



University of  
Zurich<sup>UZH</sup>

**ETH**

Eidgenössische Technische Hochschule Zürich  
Swiss Federal Institute of Technology Zurich



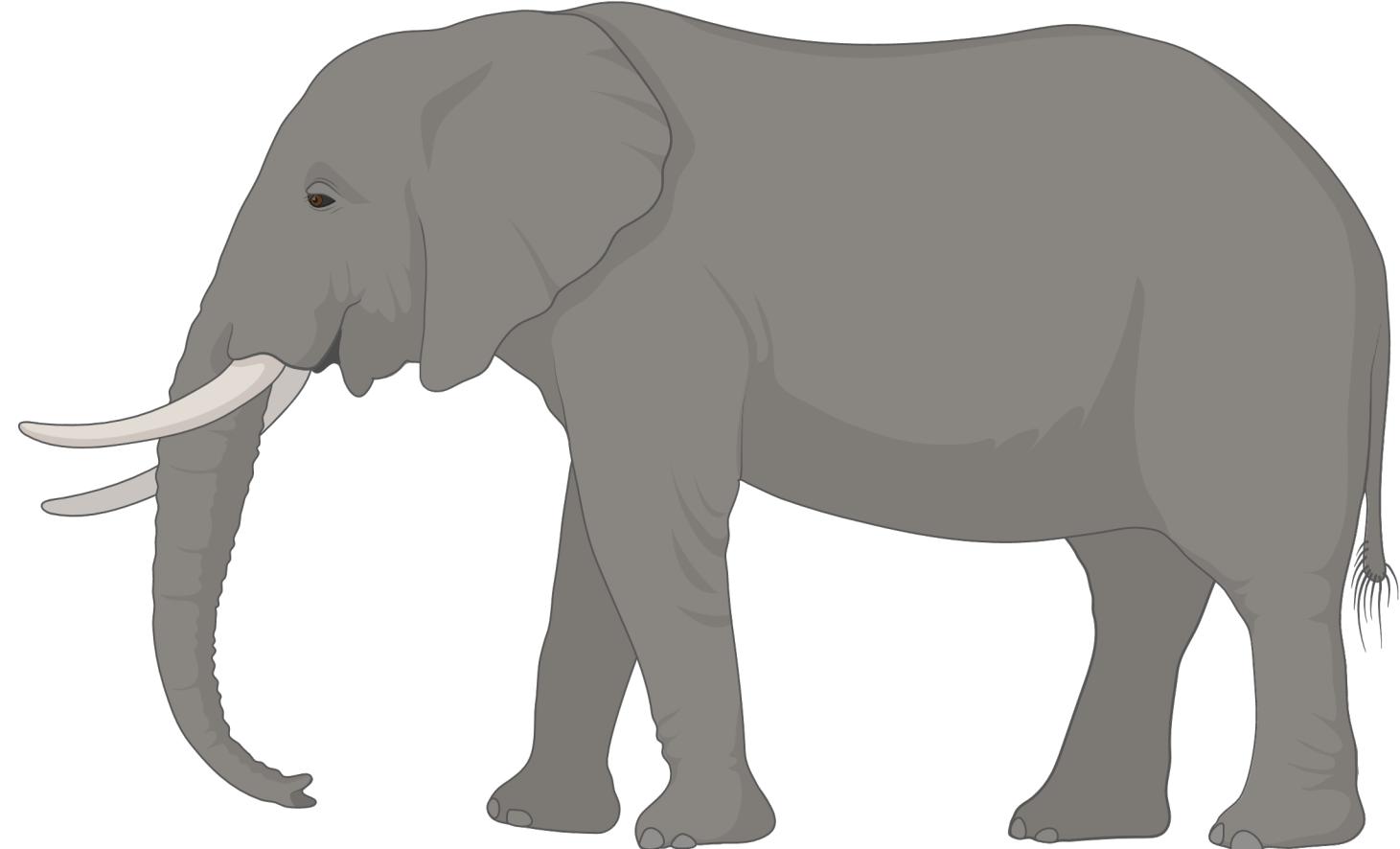
Translational Neuromodeling Unit

# Fatigue

Inês Pereira

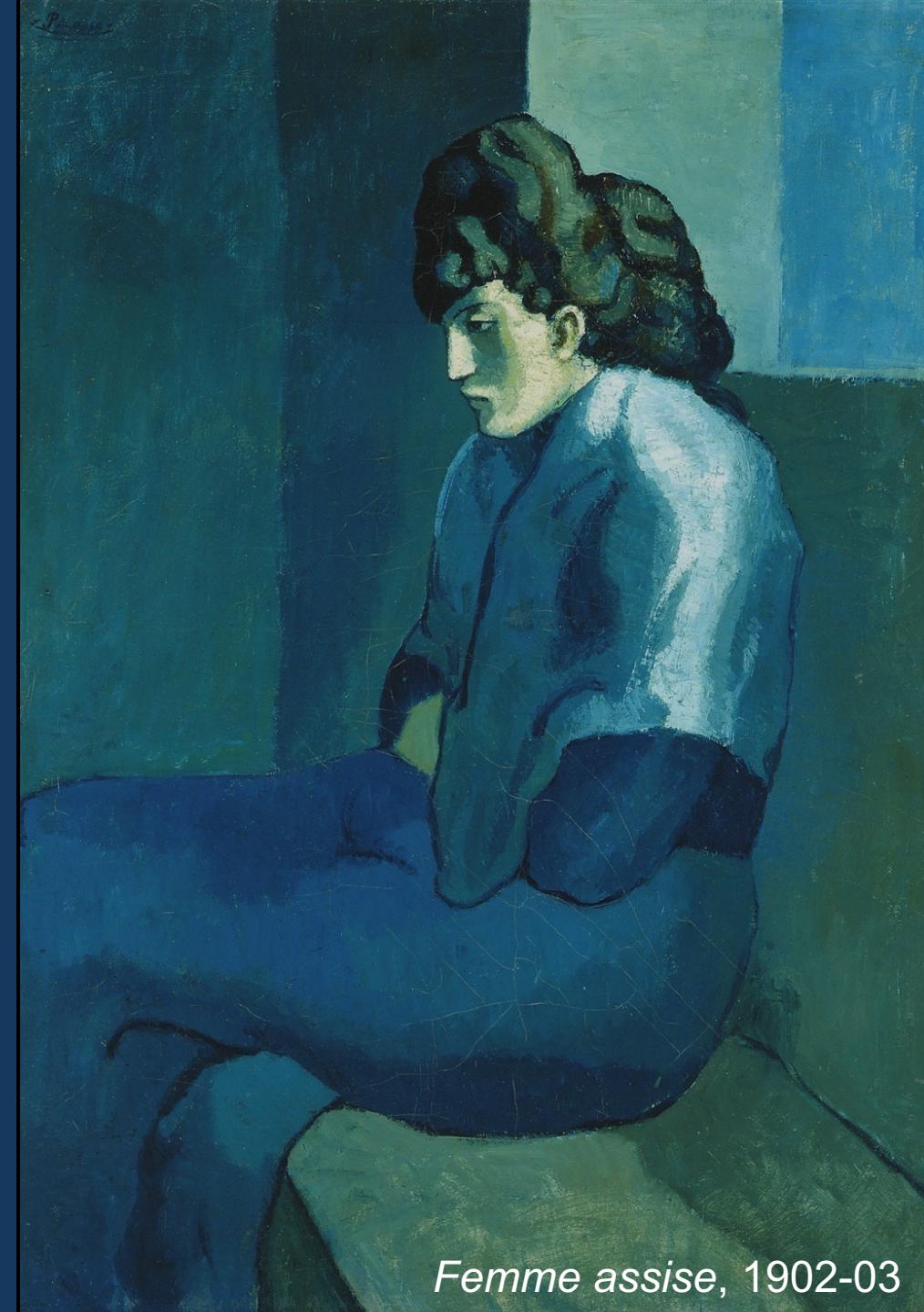
CPC Zurich 2021

*Fatigue*



# *Clinical case*

- 48-year old
- Chief complaint:
  - Depressed mood
  - Low energy
  - Sleeping excessively
  - Lost interest in previous hobbies



*Femme assise*, 1902-03

*Fatigue*

Definition?

*Fatigue*

Definition?

Common problem?

*Fatigue*

Definition?

Common problem?

*Fatigue*

Causes?

Definition?

Common problem?

*Fatigue*

Causes?

Treatment?

# Definitions

*Is there one specific biomarker?*

*Is there one specific biomarker?*

No.

*A pathognomonic clinical sign, then?*

*A pathognomonic clinical sign, then?*

No.

*Based on the patient's subjective account?*

*Based on the patient's subjective account?*

*Yes, but...*

*What do you mean by fatigue?*

Somnolence, sleepiness

*What do you mean by fatigue?*

Somnolence, sleepiness

*What do you mean by fatigue?*

Dyspnea on exertion

Somnolence, sleepiness

*What do you mean by fatigue?*

Muscle weakness

Dyspnea on exertion

Somnolence, sleepiness

Difficulty concentrating

*What do you mean by fatigue?*

Muscle weakness

Dyspnea on exertion

• • •

*"a feeling arising from difficulty in initiation of or sustaining voluntary effort"*

Chaudhuri and Behan, *Lancet*, 2004

*"feeling that relates to the lack of motivation to deploy resources and engage in high effort performance to cope with their situation"*

Dantzer et al., *Trends Neurosci*, 2014

*"an overwhelming sense of tiredness that is out of proportion (in relation to the performed activity)"*

Induruwa et al., *J Neurol Sci*, 2012

Manjaly et al., *Journal of Neurology, Neurosurgery and Psychiatry*, 2019

*Subjective human experience of physical and mental weariness, sluggishness, and exhaustion.*

Gelfand and Douglas, "Fatigue", *Harrison's principles of internal medicine*, 19th edition, 2018

*Subjective human experience of physical and mental weariness, sluggishness, and exhaustion.*

≠

*Fatigability*

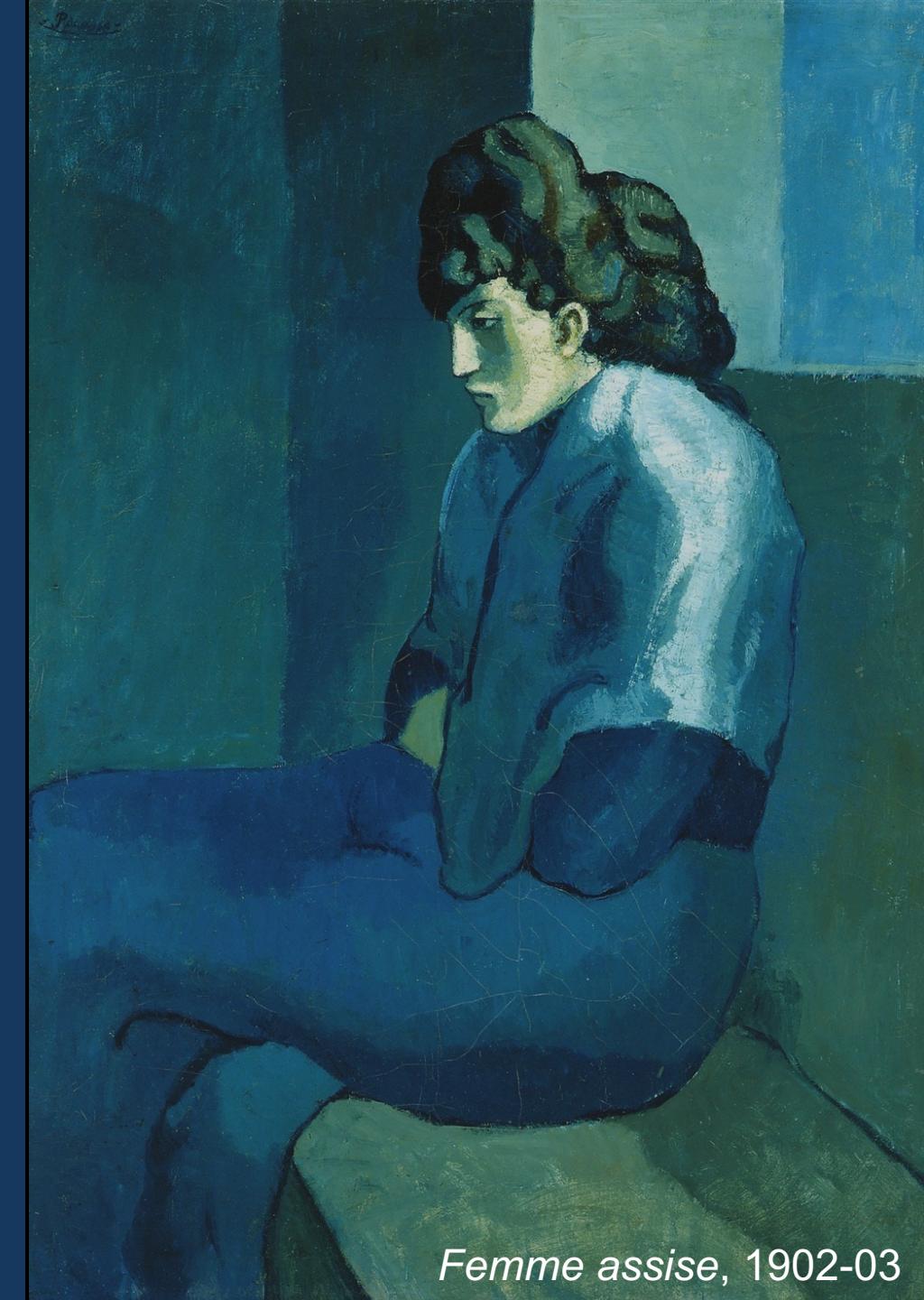
Gelfand and Douglas, "Fatigue", *Harrison's principles of internal medicine*, 19th edition, 2018

Kluger et al., *Neurology*, 2013

Penner and Paul, *Nature Reviews Neurology*, 2017

# Depressed & fatigued

- 48-year old
- Chief complaint:
  - Depressed mood
  - Low energy
  - Sleeping excessively
  - Lost interest in previous hobbies



*Femme assise*, 1902-03

# Epidemiology

# Epidemiology

- General population (U.S.):
  - 6.7% point prevalence
  - 25% lifetime prevalence
- Primary care setting (Europe and U.S.):
  - 21-33% of patients describe fatigue as an important problem
  - 10-25% of patients endorsed symptoms of subacute or chronic fatigue
- In specific conditions:
  - Multiple sclerosis: ~80% prevalence
  - Depression: fatigue is part of the diagnostic criteria

Gelfand and Douglas, "Fatigue", *Harrison's principles of internal medicine*, 19th edition, 2018

<https://www.uptodate.com/contents/approach-to-the-adult-patient-with-fatigue>

# DSM-5: Major depressive episode

- A. Five (or more) of the following symptoms have been present during the same two-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.
1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, hopeless) or observations made by others (e.g., appears tearful).
  2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation)
  3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day.
  4. Insomnia or hypersomnia nearly every day

# DSM-5: Major depressive episode

5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)
  6. Fatigue or loss of energy nearly every day
  7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)
  8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by their subjective account or as observed by others)
  9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide
- [...]

# ICD-10

In typical depressive episodes of all three varieties described below (mild (F32.0), moderate (F32.1), and severe (F32.2 and F32.3)), the individual usually suffers from depressed mood, loss of interest and enjoyment, and **reduced energy** leading to increased fatigability and diminished activity. Marked tiredness after only slight effort is common. Other common symptoms are:

- a) reduced concentration and attention;
- b) reduced self-esteem and self-confidence;
- c) ideas of guilt and unworthiness (even in a mild type of episode);
- d) bleak and pessimistic views of the future;
- e) ideas or acts of self-harm or suicide;
- f) disturbed sleep;
- g) diminished appetite.

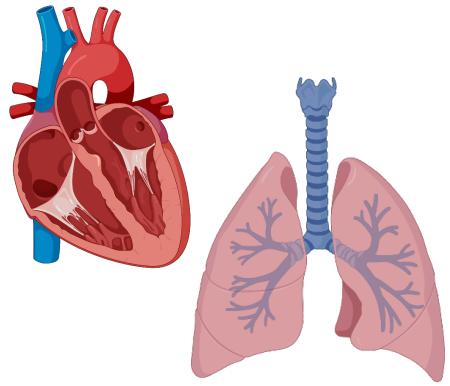
# Causes of fatigue

# Types of fatigue

- Acute (< 1 month)
- Subacute (1-6 months)
- Chronic (>6 months)

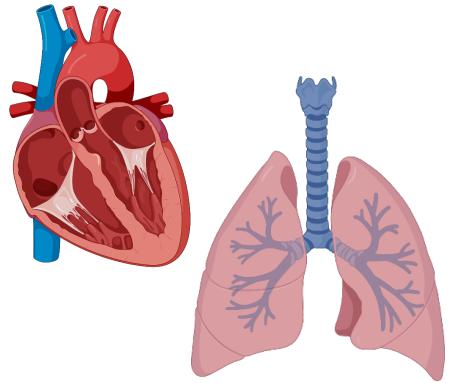
<https://www.uptodate.com/contents/approach-to-the-adult-patient-with-fatigue>

*Fatigue*

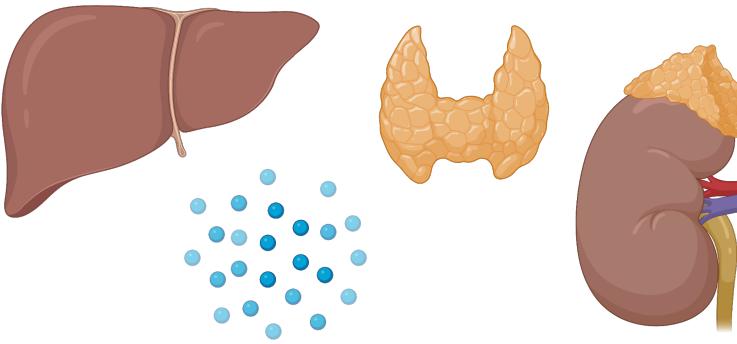


Cardiopulmonary

*Fatigue*

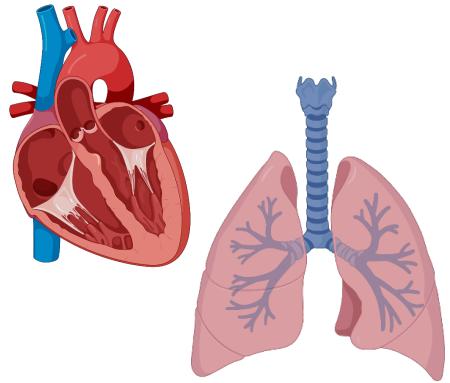


Cardiopulmonary

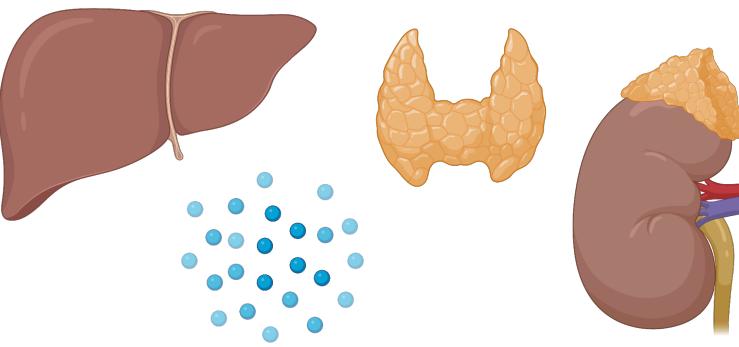


Endocrinologic/metabolic

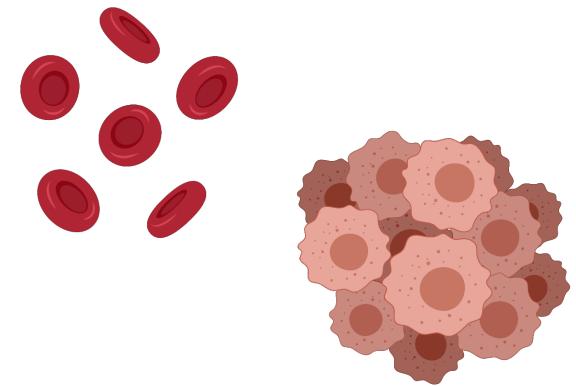
*Fatigue*



Cardiopulmonary

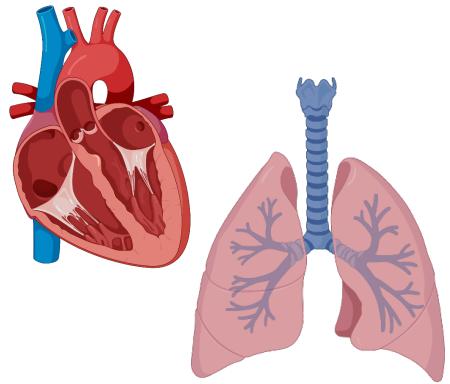


Endocrinologic/metabolic

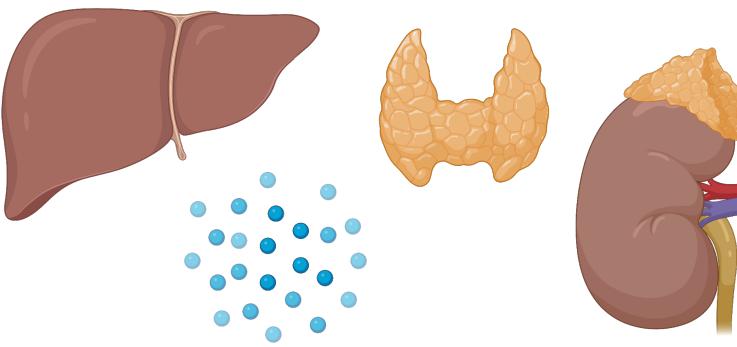


Hematologic/neoplastic

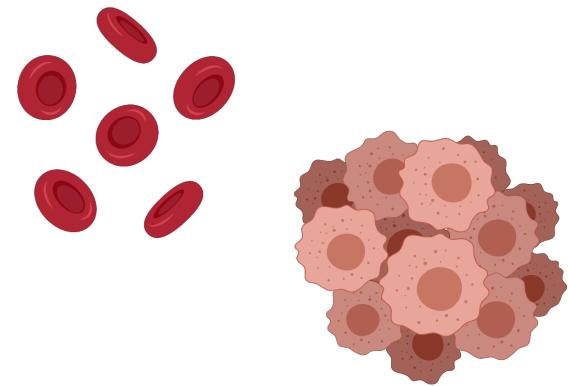
*Fatigue*



Cardiopulmonary

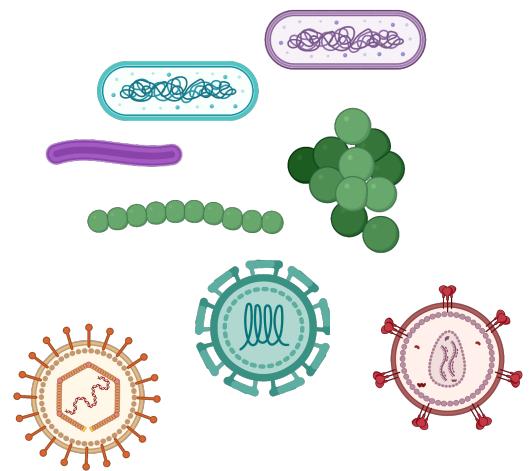


Endocrinologic/metabolic

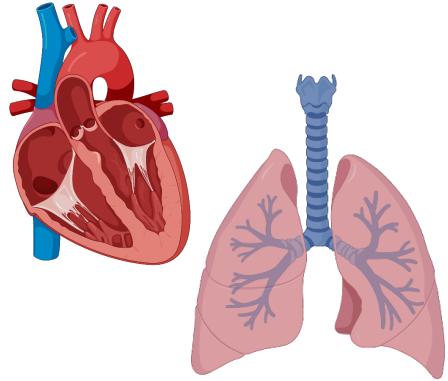


Hematologic/neoplastic

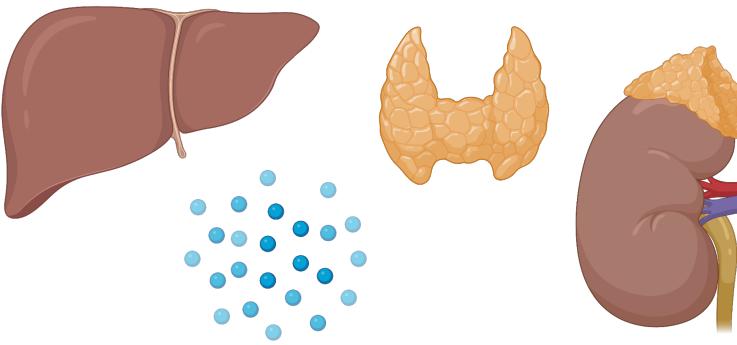
# *Fatigue*



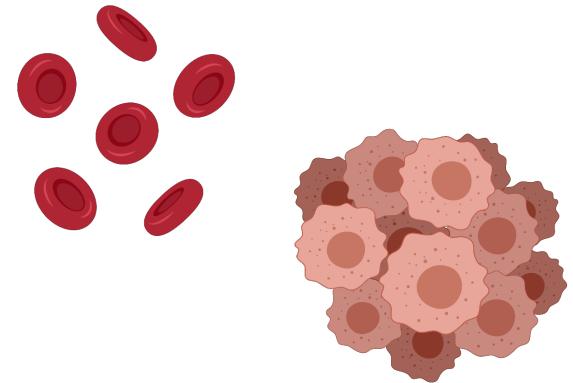
Infectious



Cardiopulmonary

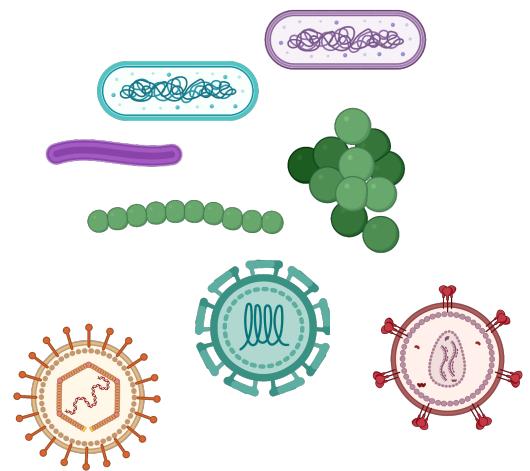


Endocrinologic/metabolic

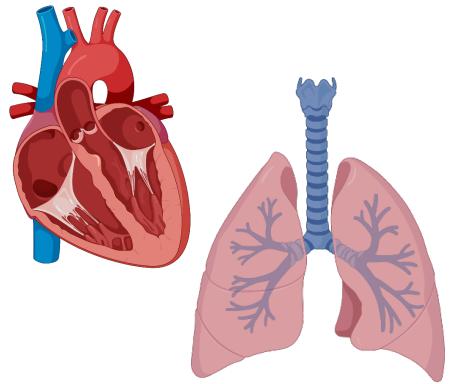


Hematologic/neoplastic

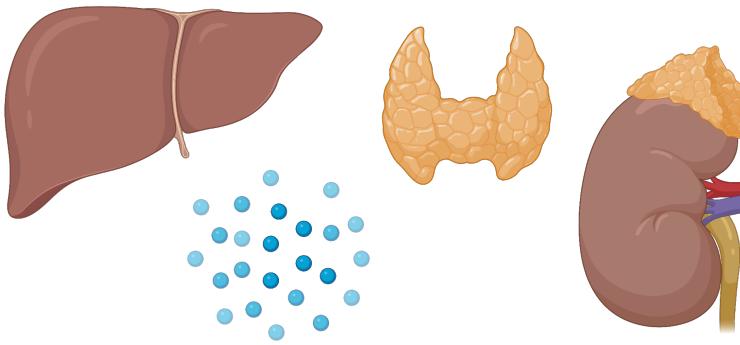
# Fatigue



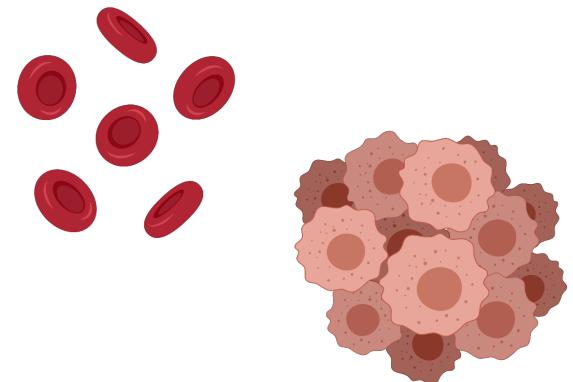
Rheumatologic



Cardiopulmonary



Endocrinologic/metabolic



Hematologic/neoplastic

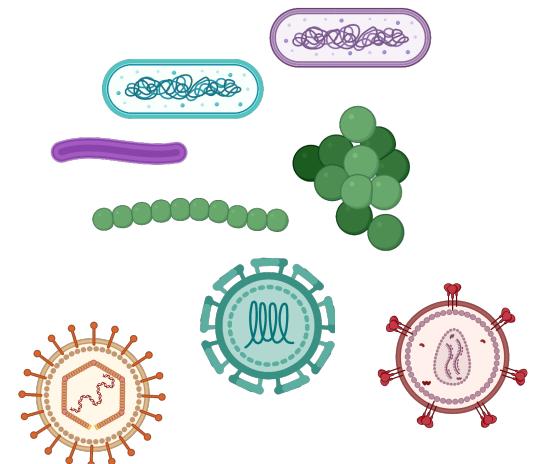
# Fatigue



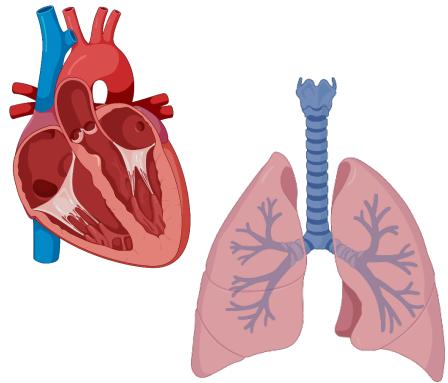
Psychiatric



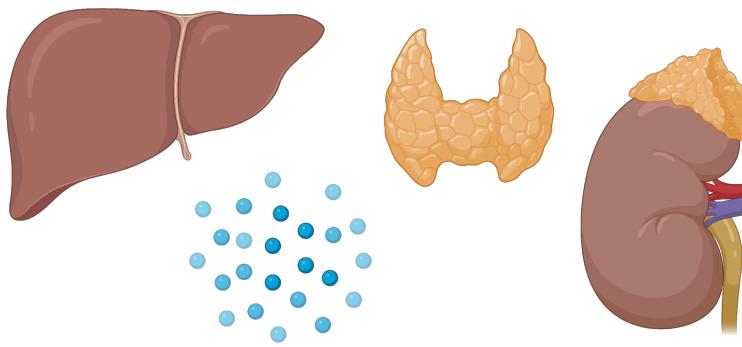
Rheumatologic



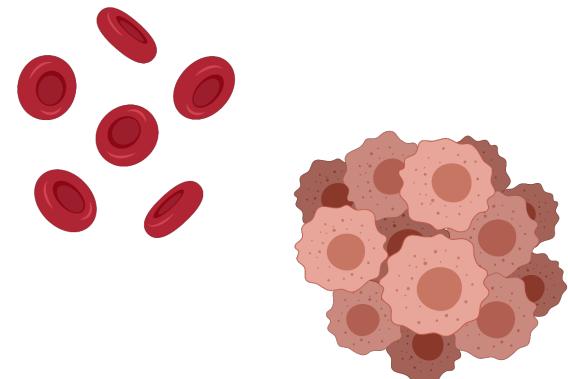
Infectious



Cardiopulmonary

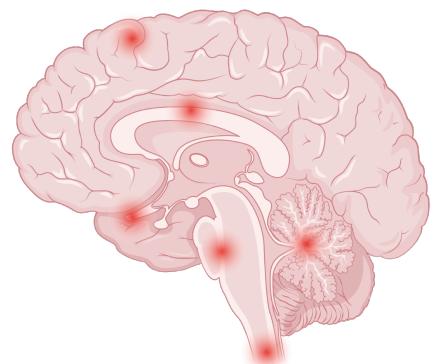


Endocrinologic/metabolic



Hematologic/neoplastic

# Fatigue



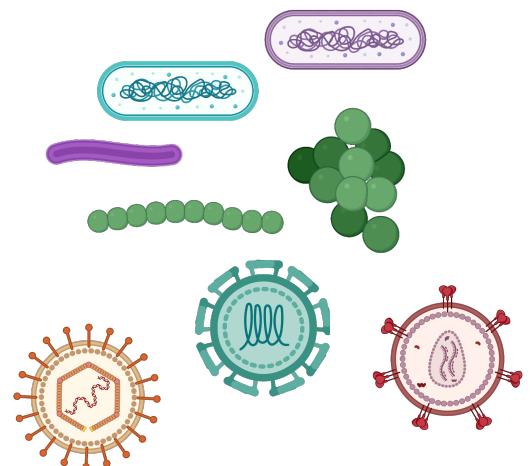
Neurologic



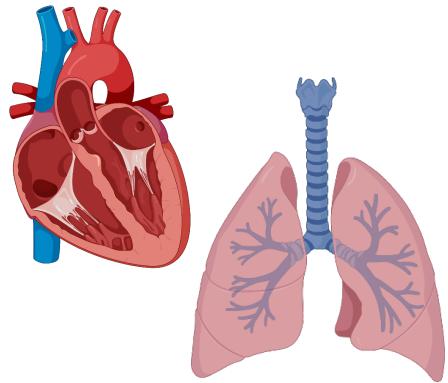
Psychiatric



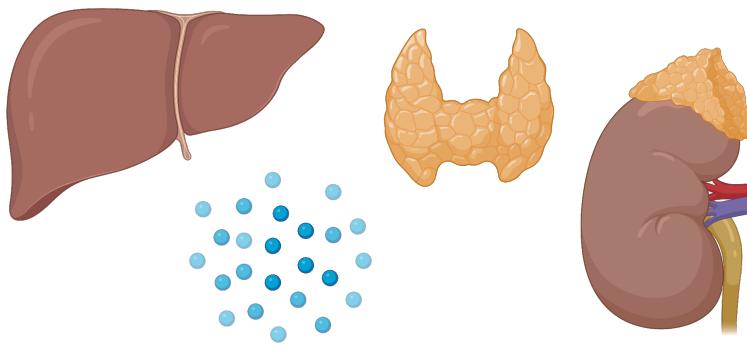
Rheumatologic



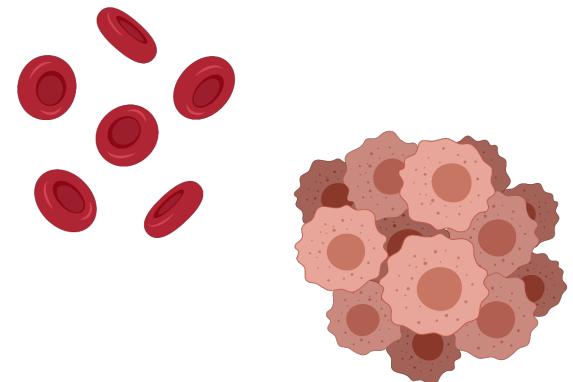
Infectious



Cardiopulmonary



Endocrinologic/metabolic

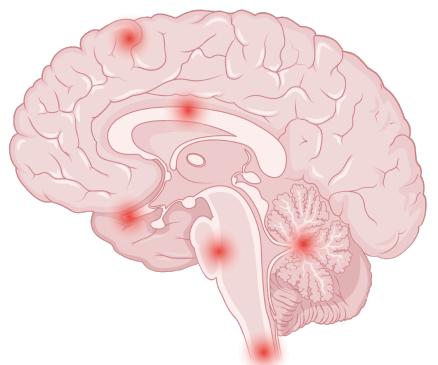


Hematologic/neoplastic

# Fatigue



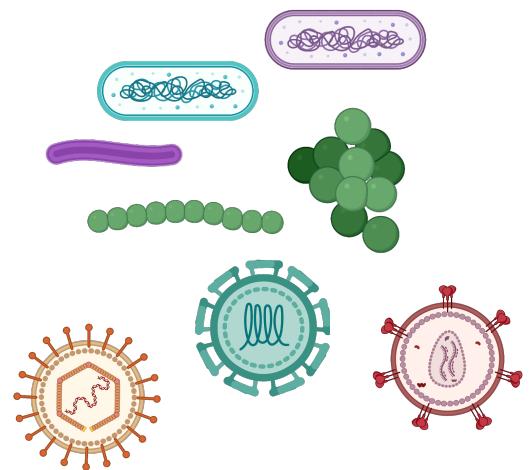
Medication



Neurologic



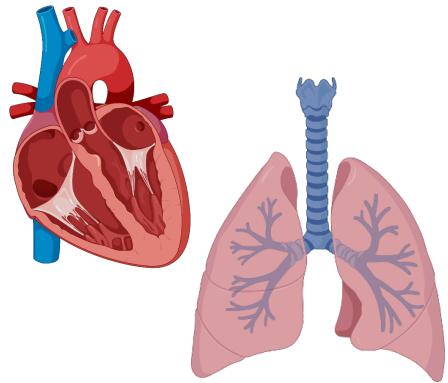
Psychiatric



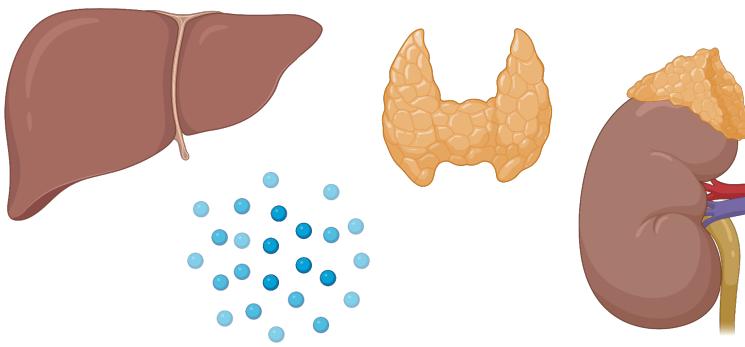
Infectious



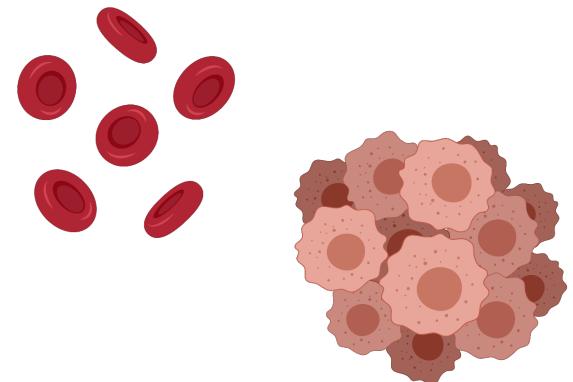
Rheumatologic



Cardiopulmonary



Endocrinologic/metabolic



Hematologic/neoplastic

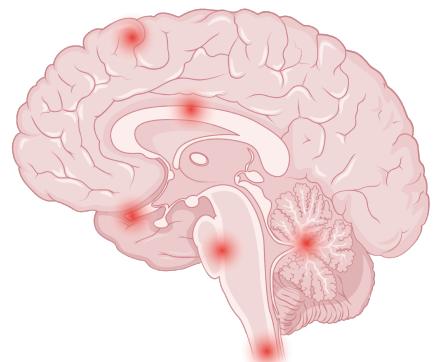


Substance use

# Fatigue



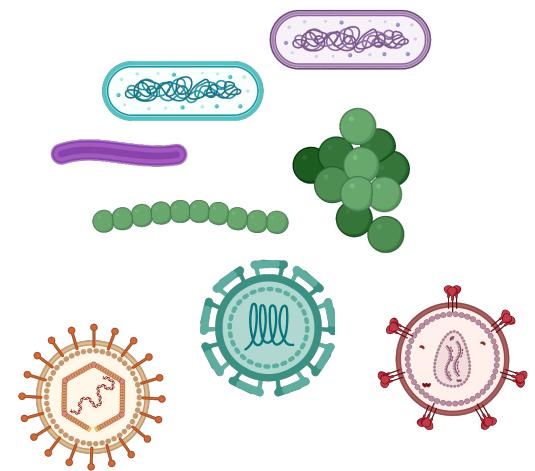
Medication



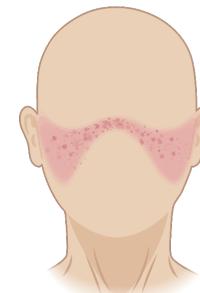
Neurologic



Psychiatric



Infectious



Rheumatologic

# Approach to the patient with fatigue

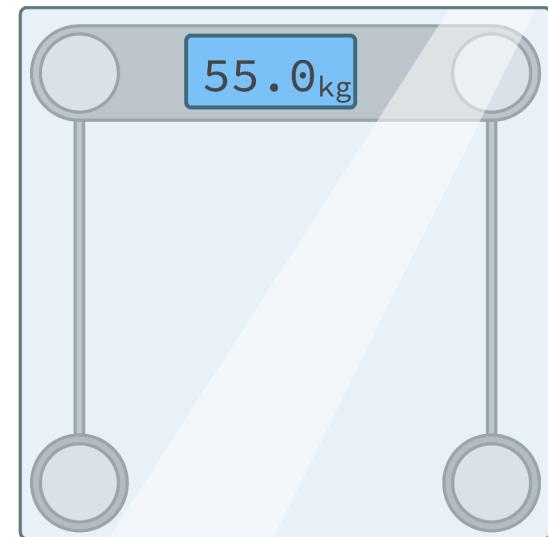
# Approach to the patient with fatigue

- Medical history





$>38\text{ }^{\circ}\text{C}$

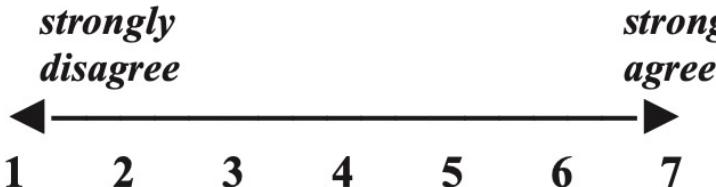


# Approach to the patient with fatigue

- Medical history



## Fatigue Severity Scale (FSS, English version)\*

							
	1	2	3	4	5	6	7
1. My motivation is lower when I am fatigued.	0	0	0	0	0	0	0
2. Exercise brings on my fatigue.	0	0	0	0	0	0	0
3. I am easily fatigued.	0	0	0	0	0	0	0
4. Fatigue interferes with my physical functioning.	0	0	0	0	0	0	0
5. Fatigue causes frequent problems for me.	0	0	0	0	0	0	0
6. My fatigue prevents sustained physical functioning.	0	0	0	0	0	0	0
7. Fatigue interferes with carrying out certain duties and responsibilities.	0	0	0	0	0	0	0
8. Fatigue is among my three most disabling symptoms.	0	0	0	0	0	0	0
9. Fatigue interferes with my work, family, or social life.	0	0	0	0	0	0	0

\*Patients are instructed to choose a number from 1 to 7 that indicates their degree of agreement with each statement where 1 indicates strongly disagree and 7, strongly agree. [Krupp et al, Arch Neurol 1989]

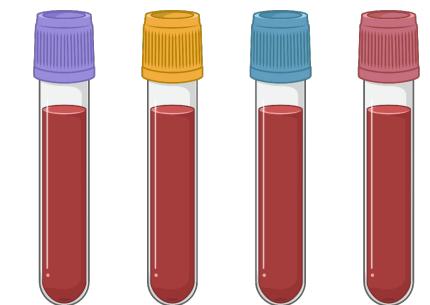
# Approach to the patient with fatigue

- Medical history
- Physical examination



# Approach to the patient with fatigue

- Medical history
- Physical examination
- Laboratory and radiological studies



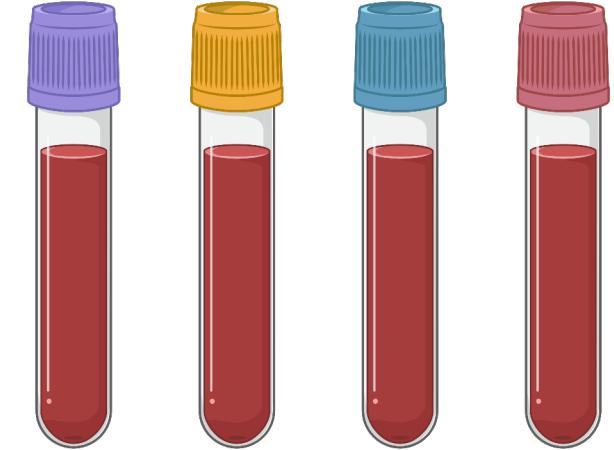
# Laboratory and radiological studies

- Initial laboratory testing
  - Complete blood count with differential count



# Laboratory and radiological studies

- Initial laboratory testing
  - Complete blood count with differential count
  - Chemistries (including glucose, electrolytes, renal and hepatic function tests)

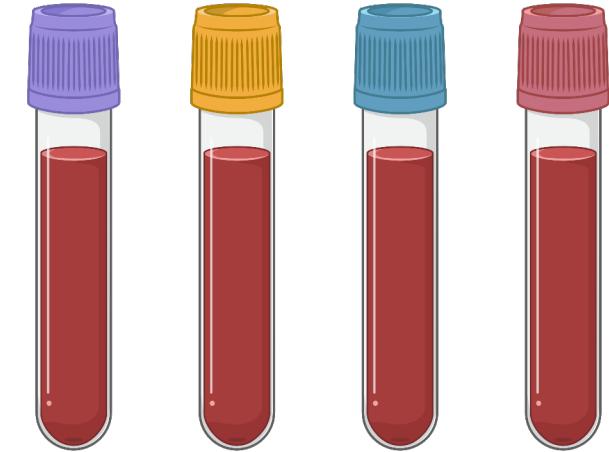


Gelfand and Douglas, "Fatigue", *Harrison's principles of internal medicine*, 19th edition, 2018

<https://www.uptodate.com/contents/approach-to-the-adult-patient-with-fatigue>

# Laboratory and radiological studies

- Initial laboratory testing
  - Complete blood count with differential count
  - Chemistries (including glucose, electrolytes, renal and hepatic function tests)
  - Thyroid-stimulating hormone

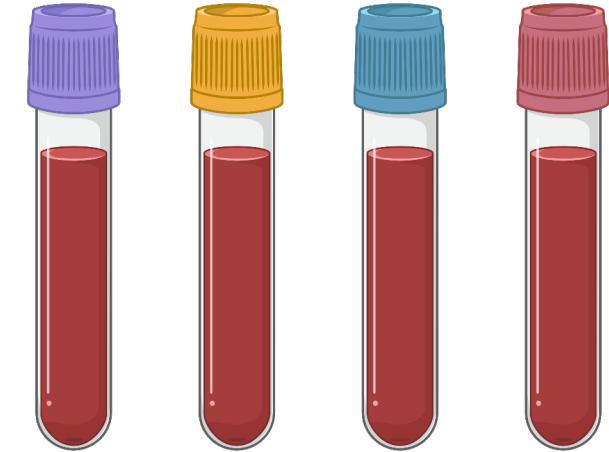


Gelfand and Douglas, "Fatigue", *Harrison's principles of internal medicine*, 19th edition, 2018

<https://www.uptodate.com/contents/approach-to-the-adult-patient-with-fatigue>

# Laboratory and radiological studies

- Initial laboratory testing
  - Complete blood count with differential count
  - Chemistries (including glucose, electrolytes, renal and hepatic function tests)
  - Thyroid-stimulating hormone
  - Serologic testing dependent on risk factors (e.g., hepatitis C virus, HIV)

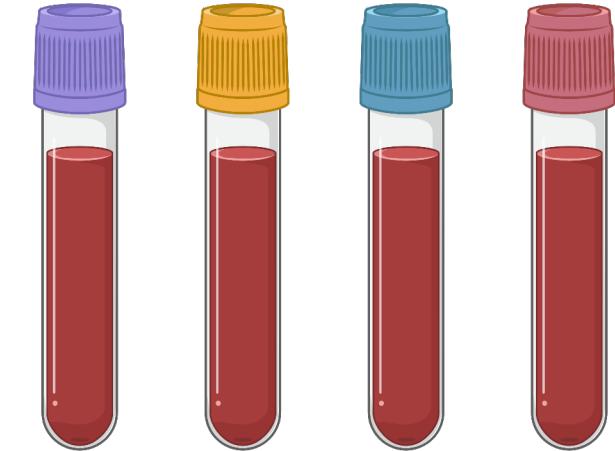


Gelfand and Douglas, "Fatigue", *Harrison's principles of internal medicine*, 19th edition, 2018

<https://www.uptodate.com/contents/approach-to-the-adult-patient-with-fatigue>

# Laboratory and radiological studies

- Initial laboratory testing
  - Complete blood count with differential count
  - Chemistries (including glucose, electrolytes, renal and hepatic function tests)
  - Thyroid-stimulating hormone
  - Serologic testing dependent on risk factors (e.g., hepatitis C virus, HIV)
  - [...]

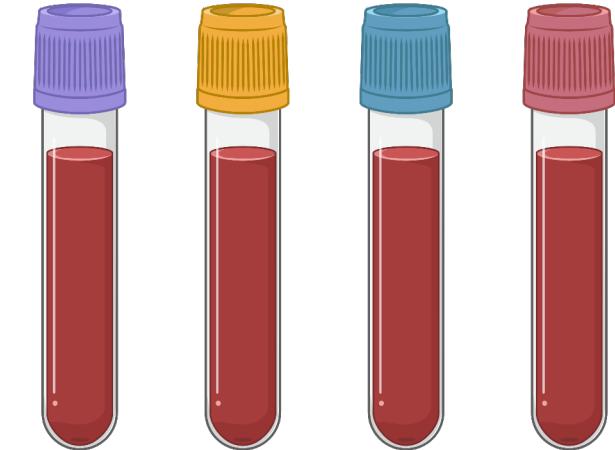


Gelfand and Douglas, "Fatigue", *Harrison's principles of internal medicine*, 19th edition, 2018

<https://www.uptodate.com/contents/approach-to-the-adult-patient-with-fatigue>

# Laboratory and radiological studies

- Initial laboratory testing
  - Complete blood count with differential count
  - Chemistries (including glucose, electrolytes, renal and hepatic function tests)
  - Thyroid-stimulating hormone
  - Serologic testing dependent on risk factors (e.g., hepatitis C virus, HIV)
  - [...]
- Updating of cancer screening interventions



Gelfand and Douglas, "Fatigue", *Harrison's principles of internal medicine*, 19th edition, 2018

<https://www.uptodate.com/contents/approach-to-the-adult-patient-with-fatigue>

# Management

# Management

- Establish therapeutic goals



# Management

- Establish therapeutic goals
- Treat underlying condition(s)



# Management

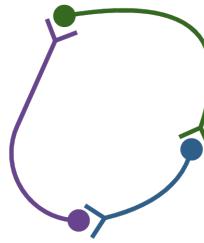
- Establish therapeutic goals
- Treat underlying condition(s)
- Address residual or idiopathic fatigue
  - Pharmacological interventions
  - Non-pharmacological interventions
    - Cognitive behavioral therapy
    - Exercise therapy
    - Occupational therapy



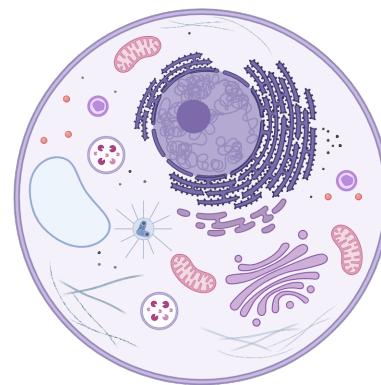
# Pathophysiology of fatigue

???

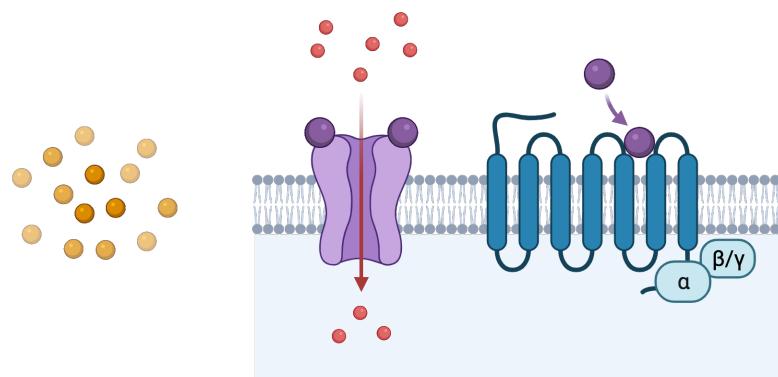
Circuit level



Cellular level



Molecular level



*IL-6*

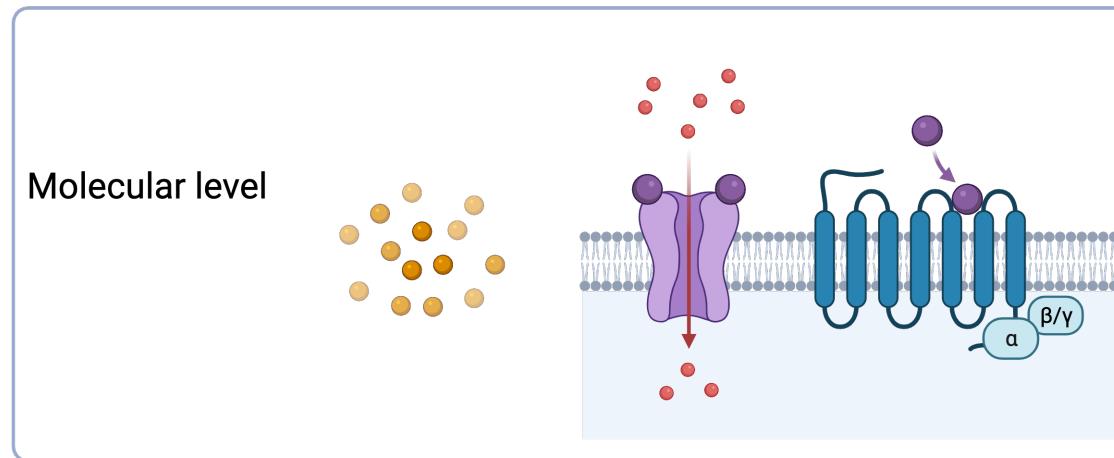
*IL-1*

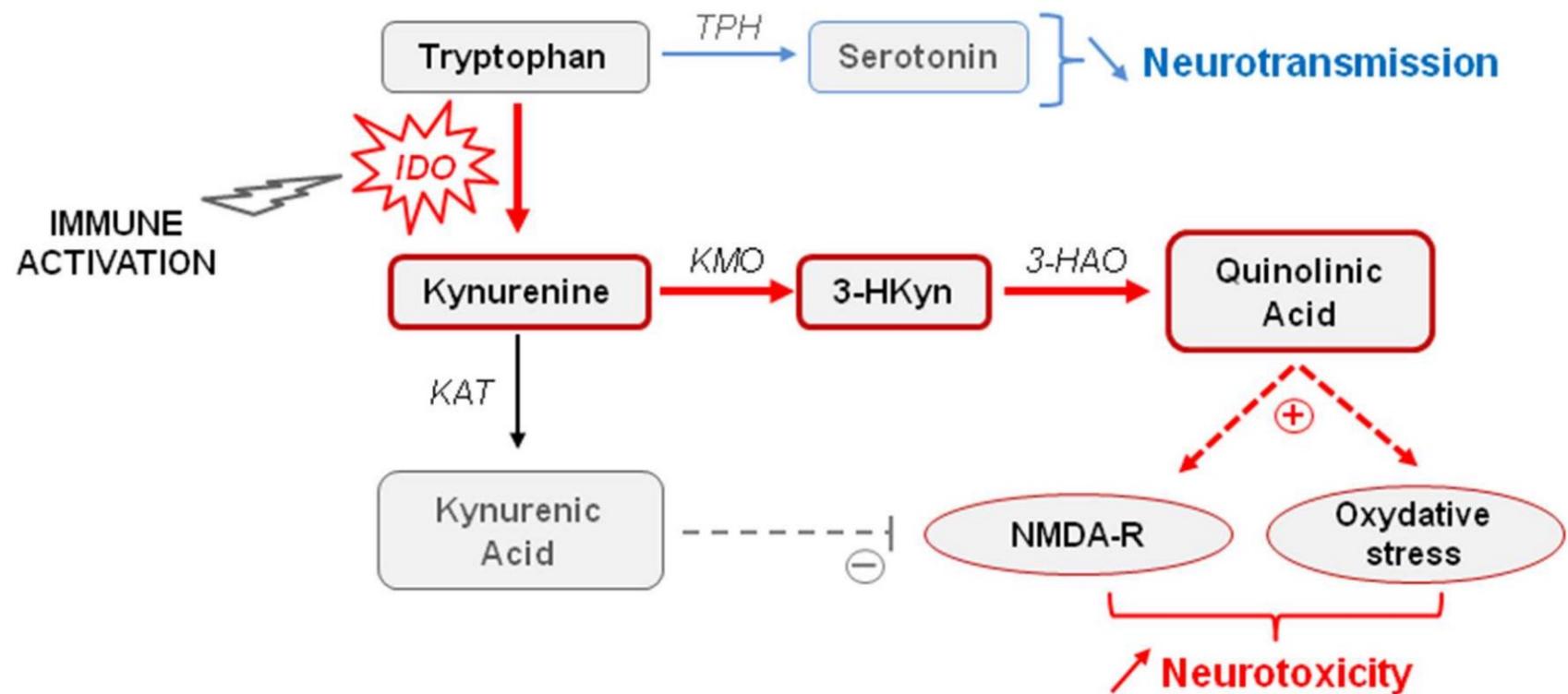
*TNF- $\alpha$*

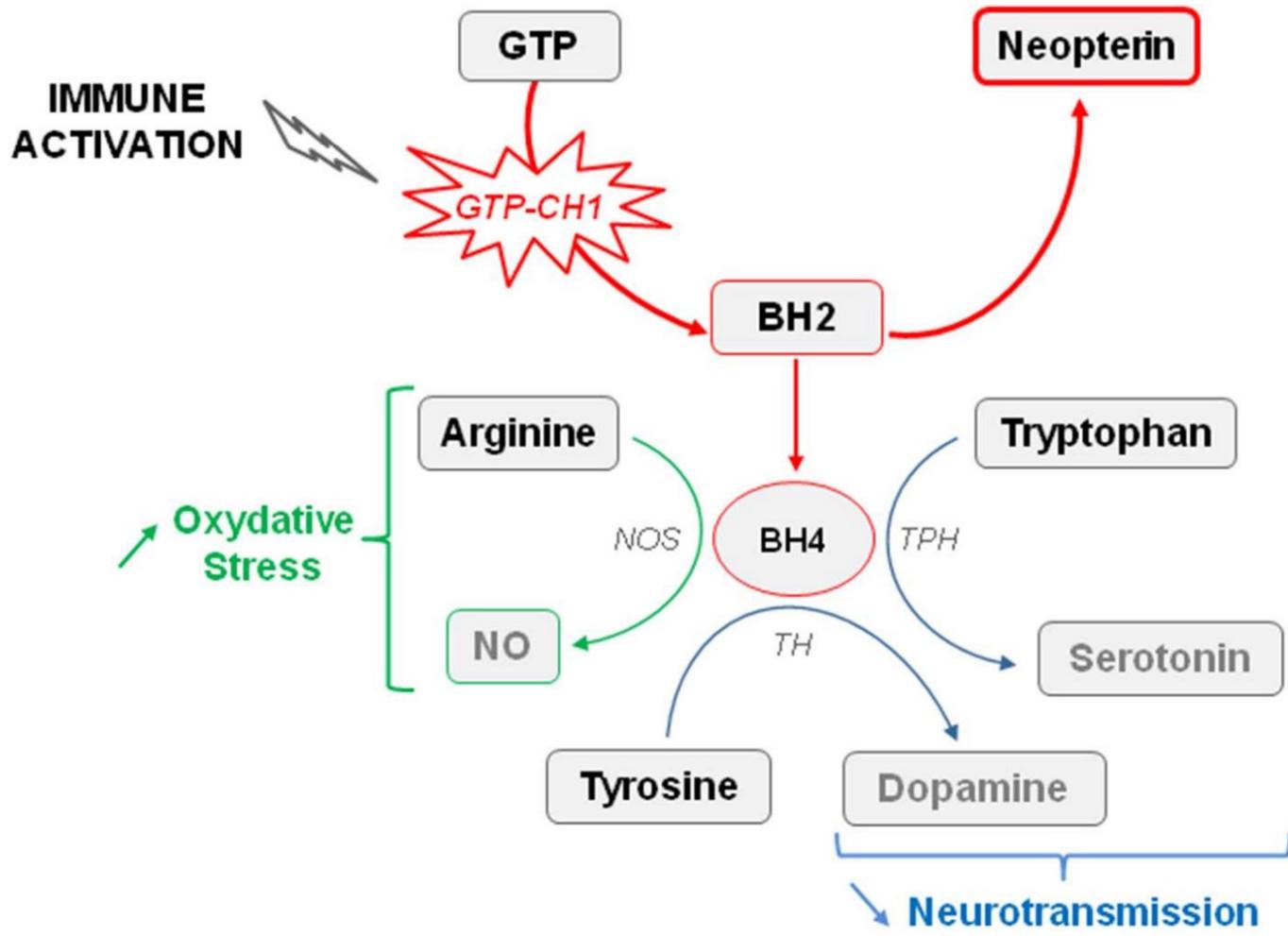
*CRP*

*INF- $\alpha$*

*INF- $\gamma$*







# **Allostatic Self-efficacy: A Metacognitive Theory of Dyshomeostasis-Induced Fatigue and Depression**

*Klaas E. Stephan<sup>1, 2, 3\*</sup>, Zina M. Manjaly<sup>1, 4</sup>, Christoph D. Mathys<sup>2</sup>, Lilian A. E. Weber<sup>1</sup>, Saeed Paliwal<sup>1</sup>, Tim Gard<sup>1, 5</sup>, Marc Tittgemeyer<sup>3</sup>, Stephen M. Fleming<sup>2</sup>, Helene Haker<sup>1</sup>, Anil K. Seth<sup>6</sup> and Frederike H. Petzschner<sup>1</sup>*

<sup>1</sup> Translational Neuromodeling Unit, Institute for Biomedical Engineering, University of Zurich and ETH Zurich, Zurich, Switzerland, <sup>2</sup> Wellcome Trust Centre for Neuroimaging, University College London, London, UK, <sup>3</sup> Max Planck Institute for Metabolism Research, Cologne, Germany, <sup>4</sup> Department of Neurology, Schulthess Clinic, Zurich, Switzerland, <sup>5</sup> Center for Complementary and Integrative Medicine, University Hospital Zurich, Zurich, Switzerland, <sup>6</sup> Sackler Centre for Consciousness Science, School of Engineering and Informatics, University of Sussex, Brighton, UK

# *Homeostasis*

*[The] maintenance of nearly constant conditions in the internal [bodily] environment*

*Walter Cannon, 1929*

# Homeostasis

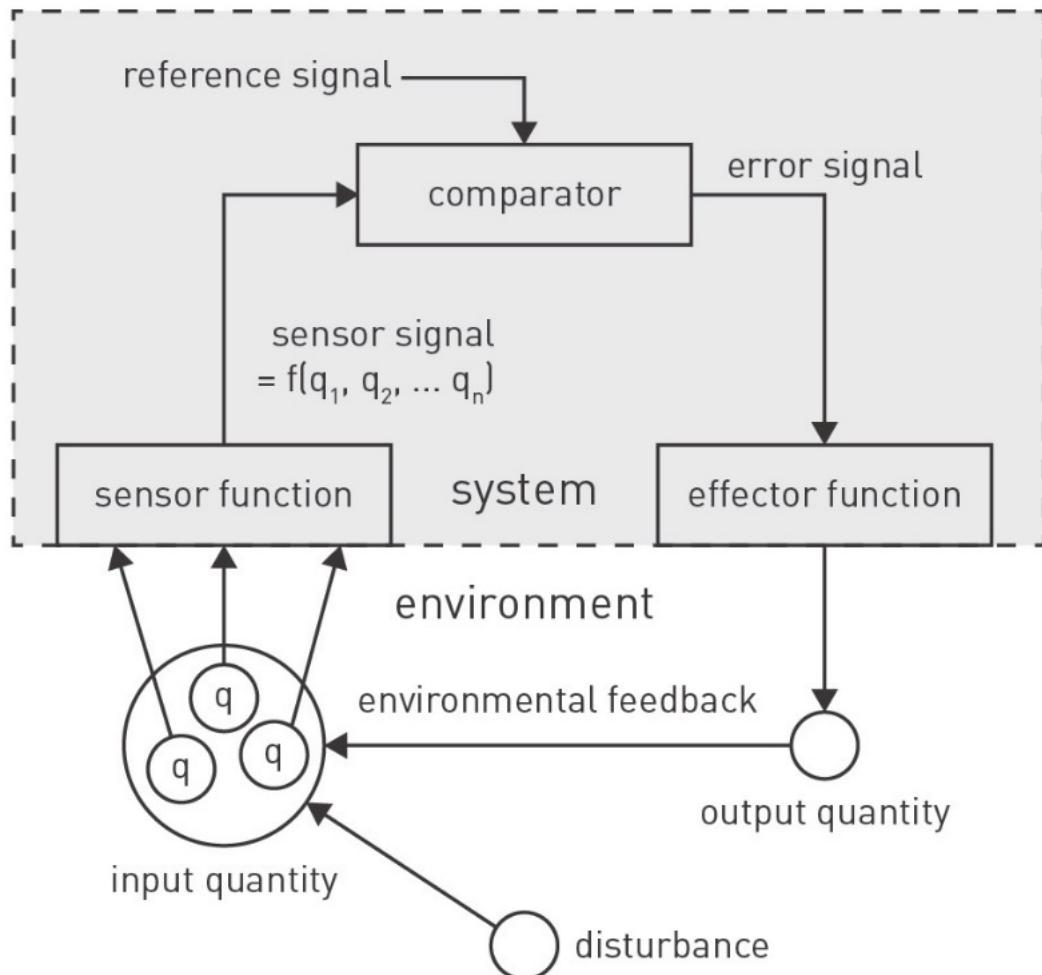


Figure from: Powers, *Science*, 1973

Based on slide from Klaas Enno Stephan

# Homeostasis

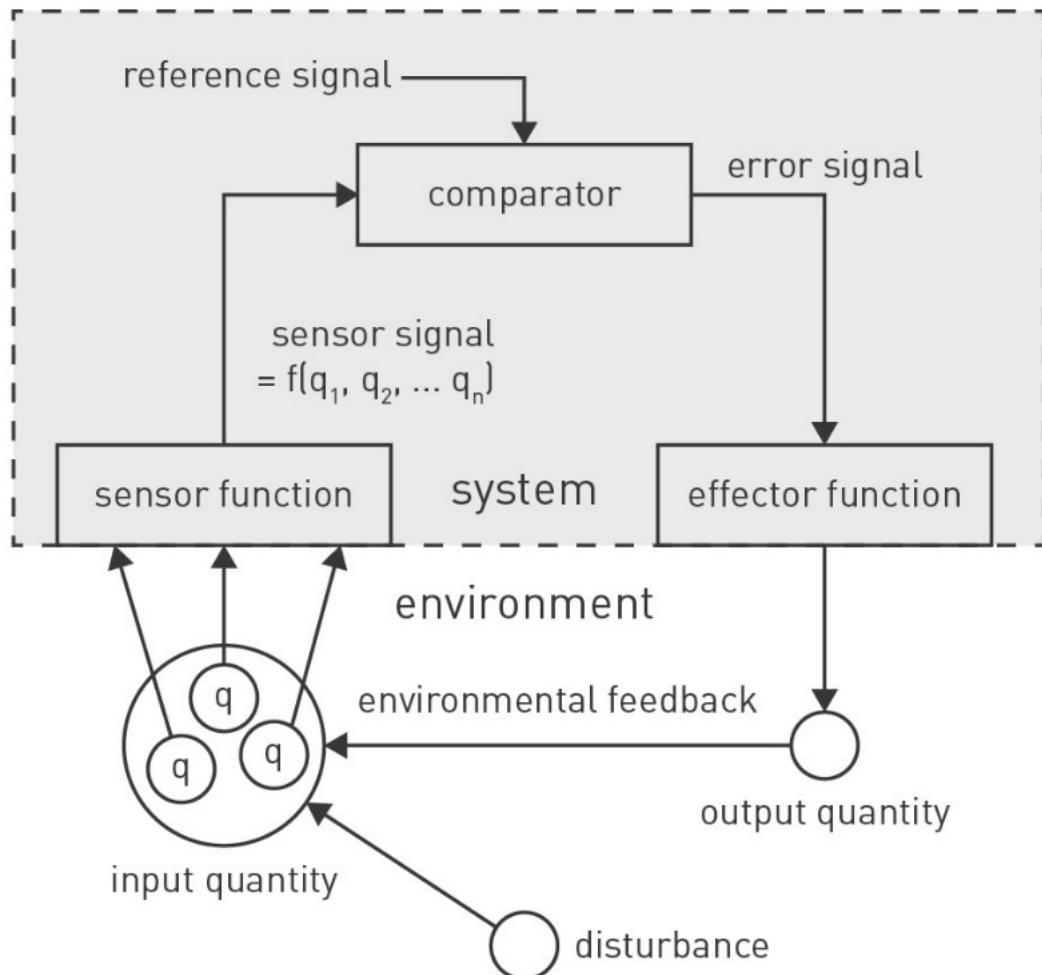


Figure from: Powers, *Science*, 1973

# Allostasis

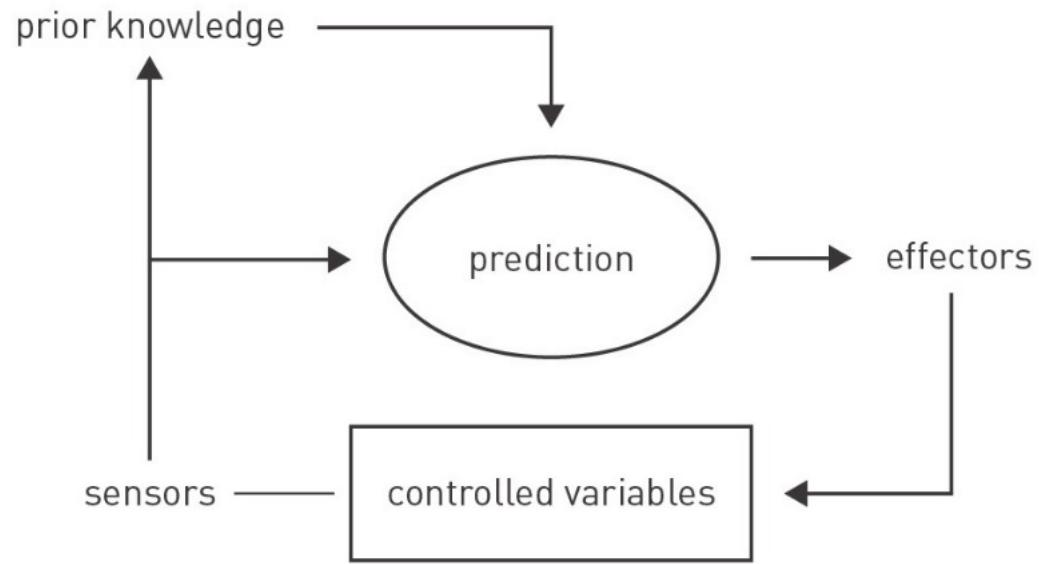
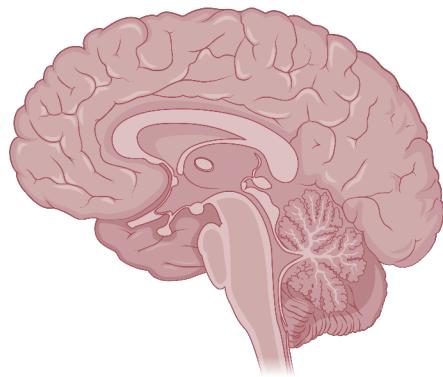


Figure from: Sterling, *Physiol. Behav.*, 2012

Based on slide from Klaas Enno Stephan



Based on figure from Stephan et al., *Frontiers in Human Neuroscience*, 2016

$$p(x|y) = \frac{p(y|x)p(x)}{p(y)}$$

prior

$$p(x|y) = \frac{p(y|x)p(x)}{p(y)}$$

$$p(x|y) = \frac{p(y|x)p(x)}{p(y)}$$

likelihood

prior

$$p(x|y) = \frac{likelihood \cdot prior}{posterior}$$
$$p(x|y) = \frac{p(y|x)p(x)}{p(y)}$$

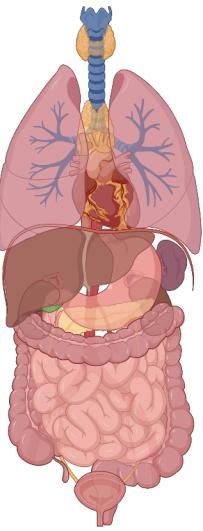
$$p(x|y, m) = \frac{\text{likelihood} \quad \text{prior}}{p(y|m)}$$

posterior

$$p(x|y, m) = \frac{\text{likelihood} \quad \text{prior}}{\text{posterior} \quad \text{model evidence}}$$
$$p(x|y, m) = \frac{p(y|x, m)p(x|m)}{p(y|m)}$$

$$p(x|y, m) = \frac{\text{likelihood} \quad \text{prior}}{\text{posterior} \quad \text{model evidence}}$$
$$= \frac{p(y|x, m)p(x|m)}{p(y|m)}$$

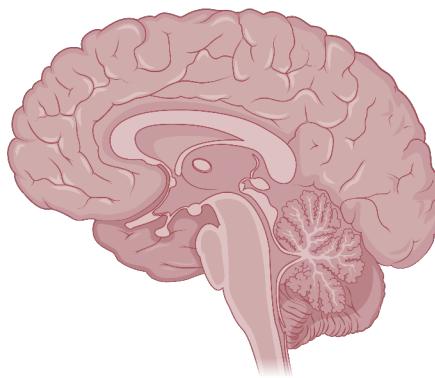
$$\log p(y|m) = -S(y|m)$$



$$p(x|y, m)$$



$$p(y|x, m)p(x|m)$$



$$p(x|y, m)$$



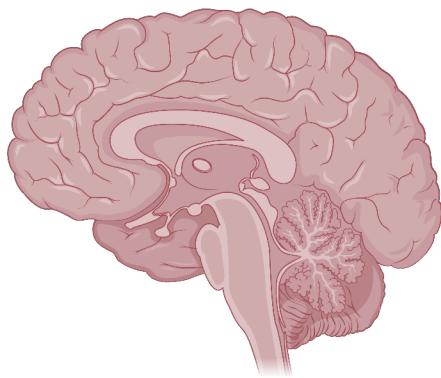
$$p(y|x, m)p(x|m)$$



Based on figure from Stephan et al., *Frontiers in Human Neuroscience*, 2016



$$\frac{p(x|y, m)}{p(y|x, m)p(x|m)}$$



$$\frac{p(x|y, m)}{p(y|x, m)p(x|m)}$$



Interoceptive surprise

Exteroceptive surprise

Based on figure from Stephan et al., *Frontiers in Human Neuroscience*, 2016

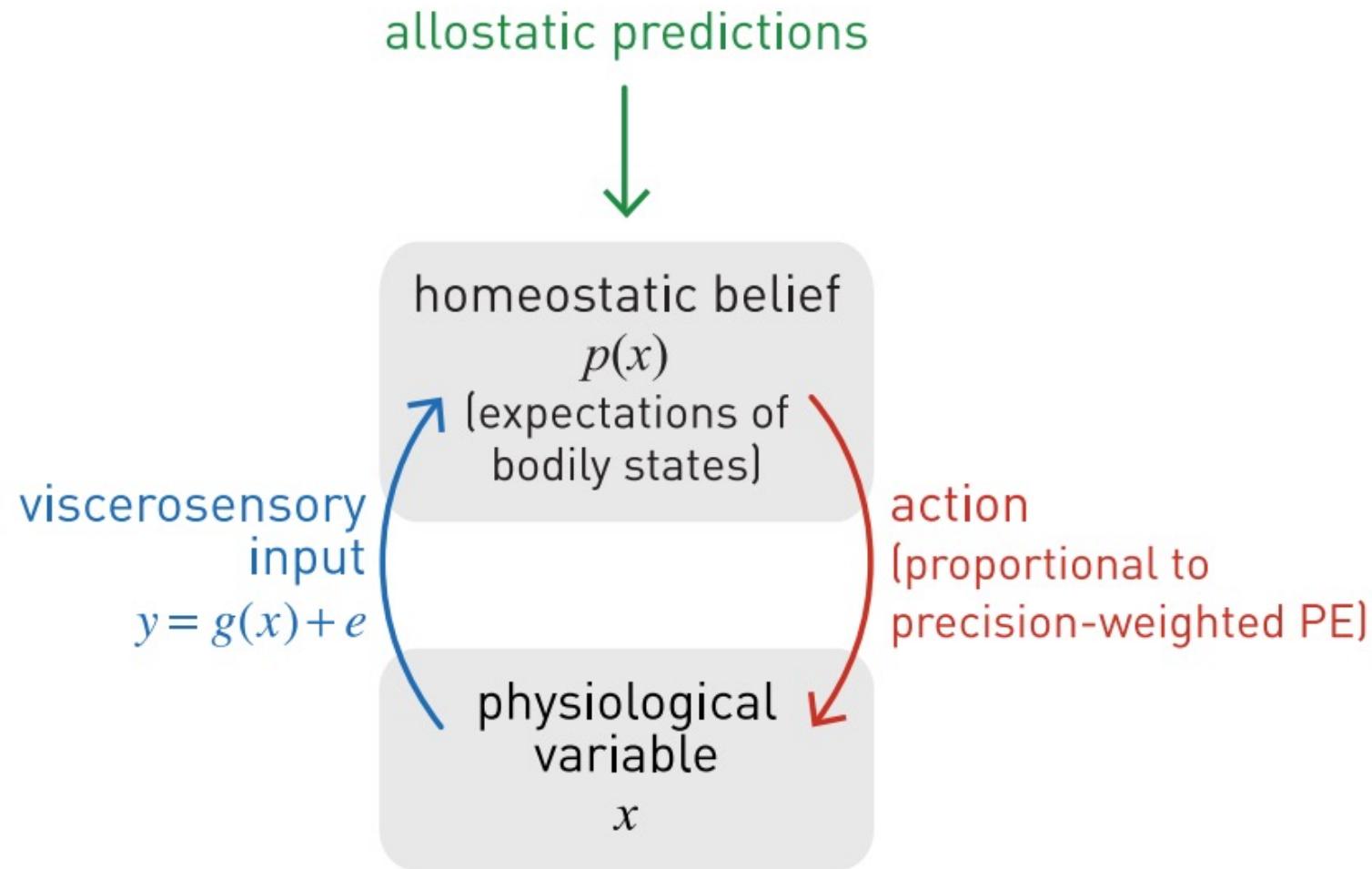
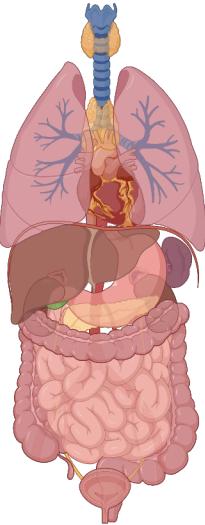
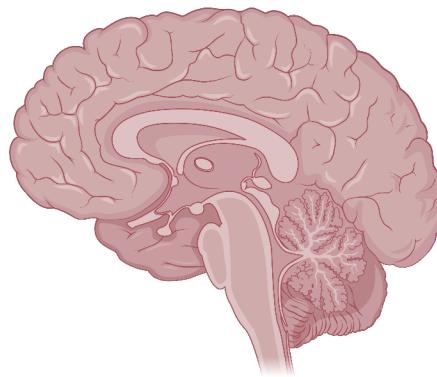


Figure from Stephan et al., *Frontiers in Human Neuroscience*, 2016

# Self-efficacy



$$\frac{p(x|y, m)}{p(y|x, m)p(x|m)}$$



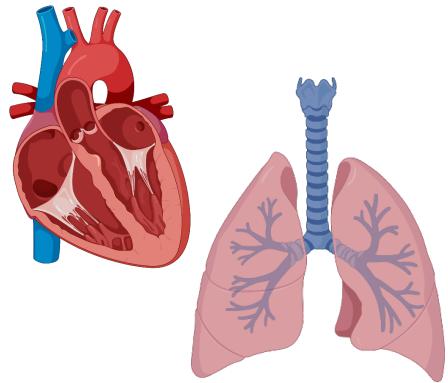
$$\frac{p(x|y, m)}{p(y|x, m)p(x|m)}$$



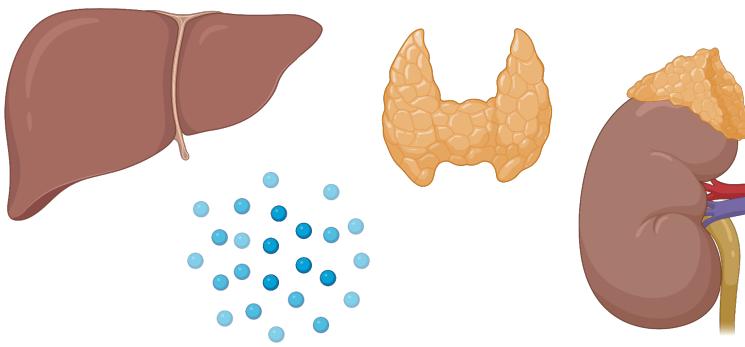
Interoceptive surprise

Exteroceptive surprise

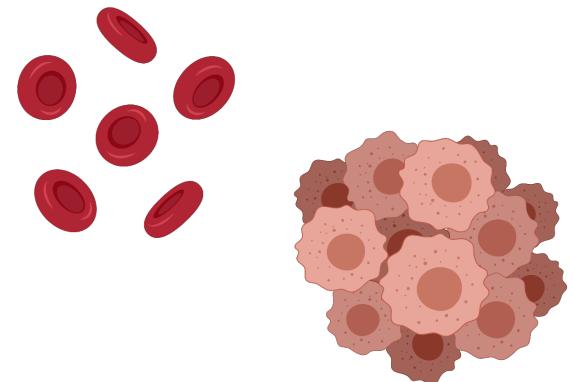
Based on figure from Stephan et al., *Frontiers in Human Neuroscience*, 2016



Cardiopulmonary



Endocrinologic/metabolic



Hematologic/neoplastic

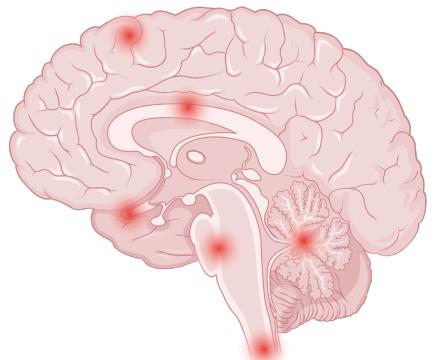


Substance use

# Fatigue



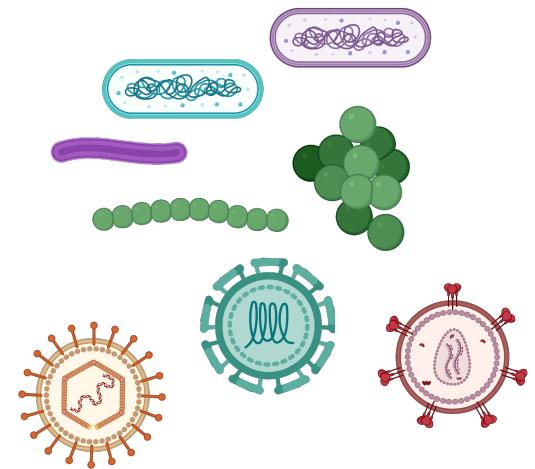
Medication



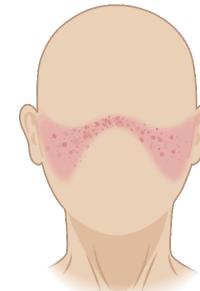
Neurologic



Psychiatric



Infectious



Rheumatologic

# *Dyshomeostasis*

Stephan et al., *Frontiers in Human Neuroscience*, 2016

# *Dyshomeostasis*

*[State of] chronically enhanced surprise about bodily signals, or,  
equivalently, low evidence for the brain's model of bodily states*

# Desiderata for a computational theory of fatigue

- Needs to account for:
  - Relation to dyshomeostasis in general
  - Role of brain-body interactions
  - Possibility that dyshomeostasis could be merely perceived  
( $\neq$  fatigue less real!)
- Needs to help with differential diagnosis

# *Metacognition*

Petzschnner et al., *Biological Psychiatry*, 2017

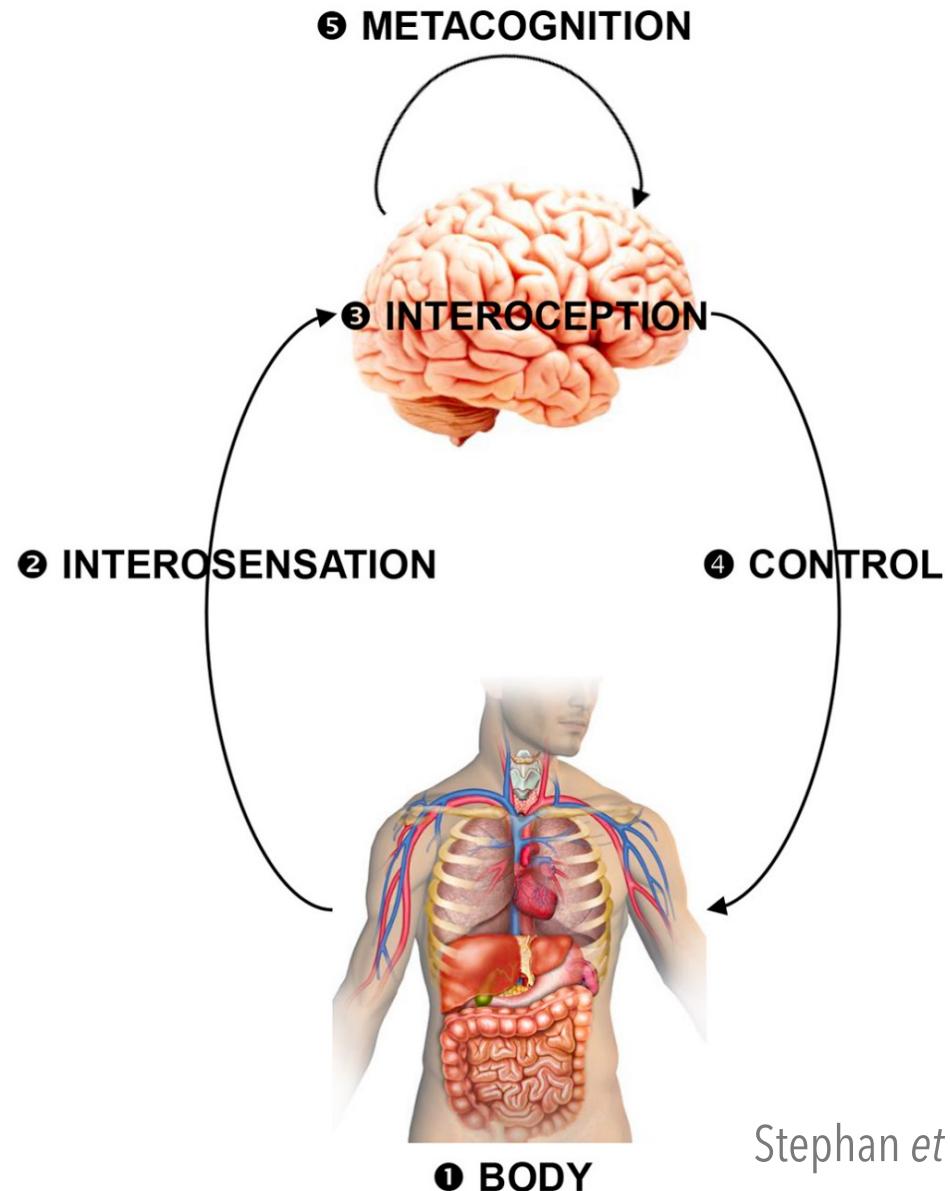
## *Metacognition*

*Self-monitoring of one's level of mastery in acting on the world... and can be seen as a high-level form of inference about one's capacity for control*

# **Allostatic Self-efficacy: A Metacognitive Theory of Dyshomeostasis-Induced Fatigue and Depression**

*Klaas E. Stephan<sup>1, 2, 3\*</sup>, Zina M. Manjaly<sup>1, 4</sup>, Christoph D. Mathys<sup>2</sup>, Lilian A. E. Weber<sup>1</sup>, Saeed Paliwal<sup>1</sup>, Tim Gard<sup>1, 5</sup>, Marc Tittgemeyer<sup>3</sup>, Stephen M. Fleming<sup>2</sup>, Helene Haker<sup>1</sup>, Anil K. Seth<sup>6</sup> and Frederike H. Petzschner<sup>1</sup>*

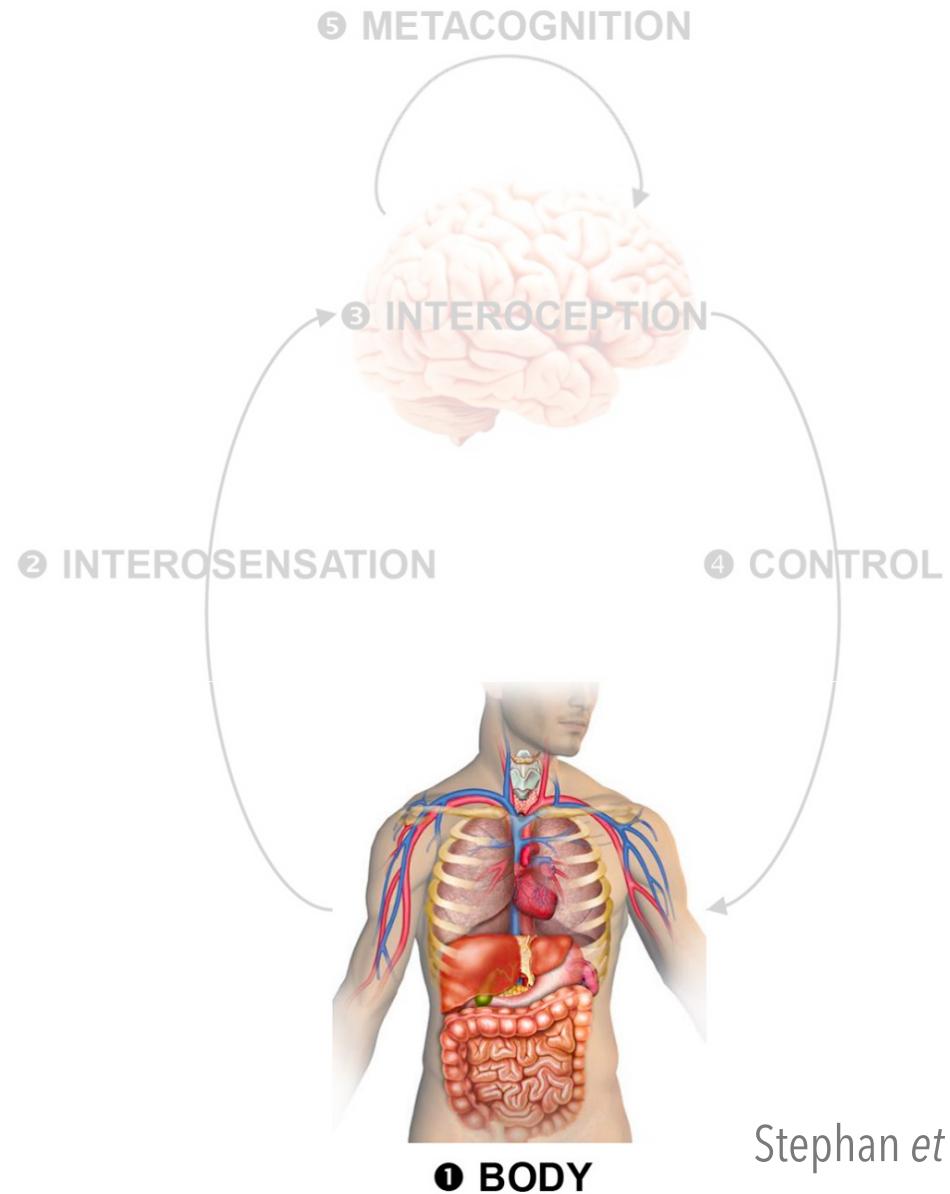
<sup>1</sup> Translational Neuromodeling Unit, Institute for Biomedical Engineering, University of Zurich and ETH Zurich, Zurich, Switzerland, <sup>2</sup> Wellcome Trust Centre for Neuroimaging, University College London, London, UK, <sup>3</sup> Max Planck Institute for Metabolism Research, Cologne, Germany, <sup>4</sup> Department of Neurology, Schulthess Clinic, Zurich, Switzerland, <sup>5</sup> Center for Complementary and Integrative Medicine, University Hospital Zurich, Zurich, Switzerland, <sup>6</sup> Sackler Centre for Consciousness Science, School of Engineering and Informatics, University of Sussex, Brighton, UK



Stephan et al., *Frontiers in Human Neuroscience*, 2016

Petzschnner et al., *Biological Psychiatry*, 2017

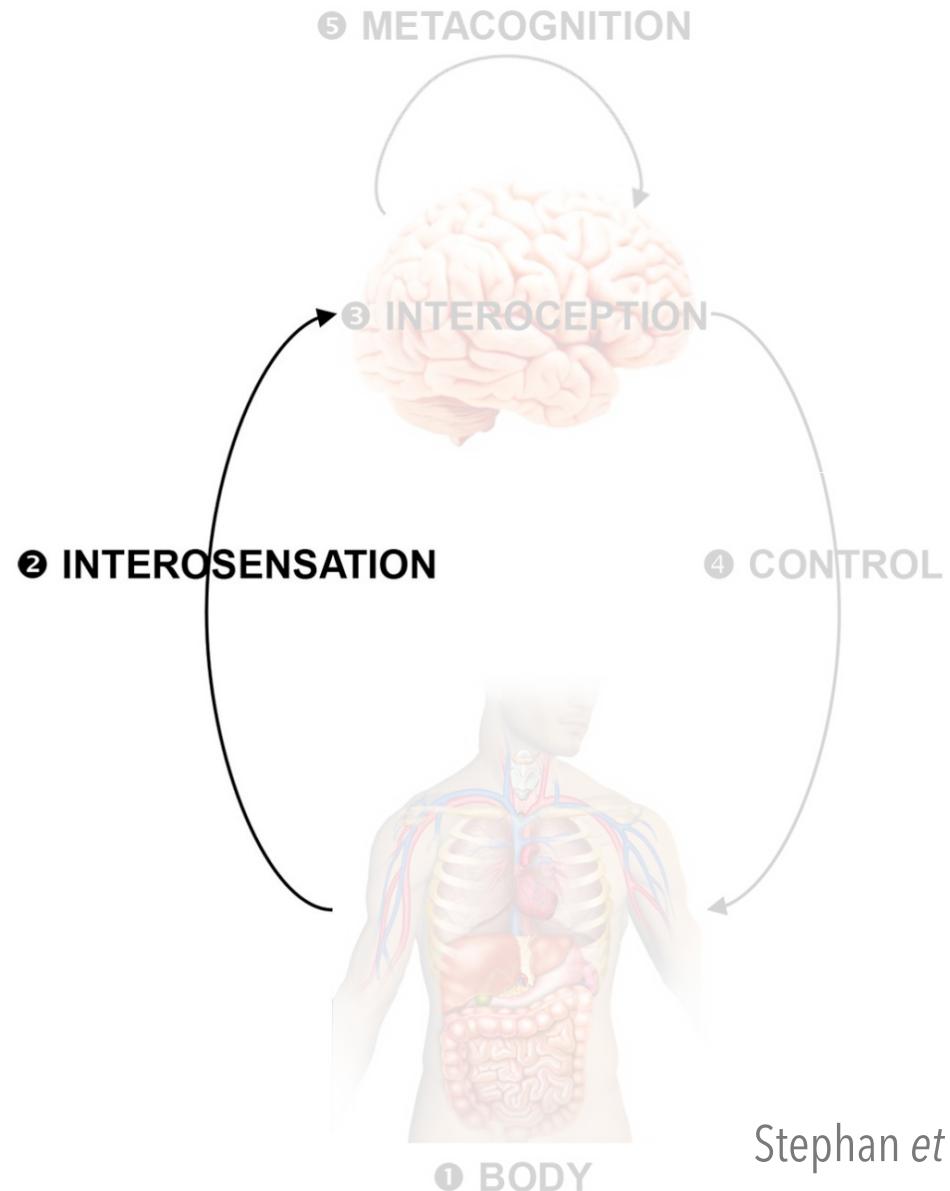
Manjaly et al., *Journal of Neurology, Neurosurgery and Psychiatry*, 2019



Stephan et al., *Frontiers in Human Neuroscience*, 2016

Petzschnner et al., *Biological Psychiatry*, 2017

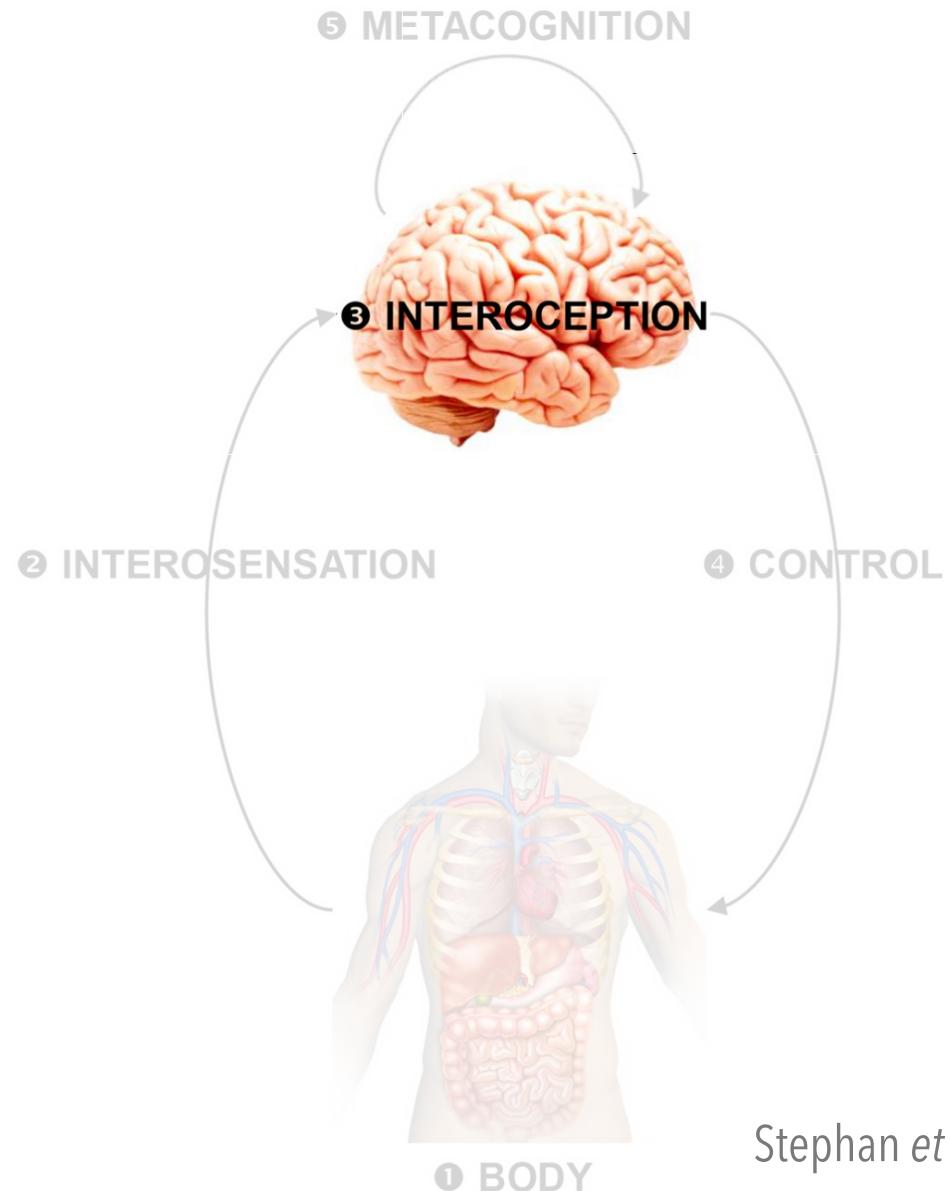
Manjaly et al., *Journal of Neurology, Neurosurgery and Psychiatry*, 2019



Stephan et al., *Frontiers in Human Neuroscience*, 2016

Petzschnner et al., *Biological Psychiatry*, 2017

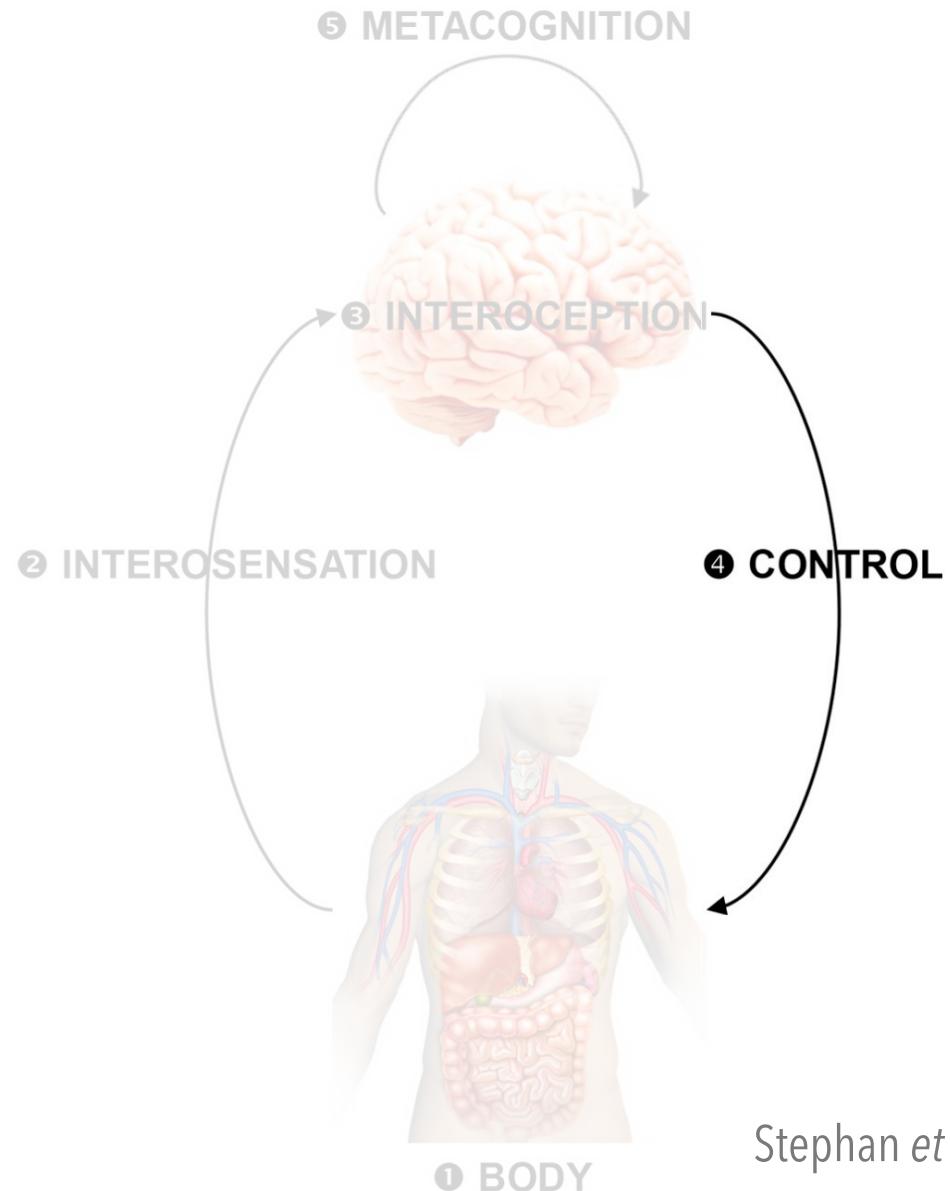
Manjaly et al., *Journal of Neurology, Neurosurgery and Psychiatry*, 2019



Stephan et al., *Frontiers in Human Neuroscience*, 2016

Petzschnner et al., *Biological Psychiatry*, 2017

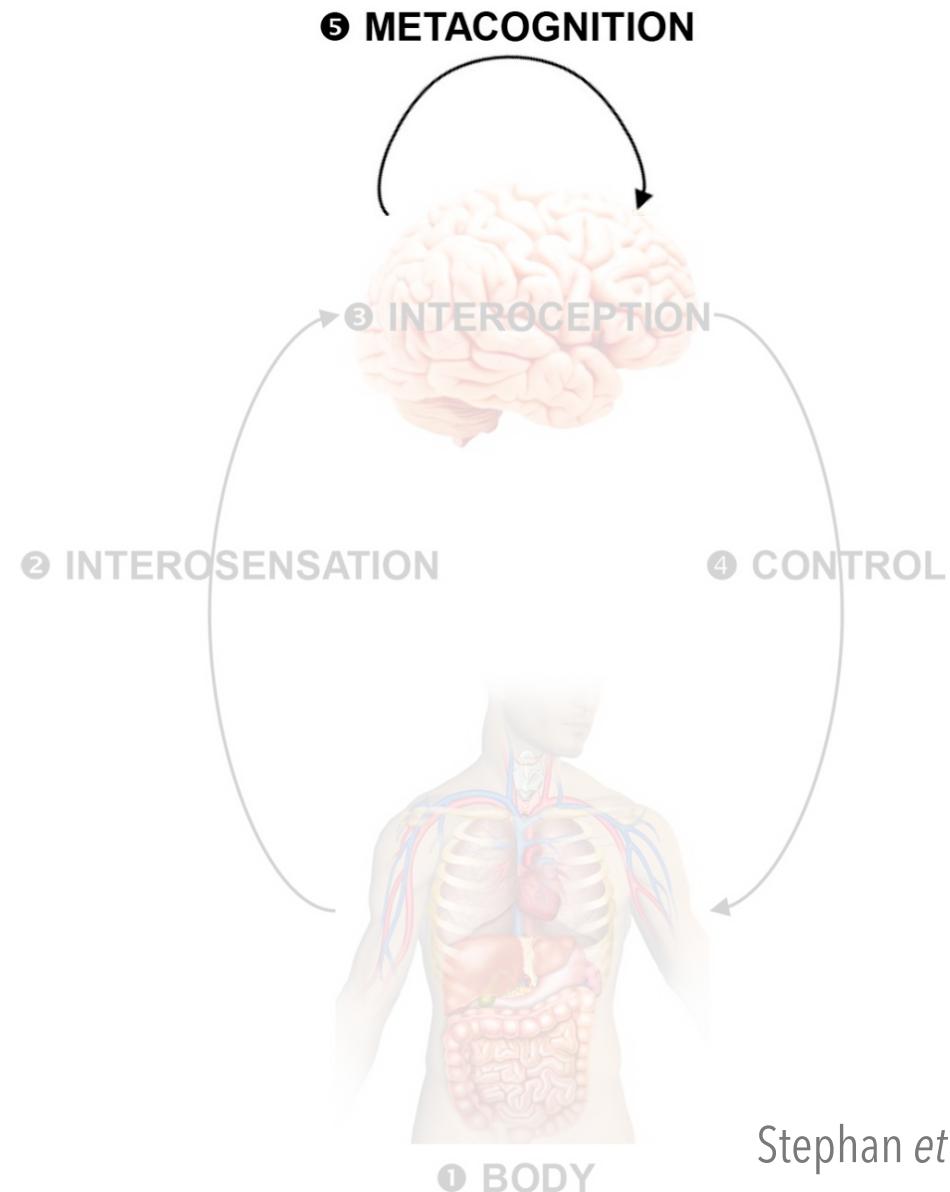
Manjaly et al., *Journal of Neurology, Neurosurgery and Psychiatry*, 2019



Stephan et al., *Frontiers in Human Neuroscience*, 2016

Petzschnner et al., *Biological Psychiatry*, 2017

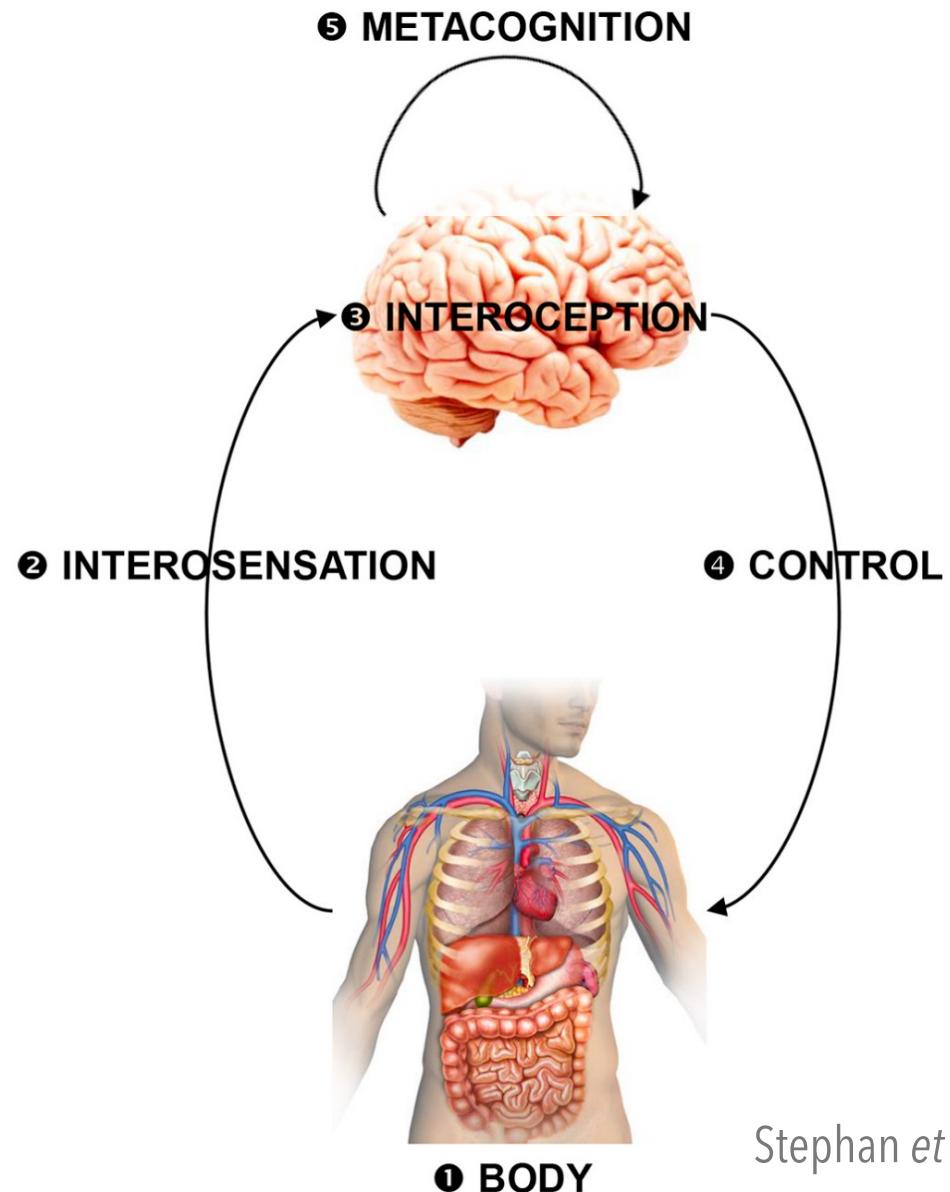
Manjaly et al., *Journal of Neurology, Neurosurgery and Psychiatry*, 2019



Stephan et al., *Frontiers in Human Neuroscience*, 2016

Petzschnner et al., *Biological Psychiatry*, 2017

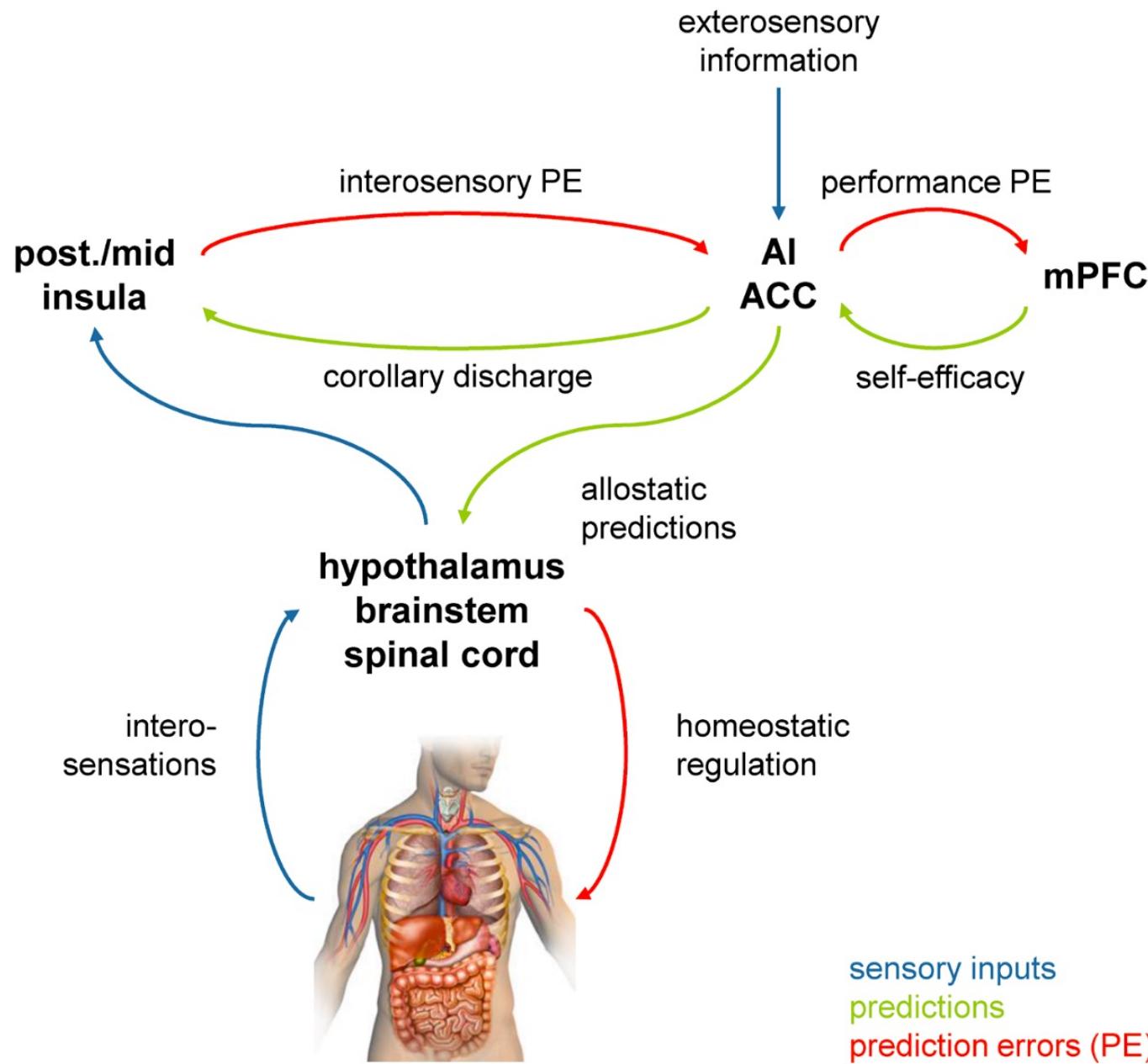
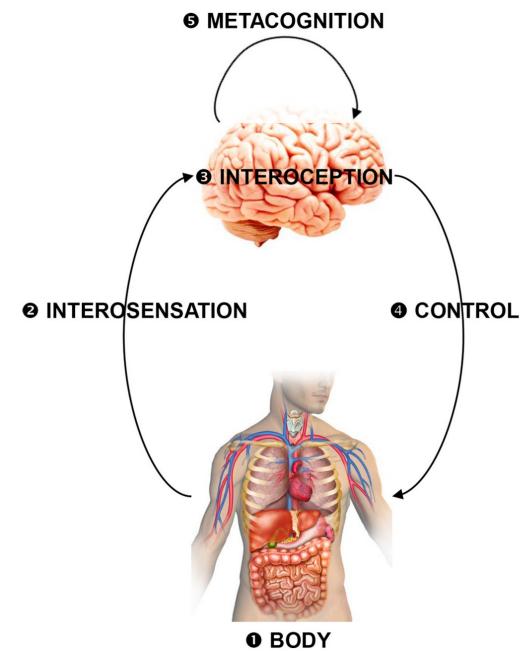
Manjaly et al., *Journal of Neurology, Neurosurgery and Psychiatry*, 2019



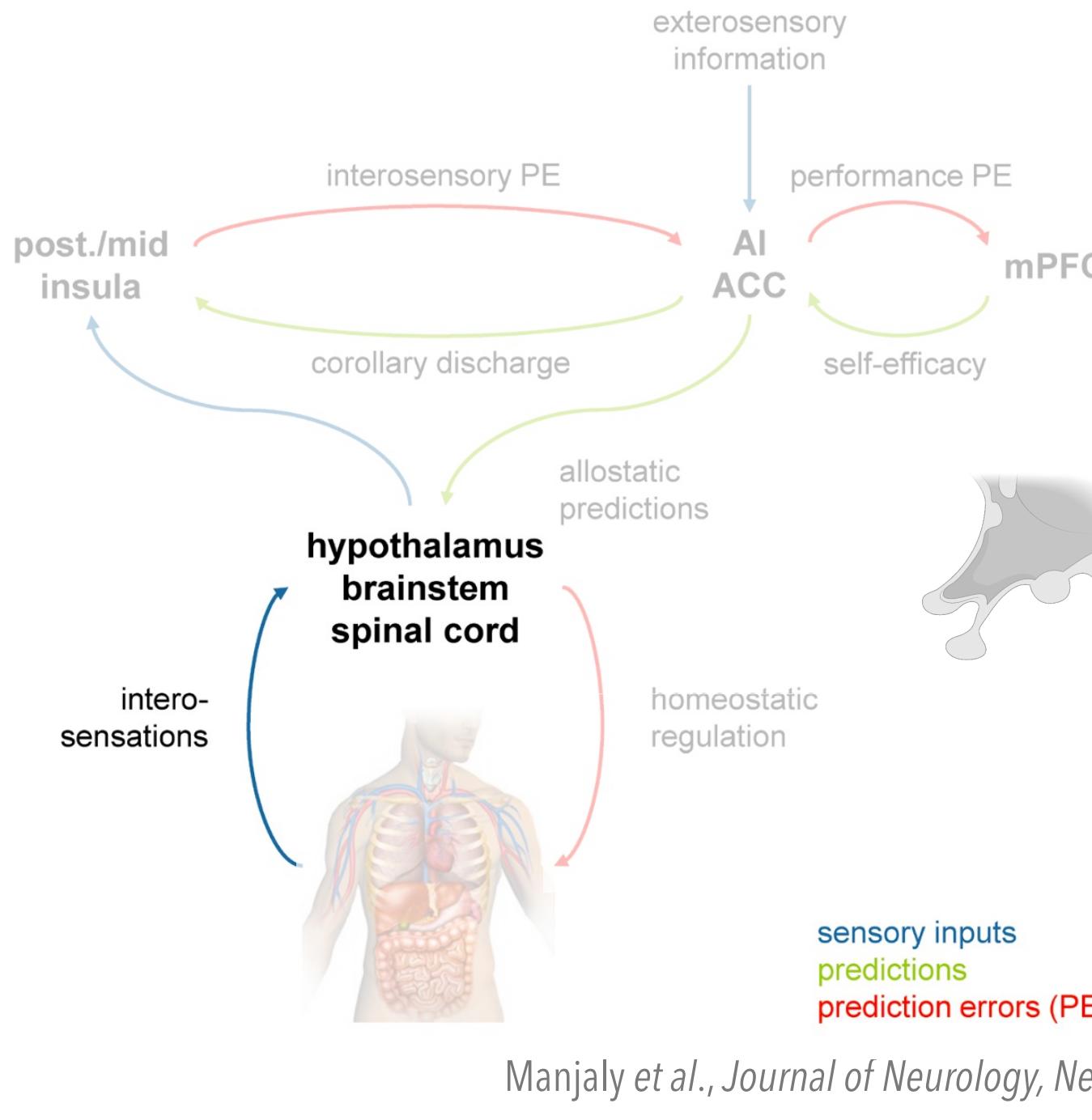
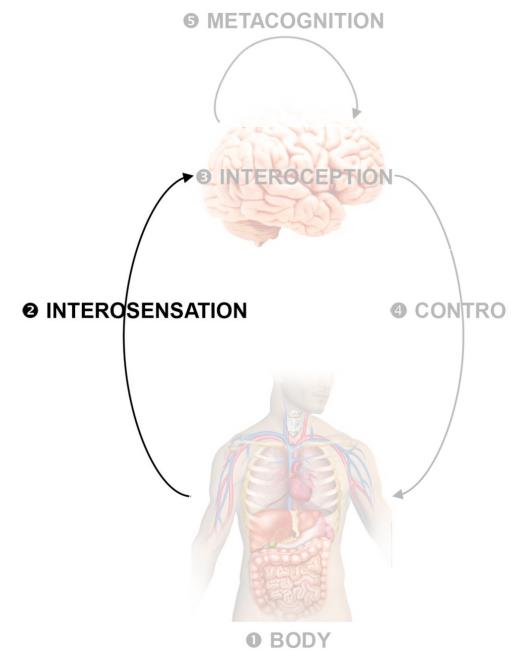
Stephan et al., *Frontiers in Human Neuroscience*, 2016

Petzschnner et al., *Biological Psychiatry*, 2017

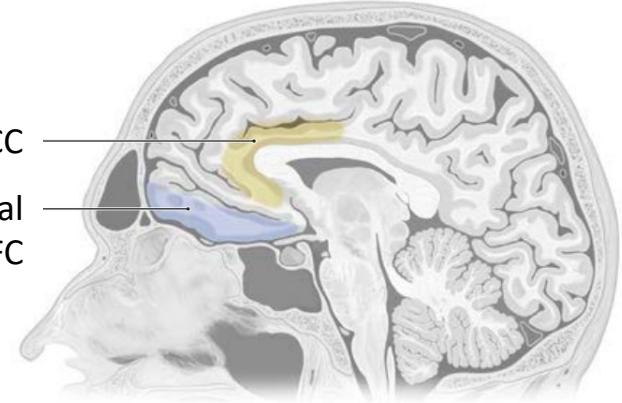
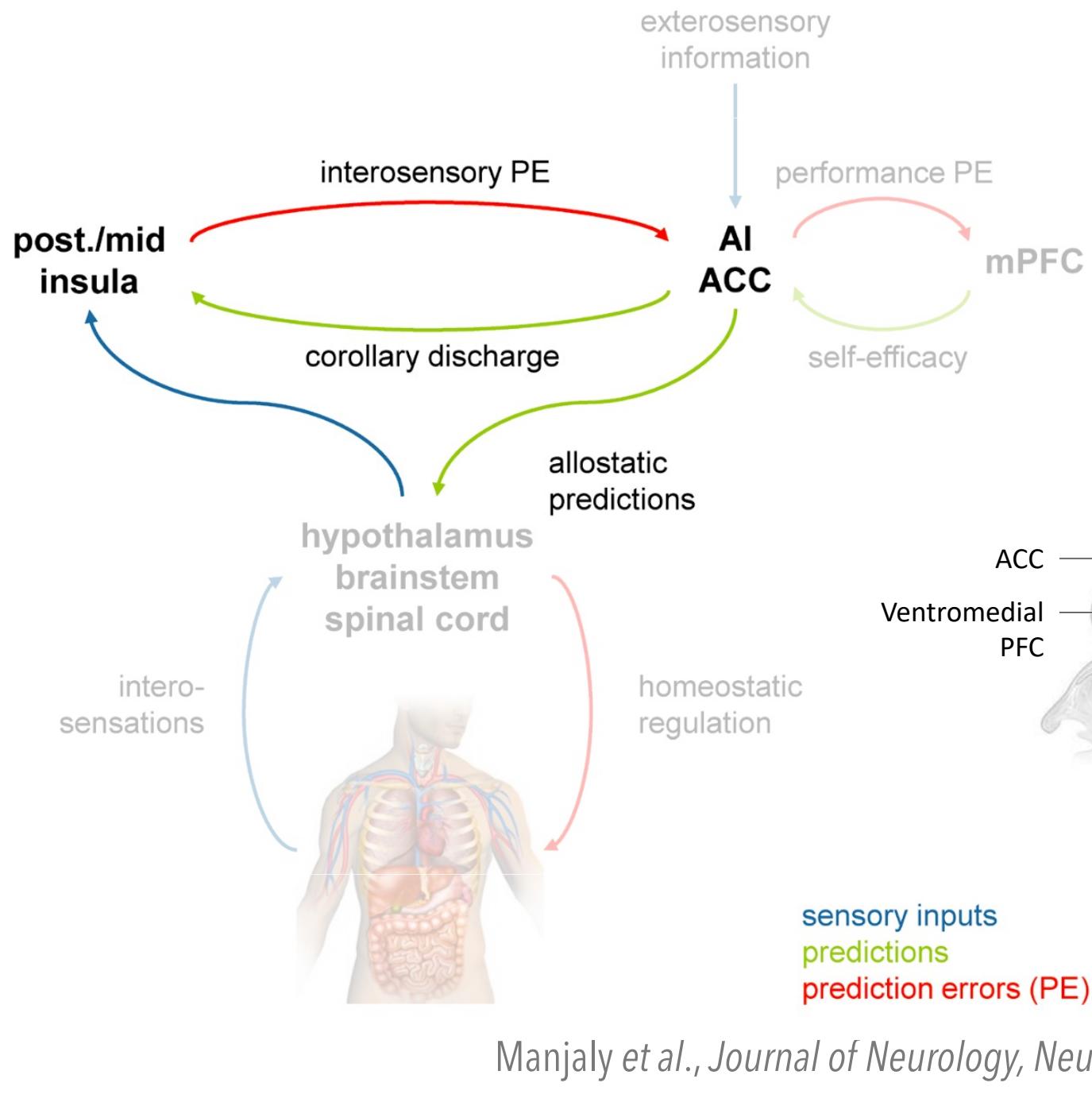
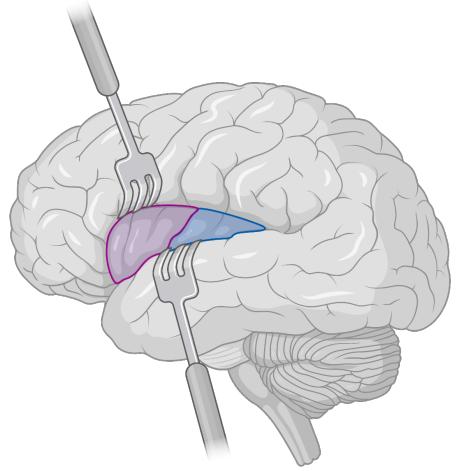
Manjaly et al., *Journal of Neurology, Neurosurgery and Psychiatry*, 2019



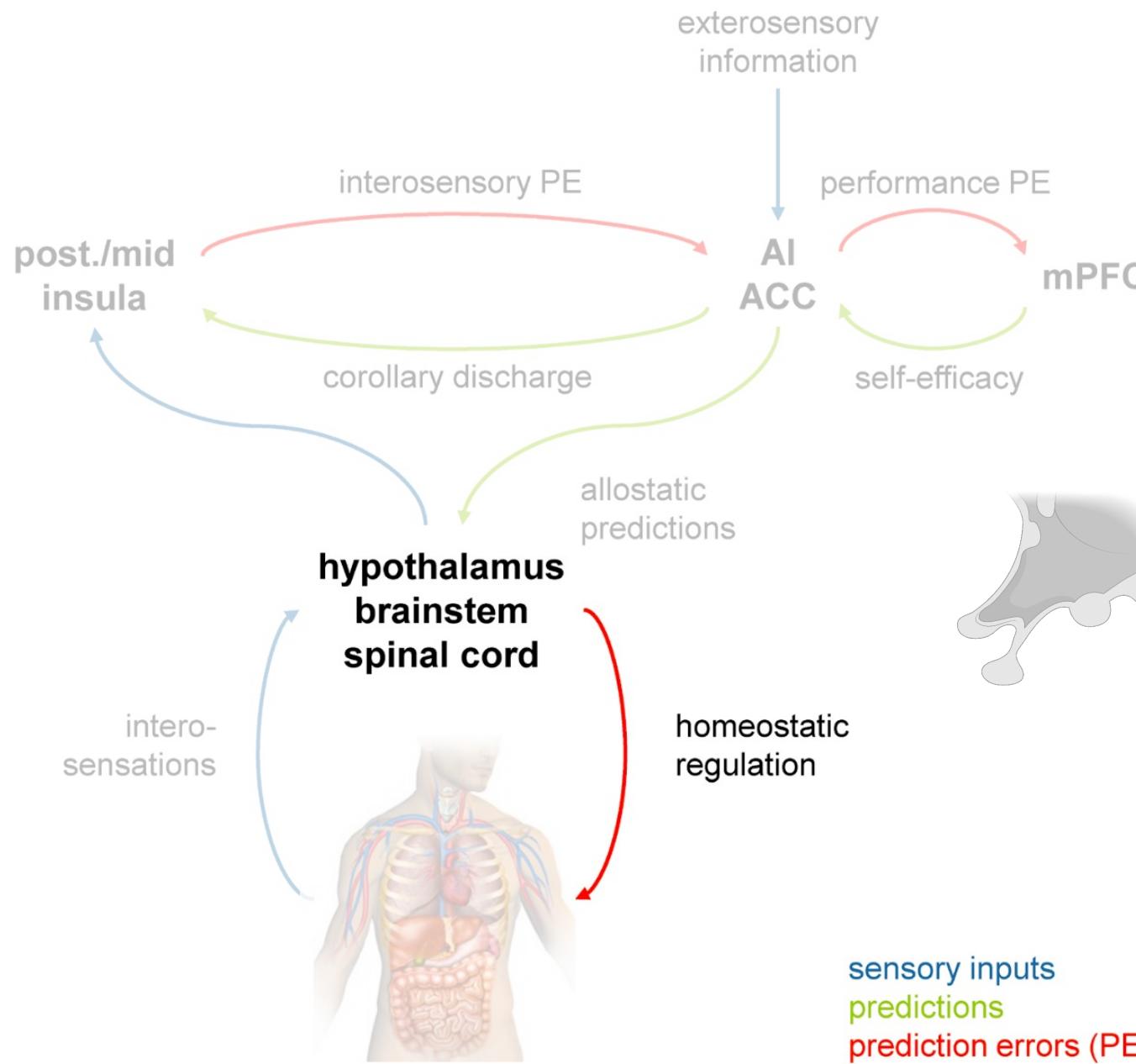
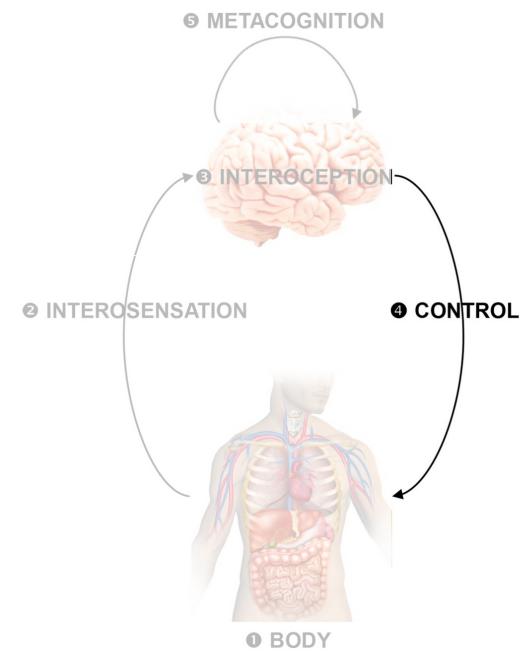
Manjaly et al., *Journal of Neurology, Neurosurgery and Psychiatry*, 2019



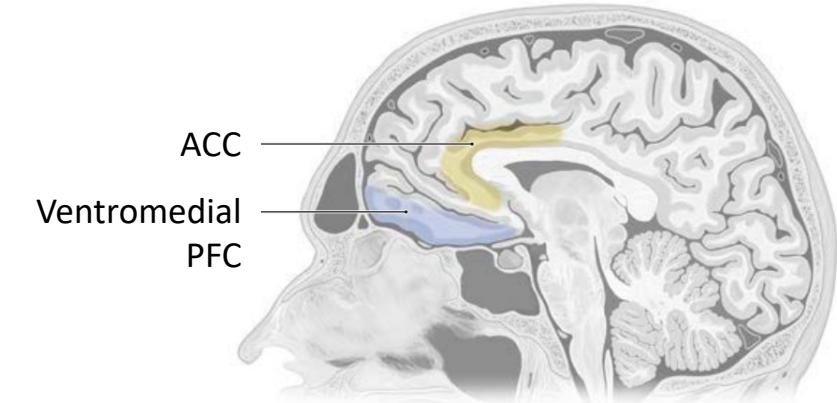
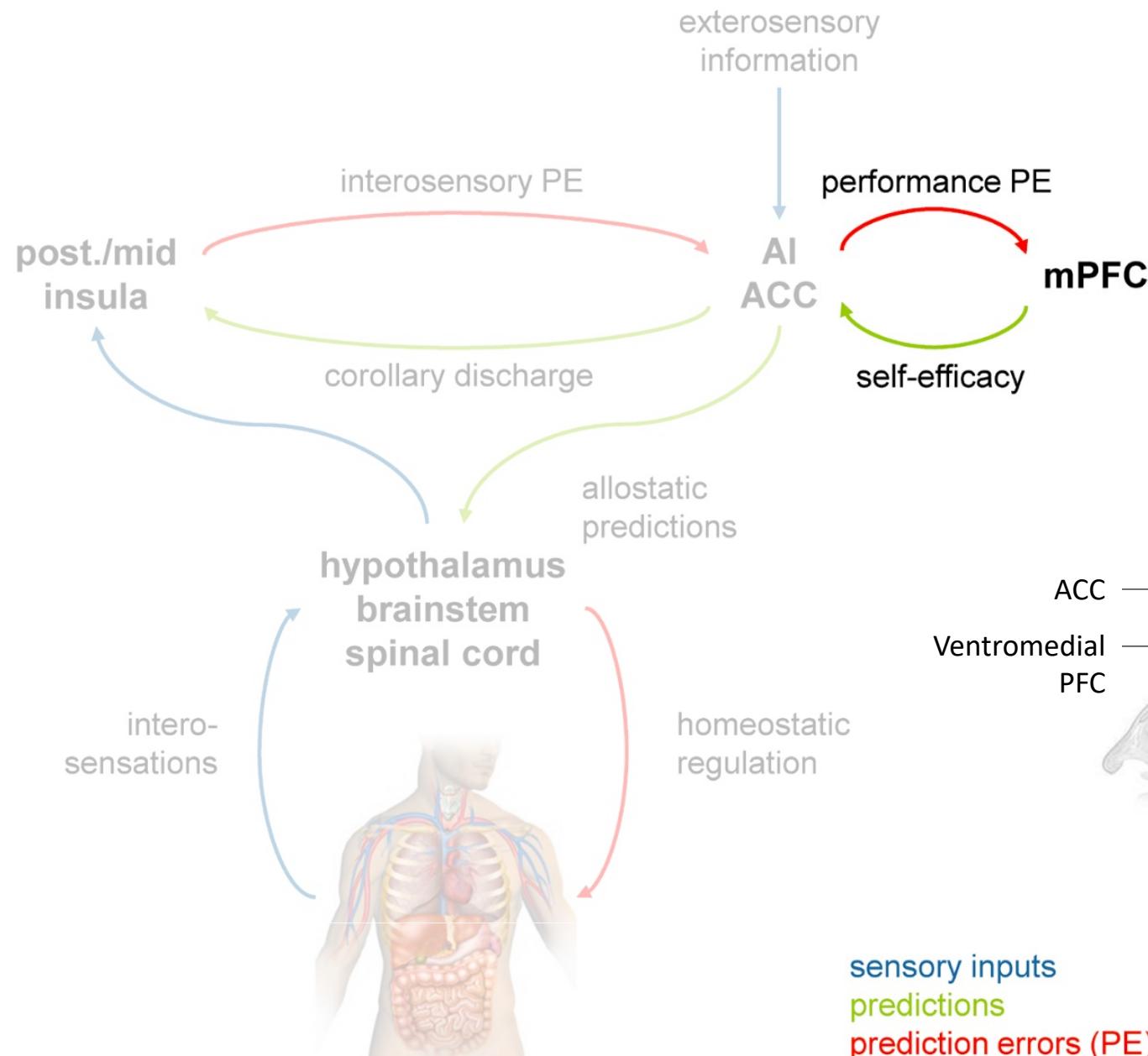
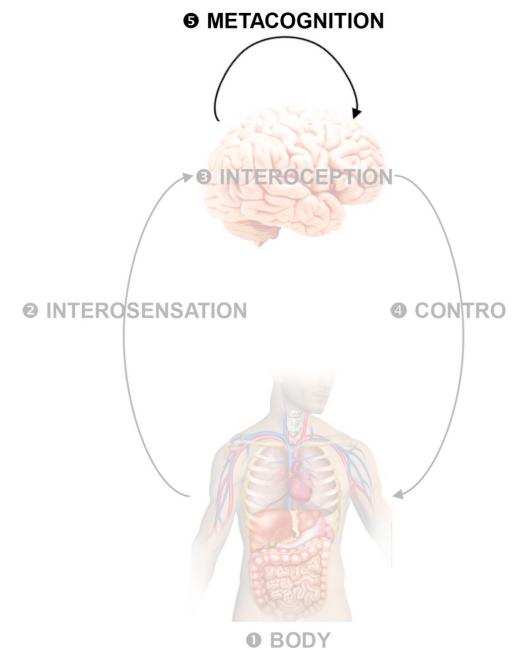
Manjaly et al., *Journal of Neurology, Neurosurgery and Psychiatry*, 2019



Manjaly et al., *Journal of Neurology, Neurosurgery and Psychiatry*, 2019



Manjaly et al., *Journal of Neurology, Neurosurgery and Psychiatry*, 2019

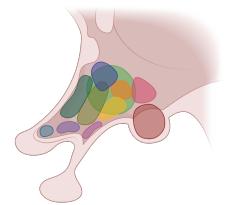
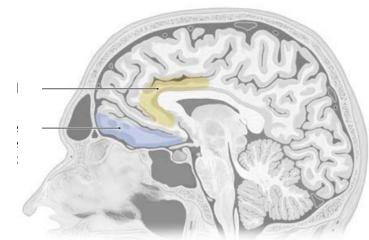
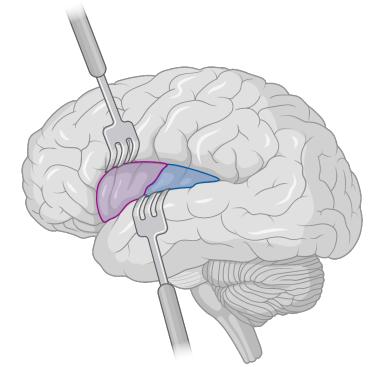


Manjaly et al., *Journal of Neurology, Neurosurgery and Psychiatry*, 2019

*Empirical evidence?*

# Anatomical areas from the circuit model

- Anterior and posterior insula:
  - Inflammation-induced microstructural changes are correlated with fatigue levels (Harrison *et al.*, 2015)
  - Among the most frequently affected cortical regions in MS (Haider *et al.*, 2016)
- Cingulate gyrus
  - Among the most frequently affected cortical regions in MS (Haider *et al.*, 2016)
- Hypothalamus
  - Biochemical/structural (Kantorová *et al.*, 2017) and structural connectivity changes (Hanken *et al.*, 2015) associated with fatigue



# Interoception (Gonzalez Campo *et al.*, 2020)

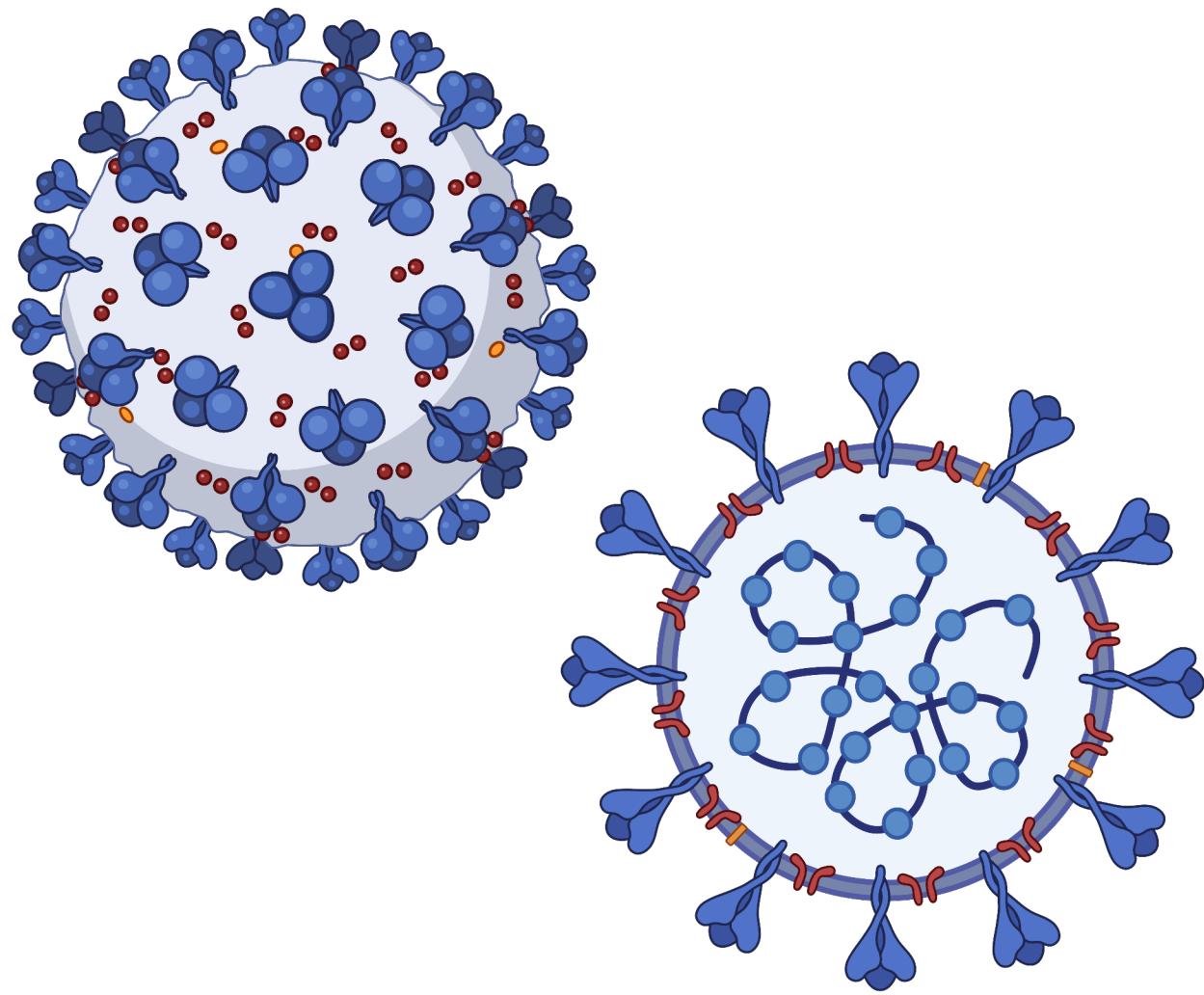
- Measures:
  - Heartbeat detection task
  - Structural and functional MRI
- Fatigued MS patients presented:
  - ↓ interoceptive accuracy
  - ↓ gray matter volume
  - ↑ functional connectivity in insula and anterior cingulate cortex
- Each of these alterations was positively associated with fatigue

# Metacognition

- Various measures of autonomic dysfunction correlate strongly with individual fatigue levels (Flachenecker *et al.*, 2003; Newton *et al.*, 2009; Cortez *et al.*, 2015)
- ... but no study has examined metacognition about interoception or homeostasis/allotasis thus far!
  - Maher-Edwards *et al.*, 2011: metacognitive factors predict individual fatigue levels.
    - However: metacognitive assessment did not specifically consider interoception
  - Delgado-Pastor *et al.*, 2015: increasing metacognitive abilities about interoception reduced worry more than increasing metacognition about other cognitive processes
    - However: study did not specifically examine fatigue

# Summary

- Fatigue
  - Subjective experience
  - Common nonspecific symptom with a broad range of etiologies
  - Acute, subacute or chronic
- Assessment of subacute and chronic fatigue
  - Comprehensive history
  - Physical examination
  - Basic laboratory studies
  - Updated cancer screening interventions
- Open research question: pathophysiology of fatigue



Thank you for your attention!

*Questions?*

# References

- Gelfand and Douglas, "Fatigue", Harrison's principles of internal medicine, 19th edition, 2018.
- Klimas *et al.*, "Biomarkers of chronic fatigue", *Brain, Behavior and Immunity*, 2012.
- Kung, Nguyen and Das, *Absolute Case-Based Neurology Review*, Springer, 2019.
- Manjaly *et al.*, "Pathophysiological and cognitive mechanisms of fatigue in multiple sclerosis", *Journal of Neurology, Neurosurgery and Psychiatry*, 2019.
- Petzschner *et al.*, "Computational Psychosomatics and Computational Psychiatry: Toward a Joint Framework for Differential Diagnosis", *Biological Psychiatry*, 2017.
- Stephan *et al.*, "Allostatic Self-efficacy: A Metacognitive Theory of Dyshomeostasis-Induced Fatigue and Depression", *Frontiers in Human Neuroscience*, 2016.
- <https://www.uptodate.com/contents/approach-to-the-adult-patient-with-fatigue>
- <https://www.uptodate.com/contents/indications-for-switching-or-stopping-disease-modifying-therapy-for-multiple-sclerosis>
- <https://www.uptodate.com/contents/manifestations-of-multiple-sclerosis-in-adults>
- <https://www.uptodate.com/contents/symptom-management-of-multiple-sclerosis-in-adults>
- ACC and cingulate cortex image: Schünke *et al.*, *Prometheus LernAtlas der Anatomie – Kopf, Hals und Neuroanatomie*, 4th edition, Thieme, 2015 (p. 498)

# Acknowledgements

- Many thanks to my TNU colleagues for all their input!
- Figures made with Biorender.com