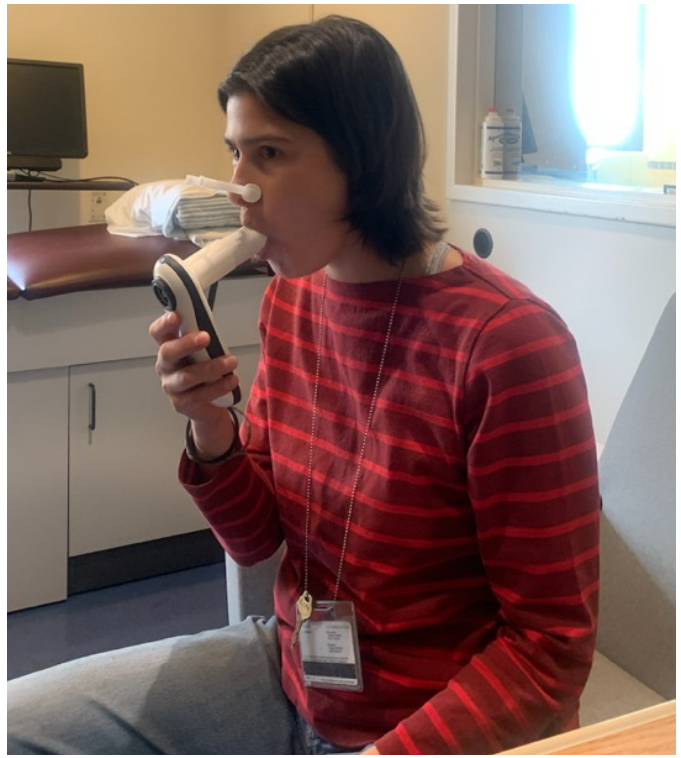
11.00 — Medical assessment

Spirometry
Hair Sample

12.00 — Lunch

Instrumentation, EKG

13.00



Step 3

Step 4

Step 5

Step 6

13.00

Instrumentation, EKG

Resting quietly (sitting)
Baseline

14.00

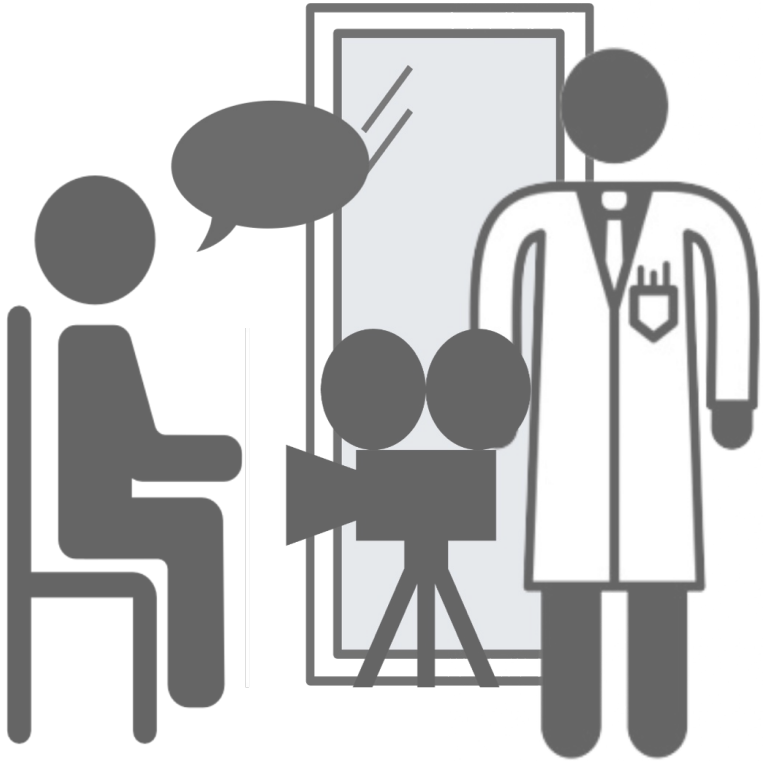
Stress Reactivity

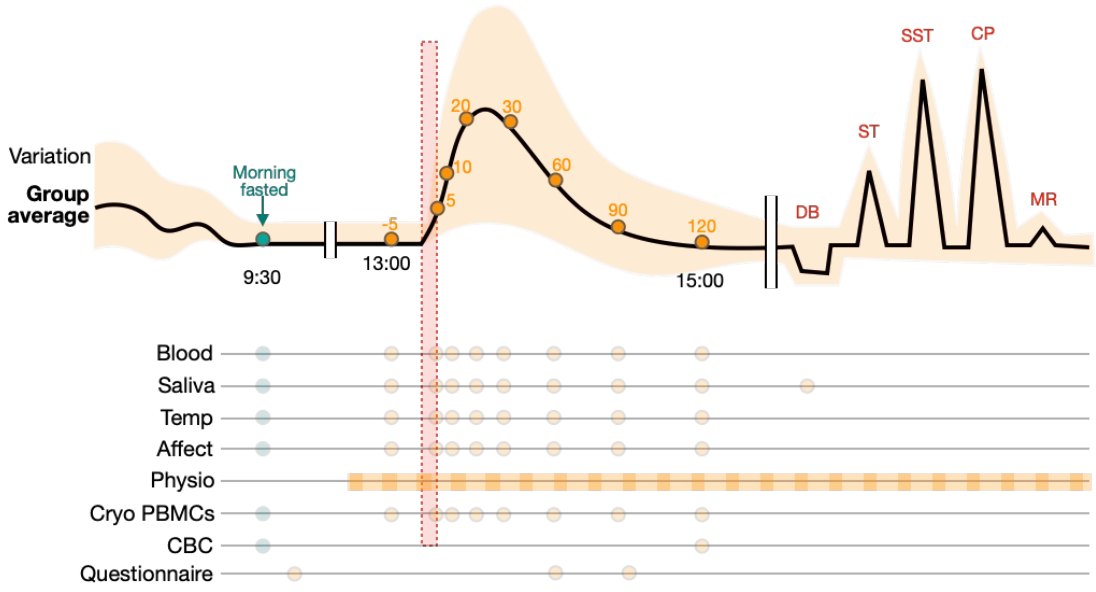
1. -5 min
Socio-evaluative stress
2. +5 min
3. +10 min
4. +20 min
5. +30 min
6. +60 min

15.00

Resting quietly (sitting)
Questionnaire Package #3

7. +90 min
8. +120 min





8. +120 min

9. Deep breathing

10. Standing

11. Functional capacity

12. Cold pressor

13. Resting metabolic rate

16.00

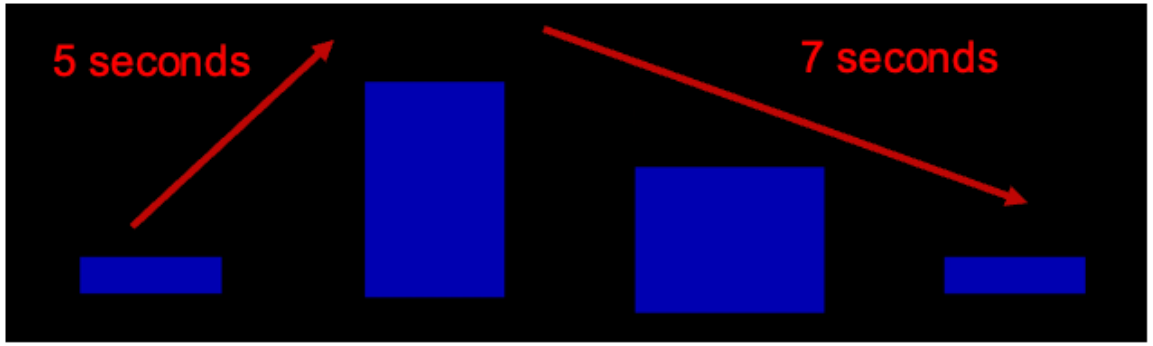
De-instrumentation

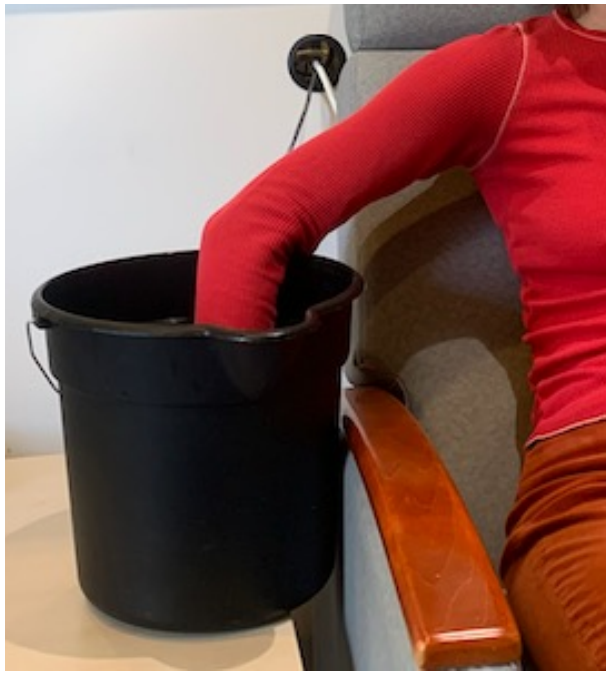
Time Estimation Task

Instructions for overnight urine collection and STRAIN

End of Day 1

17.00





Day 2

- Fasting since midnight
- Receive urine sample
  Compliance form
  Affect rating
  MRI Safety Form
  Resting metabolic rate
- Standard Breakfast
- Neuropsychological Assessment

DELIS • KAPLAN D-KEFS™ Executive Function System™

WASI–II® WECHSLER ABBREVIATED SCALE OF INTELLIGENCE®-SECOND EDITION

NAB Neuropsychological Assessment Battery®

RBANS® UPDATE

MiSBIE Mitochondria Stress Brain Epigenetics

Questionnaire package #5

Lunch

Travel to MRI

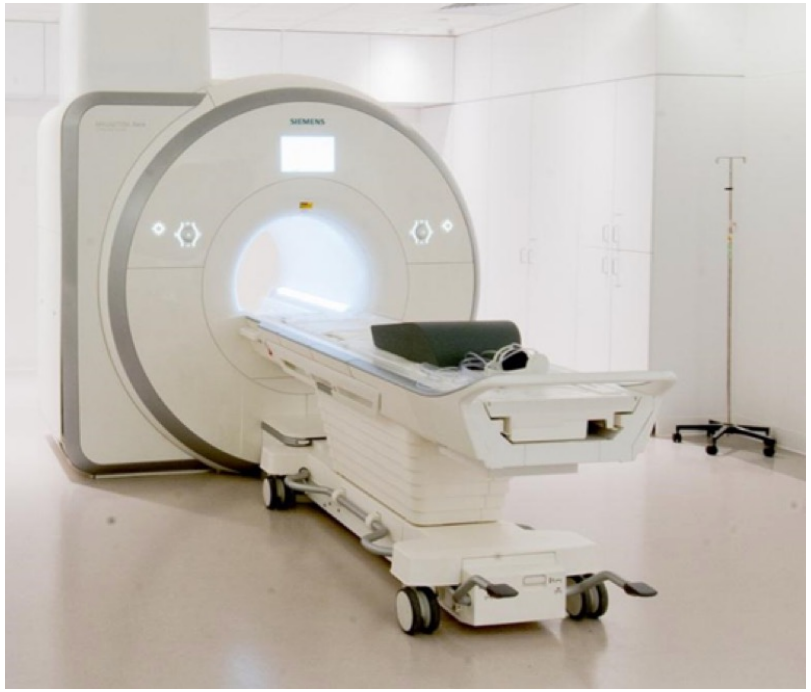
Preparation for Scan
- Gowning
- Pregnancy test
- Final metal test

Scanner setup, pulse oxymeter

1. Localizer (1min)
2. T2 scan
3. T1 scan
4. Multisensory stimulation
5. Resting state 1

6. N-back 1
7. N-back 2
8. Speech Prep Task (6 m)
9. Cold Pressor Task (6 m)
10. DTI (sequences 1-2)

11. DTI (sequences 3-6)



1.	**Scout**	**(0:14 min)**
2.	**T2 scan**	**(11:15 min)**
3.	**T1 scan**	**(5:21 min)**
4.	**Multisensory**	**(5:00 min)**
5.	**Resting state 1**	**(10:51 min)**

Affect 13 **Saliva 13**

6.	**N-back task 1**	**(4:35 min)**
7.	**N-back task 2**	**(4:35 min)**
8.	**Story task**	**(6:07 min)**
9.	**Arm wrap**	**(6:07 min)**
10.	**DTI** (seq 1-2)	**(6:27 min)**

Affect 14 **Saliva 14**

12.	**DTI** (seq 3-6)	**(14:37 min)**

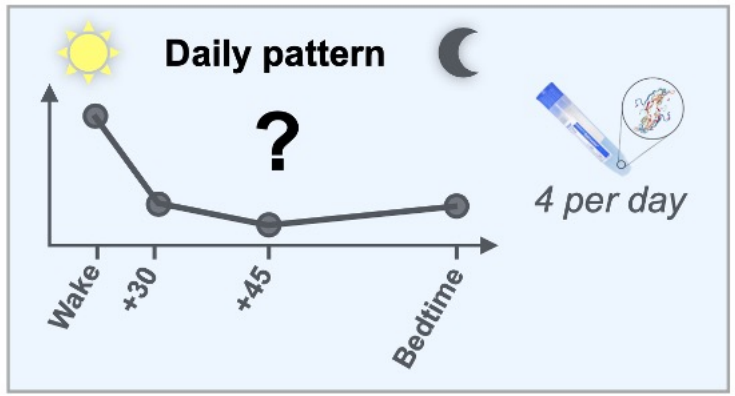
De-instrumentation

De-instrumentation
Debriefing

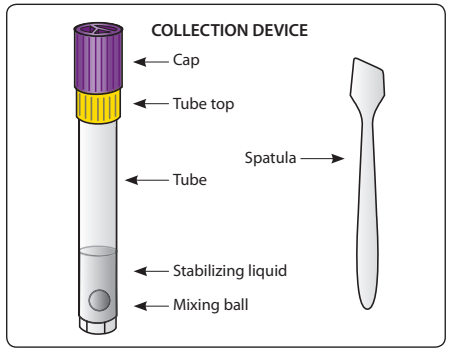
Home saliva instructions

Reimbursement form signature and Paycard

End of Day 2

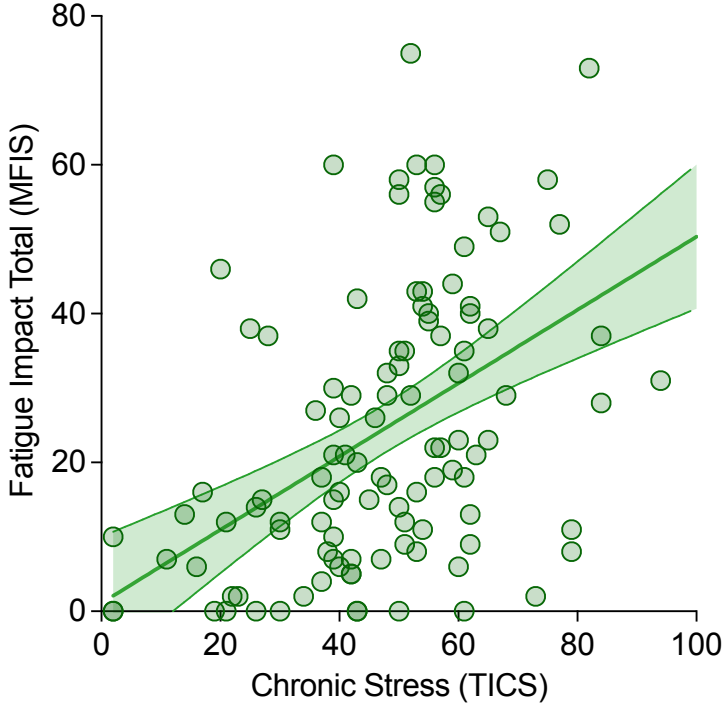


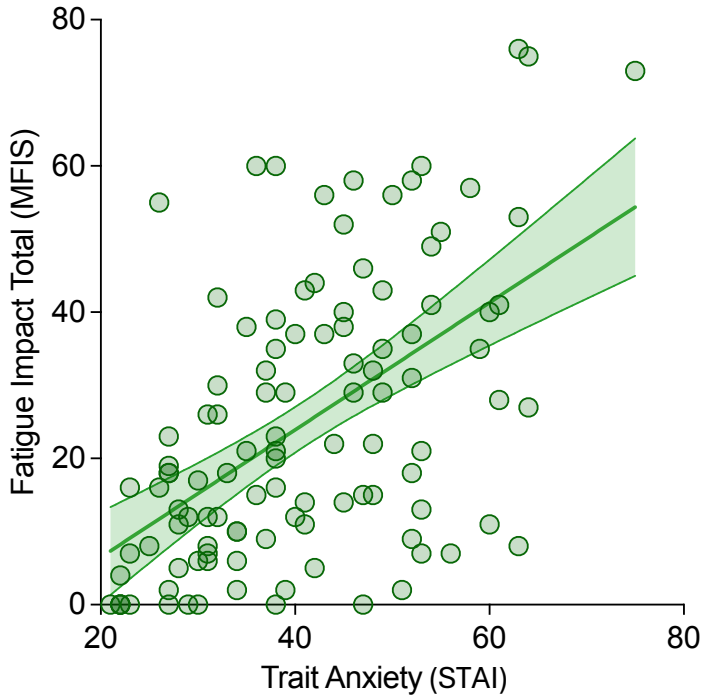
OMNIgene®·GUT
For microbiome




Sampling approaches
Biospecimens
Self-reported assessments and questionnaires
Neuroimaging and neuropsychological testing
Repeated stress reactivity measures
Home based diurnal sampling
Population
Control
n=70
without MELAS
with MELAS
m.3243 A>G mutation
n=25
Single, large-scale deletion
n=15
# People
OxPhos capacity
Data modalities
Oxygen consumption rate
ATP
Time
Mitochondrial phenotyping and body biomarkers
Self rated health
Stress
Memory complaints
Sleep quality
Fatigue
Social support
Psychosocial factors and personality
Brain structure, function, and connectivity
Relative change
Time
Stress reactivity profiles
mg/ML
Time of Day
Hormonal, metabolic, and physiological rhythms

Preliminary Results





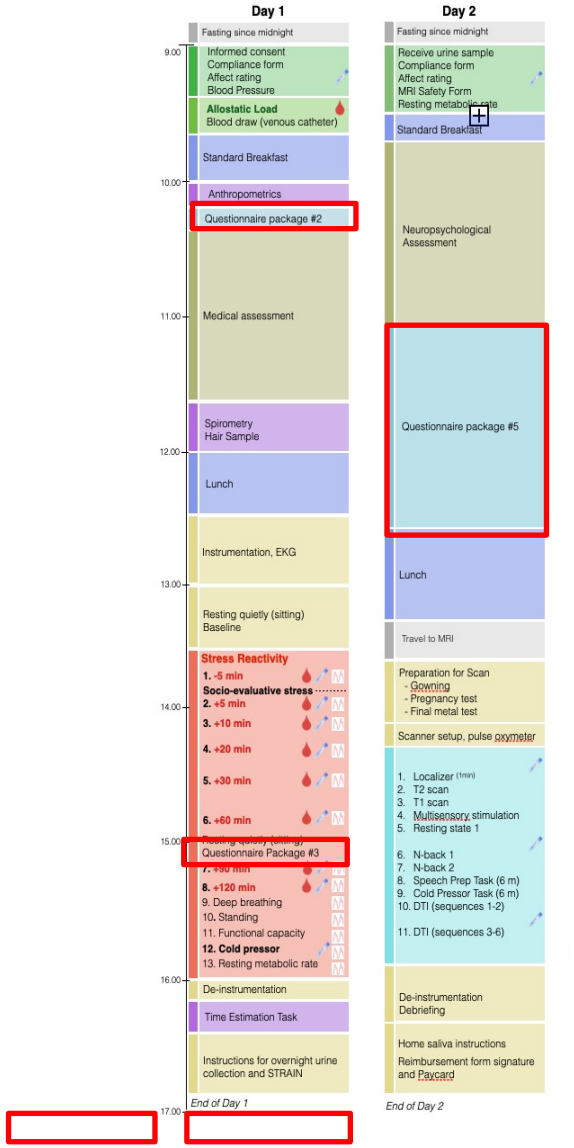
Psychosocial assessments and questionnaires

Caroline Trumpff

Columbia University Irving Medical Center

Mitochondrial Psychobiology Lab

MISBIE study questionnaires



- Hotel packages: evening Day 0 & Day 1(mDES and DISE and others, on paper).
- 3 packages during the two-day visit (Day 1 and 2) (ipad, redcap)
- Stress protocol: affect rating (stressed, nervous, angry, calm, relaxed, energetic or wornout), PASA selected items.
- AM and PM, home-based saliva collection (3 days), (ipad, redcap): affect rating, mDES and DISE

Demographics

Age, sex, ethnicity, income, level of education, language

Social life

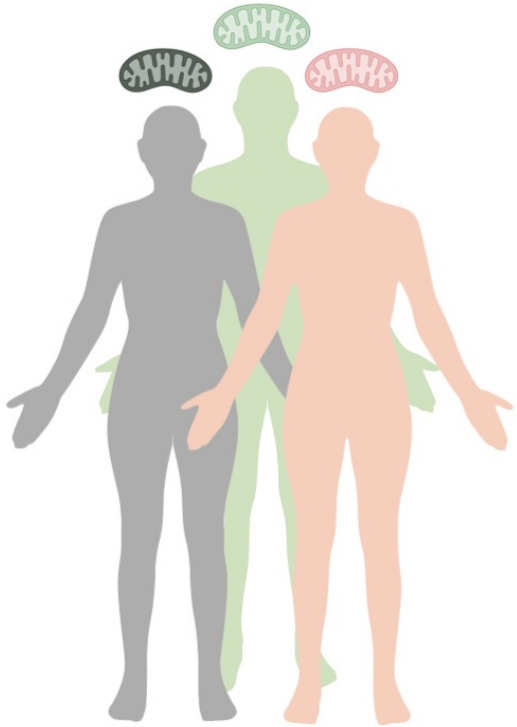
Perceived social status (Mc Arthur ladder)
Social Support (SSQ)
Perceived social support (PSSQ)
Couples Satisfaction (CSI-16)
Loneliness (ULS-8)

Personality

Personality (NEO-SF)
Gender Role (BSRI-L)
Personal Well-Being (PWB)
Sense of Coherence (SOC)

Health related-behavior

Dietary intake (FFI)
Added fat and sugar intake (SQFFS) vitamins and supplements (MESA)
Physical activity (L-Cat, IPAQ)
Sleep (PSQI)
Morningness (MEQ)



Stress and Affect

Emotions (mDES, PSA)
Perceived Stress (DISE, PSS)
Chronic Stress (TICS),Daily Hassles (DHS)
Life events (LEQ), Life adversity and childhood Trauma (STRAIN, CTQ)

Physical Symptoms

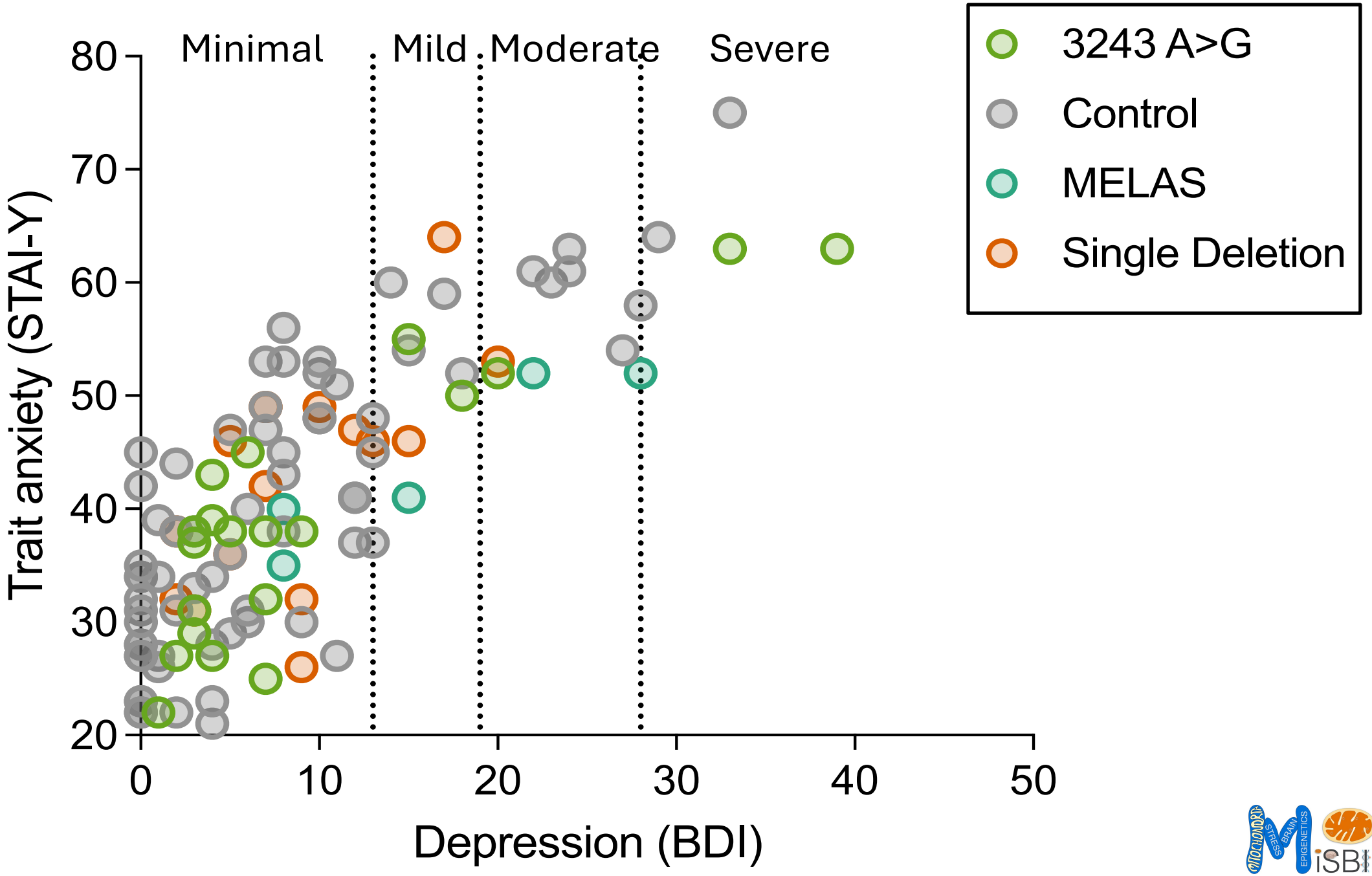
Fatigue (MFIS, PFS)
Autonomic Symptoms (COMPASS 31)
Illness Perception (BIPQ)
Self-rated health (SRH)
Memory Complaints (MCC)

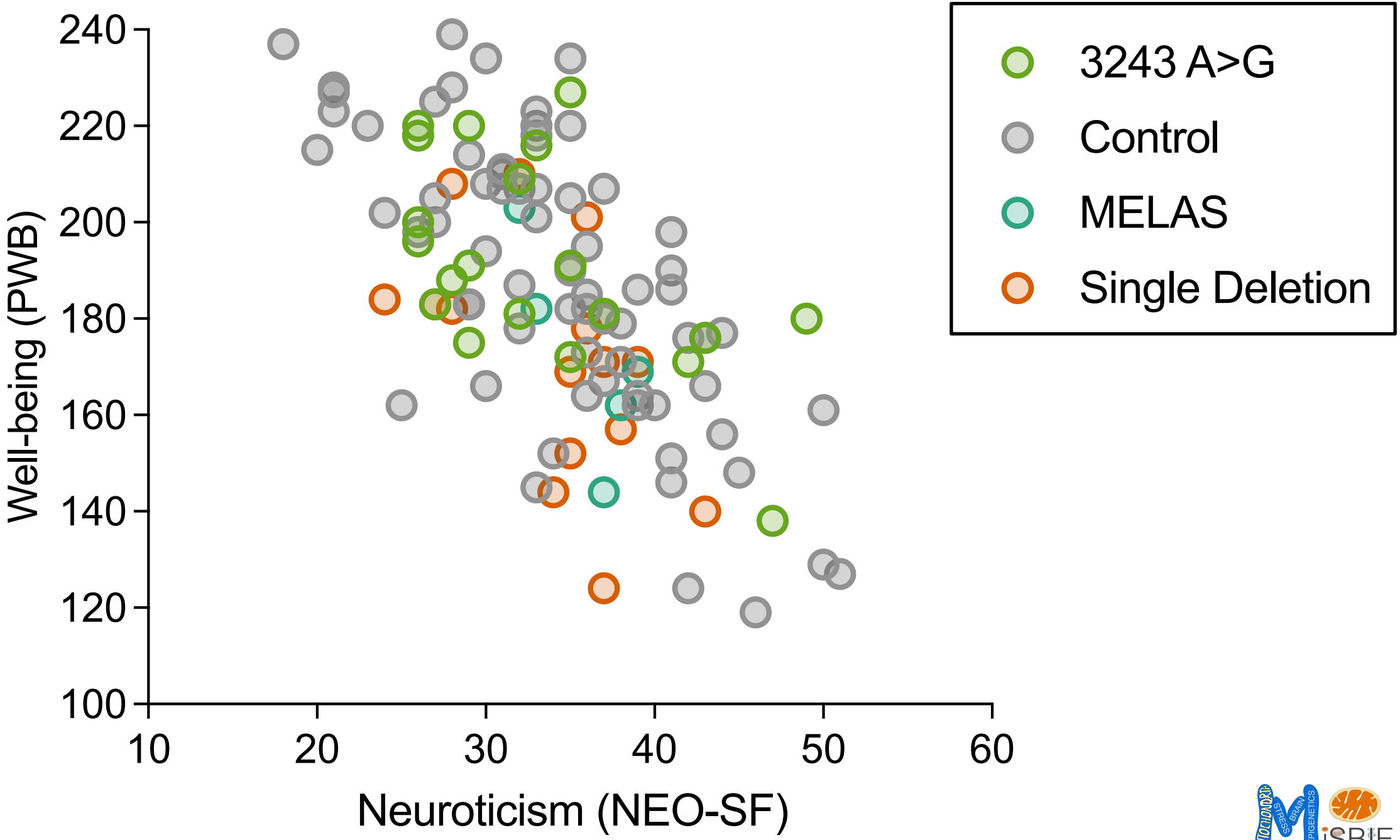
Aging

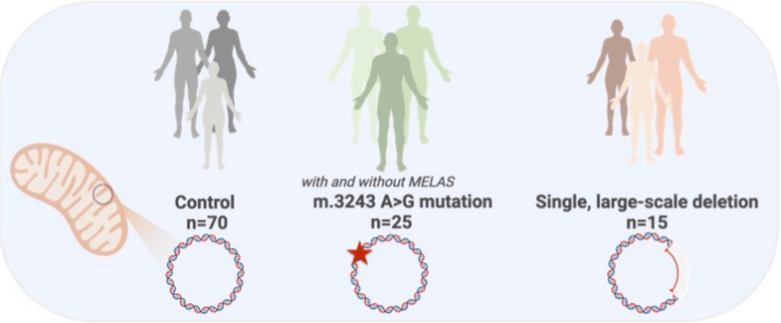
Self Perception of Aging
Perceived age

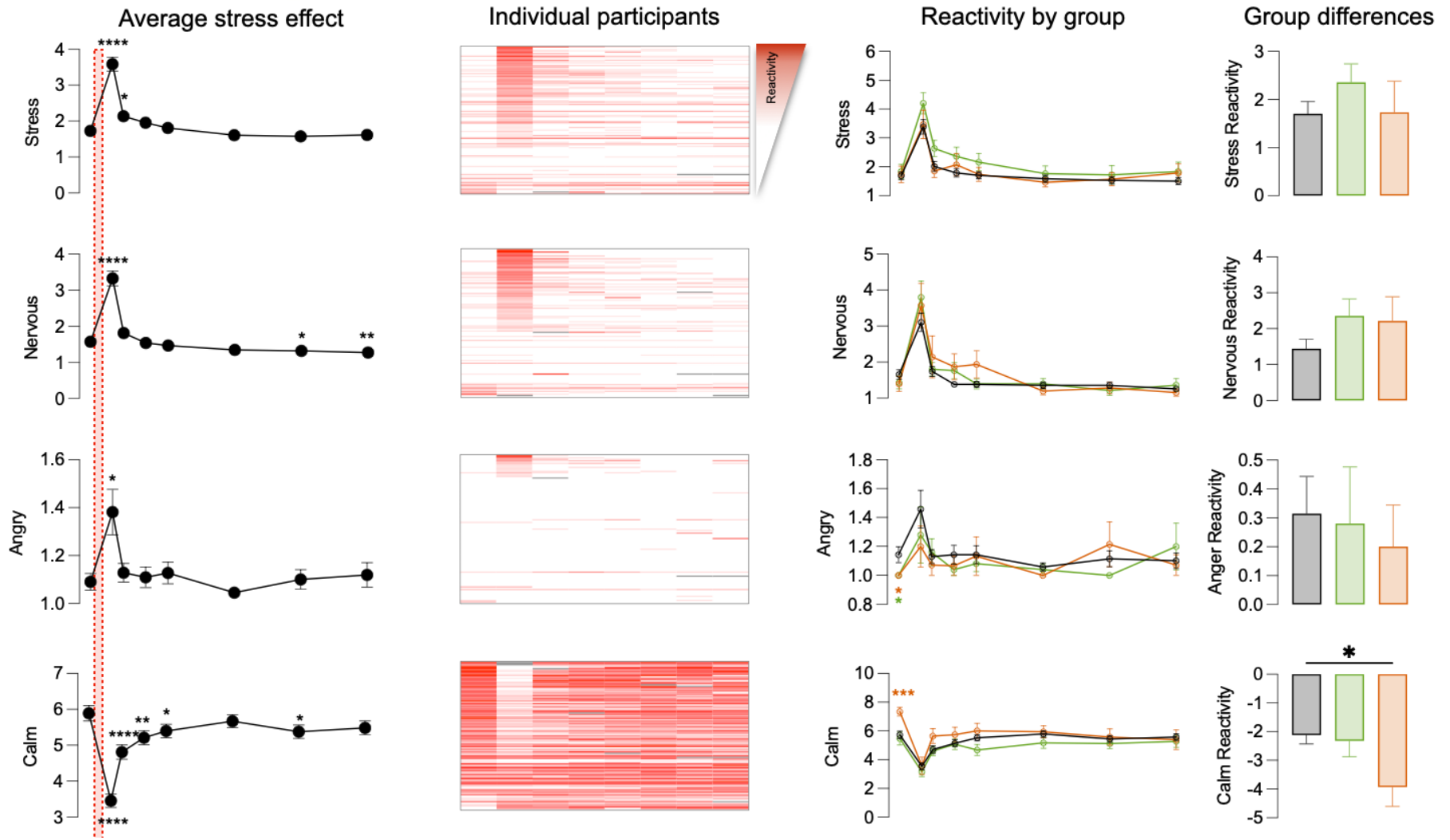
Mental Health

State and Trait Anxiety (STAI-Y)
Depressive Symptoms (BDI)
Burnout (MBI)
PSTD (PCL-C)
Mental health symptoms (DSM XC)


Minimal
Mild
Moderate
Severe
3243 A>G
Control
MELAS
Single Deletion
Trait anxiety (STAI-Y)
Depression (BDI)
80
70
60
50
40
30
20
0
10
20
30
40
50


240
220
200
180
160
140
120
100
Well-being (PWB)
10
20
30
40
50
60
Neuroticism (NEO-SF)
3243 A>G
Control
MELAS
Single Deletion


with and without MELAS
Control
n=70
m.3243 A>G mutation
n=25
Single, large-scale deletion
n=15


Average stress effect
Individual participants
Reactivity by group
Group differences
Stress
Nervous
Angry
Calm
Reactivity
Stress Reactivity
Nervous Reactivity
Anger Reactivity
Calm Reactivity

Questions?

Columbia University Irving Medical Center

Mitochondrial Psychobiology Lab

Part II

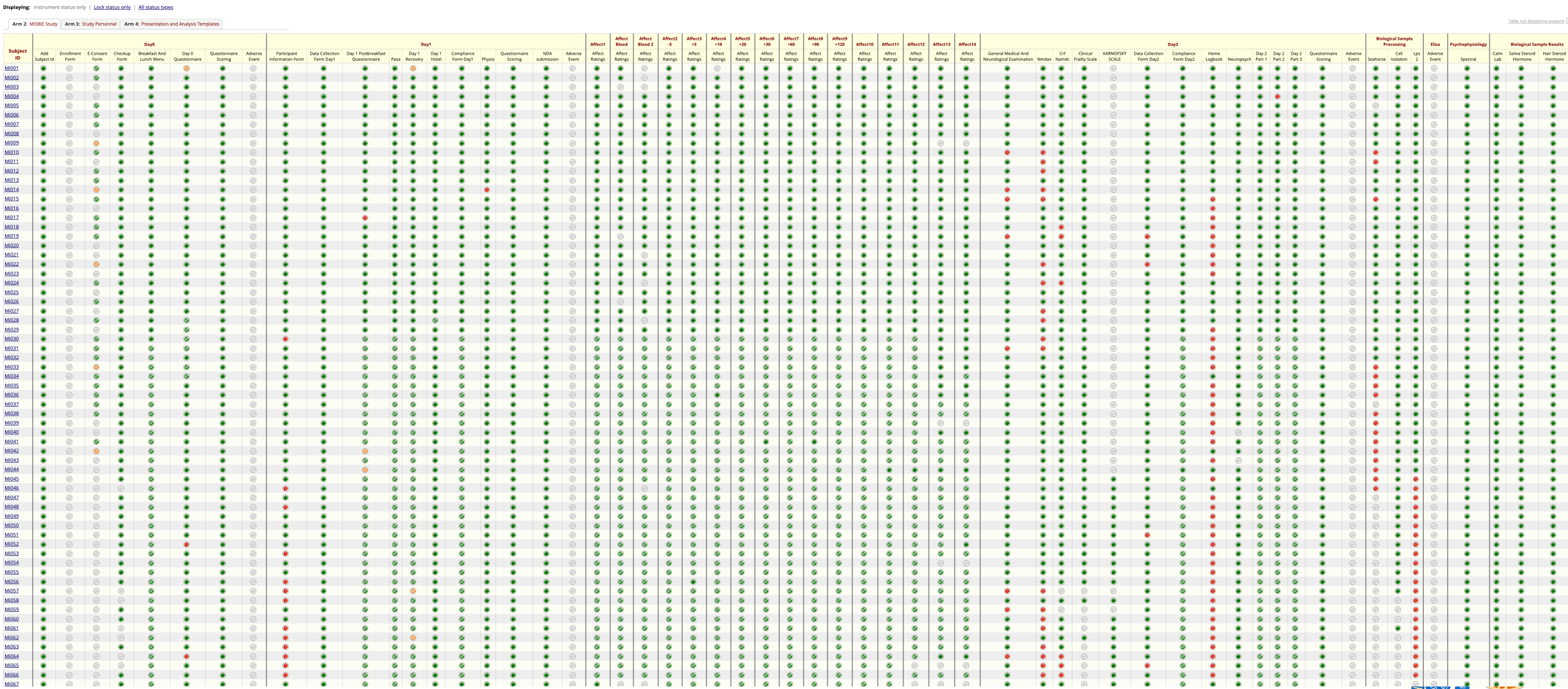
Procedures, preliminary data, and results

MiSBIE Database

Grace Liu

Columbia University / Division of Behavioral Medicine

MiSBIE Database overview



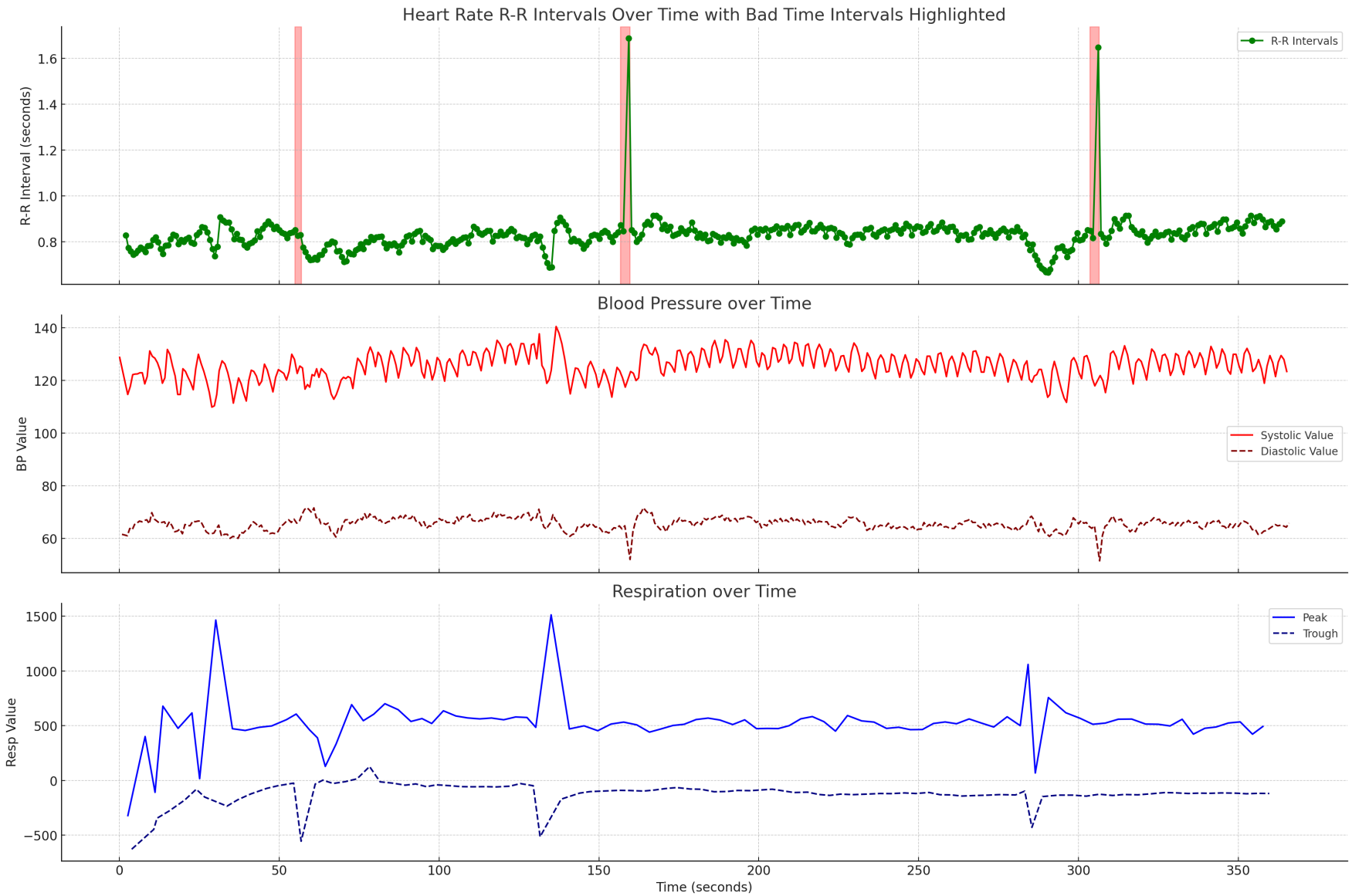
Overview and dimensionality of the MiSBIE study database.

Category	Instruments and forms	Scales and subscales	Items
Screening[1]	6	5	70
Medical assessment[2]	5	30	226
Anthropometric and other data[3]	2	3	80
Study-specific tasks[4]	1	4	24
Psychophysiology data[5]	1	82	1652
Time estimation[6]	1	2	57
Neuropsychological[7]	9	19	123
MRI procedural[8]	1	N/A	59
Neuroimaging[9]	4	16	71
Questionnaires[10]	45	134	1886
Biospecimen collection [11]	2	3	67
Biospecimen processing[12]	3	14	182
Biospecimen results[13]	3	16	229
Home based collection[14]	2	6	288
Procedural/study logistics[15]	2	N/A	66
CF DNA	1	4	925
Other[16]	2	1	17
Total	85	319	5,951

Eligibility screening and enrollment forms including phone screening, eligibility checklist, genetic counseling

Medical assessment on Day 1 including clinical scales: NMDAS, Crf Namdc, Clinical Frailty Scale, Karnofsky Scale
Collected throughout Day 1 and 2 including blood pressure, heart rate, percent body fat, resting energy expenditure
Records of timing and tasks administered on Day 1 including cold pressor, sit-stand task, and deep breathing
Pre-processed continuous physiological data from Day 1 (heart rate, blood pressure, skin conductance, ventilation)
Task to quantify time perception, includes interval estimation and production tasks administered on Day 1
Battery of tests administered on Day 2 including DKEFS, WASI-II, TOPF, RBANS, NAB
Documentation of imaging procedures including metal screening, instrumentation, discomfort ratings, scan timing
Initial measures derived from structural and functional MRI including volumetric measurements, cortical thickness, …
Questionnaires administered, 11 questionnaire packages are distributed over the study period
Documentation of blood, urine, buccal cell, and saliva collection
Procedural documentation of biological sample processing and quality for urine, saliva, buccal cell, and blood
Biofluid analytes including steroid hormones, mitochondrial parameters, PBMCs levels
Home sample collection including sampling instructions, questionnaires, biospecimen collection
Records of visit timing and detailed procedural checklist
Suicide severity rating scale, Day 1 and Day 2

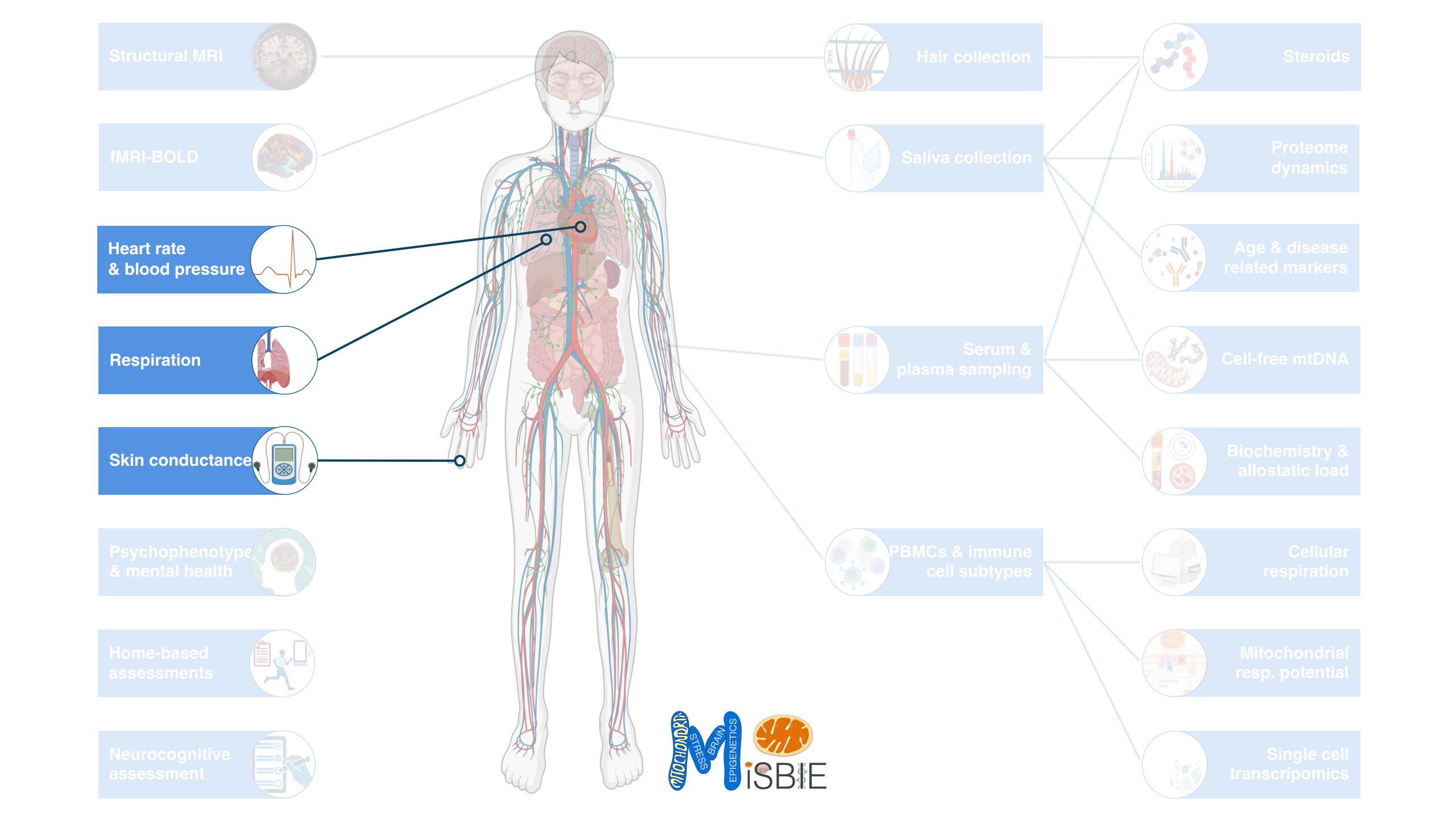
Spectral analysis/processing



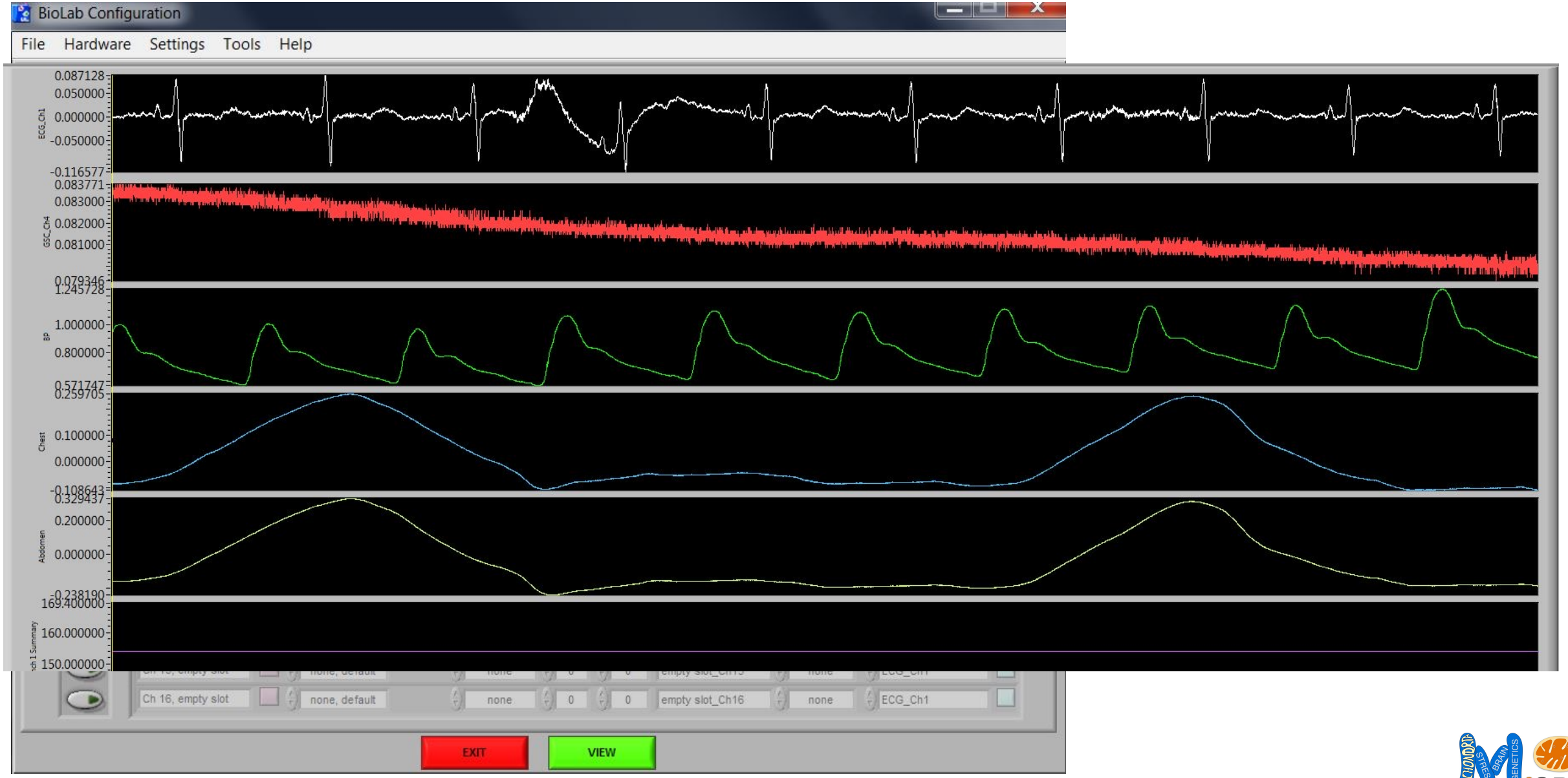
Stress Psychophisiology Session

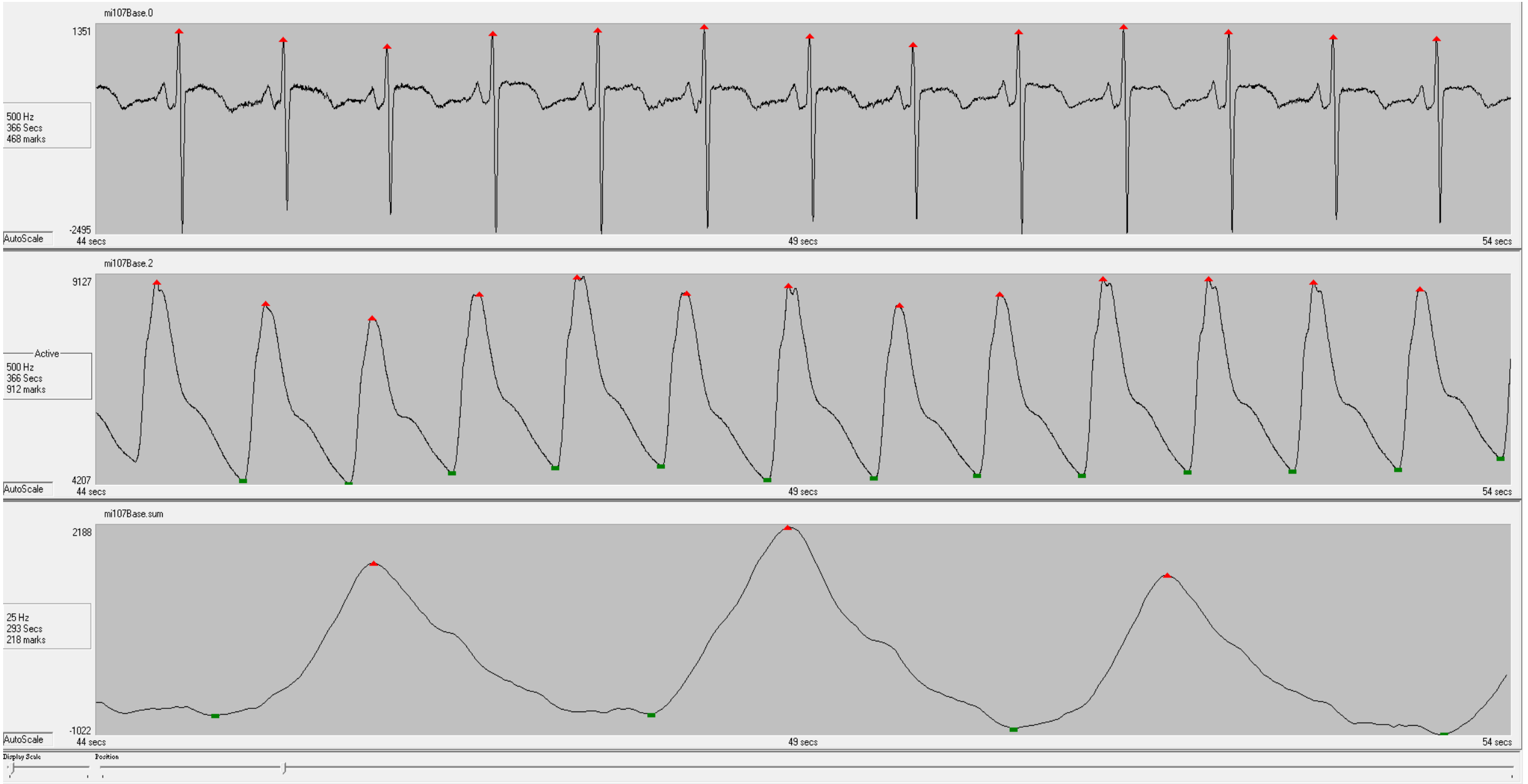
Vincenzo Lauriola

Columbia University / Division of Behavioral Medicine


Structural MRI
fMRI-BOLD
Heart rate & blood pressure
Respiration
Skin conductance
Psychophenotype & mental health
Home-based assessments
Neurocognitive assessment
Hair collection
Saliva collection
Serum & plasma sampling
PBMCs & immune cell subtypes
Steroids
Proteome dynamics
Age & disease related markers
Cell-free mtDNA
Biochemistry & allostatic load
Cellular respiration
Mitochondrial resp. potential
Single cell transcripomics
MITOCHONDRIA
STRESS
BRAIN
EPIGENETICS
MiSBIE

Task Name	Task duration	ECG Beat-to Beat BP Respiration Skin Conductance	Blood	Saliva	Affect Rating	Temperature
Baseline 1 (Base)	360	✓				
NADA2 (N2)	1440					
- 5 min (Pre)	300	✓	✓	✓	✓	✓
Psychological Stress Onset (PrepTask)	120	✓				
Psychological Stress Onset (Task)	180	✓				
+5 min (Post5)	300	✓	✓	✓	✓	✓
+10 min (Post10)	300	✓	✓	✓	✓	✓
NADA3 (N3)	300					
+20 min (Post20)	300	✓	✓	✓	✓	✓
NADA4 (N4)	300					
+30 min (Post30)	300	✓	✓	✓	✓	✓
NADA5 (N5)	1500					
+60 min (Post60)	300	✓	✓	✓	✓	✓
NADA6 (N6)	1500					
+90 min (Post90)	300	✓	✓	✓	✓	✓
NADA7 (N7)	1500					
+120 min (Post120)	300	✓	✓	✓	✓	✓
NADA8 (N8)	0					
Deep breathing task (DBT)	420	✓				
NADA9 (N9)	0					
Standing Transition (ST)	420	✓				
Standing Respiration Calibration (C3)	0	✓				
Sit-Stand Test (SST)	420	✓				
NADA10 (N10)	0					
Cold Pressor (CP)	660	✓				
NADA 11 (N11)	0					
Metabolic Rate (MR)	600	✓			✓	✓

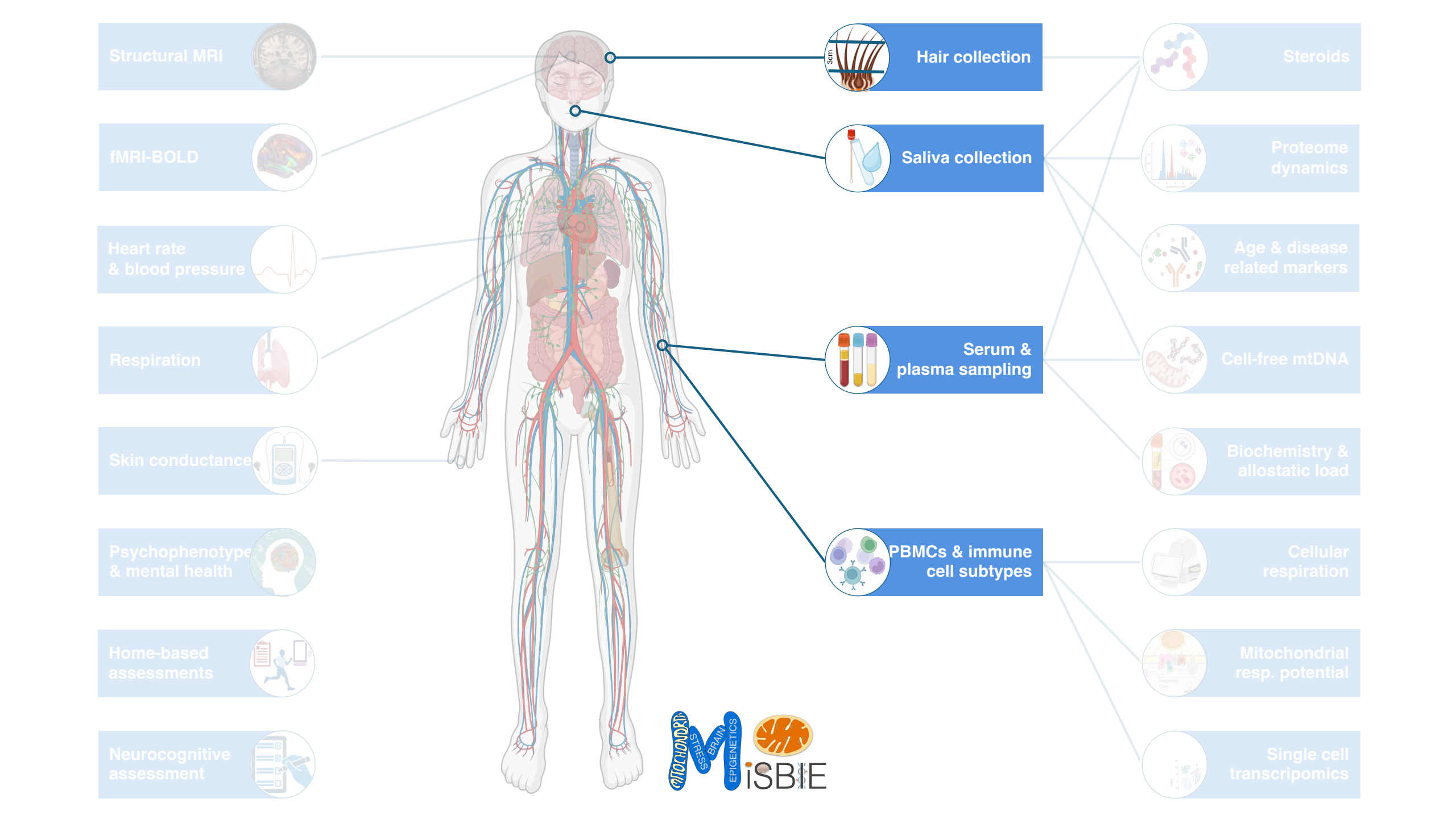

BioLab Configuration
File
Hardware
Settings
Tools
Help
ECG_Ch1
0.087128
0.050000
0.000000
-0.050000
-0.116577
GSC_Ch4
0.083771
0.083000
0.082000
0.081000
0.079346
BP
1.245728
1.000000
0.800000
0.571747
Chest
0.259705
0.100000
0.000000
-0.108643
Abdomen
0.329437
0.200000
0.000000
-0.238190
Ch 1 Summary
169.400000
160.000000
150.000000
Ch 16, empty slot
none, default
none
0
0
empty slot_Ch16
none
ECG_Ch1
EXIT
VIEW


mi107Base.0
1351
500 Hz
366 Secs
468 marks
-2495
AutoScale
44 secs
49 secs
54 secs
mi107Base.2
9127
Active
500 Hz
366 Secs
912 marks
4207
AutoScale
44 secs
49 secs
54 secs
mi107Base.sum
2188
25 Hz
293 Secs
218 marks
-1022
AutoScale
44 secs
49 secs
54 secs
Display Scale
Position

Biospecimen processing and MiSBIE biobank

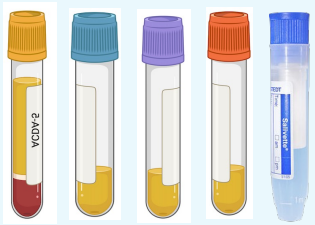
Mangesh Kurade

CUIMC - Mitochondrial Psychobiology Group


Structural MRI
fMRI-BOLD
Heart rate & blood pressure
Respiration
Skin conductance
Psychophenotype & mental health
Home-based assessments
Neurocognitive assessment
3cm
Hair collection
Saliva collection
Serum & plasma sampling
PBMCs & immune cell subtypes
Steroids
Proteome dynamics
Age & disease related markers
Cell-free mtDNA
Biochemistry & allostatic load
Cellular respiration
Mitochondrial resp. potential
Single cell transcripomics
MITOCHONDRIA
STRESS
BRAIN
EPIGENETICS
iSBIE

FASTING AND STRESS REACTIVITY COLLECTIONS

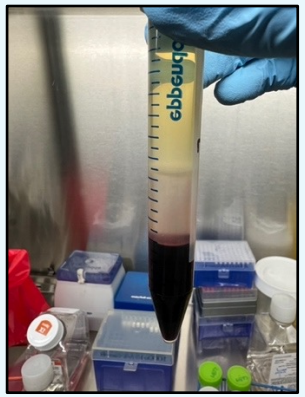
Morning fasting collections



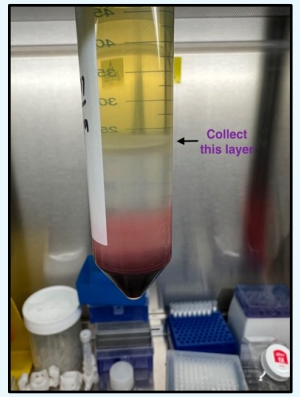
5 x ACD-A
4 x Citrate plasma
2 x Plasma
2 x Serum
1 x Salivette
1 x Buccal swab

Plasma & Serum separation

Immune cell isolation

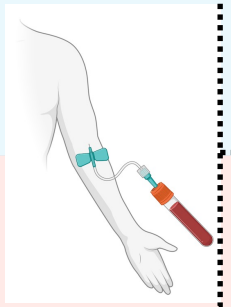


Morning PMBC isolation (Ficoll 1077)



Immune cells isolation via Ficoll double gradient (Ficoll 1077/1119)

Sample type	Aliquots
Fasting Plasma	8
Fasting Serum	6
Fasting PBMCs	7
Monocytes	4
Neutrophils	4
Lymphocytes	4
Platelets	4
Saliva	2

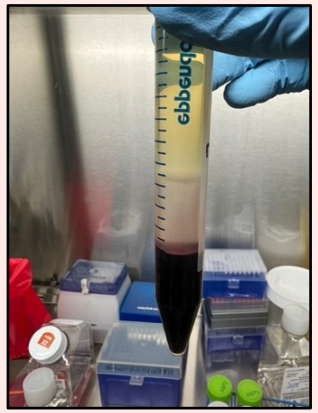


Stress reactivity collections

1 x ACD-A
8 x Plasma
8 x Serum
10 x Salivette

Plasma & Serum separation

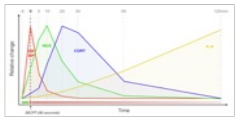
PBMC isolation



Stress reactivity PMBC isolation (Ficoll 1077)

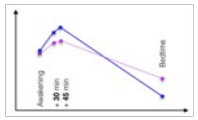
Sample type	Aliquots
Stress Plasma	24
Stress Serum	24
Stress PBMCs	20
Saliva	20

MiSBIE Samples - Processing & Storage

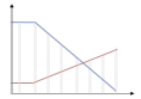


x 8

x 4

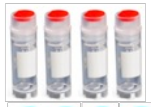


x 3



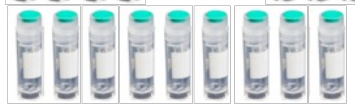
Centrifugation

Ser

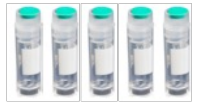


Leu

Pl

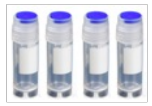


Pl

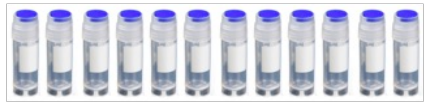


Sal

Sal



DiSal

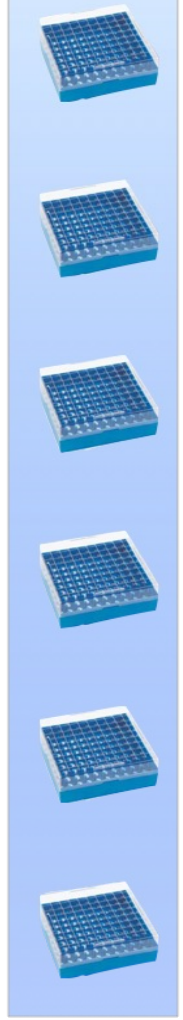


Ur

Ep

Bs

Hr



Allostatic load
Mitochondrial fx
mtDNA
nDNA/RNA

Biomarkers
Metabolomics

Biomarkers
(cortisol)

Biomarkers
(cortisol)

Biomarkers
(catecholamines)
mtDNA

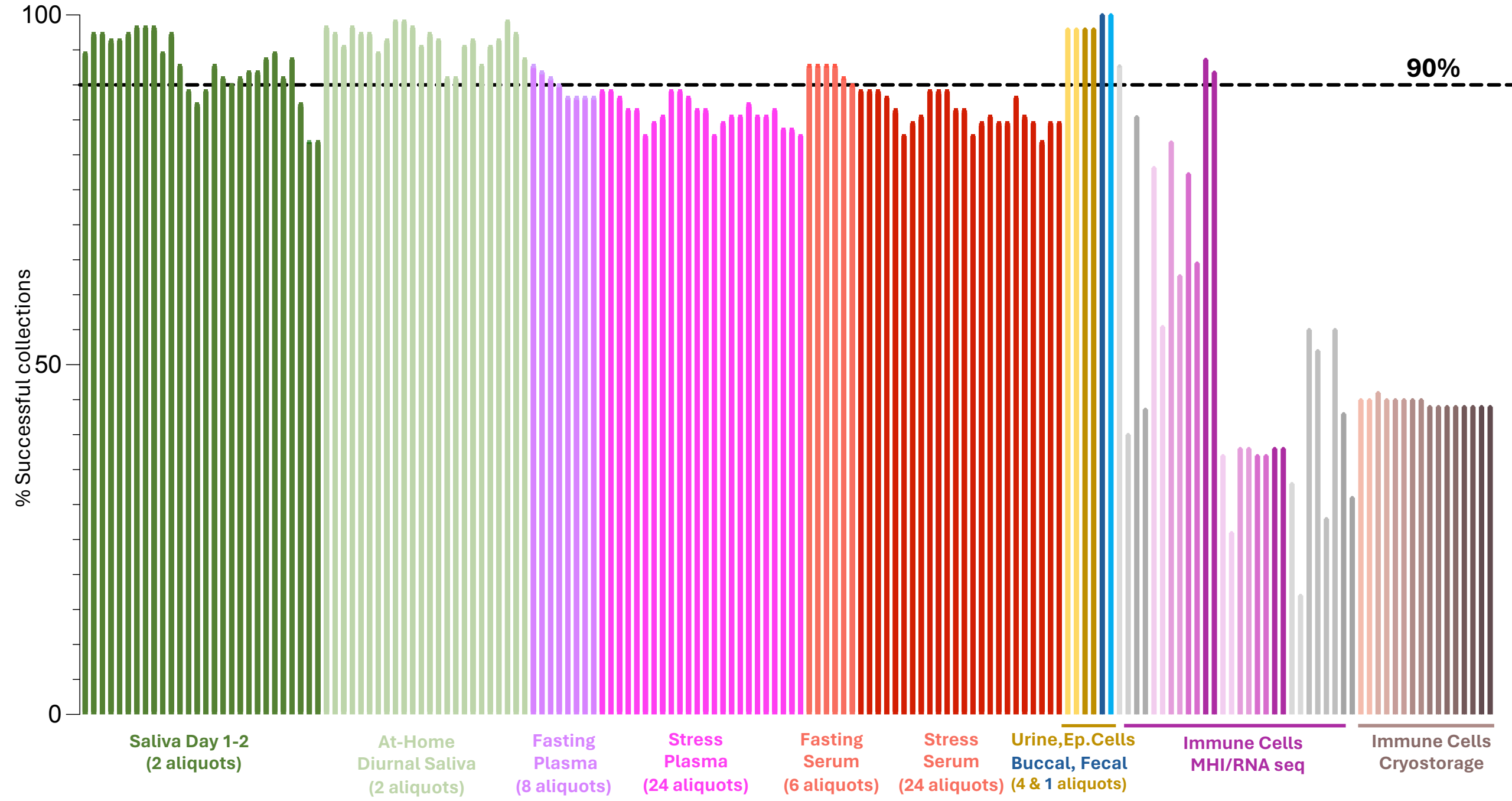
mtDNA
nDNA methyl

Biomarkers
(cortisol + others)

Room T°

MiSBIE

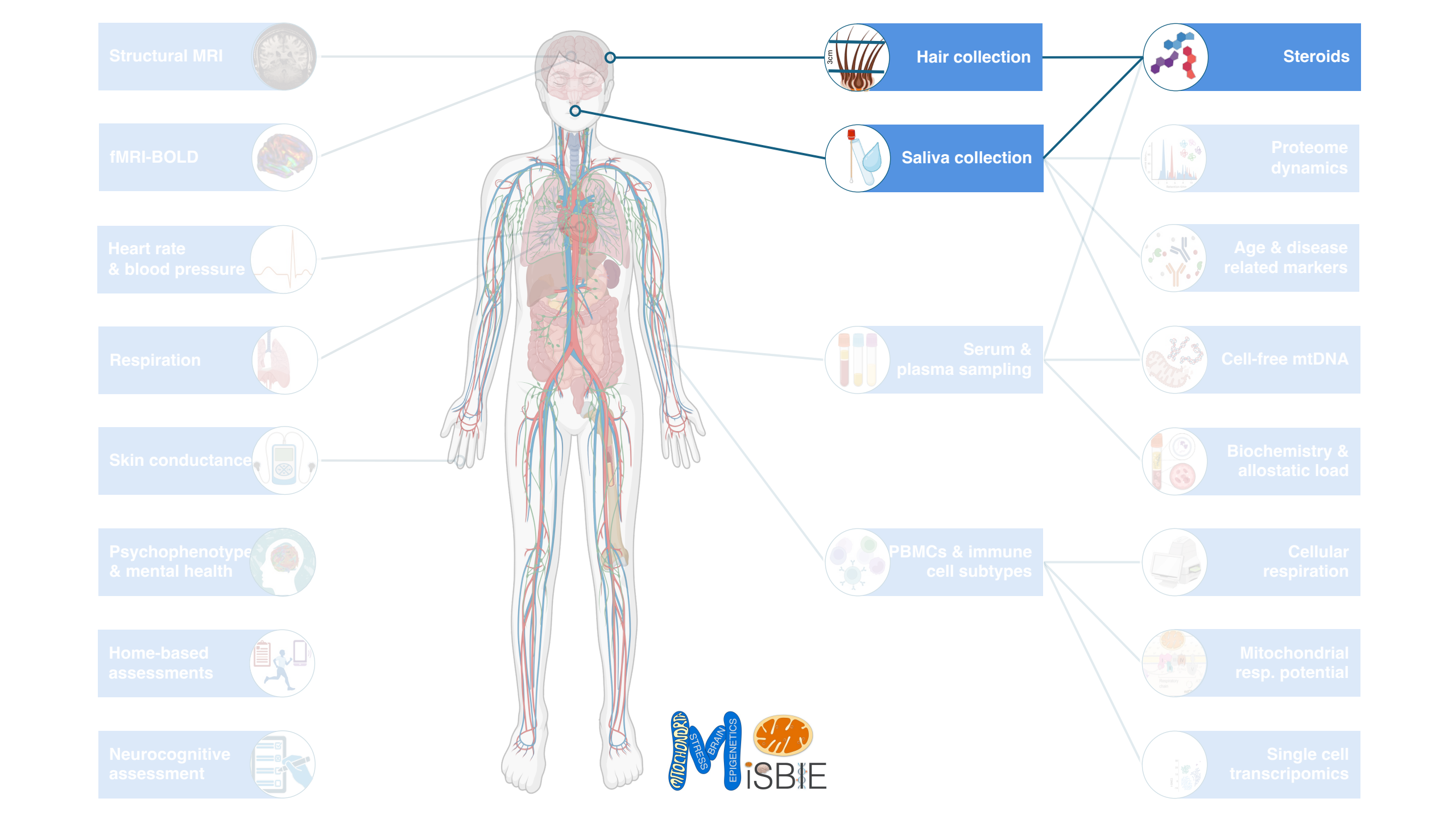
MiSBIE Biobank Overview



Steroid hormones in saliva and hair

Natalia Bobba-Alves

CUIMC - Mitochondrial Psychobiology Group

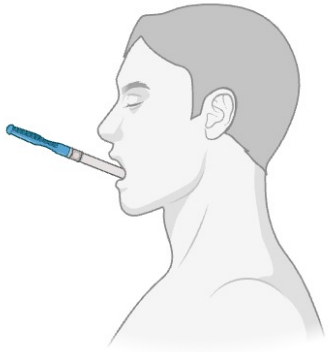

Structural MRI
fMRI-BOLD
Heart rate & blood pressure
Respiration
Skin conductance
Psychophenotype & mental health
Home-based assessments
Neurocognitive assessment
3cm
Hair collection
Saliva collection
Serum & plasma sampling
PBMCs & immune cell subtypes
Steroids
Proteome dynamics
Age & disease related markers
Cell-free mtDNA
Biochemistry & allostatic load
Cellular respiration
Mitochondrial resp. potential
Single cell transcripomics
MITOCHONDRIA
STRESS
BRAIN
EPIGENETICS
iSBSE

Sampling

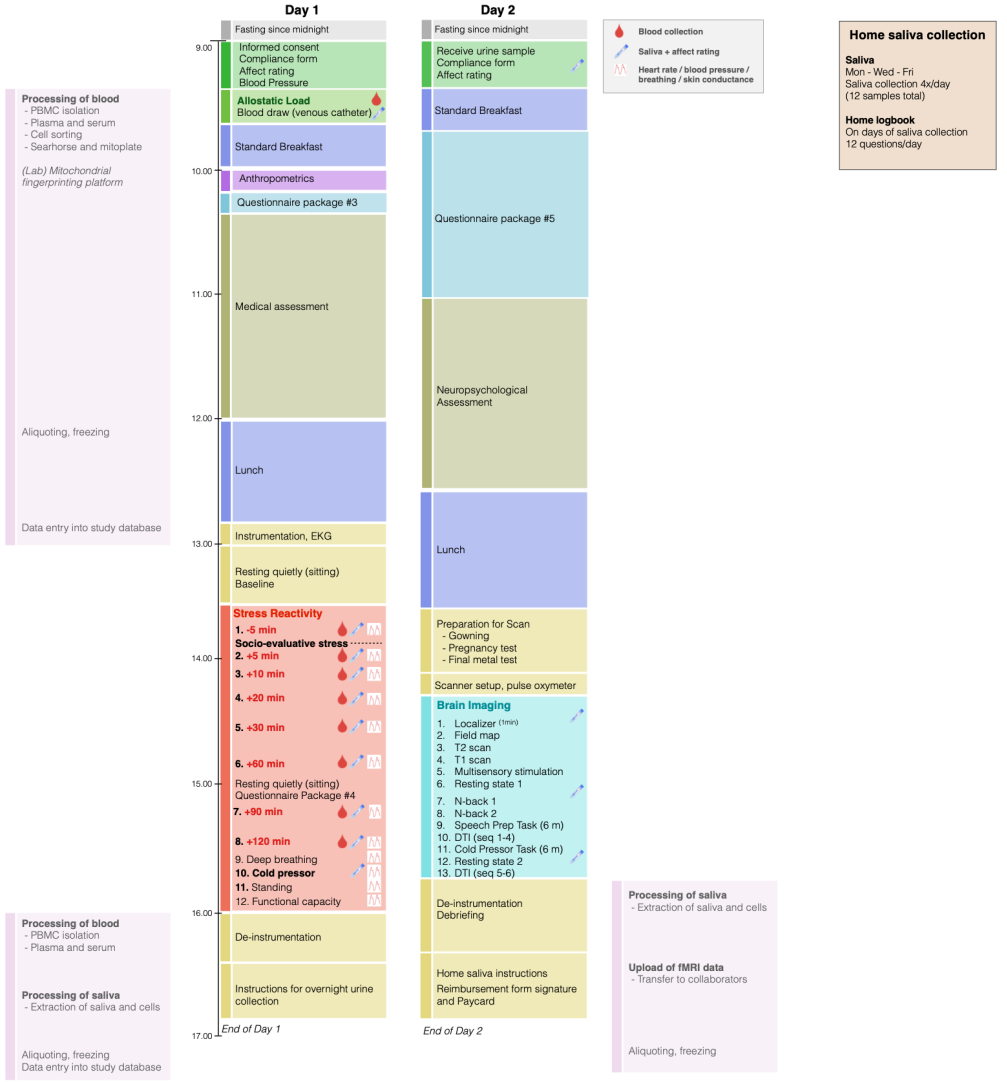
Hair

2 hair strands

Saliva



26 salivettes

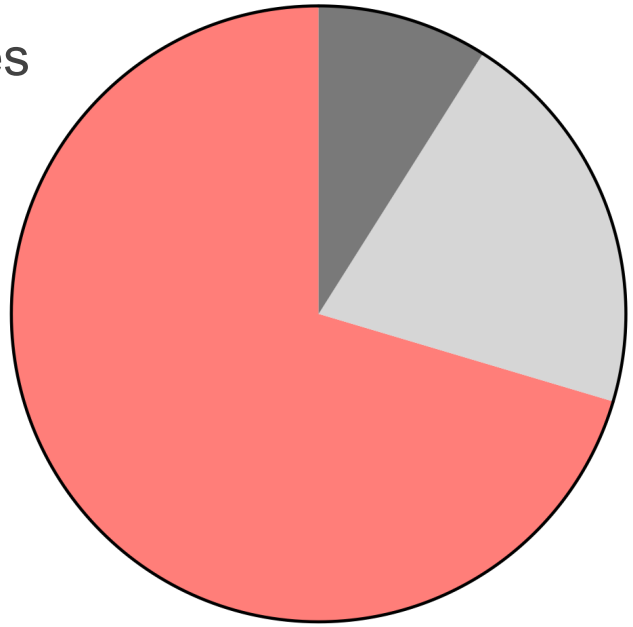


Coverage

2 Hair samples
14 Clinic Saliva samples
12 Home Saliva samples

x 110 participants

x 6 Steroid hormones = **18,480 data points**



70% Obtained values

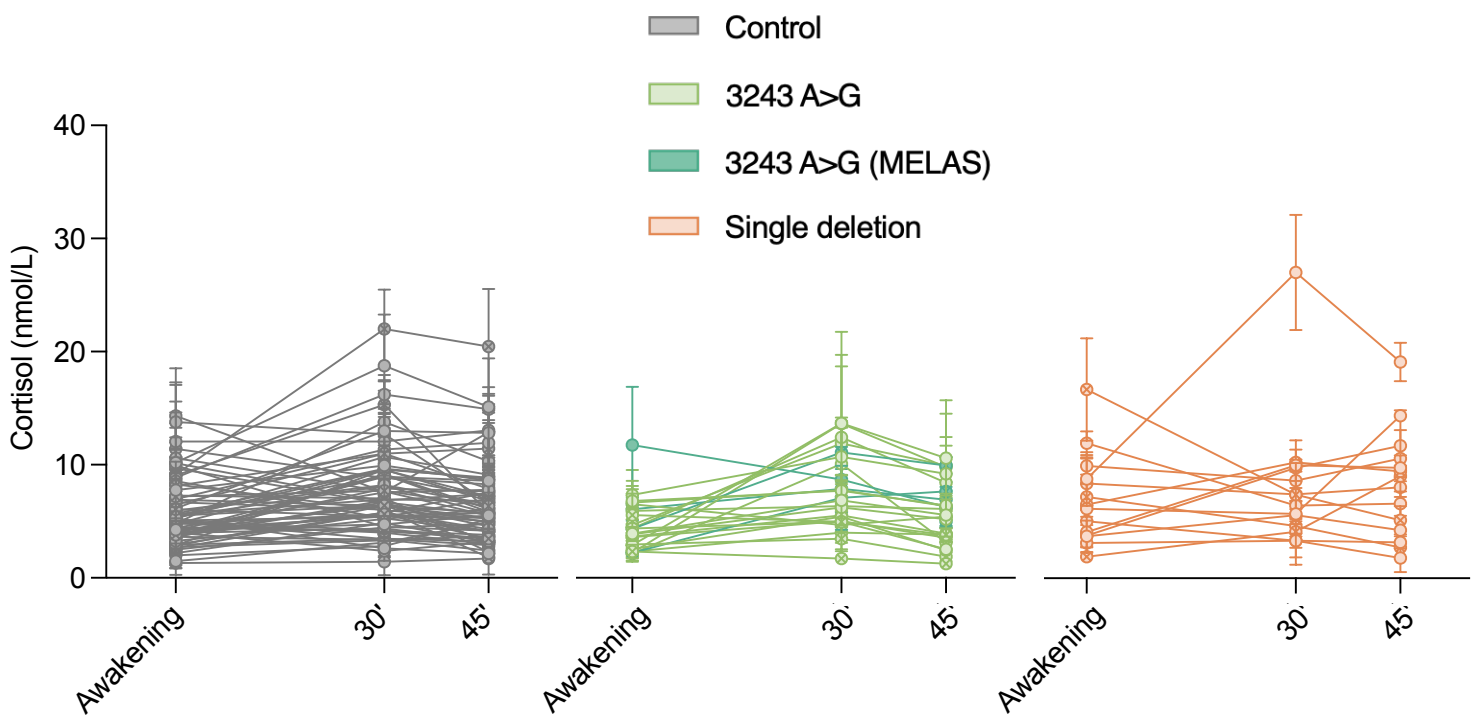
9% Missed values

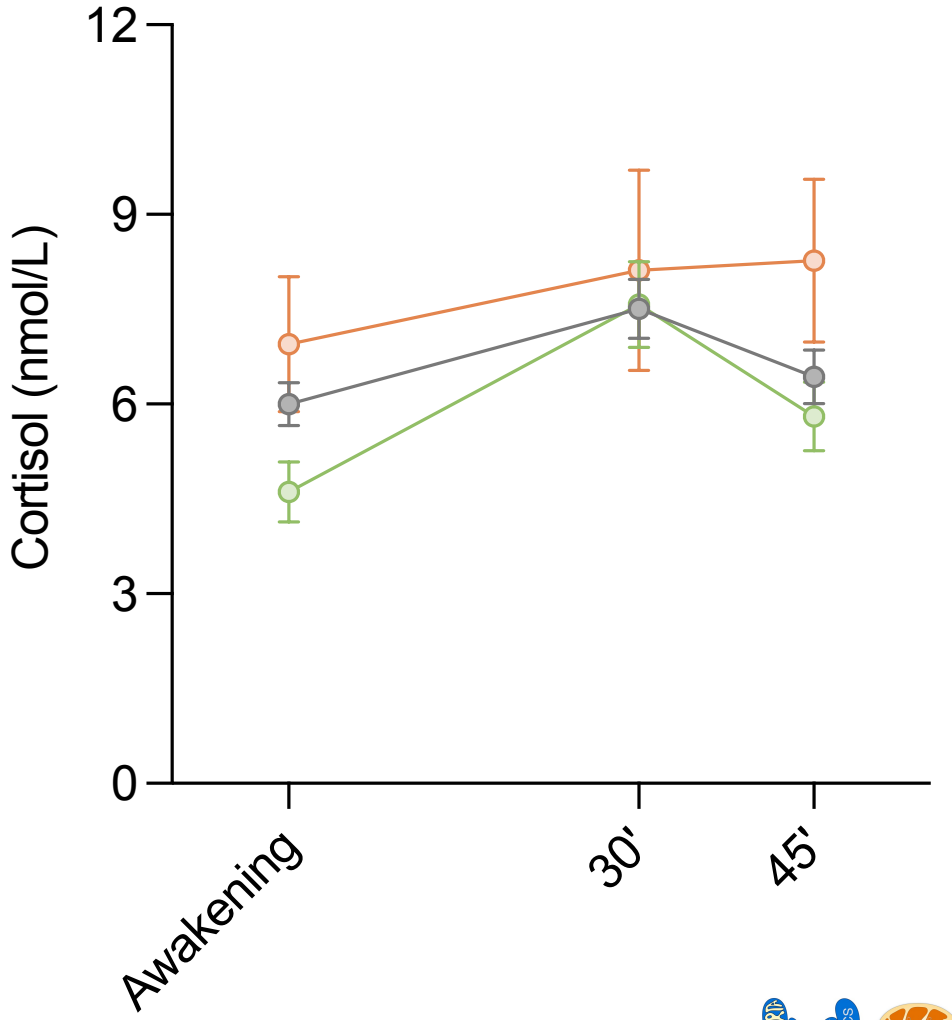
5% No sample
4% Technical problem

21% Non-detected values

11% Corticosterone
4% Progesterone
4% Testosterone
2% DHEA
~ 0% Cortisol
~ 0% Cortisone

Preliminary results – Cortisol awakening response

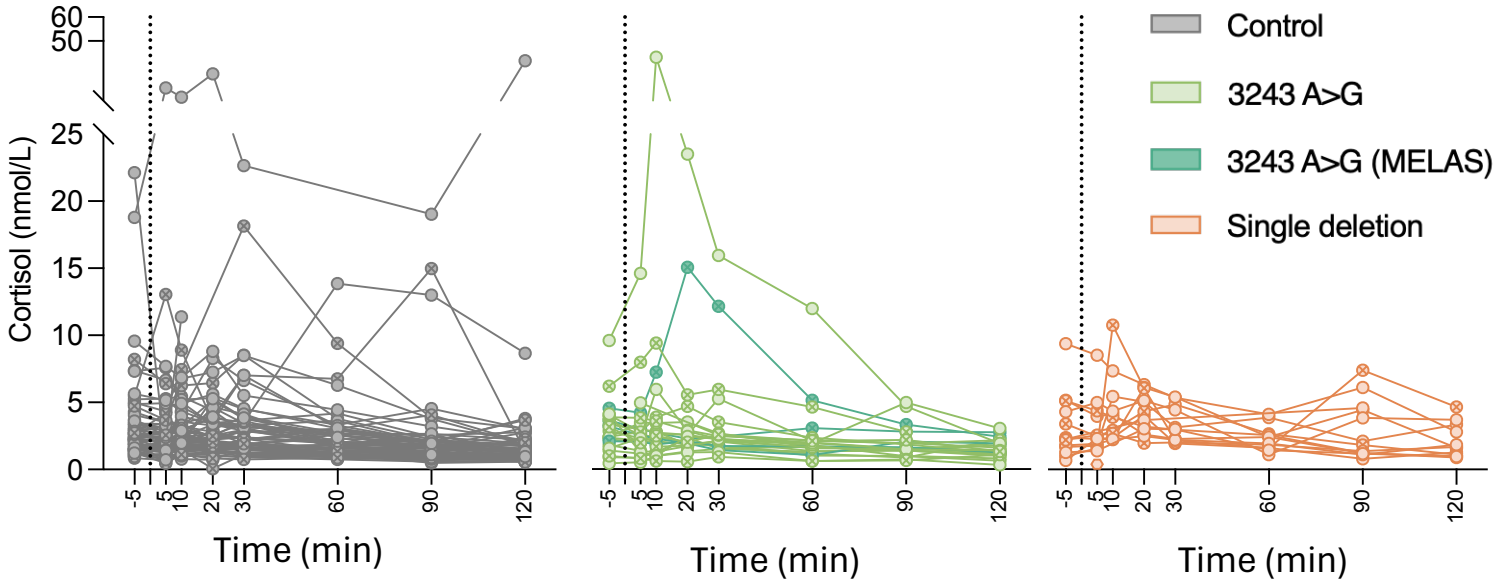


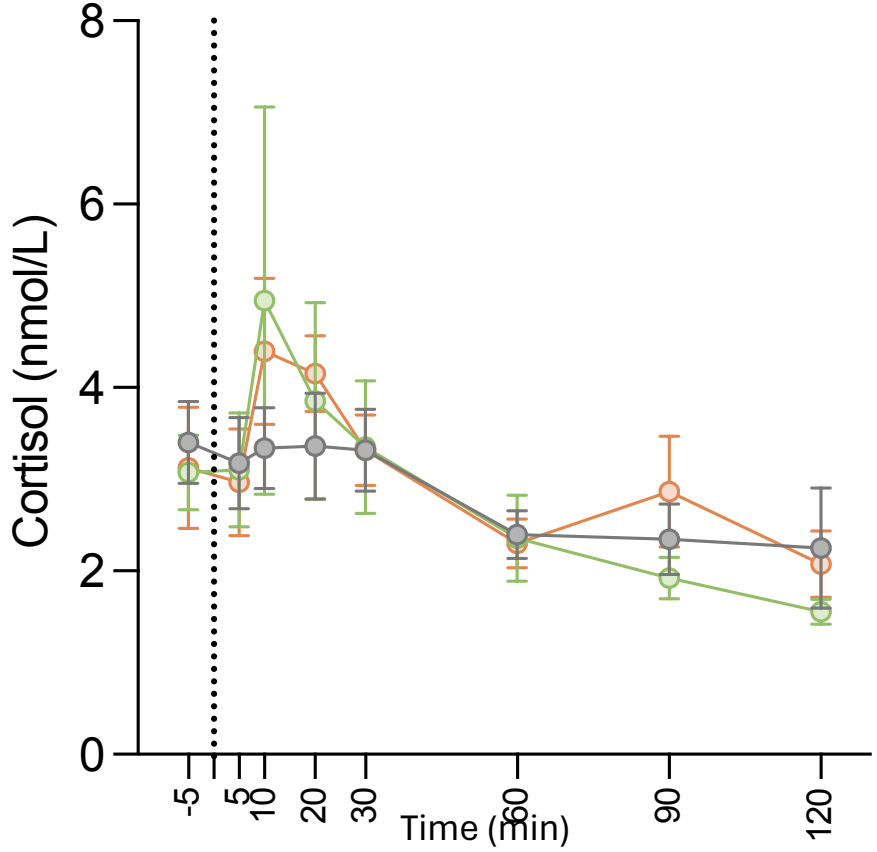


*2 Control and 1 Single deletion participants excluded

Preliminary results – Cortisol stress reactivity

Speech task



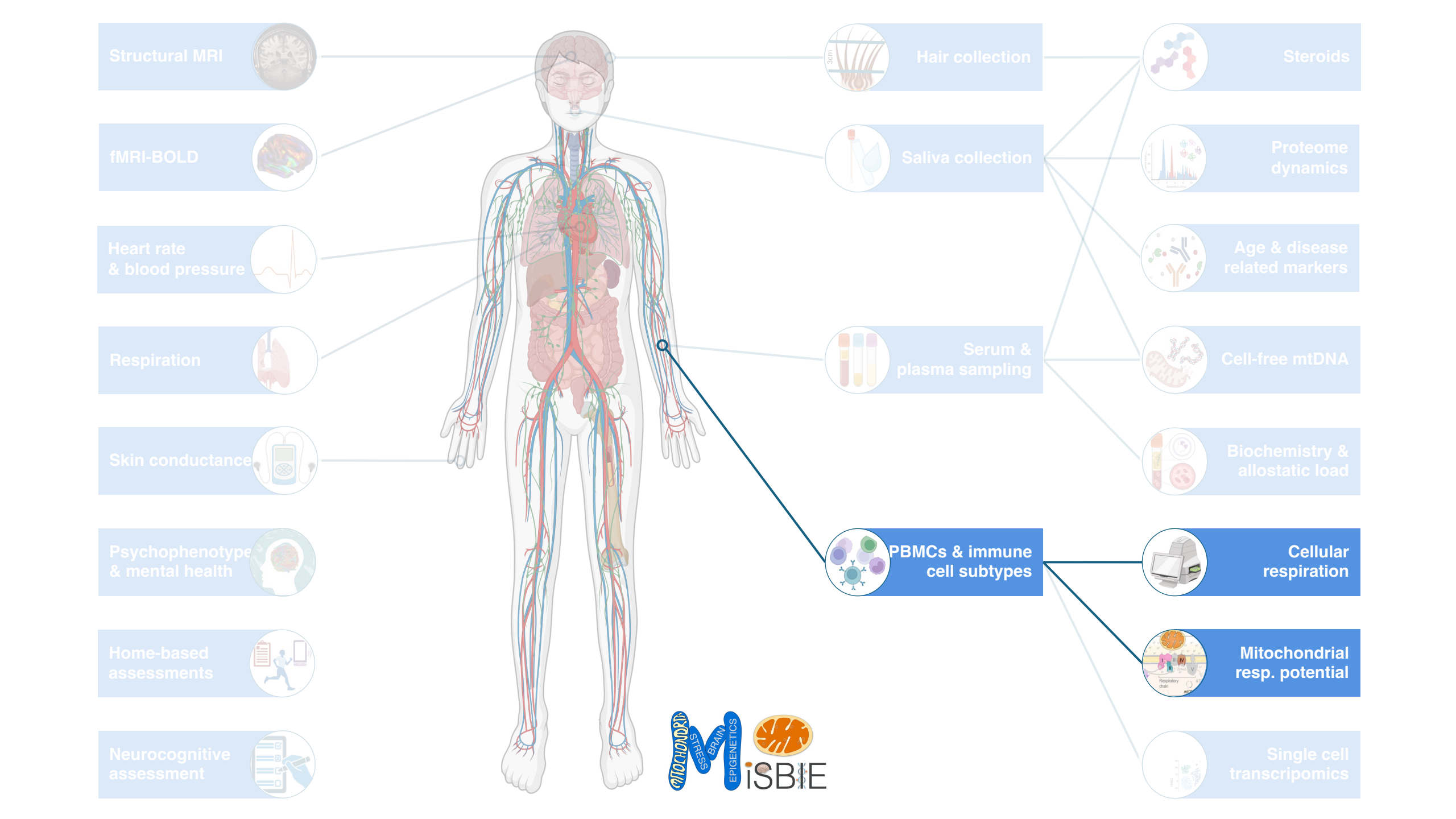


*1 Control participant excluded

Immune cell bioenergetics

Anna Monzel

CUIMC - Mitochondrial Psychobiology Group


Structural MRI
fMRI-BOLD
Heart rate & blood pressure
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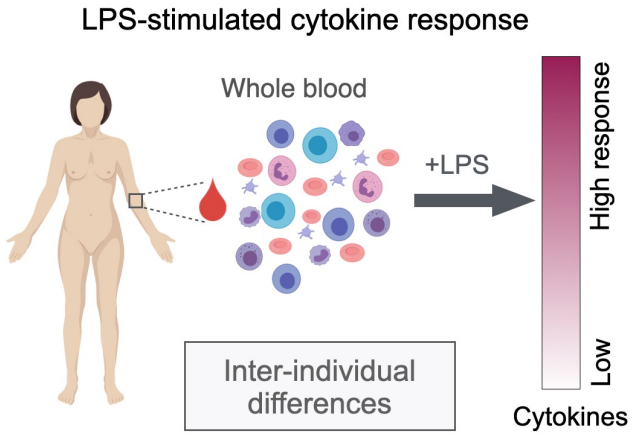
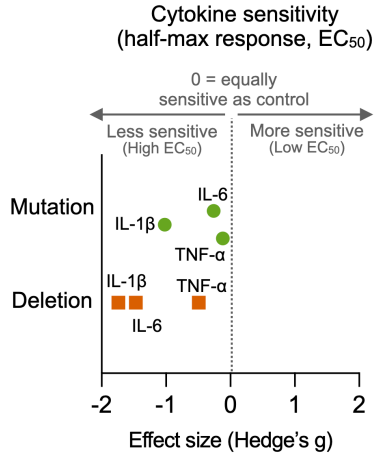
PBMCs & immune cell subtypes
Steroids
Proteome dynamics
Age & disease related markers
Cell-free mtDNA
Biochemistry & allostatic load
Cellular respiration
Mitochondrial resp. potential
Single cell transcripomics
MITOCHONDRIA
STRESS
BRAIN
EPIGENETICS
iSBIE

Background

- In mitochondrial diseases, the nature of immune system involvement is poorly understood
- Mitochondrial disease patients have higher infection susceptibility
- Mice with a genetic OxPhos defect live longer when the immune system is depleted[1]
- A study from our lab shows that patients' immune cells show blunted immune response to a challenge[2]

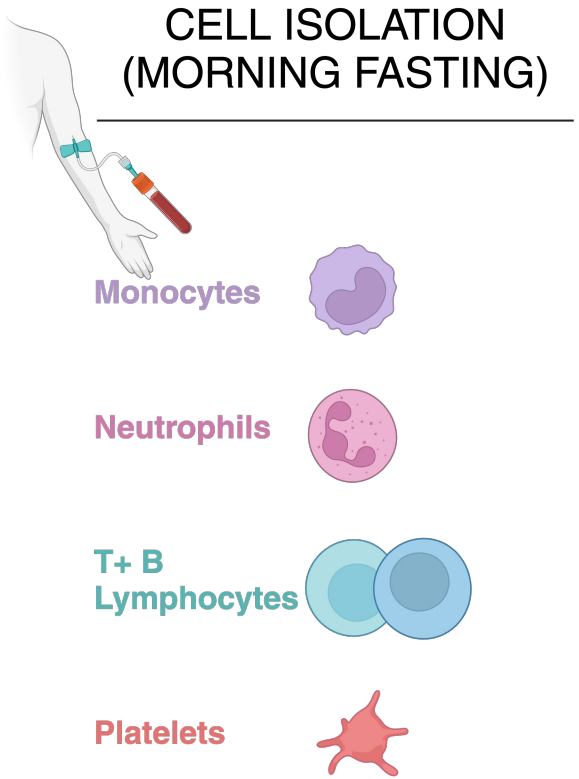




—> How do mtDNA defects influence the immune system / immune bioenergetics?

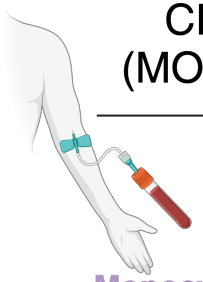
[1] Stokes *et al*. *JCI Insight* (2022).
[2] Karan *et al*. *J. Mol. Med*. (2022).

Bioenergetics - procedure



Bioenergetics - procedure

CELL ISOLATION (MORNING FASTING)



Monocytes

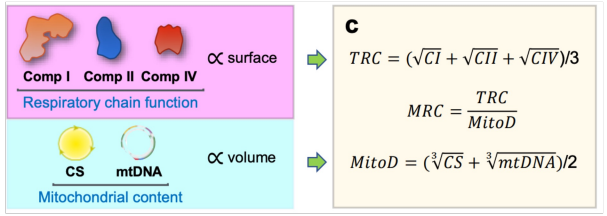
Neutrophils

T+ B Lymphocytes

Platelets

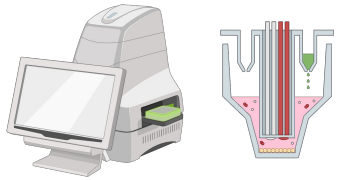
MITOCHONDRIAL OXPHOS ASSAYS

Mitochondrial respiratory capacity



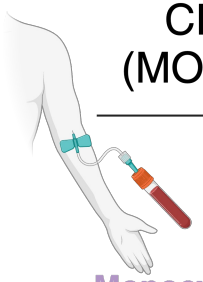
Extracellular flux analysis

Oxygen consumption (respiration) and extracellular acidification (glycolysis proxy)



Bioenergetics - procedure

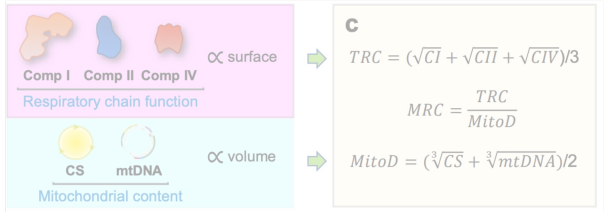
CELL ISOLATION (MORNING FASTING)



- Monocytes
- Neutrophils
- T+ B Lymphocytes
- Platelets

MITOCHONDRIAL OXPHOS ASSAYS

Mitochondrial respiratory capacity



Extracellular flux analysis

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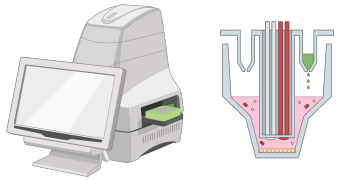
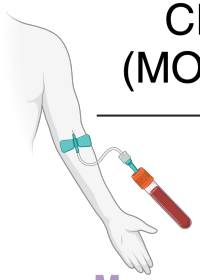


Bioenergetics - procedure

CELL ISOLATION (MORNING FASTING)



Monocytes

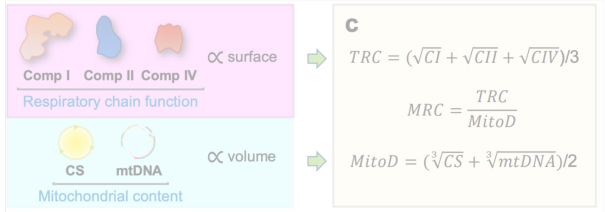
Neutrophils

T+ B Lymphocytes

Platelets

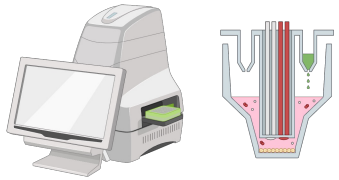
MITOCHONDRIAL OXPHOS ASSAYS

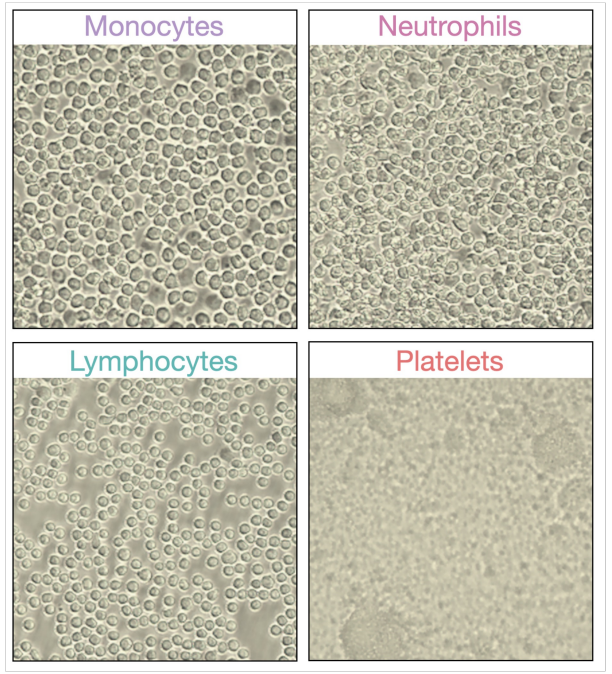
Mitochondrial respiratory capacity



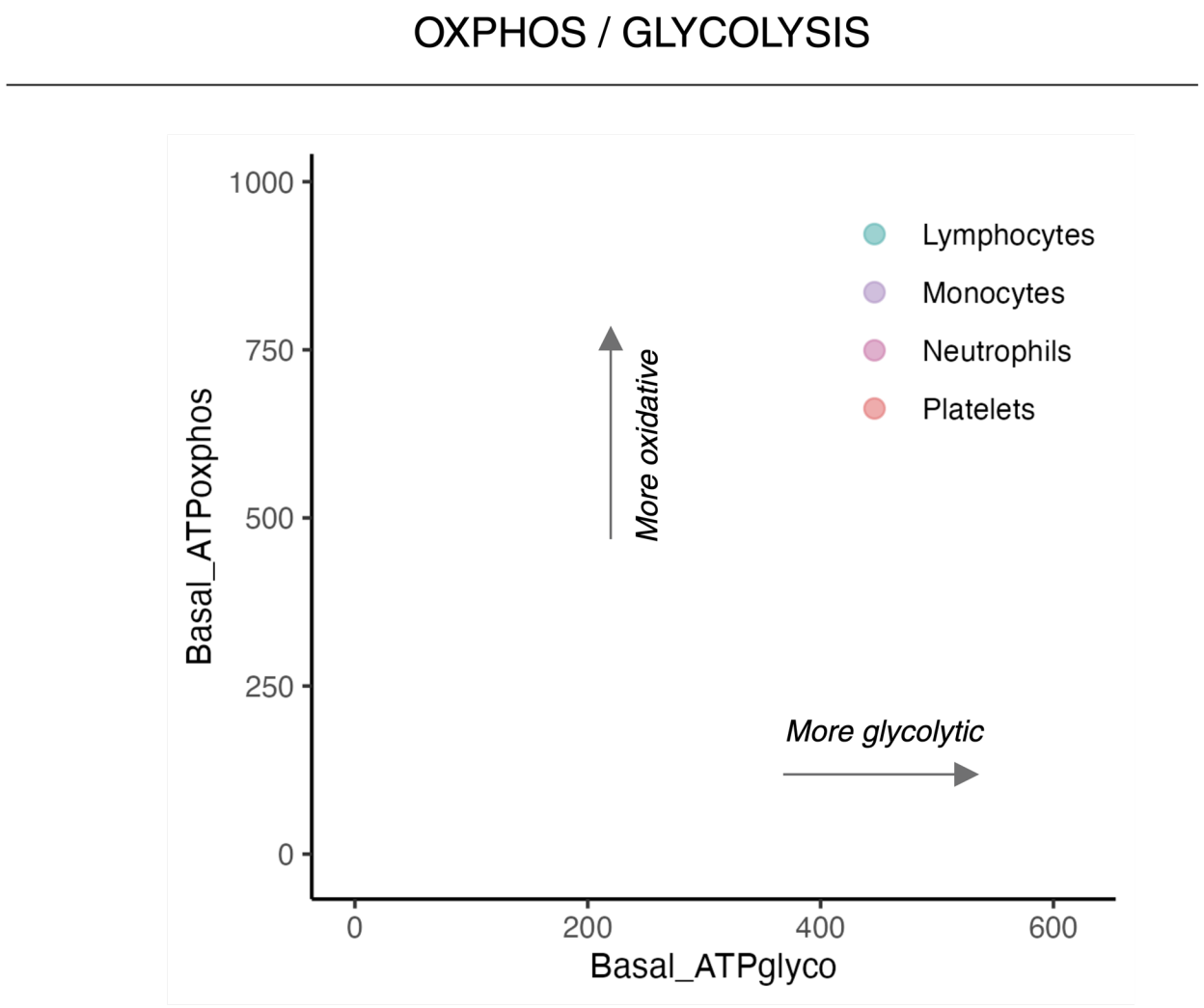
Extracellular flux analysis

Oxygen consumption (respiration) and extracellular acidification (glycolysis proxy)

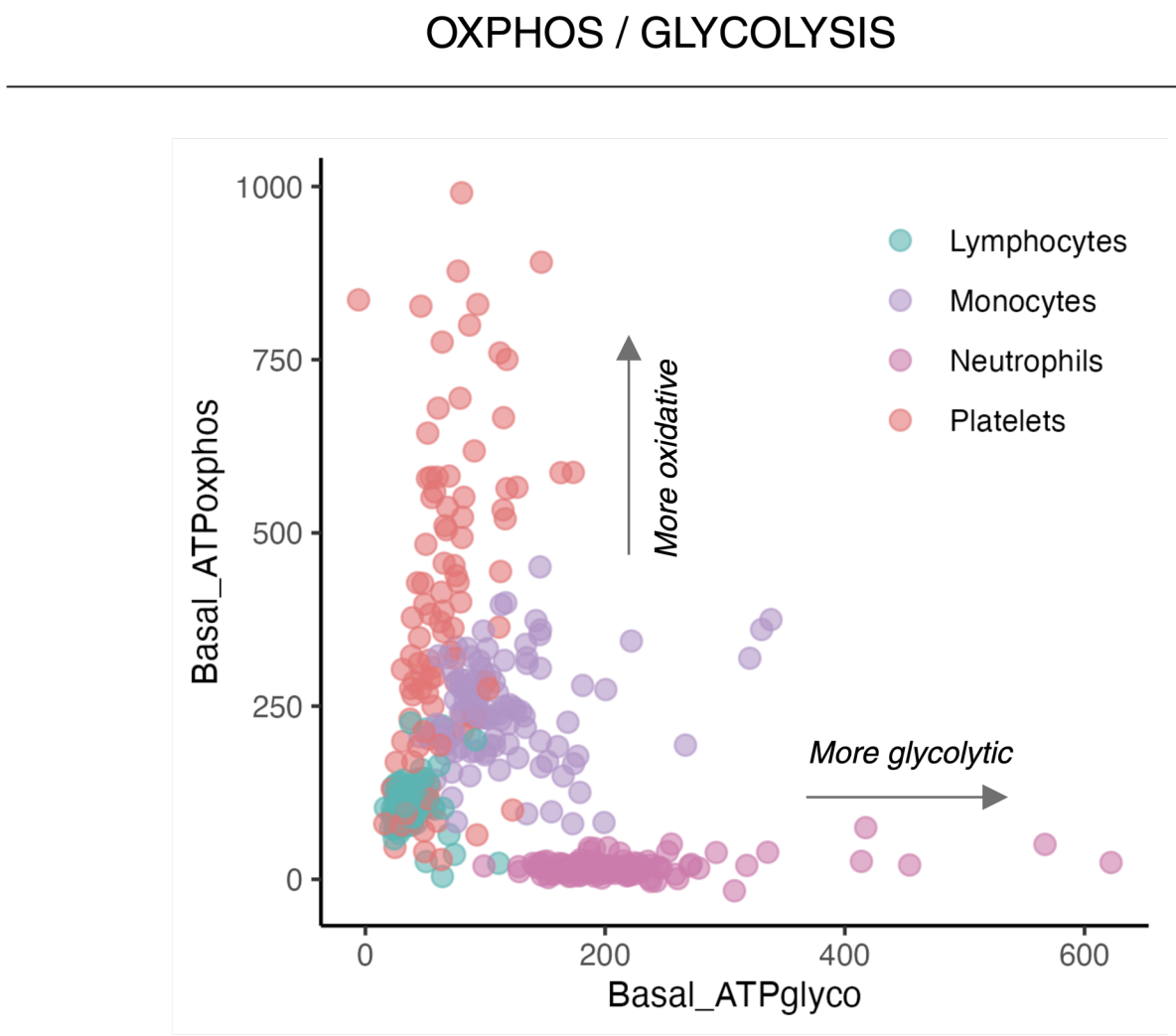




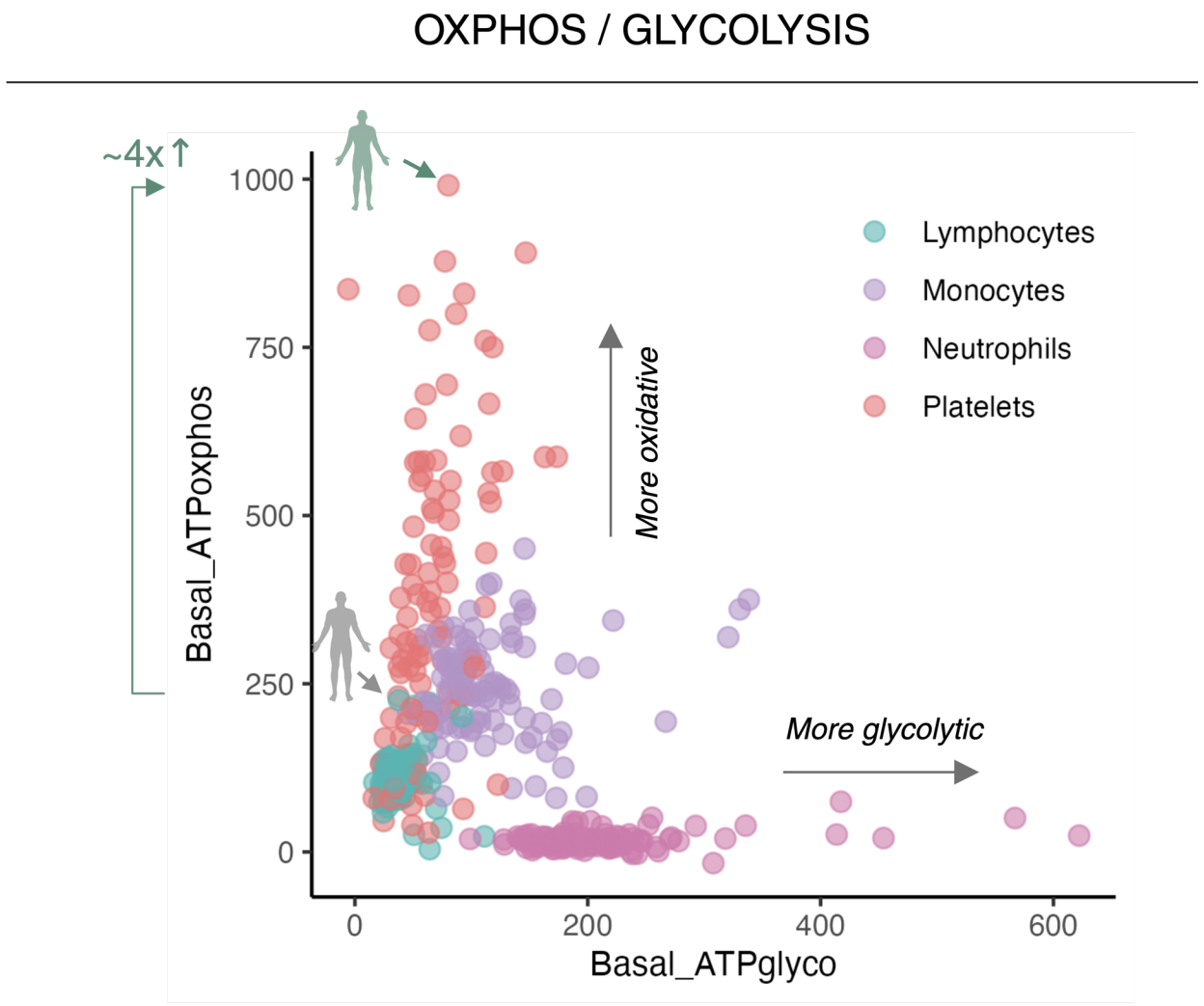
Bioenergetics - outcome



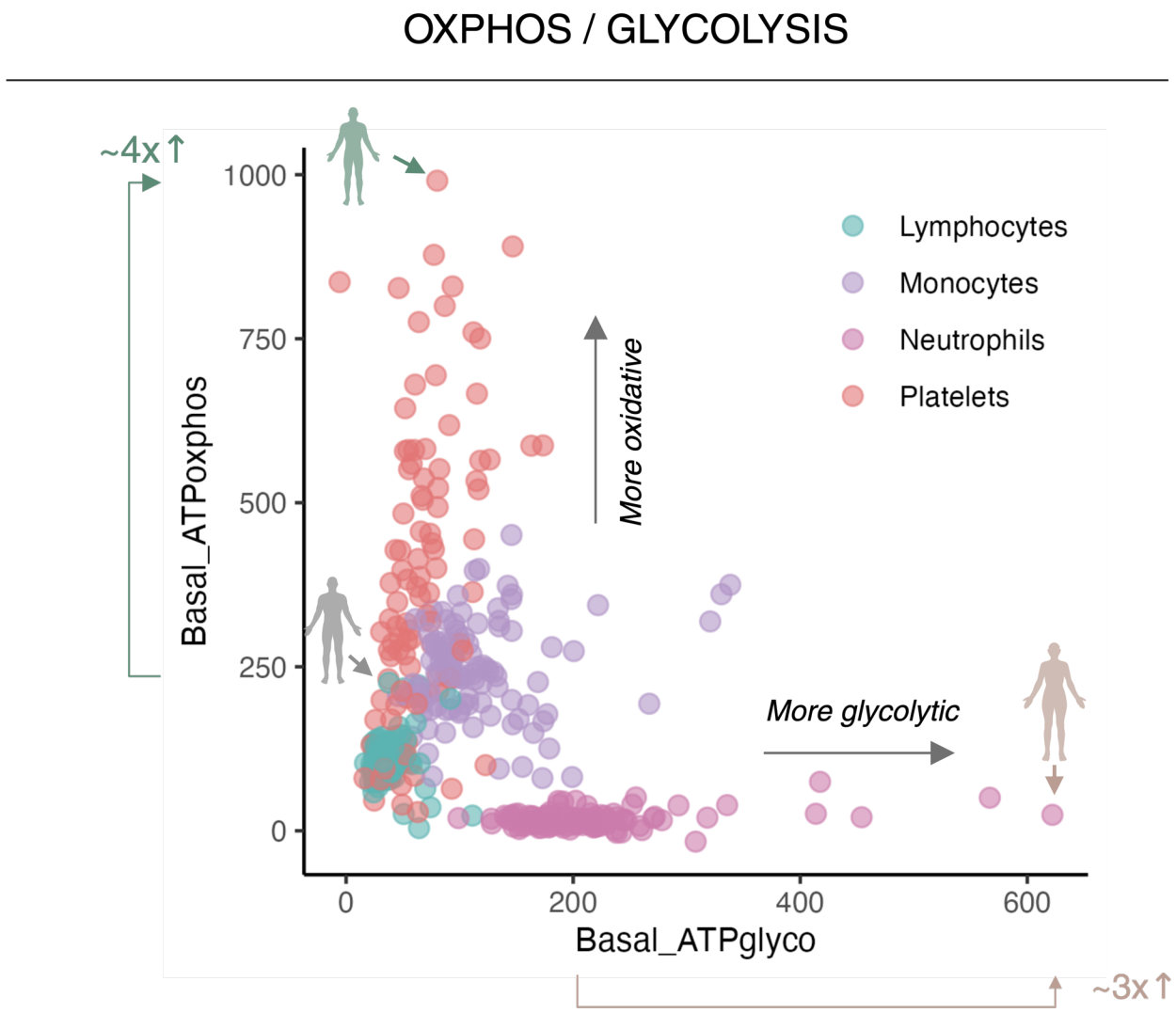
Bioenergetics - outcome



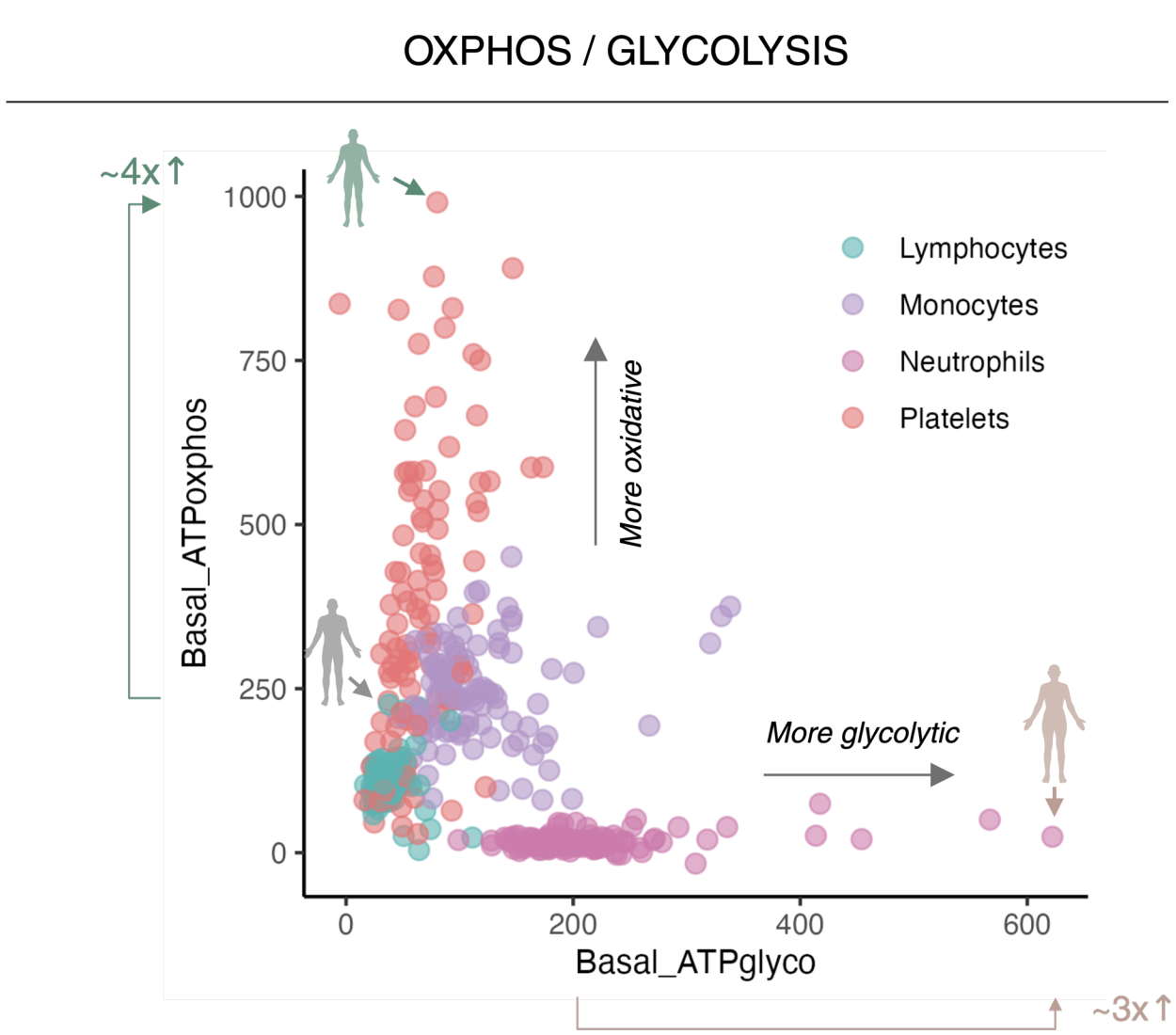
Bioenergetics - outcome



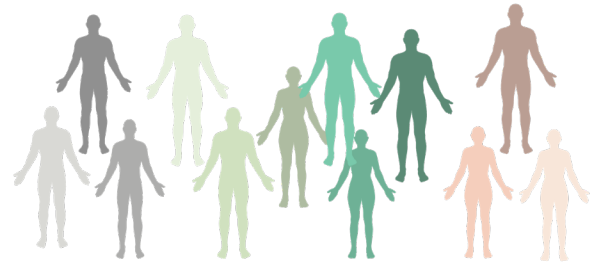
Bioenergetics - outcome



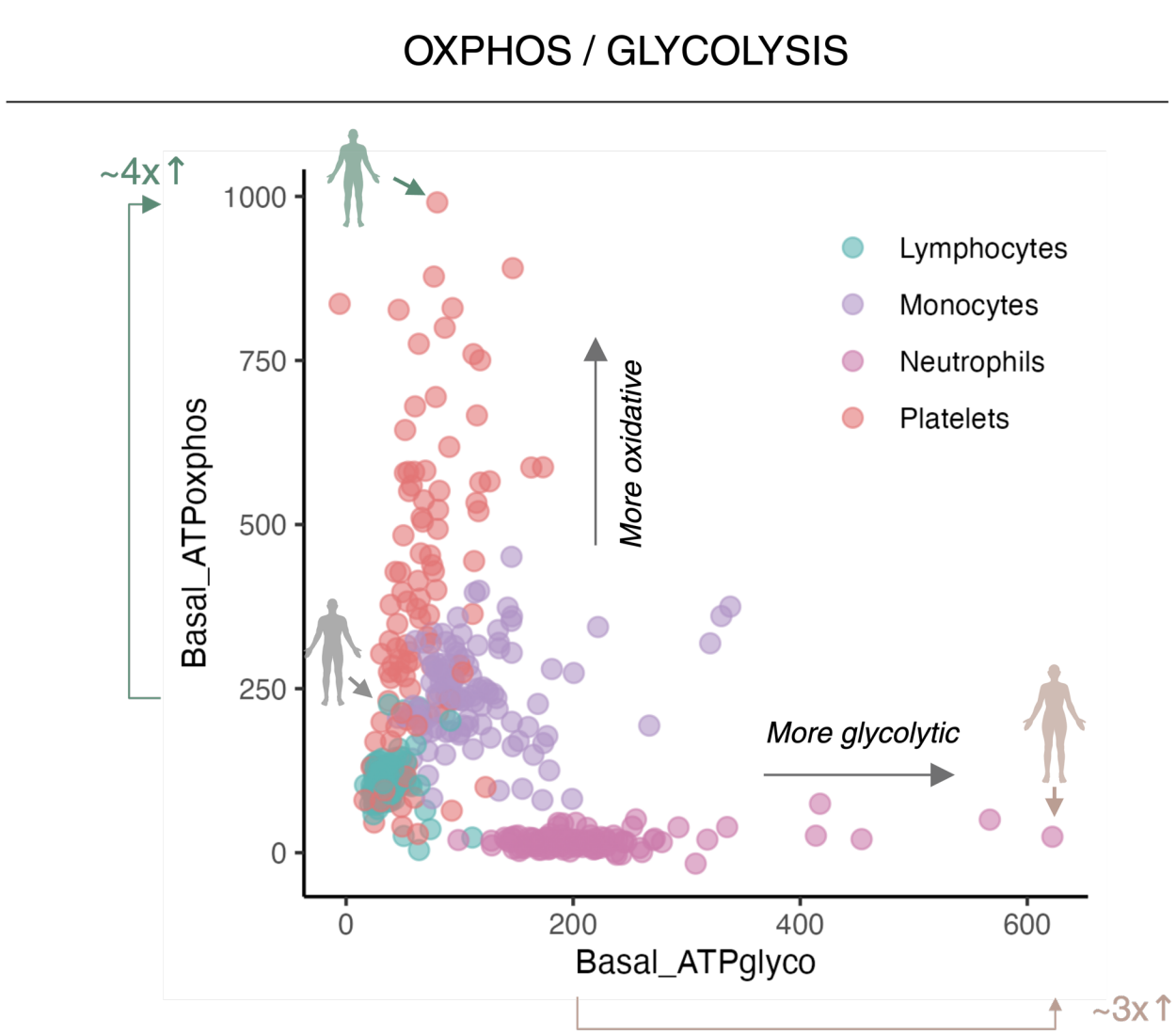
Bioenergetics - outcome



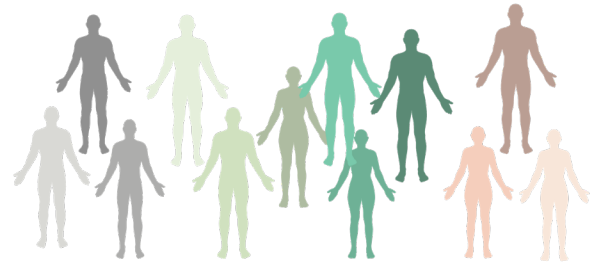
Bioenergetic profile



Bioenergetics - outcome



Bioenergetic profile



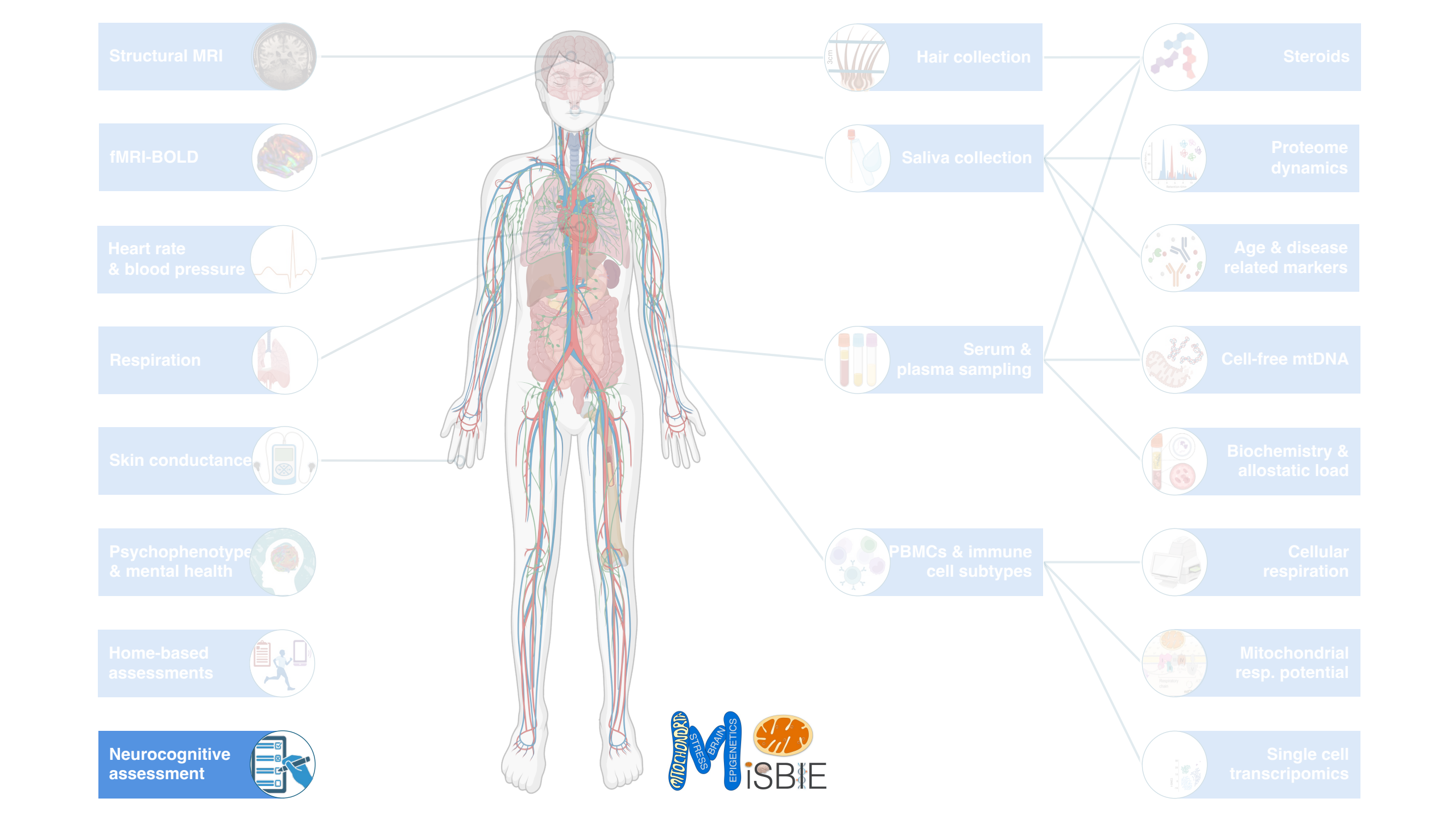
Relate to other domains of human experience:

- Clinical variables
- Psychophenotypes
- Stress reactivity
- Allostasis
- Cognition
- ...

Neuropsychological Assessment

Stephanie Assuras/Catherine Kelly

Columbia University Irving Medical Center


Structural MRI
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Heart rate & blood pressure
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Cell-free mtDNA
Biochemistry & allostatic load
Cellular respiration
Mitochondrial resp. potential
Single cell transcripomics
MITOCHONDRIA
STRESS
BRAIN
EPIGENETICS
iSBSE

- Cognitive profile and trajectory in adult mitochondrial disease poorly defined; changes in visuospatial functioning, memory, attention, processing speed and executive functions

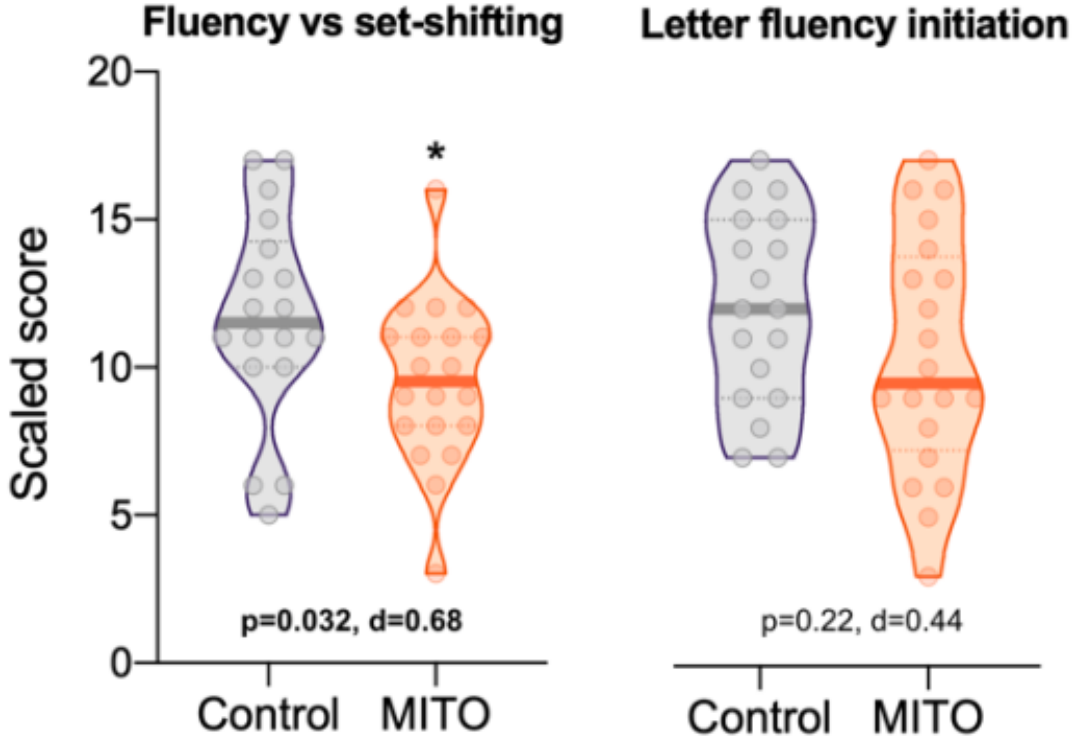
- Conclusions have been hampered by small sample sizes, variation in genotype and the breadth and depth of assessments undertaken

- Current study used a comprehensive neuropsychological assessment to evaluate all cognitive domains

Cognitive Domains	Measure	Description
Premorbid functioning	Test of Premorbid Functioning (TOPF)	Estimated verbal premorbid functioning
Intellectual functioning	WASI-II - Vocabulary and Matrix Reasoning	General intellectual ability
Visuospatial	RBANS - Line Orientation	Visuospatial judgement
Language	D-KEFS - Verbal Fluency	Letter and category fluency, verbal set-shifting
	RBANS - Picture Naming	Confrontation naming
Memory	NAB - Shape Learning	Visual learning and memory
	RBANS - List Learning, List Recall, List Recognition	Verbal learning and memory
Executive functioning and attention	NAB - Numbers and Letters	Attention and inhibition
	D-KEFS - Trail Making	Working memory, cognitive flexibility and speed
	NAB - Digits Forward and Backward	Attention and working memory
	D-KEFS - Color-Word	Response inhibition
	D-KEFS - Sorting	Mental flexibility and conceptualization
	RBANS - Coding	Processing speed
		Total time = 90 minutes

Preliminary findings:
Primary mitochondrial defects related to executive dysfunction

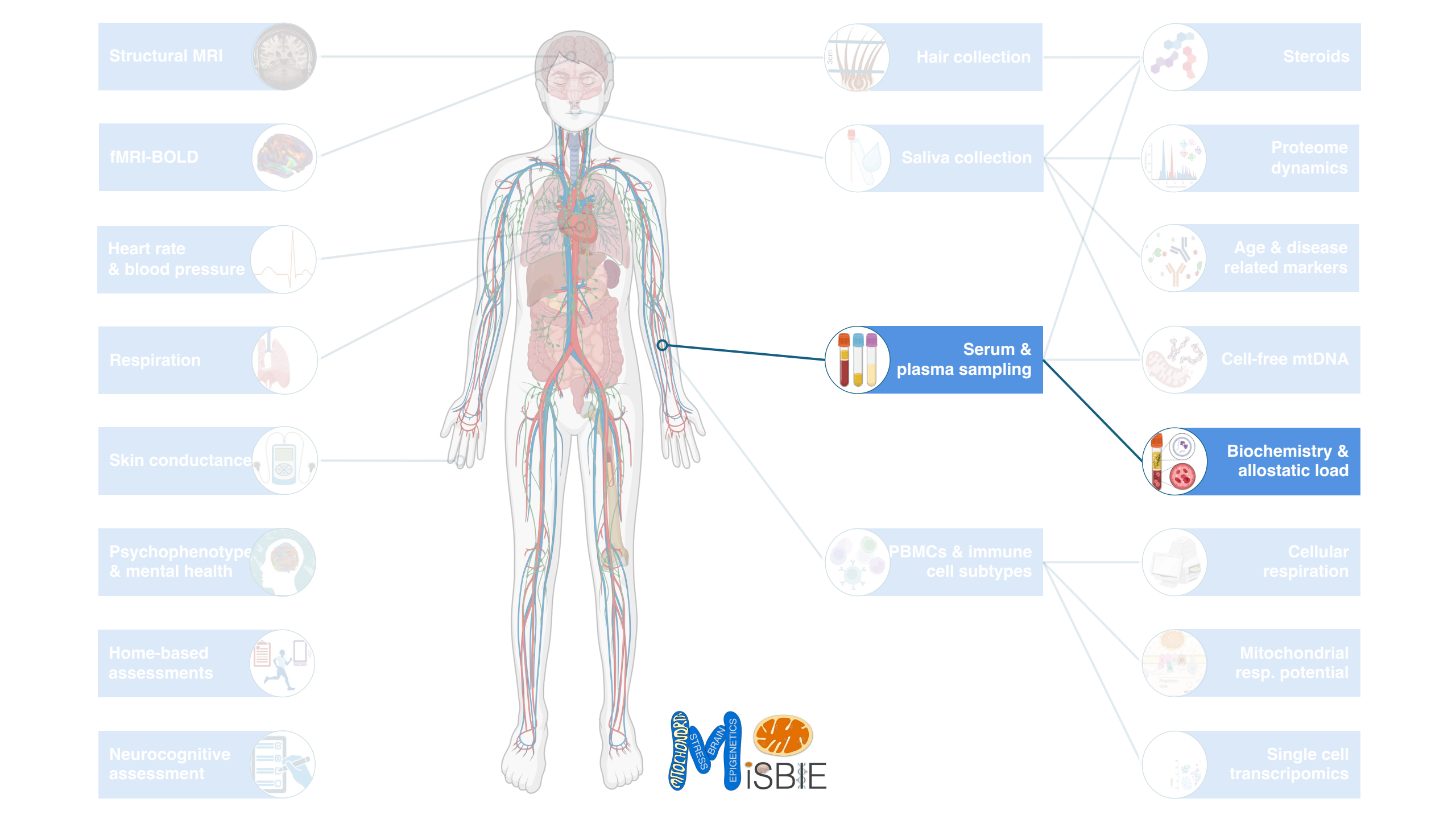
- Cognitive weaknesses in fundamental aspects of executive functioning relative to healthy controls
  - initiation/fluency
  - verbal set-shifting
- Particularly significant given the relatively young age of this cohort (Mean: 36.9 years, range: 20-52)
- Opportunity to understand the energetic basis of cognition and brain circuitry without the confounds of age or accumulated brain pathology



Clinical biochemistry and allostatic load

Alex Junker

CUIMC - Mitochondrial Psychobiology Group


Structural MRI
fMRI-BOLD
Heart rate & blood pressure
Respiration
Skin conductance
Psychophenotype & mental health
Home-based assessments
Neurocognitive assessment
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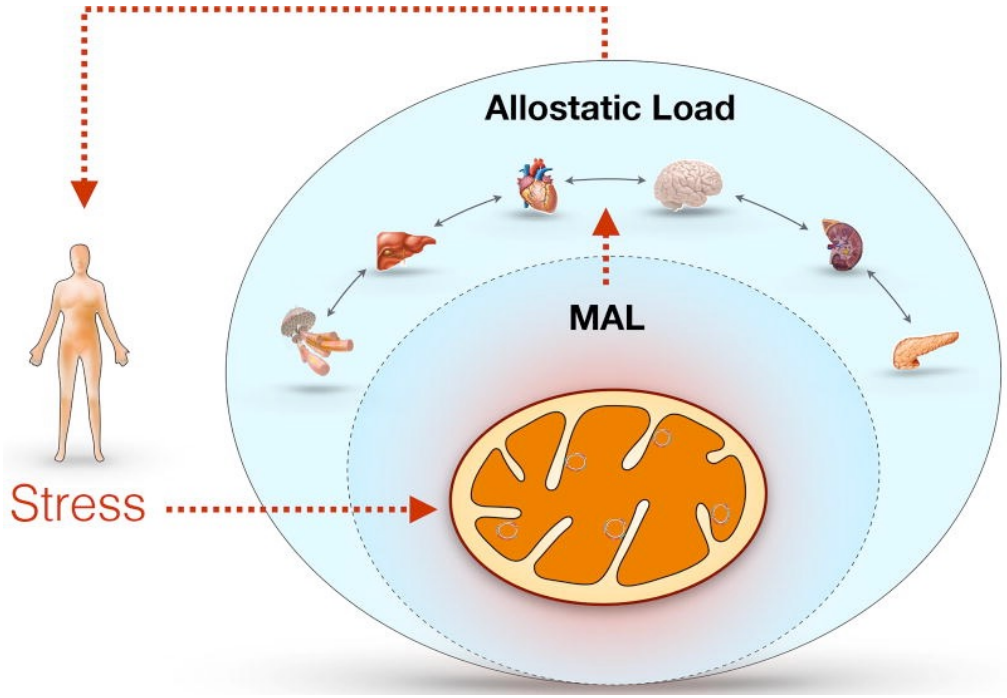
PBMCs & immune cell subtypes
Steroids
Proteome dynamics
Age & disease related markers
Cell-free mtDNA
Biochemistry & allostatic load
Cellular respiration
Mitochondrial resp. potential
Single cell transcripomics
MITOCHONDRIA
STRESS
BRAIN
EPIGENETICS
iSBSE

Allostatic load – contribution of mitochondria?

- Stressful experiences can cause ‘wear and tear’ on the body – termed allostatic load
- Mitochondrial allostatic load (MAL) can be caused by stress, or potently by mitochondrial diseases[1]
  - Decreased enzymatic activities
  - Lower respiratory capacity
- MAL influences gene expression and cellular behavior[2]
  - Mitochondrial defects alter HPA axis function in mice[3]

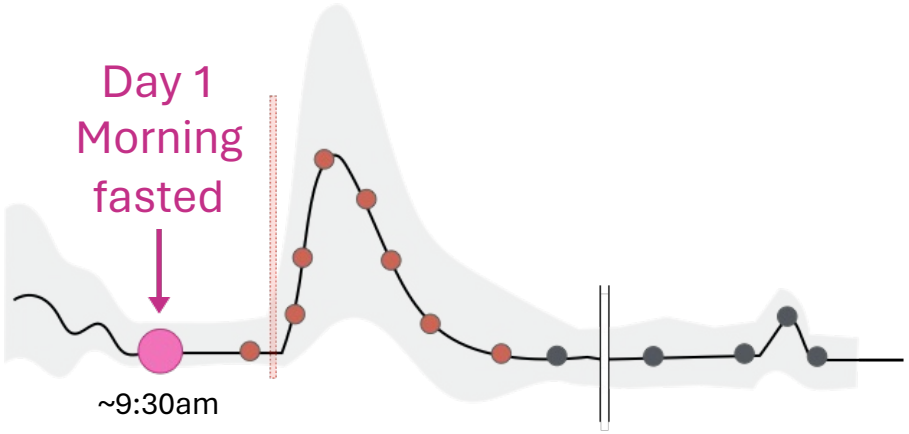
Is MAL a source of baseline, systemic AL?

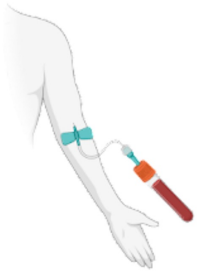
How/is this visible in standard blood biomarkers?



[1]Picard & McEwen *Nat Rev Endocrinol* (2019)
[2]Picard, Juster & McEwen *Psychosom Med* (2014)
[3]Picard et al *PNAS* (2015)

Clinical biochemistry



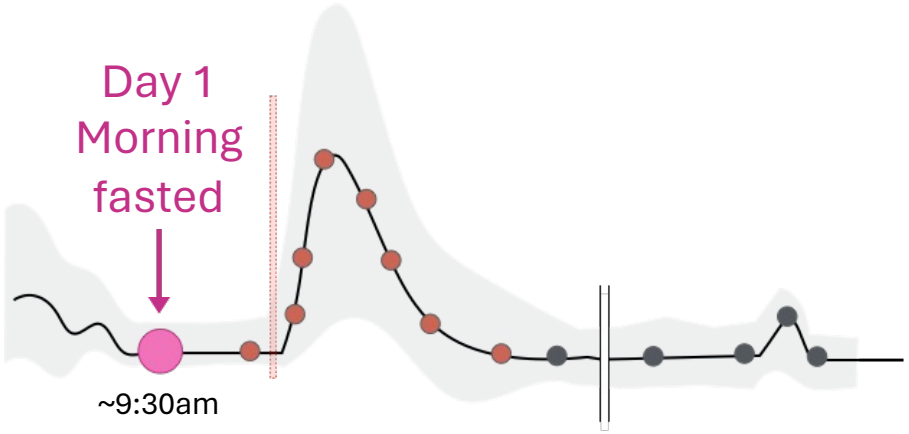


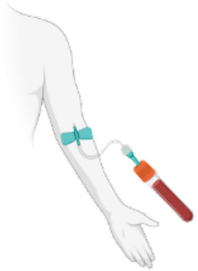
Controls, n=70

m.3243 A>G mutation, n=25

Single deletion, n=15

Clinical biochemistry





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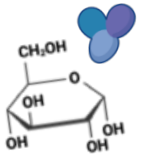


Metabolic panel
Glucose, HgbA1C, calcium, sodium, potassium, CO2, chloride, BUN, creatinine, albumin

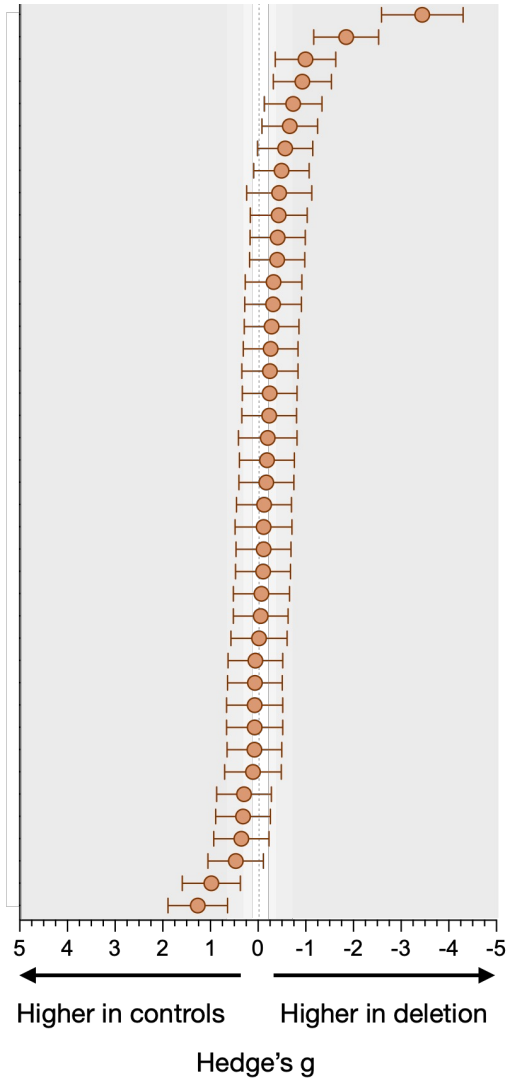
Lipid panel
Total cholesterol, LDL, HDL, triglycerides

White blood cells
Monocytes, lymphocytes, neutrophils, basophils, eosinophils (absolute and %), WBC, IG%

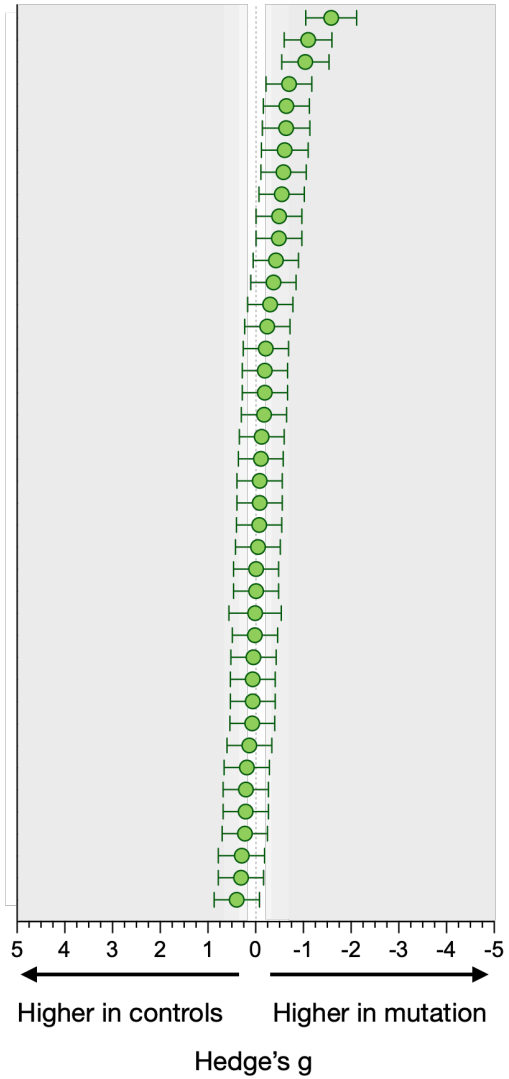
Red blood cells and platelets
RBC, hematocrit, hemoglobin, MCH, MCV, RDW, MCHC, PLT, MPV

Evidence of multisystem dysregulation in mitochondrial disease

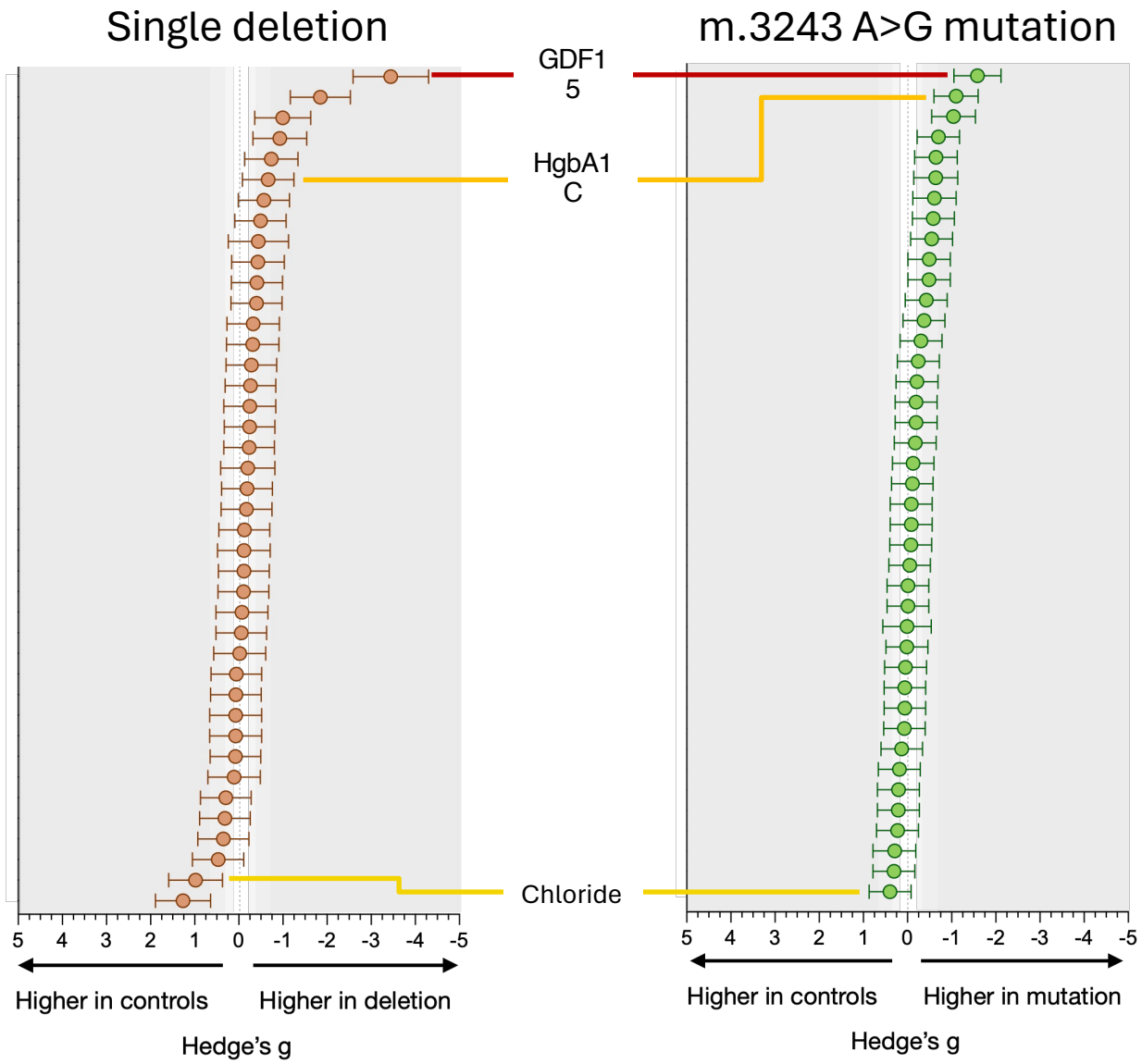
Single deletion



m.3243 A>G mutation



Evidence of multisystem dysregulation in mitochondrial disease



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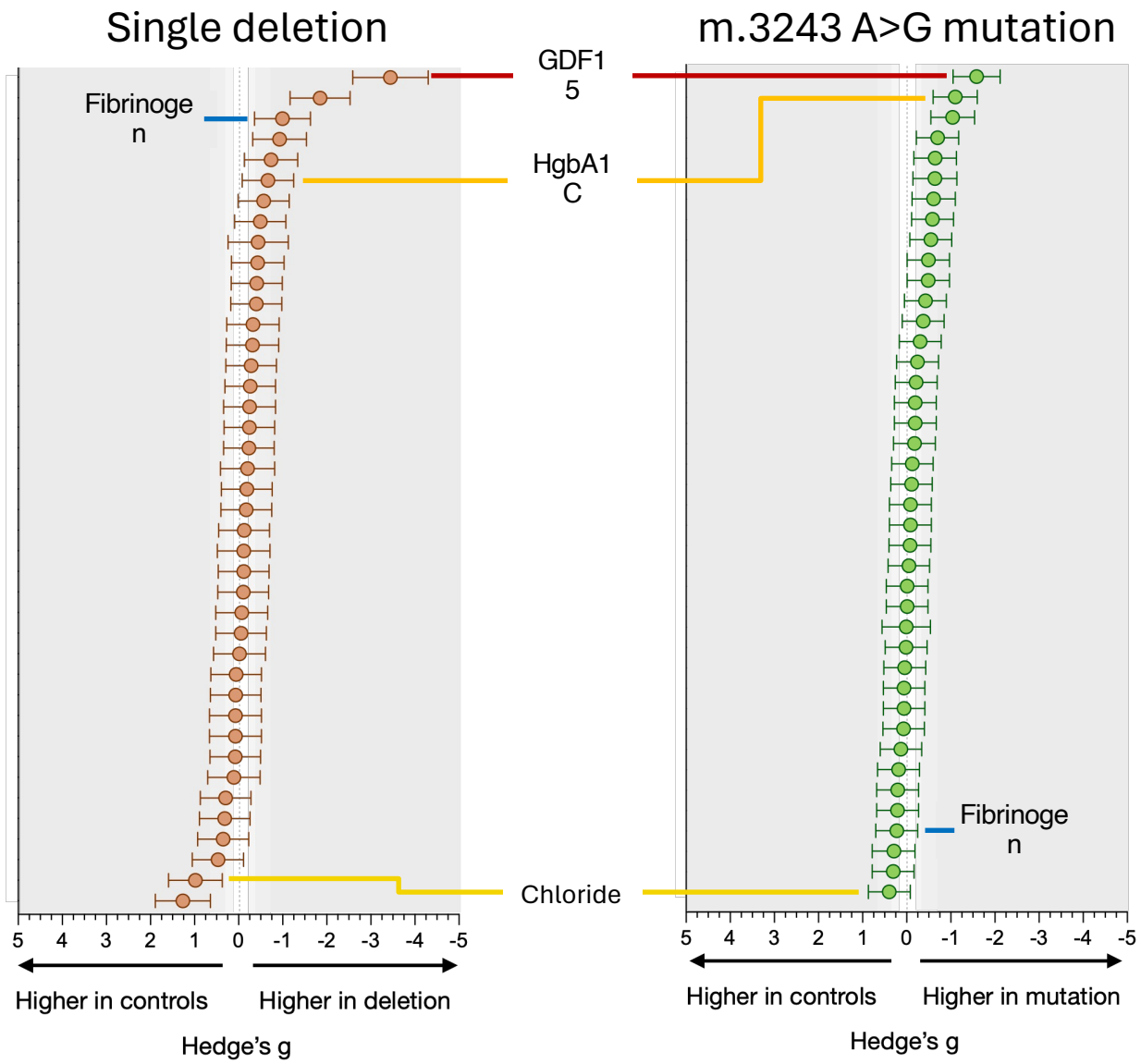
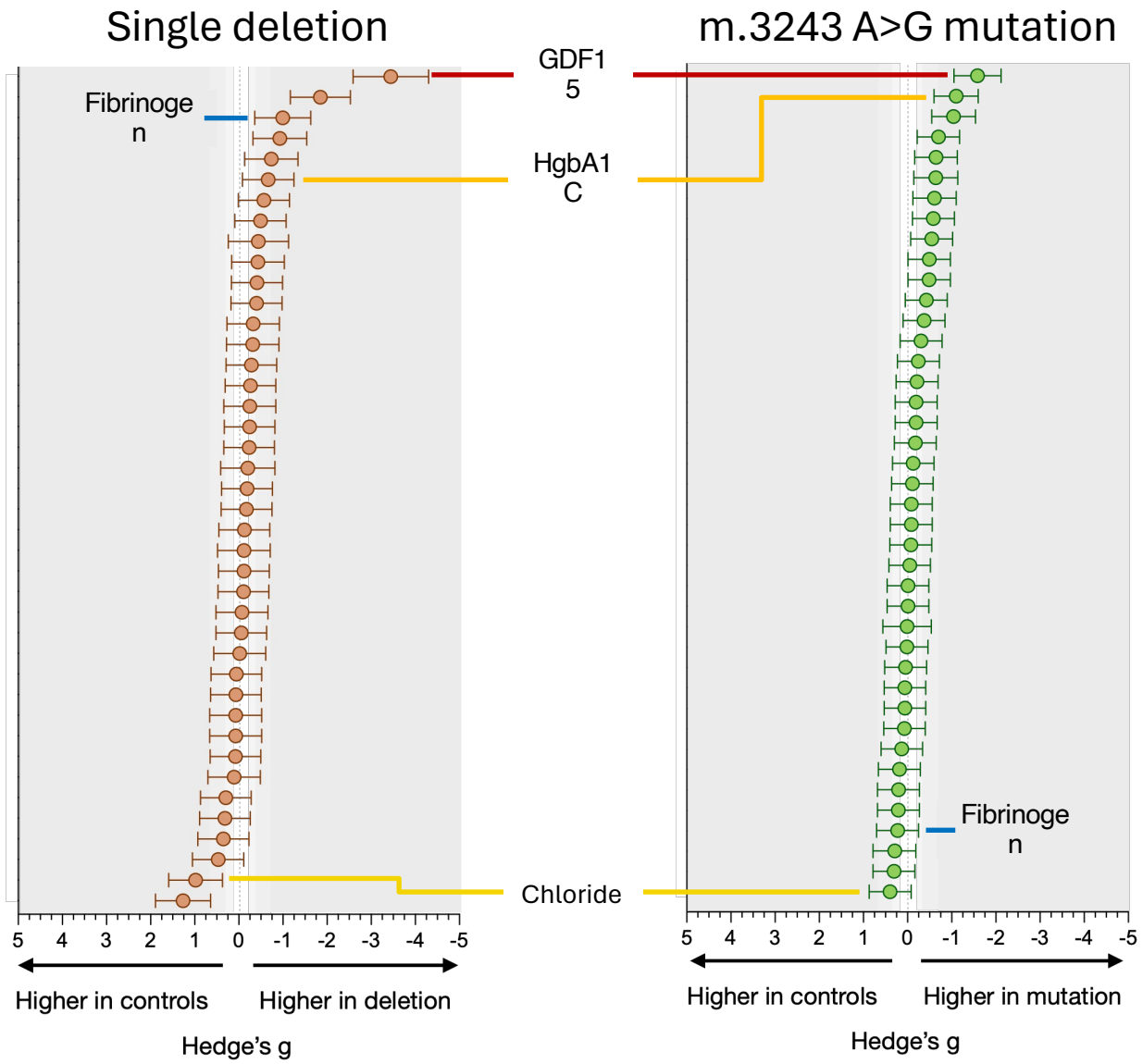


Evidence of multisystem dysregulation in mitochondrial disease



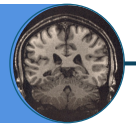
- Identify patterns of dysregulation related to baseline MAL (and its specific form)
- Relate these effects to immune cell mitochondrial respiratory capacity & bioenergetics
- Explore relevance for stress internalization & associations with clinical severity

Neuroimaging

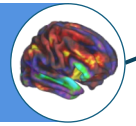
Ke Bo/ Tor Wager

Dartmouth College / Cognitive and affective neuroscience lab

Structural MRI



fMRI-BOLD



Heart rate & blood pressure

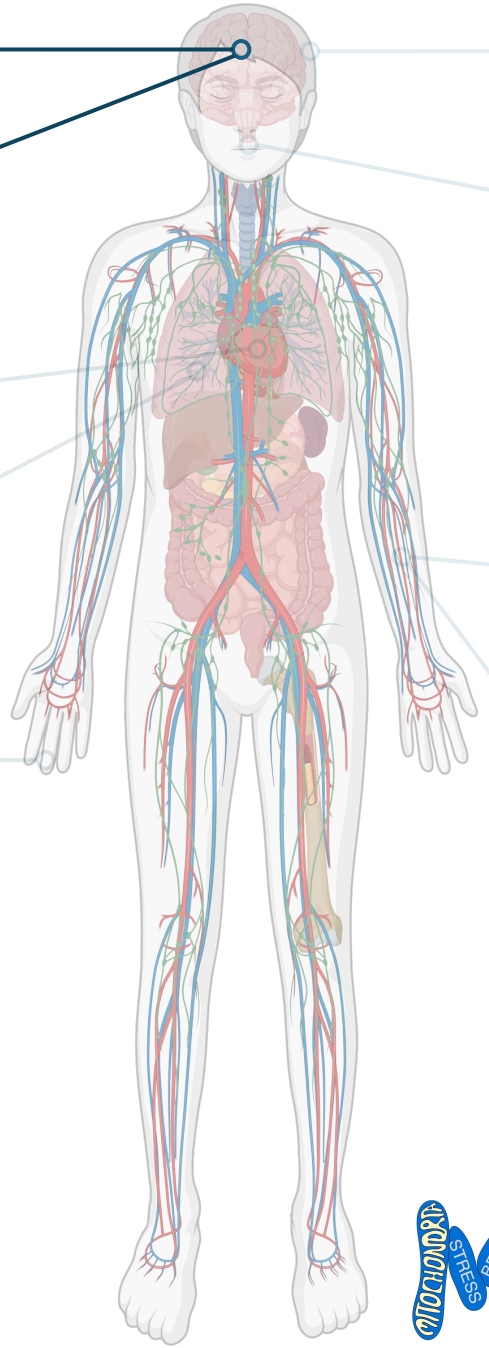
Respiration

Skin conductance

Psychophenotype & mental health

Home-based assessments

Neurocognitive assessment



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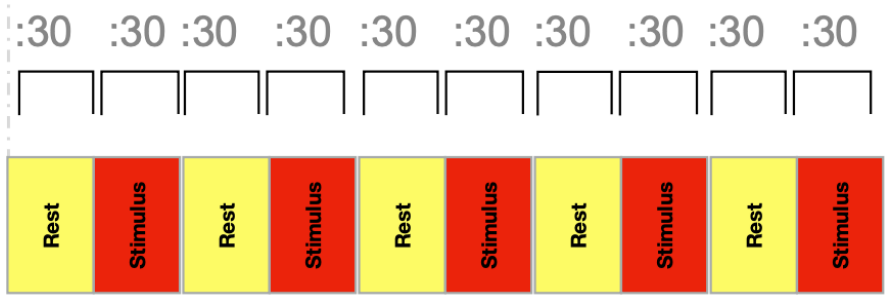
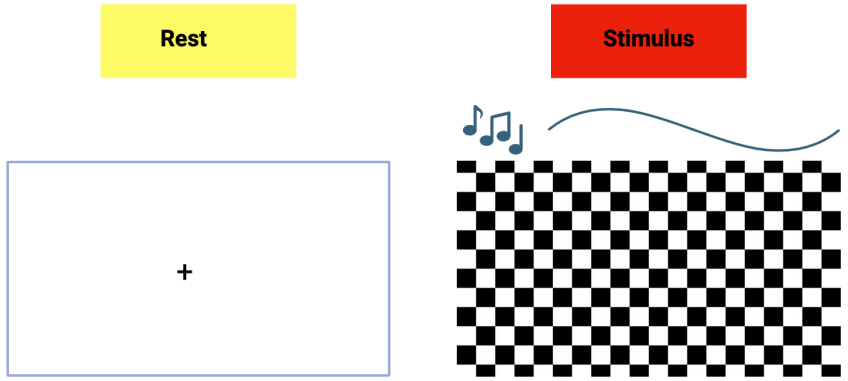
Neuroimaging Protocol

1.	Scout	(0:14 min)	Structural
2.	T2 scan	(11:15 min)	
3.	T1 scan	(5:21 min)	
4.	Multisensory	(5:00 min)	BOLD
5.	Resting state 1	(10:51 min)	
	Affect 13	Saliva 13	
6.	N-back task 1	(4:35 min)	BOLD
7.	N-back task 2	(4:35 min)	
8.	Story task	(6:07 min)	
9.	Arm wrap	(6:07 min)	
10.	DTI (seq 1-2)	(6:27 min)	Diffusion
	Affect 14	Saliva 14	
12.	DTI (seq 3-6)	(14:37 min)	

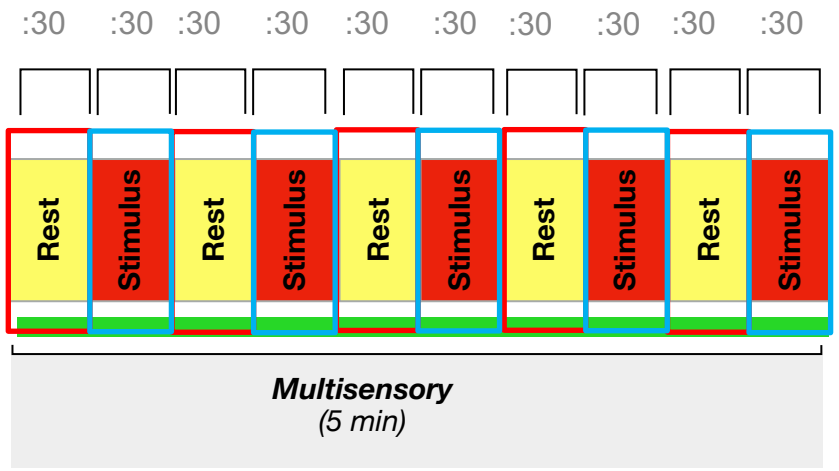
De-instrumentation



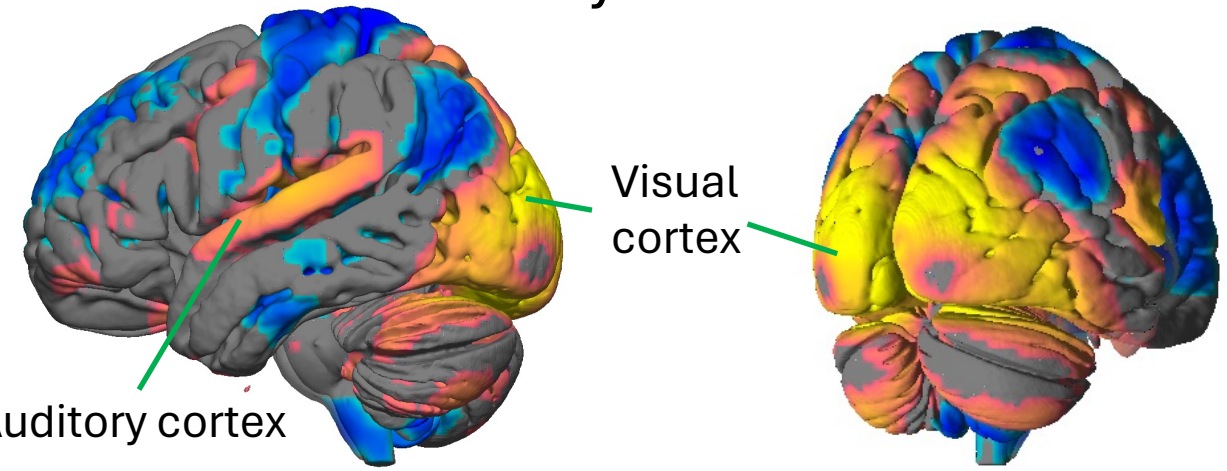


Visual: Flashing checker board
Audio : Tones that gradually change in frequency and amplitude

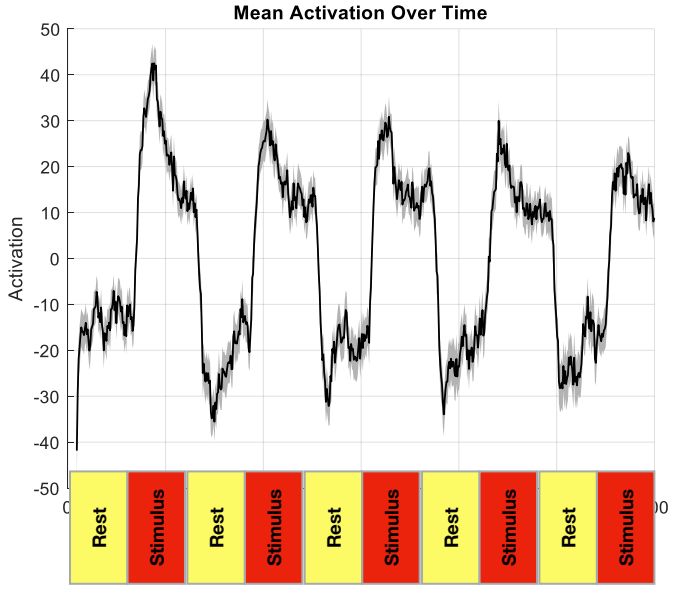
Neuroimaging- task (Multisensory)

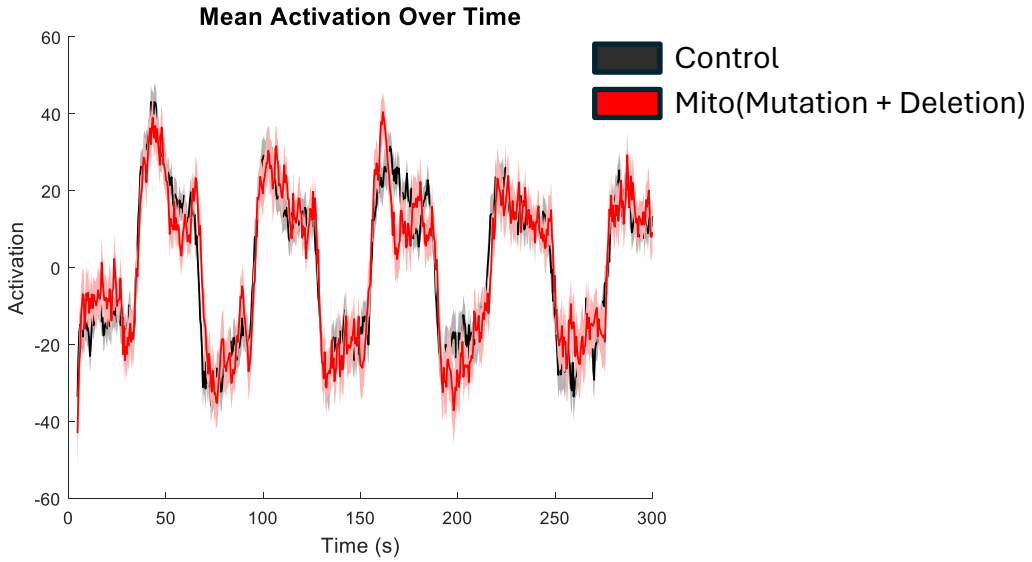


Sensory stimulus - Rest



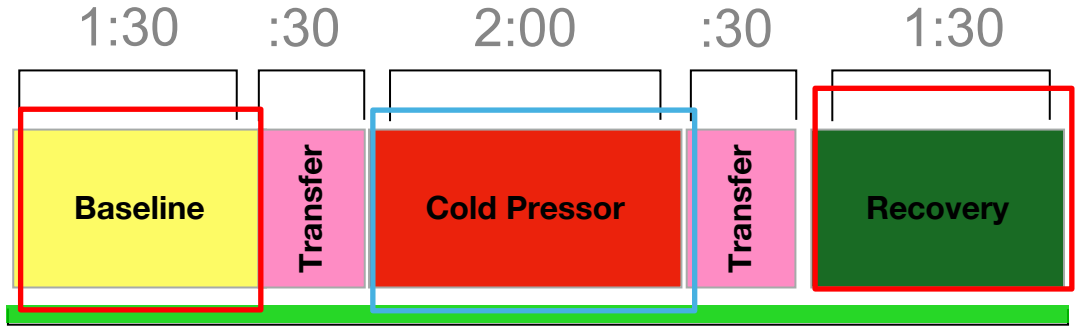
Primary visual cortex





Neuroimaging – other examples

Cold pain task



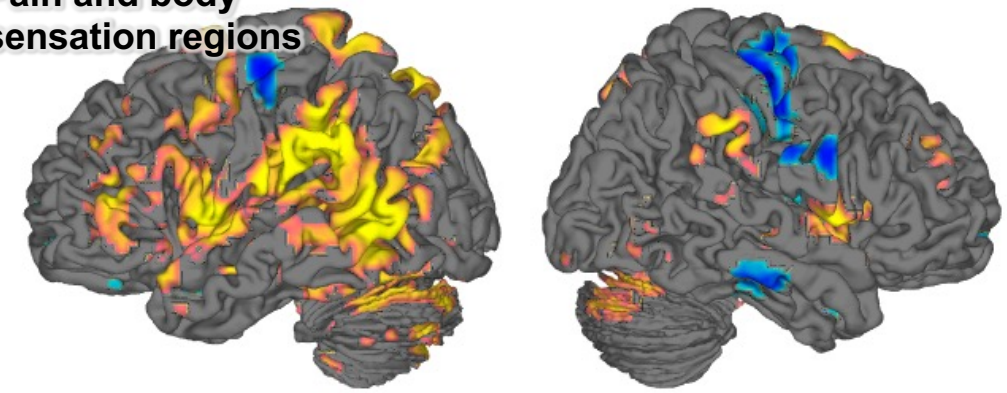
Room temperature wrapper on the right arm

Cold wrapper on the right arm

Room temperature wrapper on the right arm

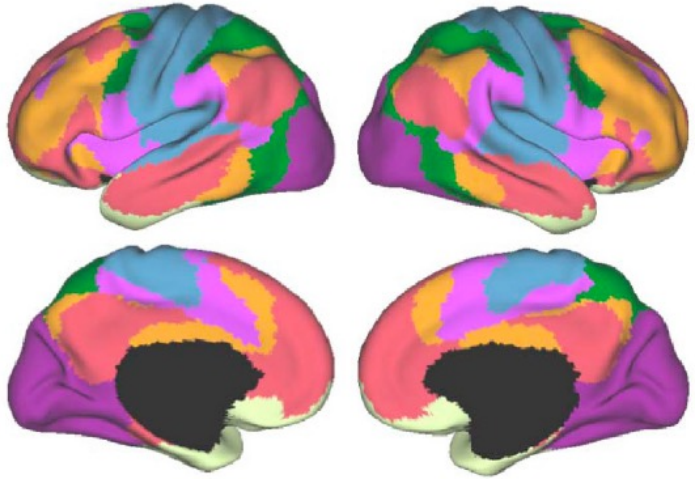
Cold pain - Rest

Pain and body sensation regions

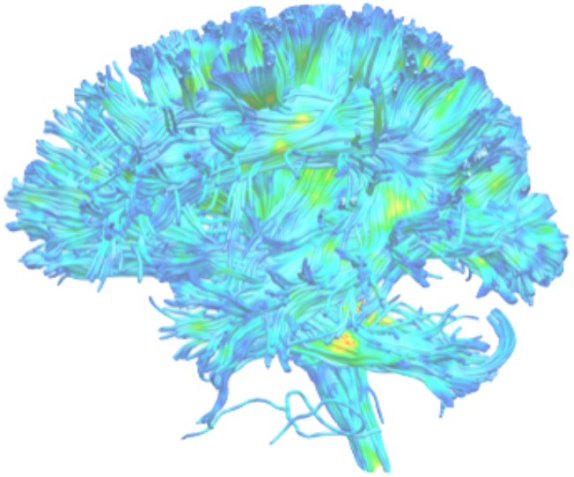


Left Right

Resting state functional imaging
large scale brain networks



DWI-visualization of white matter tracts



Dr. Michel Thiebaut de Schotten

Cell-free mitochondrial DNA

David Shire

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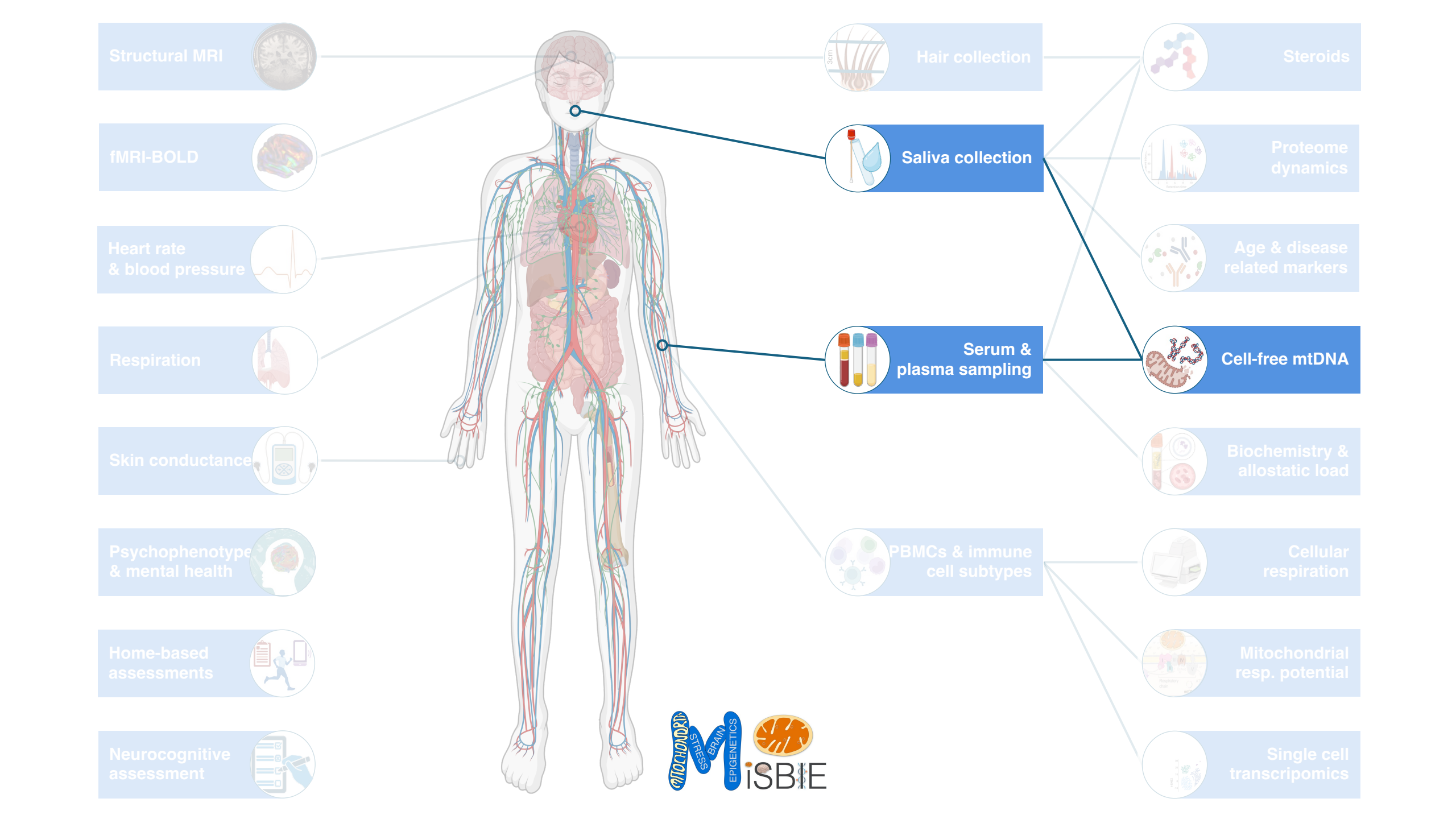
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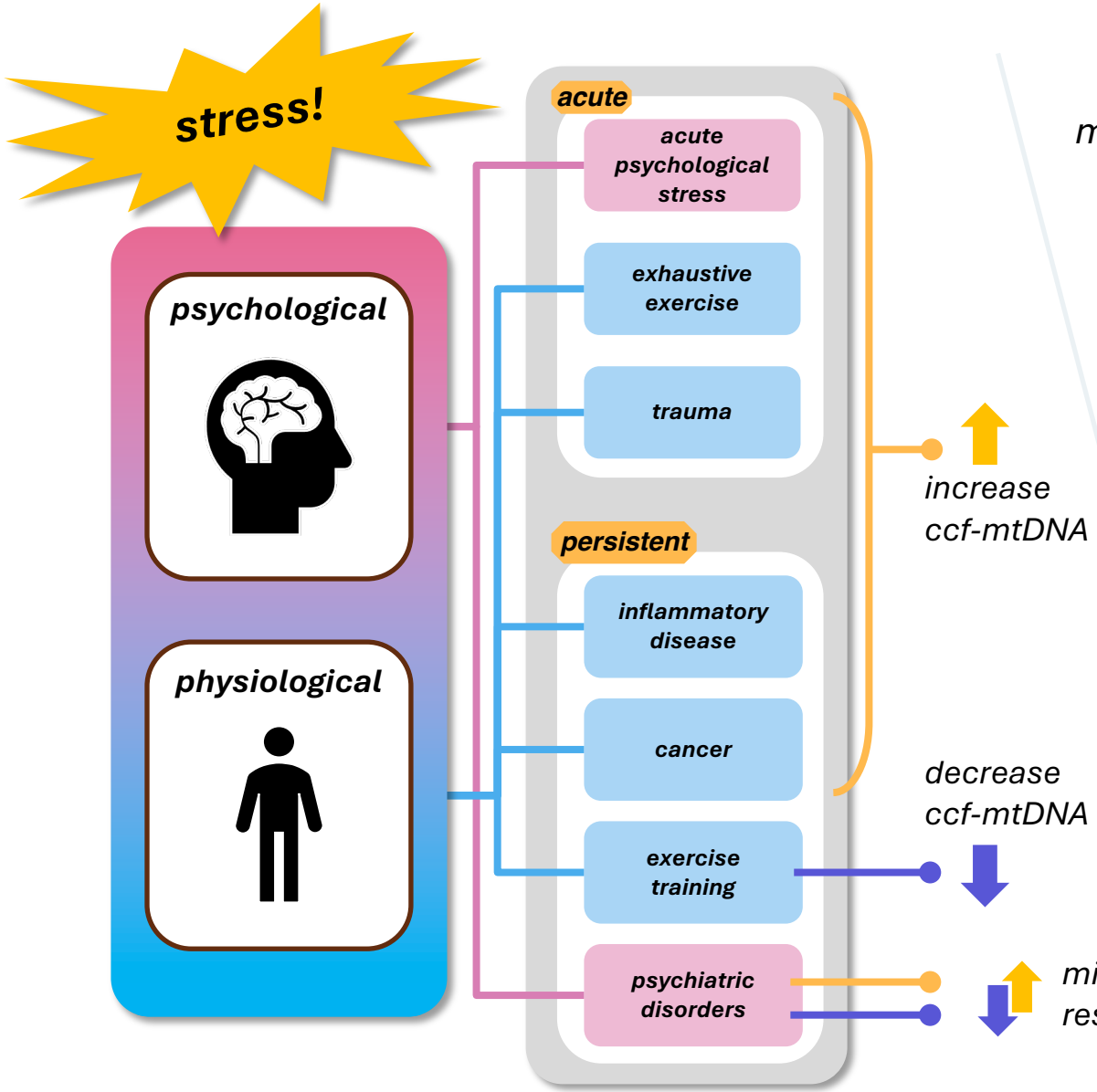
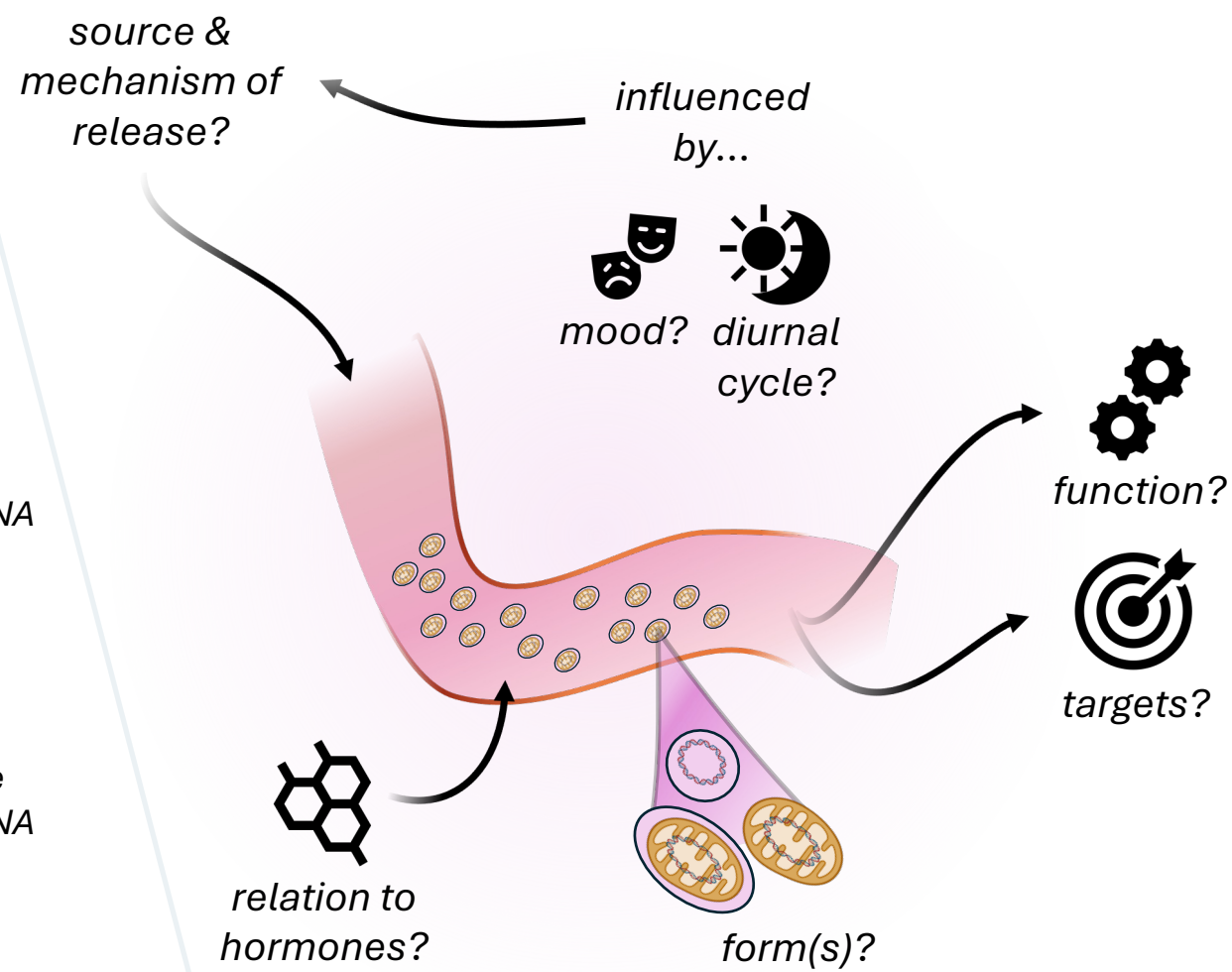
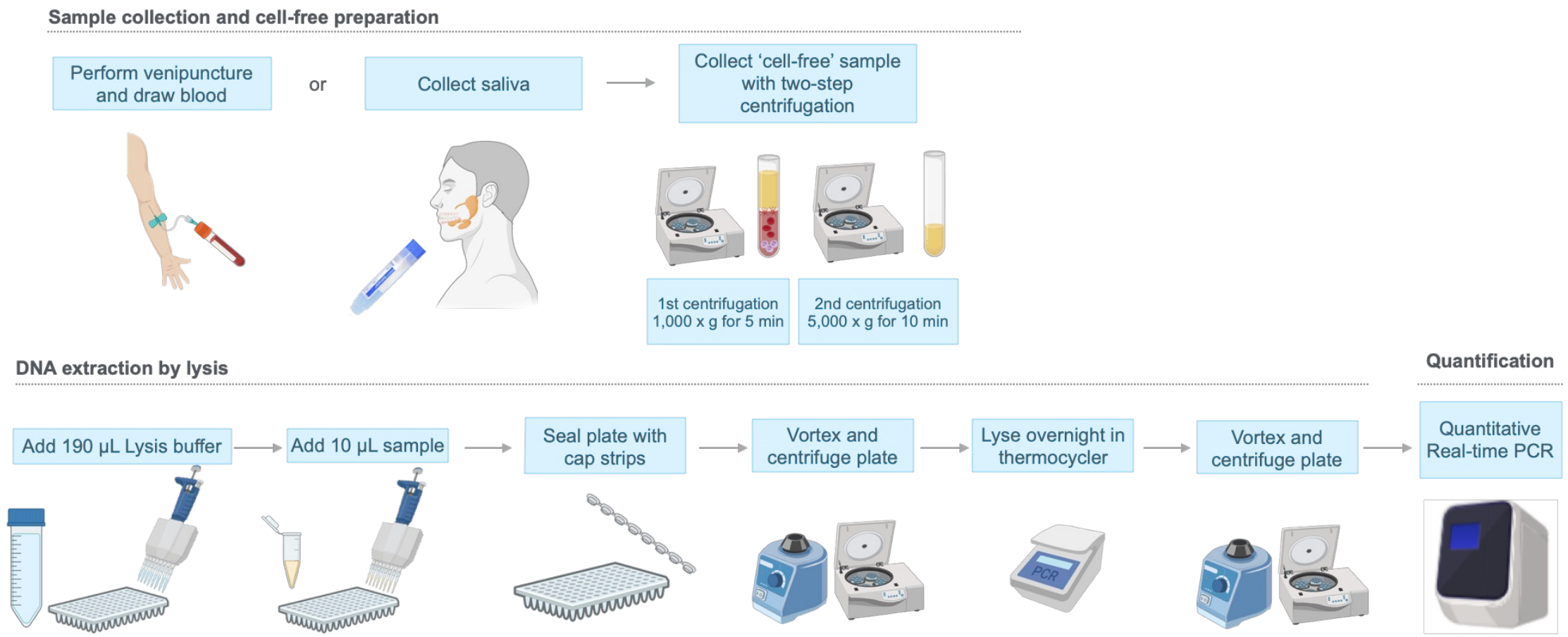
Cell-free mitochondrial DNA – background





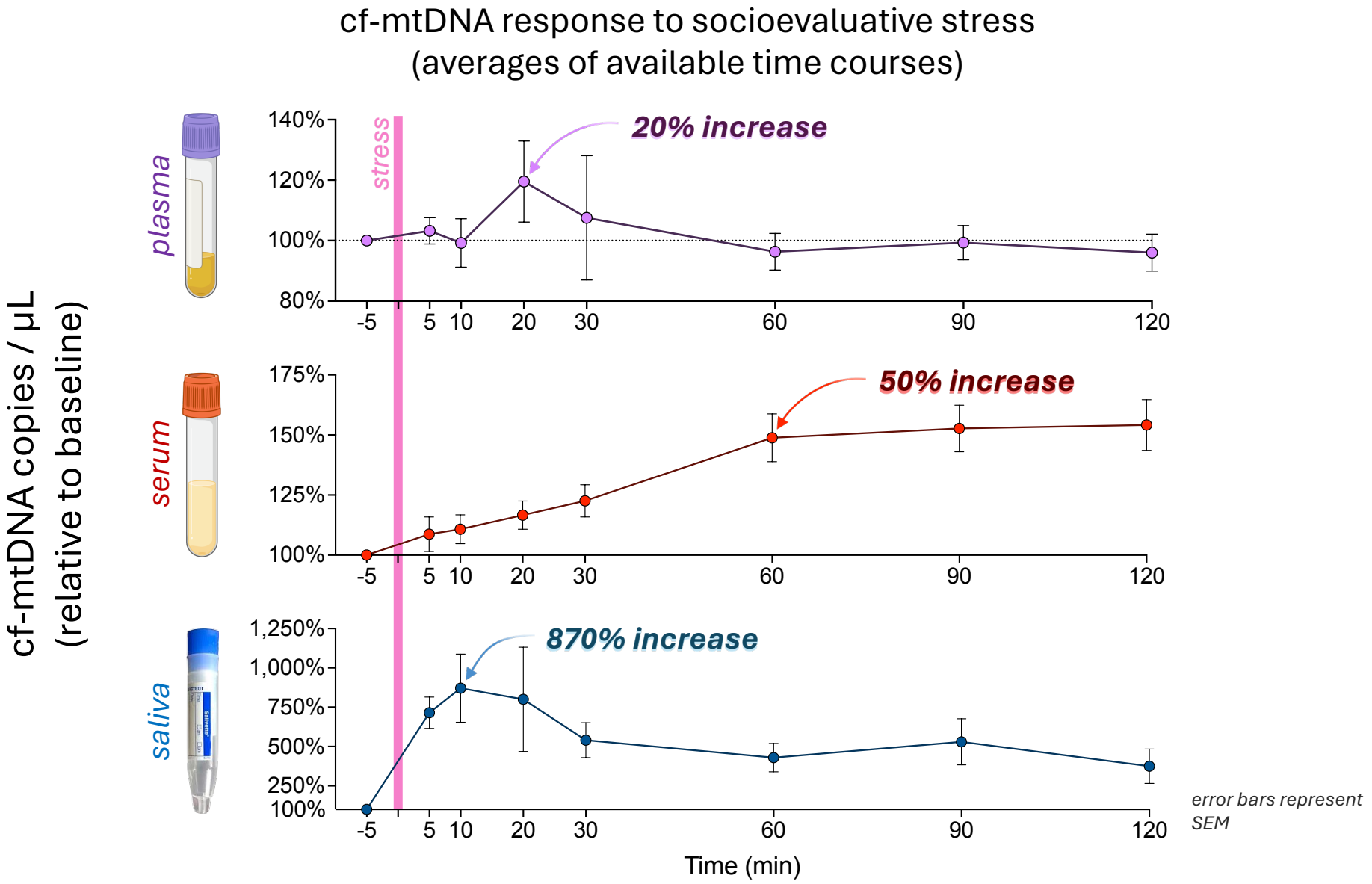
Cell-free mitochondrial DNA – procedure

Overview of MitoQuicLy method



Michelson et al., 2023

Cell-free mitochondrial DNA – results



error bars represent SEM

Actigraphy in MiSBIE

Aric A. Prather, PhD (UCSF)

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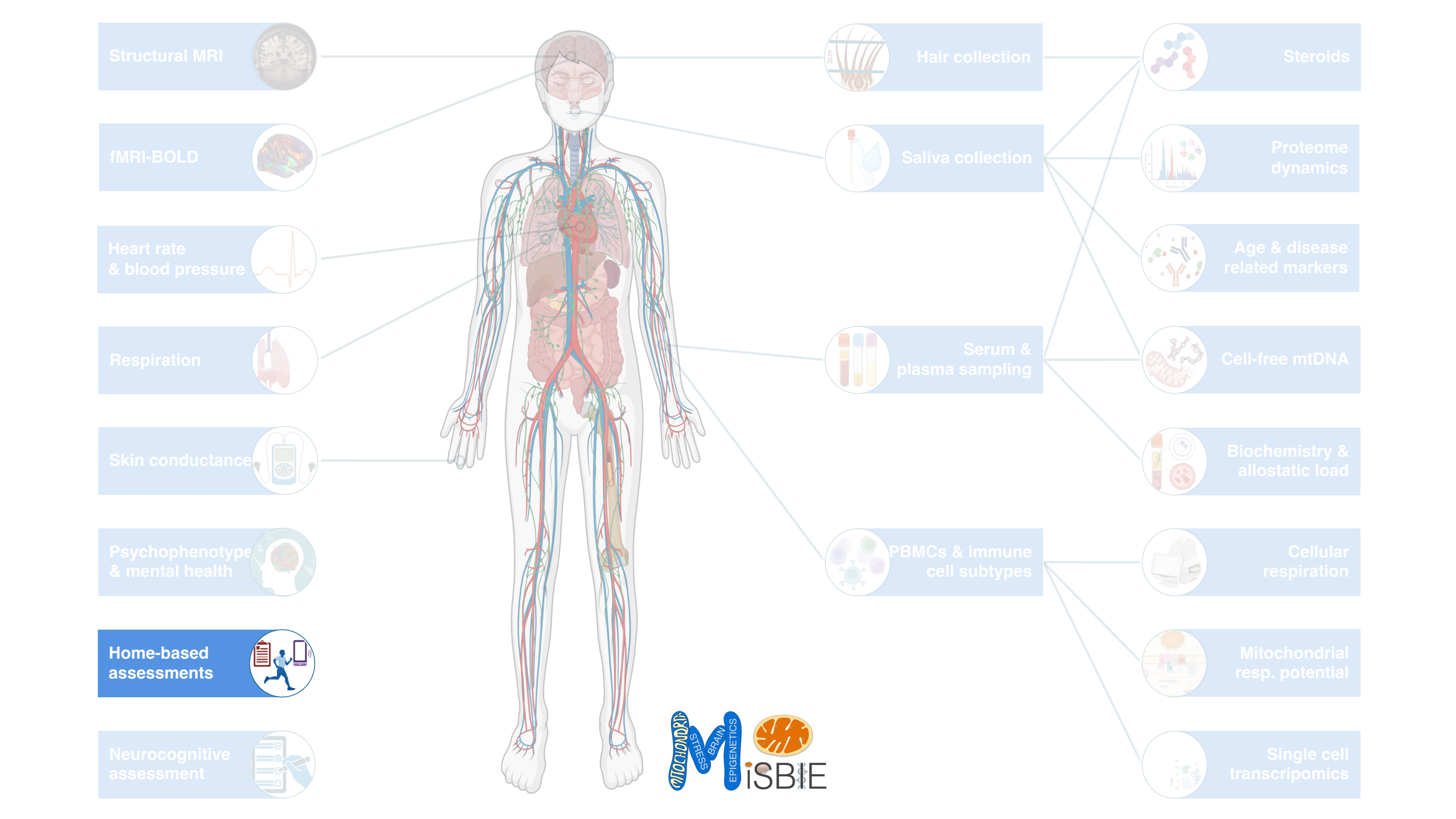
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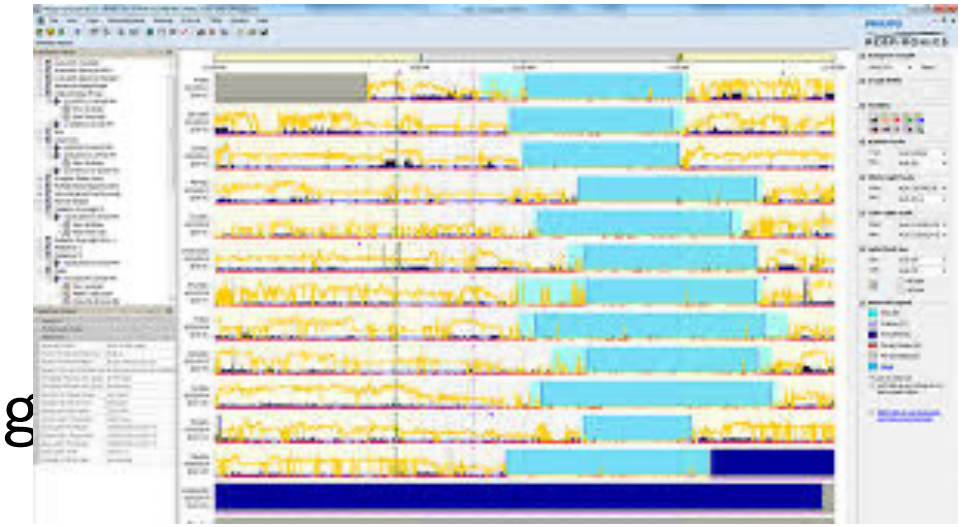
Sleep Behavior

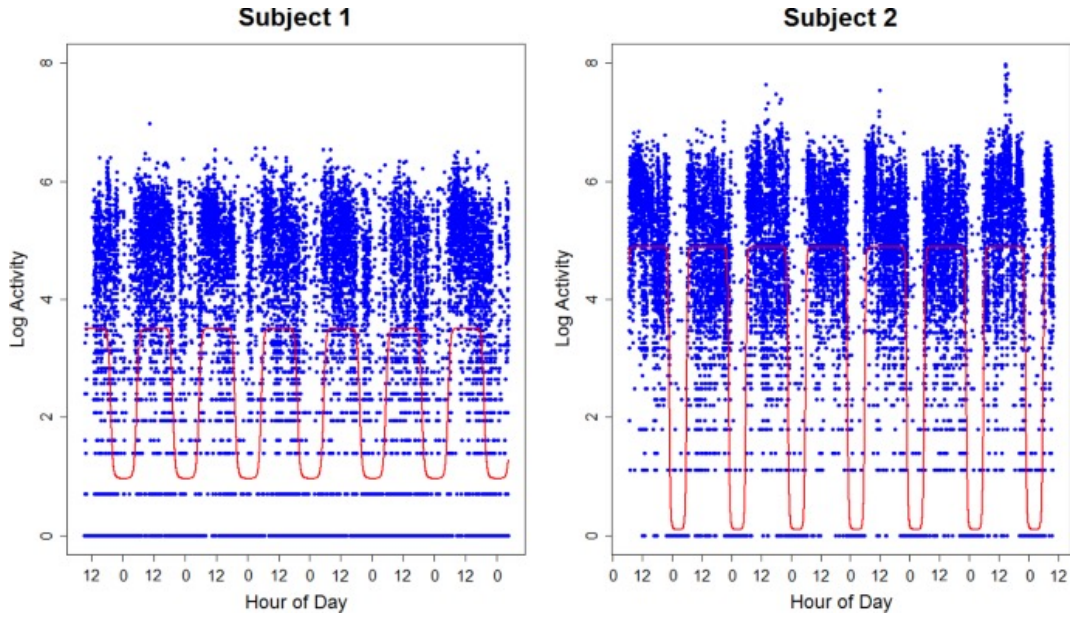
- 54 wrist actigraphy files (~ 8 days/nights of data)
  - Blinded to condition
  - Primary metrics:
    - Total sleep time
    - Sleep timing (midpoint)/Sleep Reg
    - Sleep fragmentation



Rest-Activity Rhythms and Physical Activity

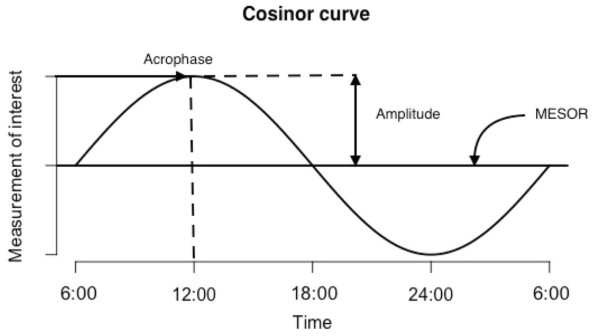
Association between accelerometer-measured amplitude of rest–activity rhythm and future health risk: a prospective cohort study of the UK Biobank

Hongliang Feng, Lulu Yang*, Sizhi Ai*, Yue Liu, Weijie Zhang, Binbin Lei, Jie Chen, Yaping Liu, Joey W Y Chan, Ngan Yin Chan, Xiao Tan, Ningjian Wang, Christian Benedict, Fujun Jia, Yun Kwok Wing†, Jihui Zhang†*



Primary outcome:

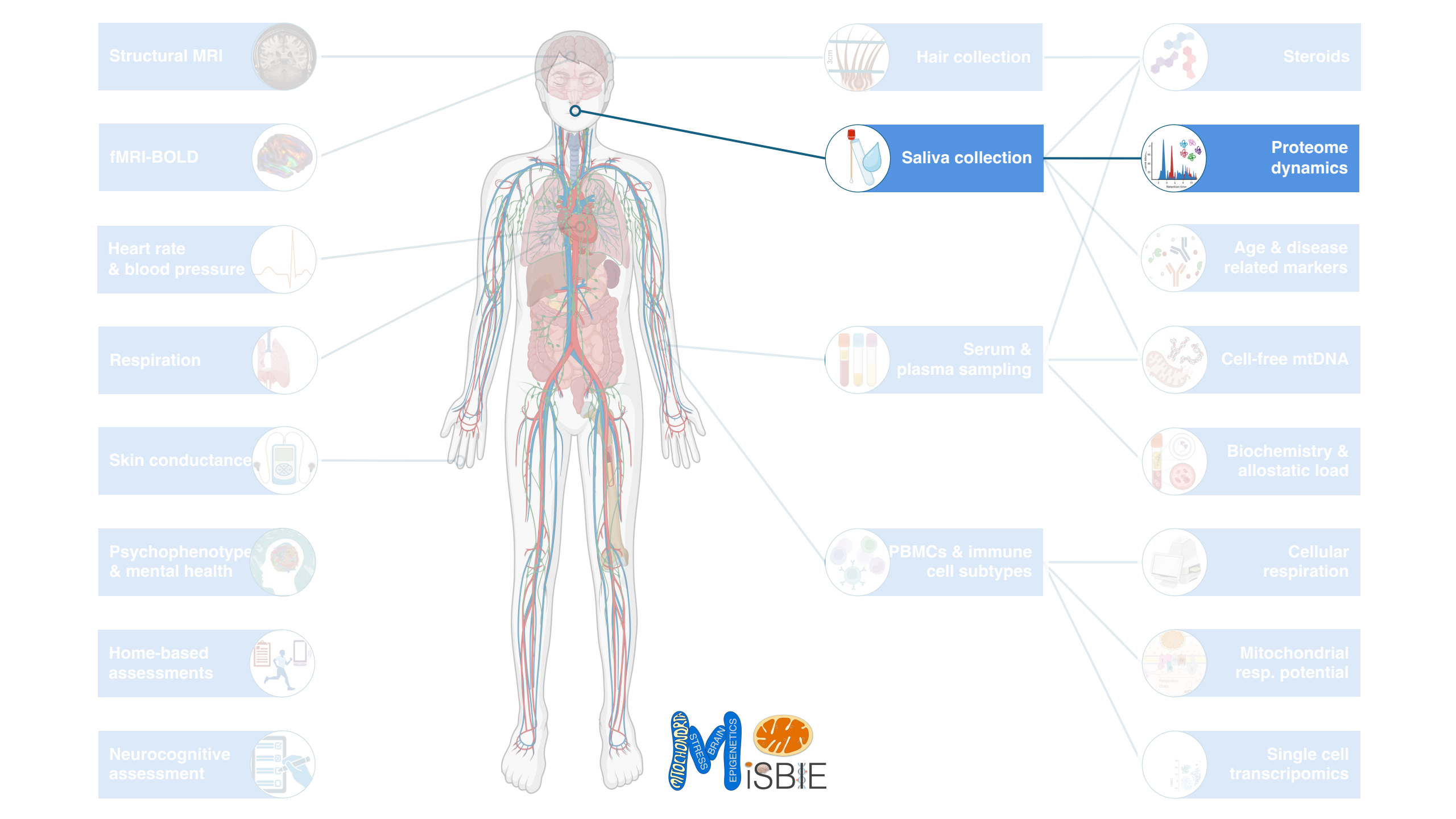
- Amplitude
- Cosine
- Mesor



Saliva Awakening Proteome Dynamics

Molei Liu, Alan Cohen et al.

Department of Biostatistics, Columbia Mailman School of Public Health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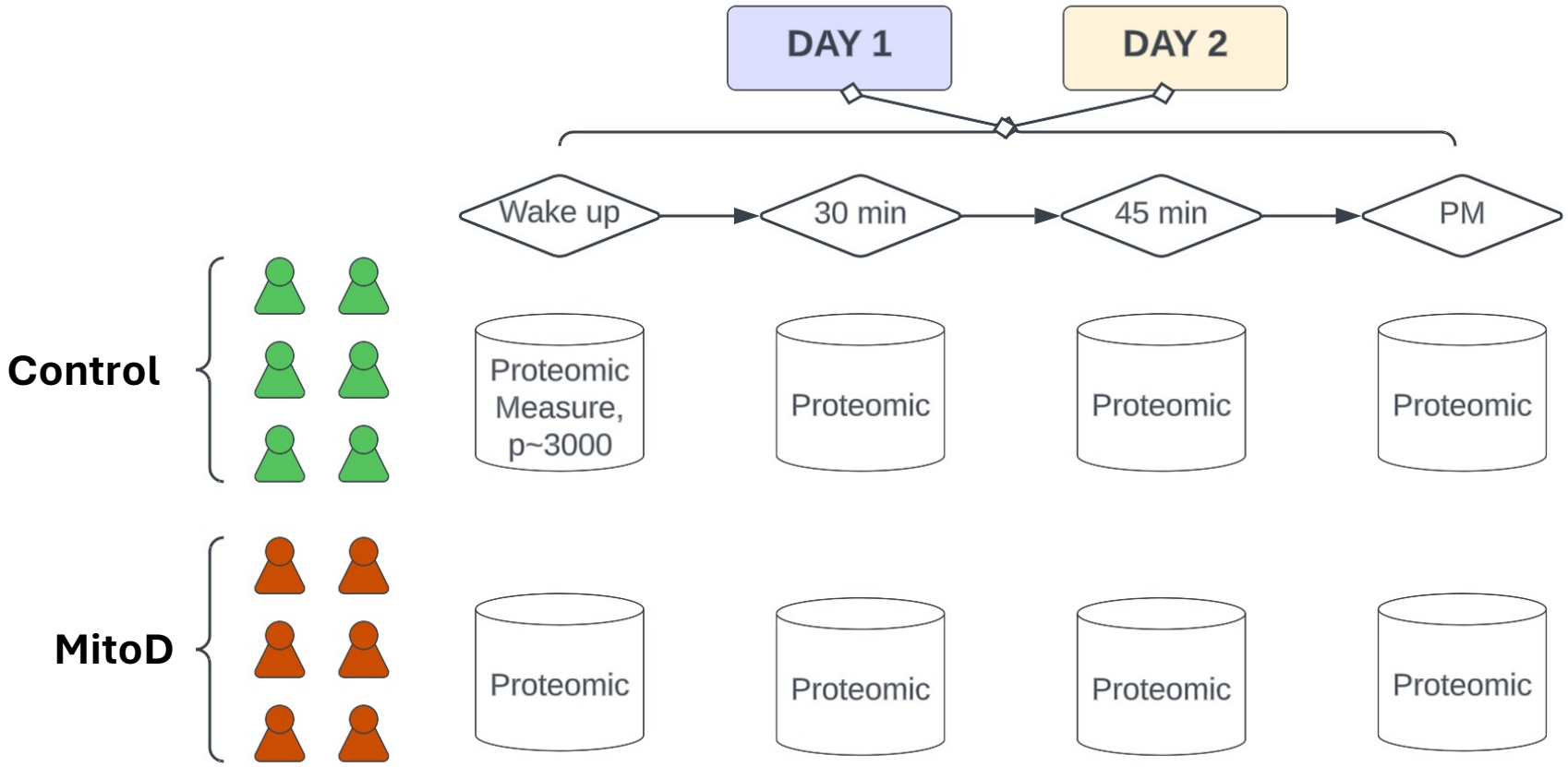
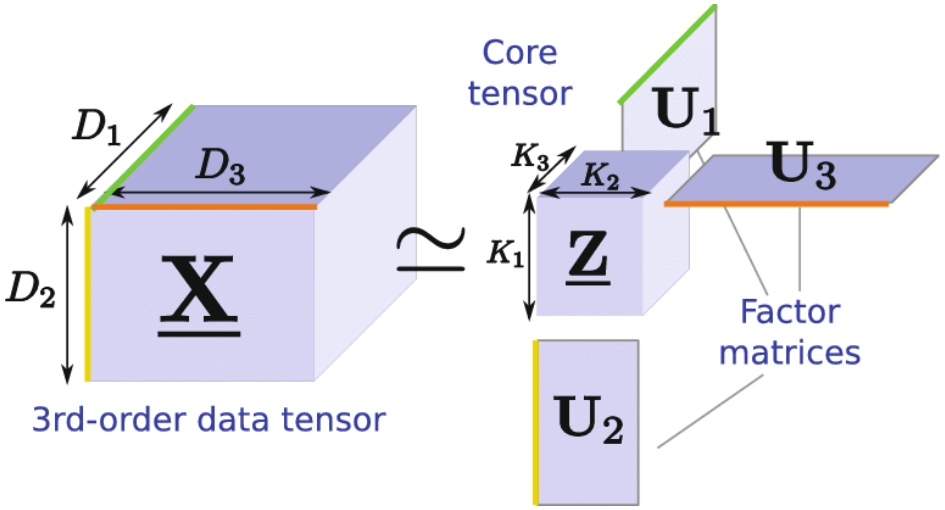
Study Design & Data Structure

- From MISBIE dataset: 6 cases + 6 matched controls.
- Proteome data (level of ~ 3000 proteins) measured by Olink platform.

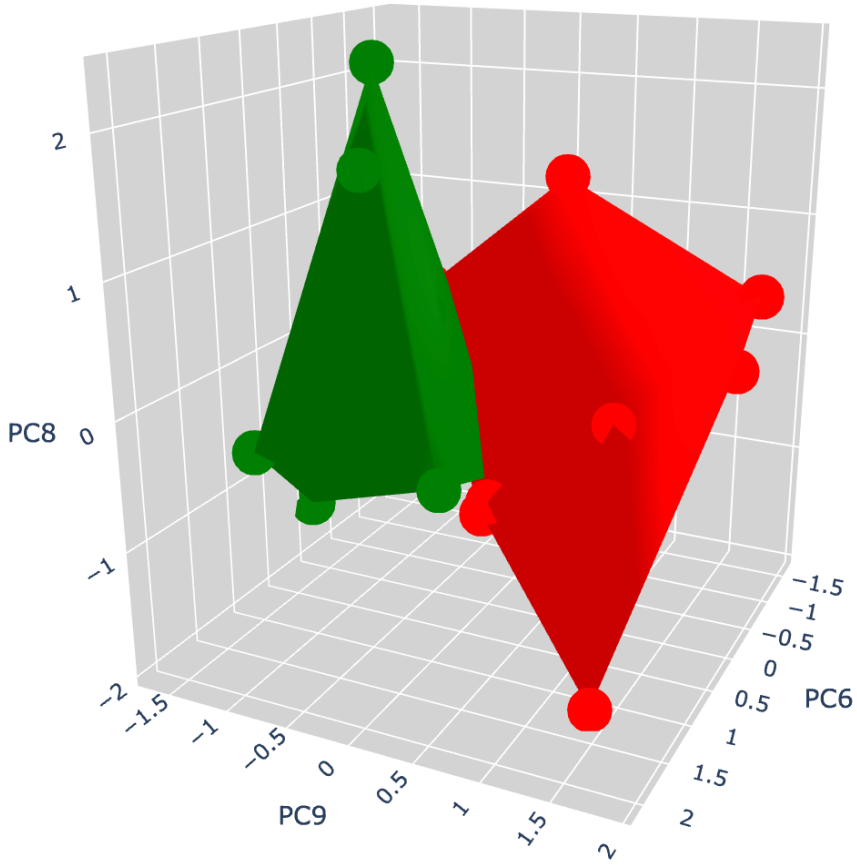


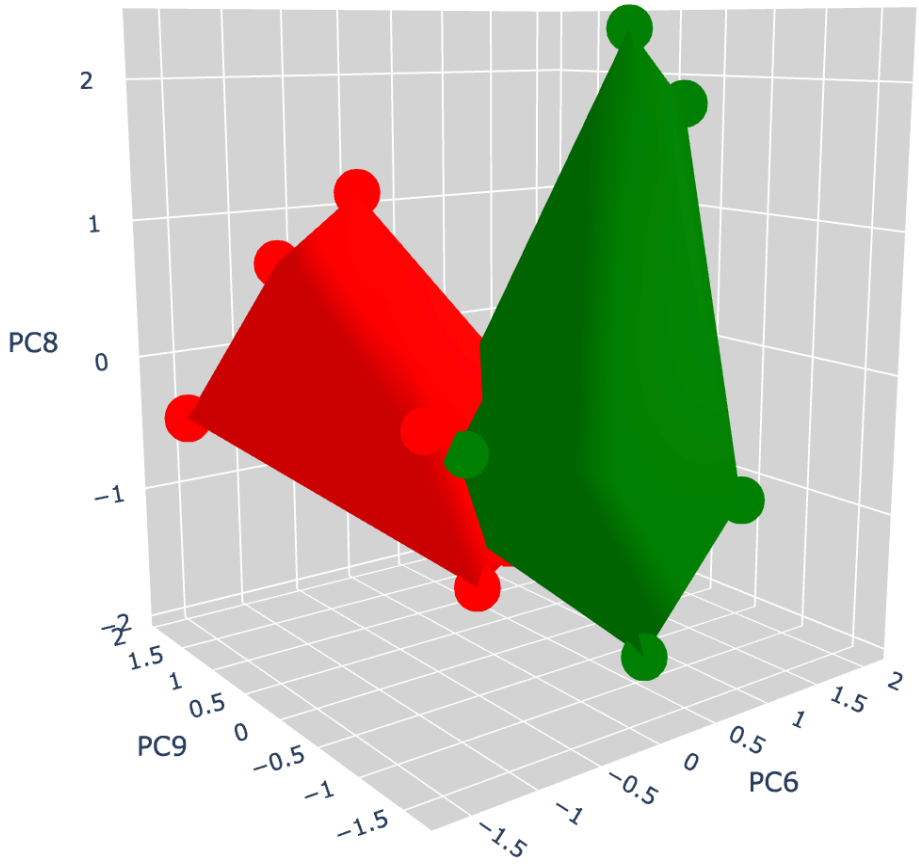
Methods

- Unsupervised: do not use the disease status for training; only for validation.
- Focus on the dynamic change (e.g., increment, elasticity)
- Capture co-expression/regulation structure.
- Challenges: small sample; high-dimensionaltiy; weak signal of a single biomarker.



Results (1/3): tensor clustering analysis

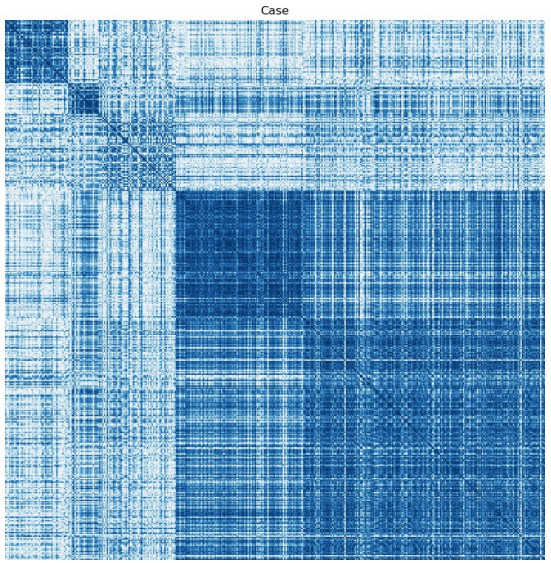




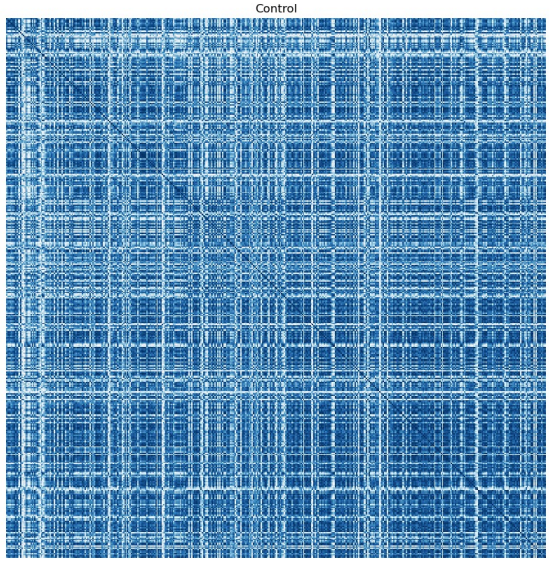
Health
- MitoD
- Control

Results (2/3): correlation of dynamic change

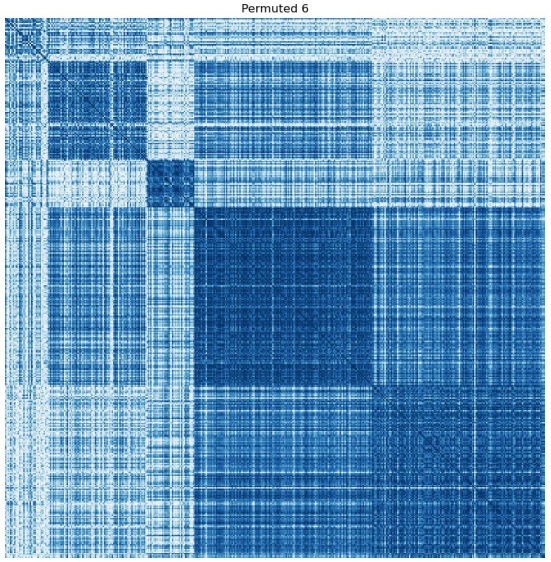
Control:



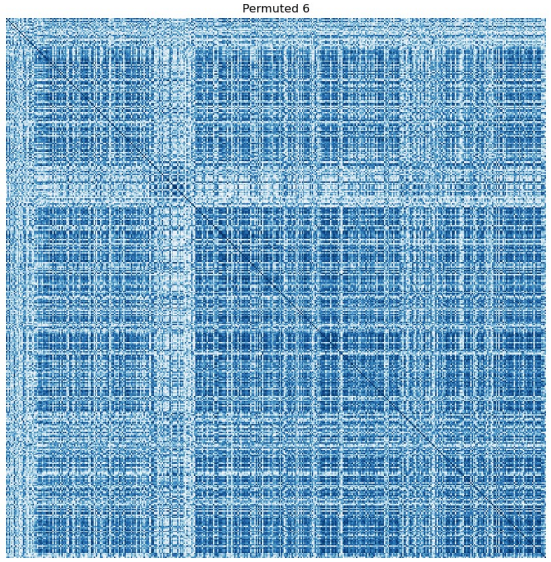
MitoD:



Random:

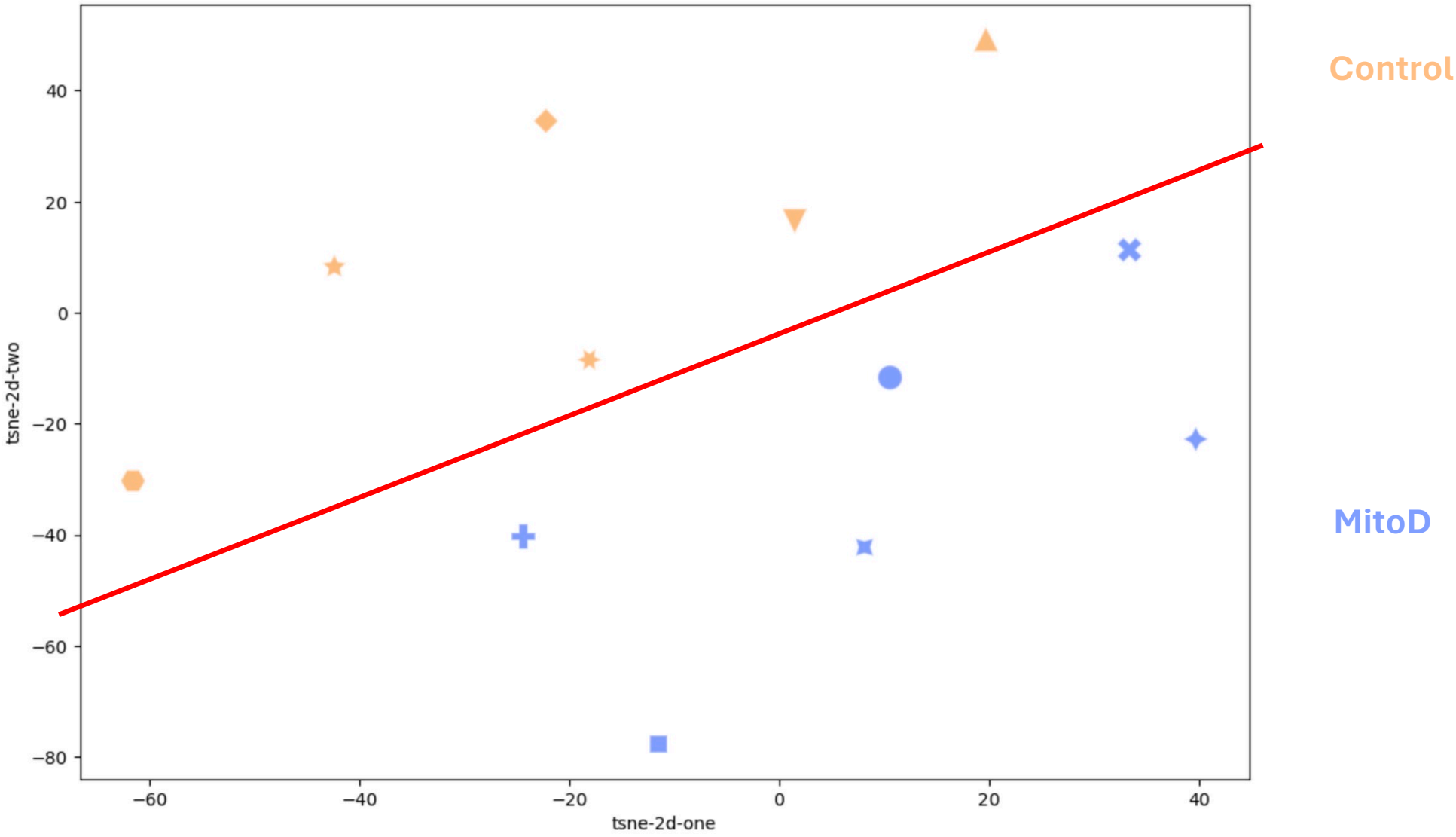


Random:



- Permutation test for the differential correlation (case v.s. control):
  P-value = 0.002
- Presented correspond to changes from 30 min to 0. Similar results for pm – 45.

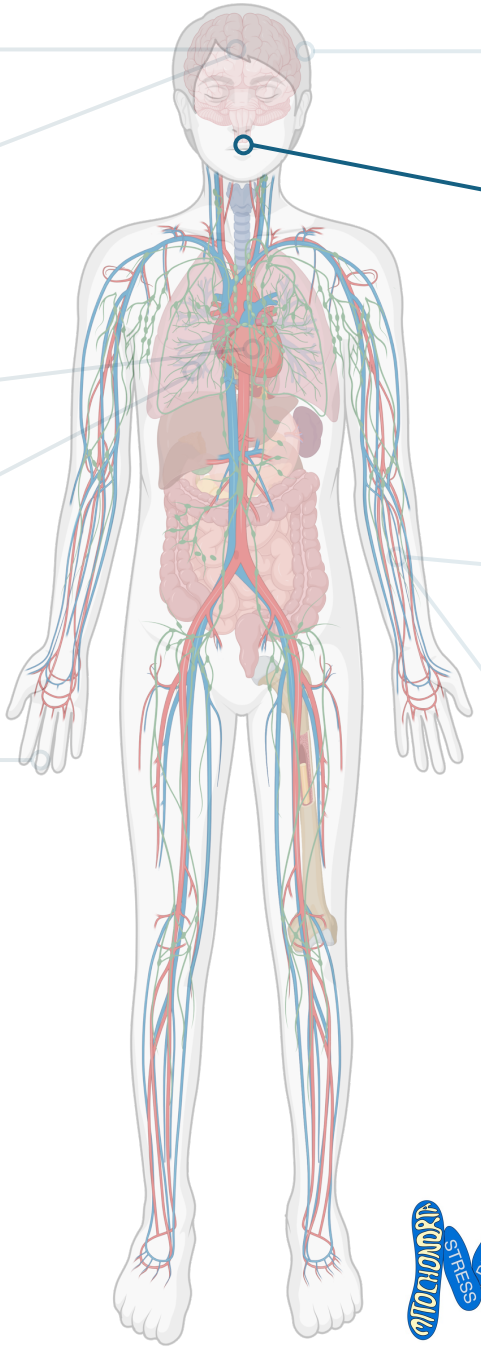
Results (3/3): t-SNE clustering with elasticity



Age-related mitochondrial disease biomarker dynamics

Hannah Huang

CUIMC - Mitochondrial Psychobiology Group



Structural MRI

fMRI-BOLD

Heart rate & blood pressure

Respiration

Skin conductance

Psychophenotype & mental health

Home-based assessments

Neurocognitive assessment

Hair collection

Saliva collection

Serum & plasma sampling

PBMCs & immune cell subtypes

Steroids

Proteome dynamics

Age & disease related markers

Cell-free mtDNA

Biochemistry & allostatic load

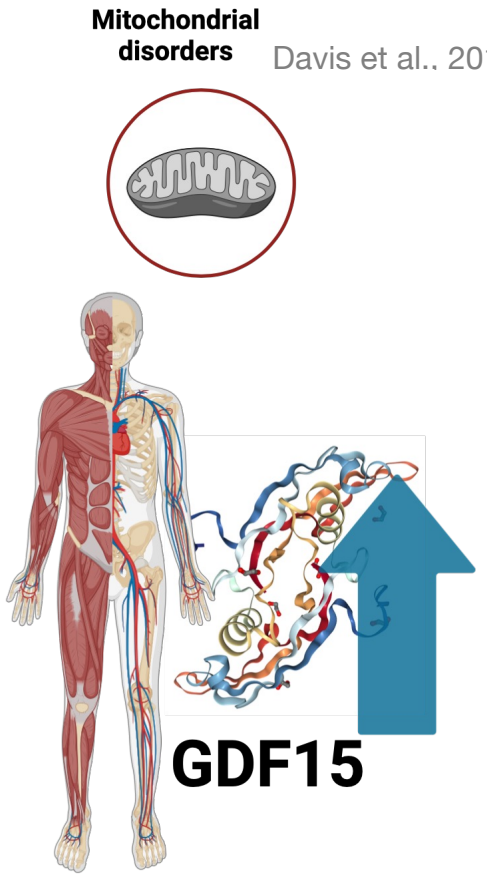
Cellular respiration

Mitochondrial resp. potential

Single cell transcripomics

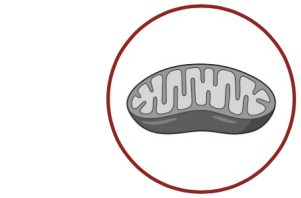
MiSBIE

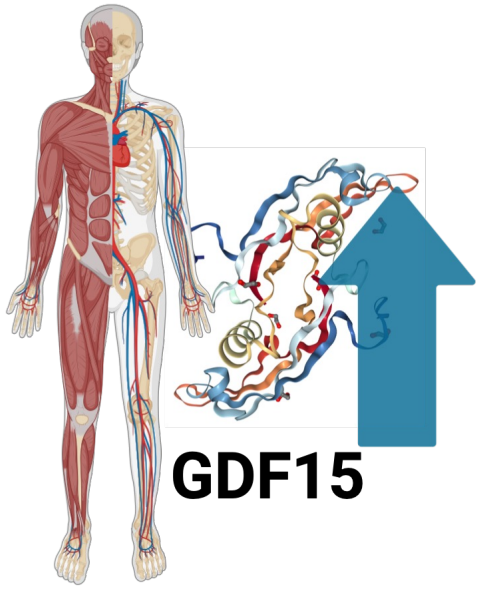
Why are we interested in GDF15?



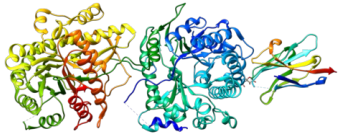
Why are we interested in GDF15?

Mitochondrial disorders Davis et al.. 2016





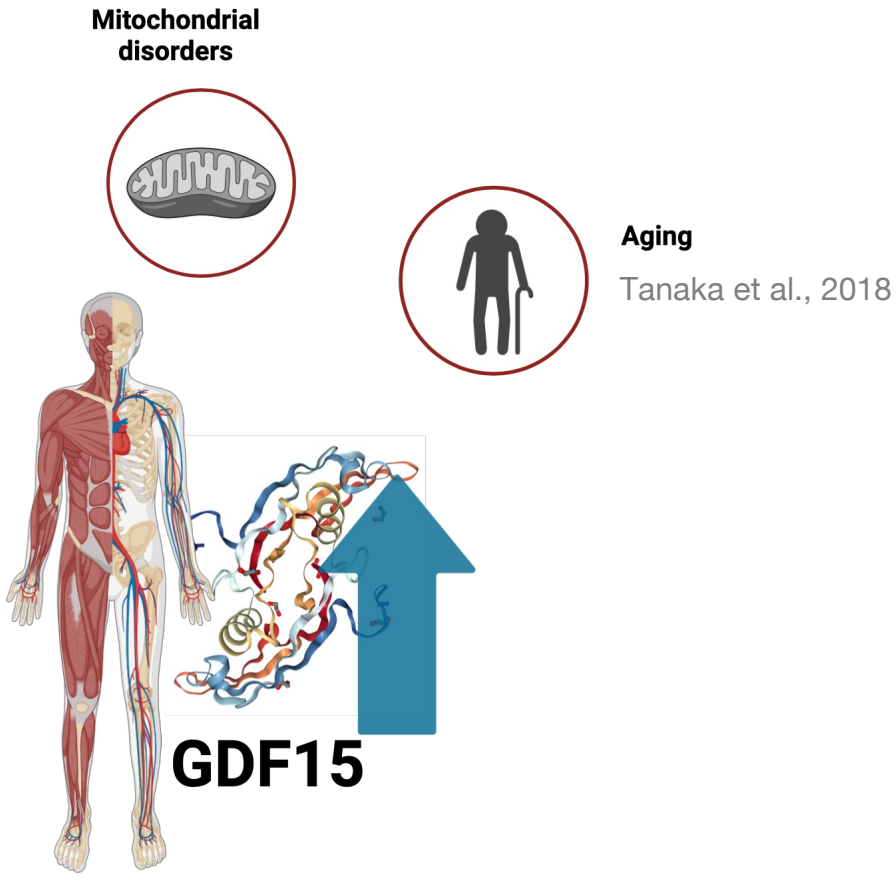
GDF15



FGF21

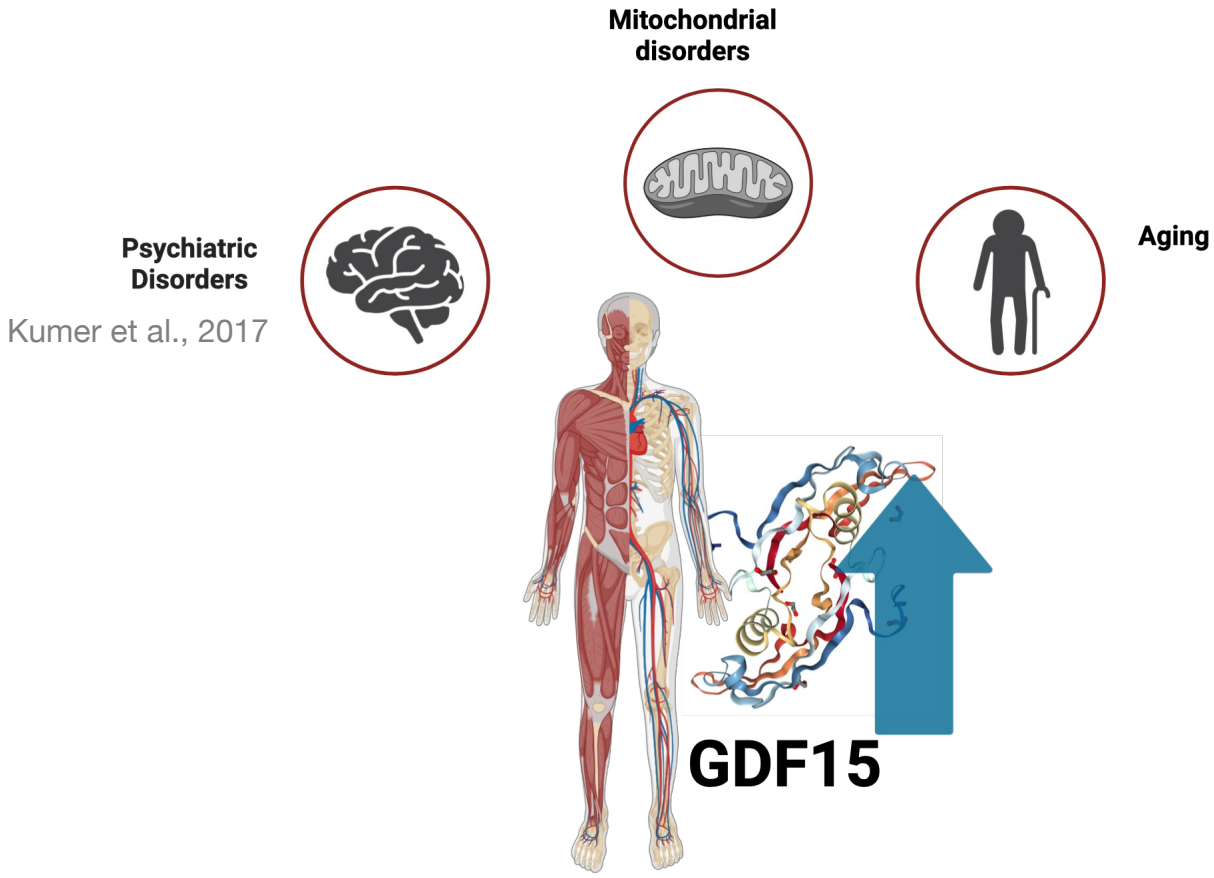
Lehtonen et al., 2016

Why are we interested in GDF15?



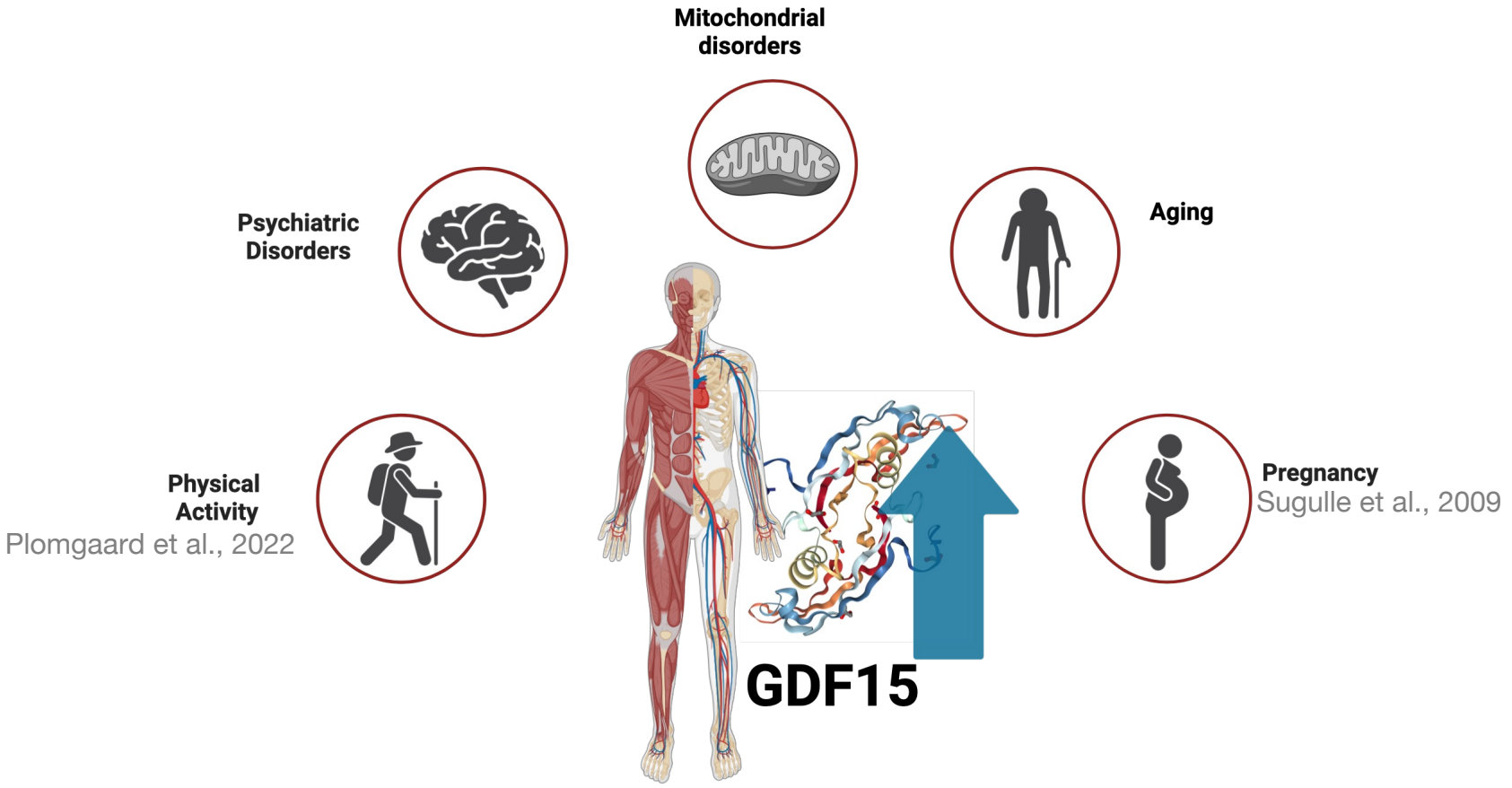
Tanaka et al., 2018

Why are we interested in GDF15?

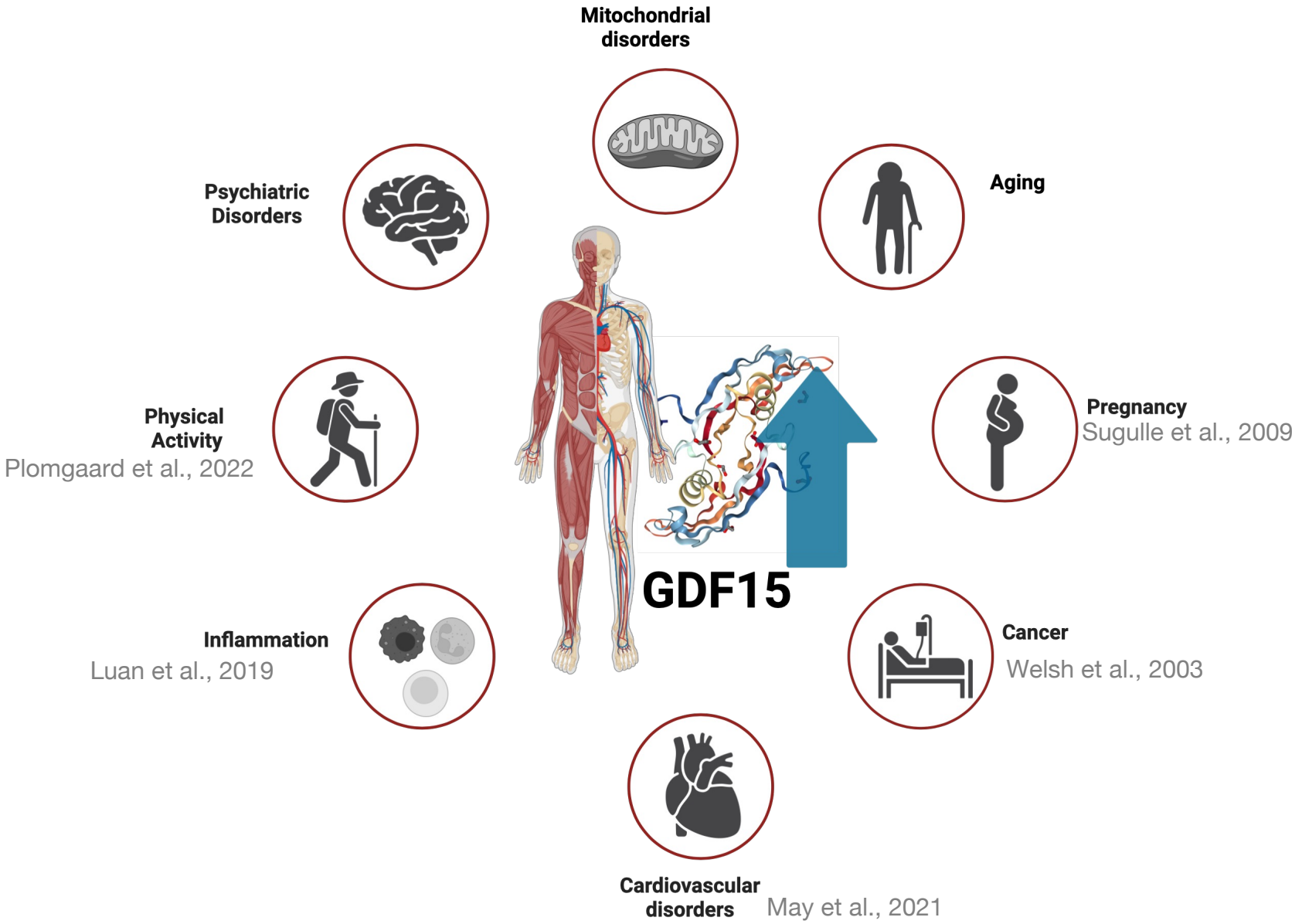


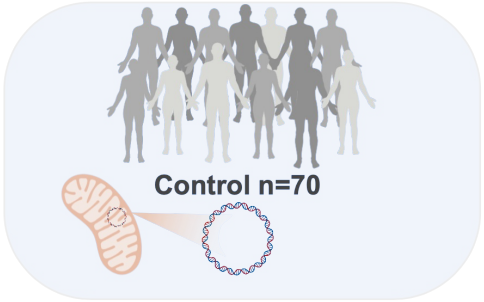
Kumer et al., 2017

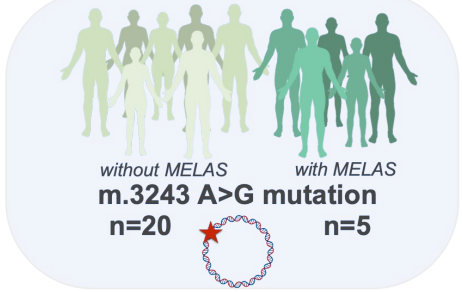
Why are we interested in GDF15?

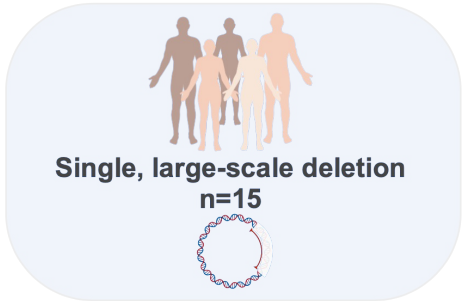


Why are we interested in GDF15?

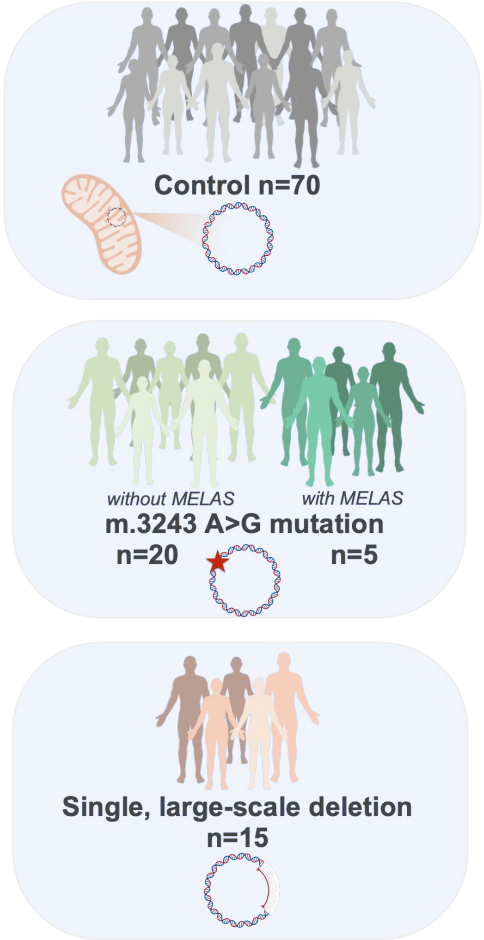


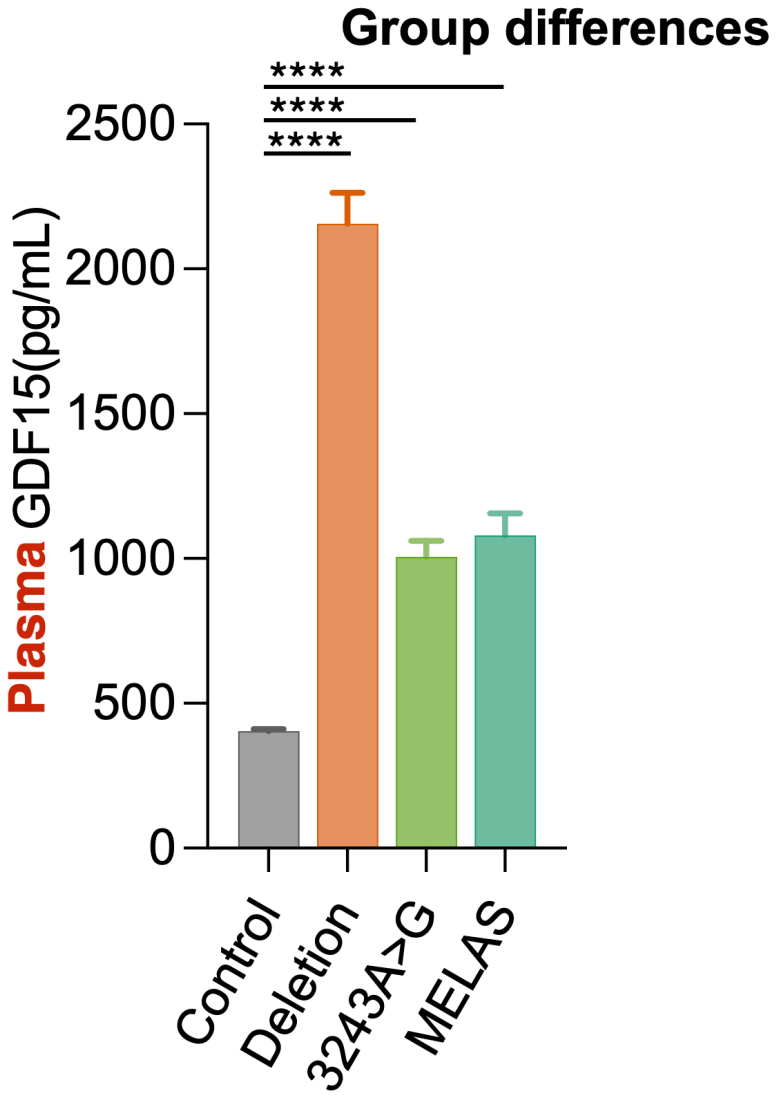

Control n=70


without MELAS
with MELAS
m.3243 A>G mutation
n=20
n=5


Single, large-scale deletion
n=15

Plasma and saliva GDF15 is elevated in MitoD patients

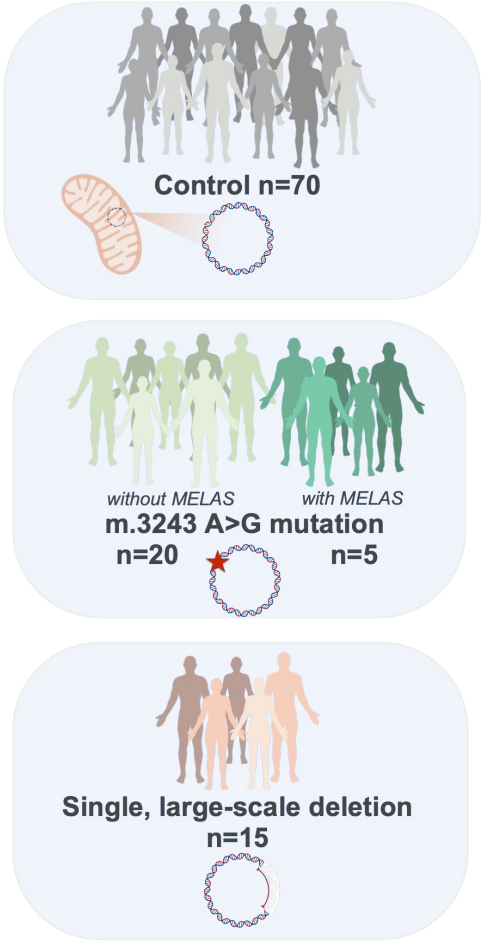


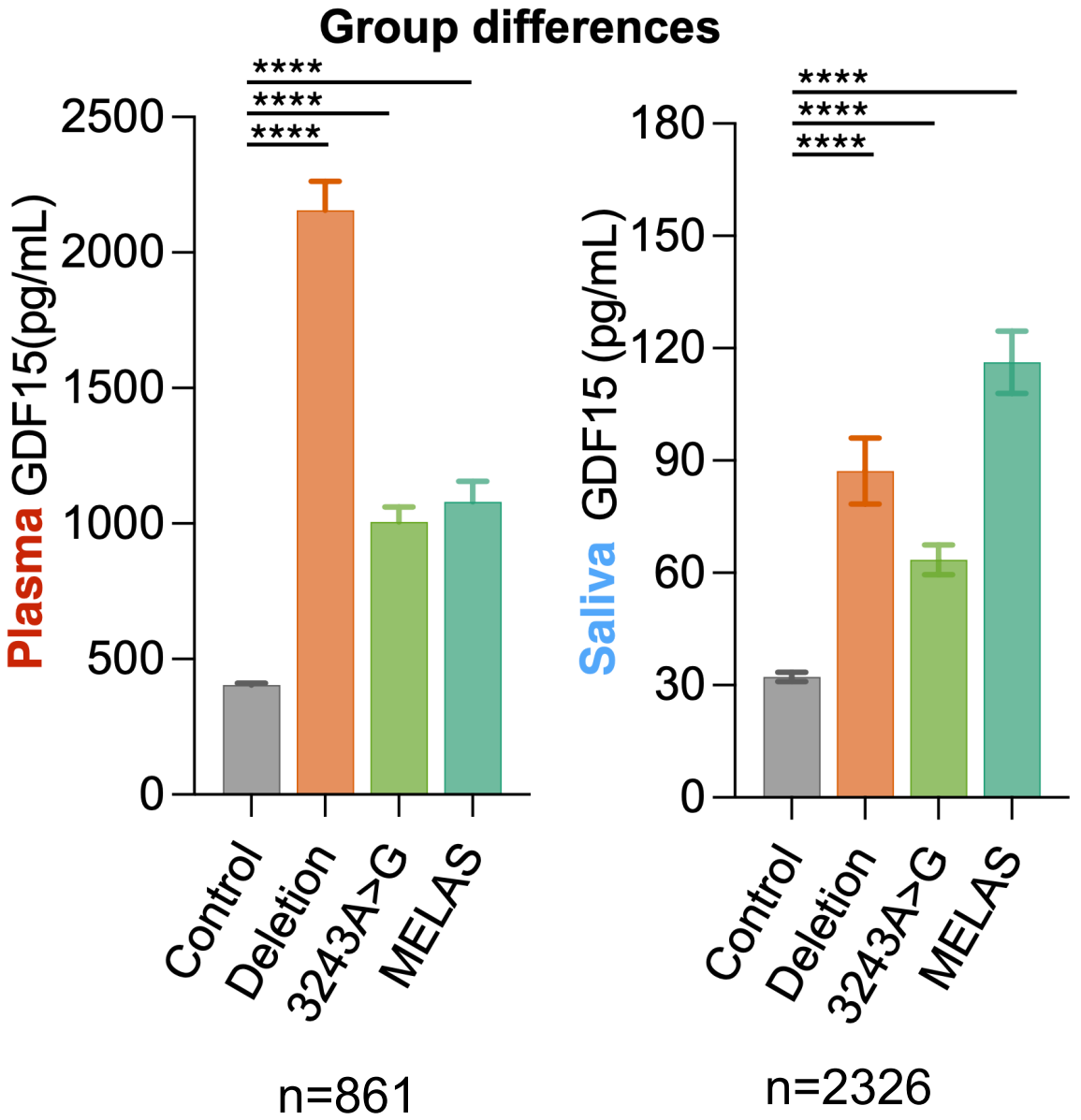


n=861

Huang and Trumpff et al., in preparation

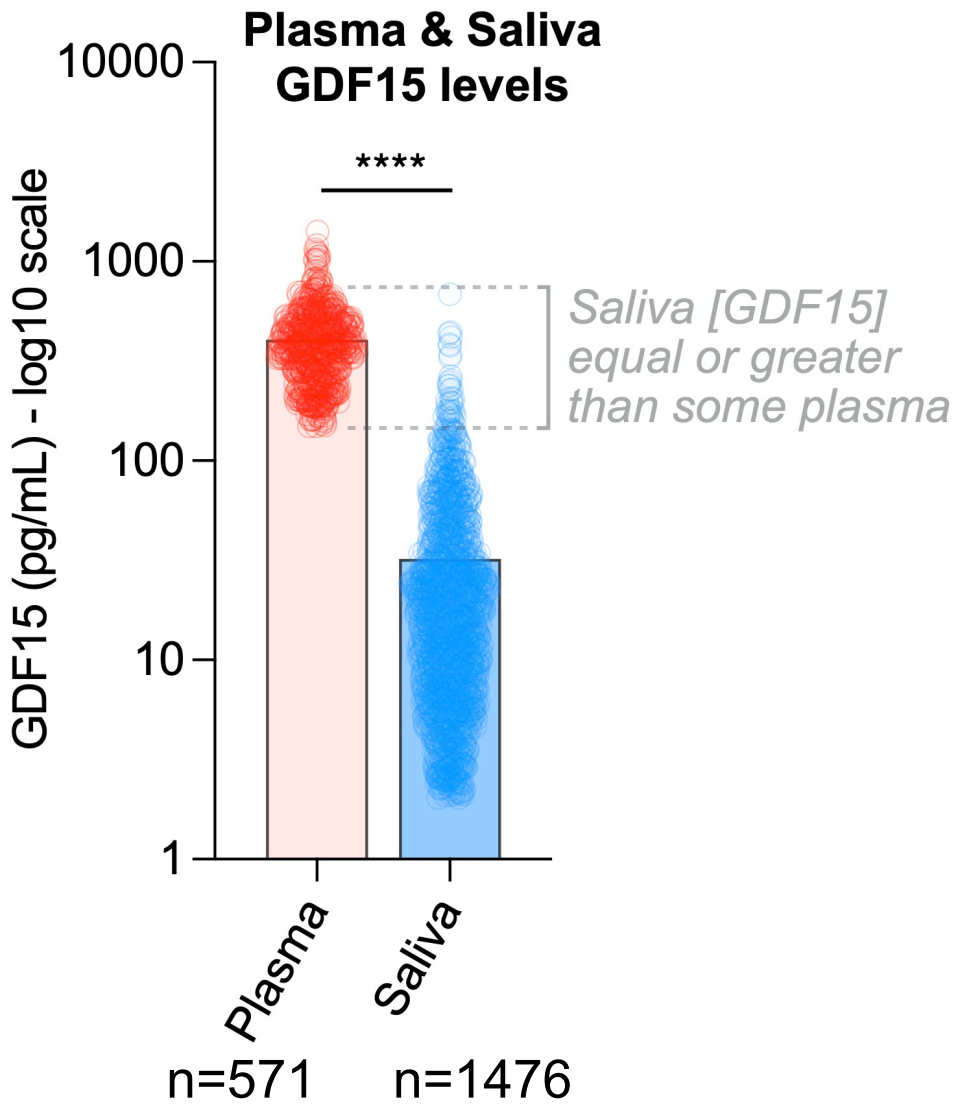
Plasma and saliva GDF15 is elevated in MitoD patients

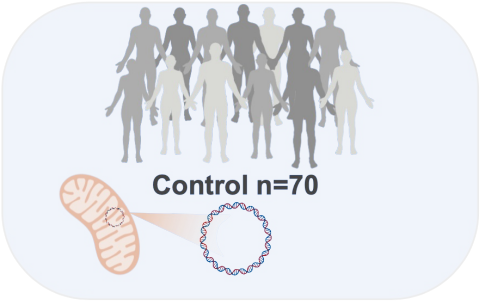




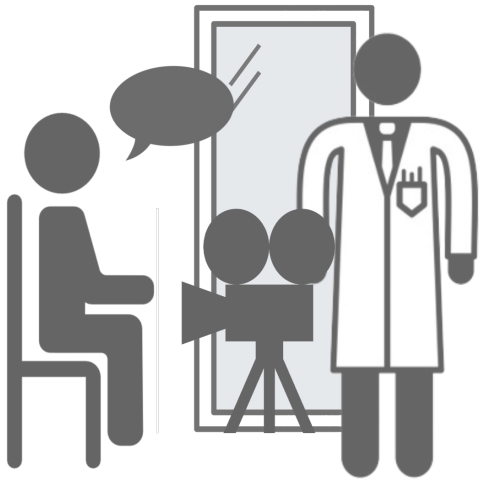
Huang and Trumpff et al., in preparation

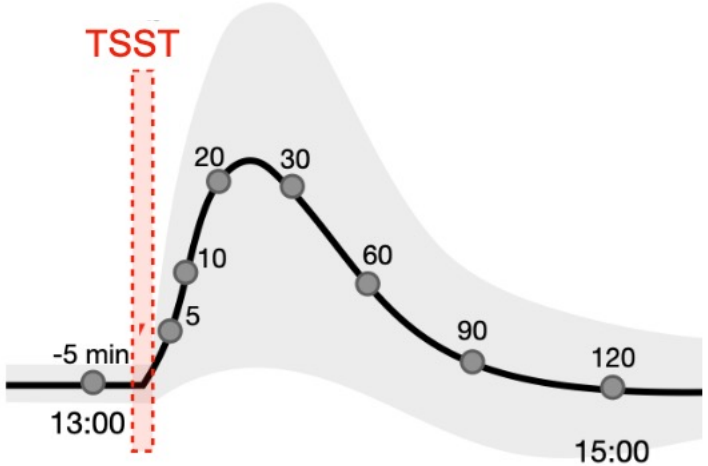
Plasma and saliva GDF15 in healthy controls



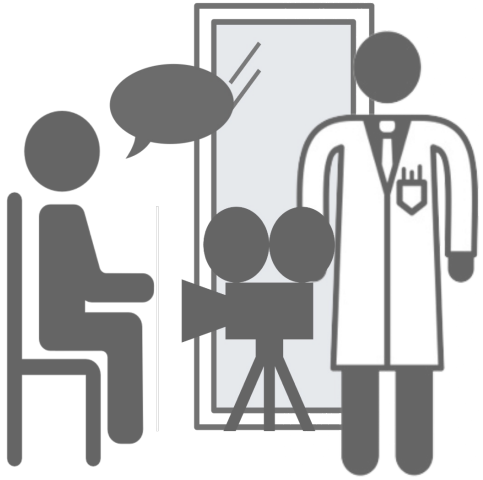


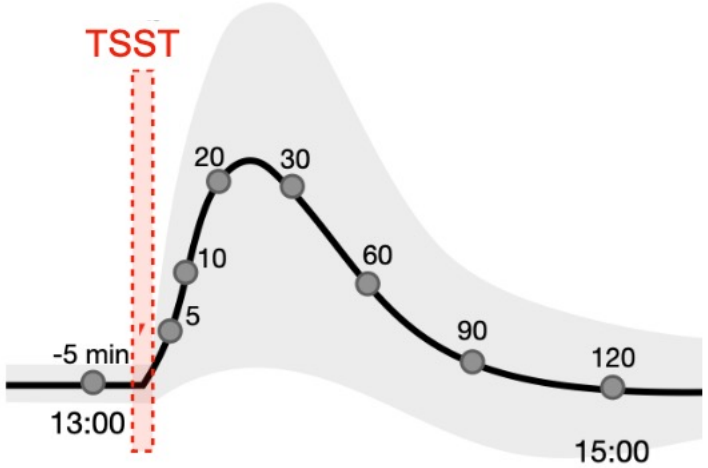
Huang and Trumpff et al., in preparation

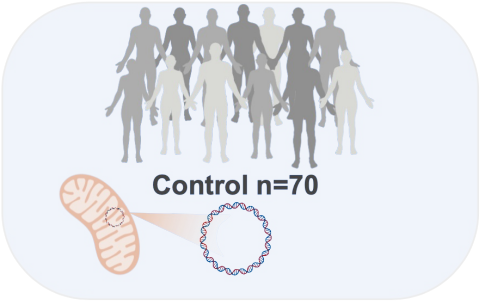


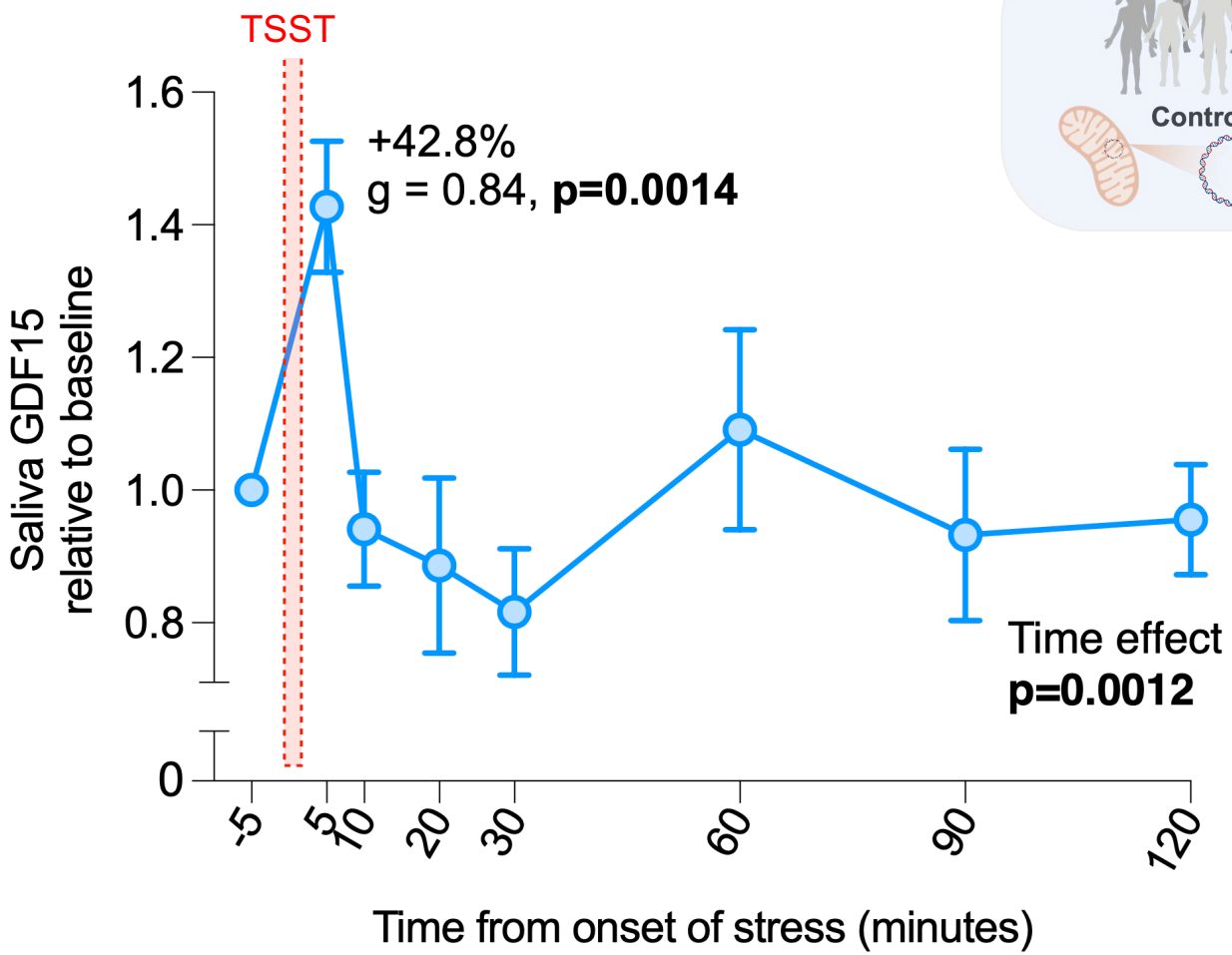

TSST
-5 min
13:00
5
10
20
30
60
90
120
15:00

Psychological stress induced rapid change in saliva GDF15



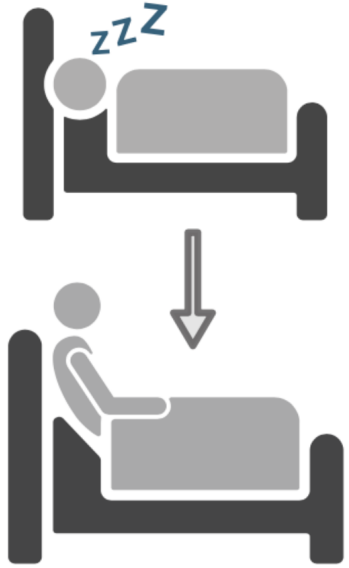


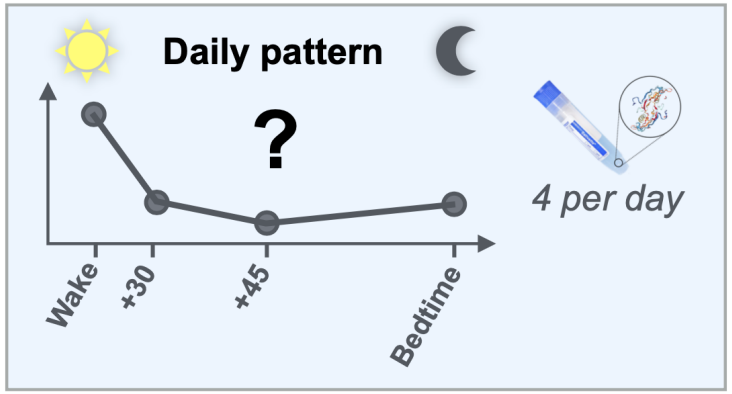




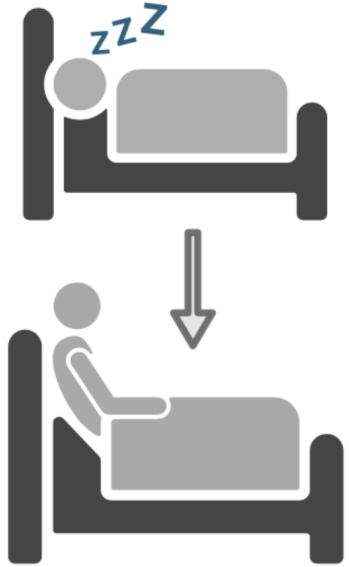
n=67, 66% female, data shown as mean ± SEM

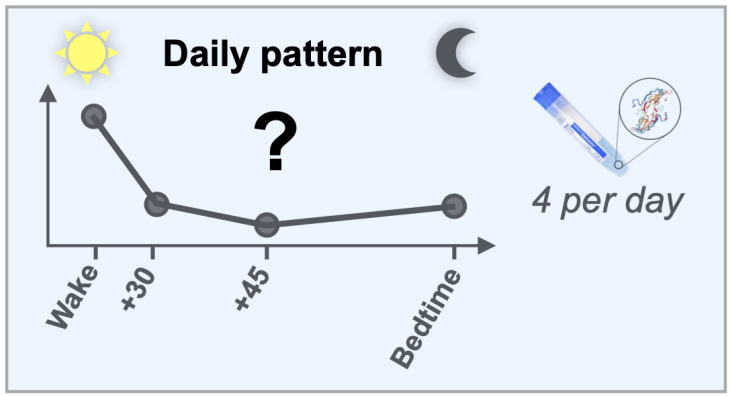
Huang and Trumpff et al., in preparation

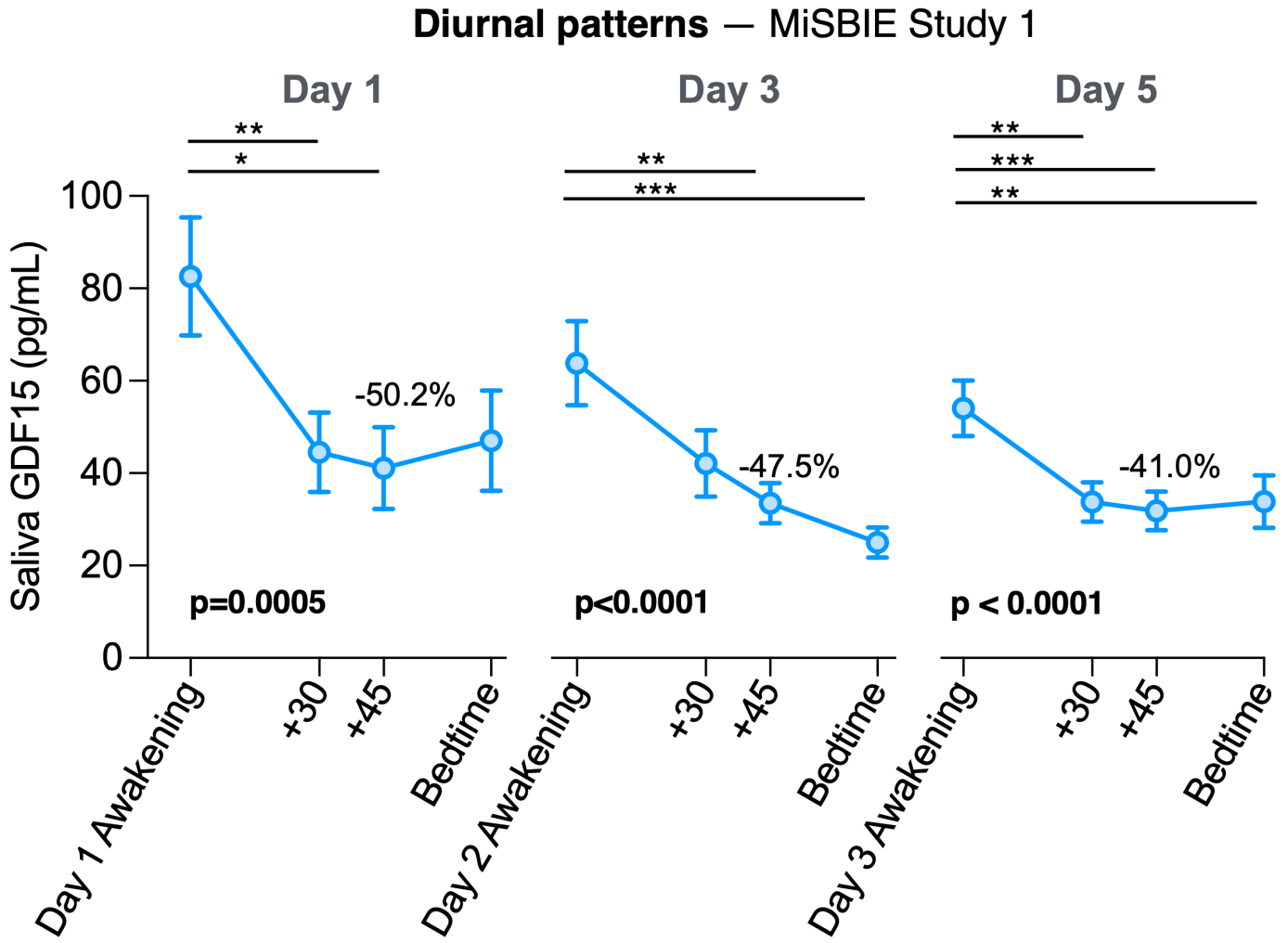

zzz


Daily pattern
?
4 per day
Wake
+30
+45
Bedtime

Saliva GDF15 presents a robust awakening response







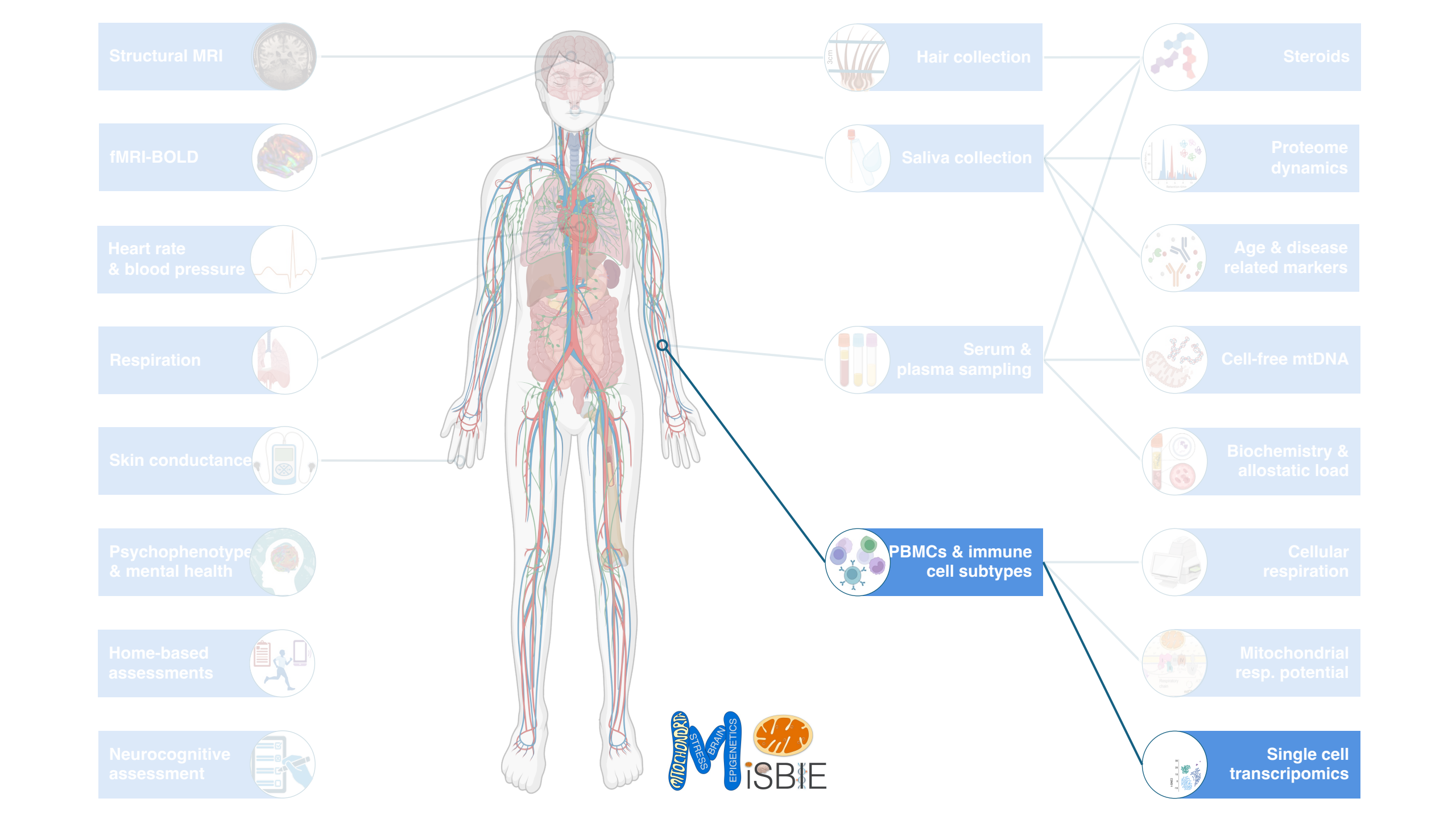
n=68, 67% female, data shown as mean ± SEM

Huang and Trumpff et al., in preparation

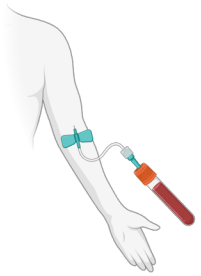
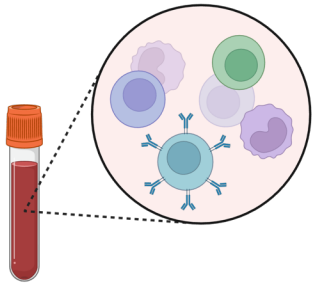
Single Cell Transcriptomics

Anna Monzel

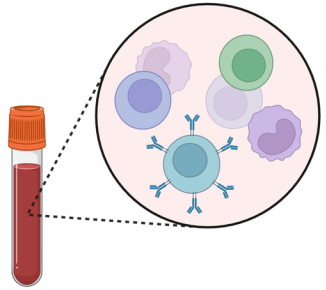
CUIMC - Mitochondrial Psychobiology Group


Structural MRI
fMRI-BOLD
Heart rate & blood pressure
Respiration
Skin conductance
Psychophenotype & mental health
Home-based assessments
Neurocognitive assessment
Hair collection
Saliva collection
Serum & plasma sampling
PBMCs & immune cell subtypes
Steroids
Proteome dynamics
Age & disease related markers
Cell-free mtDNA
Biochemistry & allostatic load
Cellular respiration
Mitochondrial resp. potential
Single cell transcripomics
MITOCHONDRIA
STRESS
BRAIN
EPIGENETICS
iSBIE

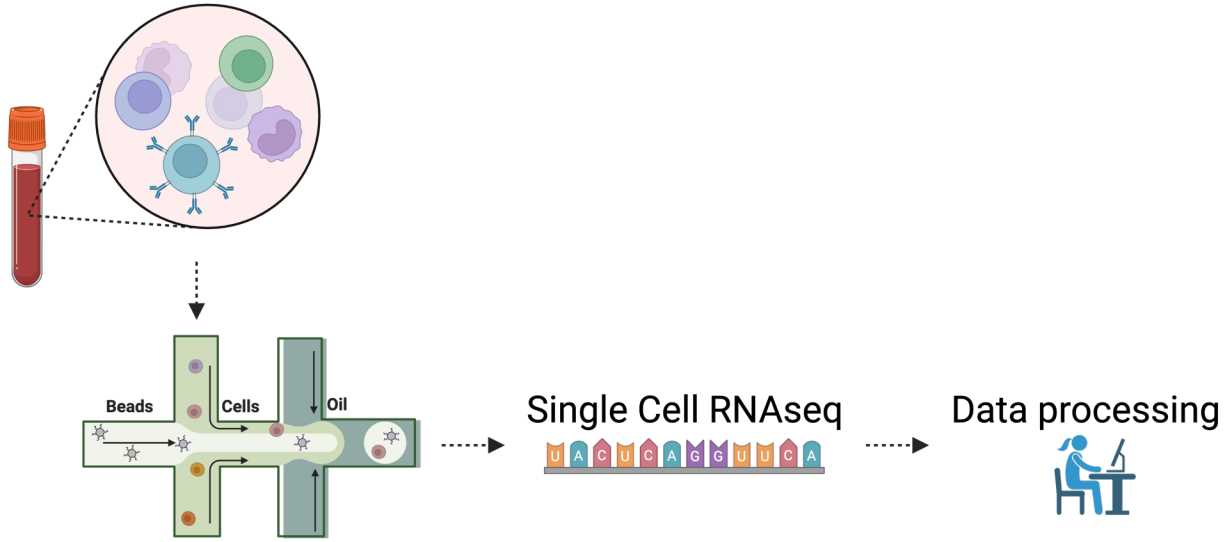
Cryopreservation – procedure

SAMPLE COLLECTION	PBMC ISOLATION	CRYOPRESERVATION
		
MORNING FASTING		**265 samples / 61 participants** (up to 6 tubes per participant)
STRESS REACTIVITY -5 +5 +10 +20 +30 +60 +90 +120		**785 samples / 50 participants** (2 tubes per time point)
STRESS RECOVERY (+120 MIN)		**81 samples / 47 participants** (up to 2 tubes per participant)

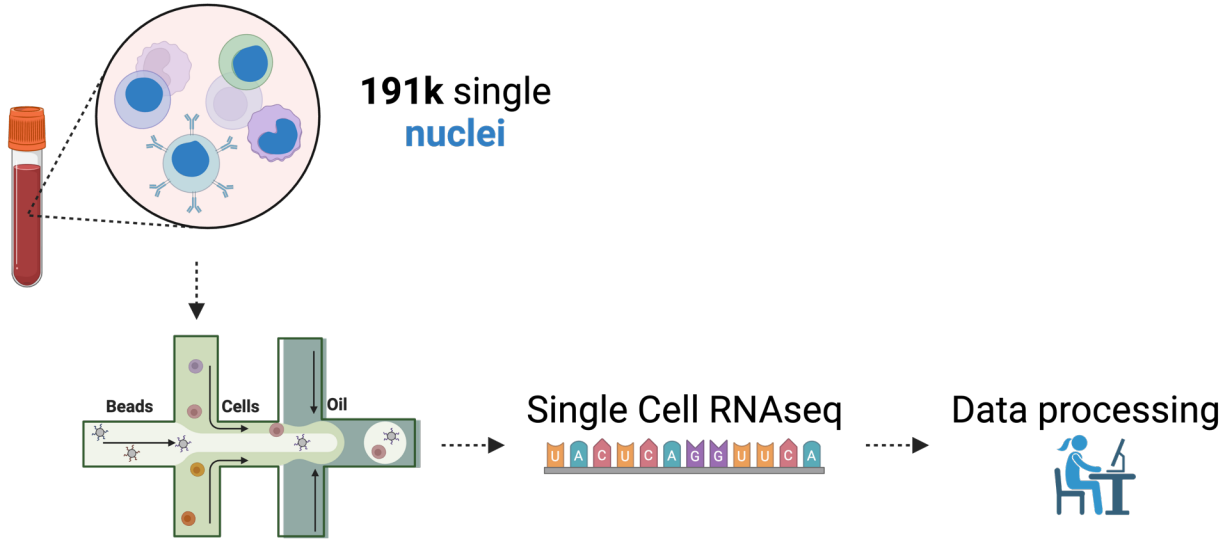
Single cell transcriptomics – procedure + outcome



Single cell transcriptomics – procedure + outcome

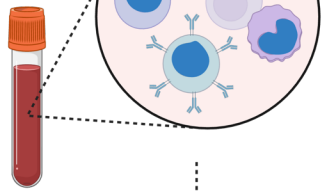


Single cell transcriptomics – procedure + outcome

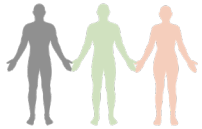


*preliminary results

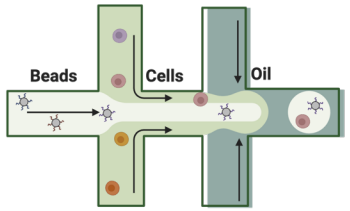
Single cell transcriptomics – procedure + outcome



191k single **nuclei**



25 participants

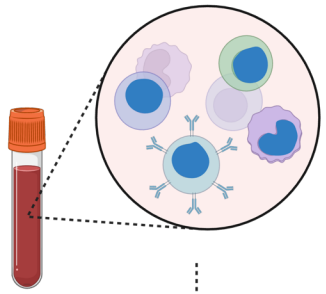


Single Cell RNAseq

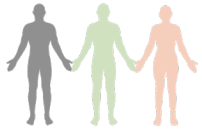
Data processing

*preliminary results

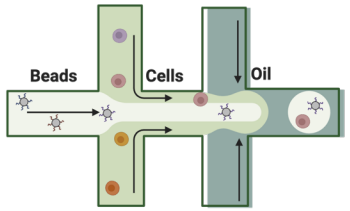
Single cell transcriptomics – procedure + outcome



191k single **nuclei**

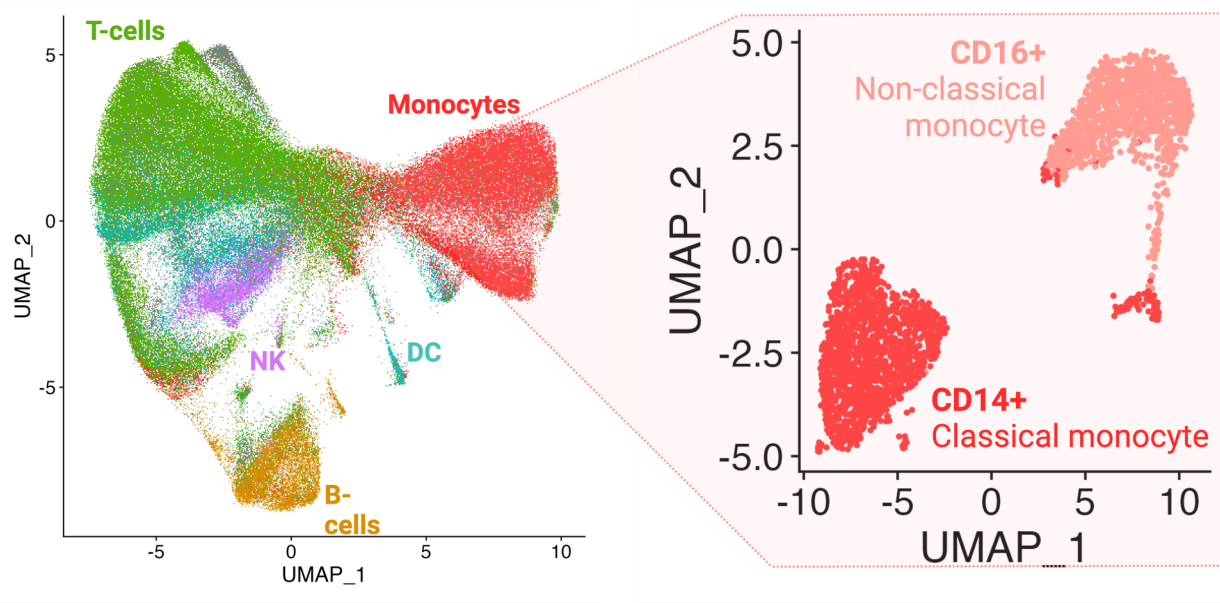


25 participants



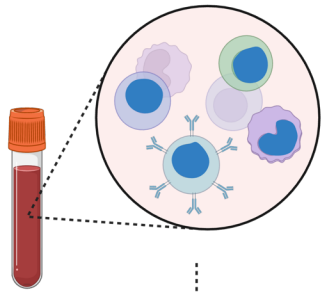
Single Cell RNAseq

Data processing

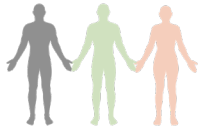


*preliminary results

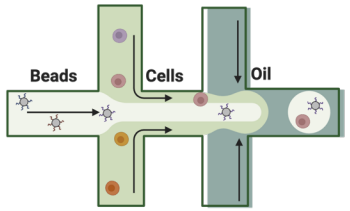
Single cell transcriptomics – procedure + outcome



191k single **nuclei**

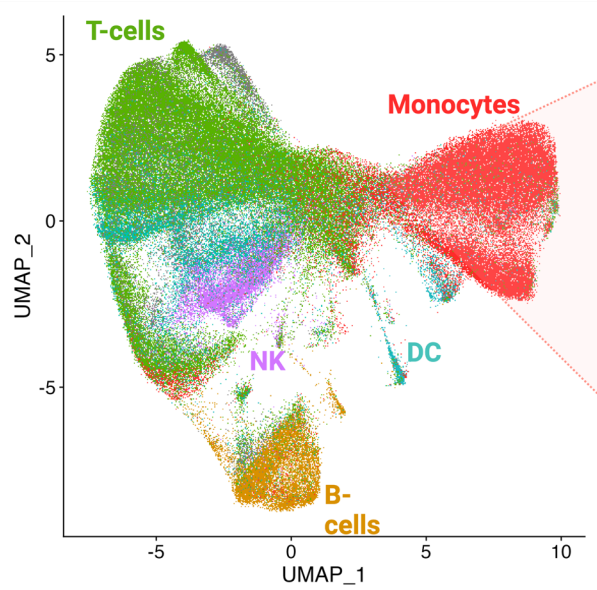


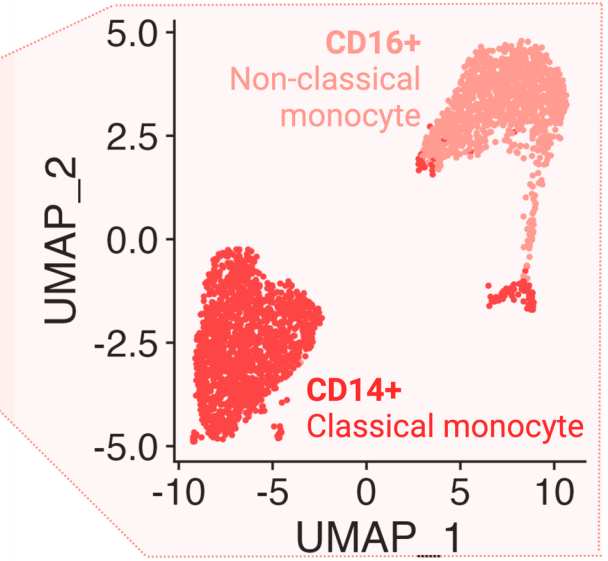
25 participants

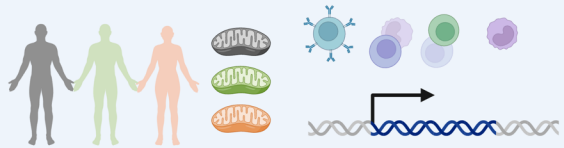


Single Cell RNAseq

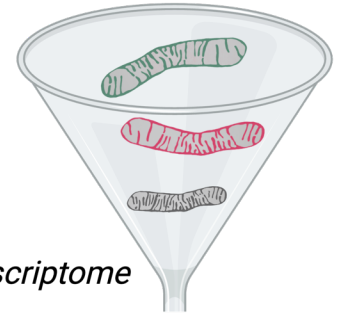
Data processing





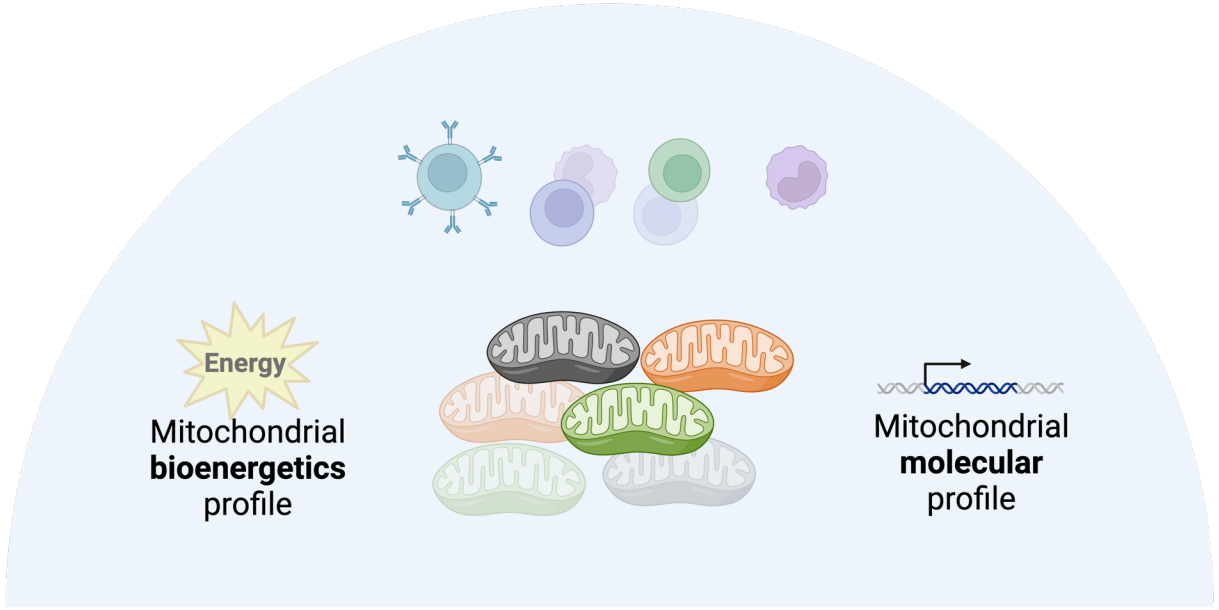


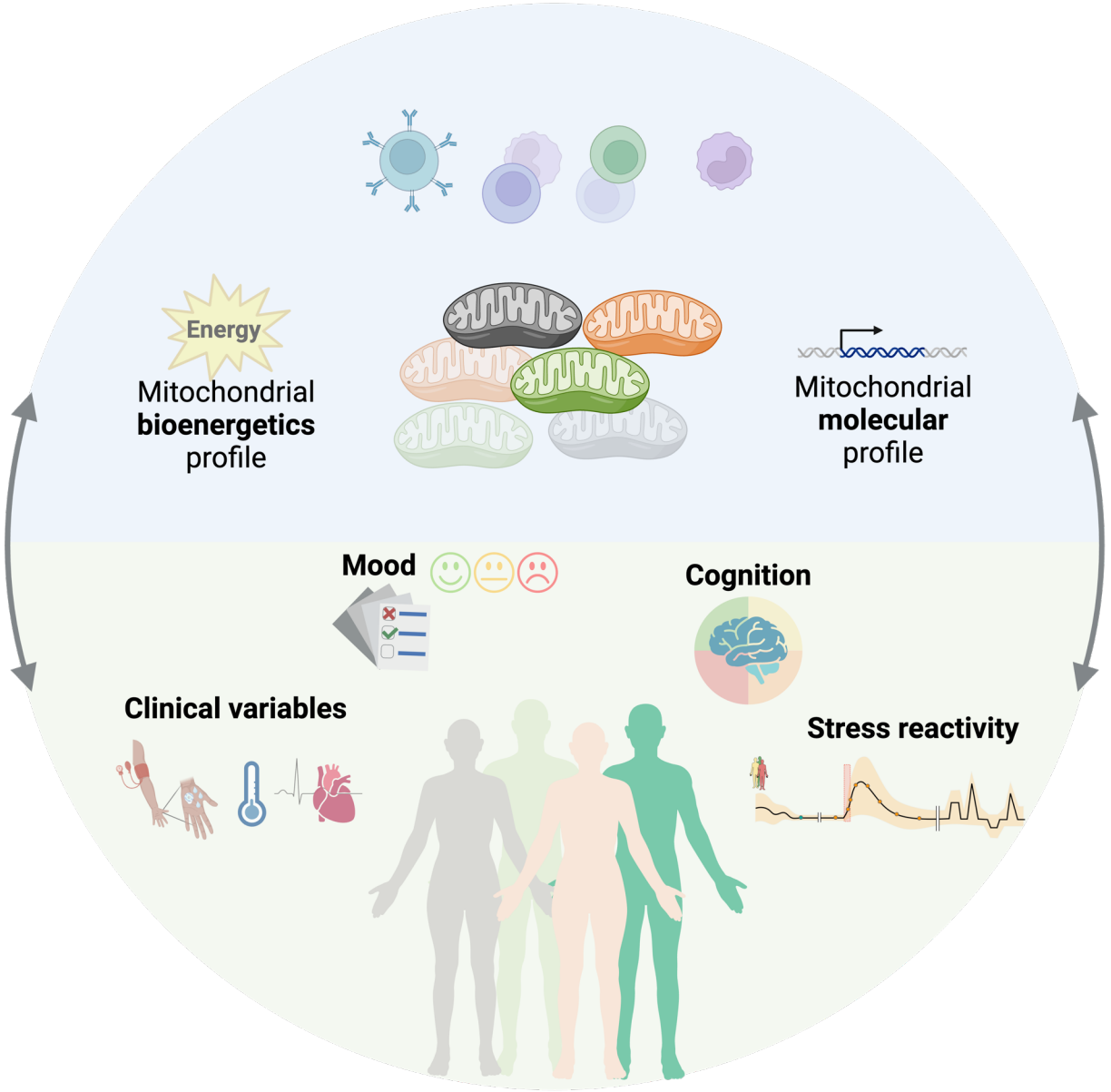
Mitochondrial molecular profile



Mitochondrial transcriptome
+
MitoPathways

***preliminary results**


Energy
Mitochondrial
bioenergetics
profile
Mitochondrial
molecular
profile


Energy
Mitochondrial
bioenergetics
profile
Mitochondrial
molecular
profile
Mood
Cognition
Clinical variables
Stress reactivity

Questions?

Columbia University Irving Medical Center

Mitochondrial Psychobiology Lab

Part III

Future plans and discussion

Congratulations!

Thank you!

Outcome variables

Mitochondrial	Stress reactivity & Allostatic load	Multi-omics	Neuroimaging	Clinical and Psychosocial

Genetic diagnosis [*categorical*]
- m.3243A>G
- Single deletion (size, position, genes affected)
- Heteroplasmy (sequencing) in blood, buccal, urine
- mtDNA haplogroups
	Allostatic load
	- Blood chemistry
	- Immune and inflammatory
	- Metabolic/neuroendocrine
	- Diurnal Cortisol
	- Hair Cortisol
		Epigenetic and genomic
		- Genome-wide (EPIC 850K)
		- Epigenetic clocks
		- Telomere length
		- Multiple tissues (blood, buccal, urine)
			Activation
			- Task-elicited
			  - Speech prep
			  - Cold pressor
			- Positive control task
			  - Checkerboard + sound
				Disease severity
				- Columbia Neurological Score
				- NMDAS
				- NAMDC CRF
				- Functional capacity
				- Autonomic symptoms
				- Data-driven clinical phenotypes

Mitochondrial bioenergetic phenotyping [*continuous*]
- OCR
- ECAR
- Metabolic flexibility (+UK5099)
- Biochemical activities (CI, CII, CIV, CS)
- mtDNAcn
	Physiological Reactivity
	- Affect and mood
	- Heart rate, HRV, BP, EDA
	- HPA axis reactivity
	- Epi/Norepi
	- Cytokines
	- Proteomics
	- Metabolomics
		Gene expression
		- RNA-Seq (monocytes, lymphocytes)
		- Pre and post-stress
		- scRNAseq PBMCs
		Fecal sample
		- Microbiome composition and complexity
			Functional connectivity
			- Resting state
			- Task-evoked
			  - Speech prep
			  - Cold pressor
			  - N-back
			- Brain-wide signatures of mitochondrial defects
				Neuropsychological testing
				- Working memory
				- Cognitive function
				- Cognitive impairment
				- Psychiatric symptoms
				Psychosocial factors

Mitochondrial molecular phenotyping - PMPC single-cell RNAseq - Single mitochondrial or nuclear genes - MitoPathways - Mitotype signatures	**Metabokines/Mitokines** - FGF21, GDF15 - cf-mtDNA (plasma, serum, saliva, urine) **Immune cytokine production** - LPS challenge ± DEX - LPS challenge ± Inhibitors	**Metabolomics** - Plasma - Baseline and stress reactivity **Proteomics** - Plasma and saliva - Baseline and stress reactivity	**Structural** - Voxel-based morphometry - Cortical surface area - Diffusion imaging & tractography	**Age of onset** **Demographic** **Psychosocial factors** **Progression** (score/yr change)

Outcome variables

Mitochondrial	Stress reactivity & Allostatic load	Multi-omics	Neuroimaging	Clinical and Psychosocial

Genetic diagnosis [*categorical*]
- m.3243A>G
- Single deletion (size, position, genes affected)
- Heteroplasmy (sequencing) in blood, buccal, urine
- mtDNA haplogroups
	Allostatic load
	- Blood chemistry
	- Immune and inflammatory
	- Metabolic/neuroendocrine
	- Diurnal Cortisol
	- Hair Cortisol
		Epigenetic and genomic
		- Genome-wide (EPIC 850K)
		- Epigenetic clocks
		- Telomere length
		- Multiple tissues (blood, buccal, urine)
			Activation
			- Task-elicited
			  - Speech prep
			  - Cold pressor
			- Positive control task
			  - Checkerboard + sound
				Disease severity
				- Columbia Neurological Score
				- NMDAS
				- NAMDC CRF
				- Functional capacity
				- Autonomic symptoms
				- Data-driven clinical phenotypes

Mitochondrial bioenergetic phenotyping [*continuous*]
- OCR
- ECAR
- Metabolic flexibility (+UK5099)
- Biochemical activities (CI, CII, CIV, CS)
- mtDNAcn
	Physiological Reactivity
	- Affect and mood
	- Heart rate, HRV, BP, EDA
	- HPA axis reactivity
	- Epi/Norepi
	- Cytokines
	- Proteomics
	- Metabolomics
		Gene expression
		- RNA-Seq (monocytes, lymphocytes)
		- Pre and post-stress
		- scRNAseq PBMCs
		Fecal sample
		- Microbiome composition and complexity
			Functional connectivity
			- Resting state
			- Task-evoked
			  - Speech prep
			  - Cold pressor
			  - N-back
			- Brain-wide signatures of mitochondrial defects
				Neuropsychological testing
				- Working memory
				- Cognitive function
				- Cognitive impairment
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iSBIE

Outcome variables

Mitochondrial	Stress reactivity & Allostatic load	Multi-omics	Neuroimaging	Clinical and Psychosocial
Genetic diagnosis [*categorical*] - m.3243A>G - Single deletion (size, position, genes affected) - Heteroplasmy (sequencing) in blood, buccal, urine - mtDNA haplogroups	**Allostatic load** - Blood chemistry - Immune and inflammatory - Metabolic/neuroendocrine - Diurnal Cortisol - Hair Cortisol	**Epigenetic and genomic** - Genome-wide (EPIC 850K) - Epigenetic clocks - Telomere length - Multiple tissues (blood, buccal, urine)	**Activation** - Task-elicited - Speech prep - Cold pressor - Positive control task - Checkerboard + sound	**Disease severity** - Columbia Neurological Score - NMDAS - NAMDC CRF - Functional capacity - Autonomic symptoms - Data-driven clinical phenotypes
Mitochondrial bioenergetic phenotyping [*continuous*] - OCR - ECAR - Metabolic flexibility (+UK5099) - Biochemical activities (CI, CII, CIV, CS) - mtDNAcn	**Physiological Reactivity** - Affect and mood - Heart rate, HRV, BP, EDA - HPA axis reactivity - Epi/Norepi - Cytokines - Proteomics - Metabolomics	**Gene expression** - RNA-Seq (monocytes, lymphocytes) - Pre and post-stress - scRNAseq PBMCs **Fecal sample** - Microbiome composition and complexity	**Functional connectivity** - Resting state - Task-evoked - Speech prep - Cold pressor - N-back - Brain-wide signatures of mitochondrial defects	**Neuropsychological testing** - Working memory - Cognitive function - Cognitive impairment - Psychiatric symptoms **Psychosocial factors**
Mitochondrial molecular phenotyping - PMPC single-cell RNAseq - Single mitochondrial or nuclear genes - MitoPathways - Mitotype signatures	**Metabokines/Mitokines** - FGF21, GDF15 - cf-mtDNA (plasma, serum, saliva, urine) **Immune cytokine production** - LPS challenge ± DEX - LPS challenge ± Inhibitors	**Metabolomics** - Plasma - Baseline and stress reactivity **Proteomics** - Plasma and saliva - Baseline and stress reactivity	**Structural** - Voxel-based morphometry - Cortical surface area - Diffusion imaging & tractography	**Age of onset** **Demographic** **Psychosocial factors** **Progression** (score/yr change)

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Scientific Questions to be Addressed

- [Stress-disease] How do mitochondria influence multisystem stress reactivity? **Bobba-Alves et al.**

- [Clinical] Can we develop robust blood or saliva-based biomarker indices (allostatic load) of mitochondrial OxPhos defects, related to disease severity/progression? **Junker, Juster et al.**

- [Neuroscience] Is there a resting state functional connectivity brain signature of mitochondrial OxPhos defects? **Bo, Wager et al.**

- [Science of Health] How is communication between physiological systems, measured from time series as *transfer entropy*, altered in mitochondrial diseases? **Pei, Cohen et al.**

- [Psychobiological] How does mitochondrial biology relate to time perception? **Kapri, Sturm et al.**

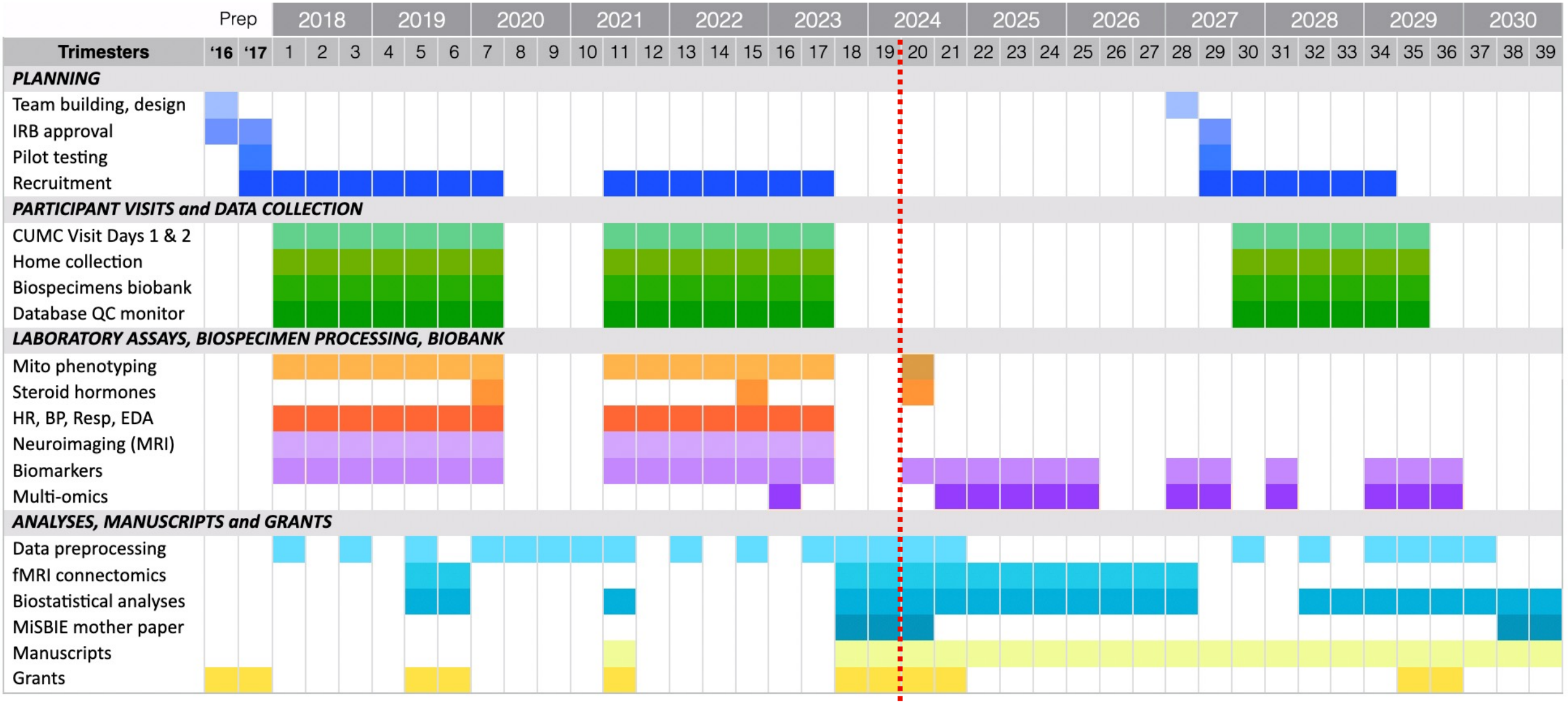
Scientific Questions to be Addressed

- [Sleep/behaviors] How do OxPhos defects influence sleep quality and quantity? **Prather et al.**
- [Human energetics] Do OxPhos defects and acute psychosocial stress cause metabolic signatures of hypermetabolism? **Shaulson et al.**
- [Psychoneuroendocrinology] Do mitochondrial defects exaggerate the influence of early life adversity on stress-induced inflammation? **Conklin, Epel et al.**
- [Psychobiological] Do metabolic signals from impaired mitochondria constrain the “state space” of mood and emotions? **Feldman Barrett et al.**
- [Aging] How do mitochondrial OxPhos defects affect aging biomarkers across organ systems? **Belsky et al.**

Biomarker analyses

- Some **Completed**
- Several **In Progress**
- **Planned** (metabolomics, proteomics)
  Human Stress Metabolome
  Human Stress Proteome
- **Biobank available** for emerging markers

Biomarker	Sample type	Description	Units	Stage
Cortisol	Hair	Fasting	pg/mg	In progress
Cortisone	Hair	Fasting	pg/mg	In progress
Corticosterone	Hair	Fasting	pg/mg	In progress
Testosterone	Hair	Fasting	pg/mg	In progress
Progesterone	Hair	Fasting	pg/mg	In progress
DHEA	Hair	Fasting	pg/mg	In progress
Cortisol	Saliva	Fasting, TSST, MRI, diurna	ng/mL	In progress
Cortisone	Saliva	Fasting, TSST, MRI, diurna	ng/mL	In progress
Corticosterone	Saliva	Fasting, TSST, MRI, diurna	ng/mL	In progress
Testosterone	Saliva	Fasting, TSST, MRI, diurna	ng/mL	In progress
Progesterone	Saliva	Fasting, TSST, MRI, diurna	ng/mL	In progress
DHEA	Saliva	Fasting, TSST, MRI, diurna	ng/mL	In progress
FGF21	Plasma	Fasting, TSST	pg/mL	Done
GDF15	Plasma	Fasting, TSST	pg/mL	Done
GDF15	Saliva	Fasting, TSST	pg/mL	Done
Epinephrine	Urine	Overnight	mcg/24 hours	Done
Norepinephrine	Urine	Overnight	mcg/24 hours	Done
IL-6	EDTA whole blood	Fasting		Not started
TNF-a	EDTA whole blood	Fasting		Not started
CRP	Serum	Fasting	mg/dL	Done
Fibrinogen	Bluetop tube	Fasting	mg/dL	Done
Glucose	Serum	Fasting	mg/dL	Done
HgbA1c	EDTA whole blood	Fasting	%	Done
Insulin	Serum	Fasting	uIU/mL	Done
Peptide C	Serum	Fasting	ng/mL	Done
Triglycerides	Serum	Fasting	mg/dL	Done
Total cholesterol	Serum	Fasting	mg/dL	Done
HDL	Serum	Fasting	mg/dL	Done
Creatinine	Serum	Fasting	mg/dL	Done
Albumin	Serum	Fasting	g/dL	Done
cf-mtDNA	Plasma	Fasting, TSST		In progress
cf-mtDNA	Serum	Fasting, TSST		In progress
cf-mtDNA	Saliva	Fasting, TSST, MRI, diurnal		Done
cf-mtDNA	Urine	Overnight		Done
MCHC	EDTA whole blood	Fasting	g/dL	Done
MPV	EDTA whole blood	Fasting		Done
pct_Neutrophils	EDTA whole blood	Fasting	%	Done
pct_Lymphs	EDTA whole blood	Fasting	%	Done
pct_Monos	EDTA whole blood	Fasting	%	Done
pct_Eos	EDTA whole blood	Fasting	%	Done
pct_Basos	EDTA whole blood	Fasting	%	Done
WBC	EDTA whole blood	Fasting	cells/L	Done
RBC	EDTA whole blood	Fasting	cells/mcL	Done
PLT	EDTA whole blood	Fasting	cells/L	Done
Hemoglobin	EDTA whole blood	Fasting	g/dL	Done
Hematocrit	EDTA whole blood	Fasting	%	Done
MCV	EDTA whole blood	Fasting	fl	Done
MCH	EDTA whole blood	Fasting	pg	Done
RDW	EDTA whole blood	Fasting	%	Done
IG%	EDTA whole blood	Fasting	%	Done
NeutroAbsolute	EDTA whole blood	Fasting	%	Done
LymphAbsolute	EDTA whole blood	Fasting	%	Done
MonoAbsolute	EDTA whole blood	Fasting	%	Done
EosAbsolute	EDTA whole blood	Fasting	%	Done
BasoAbsolute	EDTA whole blood	Fasting	%	Done
LDL	Serum	Fasting	mg/dL	Done
Sodium	Serum	Fasting	mEq/L	Done
Potassium	Serum	Fasting	mEq/L	Done
Chloride	Serum	Fasting	mEq/L	Done
CO2	Serum	Fasting	mEq/L	Done



CTSA Irving Institute

MiSBIE R21
R01MH113011
PO: Meinecke

MiSBIE parent R01
R01MH122706
PO: Meinecke

(PENDING) **MiSBIE Stress-disease follow up R01**

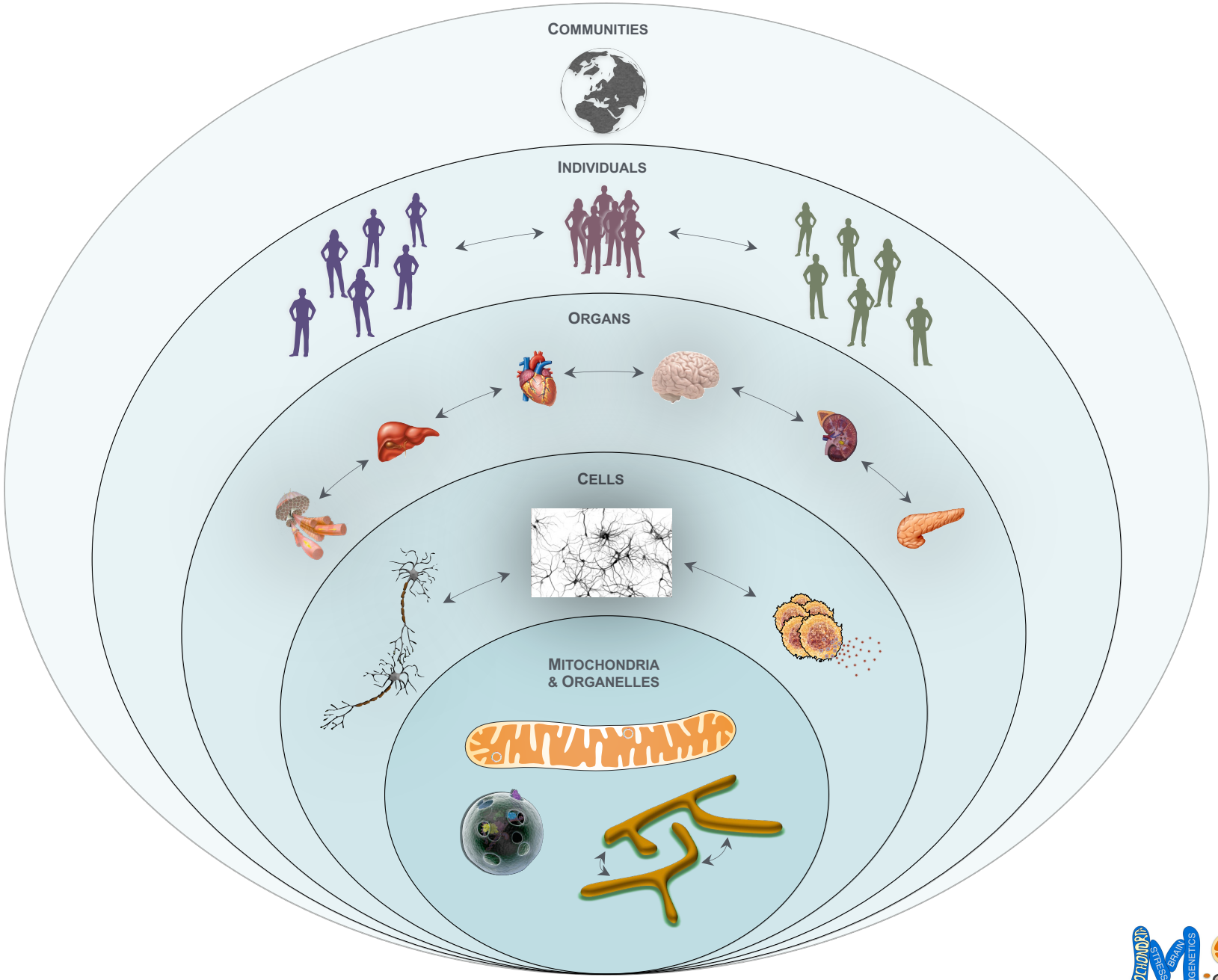
(PENDING) **MiSBIE Resilience & health R01** (Cohen)

MitoBrain RF1
RF1AG076821
PO: Max Guo

(PLANNED) **MiSBIE Multi-tissue Aging Resource R61/33**

Other questions/grants

Creating a more accurate model of human health



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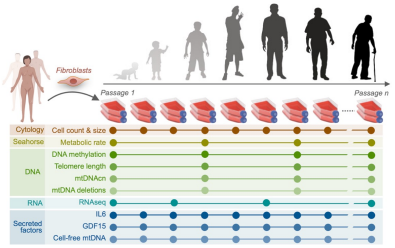
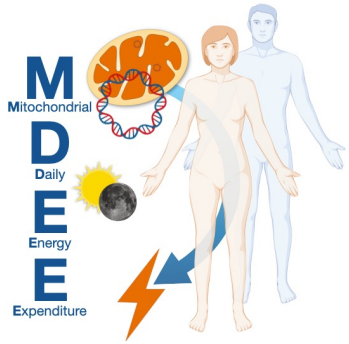
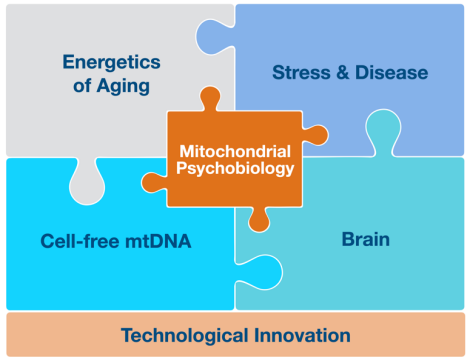


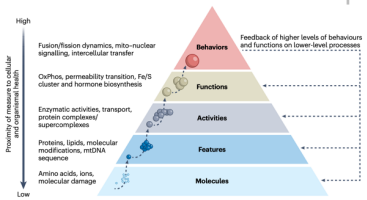
MITOCHONDRIA STRESS BRAIN EPIGENETICS iSBIE

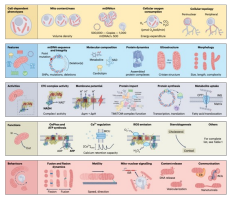


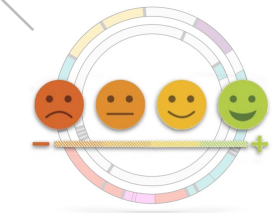
MitoBrainMap v1.0



Saliva Mitochondria Study







SHES

Mitochondrial PsychoBiology Lab

MITOCHONDRIA STRESS BRAIN EPIGENETICS iSBIE

MiSBIE Mother paper

A community resources on the rationale, design and execution of the MiSBIE study, facilitating future collaborations, follow up studies, and dissemination of results

Trends in
Endocrinology & Metabolism

CellPress

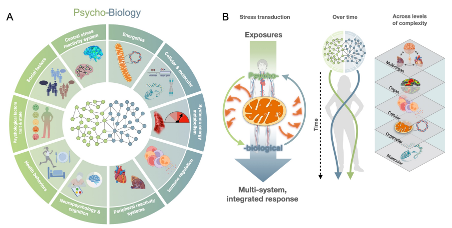
Target submission: April 2024

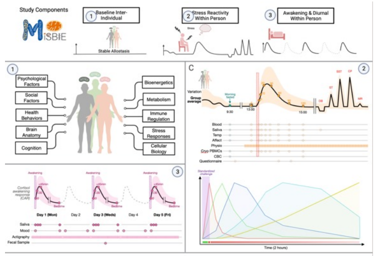
MANUSCRIPT

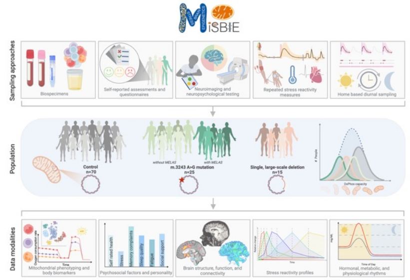
A Psychobiological Data Platform to Map the Mind-Mitochondria Connection

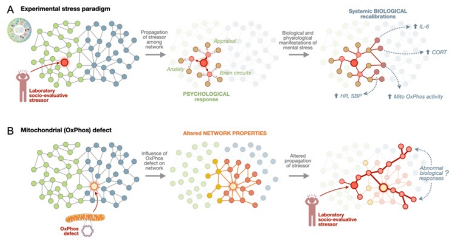
Primary author team … and **MiSBIE Group Collaborators** (listed on PubMed)

Figures









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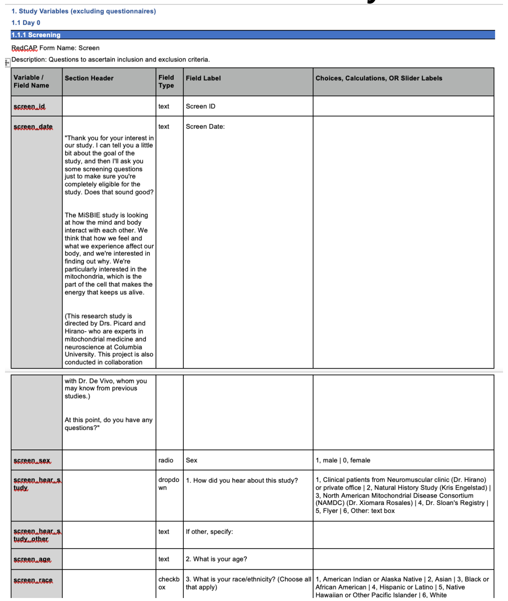


1. Study Variables (excluding questionnaires)

1.1 Day 0

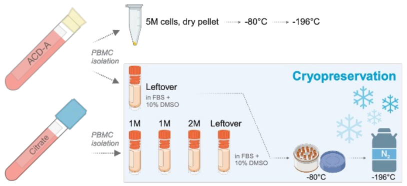
1.1.1 Screening

RedCAP Form Name: Screen

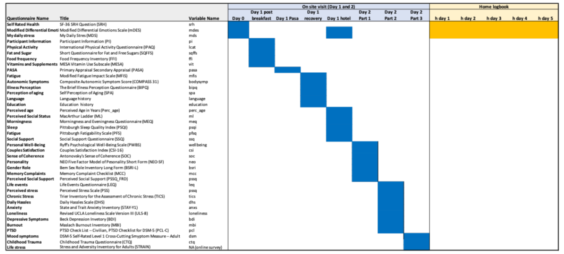
Description: Questions to ascertain inclusion and exclusion criteria.

Variable / Field Name	Section Header	Field Type	Field Label	Choices, Calculations, OR Slider Labels
screen_id		text	Screen ID	
screen_date	"Thank you for your interest in our study. I can tell you a little bit about the goal of the study, and then I'll ask you some screening questions just to make sure you're completely eligible for the study. Does that sound good? The MiSBIE study is looking at how the mind and body interact with each other. We think that how we feel and what we experience affect our body, and we're interested in finding out why. We're particularly interested in the mitochondria, which is the part of the cell that makes the energy that keeps us alive. (This research study is directed by Drs. Picard and Hirano- who are experts in mitochondrial medicine and neuroscience at Columbia University. This project is also conducted in collaboration with Dr. De Vivo, whom you may know from previous studies.) At this point, do you have any questions?"	text	Screen Date:	
screen_sex		radio	Sex	1, male | 0, female
screen_hear_study		dropdown	1. How did you hear about this study?	1, Clinical patients from Neuromuscular clinic (Dr. Hirano) or private office | 2, Natural History Study (Kris Engelstad) | 3, North American Mitochondrial Disease Consortium (NAMDC) (Dr. Xiomara Rosales) | 4, Dr. Sloan's Registry | 5, Flyer | 6, Other: text box
screen_hear_study_other		text	If other, specify:	
screen_age		text	2. What is your age?	
screen_race		checkbox	3. What is your race/ethnicity? (Choose all that apply)	1, American Indian or Alaska Native | 2, Asian | 3, Black or African American | 4, Hispanic or Latino | 5, Native Hawaiian or Other Pacific Islander | 6, White

Clinical and laboratory procedures



Questionnaires



Using MiSBIE Data and Samples

Using MiSBIE Data and Samples

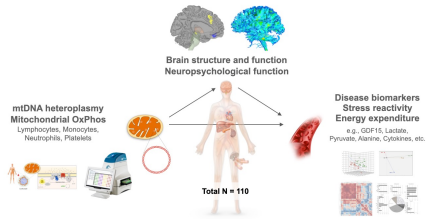
- Parent MiSBIE R01MH122706 data in **NIMH Data Archive** (NDA)
- Future OMICS data deposited in **GEO**
- All other data harmonized in sharable form in **RedCap**
- (In development) Data Request Form — online portal, early 2025
- *Project Coordinator*: Vanessa Giardino
  Data manager: Grace Liu

Annual MiSBIE Symposium

Stress reactivity & mental health

Clinical disease biomarkers

Mitochondria-microbiome



Brain-immune regulation

Energetic regulation of biological aging

Single-cell immune mitochondrial phenotypes

One-day forum to share, synthesize, and integrate new knowledge from the parent MiSBIE study and ancillary studies

Invitations to be sent early 2025

Contact: Vanessa Giardino
vg2318@cumc.columbia.edu

Slides and Recording

Link to slides and recording will be sent by email

Downloadable presentation slides

Thank you !

MiSBIE Transition meeting

Wine & Cheese

PH1505