University of Zurich[UZH]

ETH

Eidgenössische Technische Hochschule Zürich
Swiss Federal Institute of Technology Zurich

Translational Neuromodeling Unit

Fatigue

Inês Pereira

CPC Zurich 2024

Fatigue

Clinical case

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

Femme assise, 1902-03

Definition?

Common problem?

Fatigue

Treatment?

Causes?

Pathophysiology of fatigue

Definition(s)

Is there one specific biomarker?

No.

A pathognomonic clinical sign, then?

No.

Based on the person's subjective account?

Yes, but...

Somnolence, sleepiness

Difficulty concentrating

What do you mean by fatigue?

Muscle weakness

Exhaustion

"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.

≠

Fatigability

objective changes in performance in a cognitive or motor task

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*

A taxonomy of fatigue

- Fatigue
  - Subjective
  - Physical and cognitive
- Fatigability
  - Objective
  - Physical and cognitive

Kluger *et al.*, *Neurology*, 2013

Slide by Zina-Mary Manjaly

Epidemiology

Epidemiology

- General population 🇺🇸:
  - 6.7% point prevalence
  - 25% lifetime prevalence
- Primary care setting 🇪🇺🇺🇸:
  - 21-33% of patients described fatigue as an important problem
  - 10-25% of patients reported 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

[…]

Causes of fatigue

Types of fatigue

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

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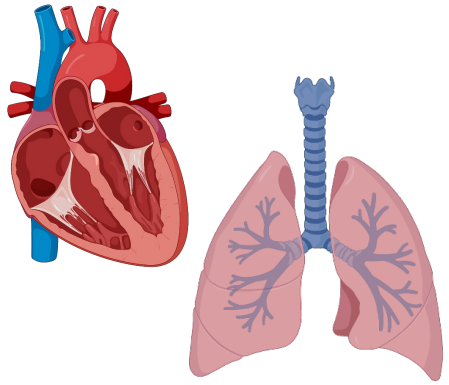
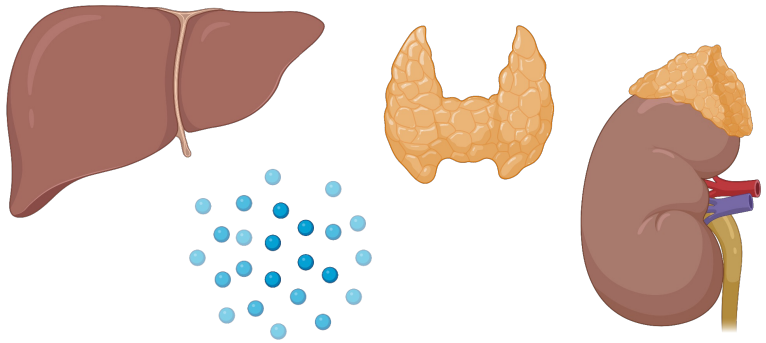
Fatigue

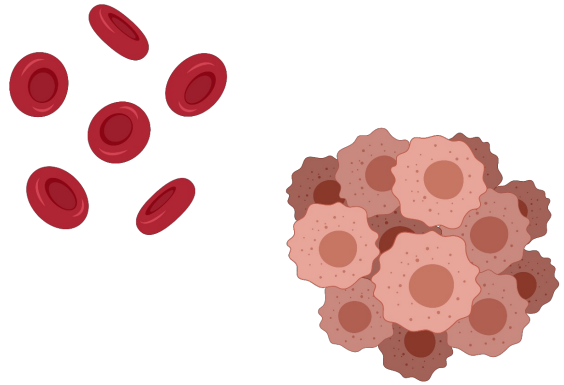
Fatigue



Cardiopulmonary

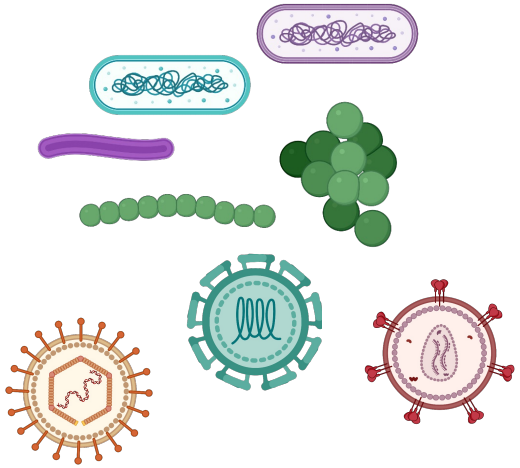


Endocrinologic/metabolic



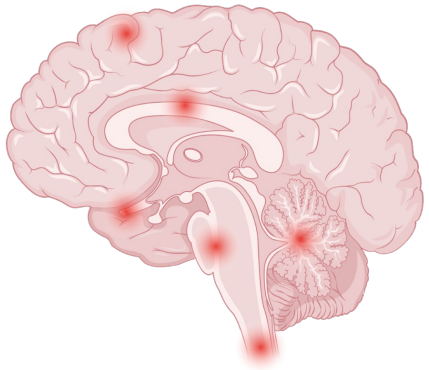
Hematologic/neoplastic

Substance use



Infectious

Medication



Neurologic

Psychiatric

Rheumatologic

Approach to the patient with fatigue

Approach to the patient with fatigue

- Medical history

Fatigue Severity Scale (FSS, English version)*

	strongly disagree 1	2	3	4	5	6	*strongly agree* 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]

Reproduced from Valko *et al.*, *Sleep*, 2008

Limitations of questionnaires

- «Snapshots»
- They do not always distinguish between physical and cognitive fatigue
- Difficult distinction between fatigue and fatigability
- No insight into the causes of fatigue

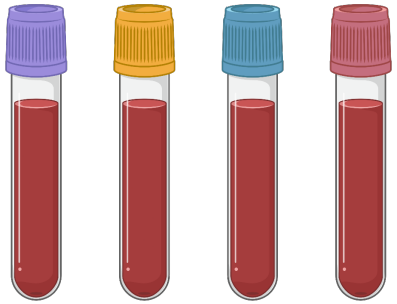
Slide by Zina-Mary Manjaly

Approach to the patient with fatigue

- Medical history

- Physical examination

- Laboratory and radiological studies



Management

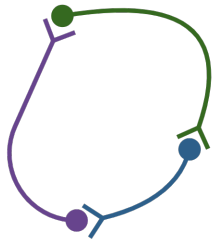
Management

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

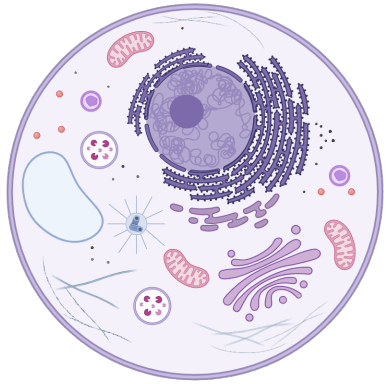
Pathophysiology of fatigue

?

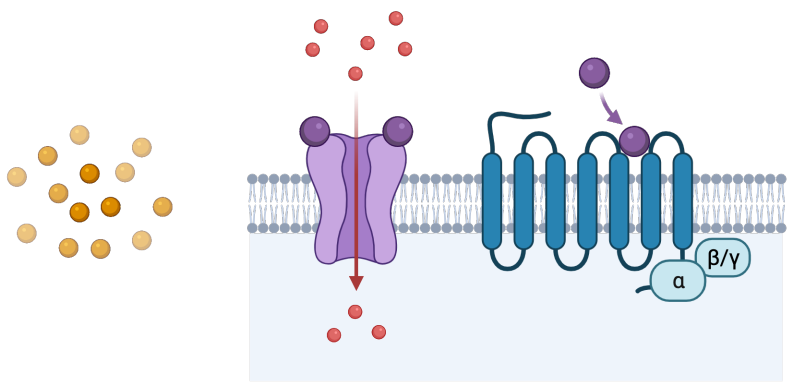
Circuit level



Cellular level



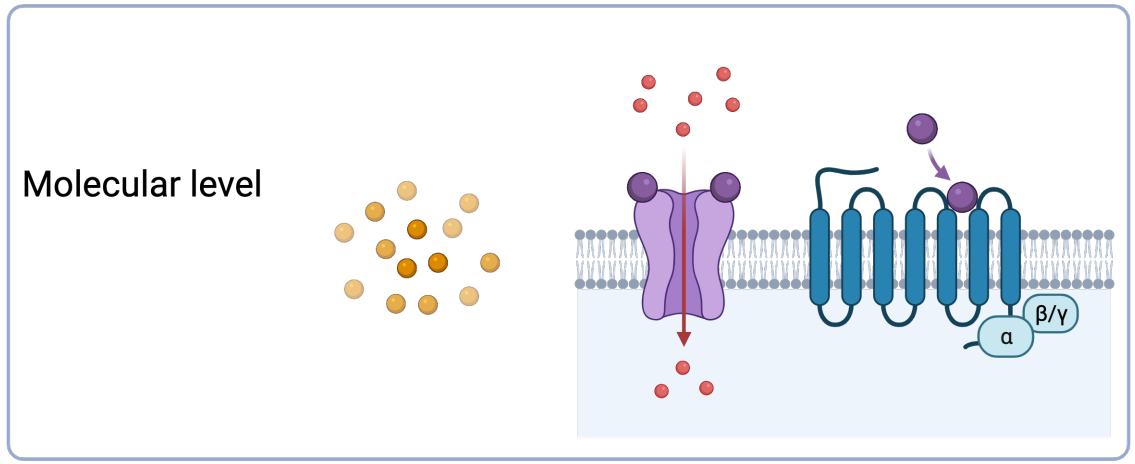
Molecular level



IL-1

CRP

INF-α

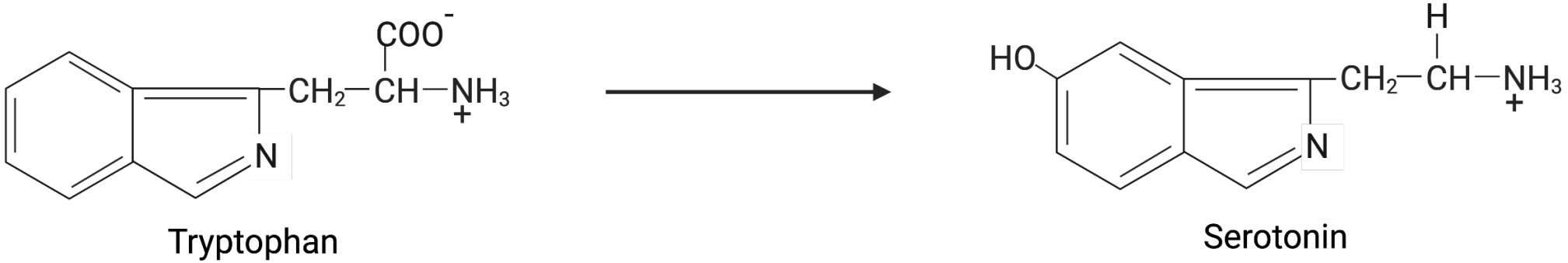


IL-6

INF-γ

TNF-α

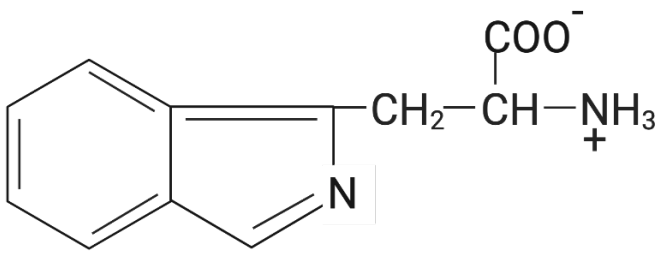
Klimas *et al.*, *Brain, Behavior, and Immunity*, 2012



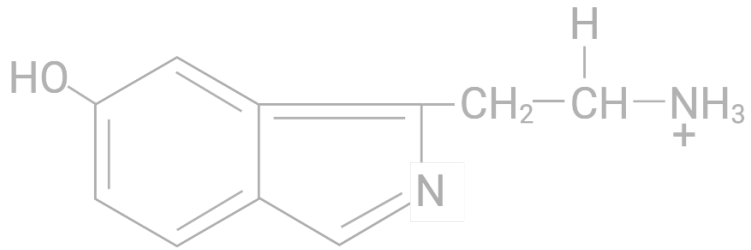
Tryptophan

Serotonin

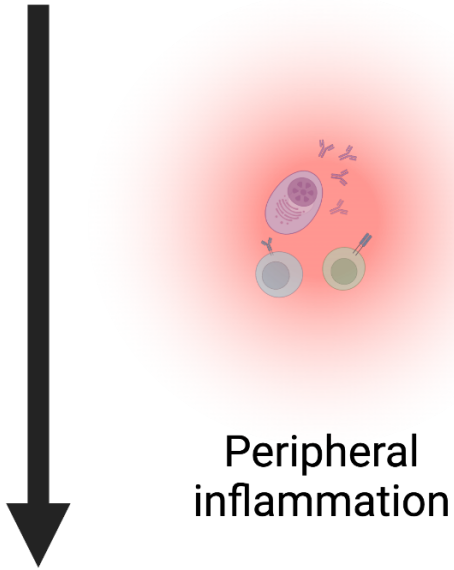
Castanon *et al.*, *Frontiers in Neuroscience*, 2015



Tryptophan



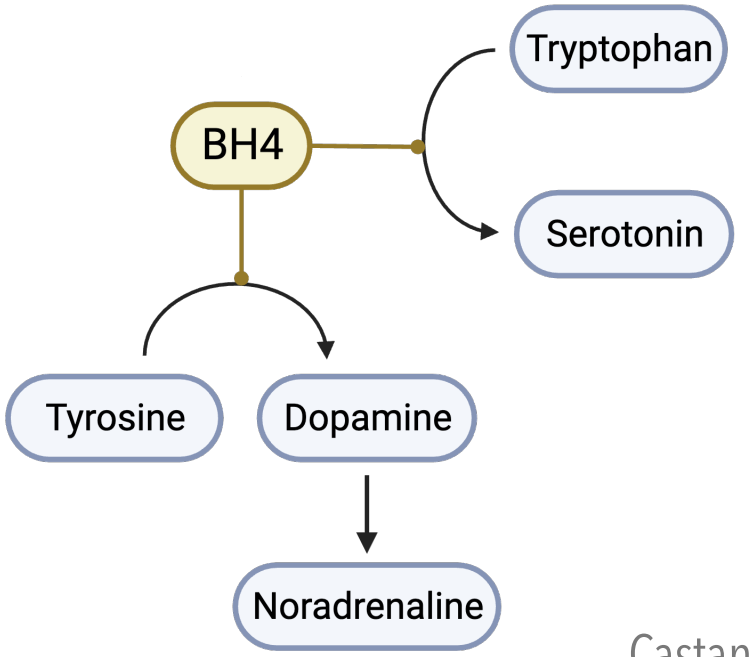
Serotonin



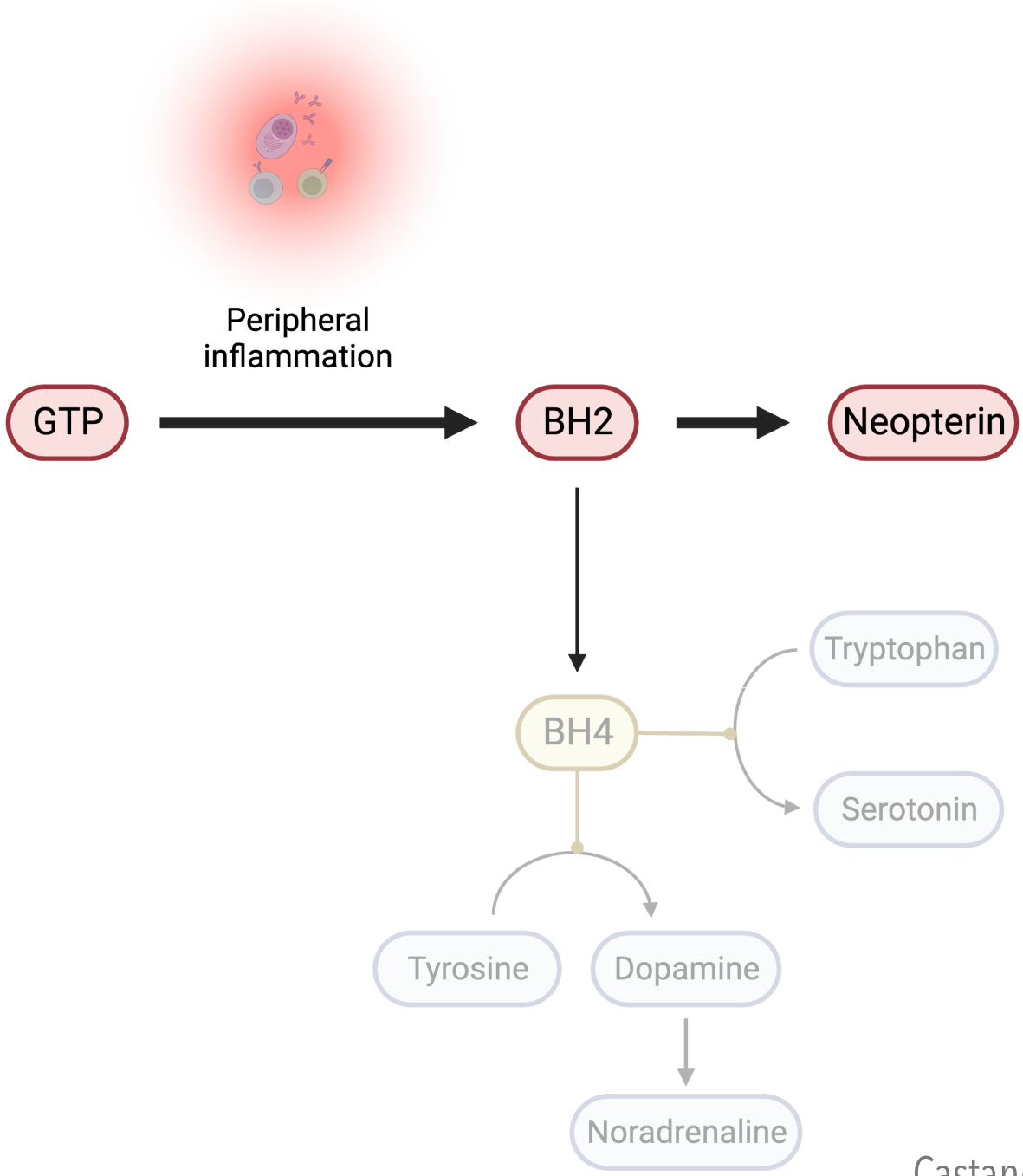
Peripheral inflammation

Kynurenine Pathway

Castanon *et al.*, *Frontiers in Neuroscience*, 2015



Castanon *et al.*, *Frontiers in Neuroscience*, 2015



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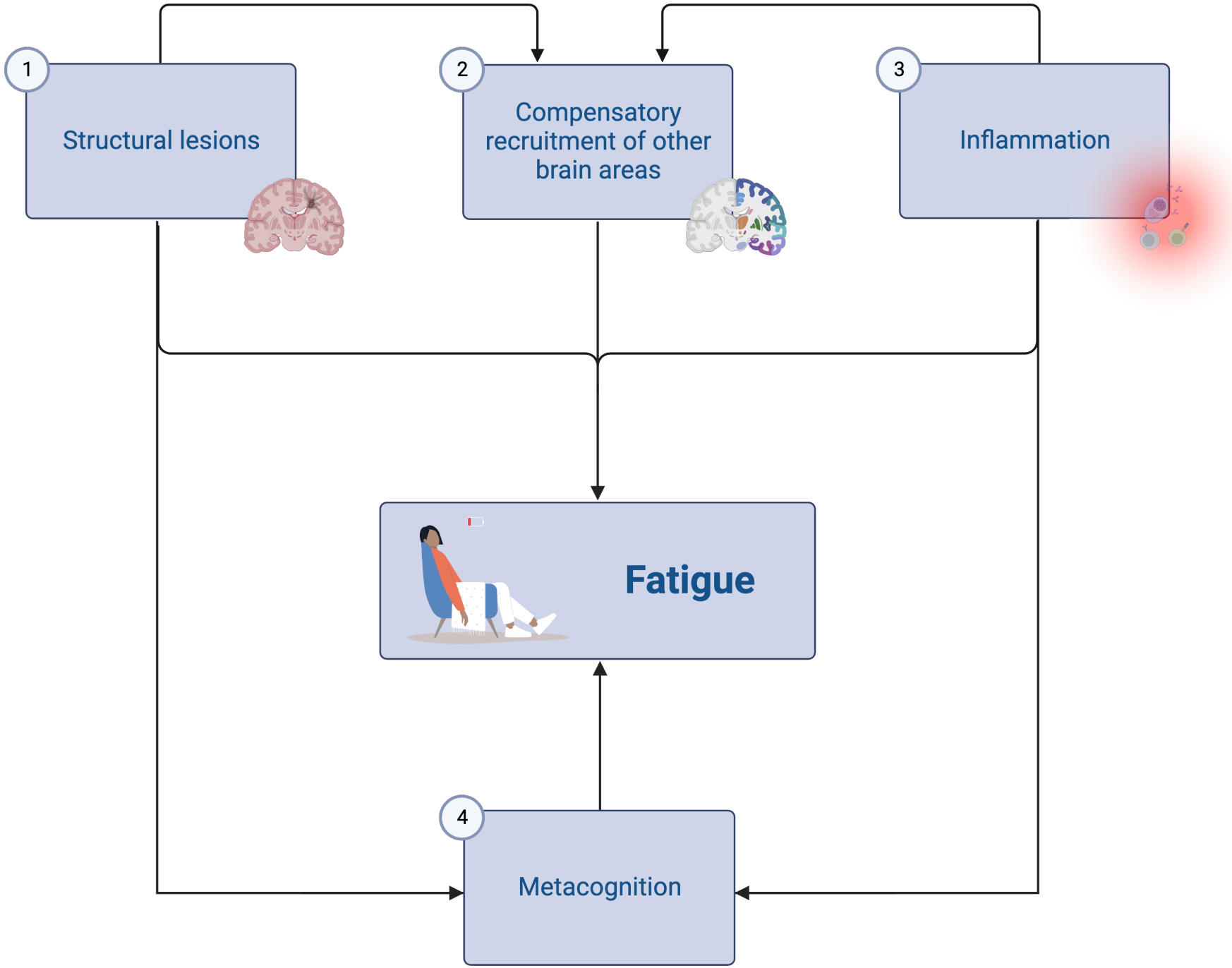
1
Structural lesions
2
Compensatory recruitment of other brain areas
3
Inflammation
Fatigue
4
Metacognition

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

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

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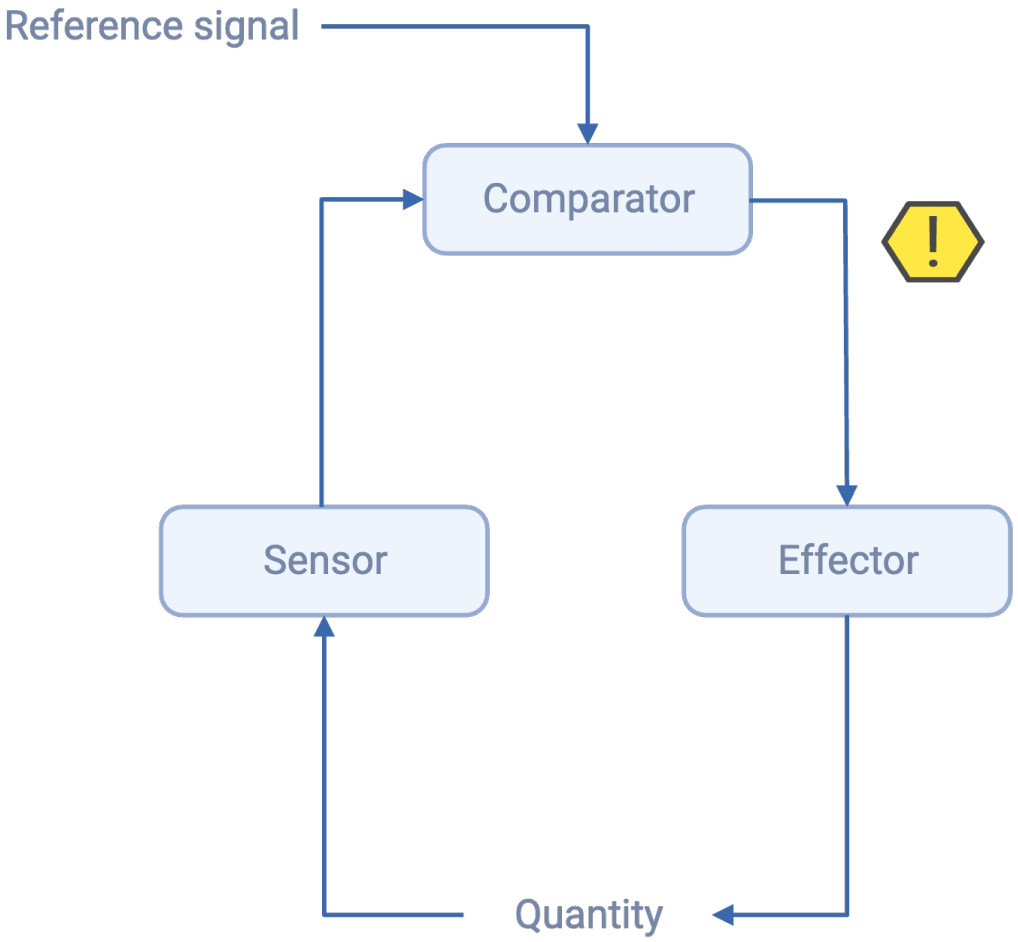
Homeostasis

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

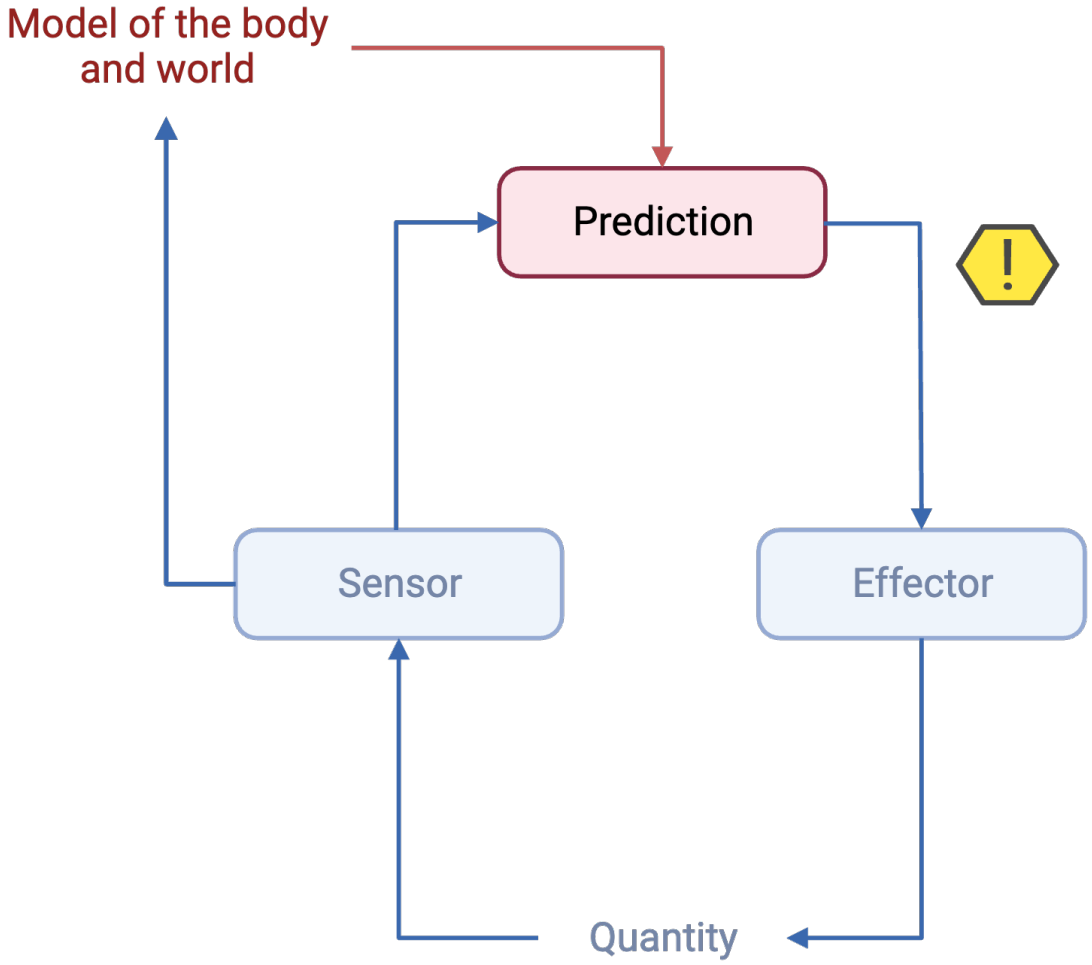
Walter Cannon, 1929

Homeostasis

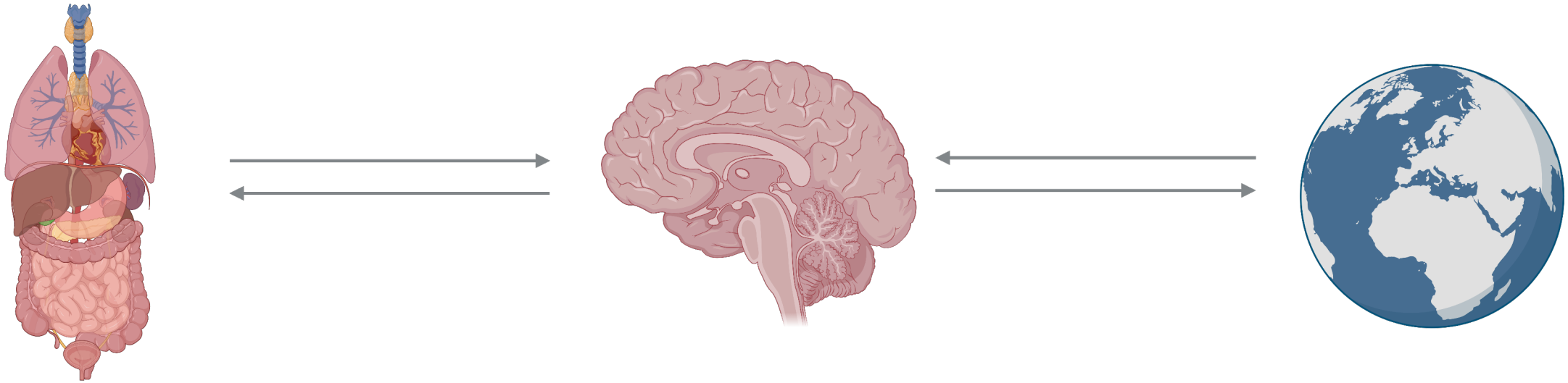


Based on figure from: Powers, *Science*, 1973

Allostasis



Based on figure from: Sterling, *Physiol. Behav.*, 2012



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likelihood prior

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

posterior

likelihood prior

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

posterior

likelihood prior

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

posterior

model evidence

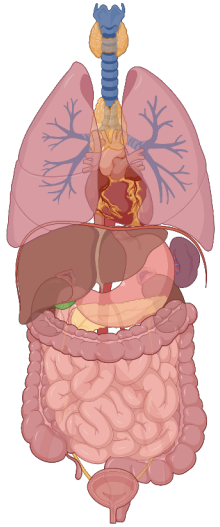
likelihood prior

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

posterior

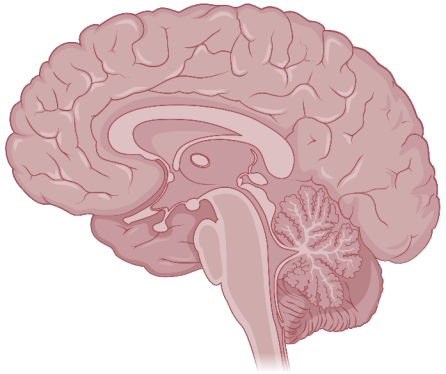
model evidence

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



$p(x|y,m)$

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



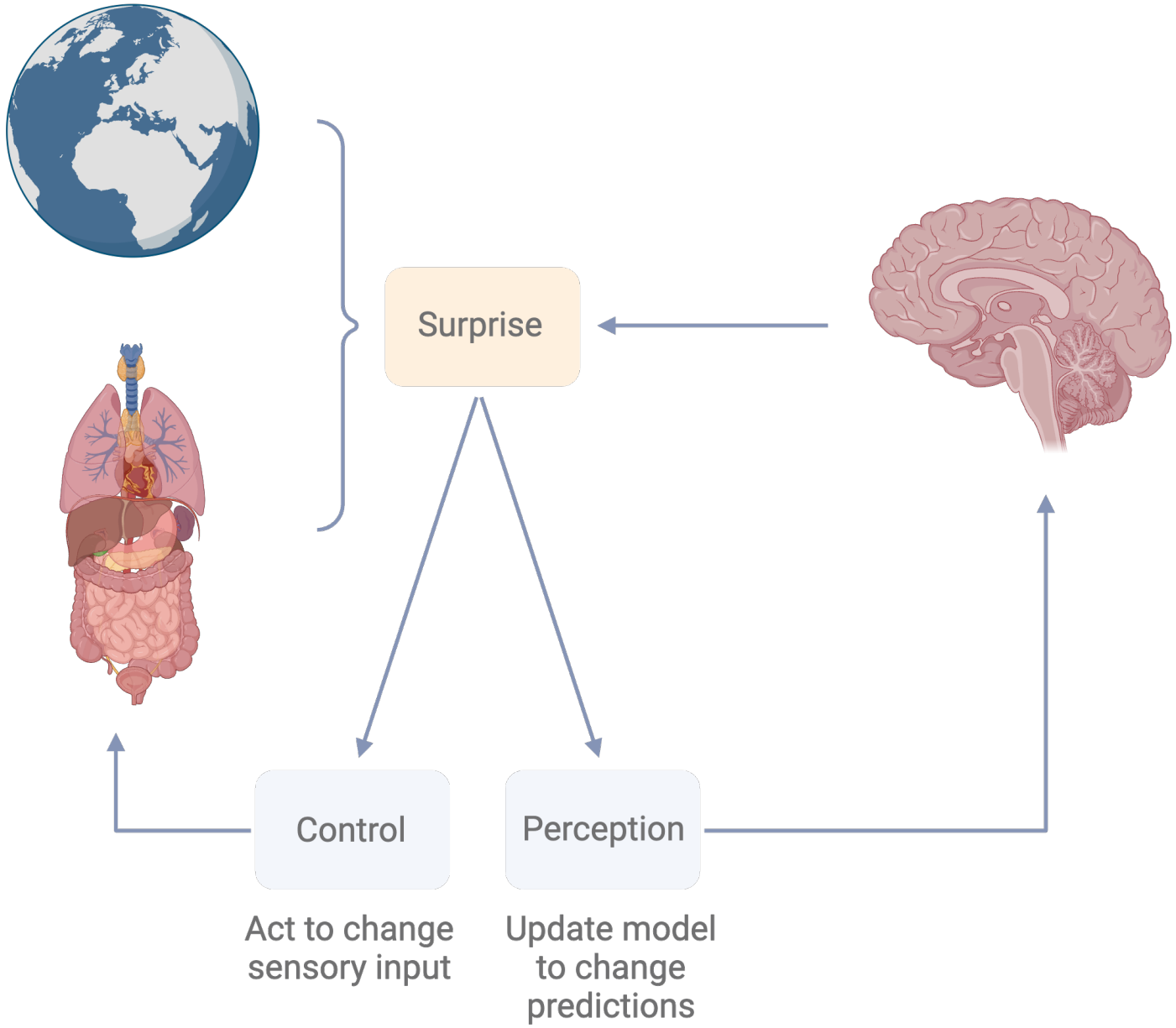
$p(x|y,m)$

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

Interoceptive surprise

Exteroceptive surprise

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



Based on slide from Prof. Klaas Enno Stephan

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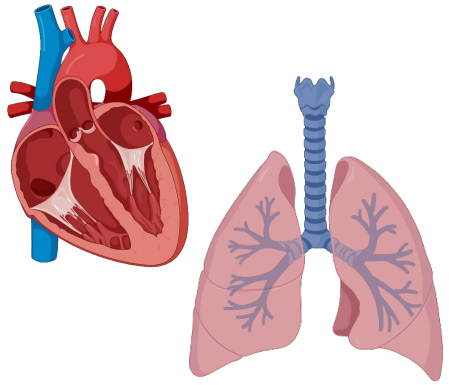
Self-efficacy

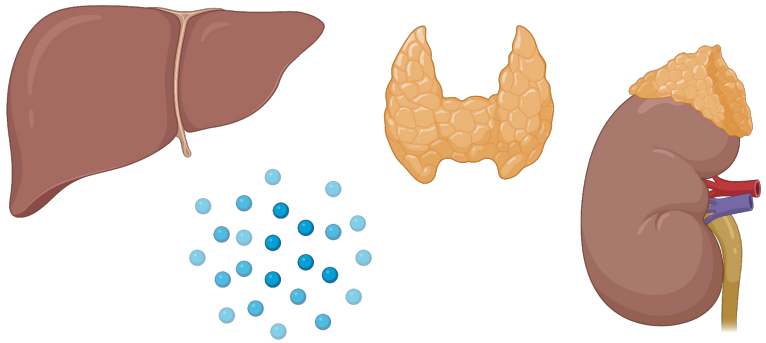
An individual's expectation of personal mastery and control

Bandura, *Psychol. Rev.*, 1977

Fatigue



Cardiopulmonary



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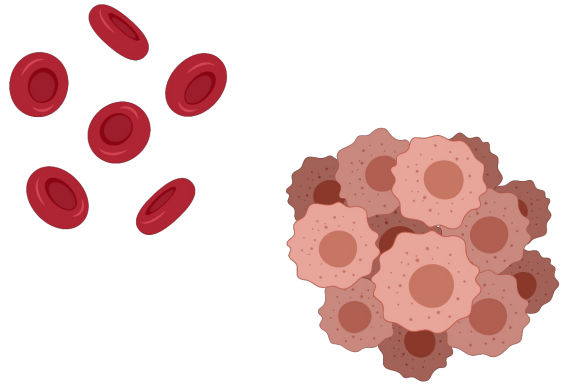
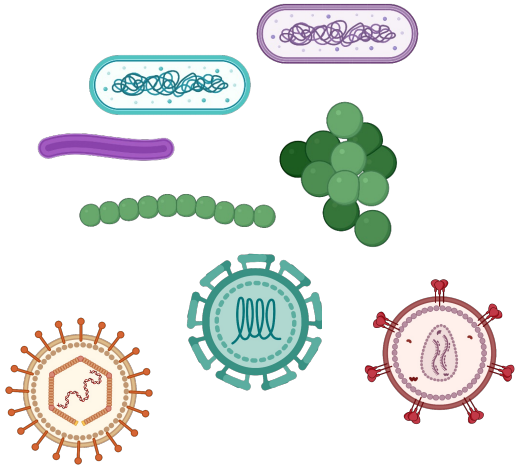


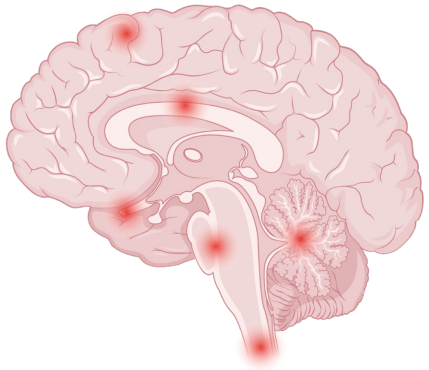
Hematologic/neoplastic

Substance use



Infectious

Medication



Neurologic

Psychiatric

Rheumatologic

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Dyshomeostasis

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

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

Key concepts

- Homeostasis
- Allostasis
- Generative models
- What is a good model?

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Metacognition

Petzschner *et al.*, *Biological Psychiatry,* 2017

Metacognition of control

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

Petzschner *et al.*, *Biological Psychiatry,* 2017

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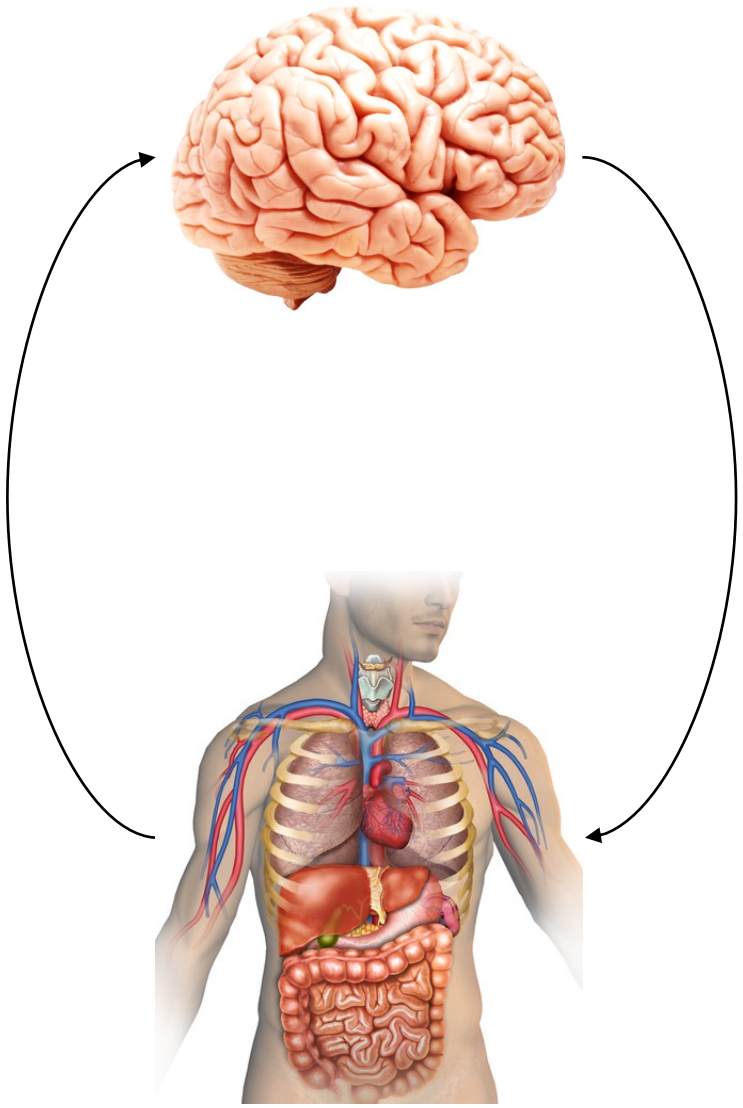
[1] Translational Neuromodeling Unit, Institute for Biomedical Engineering, University of Zurich and ETH Zurich, Zurich, Switzerland, [2] Wellcome Trust Centre for Neuroimaging, University College London, London, UK, [3] Max Planck Institute for Metabolism Research, Cologne, Germany, [4] Department of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



❶ BODY

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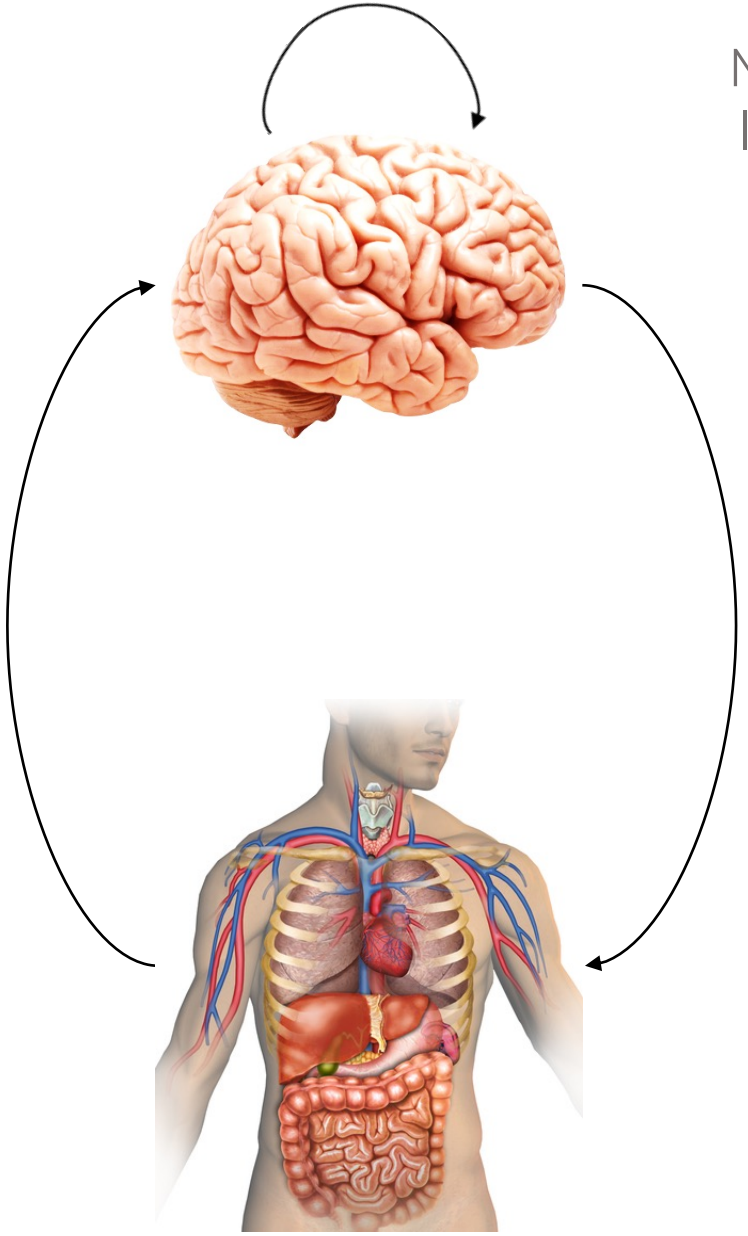

❶ BODY

Metacognitive diagnosis of low allostatic self-efficacy

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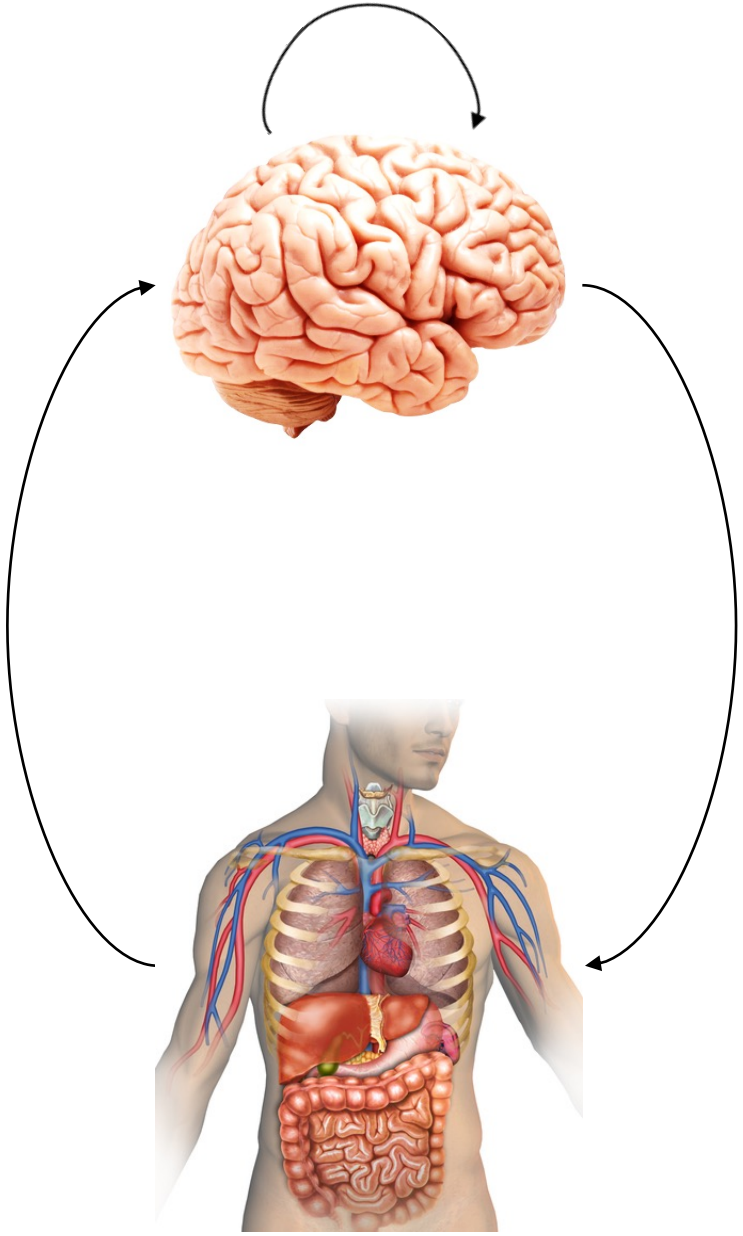

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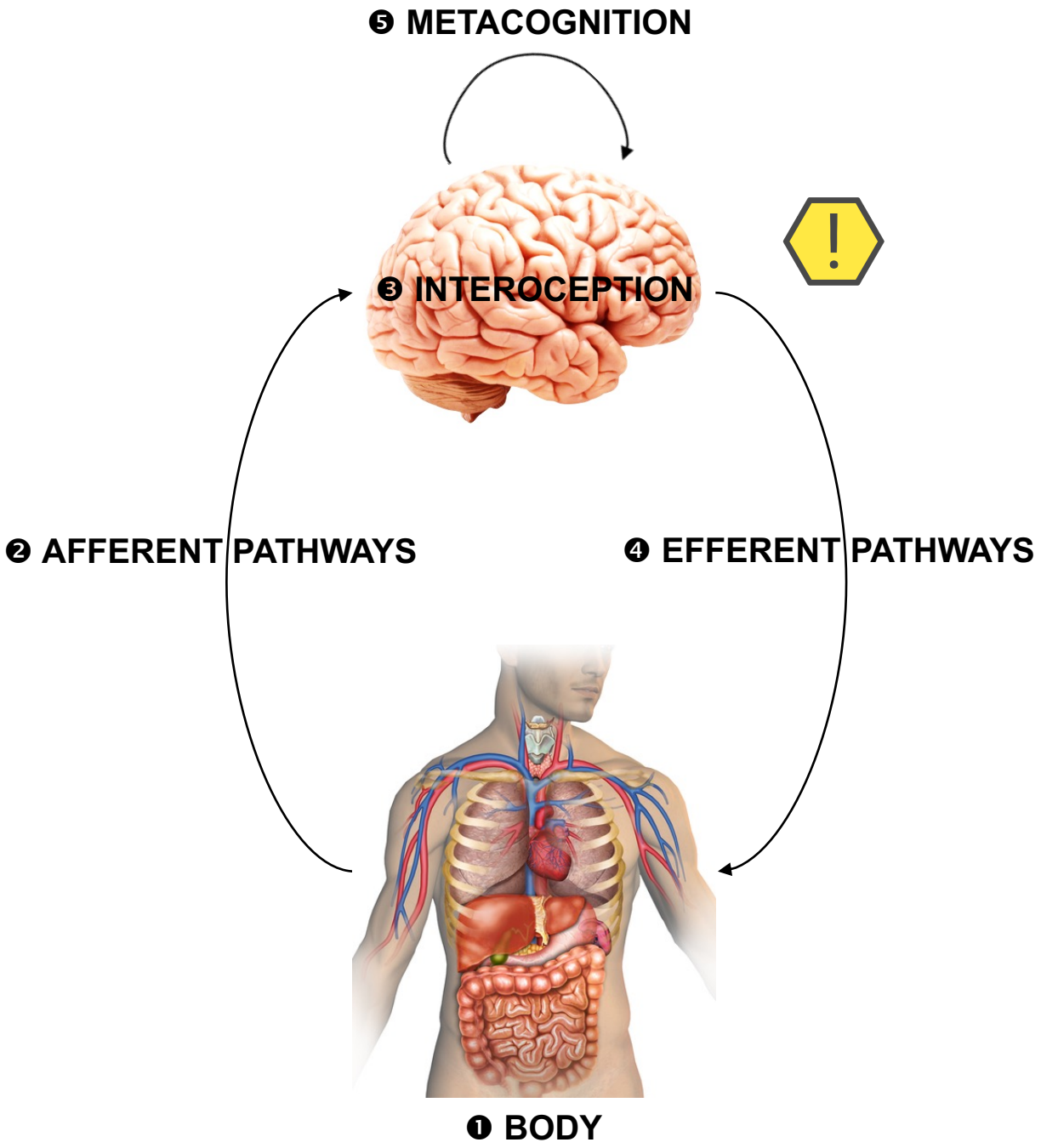
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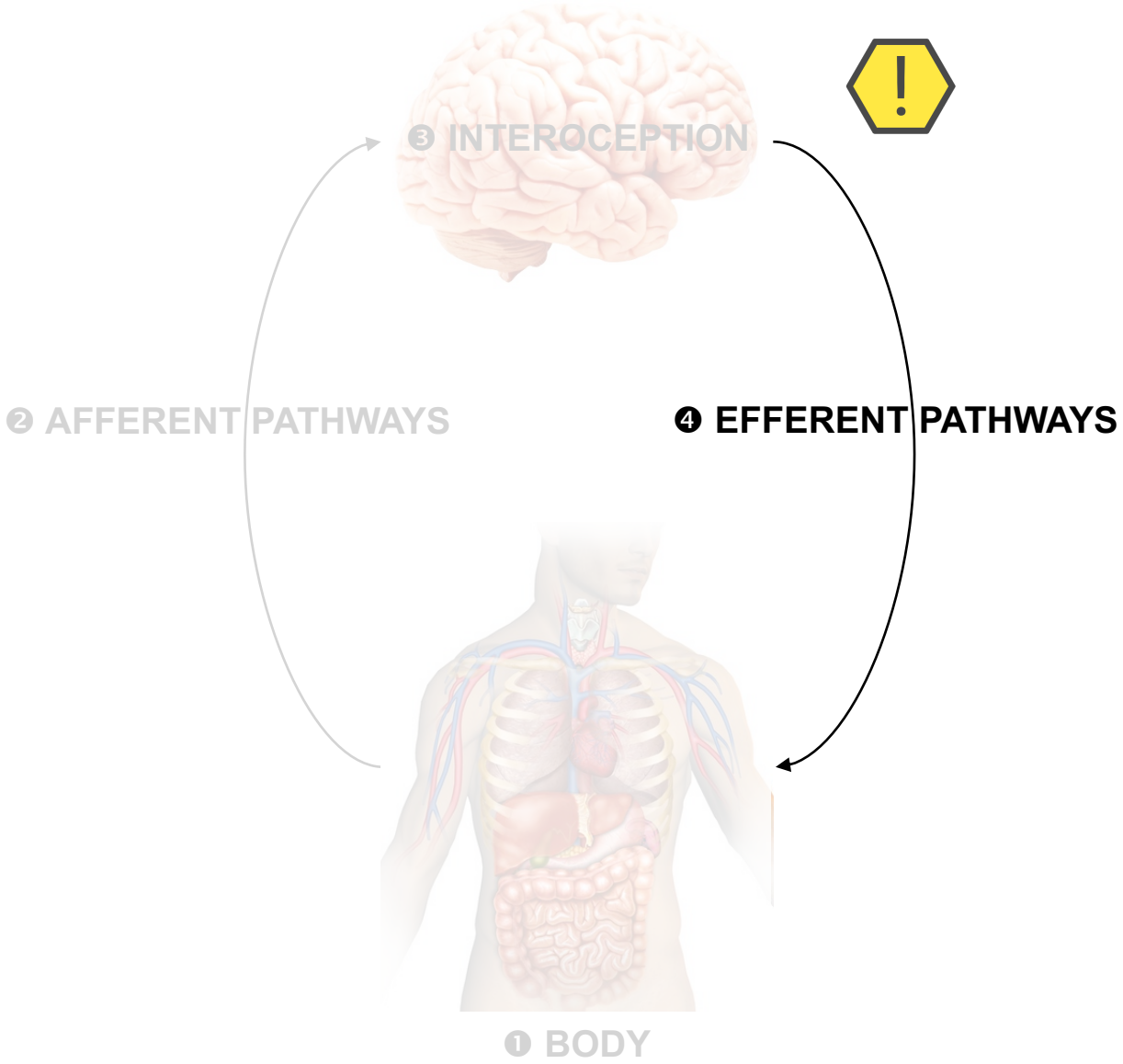
❸ INTEROCEPTION
❷ AFFERENT PATHWAYS
❹ EFFERENT PATHWAYS
❶ BODY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❷ AFFERENT PATHWAYS
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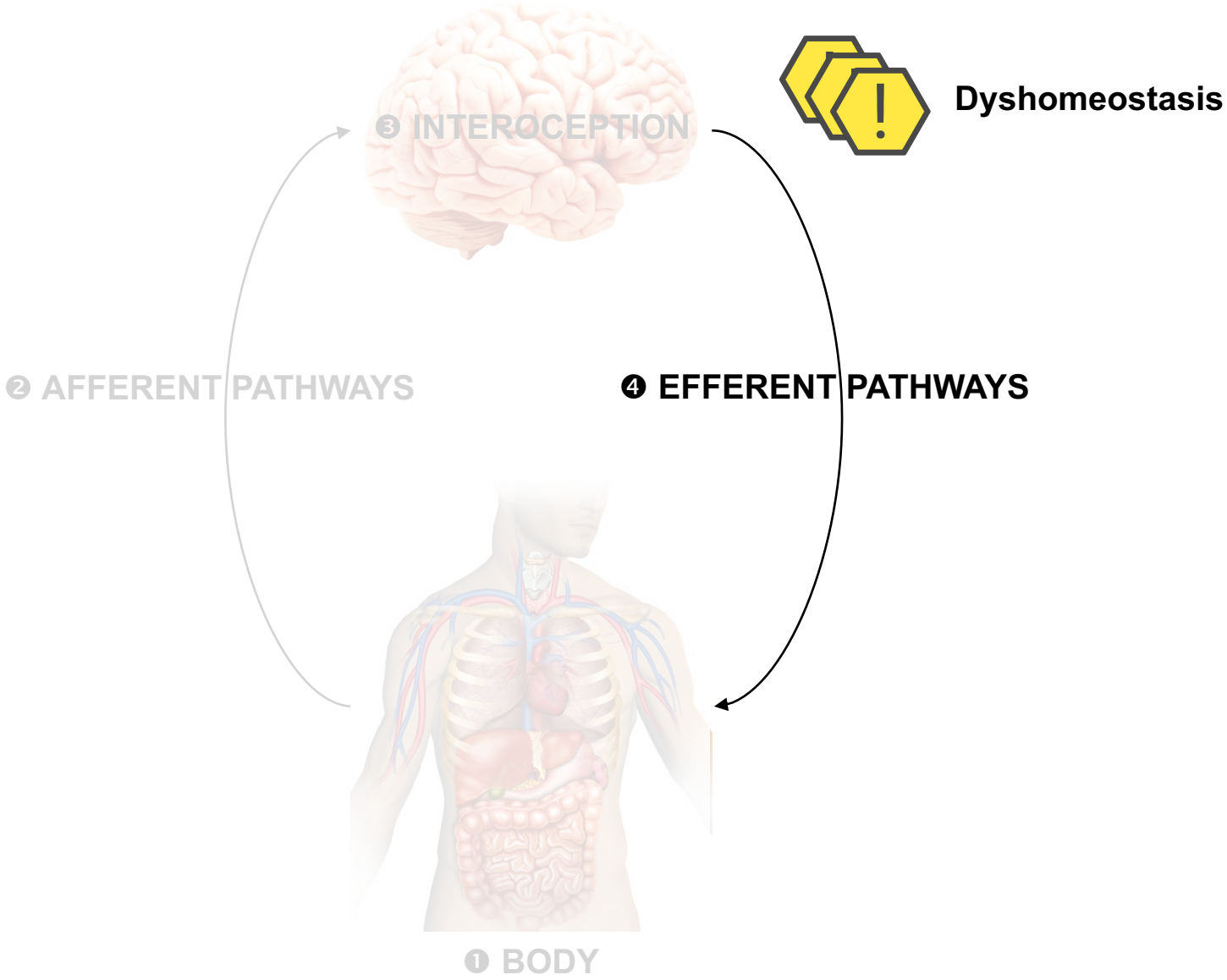
❶ BODY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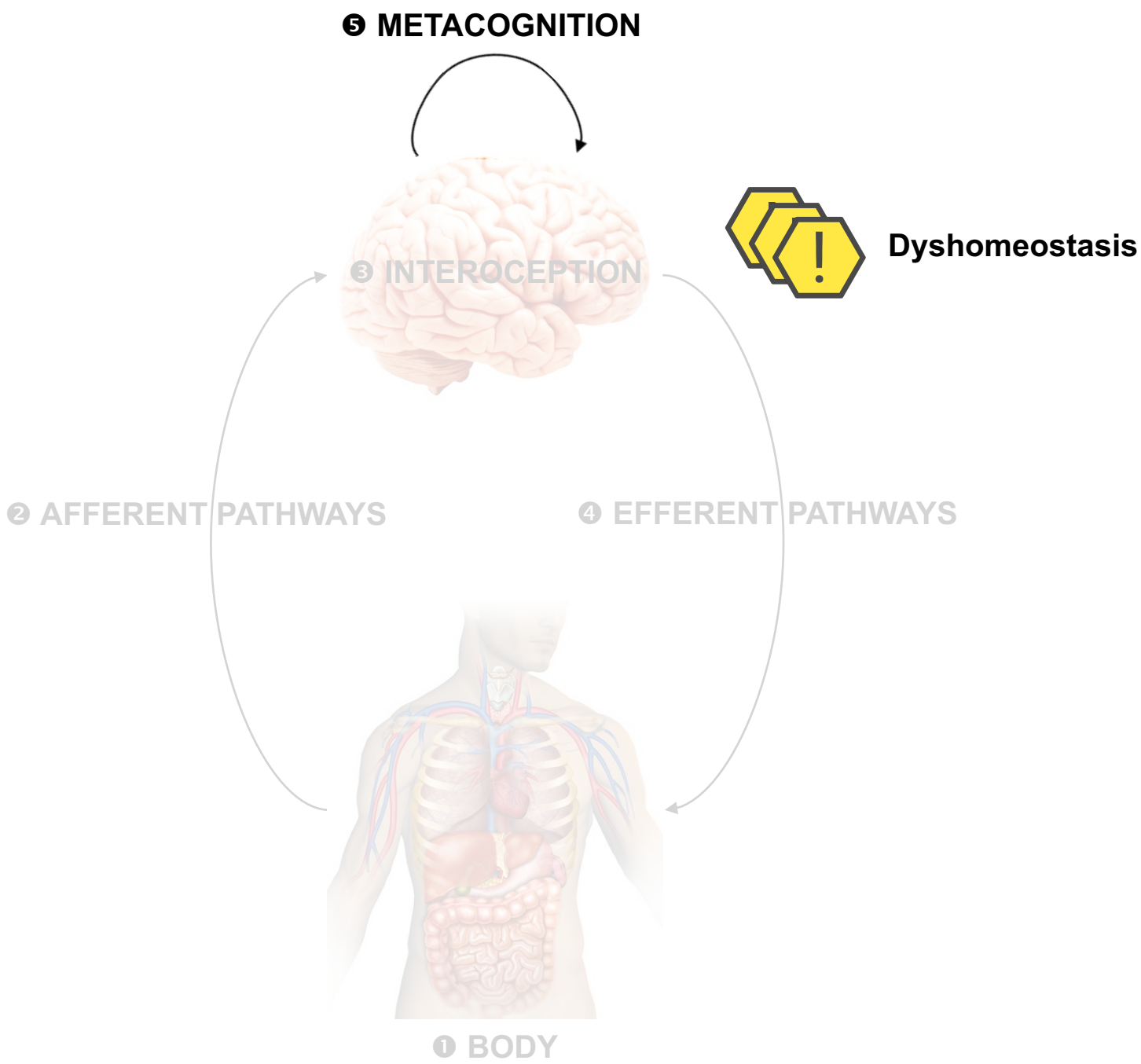
Dyshomeostasis
❷ AFFERENT PATHWAYS
❹ EFFERENT PATHWAYS
❶ BODY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❸ INTEROCEPTION
Dyshomeostasis
❷ AFFERENT PATHWAYS
❹ EFFERENT PATHWAYS
❶ BODY

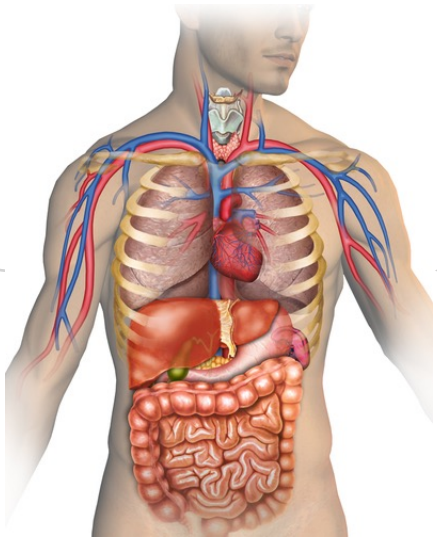
❺ METACOGNITION

❸ INTEROCEPTION

Dyshomeostasis

❷ AFFERENT PATHWAYS

❹ EFFERENT PATHWAYS



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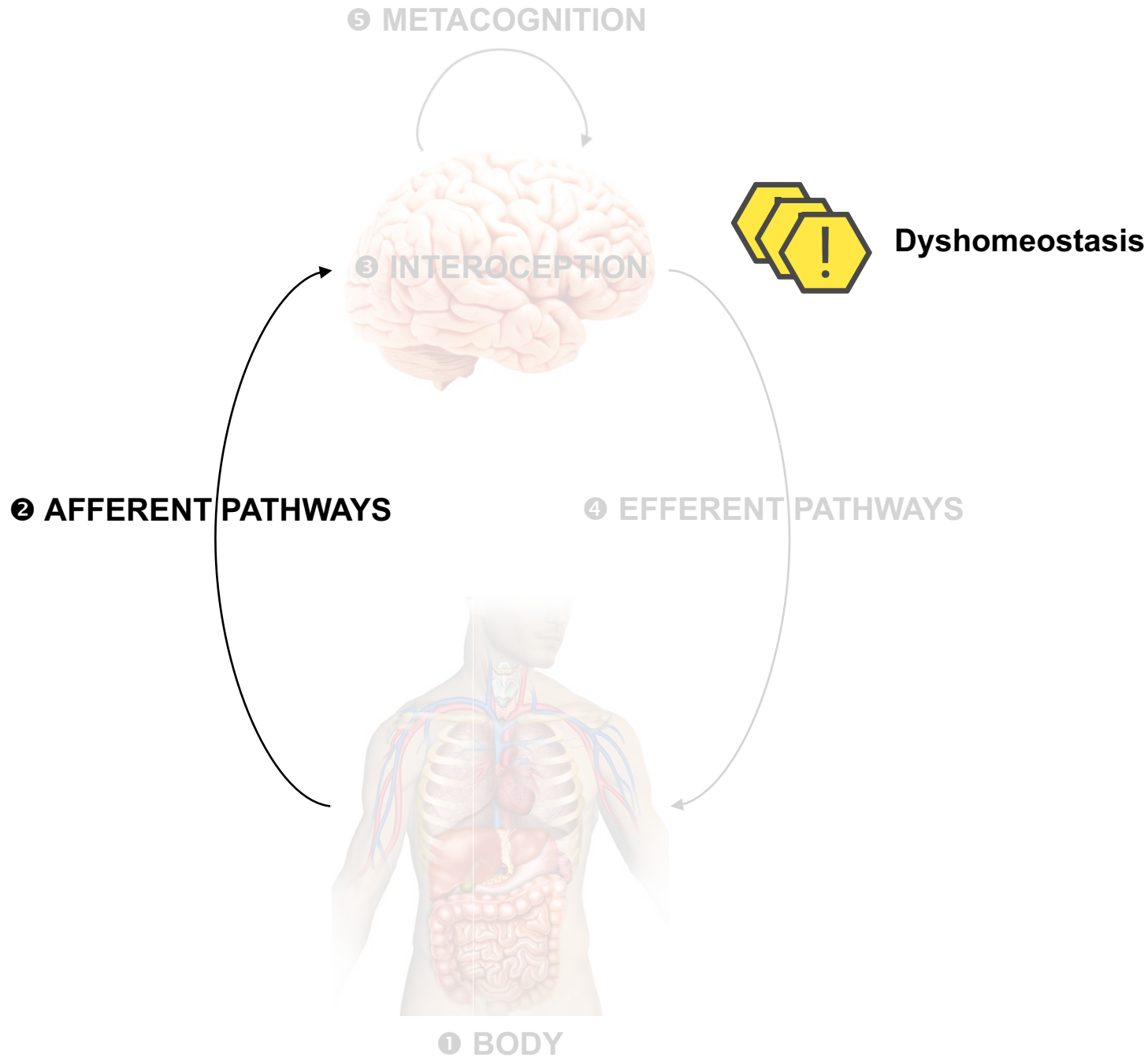
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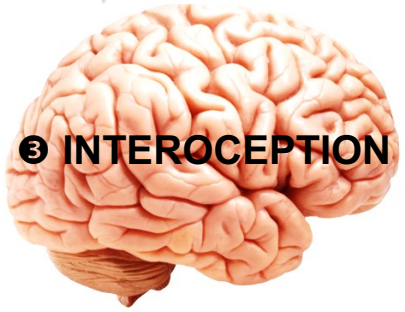
❸ INTEROCEPTION
Dyshomeostasis
❷ AFFERENT PATHWAYS
❹ EFFERENT PATHWAYS
❶ BODY

❺ METACOGNITION



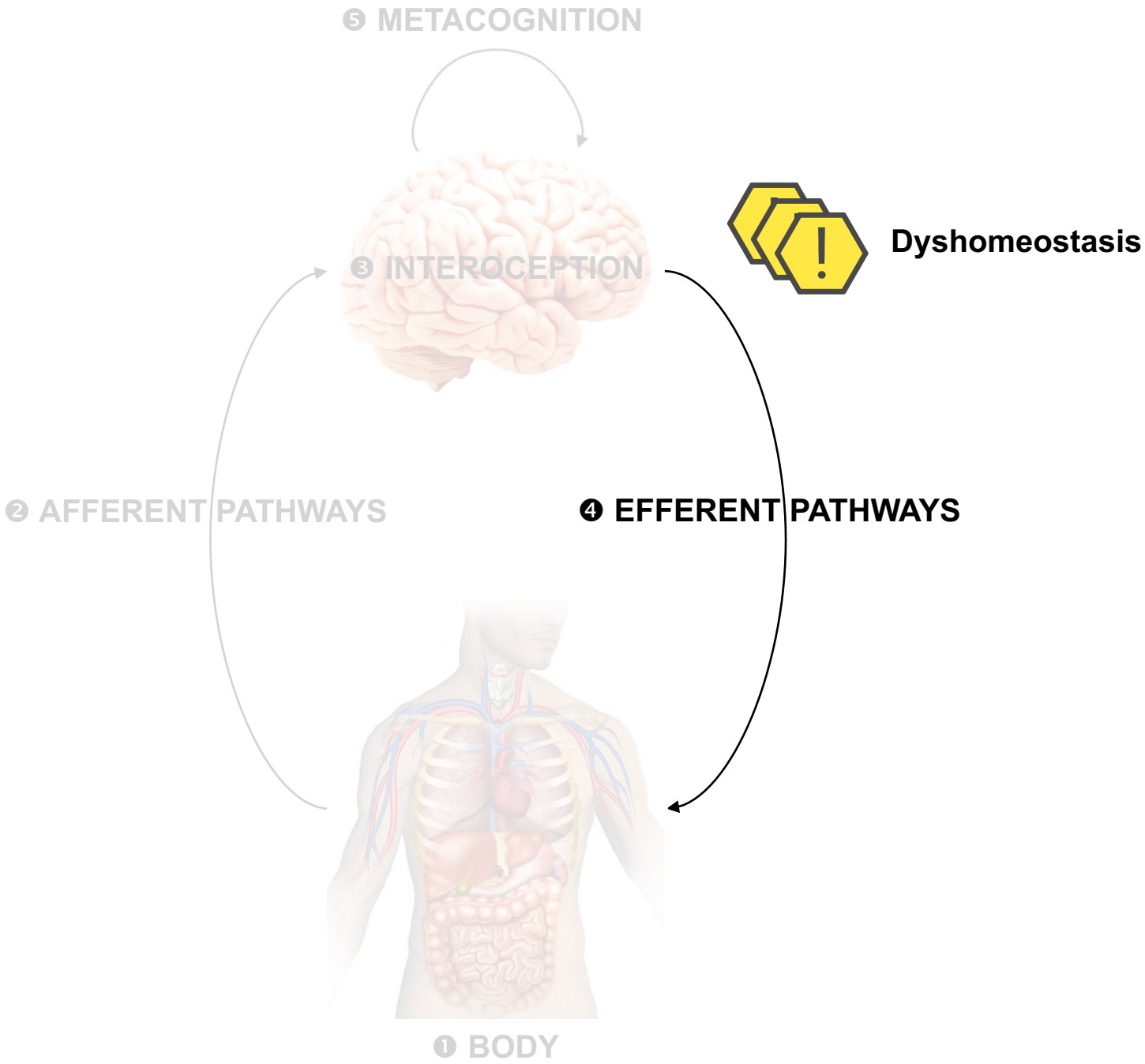
❸ INTEROCEPTION

Dyshomeostasis

❷ AFFERENT PATHWAYS

❹ EFFERENT PATHWAYS

❶ BODY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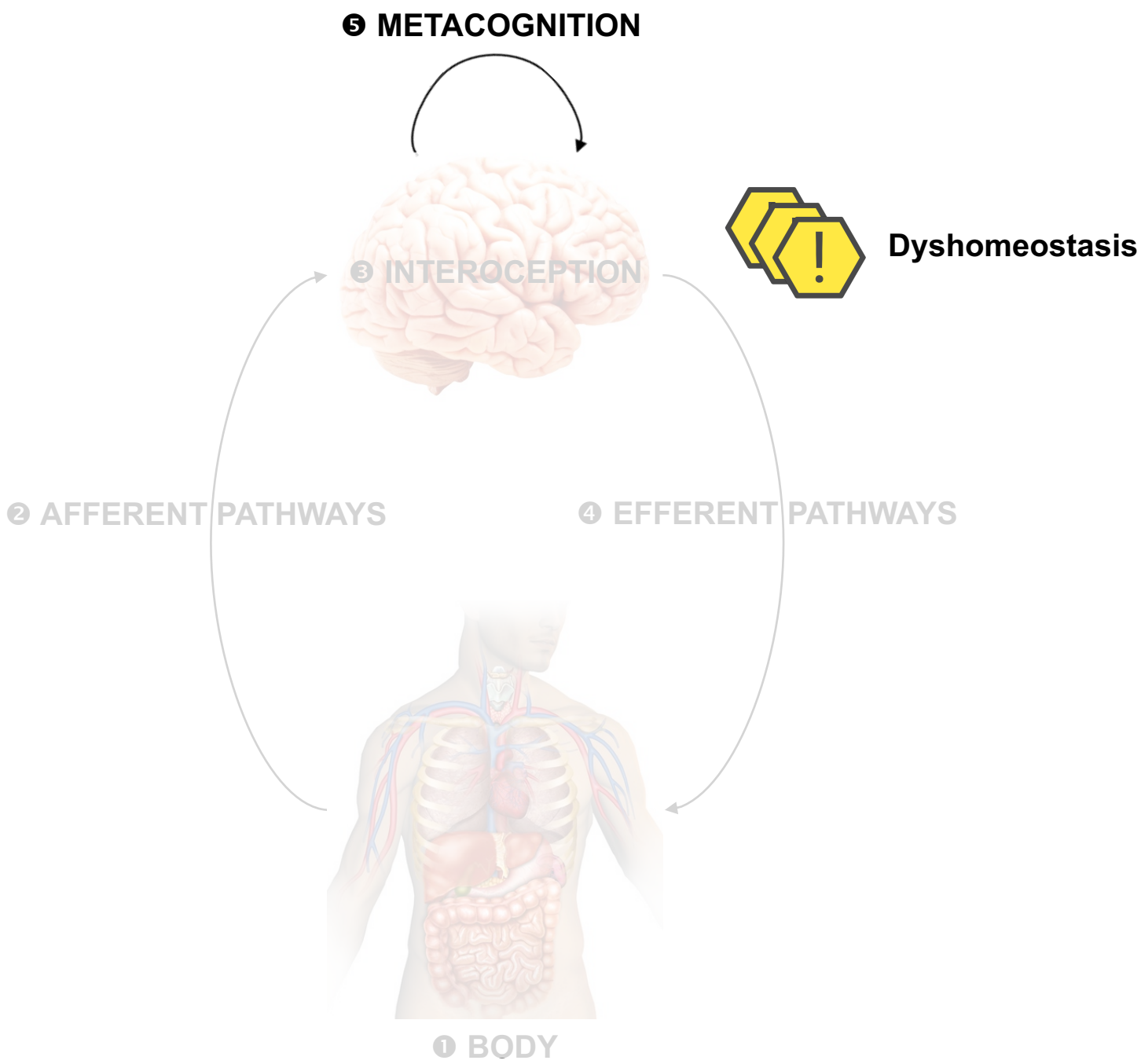
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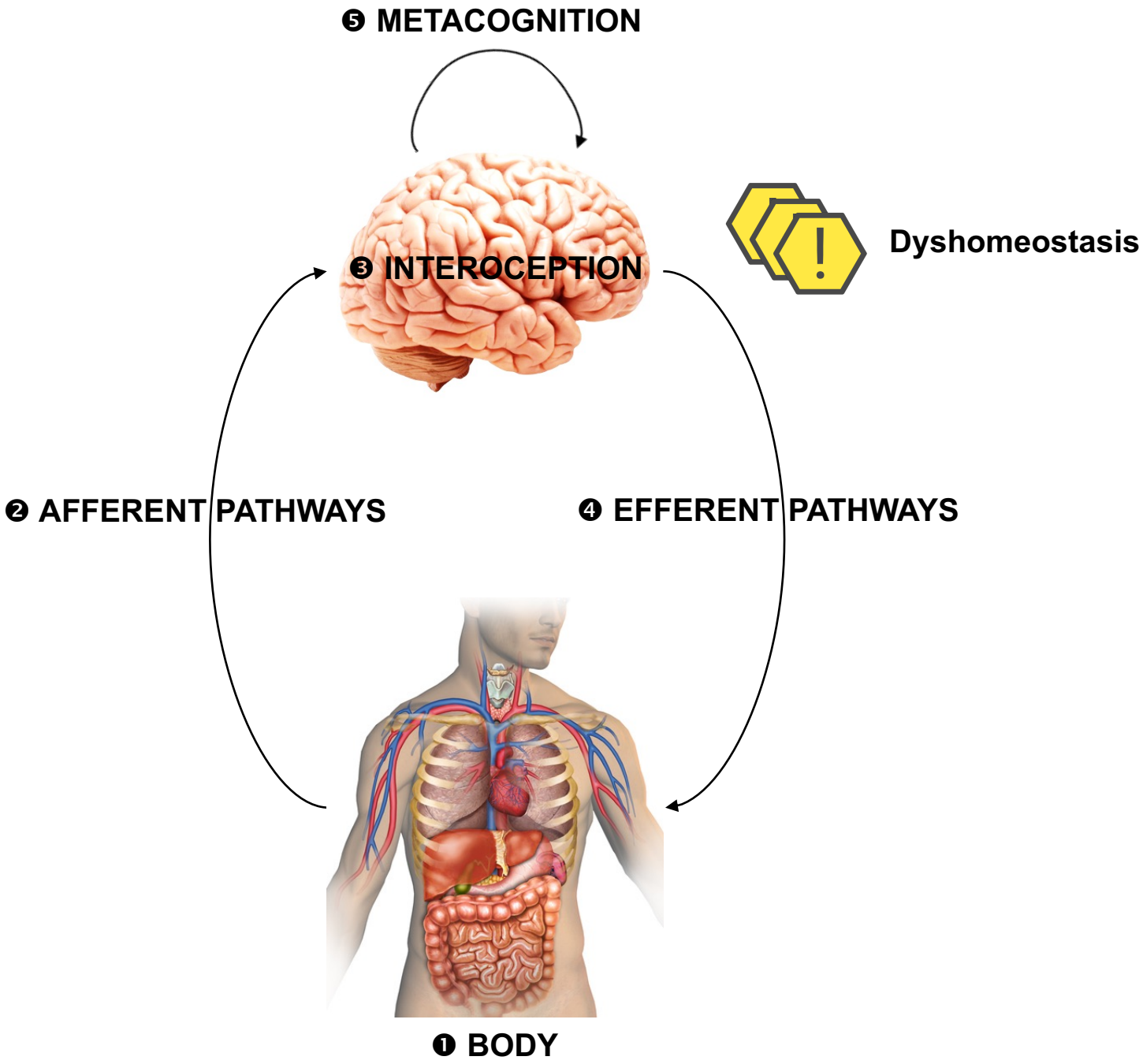
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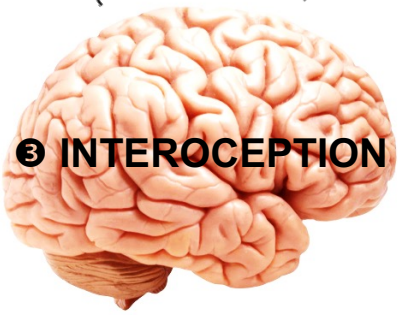
❺ METACOGNITION



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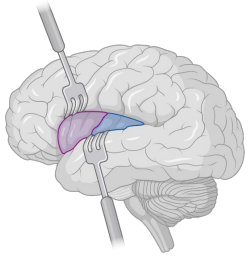
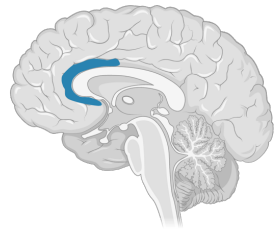
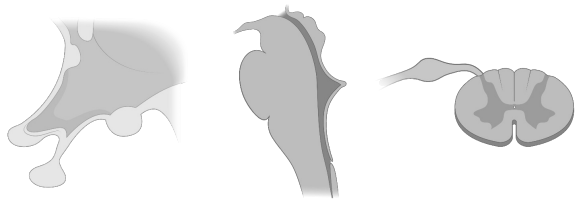
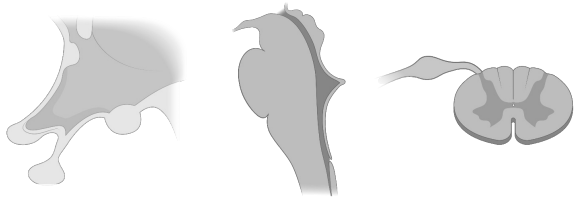


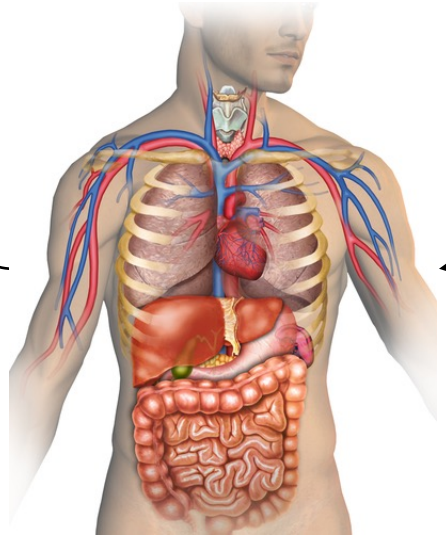


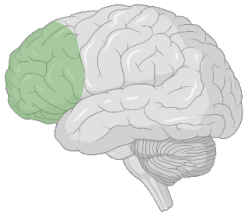


❷ AFFERENT PATHWAYS

❹ EFFERENT PATHWAYS

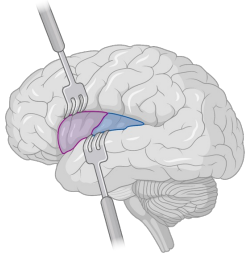


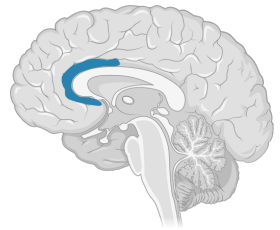


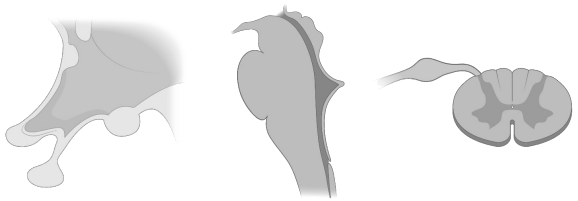


❺ METACOGNITION

❸ INTEROCEPTION







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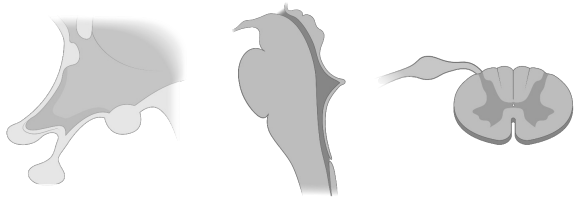
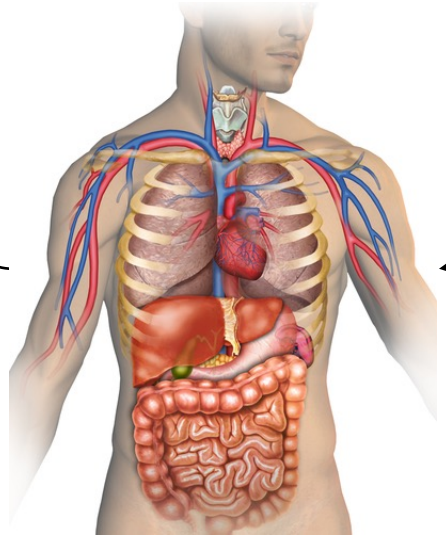
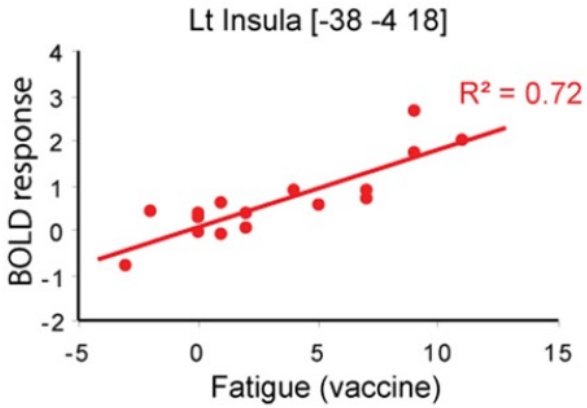


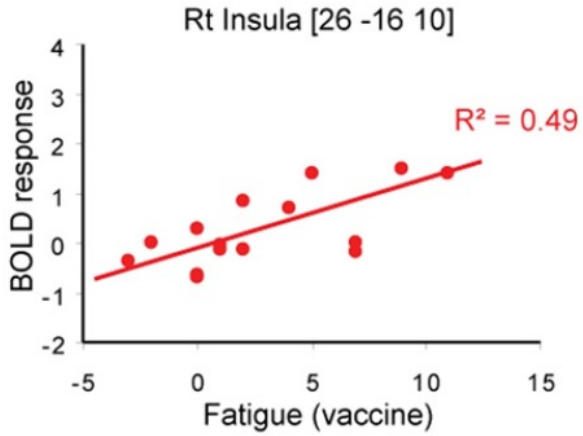


Empirical evidence?

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



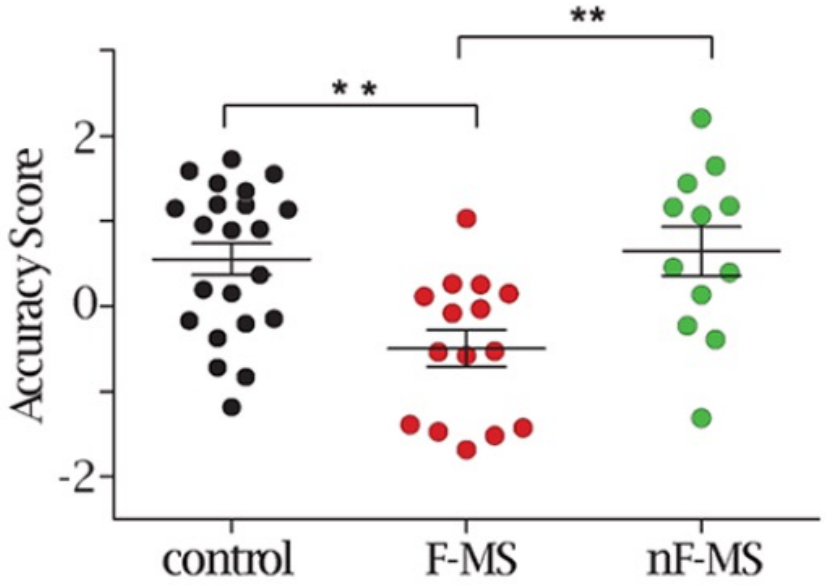


Harrison *et al., 2009*

Based on slide from Klaas Enno Stephan

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



Based on slide from Klaas Enno Stephan

Analysis plan

RESEARCH REPORT

EJN European Journal of Neuroscience FENS WILEY

Interoceptive and metacognitive facets of fatigue in multiple sclerosis

Marion Rouault[1,2] | Inês Pereira[3] | Herman Galioulline[3] | Stephen M. Fleming[4,5,6] | Klaas Enno Stephan[3,7] | Zina-Mary Manjaly[8,9]

Collected data

71 persons with multiple sclerosis

Questionnaires

- Fatigue (MFIS & FSS)
- Interoceptive awareness (MAIA)

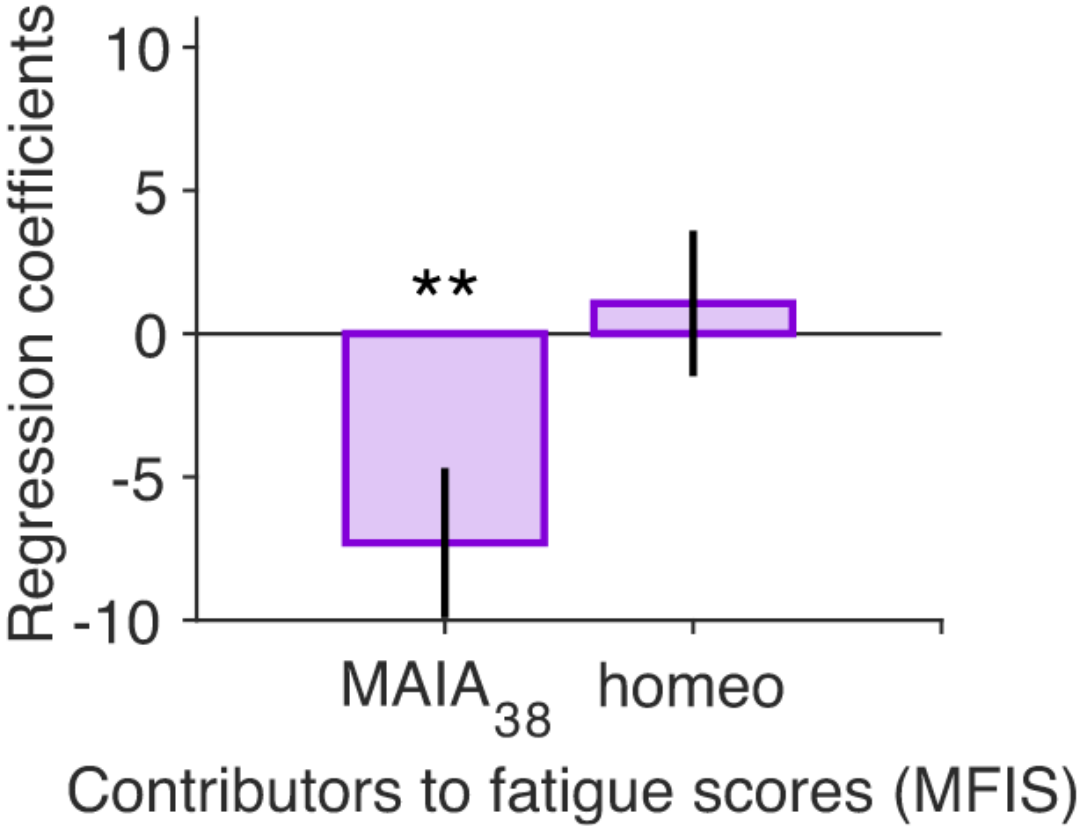
Physiological measurements

- Heart Rate Variability
- Orthostatic blood pressure and heart rate changes
- Sudomotor activity
- Body temperature

Metacognitive tasks

- Indices of metacognition based on quantitative modeling of choice and confidence behaviour

Results



Rouault *et al.*, *European Journal of Neuroscience, 2023*

Zina-Mary Manjaly

Réka Enz

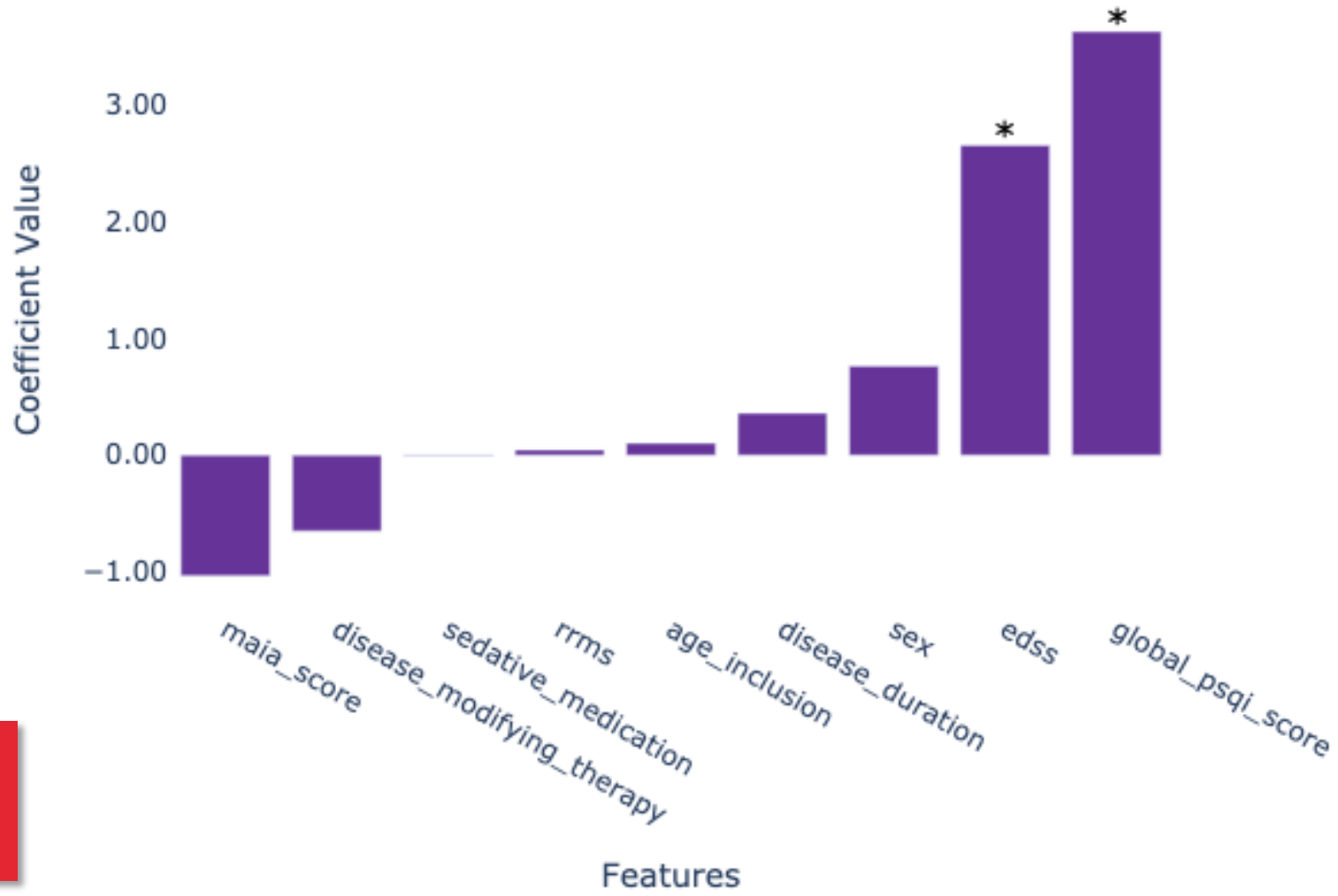
Delania Meng

Stefania Mare

Laura Köchli

Inês Pereira

COMPUTATIONAL PSYCHIATRY COURSE ZURICH 2024
10TH ANNIVERSARY EDITION
#16



Analysis plan

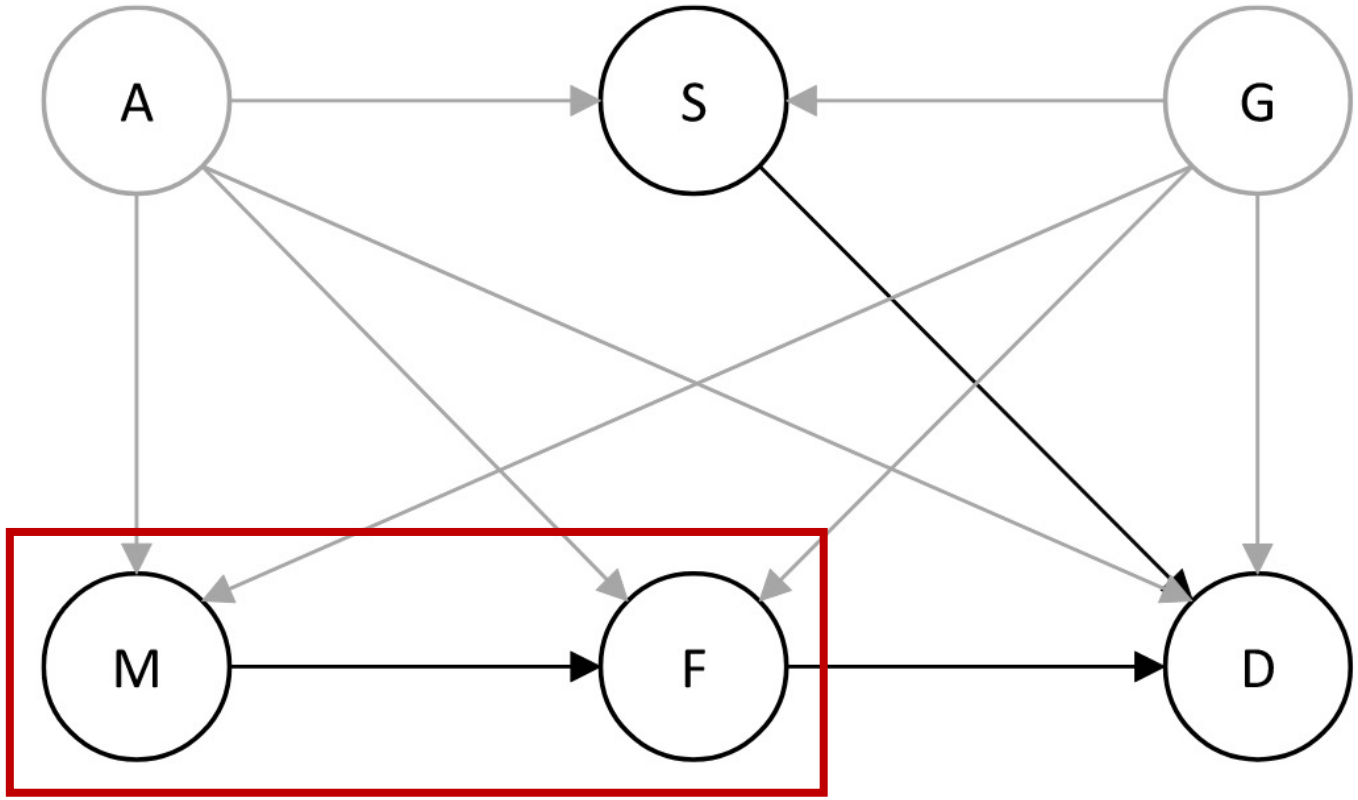
ECTRIMS
EUROPEAN COMMITTEE FOR TREATMENT AND RESEARCH IN MULTIPLE SCLEROSIS

Refining the Allostatic Self-Efficacy Theory of Fatigue and Depression Using Causal Inference

Alexander J. Hess, Dina von Werder, Olivia K. Harrison, Jakob Heinzle, Klaas Enno Stephan

doi: https://doi.org/10.1101/2024.06.17.24309015

Analysis plan



M: metacognition of allostatic control
F: fatigue
S: general self-efficacy
D: depression
A: age
G: gender

Figure 1: Directed acyclic graph (DAG) J_0 summarizing the key proposal of the allostatic self-efficacy theory (ASE; [40]). The DAG J_0 is representative for the induced observational distribution $\mathbb{P}$ and the interventional distributions induced by interventions on metacognition of allostatic control (M; $\mathbb{P}_{do(M:=m)}$), fatigue (F; $\mathbb{P}_{do(F:=f)}$) or general self-efficacy (S; $\mathbb{P}_{do(S:=s)}$). The other variables in the graph are depression (D), age (A) and gender (G). Black edges represent causal directions as proposed by the ASE theory, grey edges represent effects that are not explicitly part of the ASE theory but are likely to exist.

In short…

- Fatigue
  - Subjective experience
  - Common nonspecific symptom with a broad range of etiologies
  - Acute, subacute or chronic
- Assessment of fatigue
- Open research question: pathophysiology of fatigue
  - Molecular hypotheses
  - Structural changes
  - Functional changes
  - Metacognition and low allostatic self-efficacy

Thank you for your attention!

@nespereira_

Questions?

Acknowledgements

- Many thanks to
  - My TNU colleagues
  - Klaas Enno Stephan
  - Zina-Mary Manjaly

  … for all their input!
- Figures made with Biorender.com

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- https://www.uptodate.com/contents/symptom-management-of-multiple-sclerosis-in-adults

Thank you for your attention!

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