A photograph of the International Space Station (ISS) in orbit above the Earth. The station's complex structure, including solar panels and modules, is clearly visible against the blue and white horizon of the planet. The background shows the vast expanse of the Earth's surface with clouds and landmasses.

# **Gravity and Nervous Systems: From Mechanotransduction to Neuromuscular Adaptation**

Dr. Alberto Griffoni

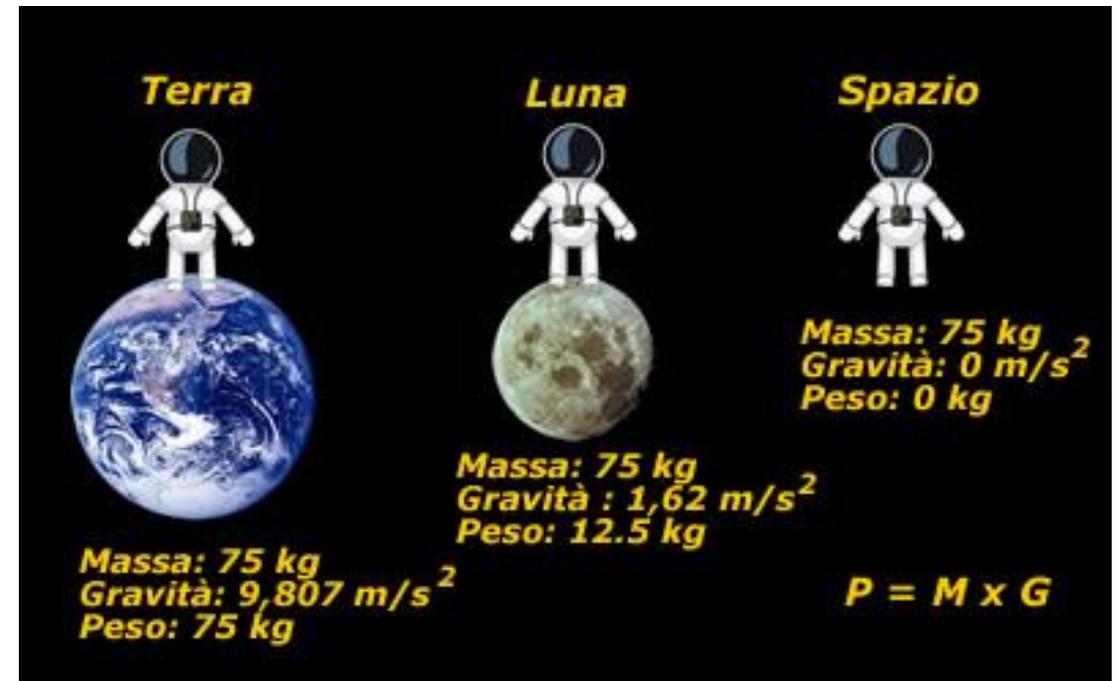
Department of Life Science

University of Trieste

# The invisible force shaping biology

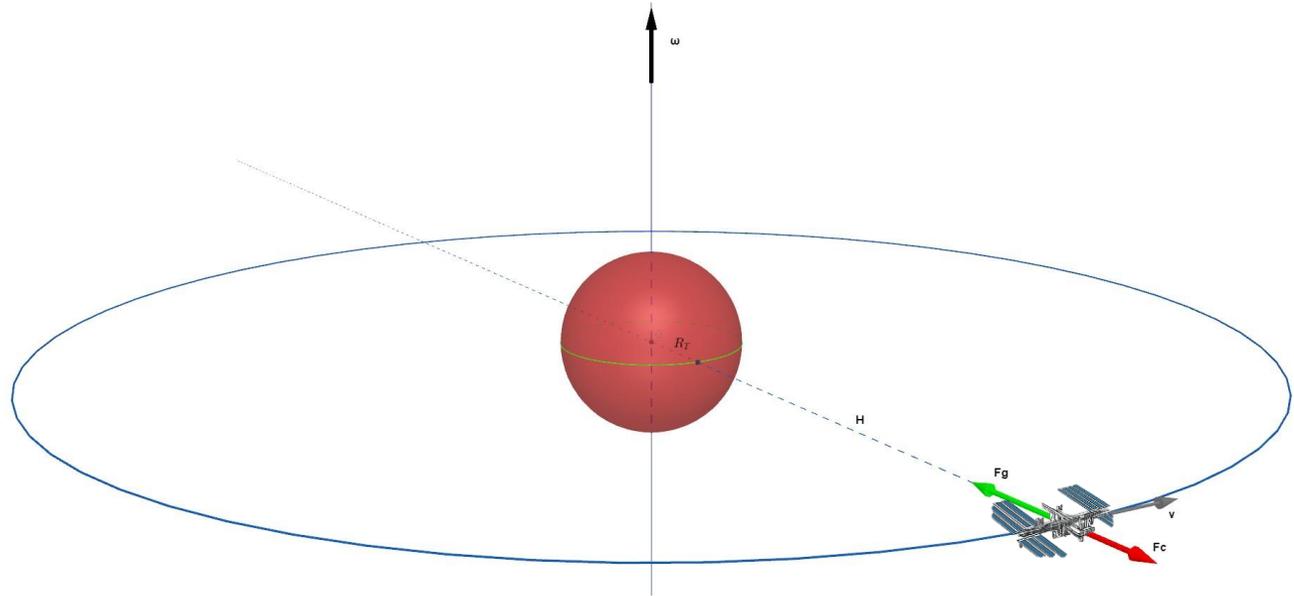
**Gravity is the constant mechanical cue that has guided the evolution of life.**

Its intensity depends on each planet's mass and radius, determining the gravitational acceleration that sets the mechanical environment for every living organism.



# What is microgravity?

- Microgravity does not mean zero gravity. It refers to environments where gravity is drastically reduced ( $\sim 10^{-3}$ – $10^{-6}$  g).
- Occurs aboard the International Space Station (ISS).
- The station's orbital velocity keeps it in a state of continuous free fall, creating the condition of microgravity.



# **Do we adapt? Do we recover?**

- 1. Does the human body truly adapt to prolonged microgravity?**
- 2. Once we return to Earth, do those altered physiological functions recover completely?**

# Effects of permanence in the space



Chris Cassidy and Samantha Cristoforetti returning from their expedition

# The NASA Twins Study

## RESEARCH ARTICLE SUMMARY

### HUMAN PHYSIOLOGY

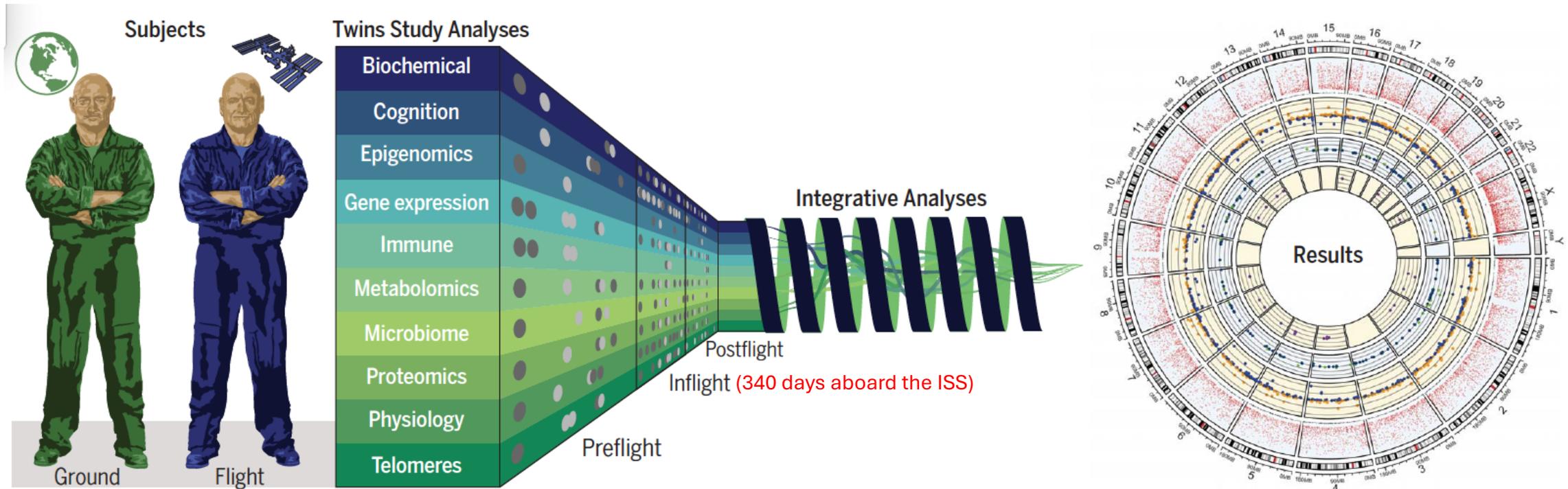
## The NASA Twins Study: A multidimensional analysis of a year-long human spaceflight

Garrett-Bakelman *et al.*, *Science* **364**, 144 (2019)



NASA's astronauts Marc (Ground) and Scott Kelly (Flight)

# The NASA Twins Study: the experimental approach



(50 years of age at the time of study initiation)

**Multidimensional, longitudinal assays of the NASA Twins Study.** (Left and middle) Genetically identical twin subjects (ground and flight) were characterized across 10 generalized biomedical modalities before (preflight), during (inflight), and after flight (postflight) for a total of 25 months (circles indicate time points at which data were collected). (Right) Data were integrated to guide biomedical metrics across various “-omes” for future missions (concentric circles indicate, from inner to outer, cytokines, proteome, transcriptome, and methylome).

# The NASA Twins Study: key findings

## Mild / Adaptive Physiological Effects

1. Reduction in body mass
2. Elongation of average telomere length
3. Transient alterations of the microbiome
4. Changes in blood volume and water-salt balance

## Moderate Physiological Effects / Compensatory Responses

1. Immune and inflammatory alterations (transient activation)
2. Regulation of water-salt balance and diuresis
3. Telomere shortening upon return
4. Pressure and cardiovascular variations ( $\downarrow$  plasma volume,  $\downarrow$  MAP)

## Significant Clinical or Structural Effects

1. Spaceflight-Associated Neuro-Ocular Syndrome (SANS)
2. Increased arterial wall thickness ( $\uparrow$  cIMT)
3. Persistence of gene expression alterations ( $\sim 7\%$ )
4. Temporary post-flight cognitive decline

# Simulated microgravity

## 🌍 Simulated microgravity on Earth

- Tries to simulate the condition astronauts lives during their missions

## 🔬 Scientific relevance

- Allows us to study how cells, tissues, and organs behave when the mechanical load of gravity is almost eliminated.



Microgravity simulation on Earth



# Weightlessness on Earth (in vivo)



6° head-down bed rest (HDBR)

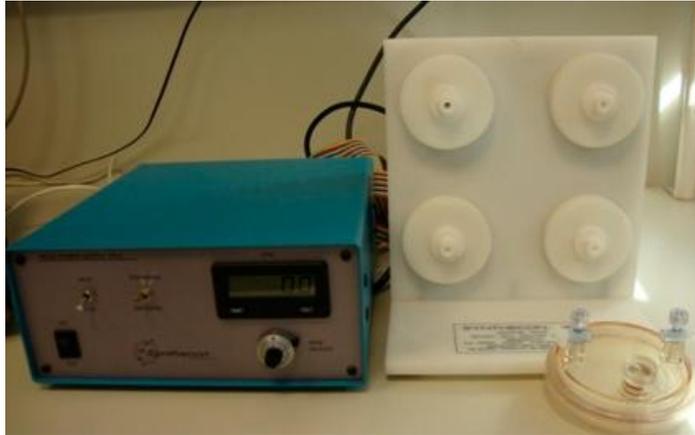


Water immersion (WI)



Dry water immersion (DWI)

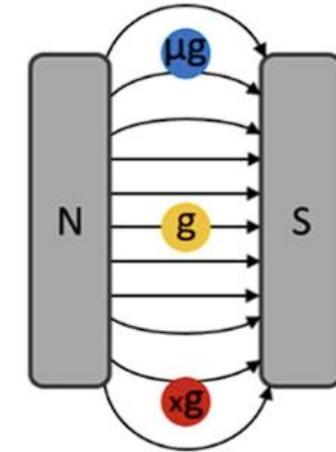
# Weightlessness on Earth (in vitro)



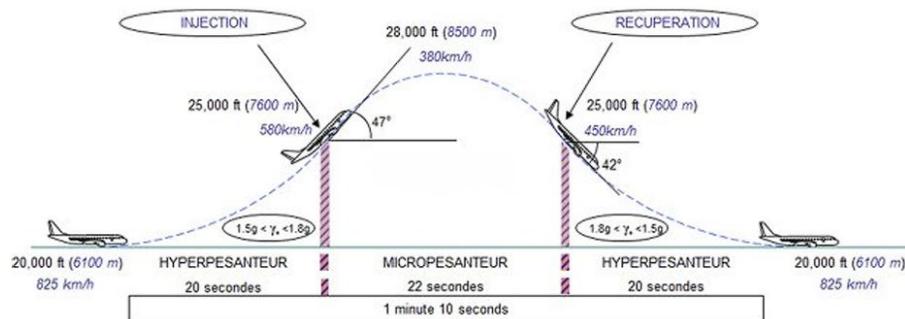
Rotating wall vessel (RWV)



Three-dimensional clinostat



Modular magnetic suspension



Parabolic flight

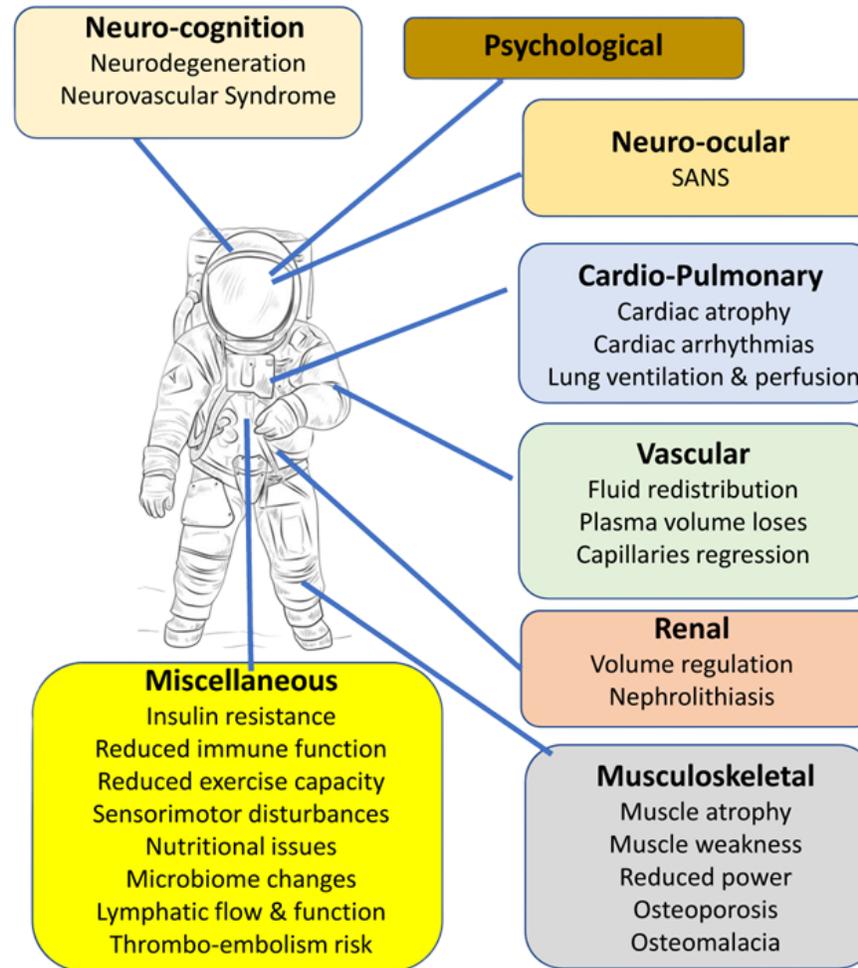


Drop tower



Suborbital flight

# Systemic effects of microgravity



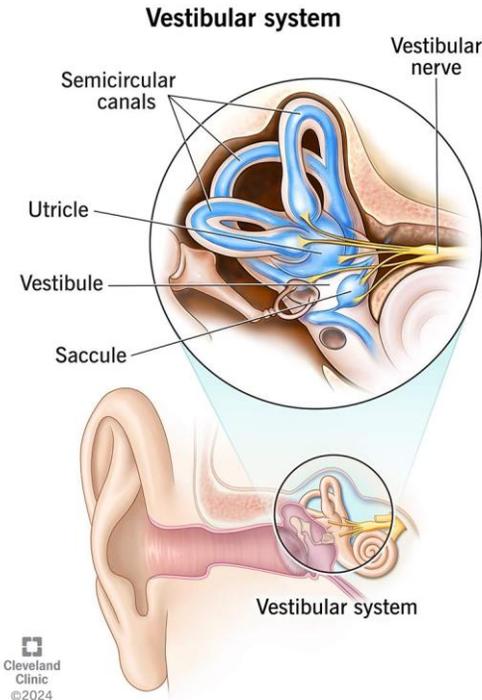
Overview of the main physiological systems affected by microgravity

## Neuro-cognition

Neurodegeneration  
Neurovascular Syndrome

Siddiqui et al., *Life* 11(10):1008 (2021).

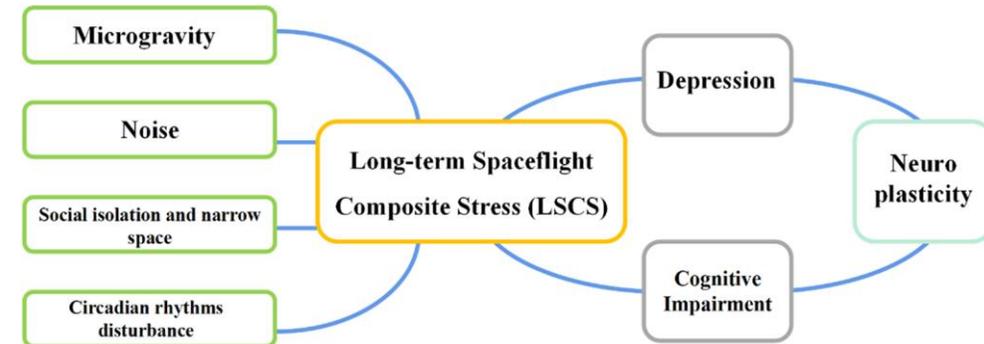
- Loss of gravitational reference disrupts vestibular inputs, causing disorientation and motion sickness.
- Oxidative and mitochondrial stress may accelerate neurodegeneration during long missions.



## Psychological

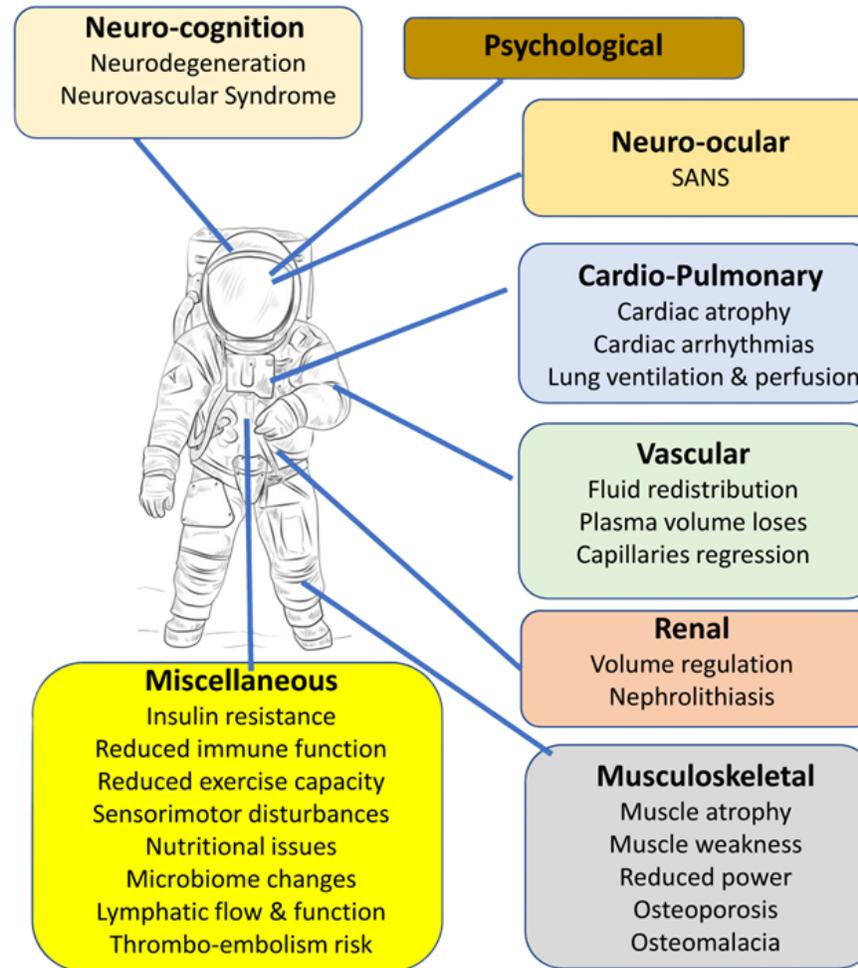
Yin et al., *Transl Psychiatry* 13, 342 (2023).

- Emotional and behavioral changes during long-term adaptation.
- Stress, isolation, and disrupted circadian rhythm.
- Sleep disturbances and reduced cognitive performance.



These alterations bring cortical and subcortical reorganization within days called 'space-induced neuroplasticity'

# Systemic effects of microgravity

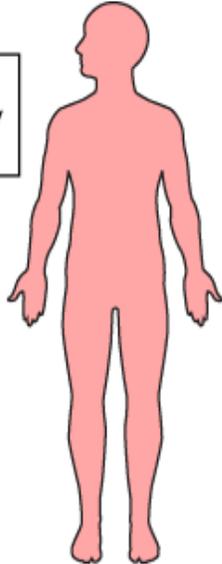


Overview of the main physiological systems affected by microgravity

**Vascular**  
Fluid redistribution  
Plasma volume loses  
Capillaries regression

**On Earth**

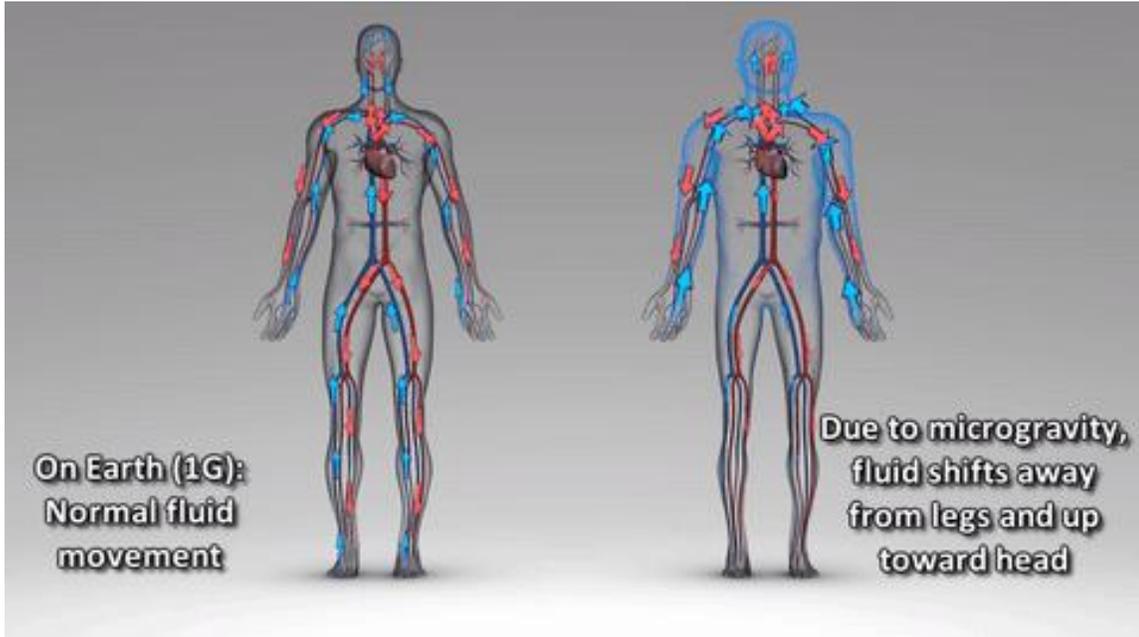
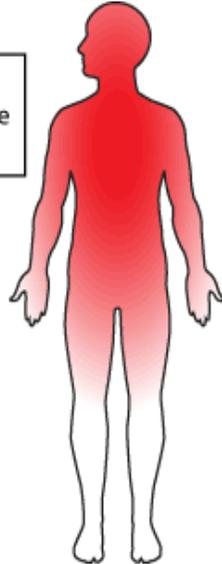
Gravity and muscles spread fluids out evenly inside the body.



Gravity pulls fluids down

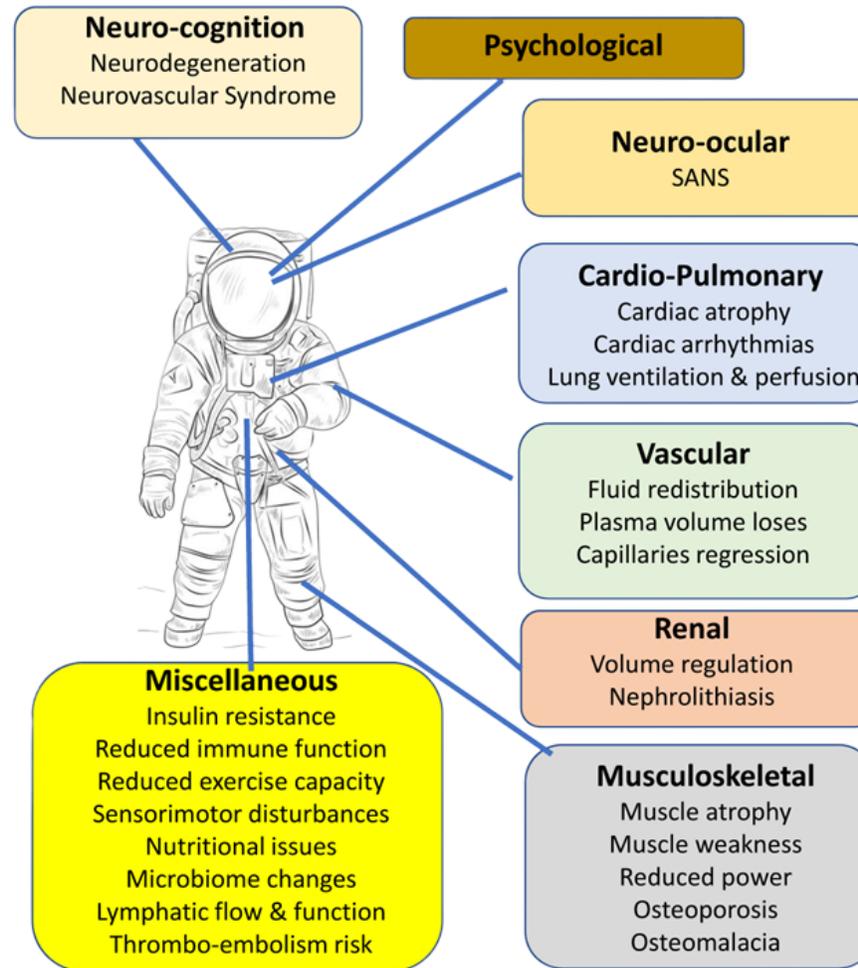
**In Space**

Without gravity, fluids pool near the chest and heart.



«Puffy face», «stuffed nose» and «bird legs»

# Systemic effects of microgravity



Overview of the main physiological systems affected by microgravity

## Neuro-ocular SANS

## Cardio-Pulmonary

Cardiac atrophy  
Cardiac arrhythmias  
Lung ventilation & perfusion

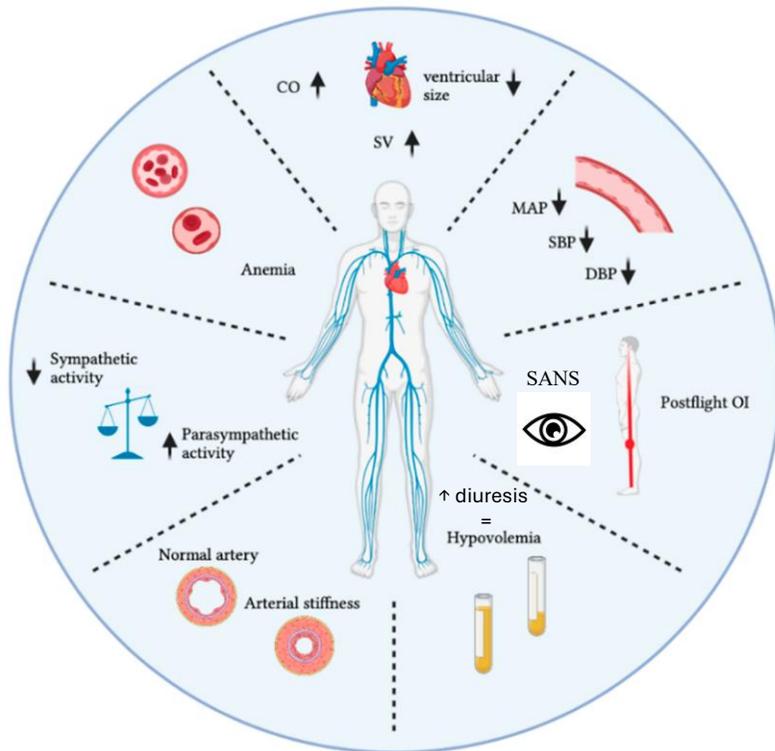


Table 1. Microgravity-induced cardiovascular adaptations.

Ref	Variables	Initial Reaction	ST Response	LT Response
[2]	Blood volume	↑	↓ 10–15%	↓ 10–15%
[2,16]	Haematocrit	↑	↓ 10–15%	Unchanged or ↓
[17–20]	CO	↑	↑ 18–24%	↑ 41%
[19,20]	SV	↑	↑ 46%	↑ 35%
[21–23]	Ventricular size	↑ 20%	↓ 10%	↓ 10%
[24–26]	CVP	↓	↓	↓
[20,27–29]	MAP	Unchanged	Unchanged	↓ 10 mmHg
[20,27–29]	SBP	Unchanged	Unchanged	↓ 8 mmHg
[20,27–29]	DBP	Unchanged	↓ 5 mmHg	↓ 9 mmHg
[20,29]	SVR	Unchanged	Unchanged	↓ 39%
[24,30]	HR	Unchanged	Unchanged or ↓	Unchanged or ↓
[31,32]	cIMT			↑ 10–12% (6 M) ↑ 20% (1 Y)
[31,32]	Femoral IMT			↑ 10%–15%
[33–35]	Arterial stiffness			↑ 17%–30%

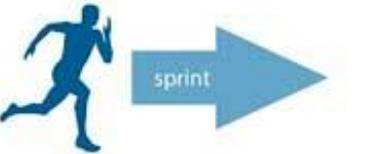
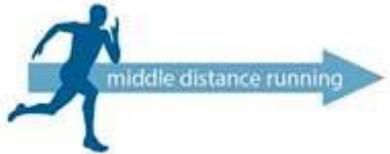
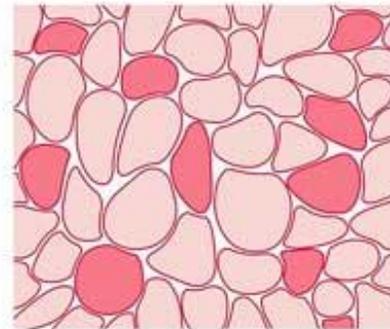
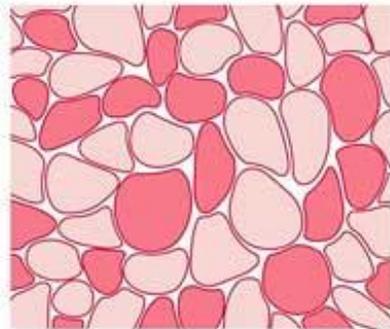
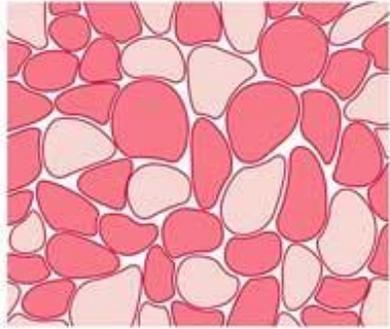
Abbreviations: References (Ref); short-term (ST); long-term (LT); cardiac output (CO); stroke volume (SV); central venous pressure (CVP); mean arterial pressure (MAP); systolic blood pressure (SBP); diastolic blood pressure (DBP); systemic vascular resistance (SVR); heart rate (HR); carotid intima media thickness (cIMT); femoral intima media thickness (femoral IMT); months (M); year (Y); increase (↑); decrease (↓).

A summary of spaceflight-induced cardiovascular diseases. Abbreviations: cardiac output (CO); stroke volume (SV); mean arterial pressure (MAP); systolic blood pressure (SBP); diastolic blood pressure (DBP); orthostatic intolerance (OI); increase (↑); decrease (↓).

Spaceflight-associated neuro-ocular syndrome (SANS)

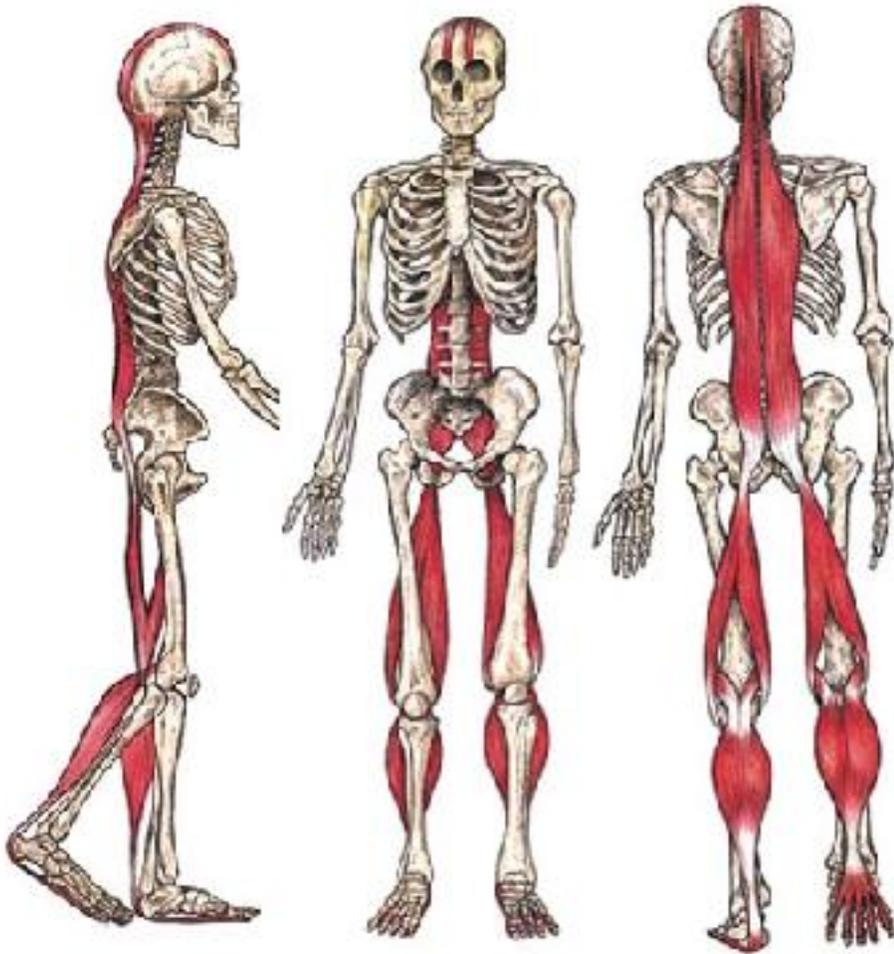
# Composition of skeletal muscle:

## Slow (type I), Intermediate (type IIa) and Fast (type IIb) muscular fibers



	FAST FIBERS	INTERMEDIATE FIBERS	SLOW FIBERS
ENERGETIC METABOLISM	ANAEROBIC	ANAEROBIC AEROBIC	AEROBIC
MITOCHONDRIA	FEW	MEDIUM	MANY
CAPILLARY DENSITY	LOW	MEDIUM	HIGH
FATIGUE	FAST	MEDIUM	SLOW
FIBER DIAMETER	BIG	MEDIUM	SMALL
CONTRACTION SPEED	FAST	MEDIUM	SLOW

# Postural (or antigravitary) muscles: enriched in type I fiber



## POSTURAL

Gastrocnemius  
Soleus  
Sartorius  
Hamstrings  
Iliopsoas  
Rectus femoris  
Tensor fasciae latae (TFL)  
Adductors  
Piriformis  
Erector spinae (quadratus lumborum region)  
Scalenes  
Pectoralis major  
Levator scapulae  
Upper trapezius  
Biceps brachii

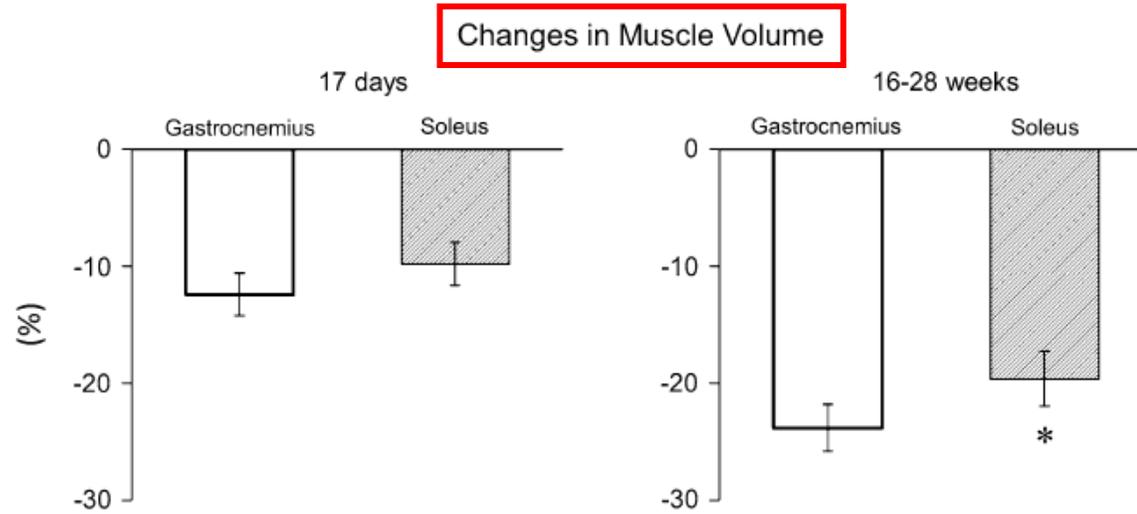
## PHASIC

Tibialis anterior  
Vastus medialis  
Vastus lateralis  
Gluteus medius / gluteus maximus / gluteus minimus  
Perineal muscles  
Erector spinae (thoracic level)  
Rhomboids  
Lower trapezius  
Triceps brachii

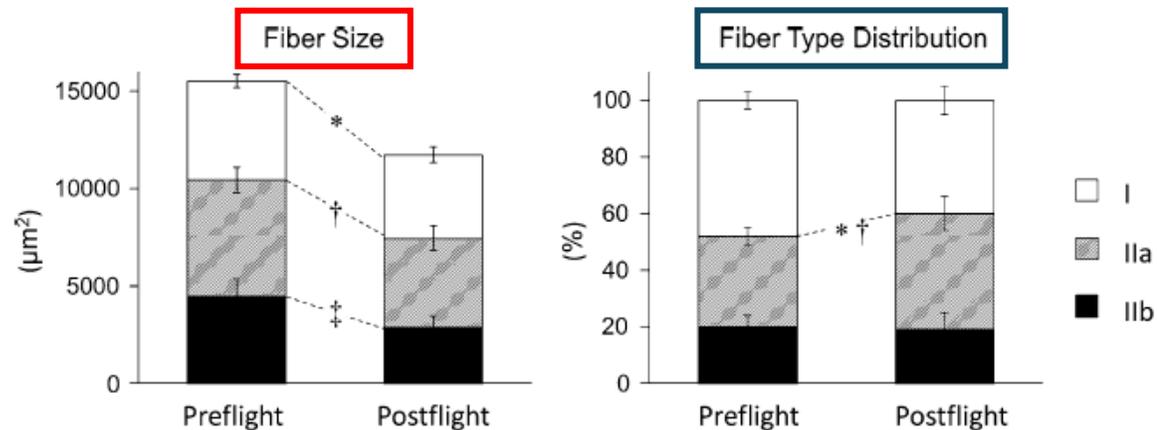
# Cellular effects of microgravity on the skeletal muscle: disuse atrophy

J Physiol Sci (2017) 67:271–281

**Fig. 1** Changes in muscle volume of triceps surae in astronauts after short (17 days) and long (16–28 weeks) spaceflights (drawn from data in Ref. [27]). \* $p < 0.05$  vs gastrocnemius



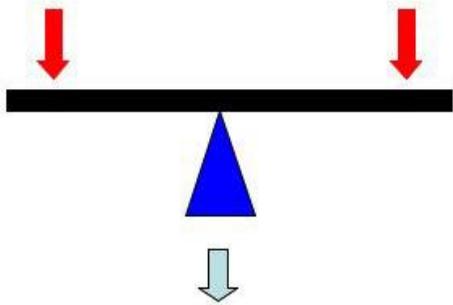
**Fig. 2** Changes in muscle fiber size (left panel) and fiber type distribution (right panel) of the vastus lateralis in astronauts after 11 days of spaceflight (drawn from data in Ref. [28]). \* $p < 0.05$  vs type I of preflight, † $p < 0.05$  vs type IIa of preflight, ‡ $p < 0.05$  vs type IIb of preflight



# Molecular mechanisms of muscle atrophy under microgravity

On the Ground, or  
In a Loading Environment

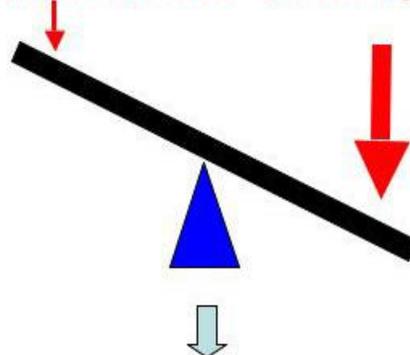
Skeletal muscle protein synthesis      Skeletal muscle protein degradation



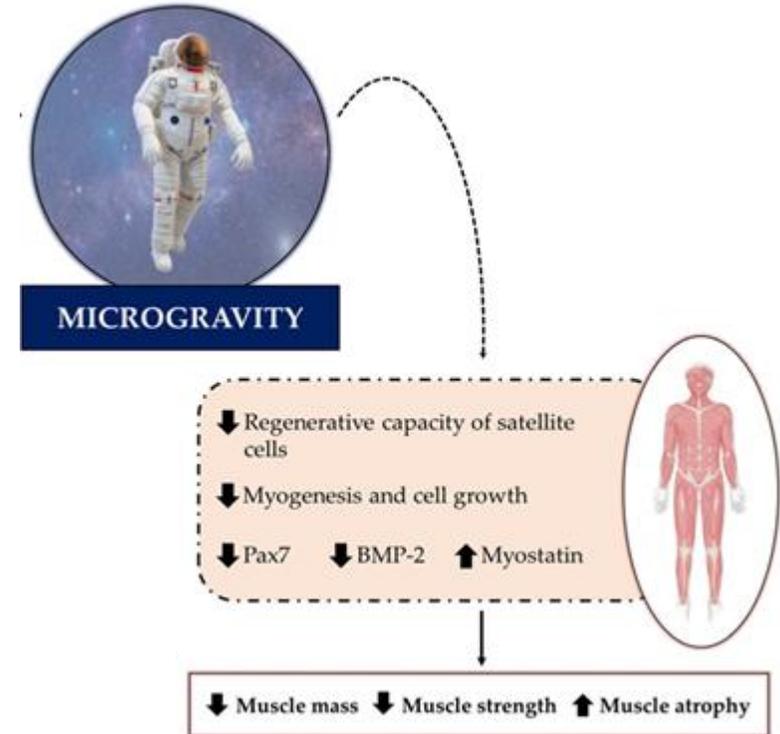
Conservation of muscle mass

In Space, or  
In an Unloading Environment

Skeletal muscle protein synthesis      Skeletal muscle protein degradation

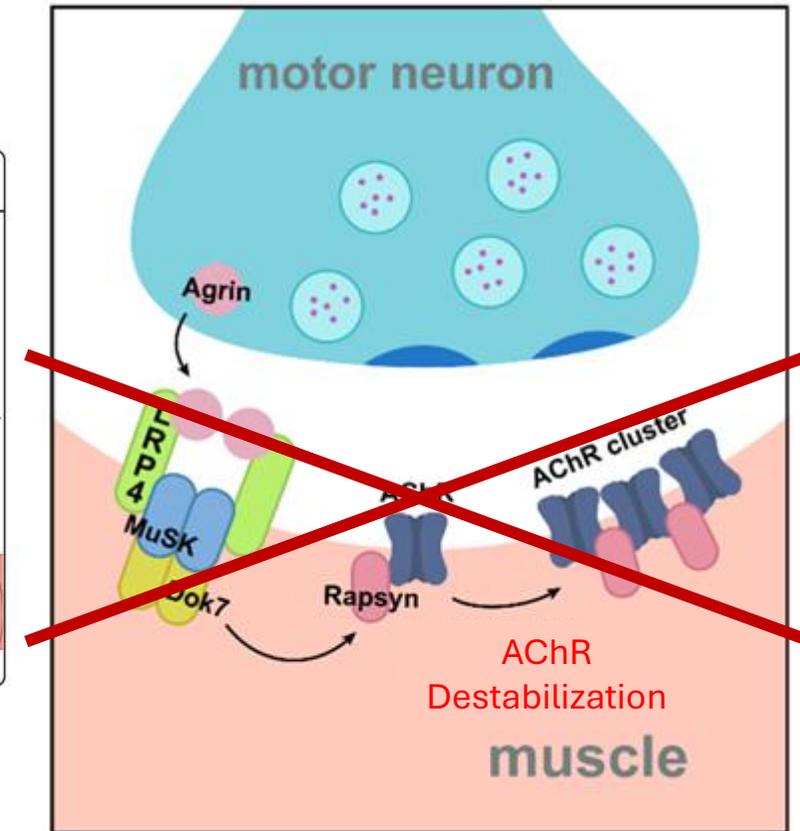
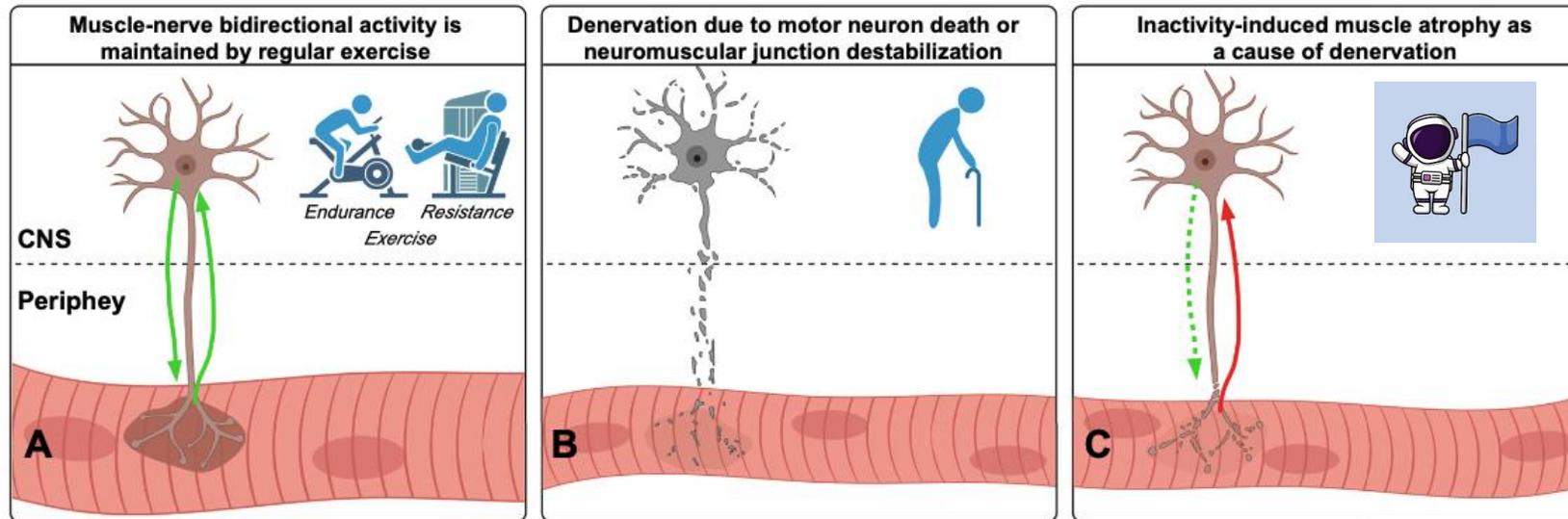


Muscle atrophy



- ↓ **IGF-1 / BMP-2** → reduced Akt–mTOR signaling → ↓ protein synthesis
- ↑ **Myostatin** → activation of catabolic pathways (autophagy)
- Reduction of satellite cells activity (↓ **Pax7**) → ↓ muscle regeneration
- The muscle enters a **metabolic “energy-saving” state**, losing mass and repair capacity

# From muscle atrophy to synapse instability

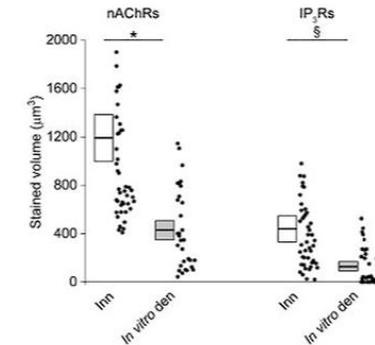
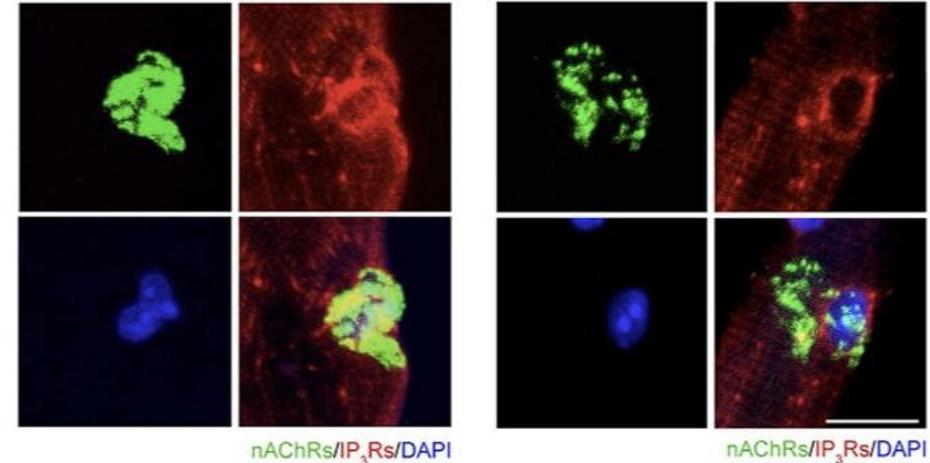
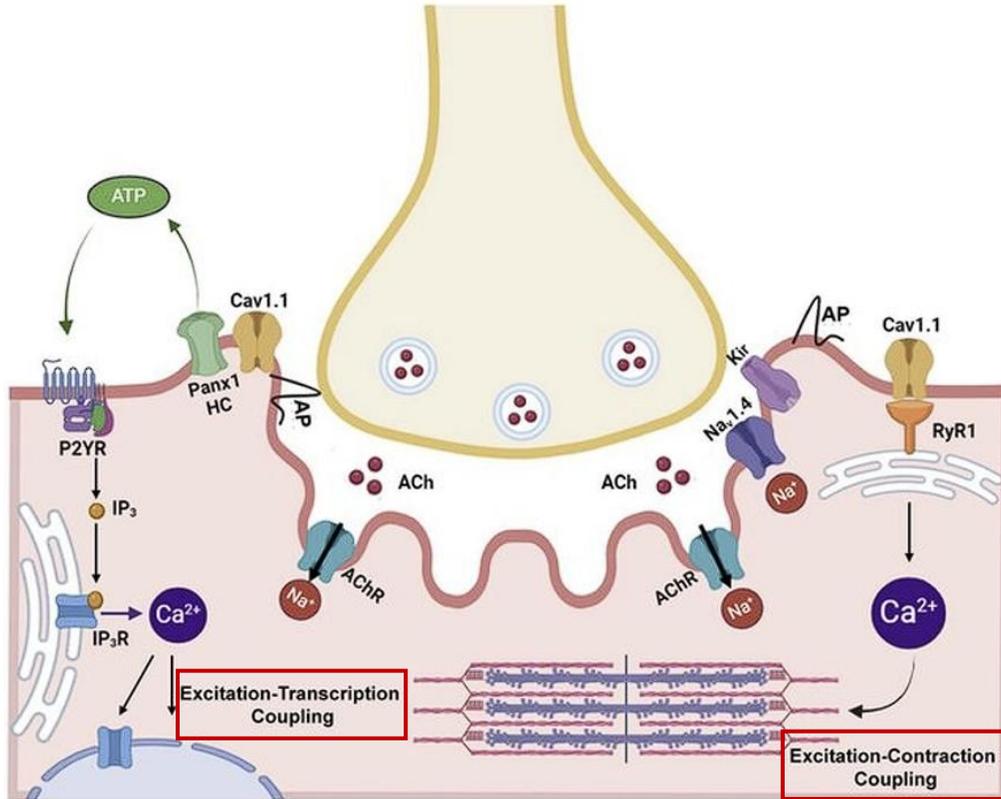


The figure summarizes the bidirectional communication between motor neurons and muscle fibers: **(A)** regular activity preserves NMJ stability, **(B)** neuronal deterioration causes muscle atrophy, and **(C)** inactivity or unloading leads to atrophy first, followed by denervation.

Agrin–MuSK–Lrp4 cascade permits nAChR stabilization

# Calcium microdomains and IP<sub>3</sub>R1 signaling

Vásquez et al., *J Physiol.* 603(15):4213-4235 (2025).



Representation of the E–C and E–T coupling mechanisms. Local IP<sub>3</sub>R1-dependent Ca<sup>2+</sup> release regulates transcription of synaptic genes at the NMJ

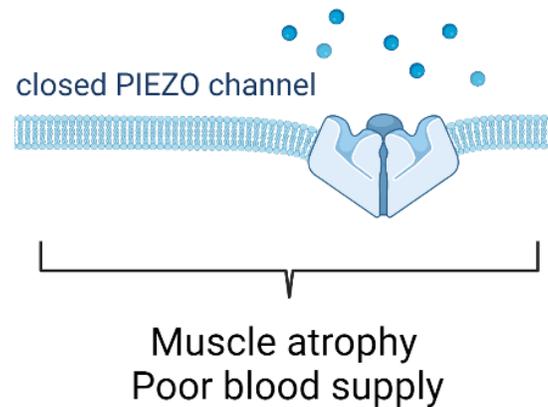
Co-localization of nAChRs (green) and IP<sub>3</sub>R1 (red) in muscle fibers.

Reduced expression and clustering are observed in in vitro denervated models

Volpe et al., *Journal of General Physiology.* 154(1):e202213128 (2022).

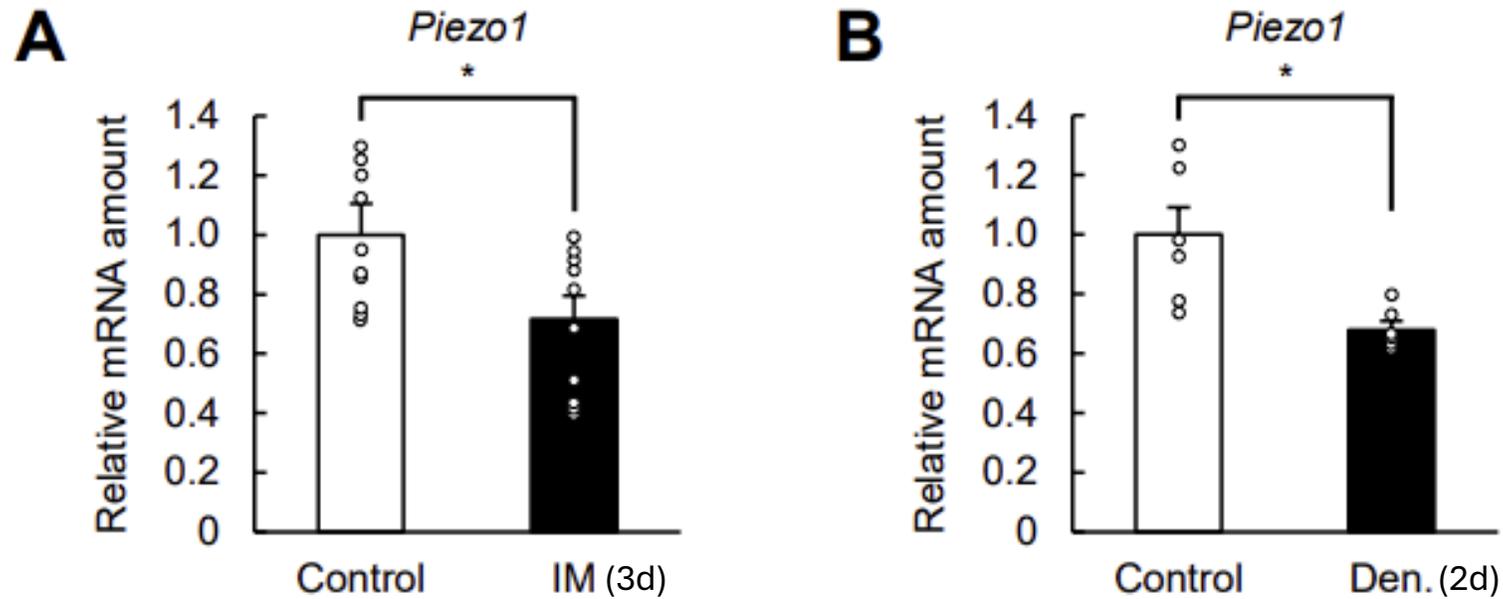
# Mechanotransduction: cells feel force

Muscle pathology  
(Microgravity, aging, disuse)



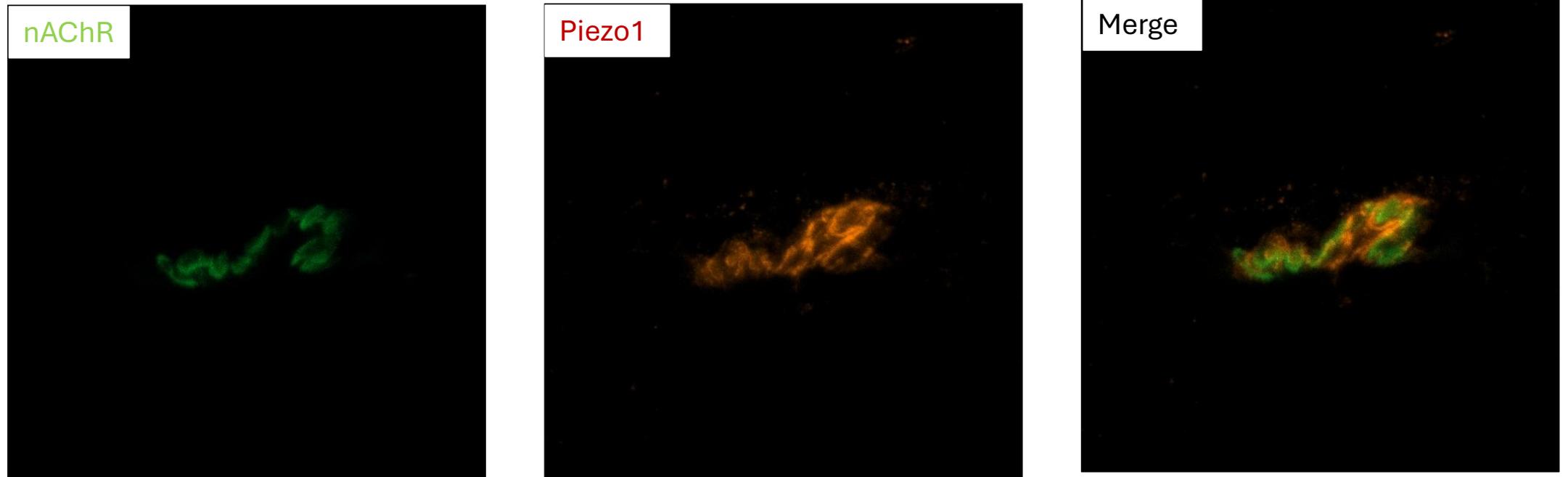
Mechanical stimulation/Piezo activation →  $\text{Ca}^{2+}$  influx → cellular response

# Immobilization and denervation effects on Piezo1 expression



Quantitative RT-PCR analysis of Piezo1 mRNA in gastrocnemius of control or cast-immobilized mice (n = 10 mice) (A) or of control or denervated mice (n = 6 mice) (B).

# Piezo1 expression at the NMJ



Maximal projection in confocal microscopy of muscle fibers ex vivo (rat).

# Physical countermeasures: exercise and stimulation



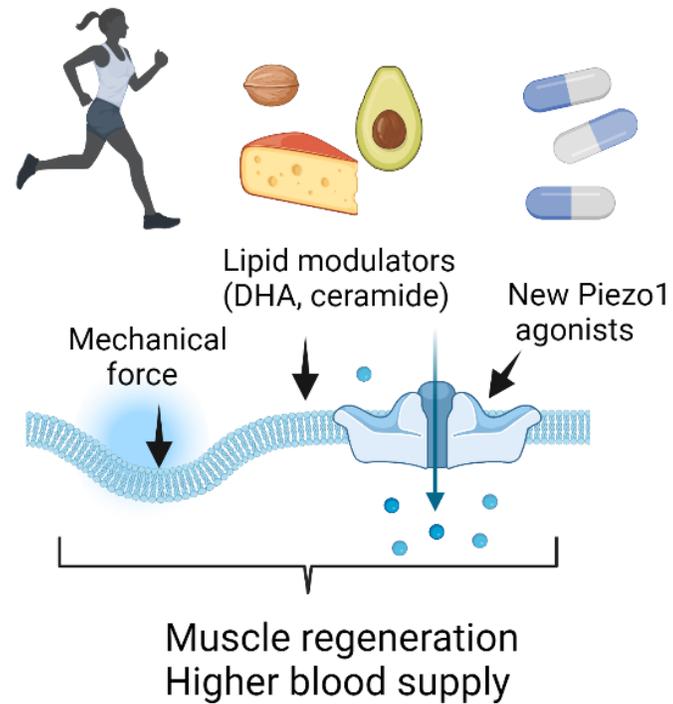
ARED system



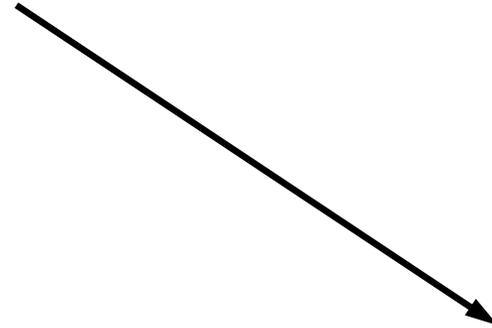
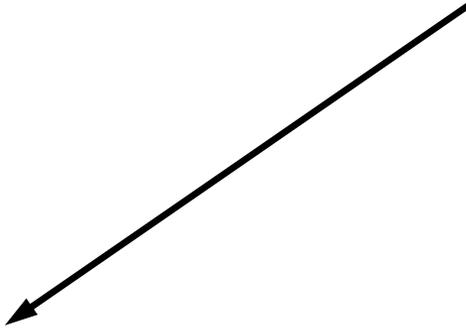
NMES system

# Pharmacological and nutritional approaches

## Modulation and treatment



# From space to Earth: translational implications



Neuromuscular disorders  
(disuse atrophy)



Aging (sarcopenia)

**Thanks for attention**

