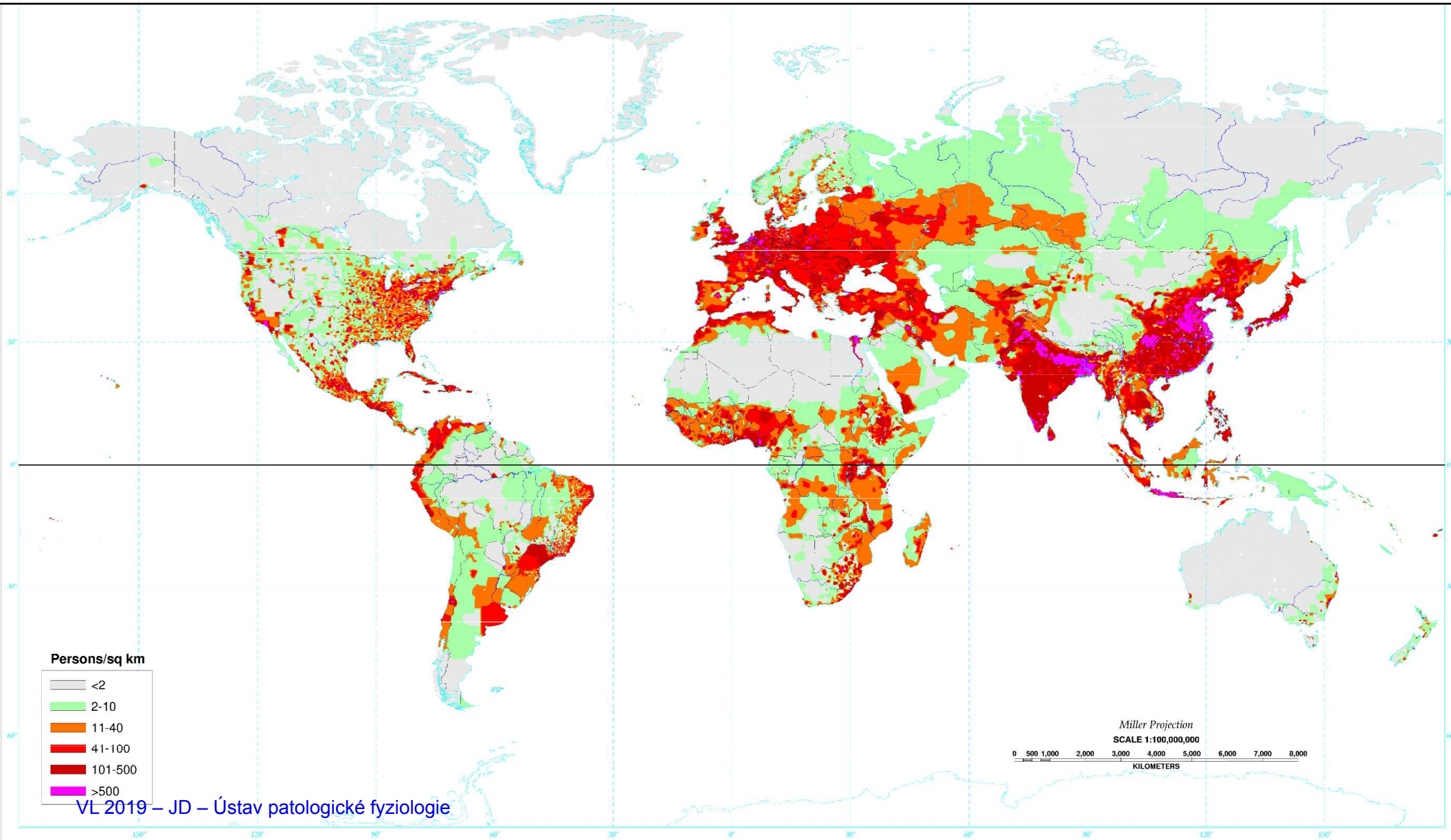


**MUNI  
MED**

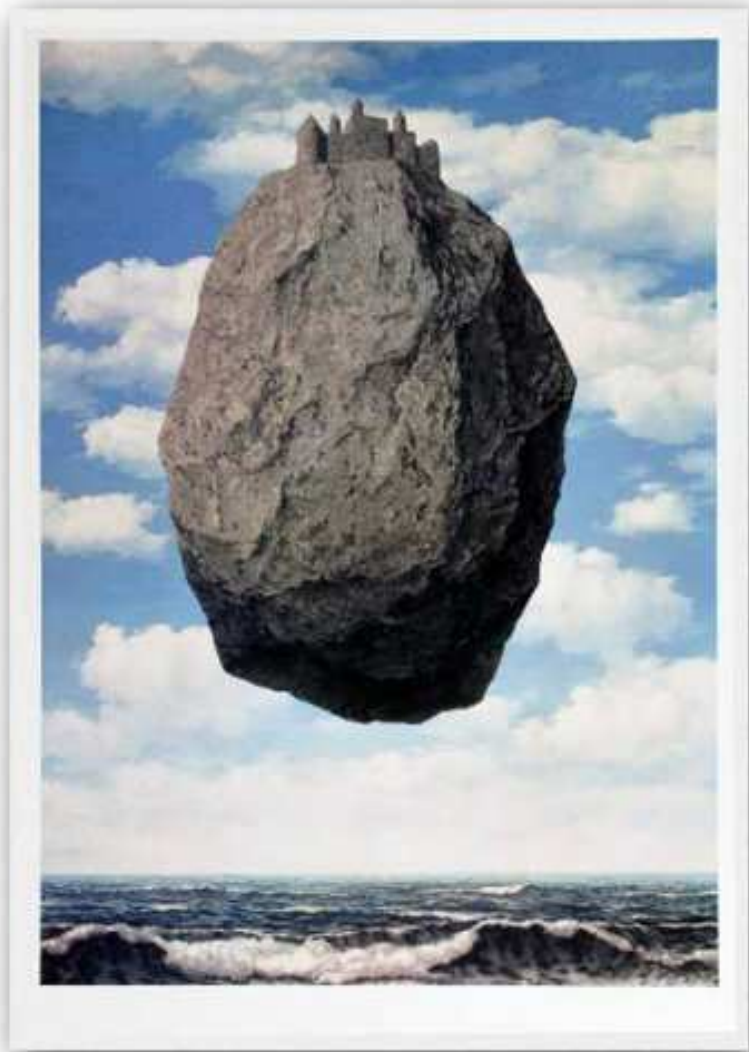
# **Pathophysiology of endocrine system II– homeostasis, principles of regulation and its disorders) -stress reaction and stress as a pathophysiological phenomenon**

Julie Dobrovolná

Department of Pathological Physiology MED MUNI



VL 2019 – JD – Ústav patologickej fyziologie









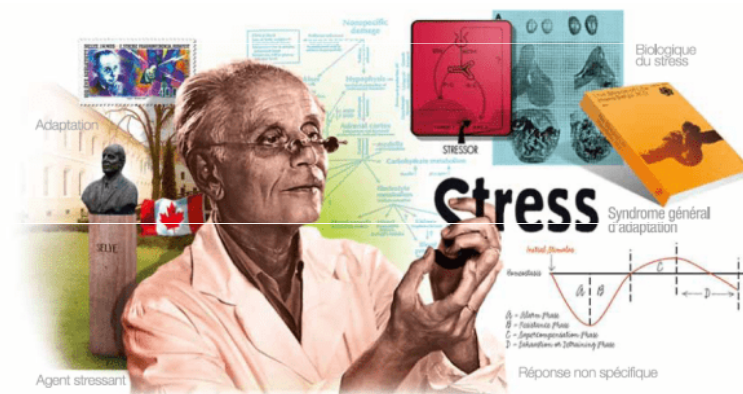
To be totally without  
stress is to be dead.

Hans Selye

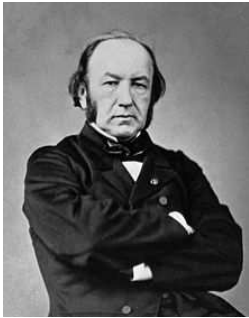
 quote fancy

## Stress and environment

# So what is stress?



# Evolution of the term „stres“



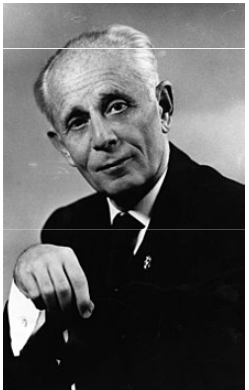
## Claude Bernard (1813-1878)

- *Leçons sur les phénomènes de la vie communs aux animaux et aux végétaux*
- Vnitřní prostředí je udržováno jako stálé



## Walter Cannon (1871-1945)

- *The Wisdom of the Body*
- Homeostáza, stres, autonomní (sympatický) nervový systém



## Hans Selye (1907-1982)

- *The Physiology and Pathology of Stress; a Treatise Based on the Concepts of the General-Adaptation-Syndrome and the Diseases of Adaptation*
- Hypotalamo-hypofyzárně nadledvinková osa (HPA)

# Evolution of the term „stres“

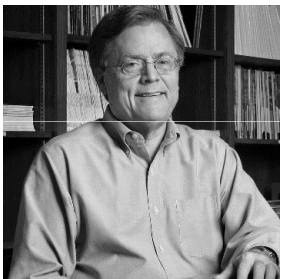


## Robert Sapolsky

*Stress, the Aging Brain, and the Mechanisms of Neuron Death*

*Why Zebras Don't Get Ulcers: an Updated guide to Stress, Stress-Related Diseases, and Coping*

Úloha limbického systému (hippocampus) v regulaci HPA



## Bruce McEwen & Theresa E. Seaman

- *The End of Stress as We Know It*
- Allostáza, homeodynamika



## Gordon Lithgow a další

- Hormeze, endokrinní regulace délky života u much, hlístů a myší



# So what is stress?



## Social aspects of stress

Social factors such as lack of education, a low standard of housing, noise and crowding, homelessness, lack of social support, domestic violence, and economic hardship put individuals under greater stress, contributing to poor health and family problems.



## ***Effects of long-term exposure to poverty in childhood Evans and Kim (2007)***



The aim of the study was to investigate the long-term relationship between poverty or low socioeconomic status, cumulative risk factors and physiological stress.

## ***Effects of long-term exposure to poverty in childhood*** ***Evans and Kim (2007)***

Participants were 200 seven-year-olds.

The researchers measured blood pressure and cortisol levels.

Stress regulation was assessed by measurement of the heart's reactivity to a standard acute stressor, and recovery after exposure to the stressor.

Exposure to risk factors such as substandard housing, and family violence were included to have a measure of cumulative stress factors.

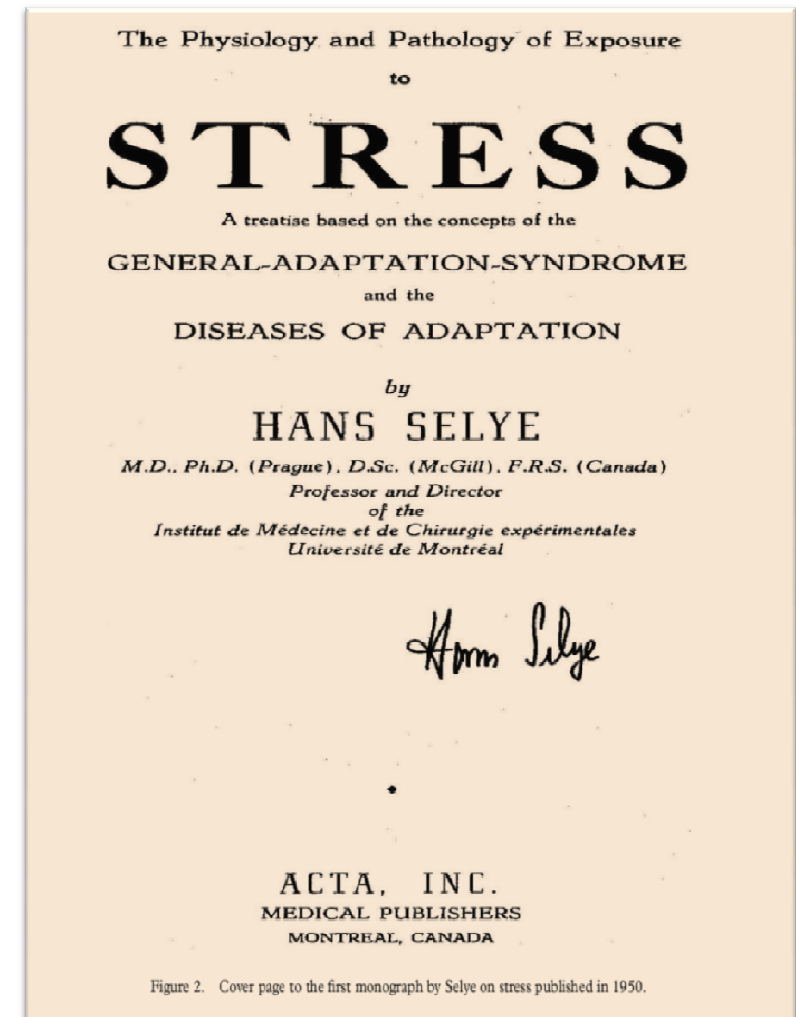




# Definition?

**The Stress of Life, Hans Selye, 1956:**

*„... the non-specific response of the body to any demand made upon it, whether it is caused by, or results in, pleasant, or unpleasant conditions“*



## ***Cannon (1914) The fight or flight theory***



The fight or flight response is a physiological stress response evolved to help organisms (i.e. animals and humans) to survive immediate danger. Activation of the sympathetic nervous system.

## ***Cannon (1914) The fight or flight theory***

The theory proposes that when an organism faces an imminent danger (acute stressor), the body is rapidly aroused and motivated to act via two systems: the sympathetic nervous system and the endocrine system. These two physiological systems interact to mobilize the organism to [fight](#) against or [flee](#) the danger.



# Fight or Flight?



The fight or flight theory is only addressing the physiological aspects of stress.

This could be because Cannon only studied animals. The exclusive focus on physiological aspects of stress is a limitation in relation to humans.

It is now known that cognitive factors can mediate the stress response.



# ***GAS (General Adaptation Syndrome)*** ***Selye (1956)***

The theory is based on animal research (rats) and it extends Cannon's theory.

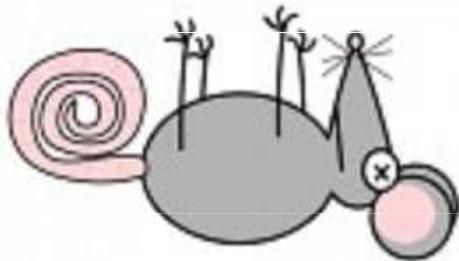
Selye did experiments where he exposed rats to various stressors (e.g. cold, surgical injury, excessive exercise).



# ***GAS (General Adaptation Syndrome)*** ***Selye (1956)***

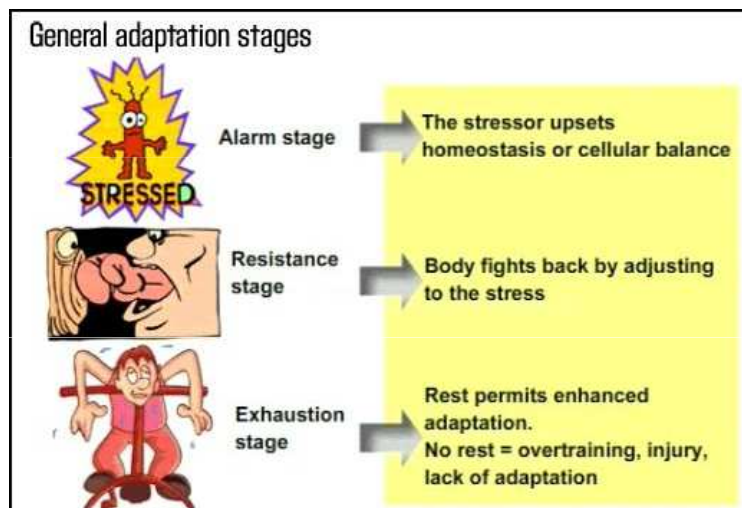


The animals all showed the same general physiological responses such as enlarged adrenal glands, diminished thymus (important organ in the immune system) and ulcers when they were exposed to stressors. Some of them died.



# ***GAS (General Adaptation Syndrome)***

## ***Selye (1956)***



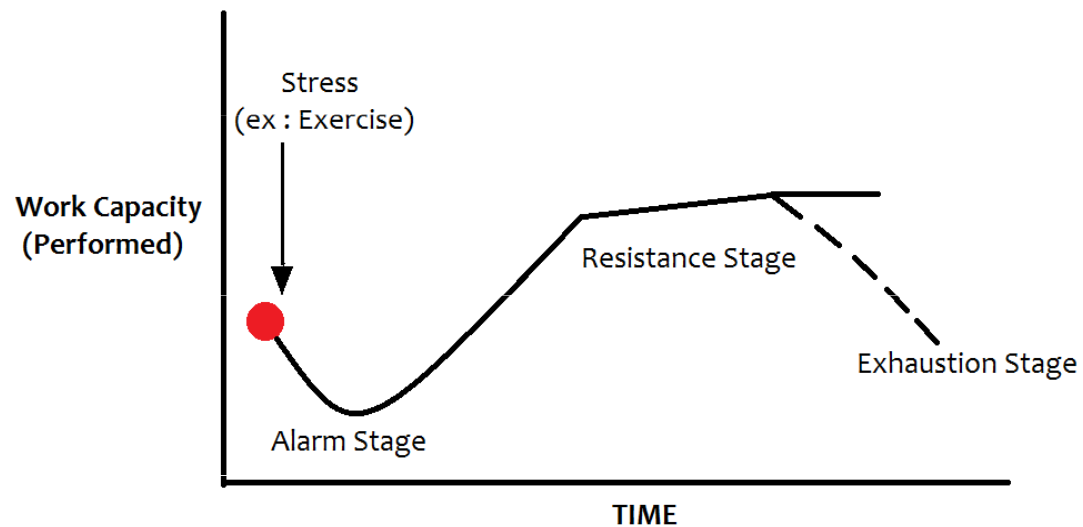
The three stages of stress

**Alarm:** Physiological mobilization to respond to the danger. It is the same as the fight or flight response.

**Resistance:** Attempts to cope with the stress response.

**Exhaustion:** Occurs when the organism fails to overcome the danger and is incapable of further coping.

# ***GAS (General Adaptation Syndrome)*** ***Selye (1956)***





## ***GAS (General Adaptation Syndrome)*** ***Selye (1956)***

Selye concluded that rats (and humans) would respond with the same physiological pattern of physiological changes no matter the stressor.

With prolonged exposure to stress (chronic stress), the physiological system will be damaged and the organism may eventually die.

It may be problematic to generalize such results to humans but research in health psychology has confirmed a link between stress and low immune functioning.



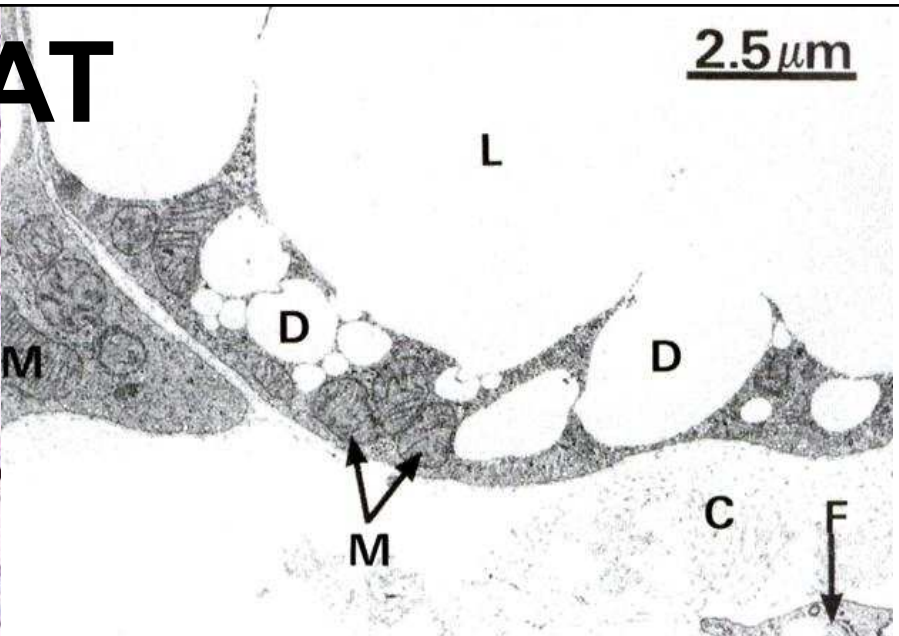
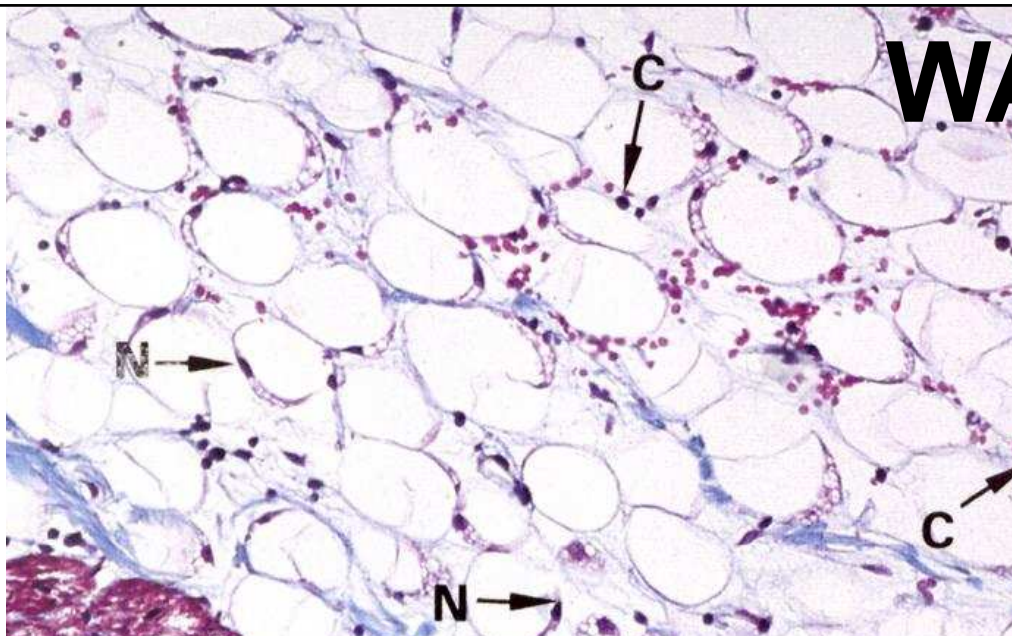
**Which organ systems are involved in stress reaction?**

---

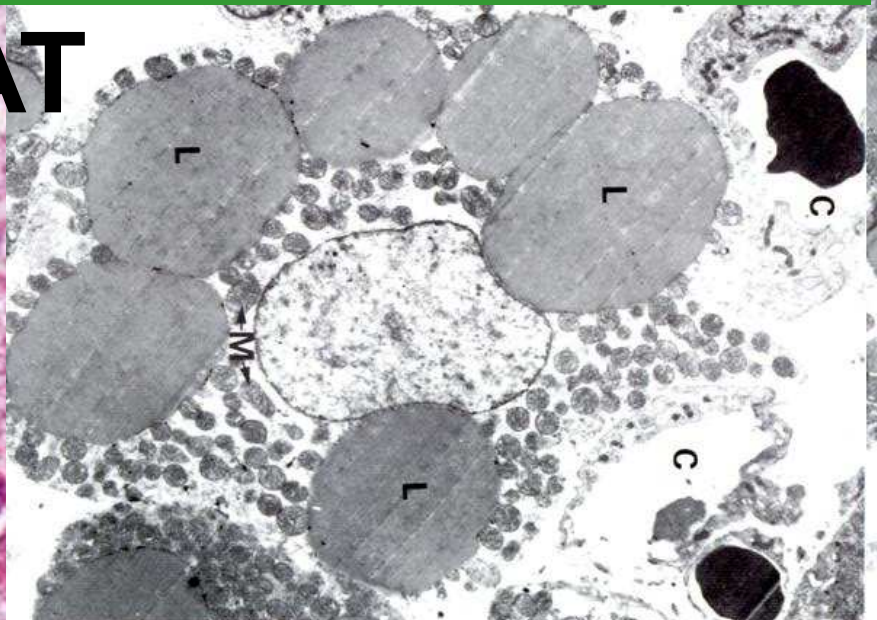
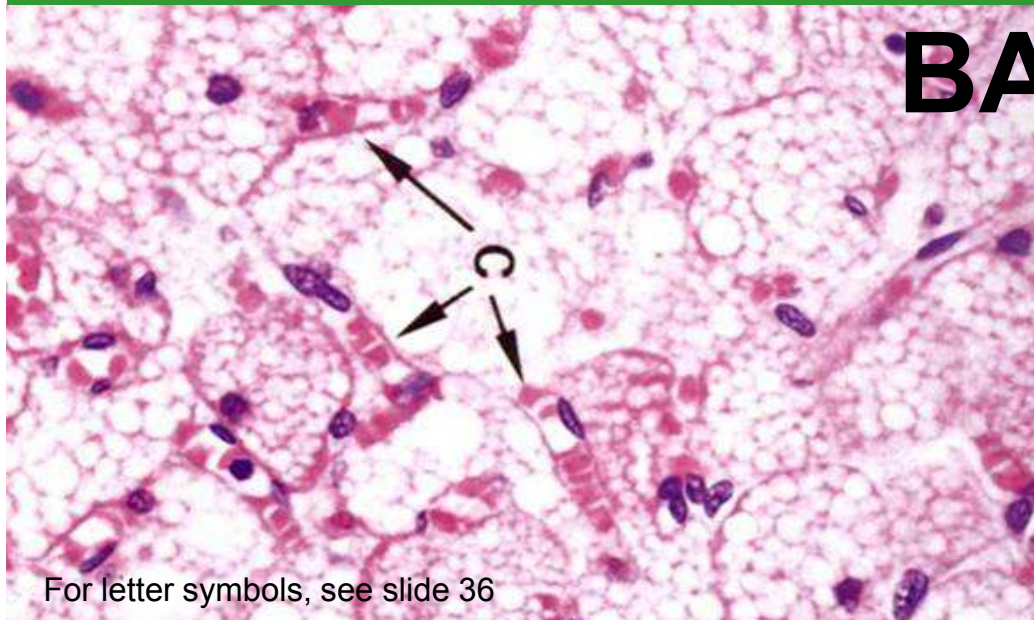
Stress and control of adaptation

# **The role of the adipose tissue**

# WAT



# BAT

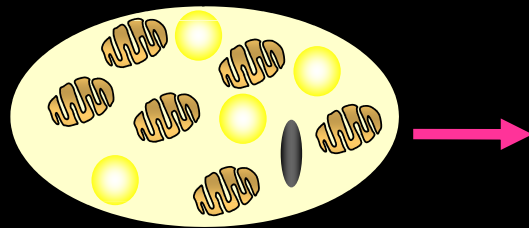


For letter symbols, see slide 36



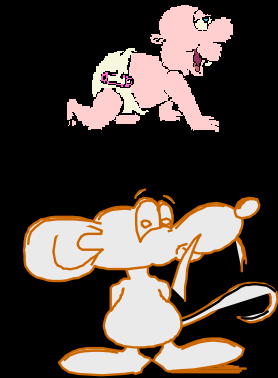
# White and brown adipocytes

## Brown adipocyte

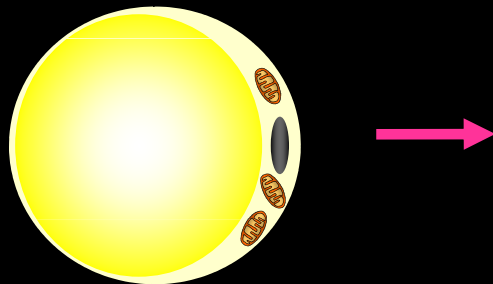


Multilocular  
Storage and mobilization of lipids (++)  
Mitochondria (+++)  
Beta oxidation (+++)  
Respiratory chain (+++)  
UCP1 (+++)

PGC-1 $\alpha$  (+++)



## White adipocyte



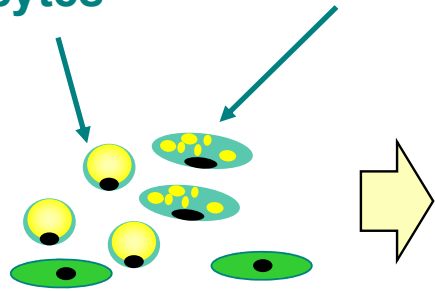
Unilocular ( $\rightarrow$  200 $\mu$ m)  
Storage and mobilization of lipids(+++)  
Mitochondria (+)  
Beta oxidation (+)  
Respiratory chain (+)  
UCP1 (0)

PGC-1 $\alpha$  (+)

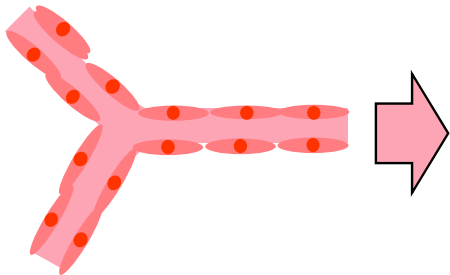


# Adipose tissue – there is more than just pure differentiation

Mature adipocytes      Preadipocytes



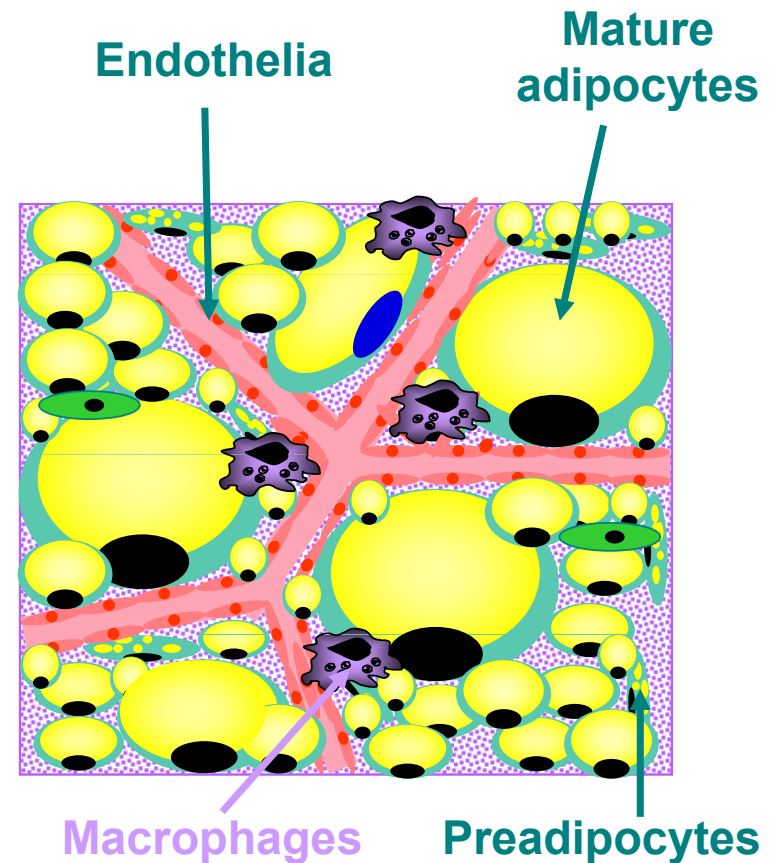
Hypertrophy and hyperplasia



Angiogenesis

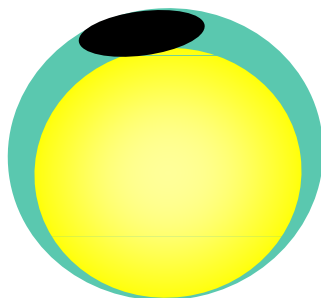


Inflammation



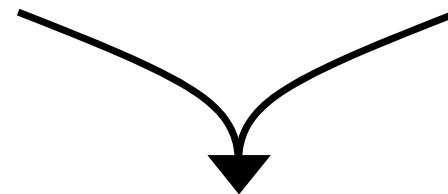
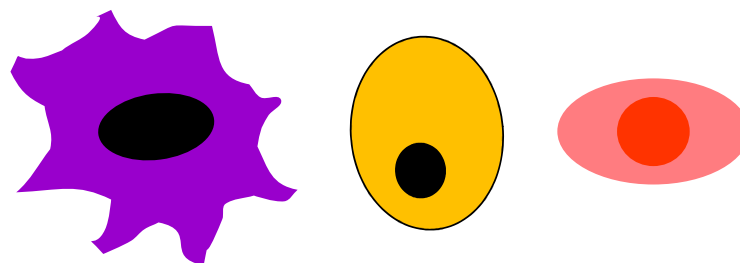
# Cellular origin of secreted molecules

Adipocytes → Adipokines



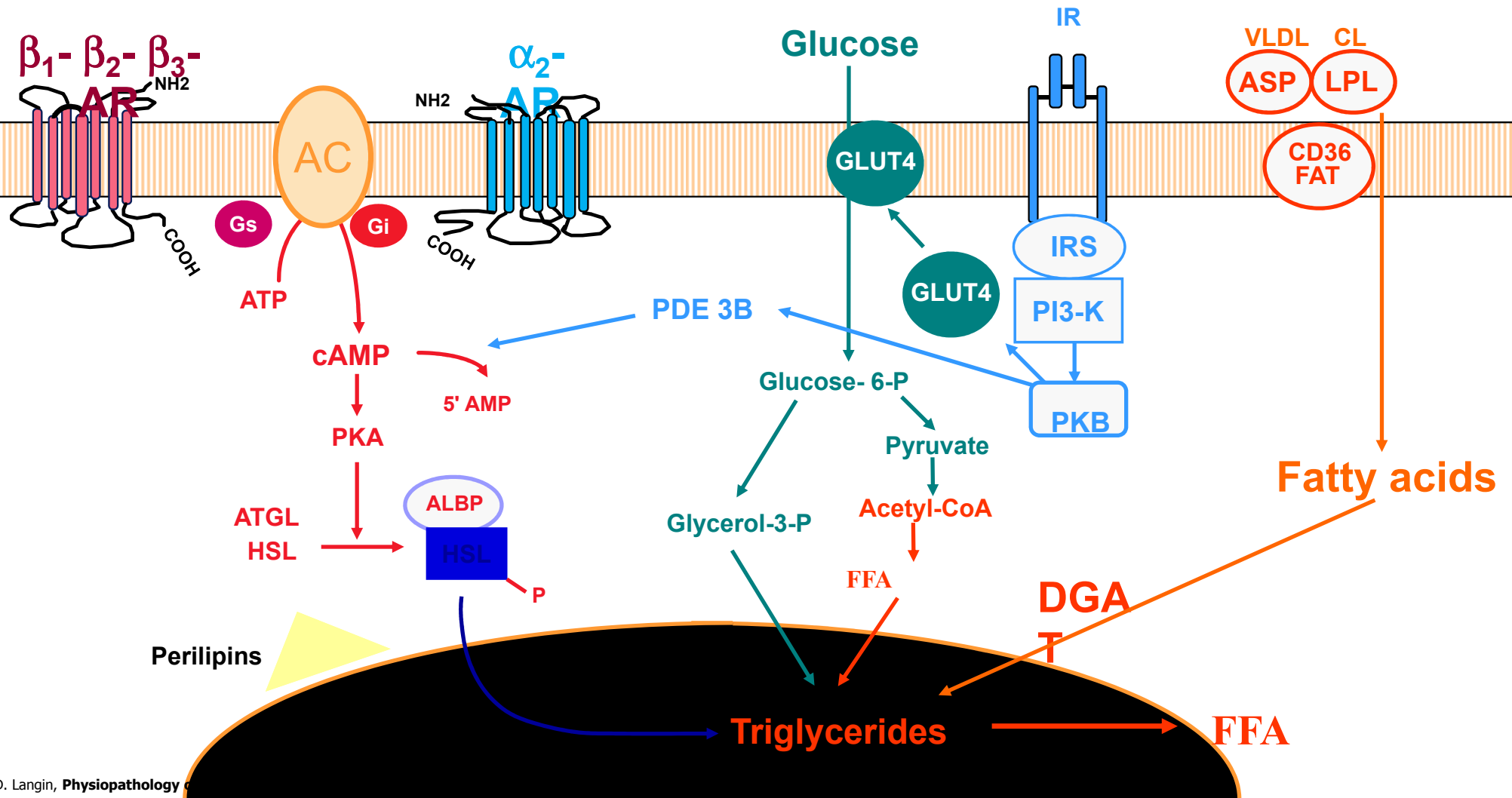
Leptin  
Adiponektin  
Serum amyloid  
Retinol binding protein 4 (RBP4)  
Apelin

Stromal vascular fraction cells  
→ cytokines & chemokines



Monocyte chemoattractant protein 1 (MCP-1)  
Macrophage inflammatory protein (MIP)  
Tumor necrosis  $\alpha$  (TNF $\alpha$ )  
Interleukins 1 $\beta$ , 6, 8, 10, ....  
Chemokines  
Resistin

# Adipocytes and nerves



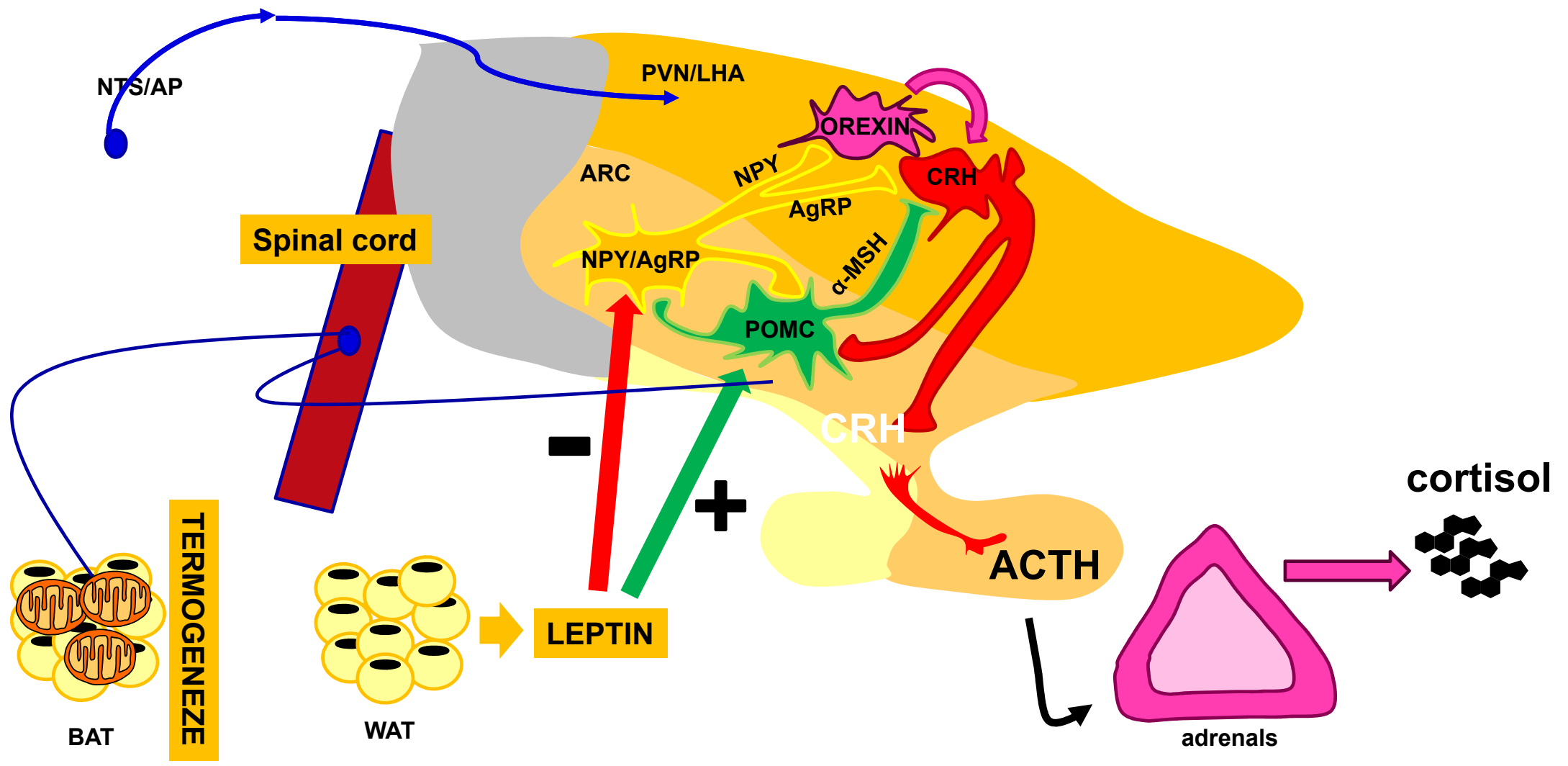
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Stress and metabolic control

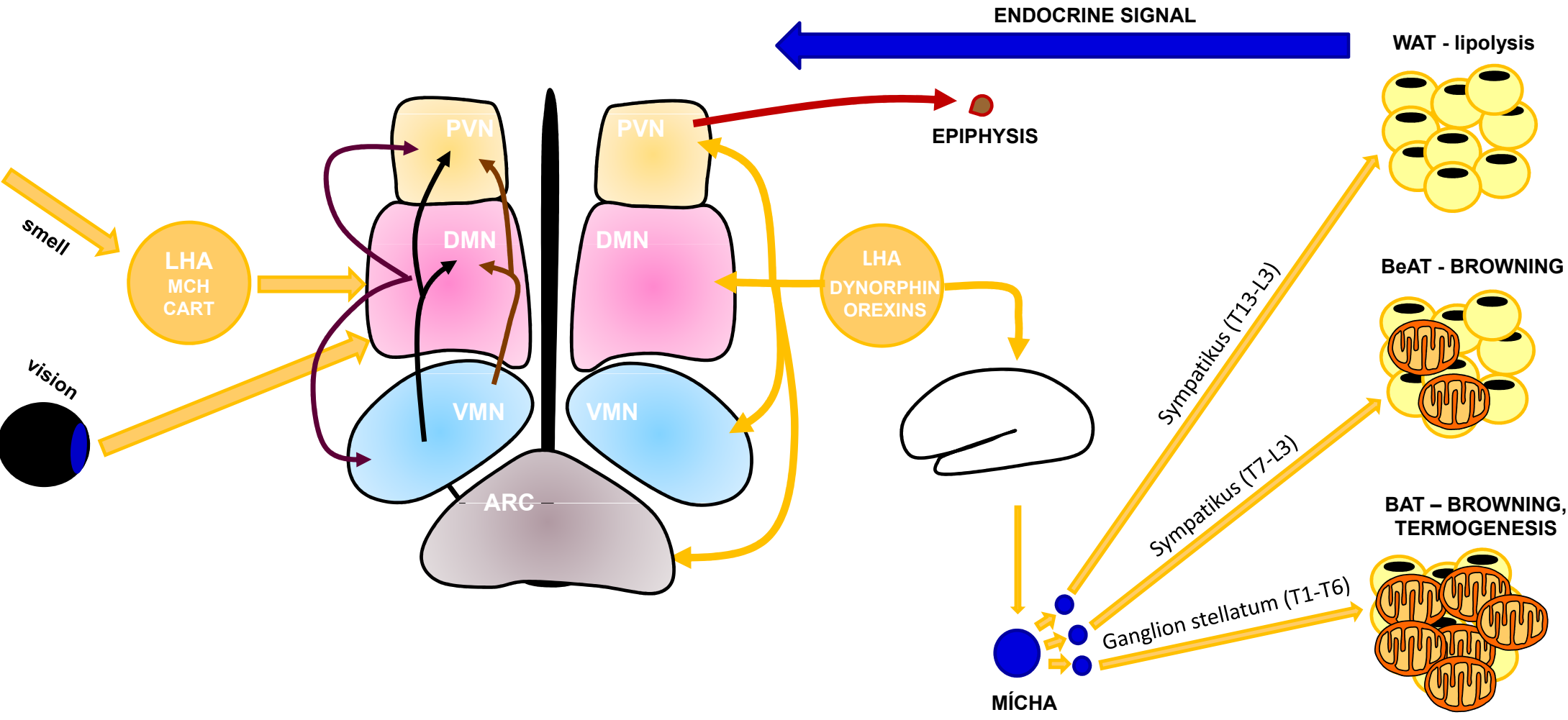
# **Brain vs. adipose tissue**



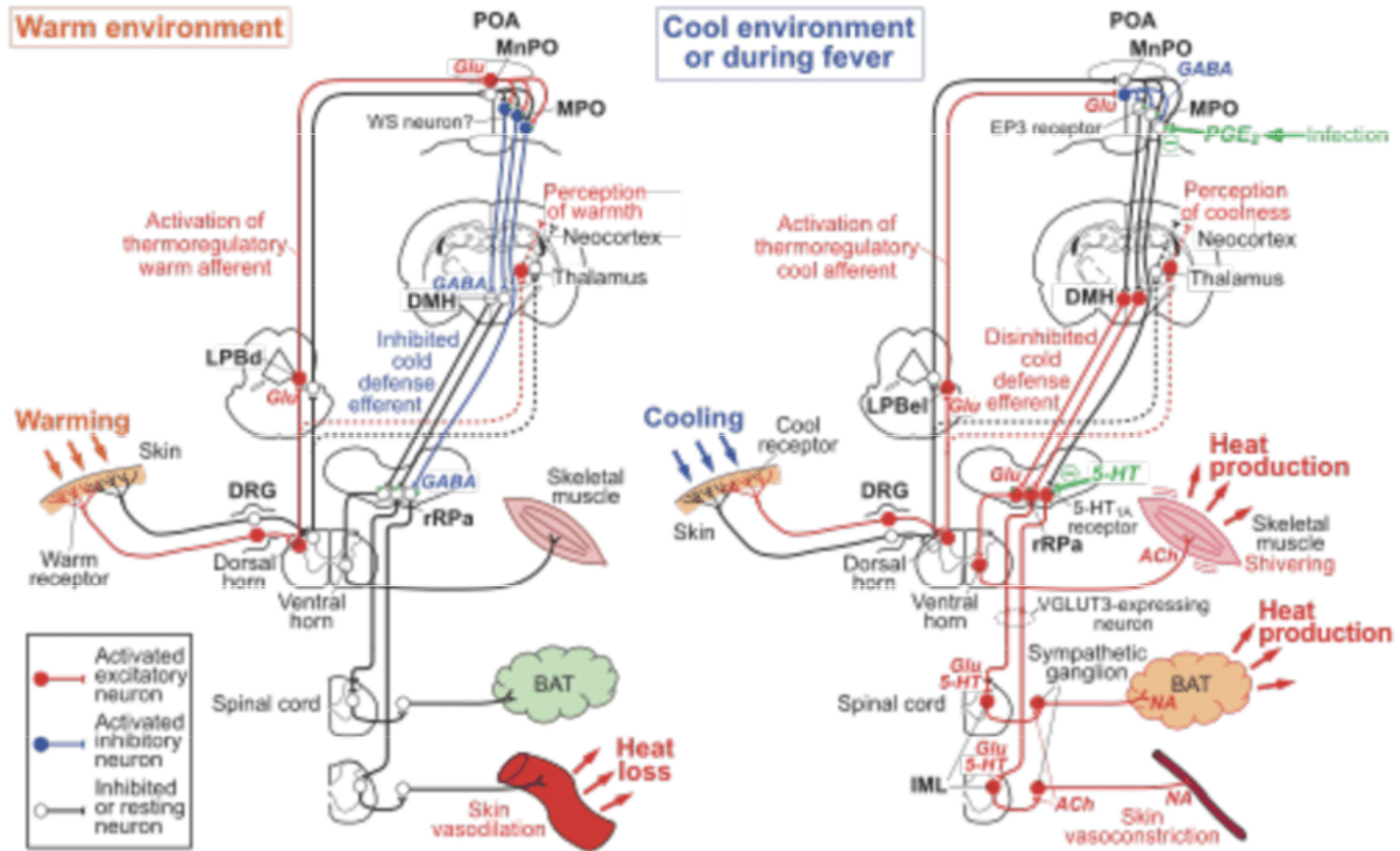
# Brain-adipose tissue axis I



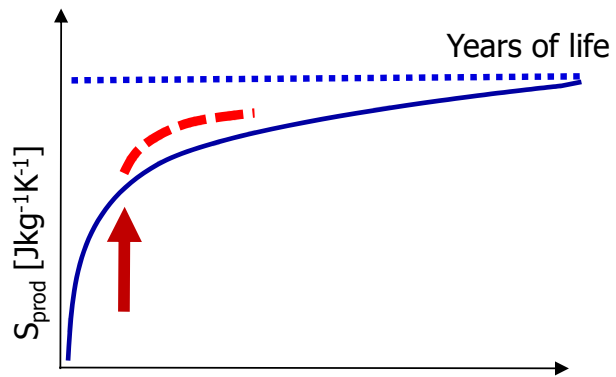
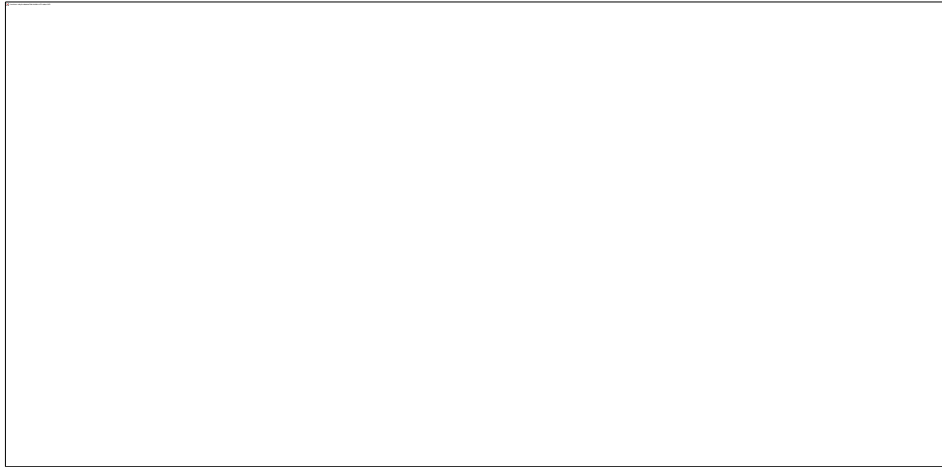
# Brain-adipose tissue axis II



# Can stress be calculated? Can temperature be calculated?



# Really?



Stress and metabolic control

## **What it all means?**

Impaired social environment?

Impaired social context?

Isolated „social animals“?

Loneliness?

Perceived discrimination?

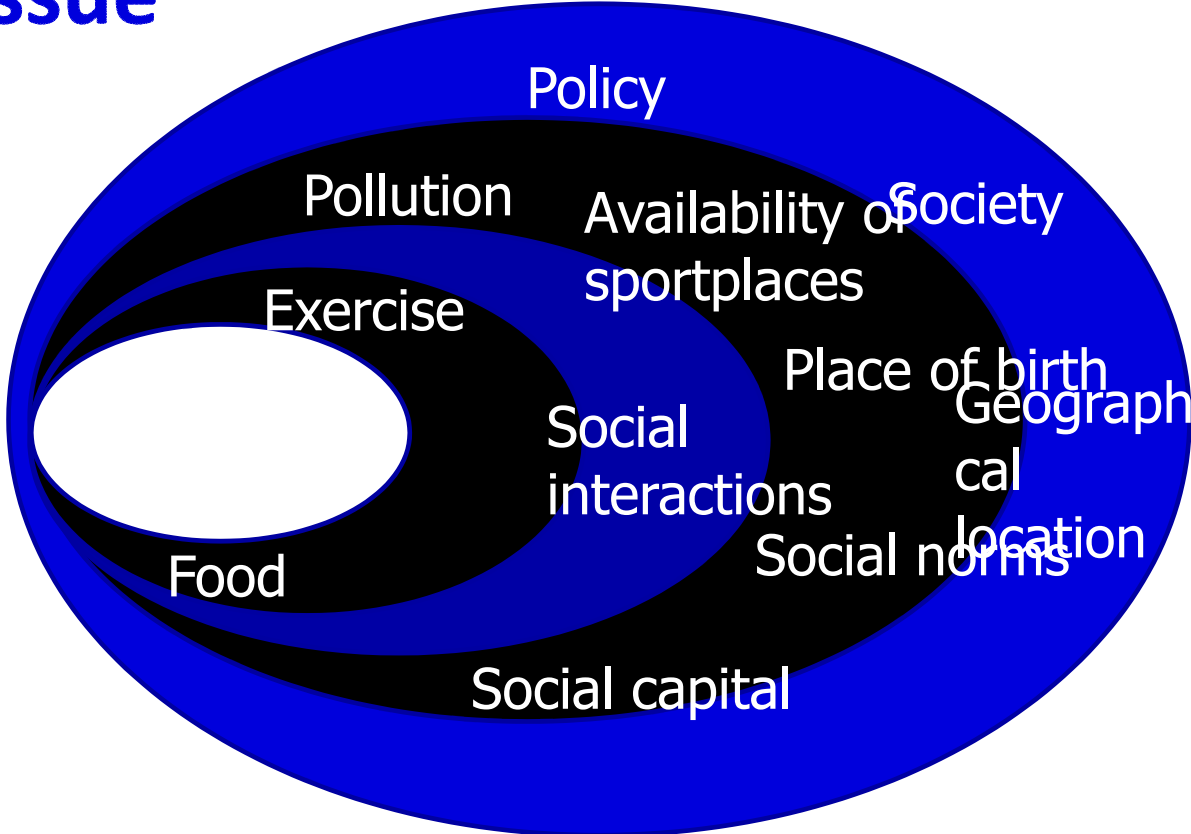
Prenatal modelling?

Absence of contact with the „real“ environment?

...



# Changing the paradigm of understanding of adipose tissue



Is it more practical to attempt to change the human or the environment?

# Adipose tissue and change of paradigm?

---

*„Obesity is not simply about bodyweight or body image. It is about human vulnerability arising from excess body fat, the origins of which lie in multiple determinants ranging from molecular genetics to market forces.“*

Ralston J, Brinsden H, Buse K, Candeias V, Caterson I, Hassell T, Kumanyika S, Nece P, Nishtar S, Patton I, Proietto J, Salas XR, Reddy S, Ryan D, Sharma AM, Swinburn B, Wilding J, Woodward E. Time for a new **obesity** narrative. **Lancet**. 2018 Oct 20;392(10156):1384-1386.



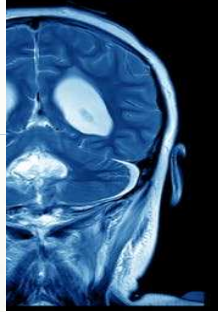
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Let's get back to adaptation!



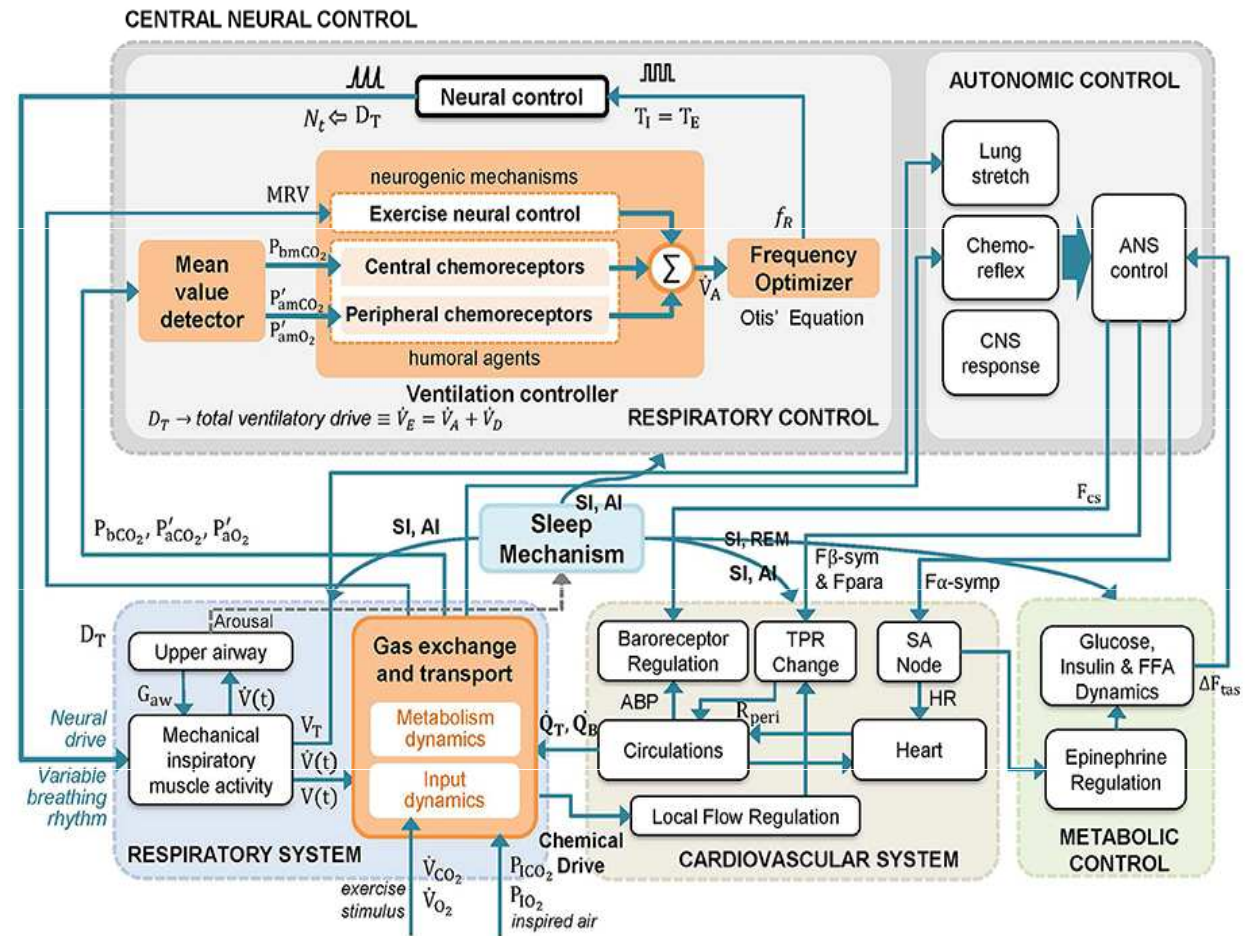


Marine diet





# Breathable air?



## Breathable air

Most of the adaptation during the first 2 weeks to 2 months after arrival to the high altitude area, but in permanently living populations the changes occur prenatally already  
Most of the changes go unnoticed  
Typical morphology of populations living in the high altitude – the barrel chest  
Different mechanism of adaptation (decreased or increased hemoglobin levels, etc.)  
Higher hydration  
Different distinct populations: Tibetans, Andians, Ethiopians.





# Breathable air: record



# :Shelter: cold and heat - records

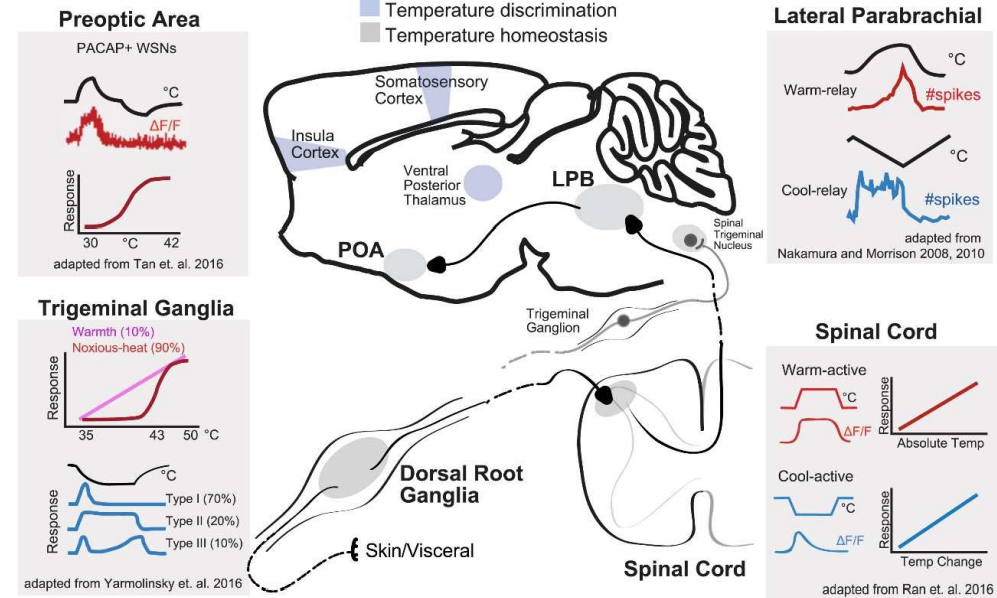
Very dry air: 120+ °C (248+ °F)  
 short-term, 70+ °C (158+ °F) long-term  
 (with access to water with lower temperature)

Tropical air: 60+ °C (140 °F) short-term,  
 47 °C (117 °F) long-term

Saturated air: 48 °C (118 °F)

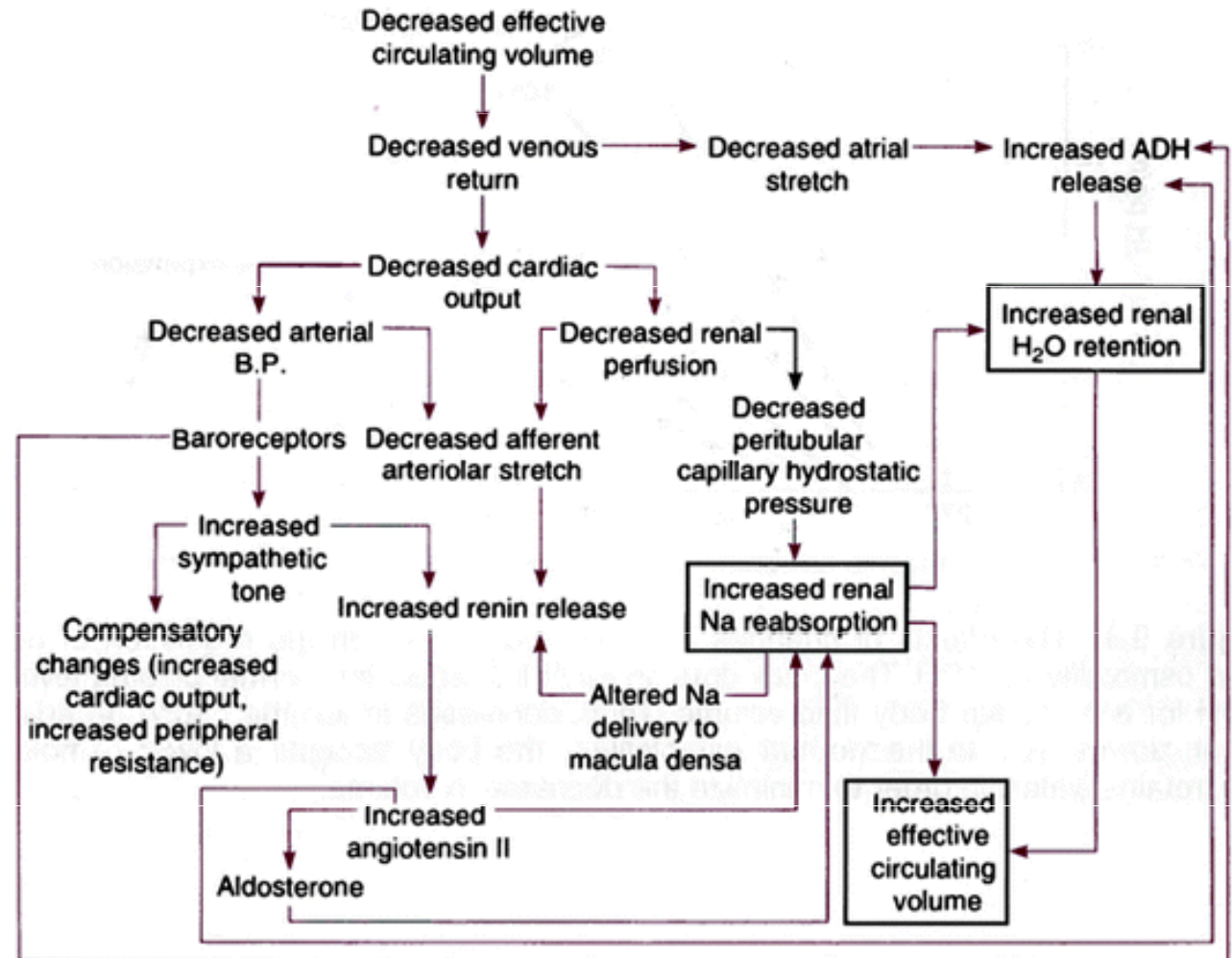
short-term, 35 °C (95 °F) long-term

Water: 46° C (115 °F) short-term  
 and 41°C (106 °F) long-term



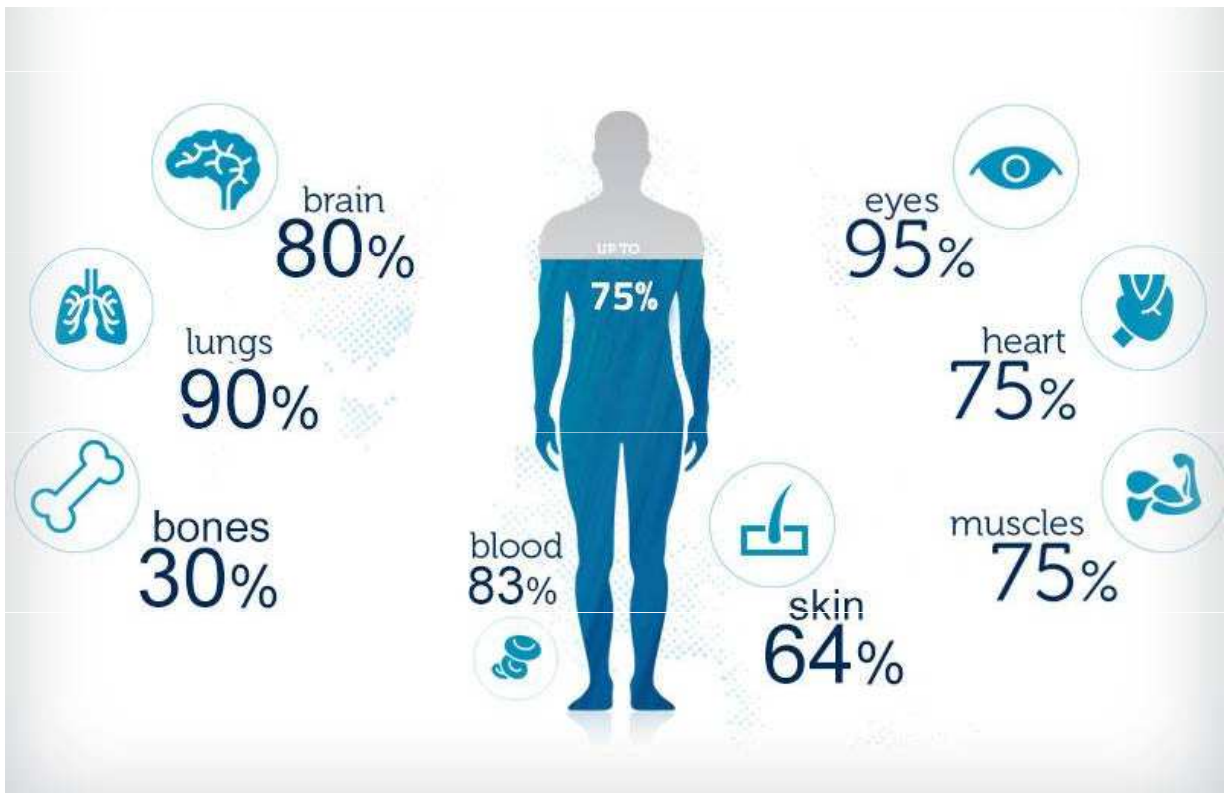
**Regulation of Body Temperature by the Nervous System**  
 Chan LekTan<sup>1</sup>Zachary A.Knight<sup>1234</sup>

# Water?

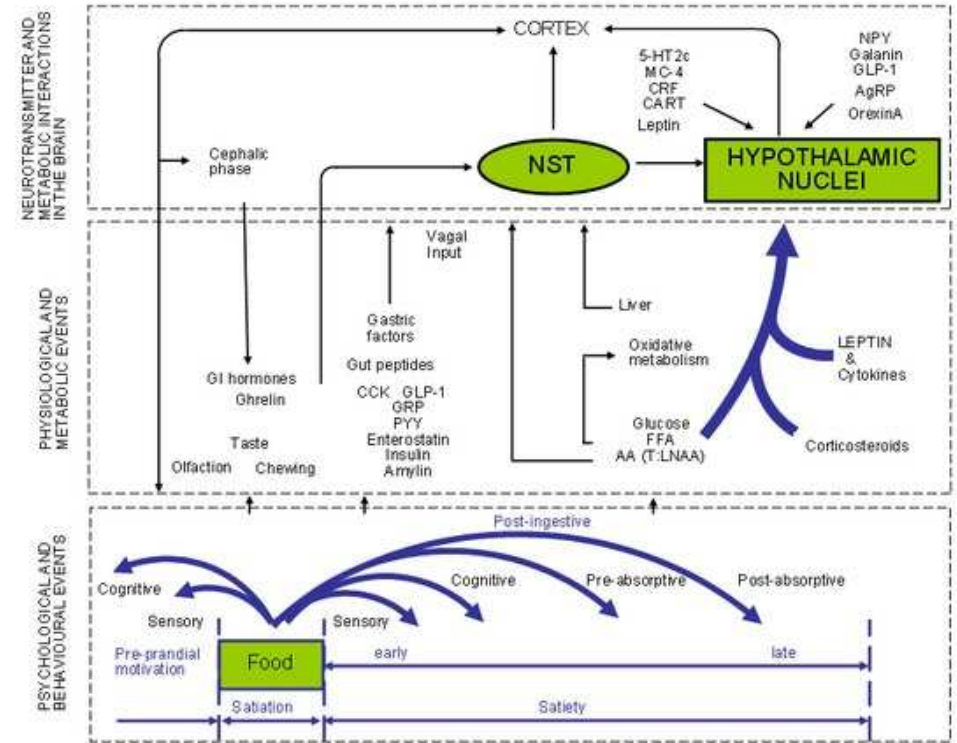




# Water: physiological demands: record



# Food intake?





# Food: physiological demands, record?



**74 vs. 382 days?**

# Stress and the surrounding environment

What do we know?

# Human wellbeing vs stress

*Epictetus: "If you wish your house to be well managed, imitate the Spartan Lysurgus. For as he did not fence his city with walls, but fortified the inhabitants by virtue and preserved the city always free; so do you not cast around (your house) a large court and raise high towers, but strengthen the dwellers by goodwill and fidelity and friendship, and then nothing harmful will enter it, not even if the whole band of wickedness shall array itself against it. Also, that city is well fortified which has a wall of men instead of brick."*

*There is increasing acknowledgement that design of urban spaces can contribute to the health and well-being of residents. Development of green spaces, design of parks and appropriate proximate infrastructure may promote increased physical activity leading to improved health outcomes within populations (Honold et al., 2015, Nordh et al., 2011, [Nordh et al., 2009](#), Nordh and Østby, 2013).*

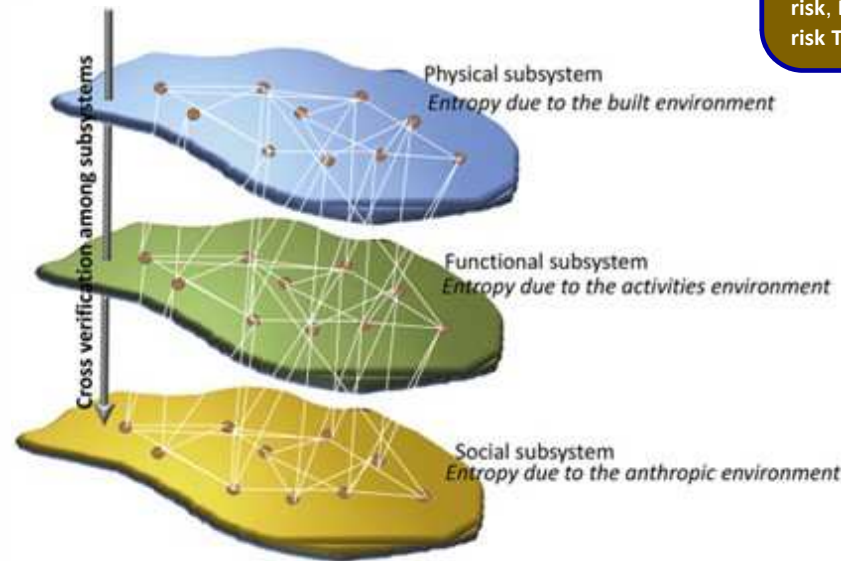
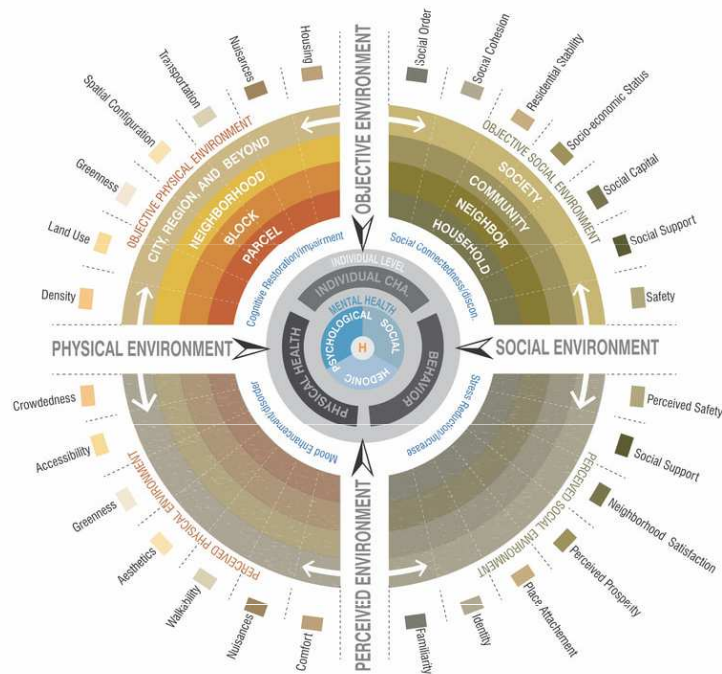




# The WHO Expert Committee on Environmental Health in Urban Development

*"The **health of a city's people** is strongly determined by physical, social, economic, political and cultural factors in the urban environment, including the processes of social aggregation, migration, modernisation and industrialisation, and the circumstances of urban living..... [T]he impact of urban processes on health is not just the sum of the effects of the various factors taken individually, since they interact synergistically with each other." (WHO, 1991, pag.11)*

# So, what constitutes human wellbeing?



Percentage of Energy-efficient buildings  
 Density of disused buildings, Roads conditions  
 Traffic intensity, Quality of the Local Transport Network  
 Percentage of soft mobility lanes, Density of areas subjected to flooding risk,  
 Density of areas subjected to seismic risk, Density of areas subjected to hydrogeological risk  
 Territorial utilization for agriculture

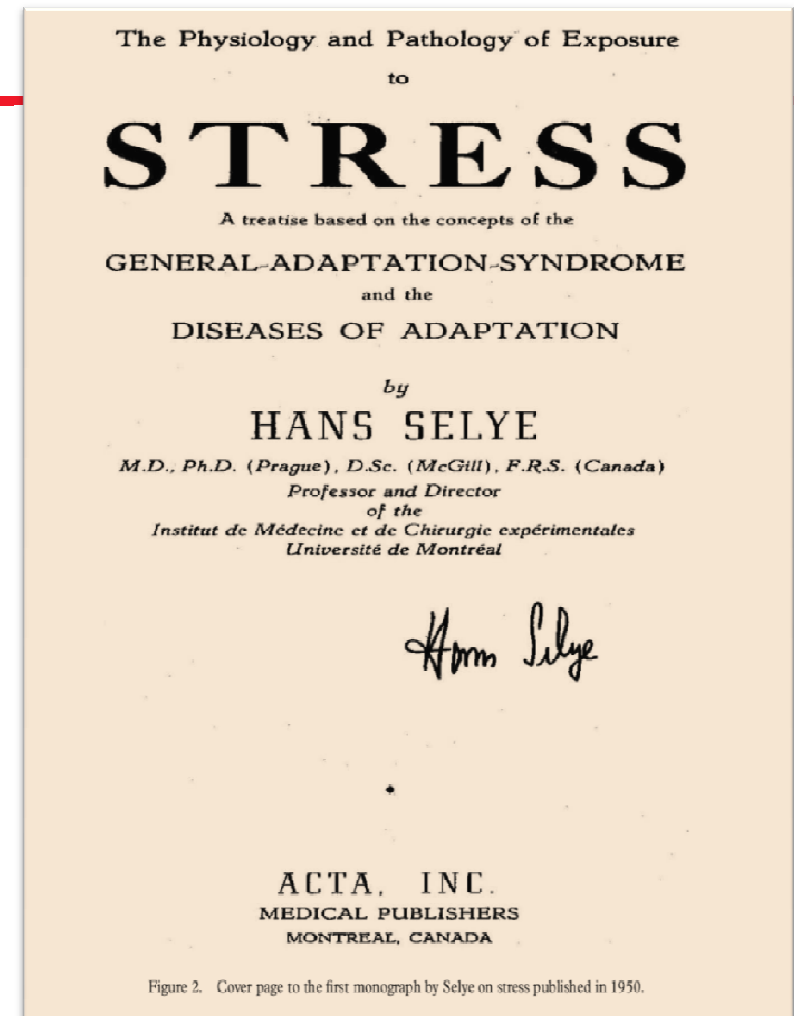
Population density  
 Presence of metropolitan functions  
 Percentage of Tertiary activities  
 Status of the housing stock, Waste production  
 Building obsolescence  
 Bigger emission sources  
 Building quality  
 Clime characteristics, Density of Illegal buildings  
 Density of Sport and recreational structures  
 Crowding index

Noise pollution  
 Electromagnetic pollution  
 Unemployment rate  
 Multi-ethnic composition of residential population  
 Safety and care of elder population

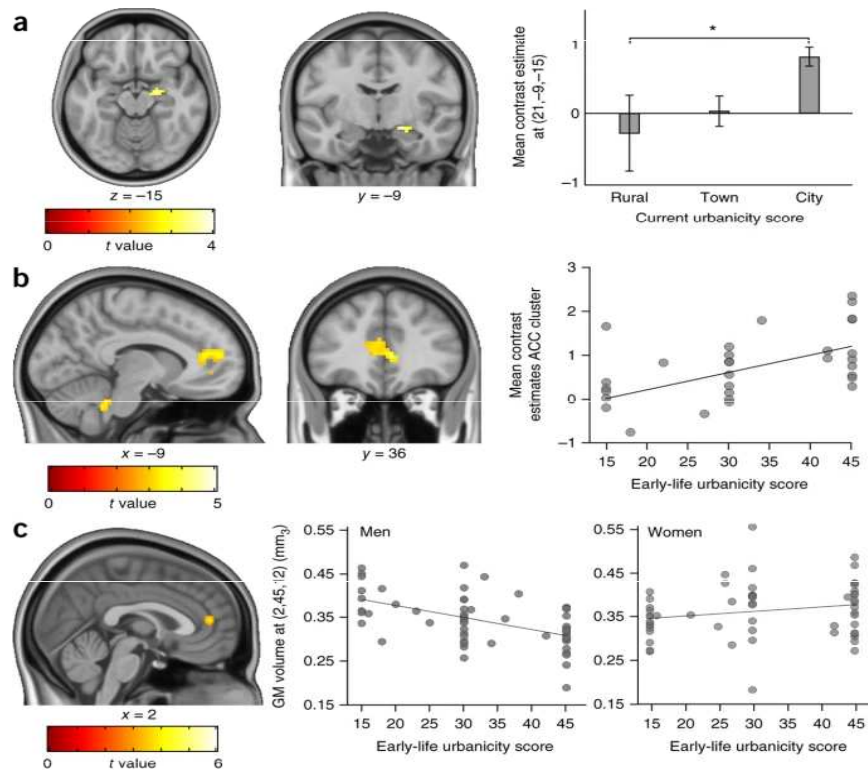
Urban form and mental wellbeing: scoping a theoretical framework for action  
 Amir Hajrasouli(1), Vicente del Rio(1), James Francis (1) and Jessica Edmondson(2)  
 The Journal of Urban Design and Mental Health

## The Stress of Life, Hans Selye, 1956:

*„... the non-specific response of the body to any demand made upon it, whether it is caused by, or results in, pleasant, or unpleasant conditions“*



# So what is the problem?



How does extent of a given land cover type in a citizens' view affect her or his level of emotional arousal, while controlling for walk speed, direction, and distance to automobile roads, and how do changes in direction (turns) explain additional variation in physiological parameters when the other variables are accounted for?

# So what is urban stress in terms of human health?



A state of bodily or mental tension developed through city living, or the physical, chemical, or emotional factors that give rise to that tension.

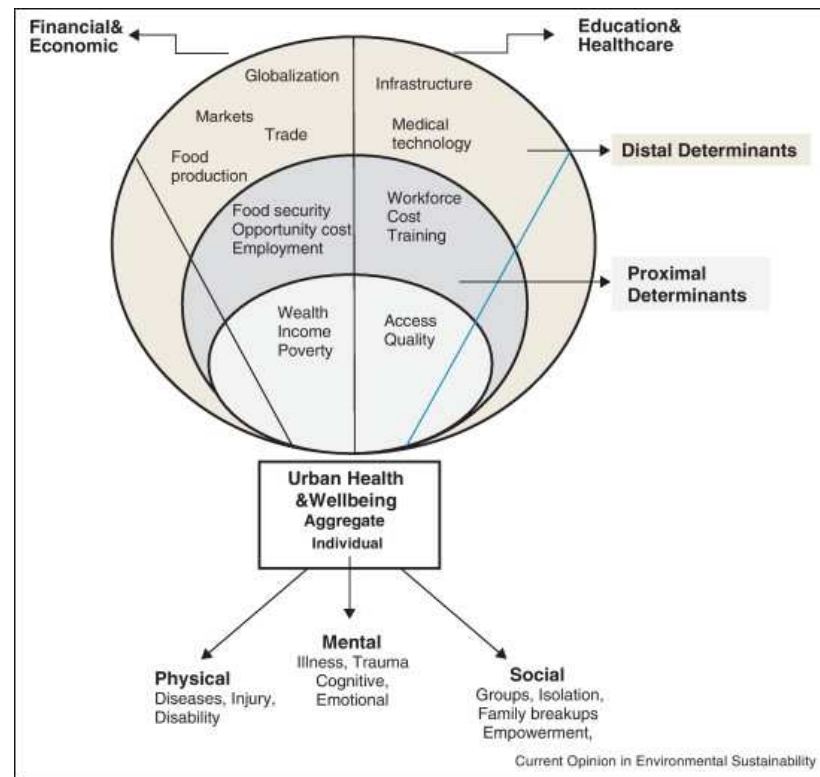
**Urban health: an example of a "health in all policies" approach in the context of SDGs implementation** [Oriana Ramirez-Rubio](#), [Carolyn Daher](#), [Gonzalo Fanjul](#), [Mireia Gascon](#), [Natalie Mueller](#), [Leire Pajin](#), [Antoni Plasencia](#), [David Rojas-Rueda](#), [Meelan Thondoo](#) & [Mark J. Nieuwenhuijsen](#) *Globalization and Health* volume 15, Article number: 87 (2019)



# So what are the determinants of urban health?

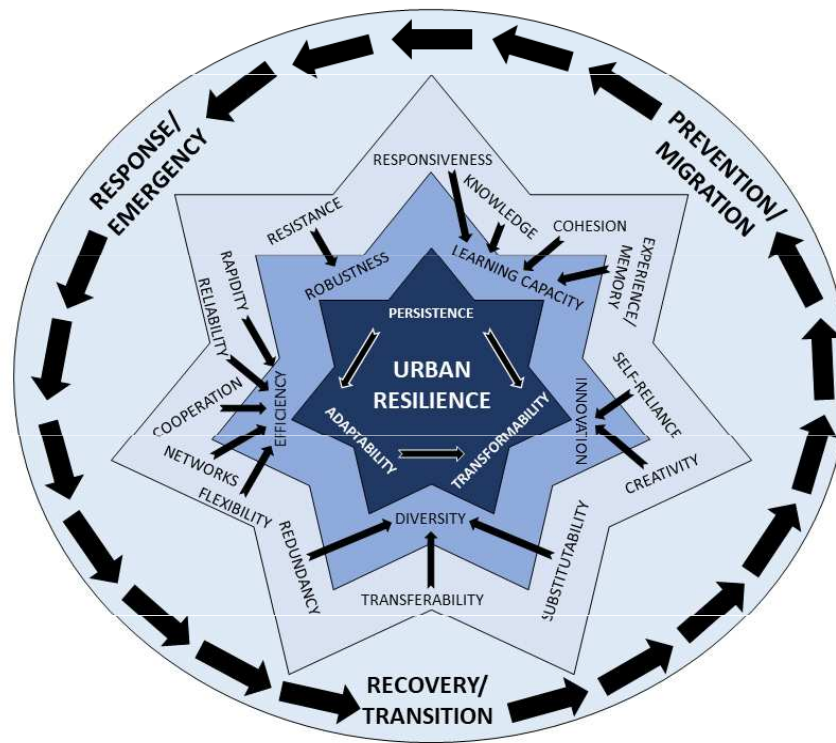


J. Boydell et al. *Br. J. Psychiatry* **182**, 45–49; 2003



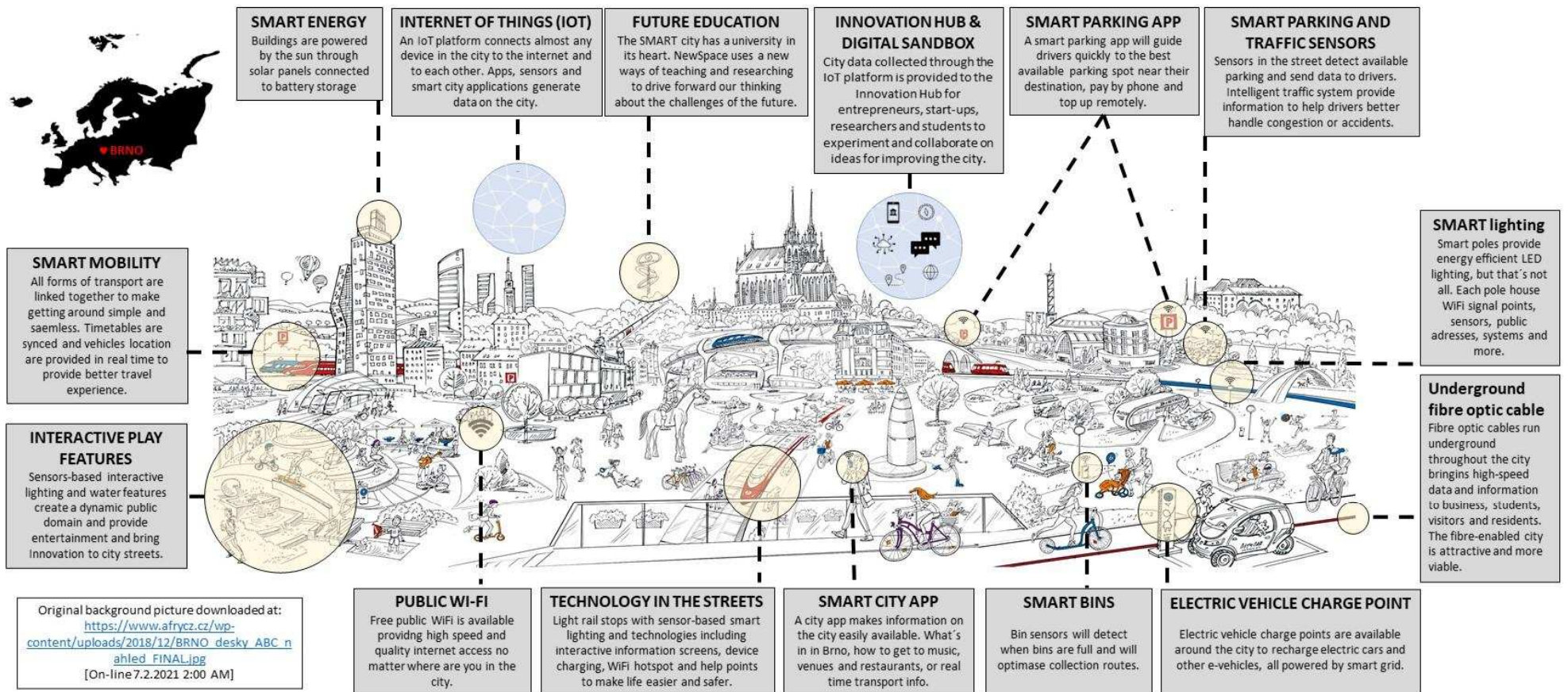
Health and wellbeing in the changing urban environment: complex challenges, scientific responses, and the way forward Xuemei Bai Indira Nath Anthony Capon Nordin Hasan Dov Jaron, *Current Opinion in Environmental Sustainability* Volume 4, Issue 4, October 2012, Pages 465-472

# Why is it important?



„Urban resilience has conventionally been defined as the "measurable ability of any urban system, with its inhabitants, to maintain continuity through all shocks and stresses, while positively adapting and transforming towards sustainability".<sup>[1]</sup> Therefore, a resilient city is one that assesses, plans and acts to prepare for and respond to hazards - natural and human-made, sudden and slow-onset, expected and unexpected. Resilient Cities are better positioned to protect and enhance people's lives, secure development gains, foster an investible environment, and drive positive change.<sup>[1]</sup> Academic discussion of urban resilience has focused primarily on three distinct threats; climate change, natural disasters, and terrorism.“ – Wikipedia as of 2021

# Smart cities – where we want-could be

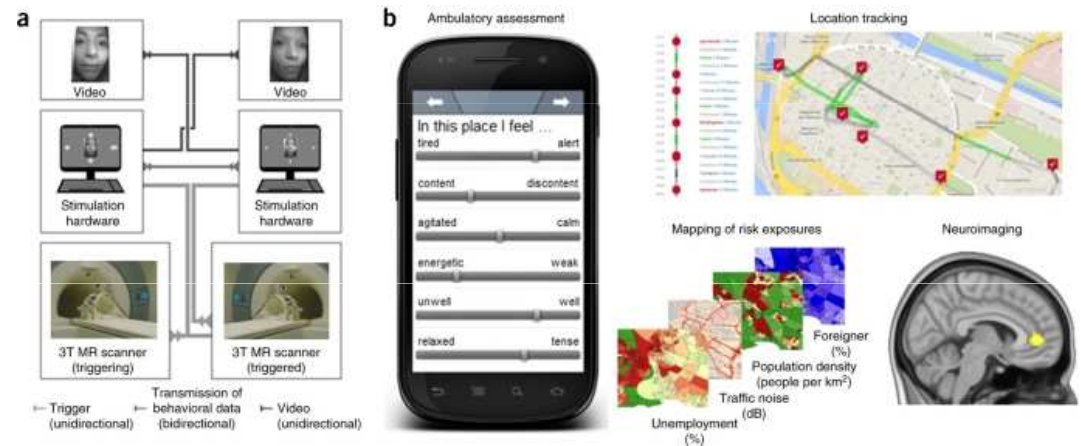
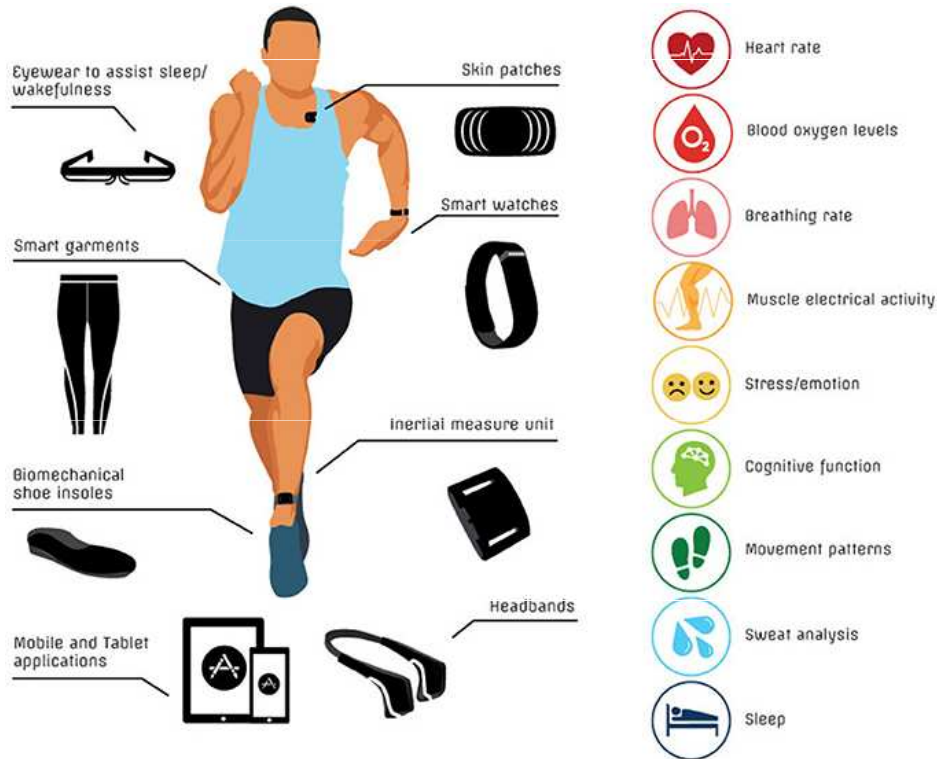


# So what can physiology offer to urbanism?

- Deep understanding of pathogenic processes behind common illnesses
- Deep insight into methodology of measurement of various urban-stress-related variables
- Explanations of pathways between exposure and final health outcome, instead of plain association of exposure with disease
- Looking at the city as a platform capable of managing ENVIRONMENTAL DATA (pollution levels, water and waste management), SECURITY (health of buildings, bridges and dams or emergency situations), TRANSPORTATION (lighting on roads, real-time traffic, reduction of travel times and refueling), QUALITY OF LIFE (health, accessibility, sport and leisure) and BUILDINGS (energy consumption and user comfort), should enable major short-term improvements in health of citizens.



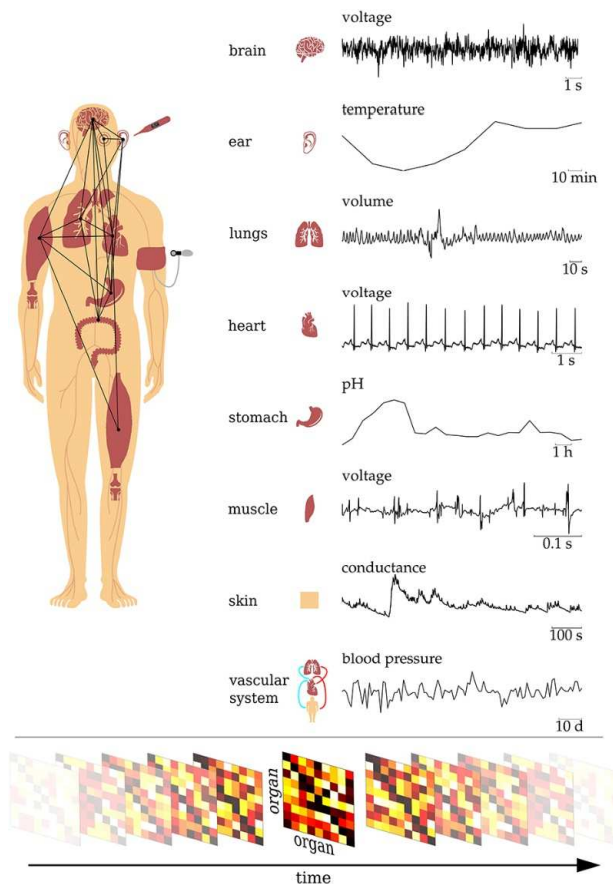
# And, how do we measure stress in real world?



[A Critical Review of Consumer Wearables, Mobile Applications, and Equipment for Providing Biofeedback, Monitoring Stress, and Sleep in Physically Active Populations.](#) **Peake JM**, Kerr G, Sullivan JP. *Front Physiol.* 2018 Jun 28;9:743. doi: 10.3389/fphys.2018.00743.



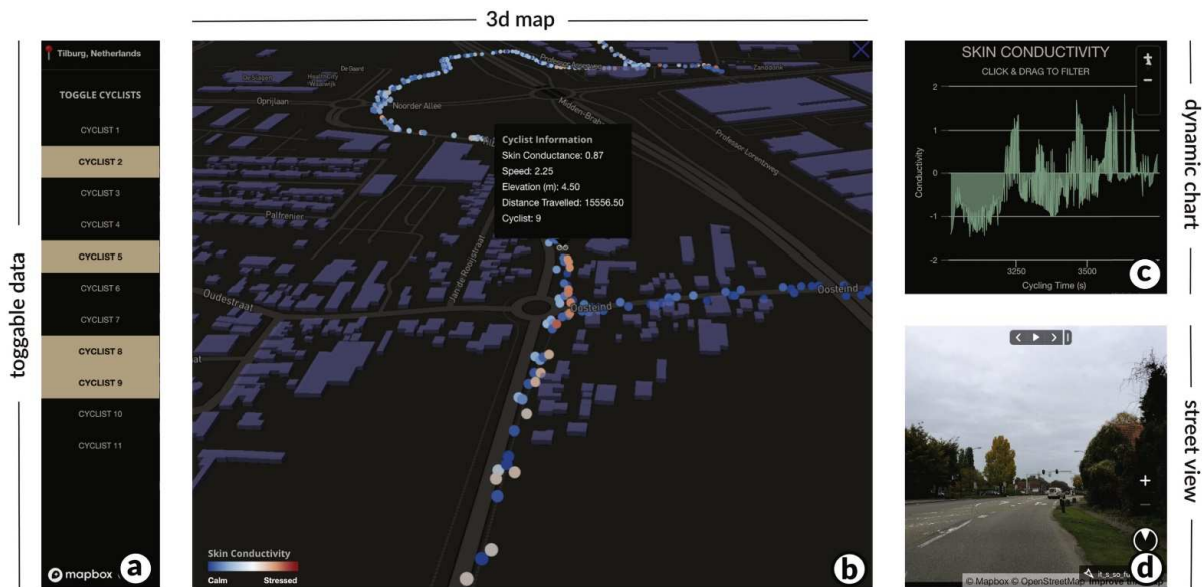
# Humans as sensors



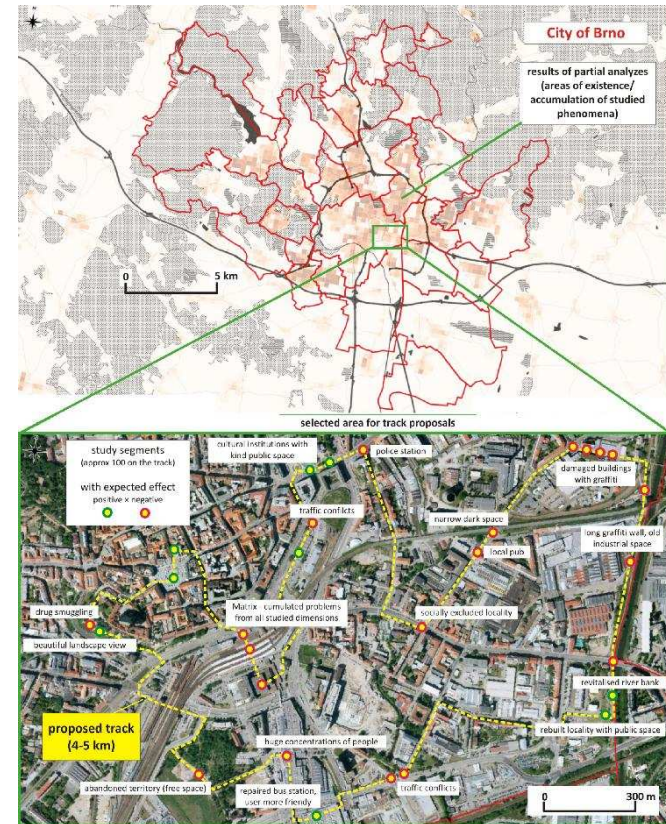
- We often do not know exactly the systems' equations of motion;
- We lack knowledge as to how to merge/combine these equations (e.g., due to the issue of time-scale matching);
- We may have insufficient knowledge about relevant structural connections;
- We may not have direct access to interactions between systems (e.g., via probing).

[The Human Organism as an Integrated Interaction Network: Recent Conceptual and Methodological Challenges.](#)  
**Lehnertz K**, Bröhl T, Rings T. *Front Physiol.* 2020 Dec 21;11:598694. doi: 10.3389/fphys.2020.598694. eCollection 2020.

# Collective sensing

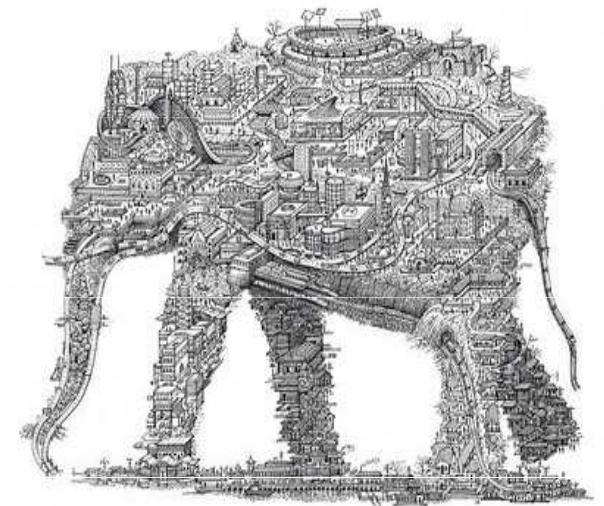


Space-time analytics of human physiology for urban planning  
 Garrett C. Millara,\*, Ondrej Mitasb, Wilco Boodeb, Lisette Hoekeb, Joost de Kruijfb,  
 Anna Petrasovaa, Helena Mitasova, Computers, Environment and Urban Systems 85 (2021) 101554



# What is the point? Change of paradigm?

Formal structures of cities are often inspired by a combination of human geometry and cosmological patterns in both Eastern and Western civilizations, from early representations in mandalas to the Vitruvian Man. Cities have also been understood **as a living system**, a macroscopic organism, linked through its collective consciousness, communicative structure and relationship to natural resources and cycles. Like the human body or other natural organisms, the city is comprised of multiple parts, organs, cells and functions, each autonomously working with its own requirements. However, we need to learn much more about the interconnectedness to understand better the processes.

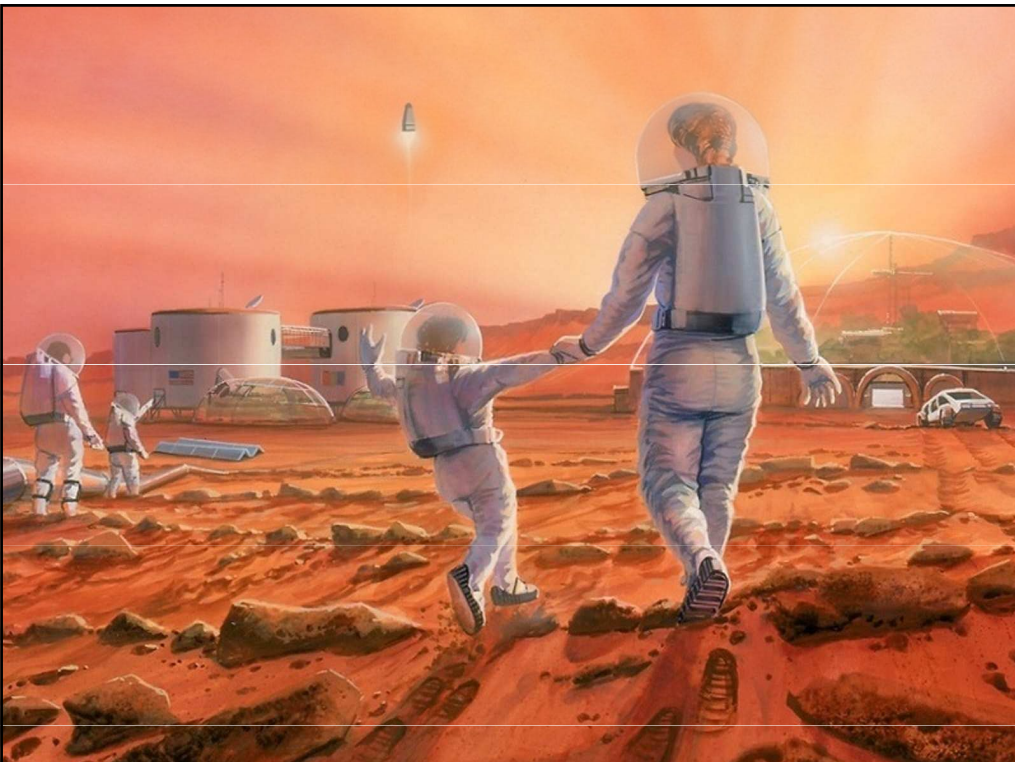






***“It is our attitude toward events, not events themselves, which we can control. Nothing is by its own nature calamitous -- even death is terrible only if we fear it.”  
— Epictetus***

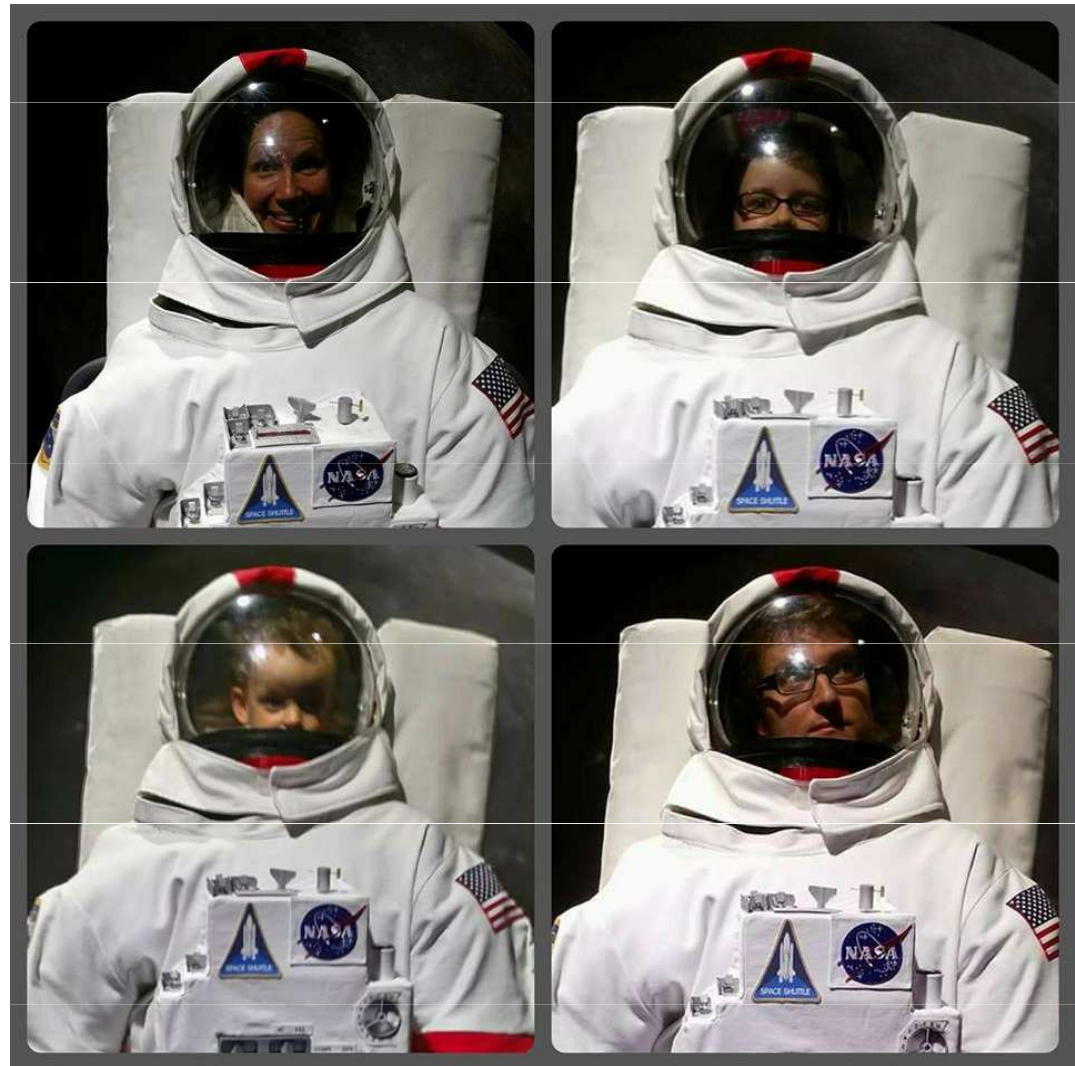






# Budeme u toho?

– Ano!



**MASARYKOVA  
UNIVERZITA**