



University of
Zurich^{UZH}

ETH

Eidgenössische Technische Hochschule Zürich
Swiss Federal Institute of Technology Zurich



Translational Neuromodeling Unit

Fatigue

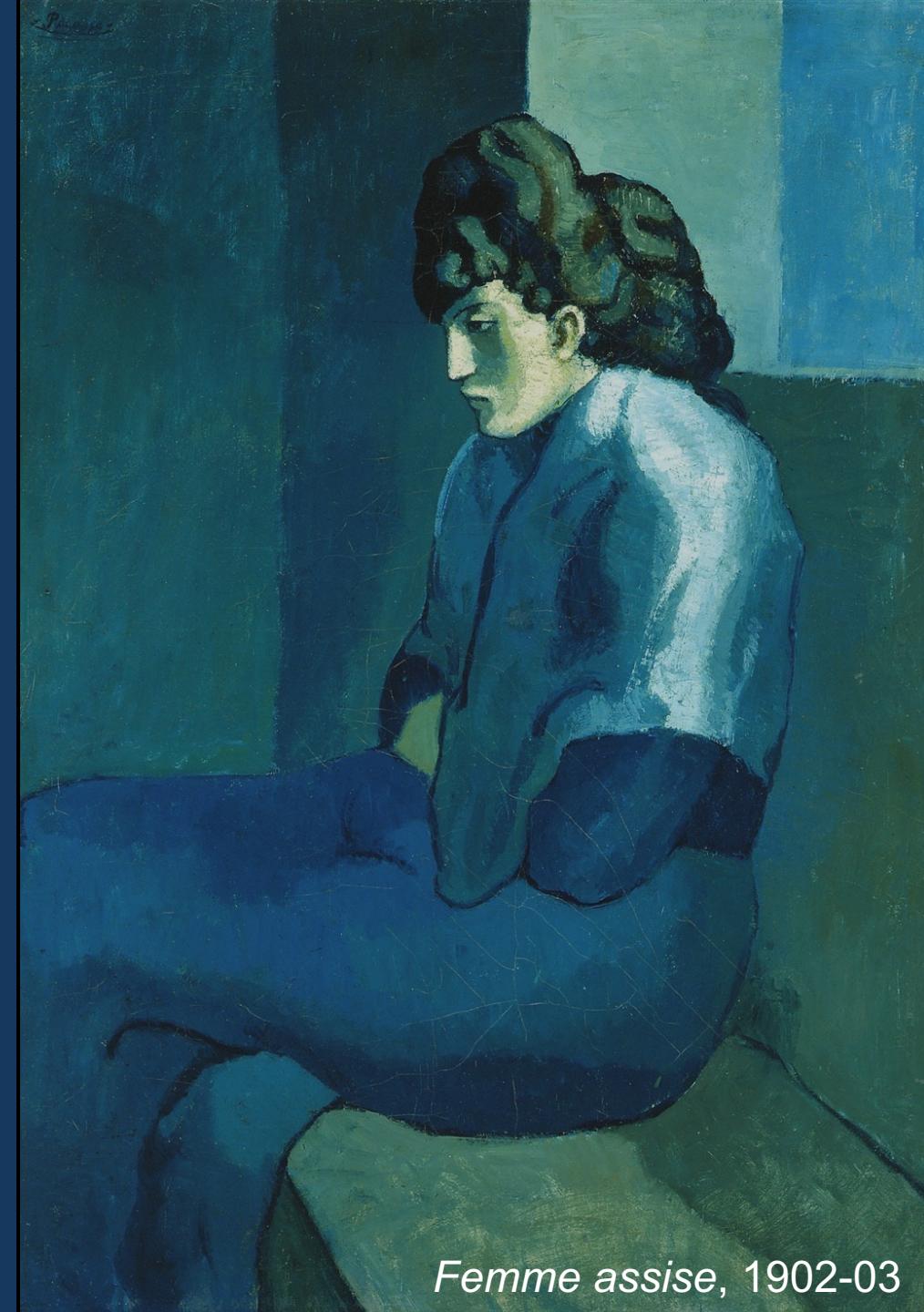
Inês Pereira

CPC Zurich 2025

Fatigue

Clinical case

- 47-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?

Pathophysiology of fatigue

Definition(s)

*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 person's
subjective account?*

*Based on the person'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?

Exhaustion

Somnolence,
sleepiness

What do you mean by fatigue?

Muscle weakness

Exhaustion

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

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

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

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Fatigability

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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

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

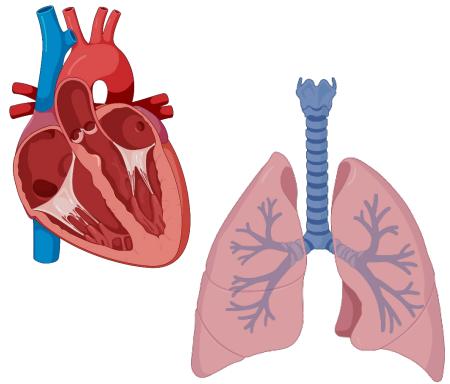
[...]

Causes of fatigue

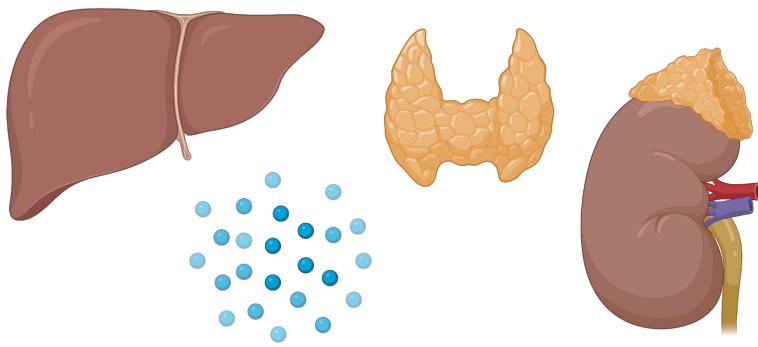
Types of fatigue

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

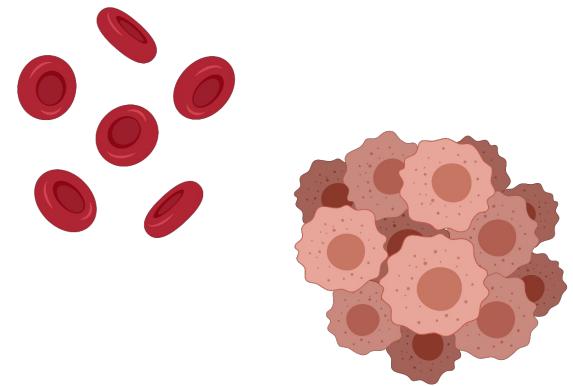
Fatigue



Cardiopulmonary



Endocrinologic/metabolic



Hematologic/neoplastic

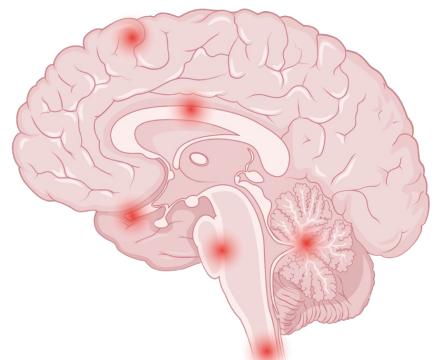


Substance use

Fatigue



Medication



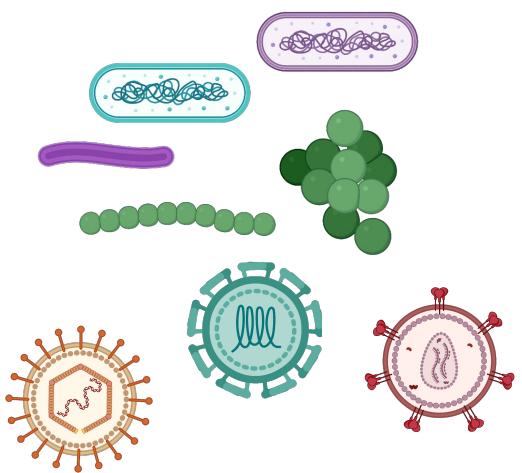
Neurologic



Psychiatric



Rheumatologic



Infectious

Approach to the patient with fatigue

Approach to the patient with fatigue

- Medical history



Fatigue Severity Scale (FSS, English version)*

	strongly disagree			strongly agree			
	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]*

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

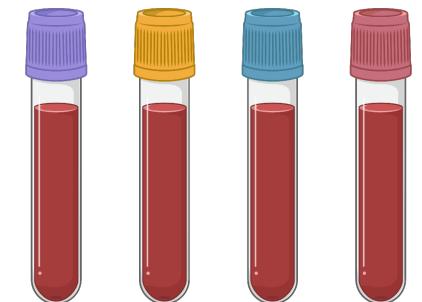
Approach to the patient with fatigue

- Medical history
- Physical examination



Approach to the patient with fatigue

- Medical history
- Physical examination
- Laboratory and radiological studies



Management

Management

- Establish therapeutic goals



Management

- Establish therapeutic goals
- Treat underlying condition(s)



Management

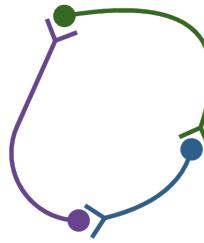
- Establish therapeutic goals
- Treat underlying condition(s)
- Address residual or idiopathic fatigue
 - Pharmacological interventions
 - Non-pharmacological interventions
 - Cognitive behavioral therapy
 - Exercise therapy
 - Occupational therapy



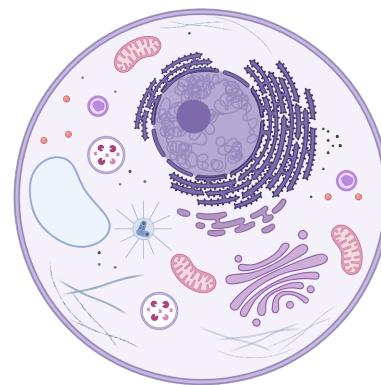
Pathophysiology of fatigue

?

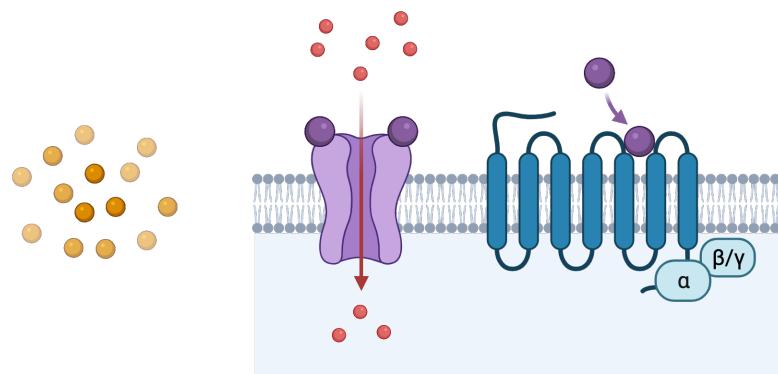
Circuit level



Cellular level



Molecular level



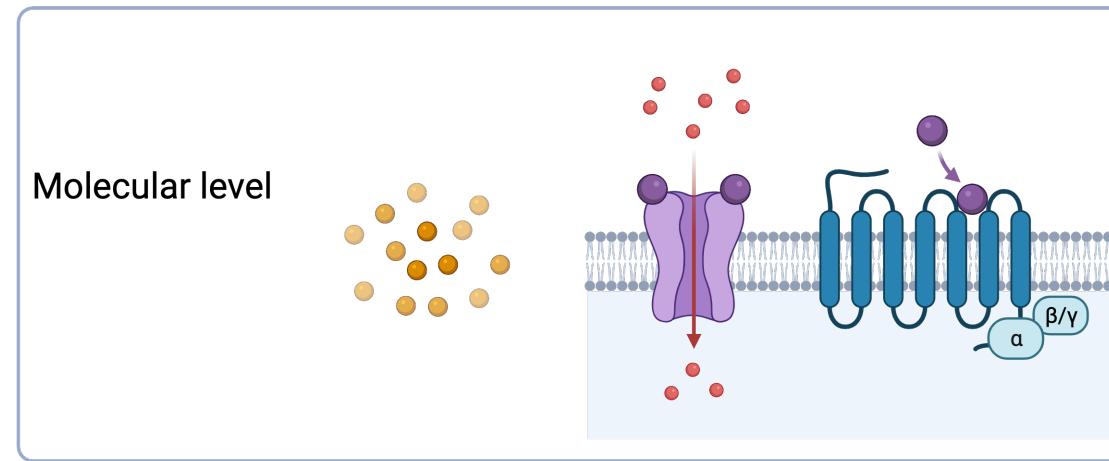
IL-6

IL-1

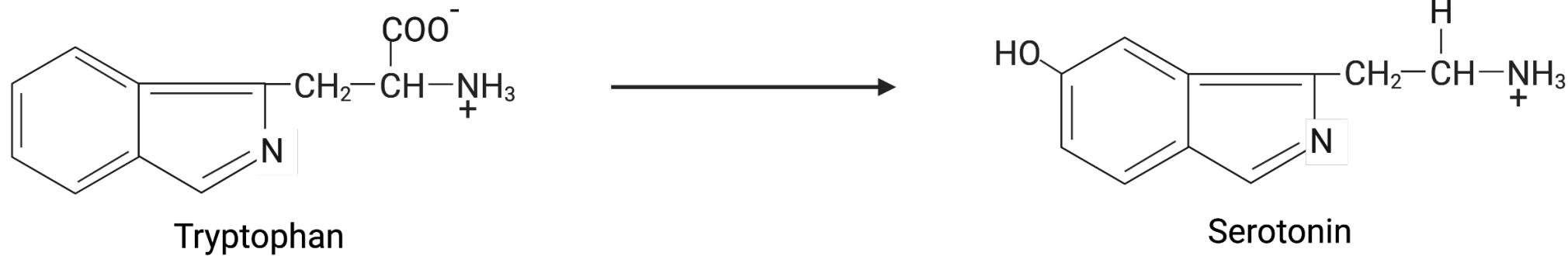
CRP

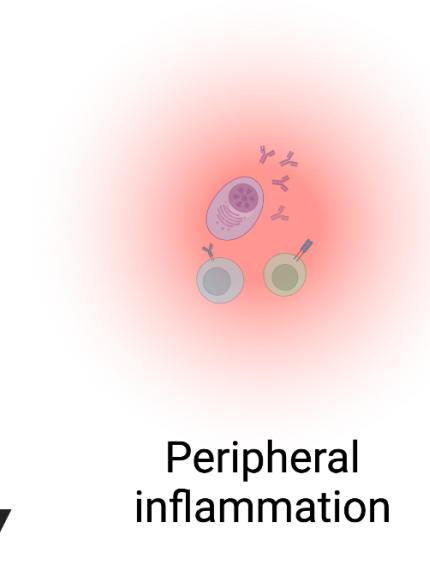
INF- α

TNF- α



INF- γ

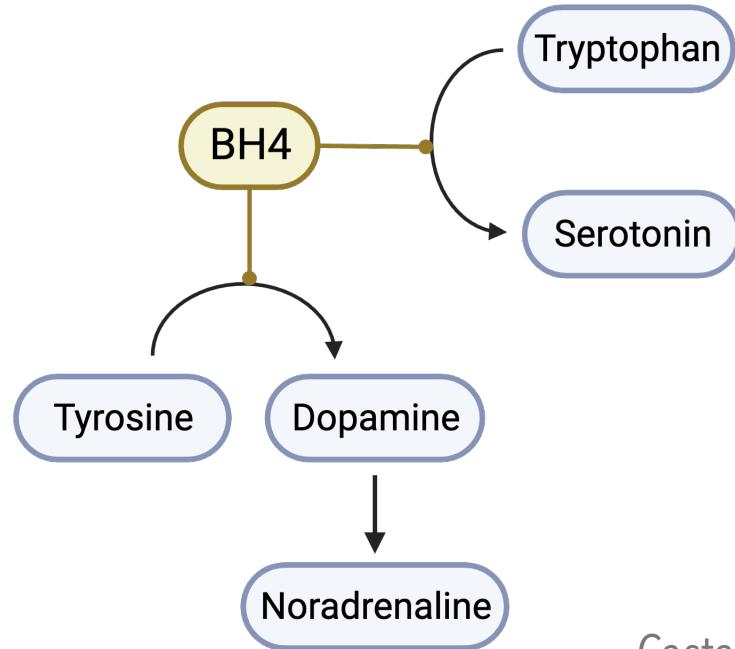


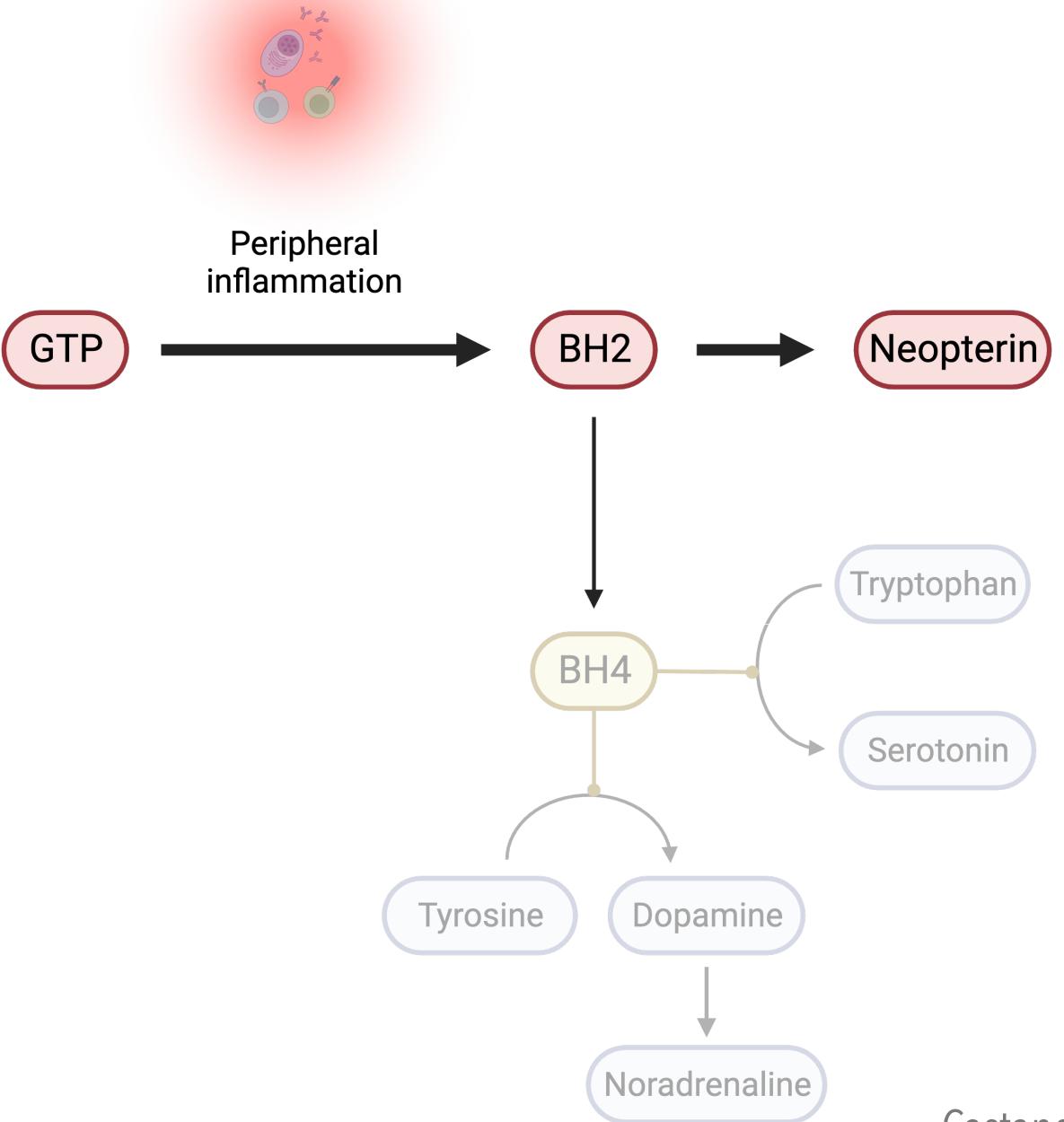


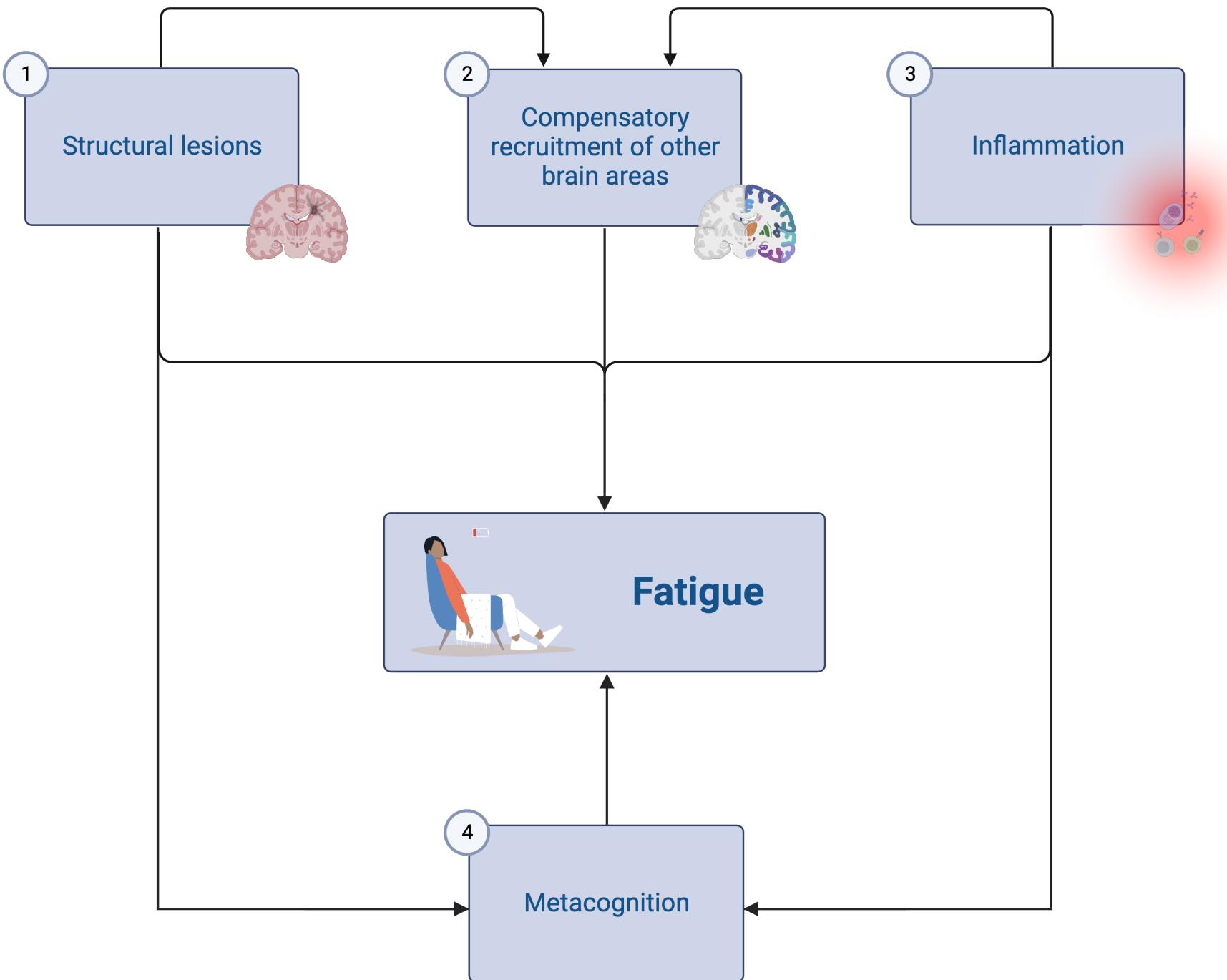
Peripheral
inflammation

Kynurenine Pathway

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







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. Mathys², Lilian A. E. Weber¹, Saeed Paliwal¹, Tim Gard^{1, 5}, Marc Tittgemeyer³, Stephen M. Fleming², Helene Haker¹, Anil K. Seth⁶ and Frederike H. Petzschner¹*

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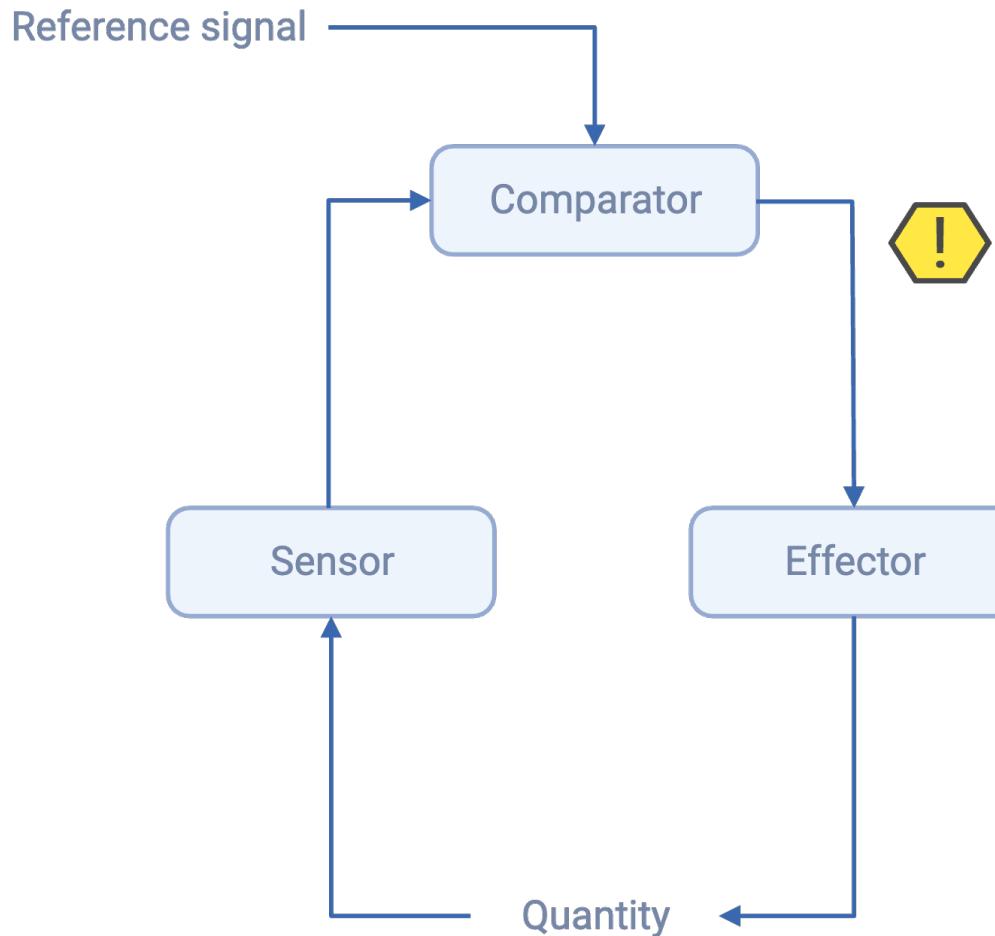
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Homeostasis

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

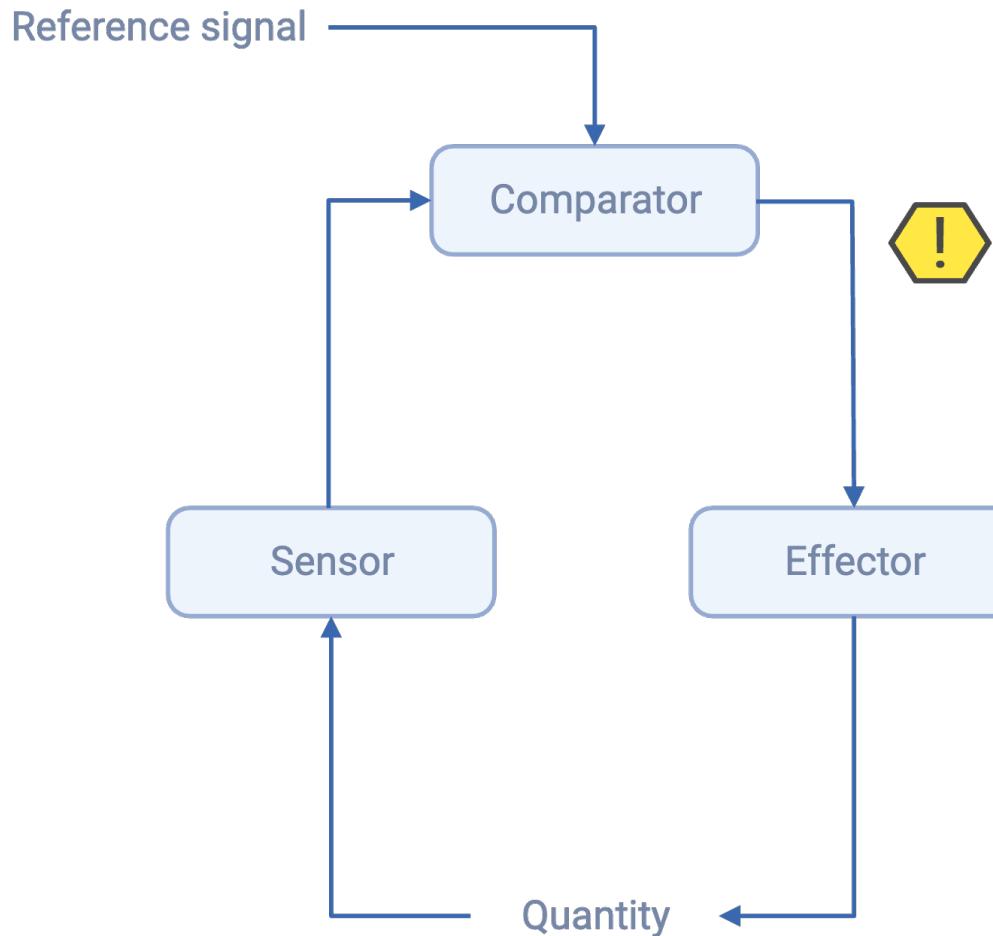
Walter Cannon, 1929

Homeostasis



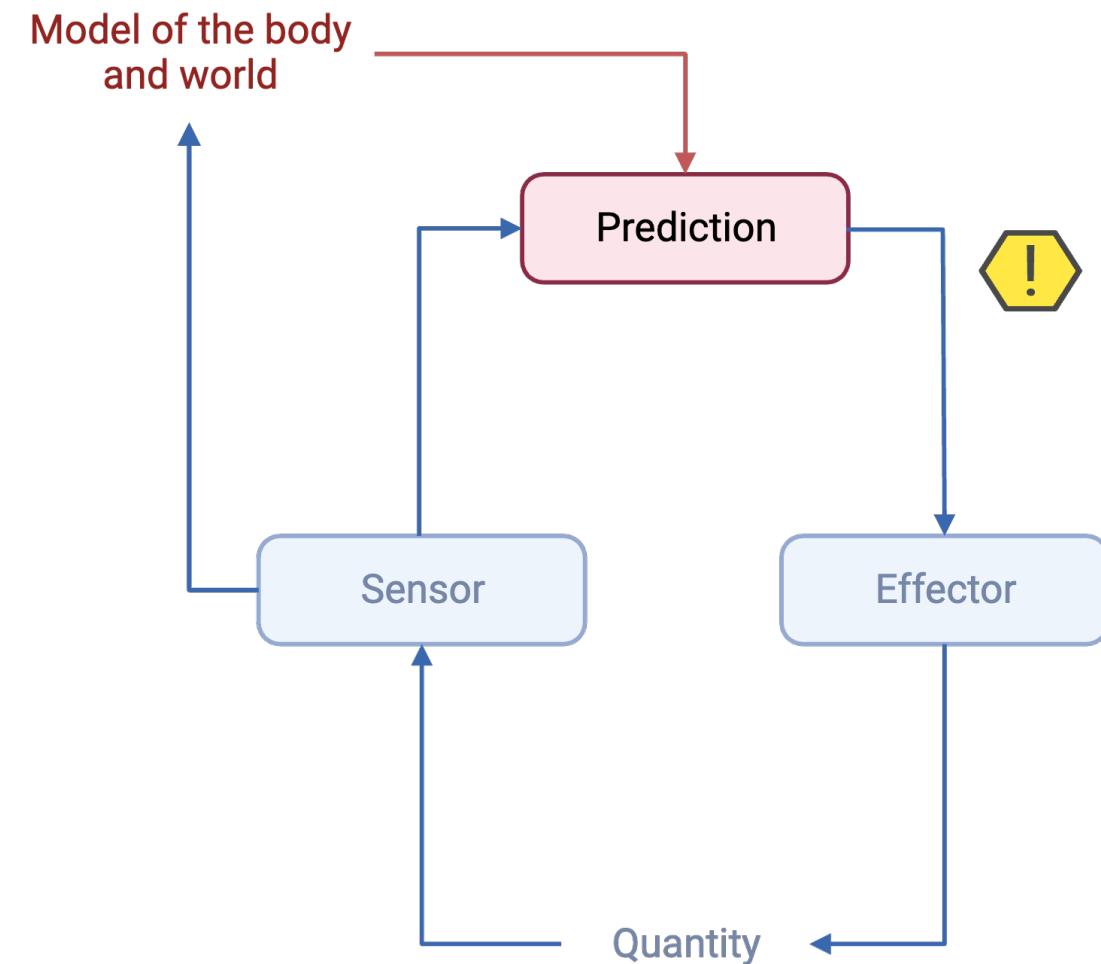
Based on figure from: Powers,
Science, 1973

Homeostasis

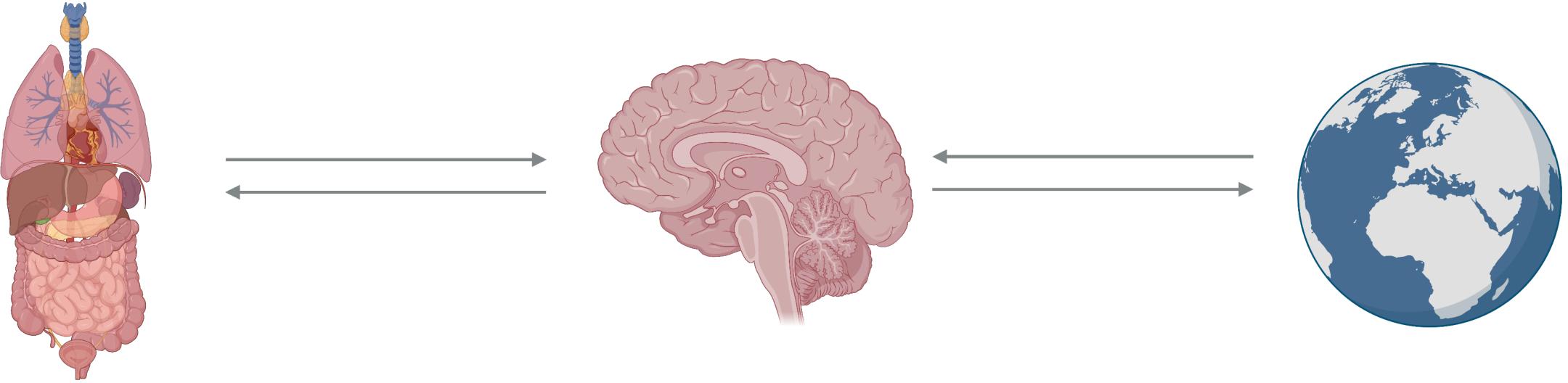


Based on figure from: Powers,
Science, 1973

Allostasis



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



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

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

prior

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

likelihood 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

posterior

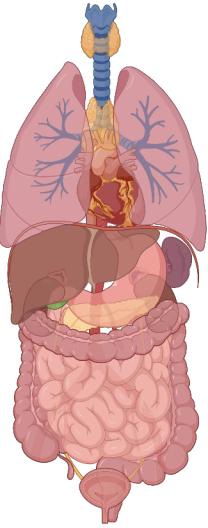
$$p(x|y, m) = \frac{\text{likelihood} \quad \text{prior}}{p(y|m)}$$

posterior

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

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

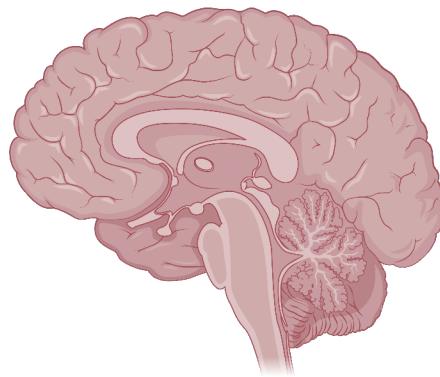
$$\log p(y|m) = -S(y|m)$$



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

$$\xrightarrow{\hspace{1cm}}$$

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



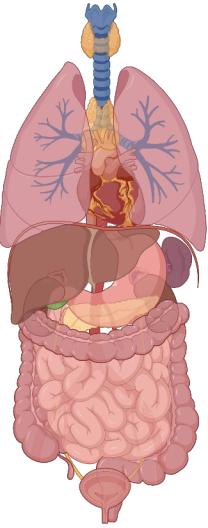
$$p(x|y, m)$$

$$\xleftarrow{\hspace{1cm}}$$

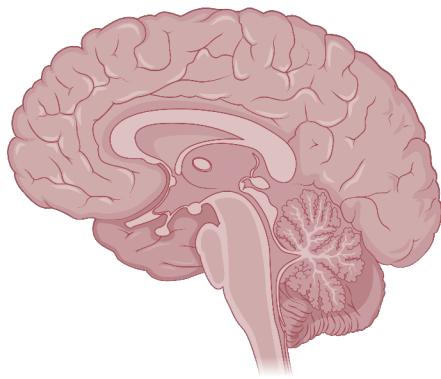
$$p(y|x, m)p(x|m)$$



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



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



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



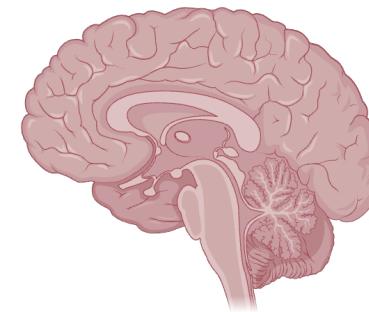
Interoceptive surprise

Exteroceptive surprise

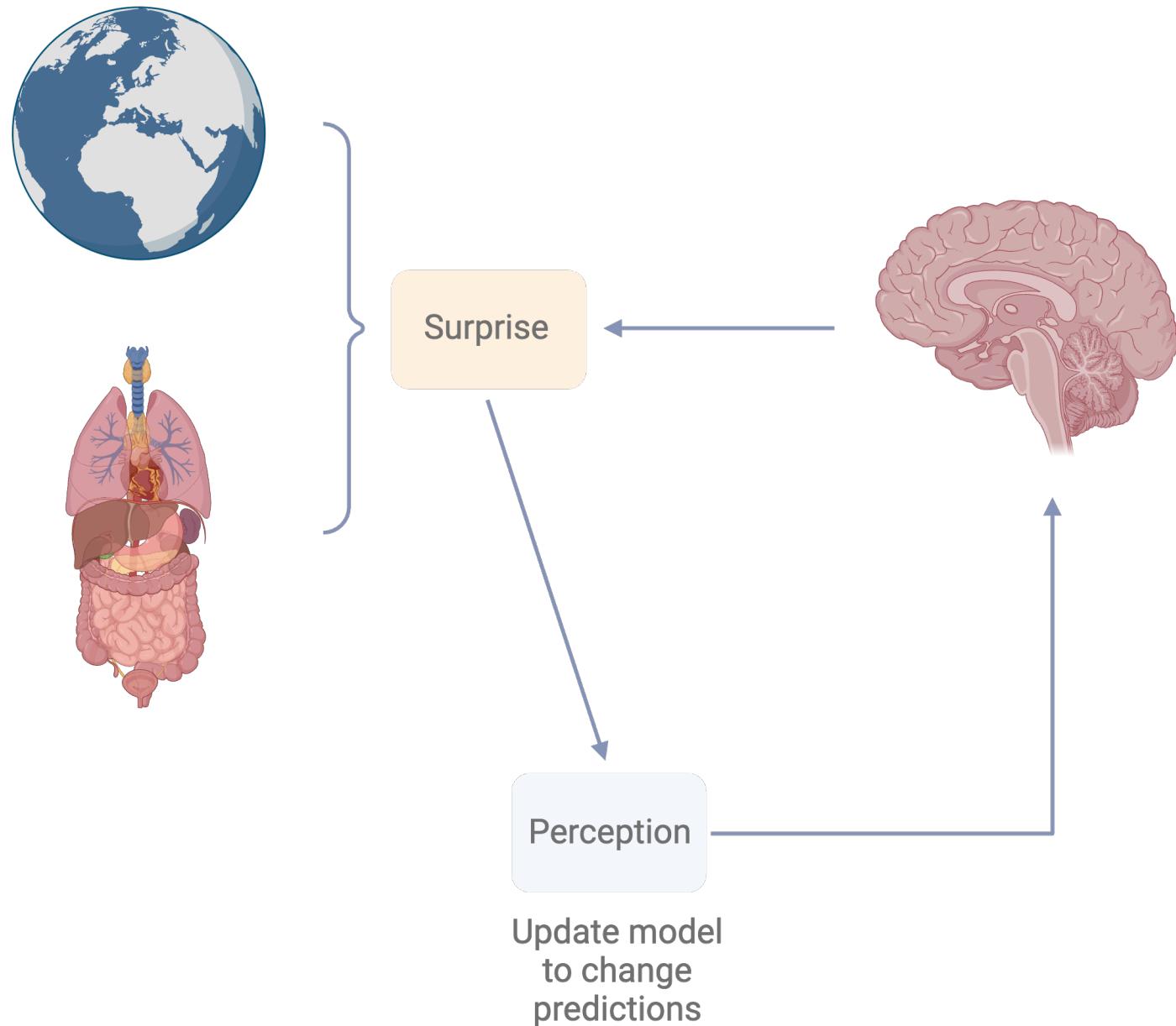
Based on figure from Stephan *et al.*, *Frontiers in Human Neuroscience*, 2016



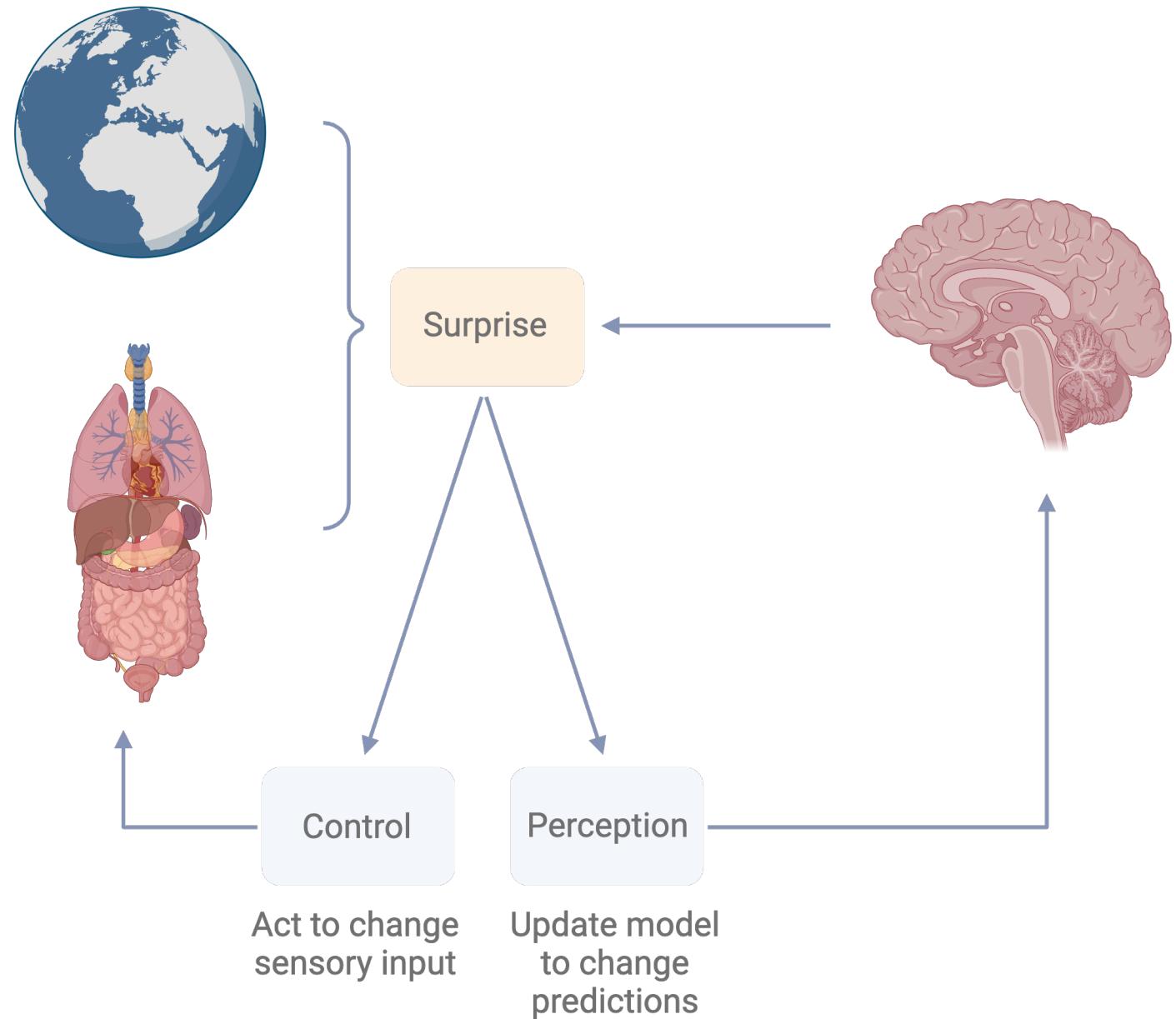
Surprise



Based on slide from Klaas Enno Stephan



Based on slide from Klaas Enno Stephan



Based on slide from Klaas Enno Stephan

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

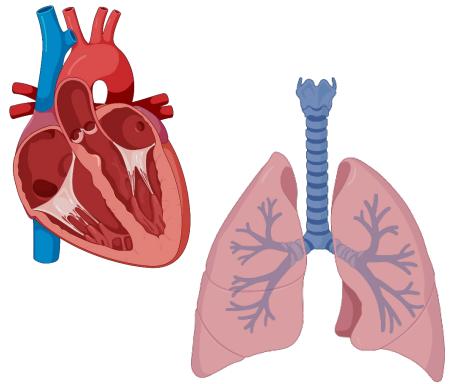
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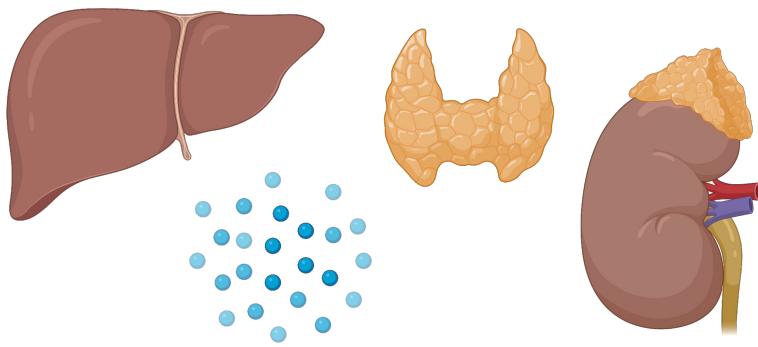
Self-efficacy

An individual's expectation of personal mastery and control

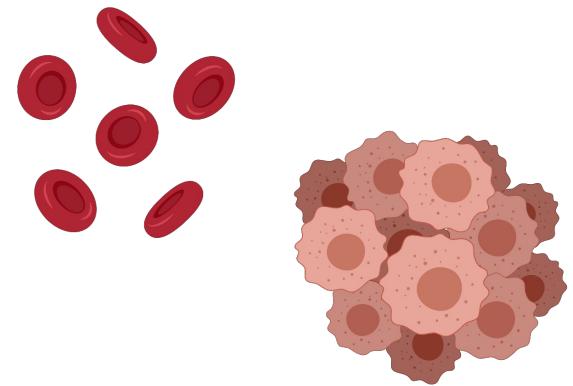
Bandura, *Psychol. Rev.*, 1977



Cardiopulmonary



Endocrinologic/metabolic



Hematologic/neoplastic

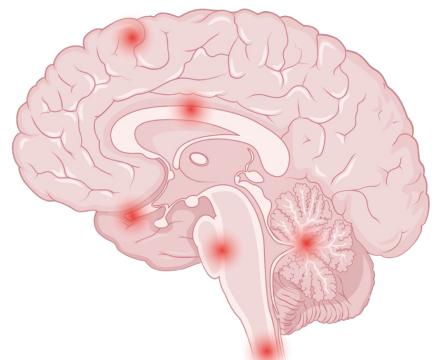


Substance use

Fatigue



Medication



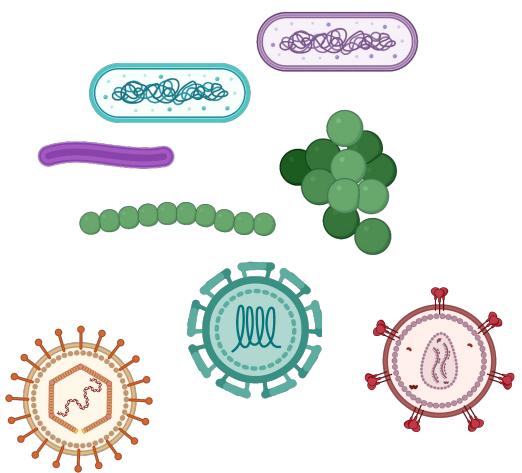
Neurologic



Psychiatric



Rheumatologic



Infectious

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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*

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Key concepts

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

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Metacognition

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

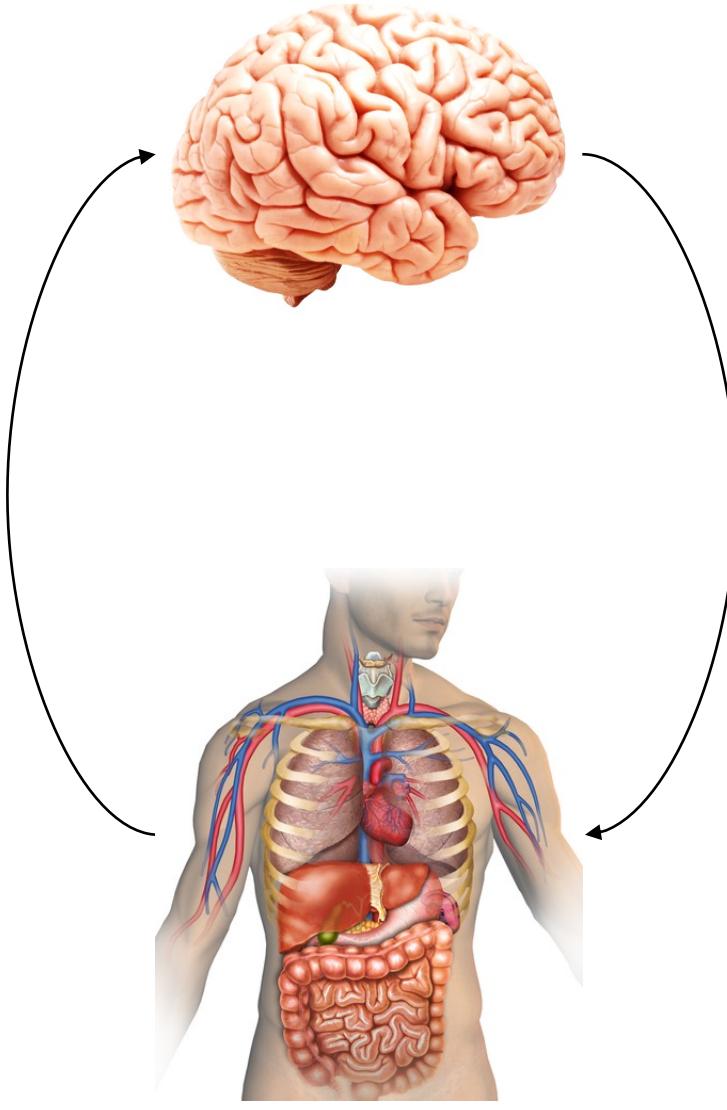
Metacognition of control

*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*

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

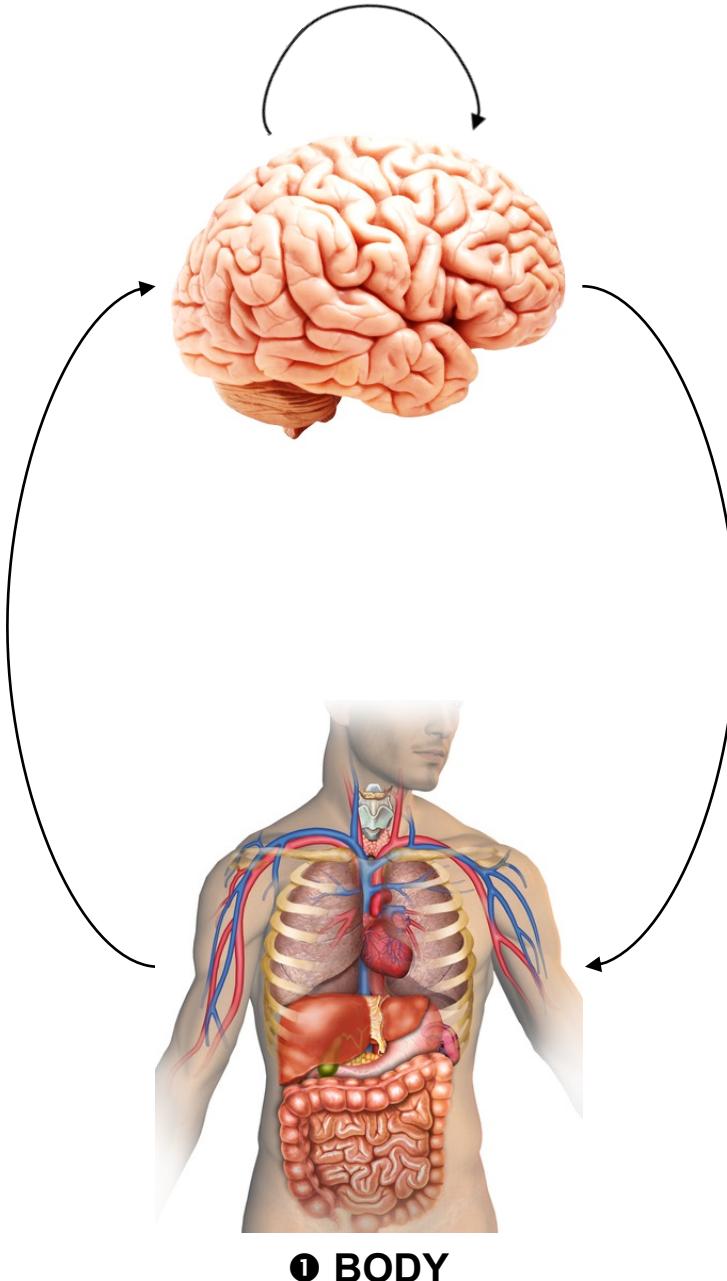
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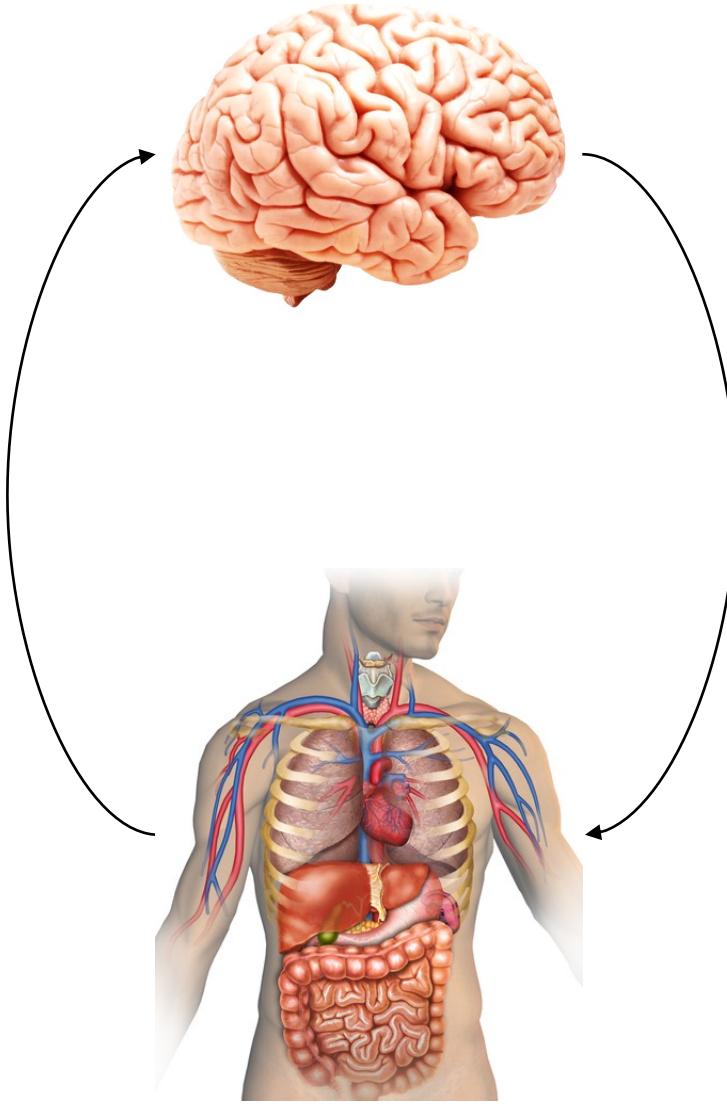


❶ BODY

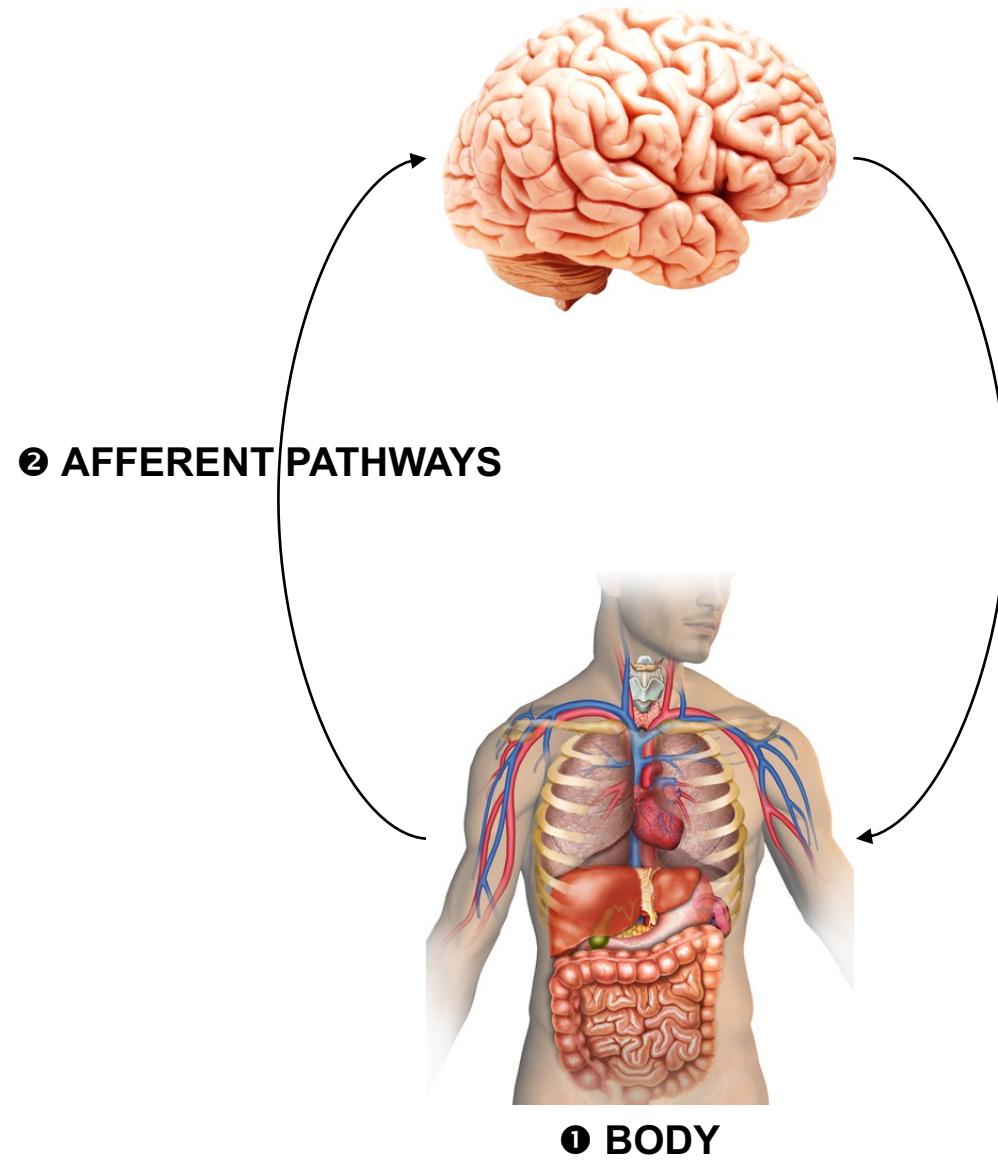
⑤ METACOGNITION

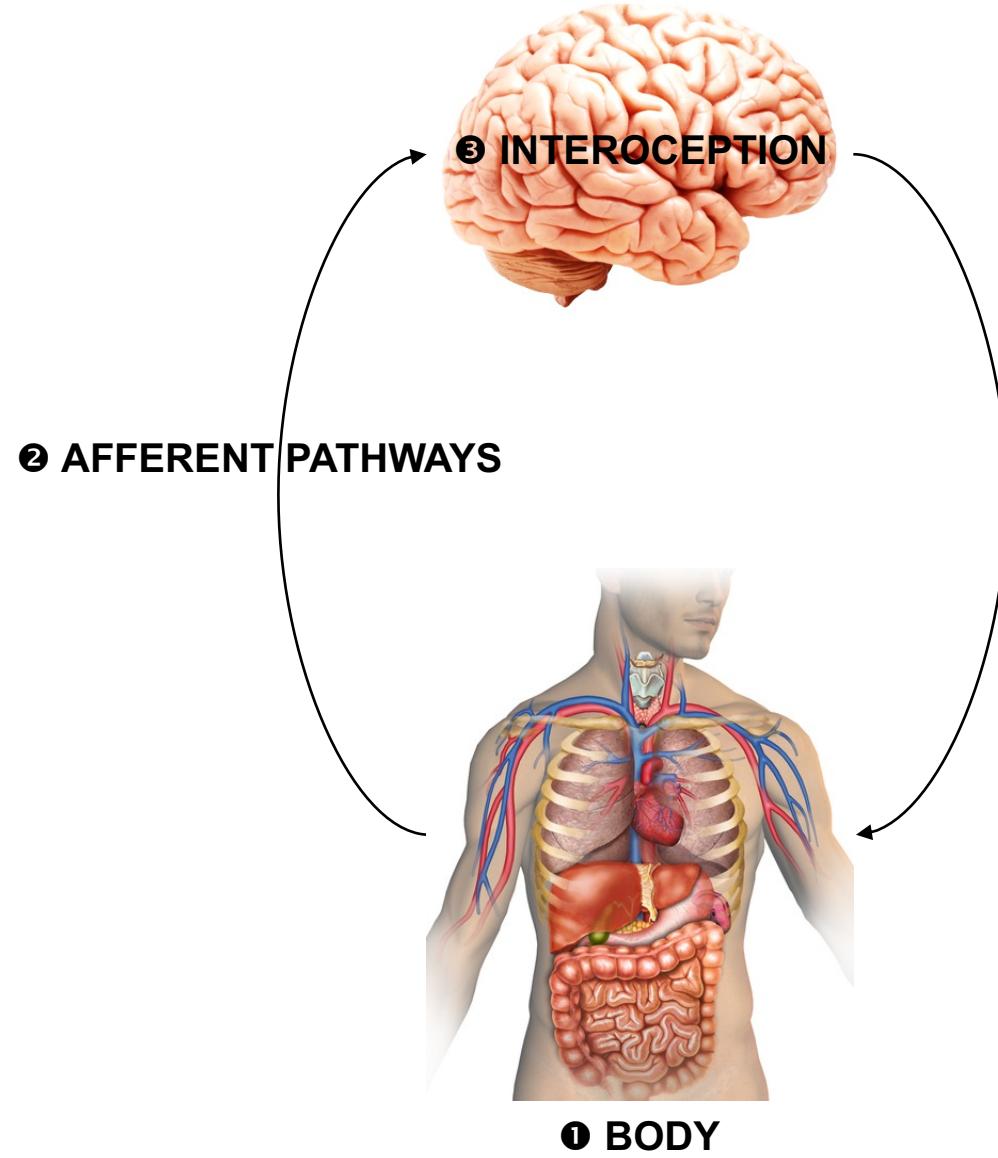


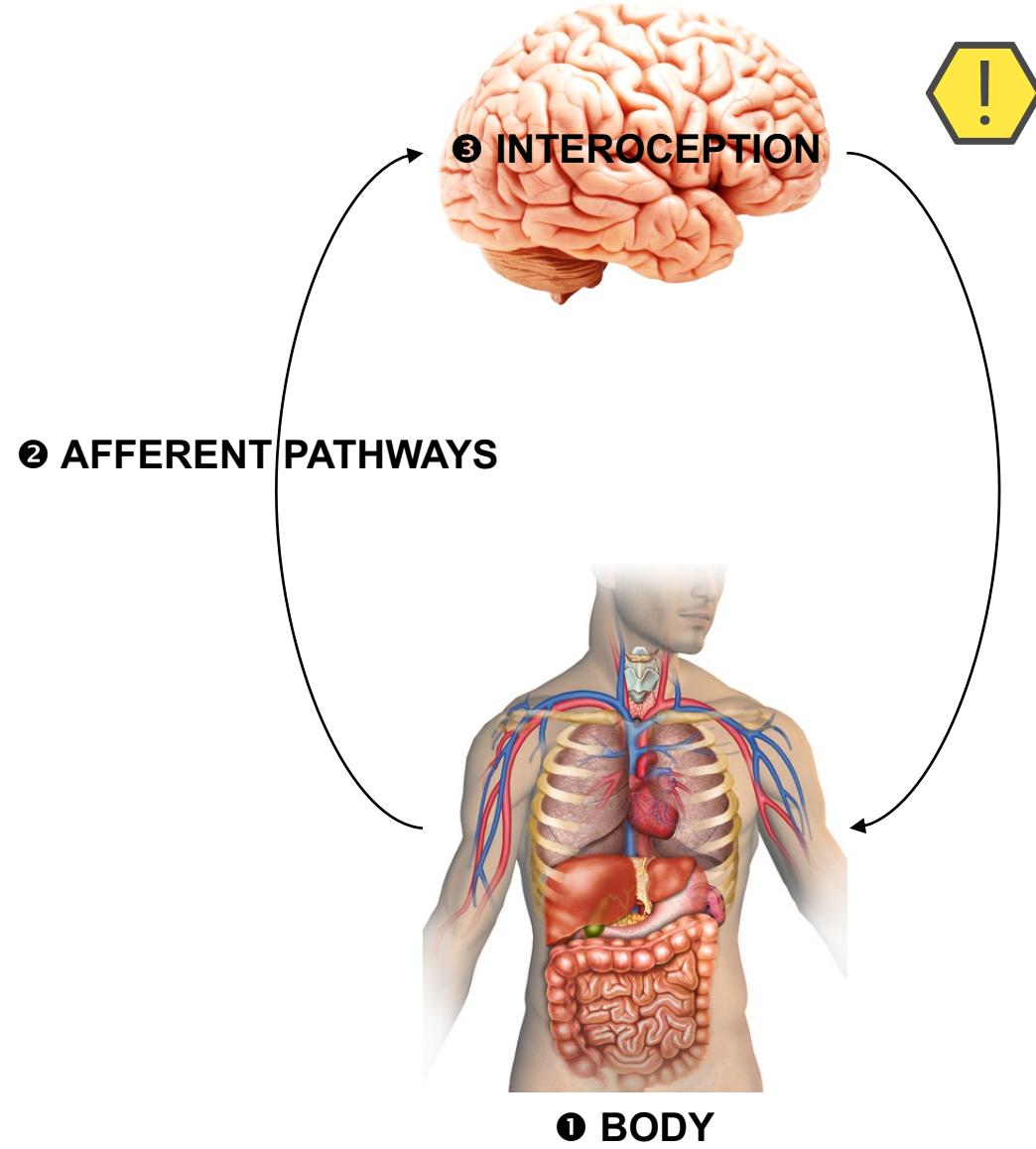
Metacognitive diagnosis of
low allostatic self-efficacy

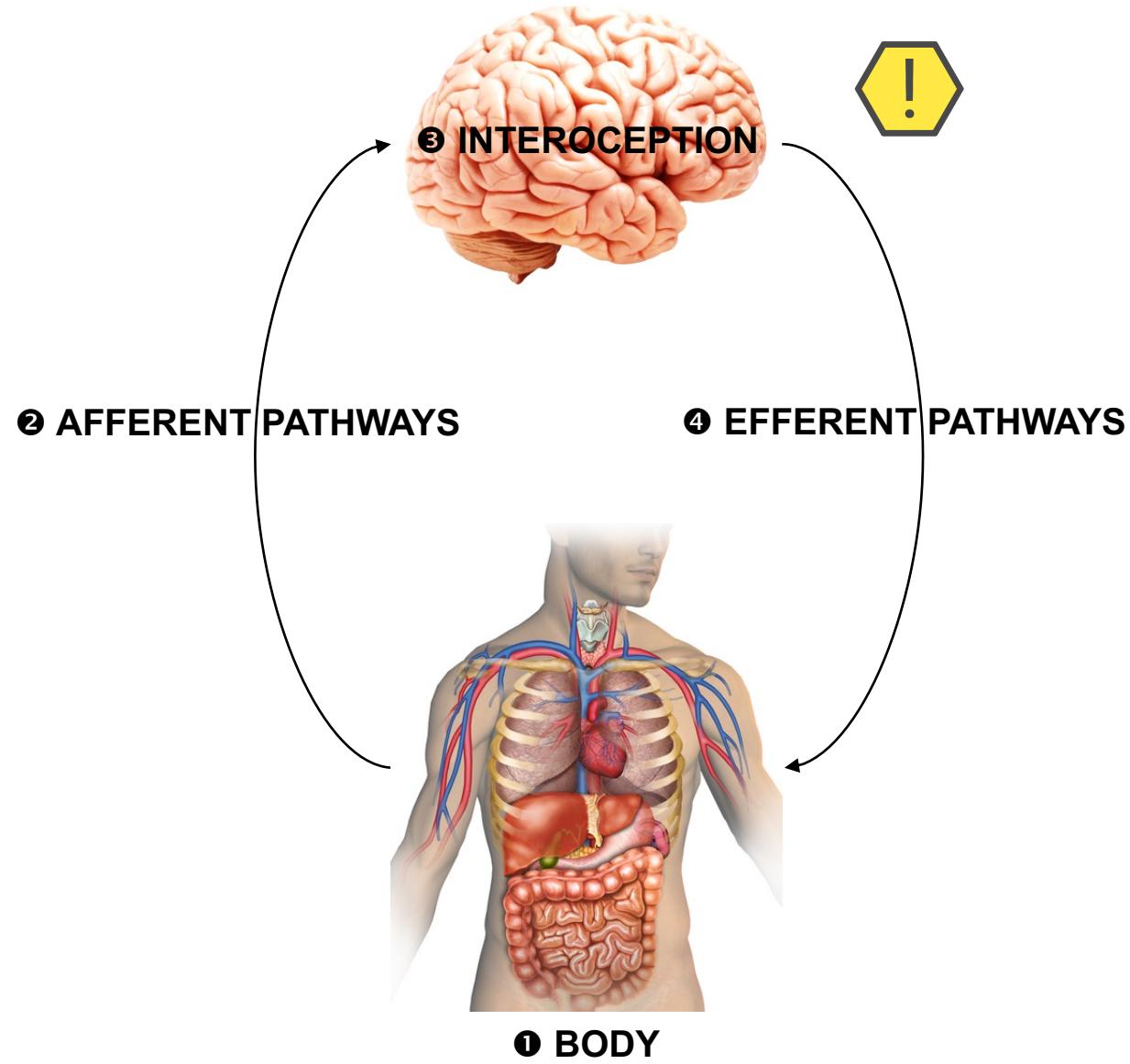


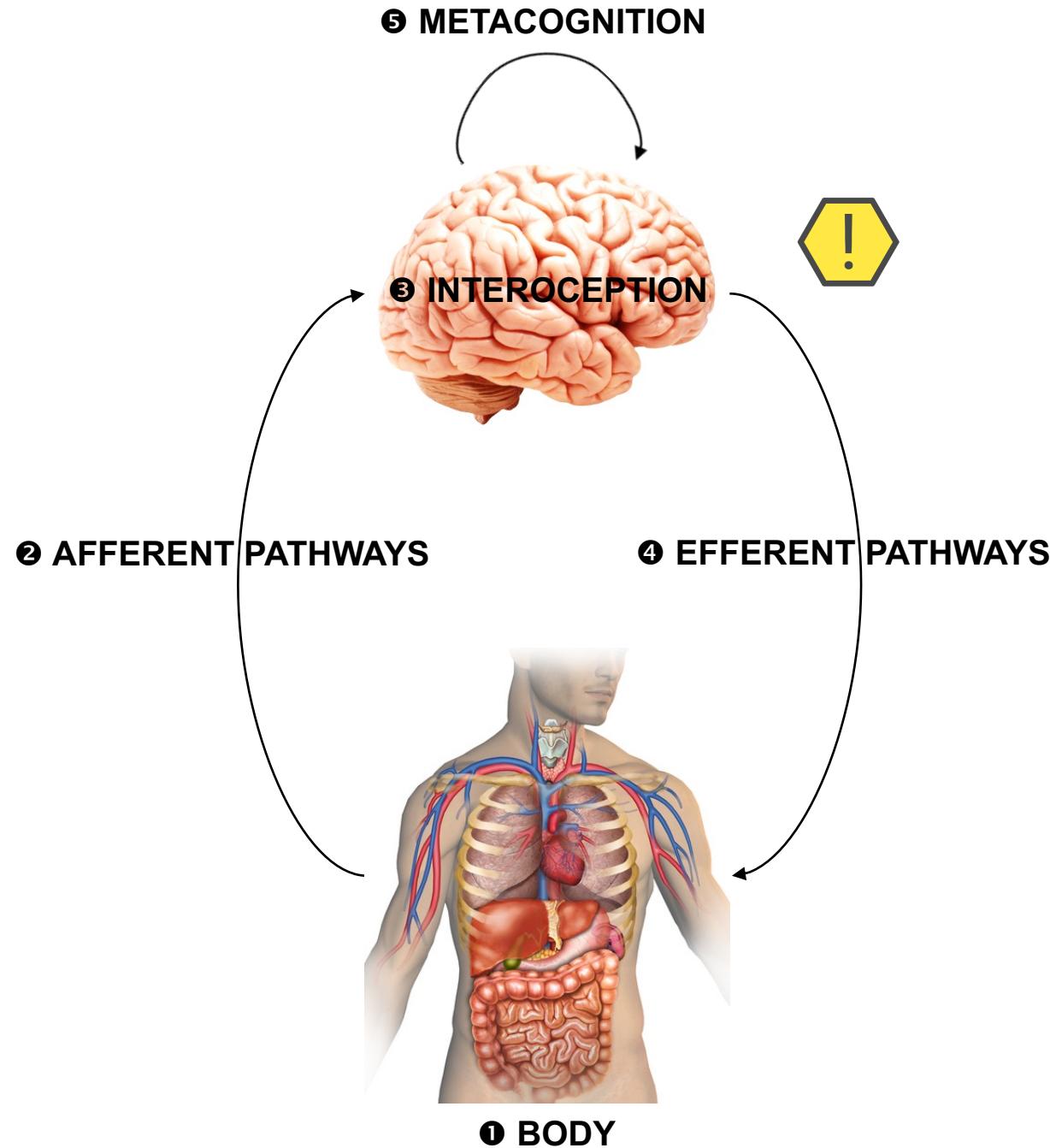
❶ BODY

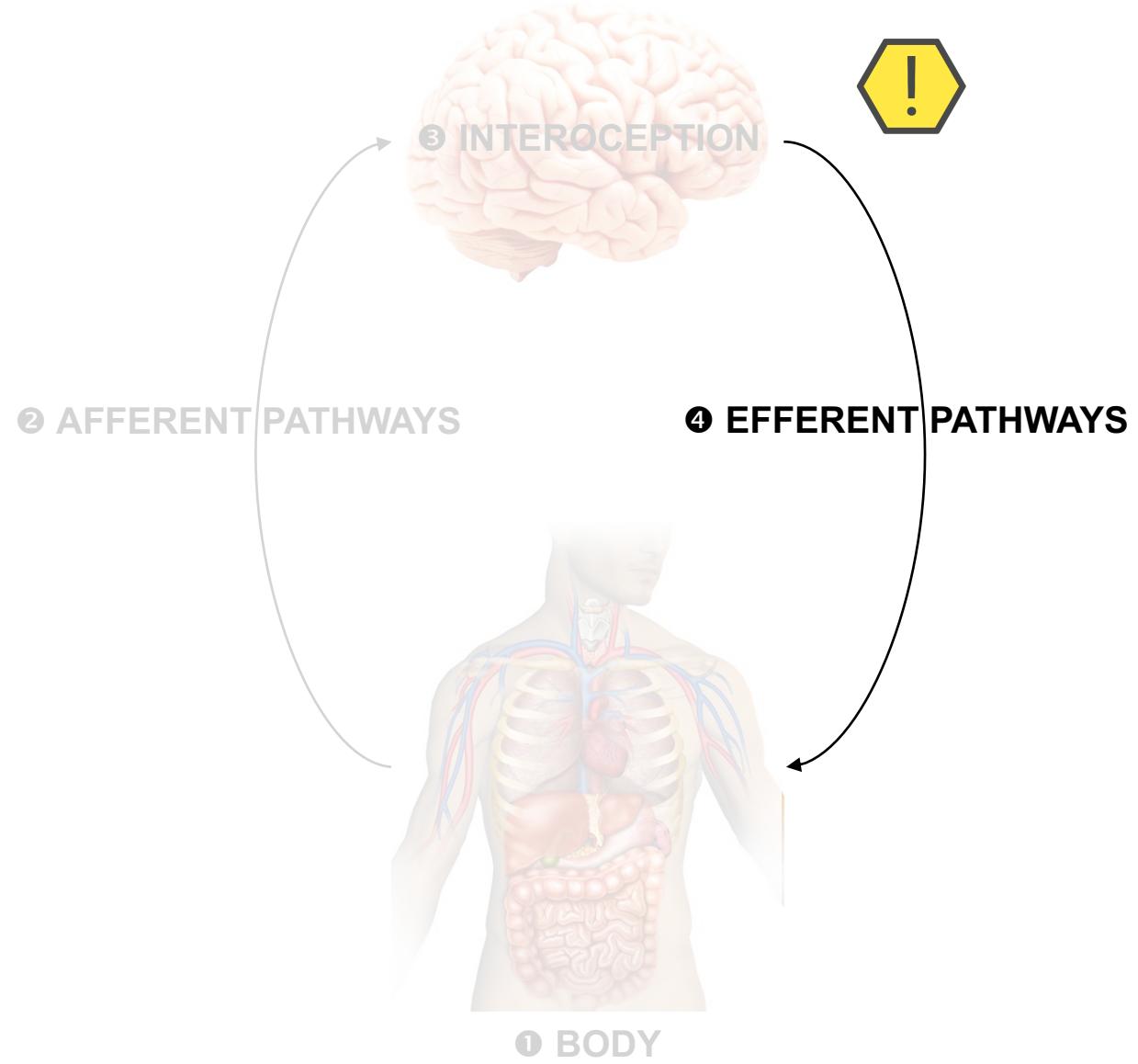


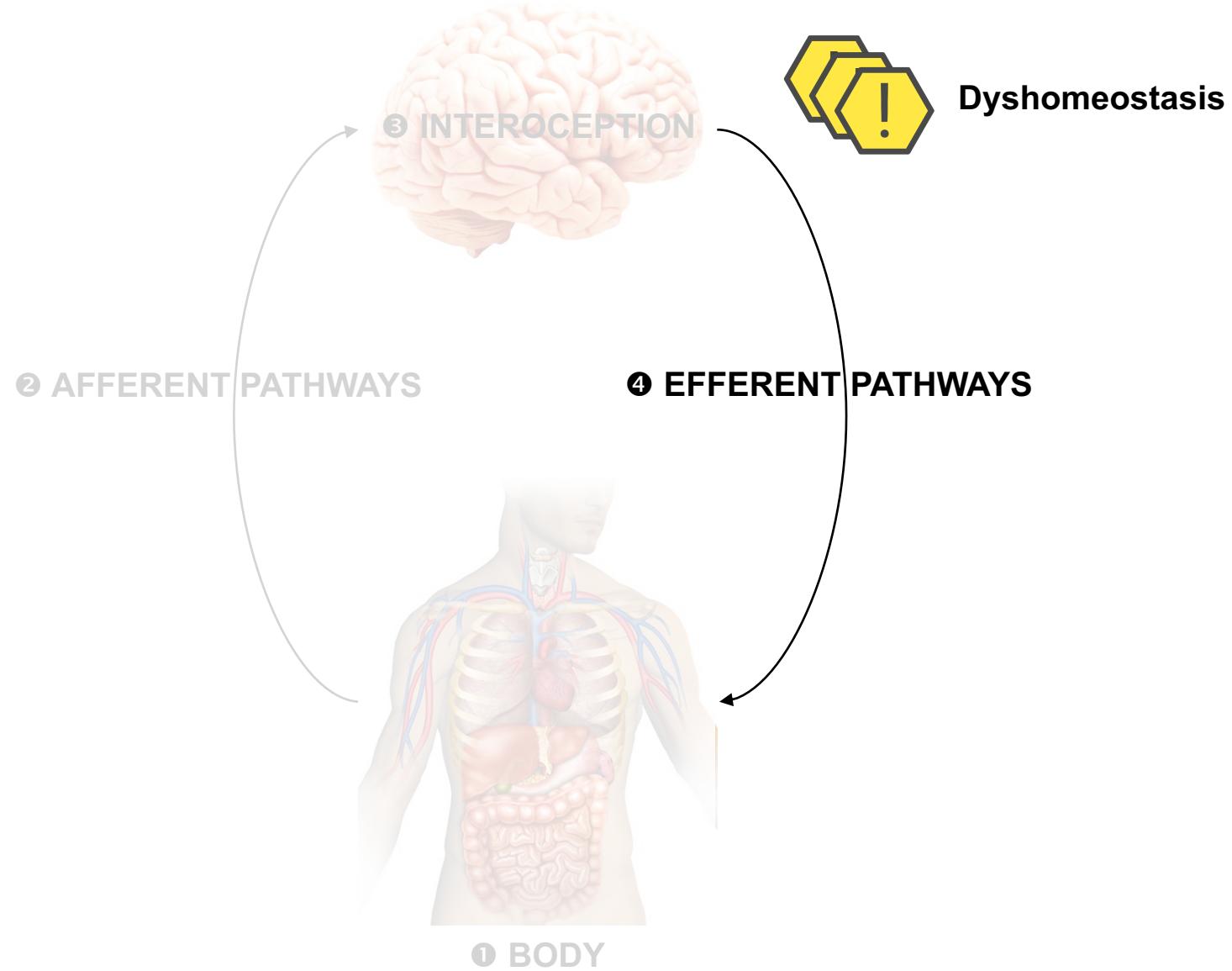




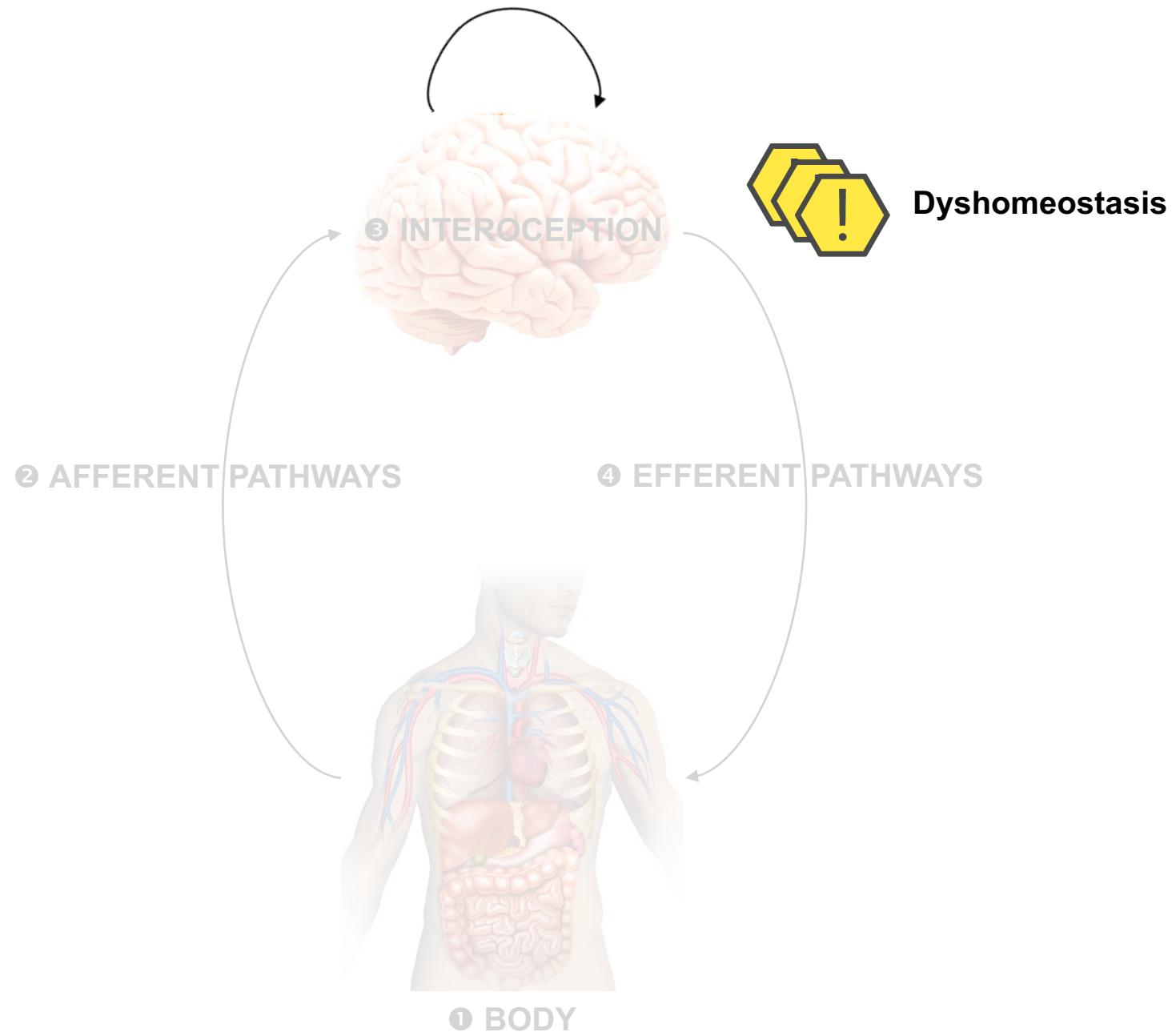


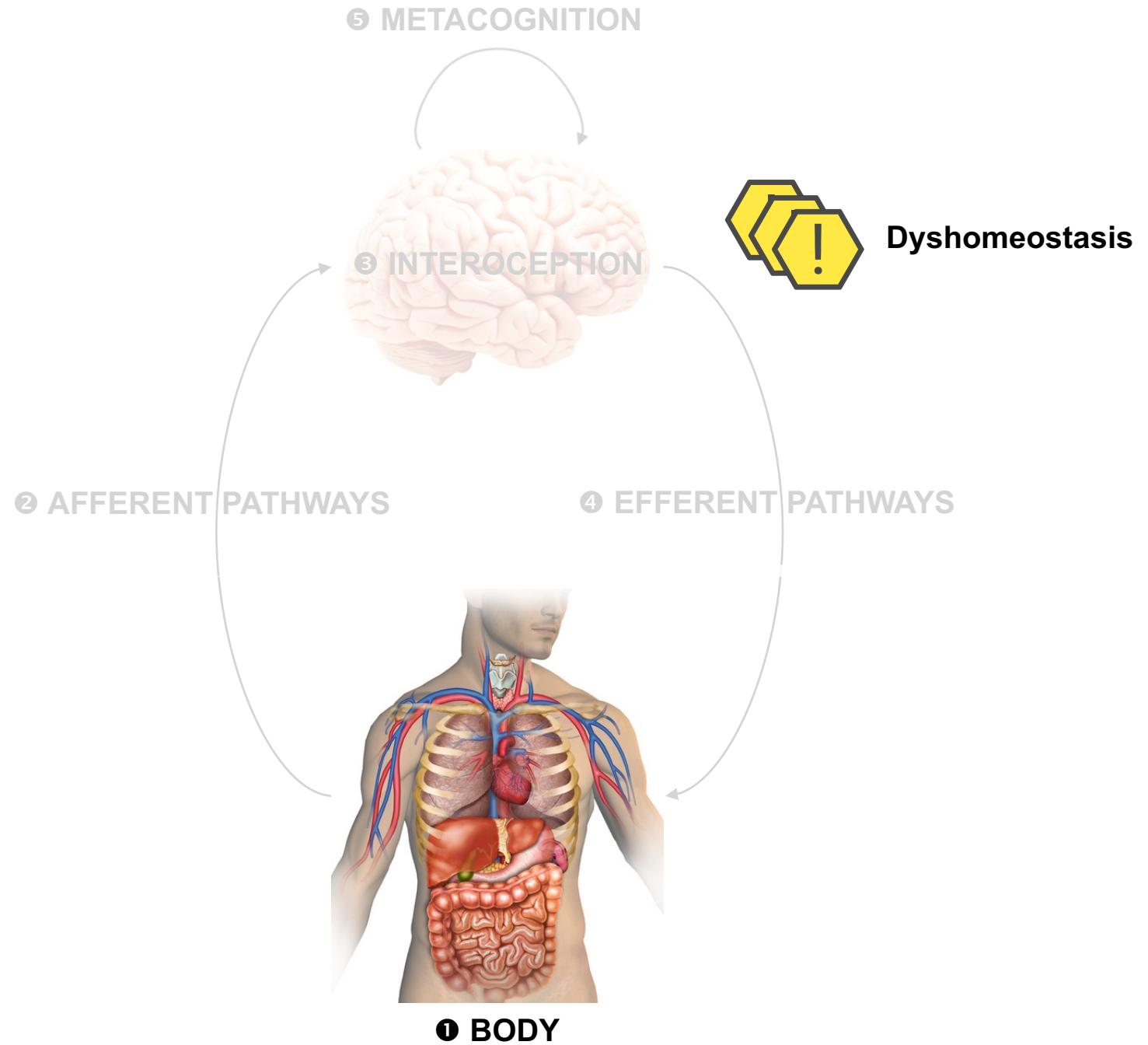


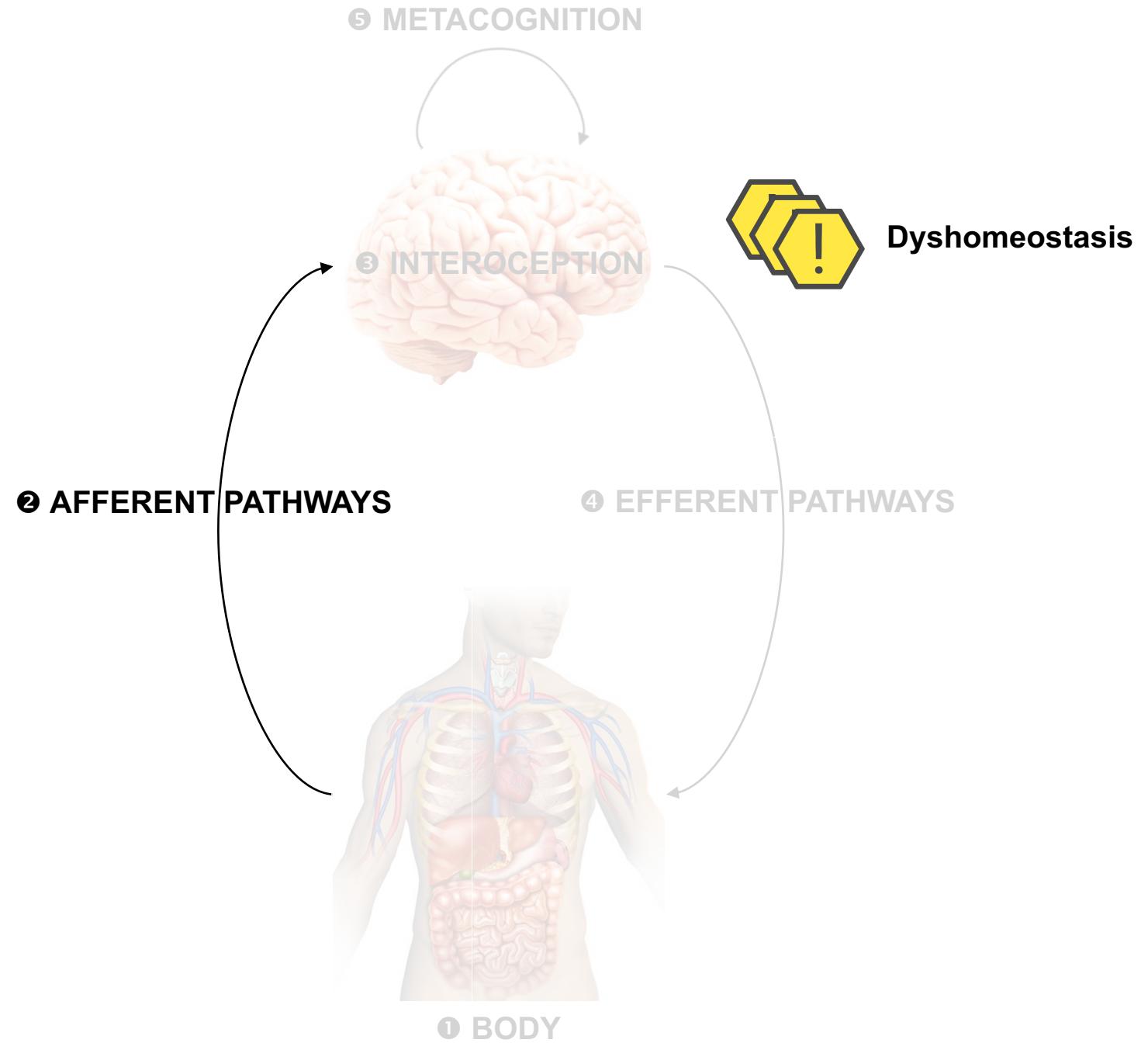


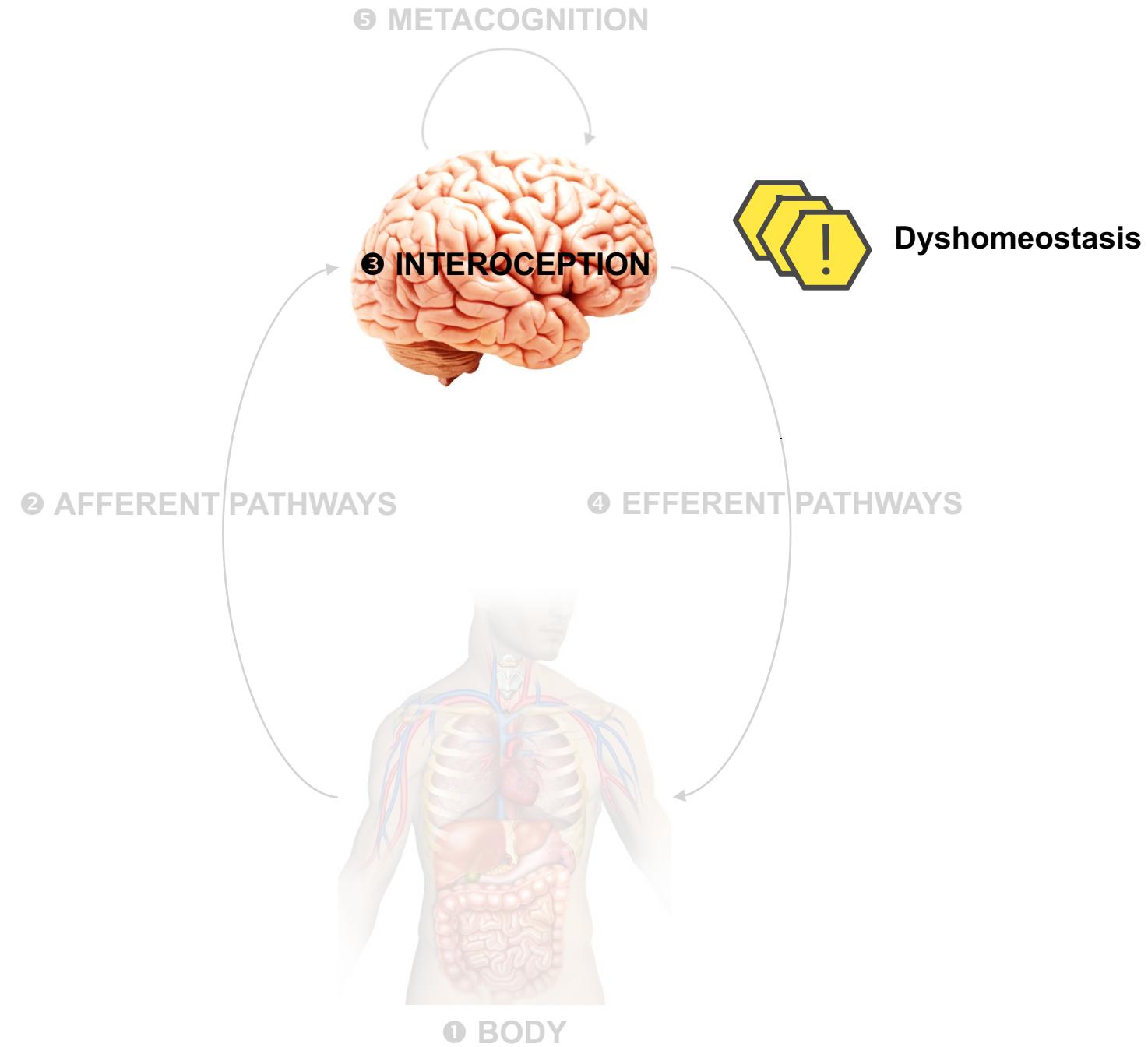


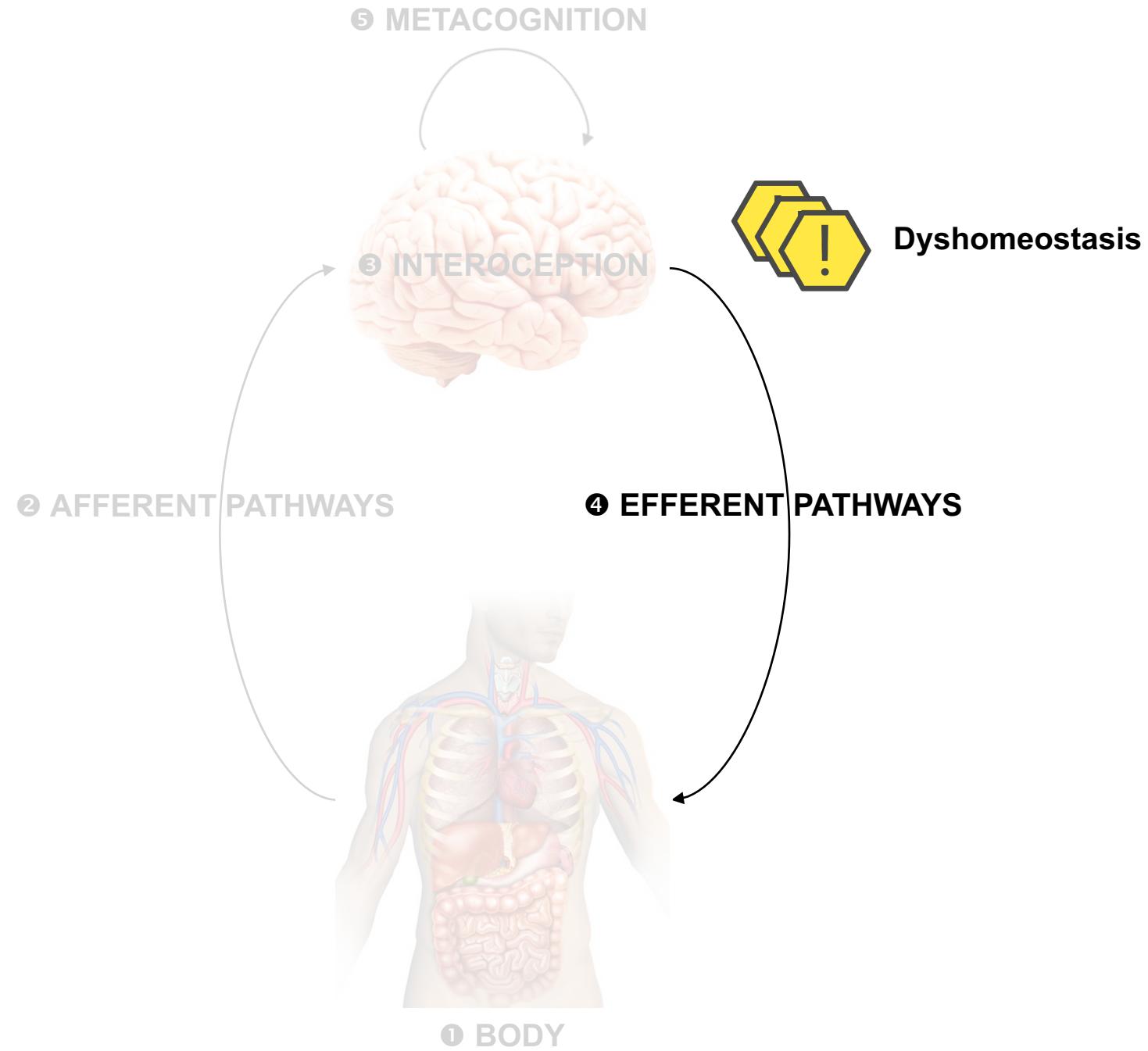
⑤ METACOGNITION



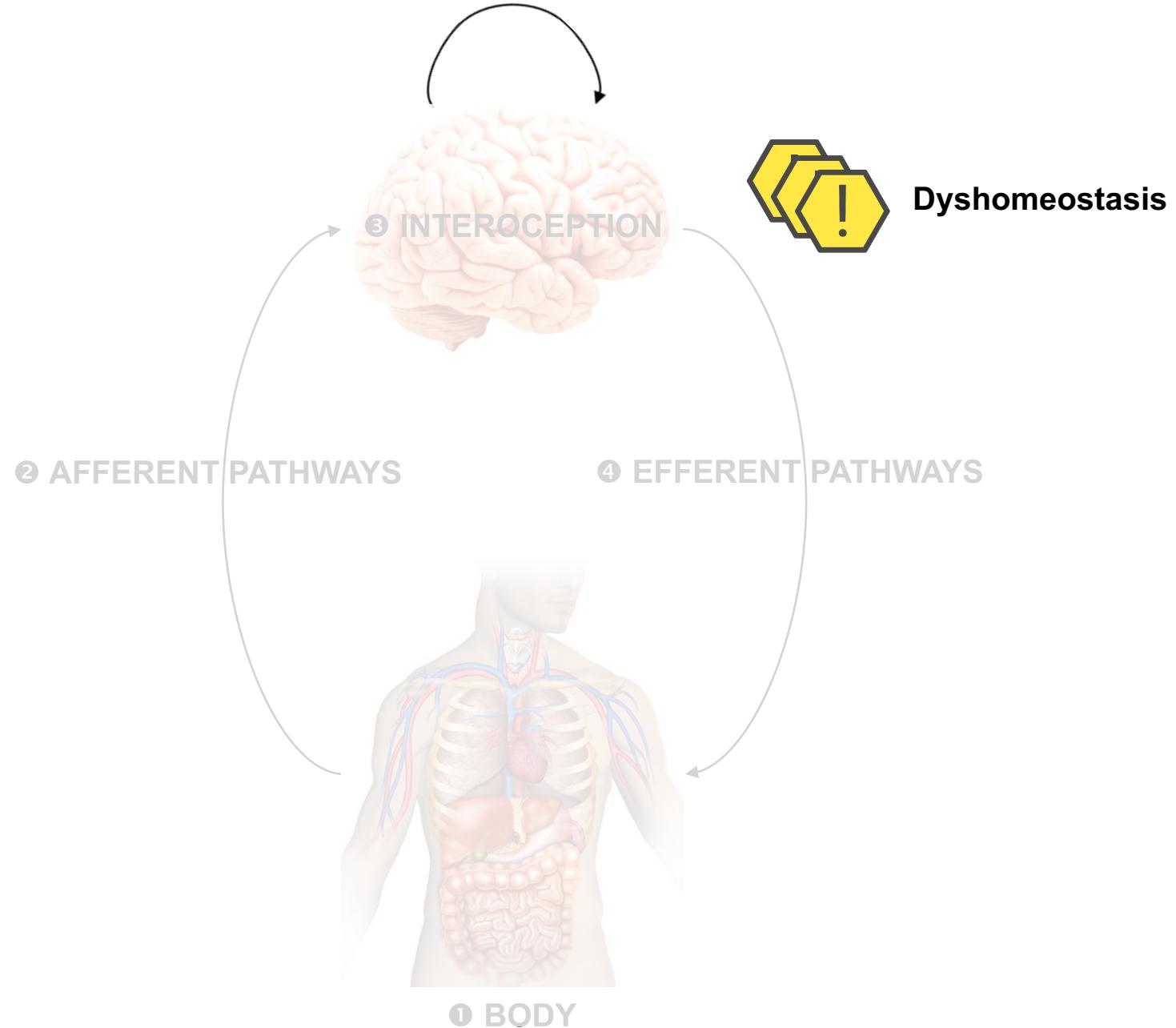


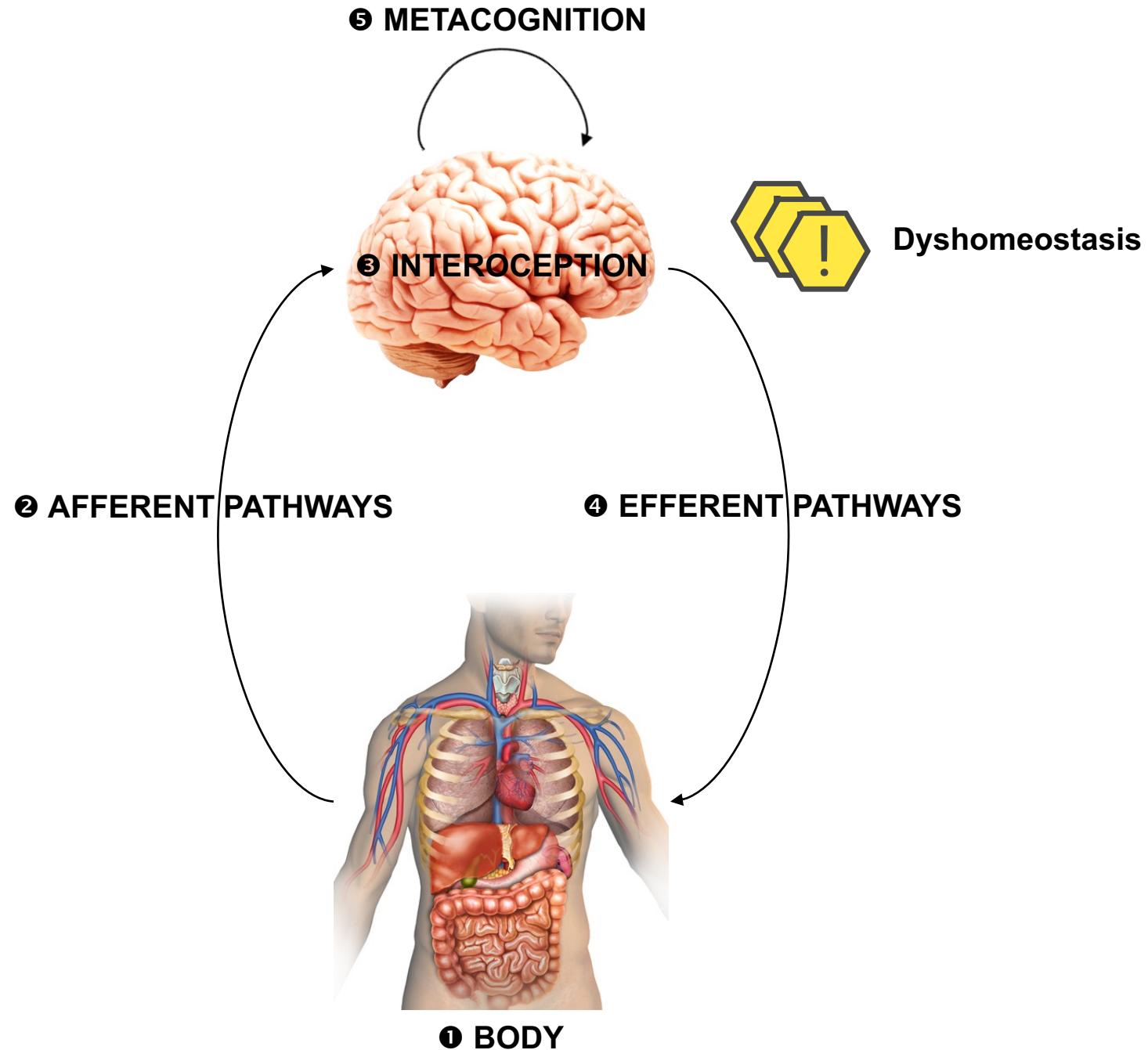


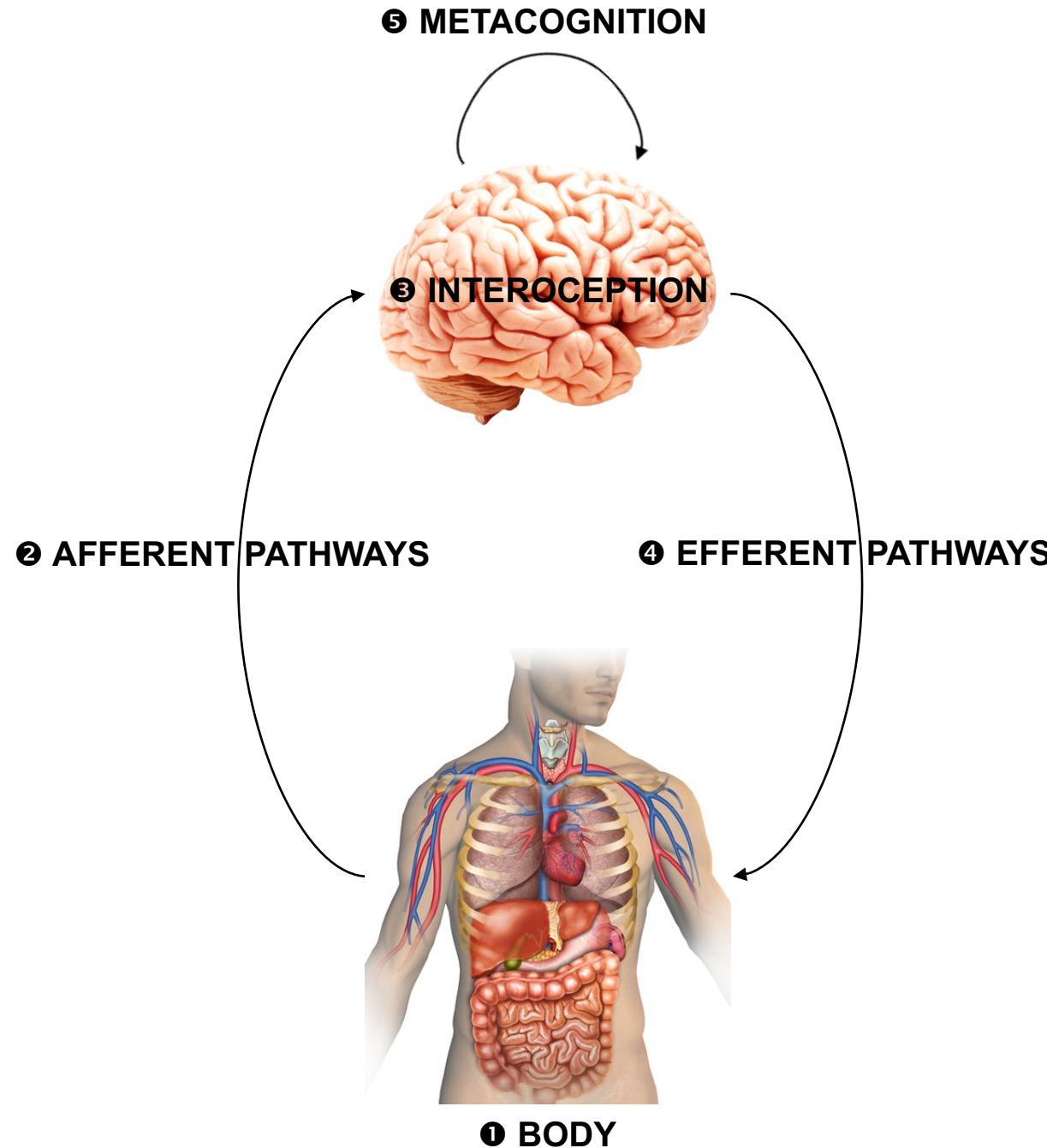
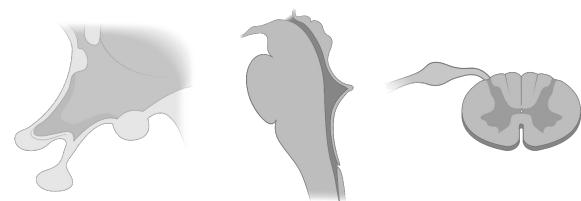




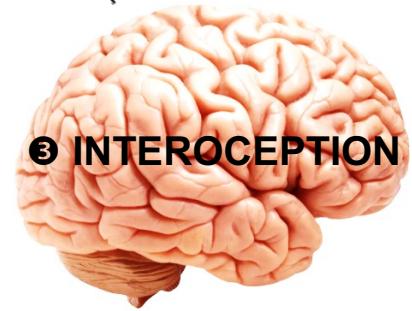
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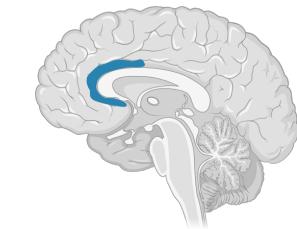
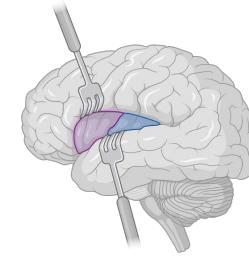




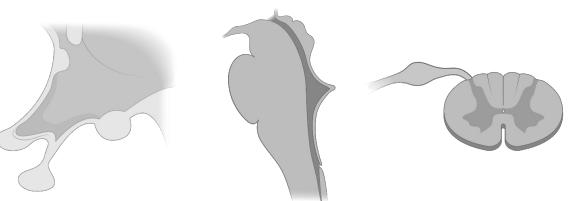
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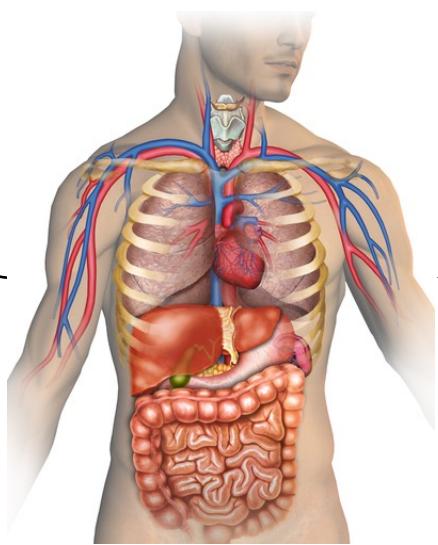
③ INTEROCEPTION



② AFFERENT PATHWAYS

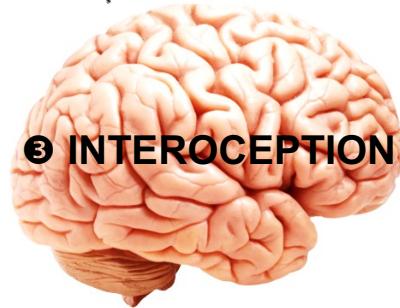


④ EFFERENT PATHWAYS

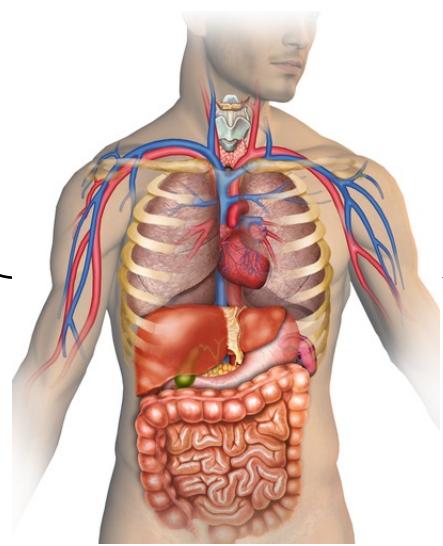


① BODY

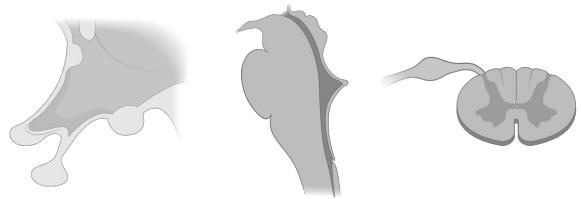
⑤ METACOGNITION



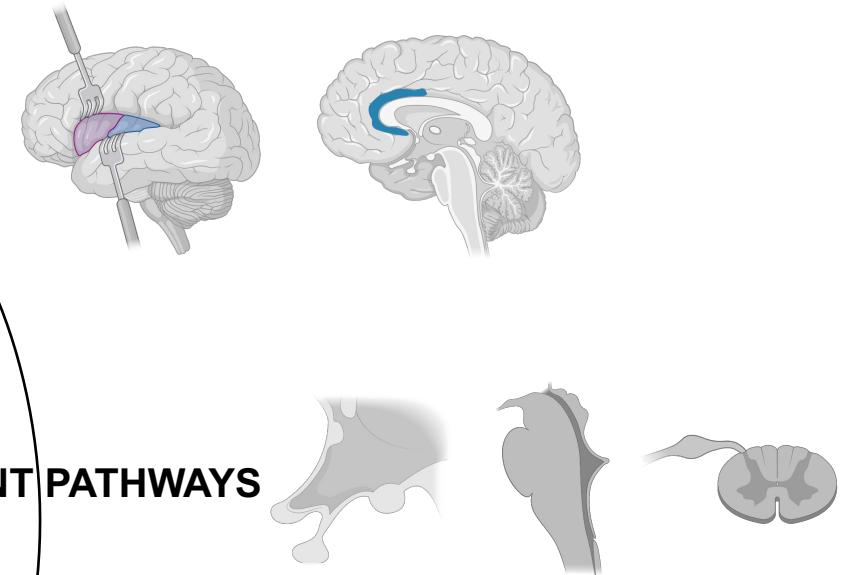
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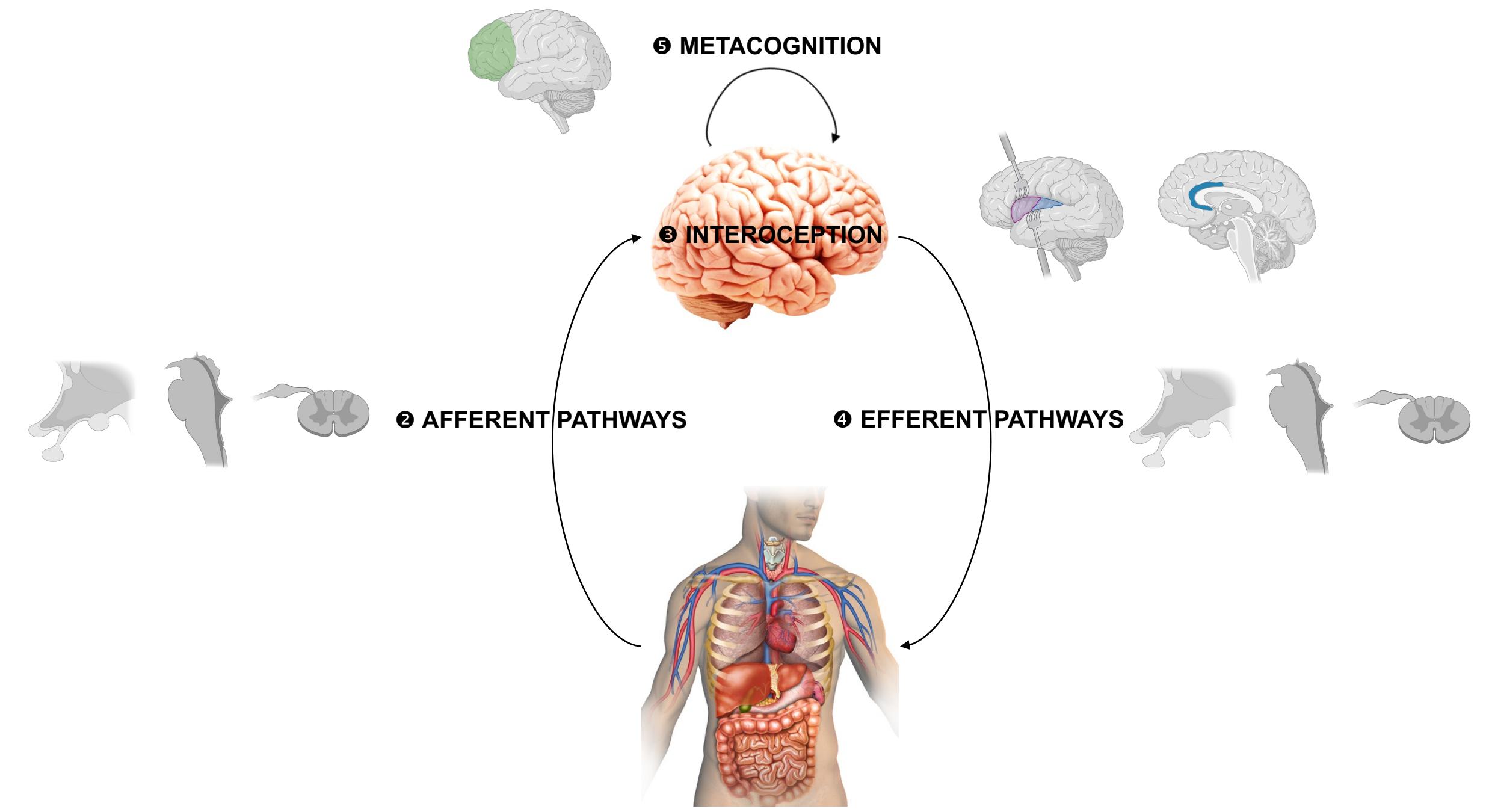


② AFFERENT PATHWAYS



④ EFFERENT PATHWAYS

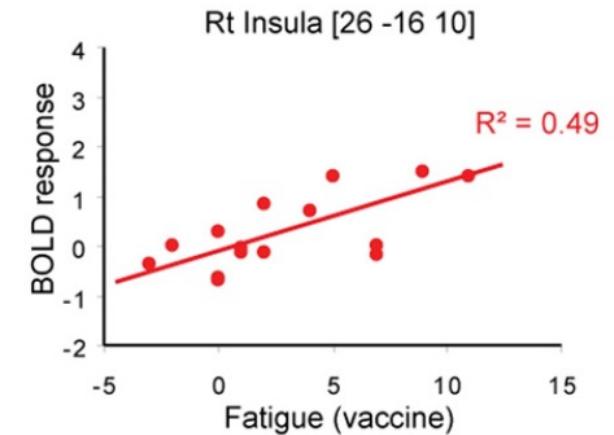
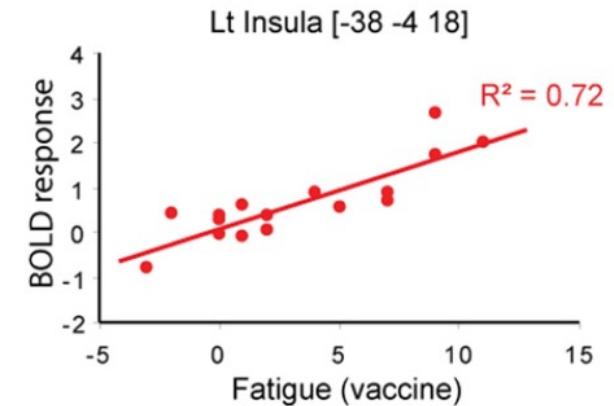




Empirical evidence?

Anatomical areas from the circuit model

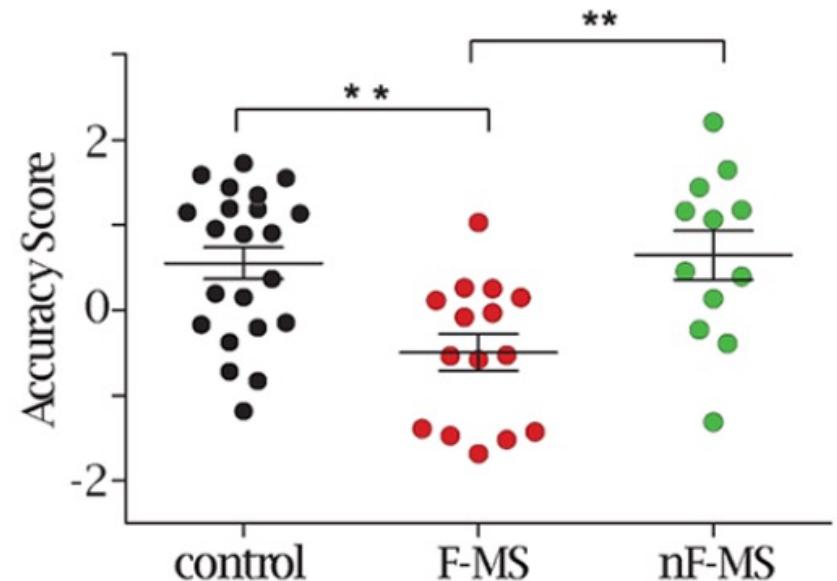
- Anterior and posterior insula:
 - Inflammation-induced microstructural changes are correlated with fatigue levels (Harrison *et al.*, 2015)
 - Among the most frequently affected cortical regions in MS (Haider *et al.*, 2016)
- Cingulate gyrus
 - Among the most frequently affected cortical regions in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

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





Analysis plan

RESEARCH REPORT

EJN European Journal of Neuroscience FENS Federation of European Neuroscience Societies

WILEY

Interoceptive and metacognitive facets of fatigue in multiple sclerosis

Marion Rouault^{1,2}  | Inês Pereira³  | Herman Galioulline³  |
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

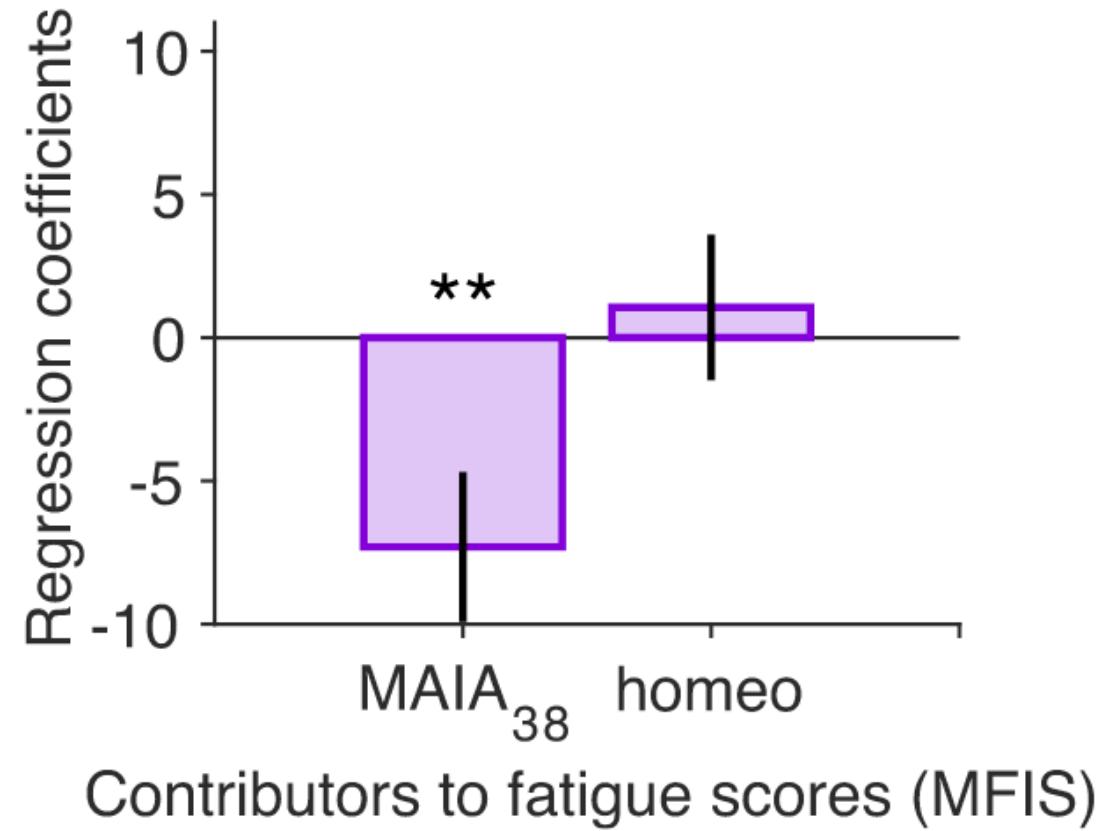


Table 4. Final Multidimensional Conceptual Framework of Body Awareness and Scales.

1) *Awareness of Body Sensations*

Noticing: Awareness of uncomfortable, comfortable, and neutral body sensations

2) *Emotional Reaction and Attentional Response to Sensations*

Not Distracting: Tendency to ignore or distract oneself from sensations of pain or discomfort

Not Worrying: Emotional distress or worry with sensations of pain or discomfort (reversed)

3) *Capacity to Regulate Attention: ability to stay focused when facing numerous sensory stimuli competing for attention*

Attention Regulation: Ability to sustain and control attention to body sensation

4) *Awareness of Mind-Body Integration: access to more developed levels of body awareness*

Emotional Awareness: Awareness of the connection between body sensations and emotional states

Self-Regulation: Ability to regulate psychological distress by attention to body sensations

Body Listening: Actively listens to the body for insight

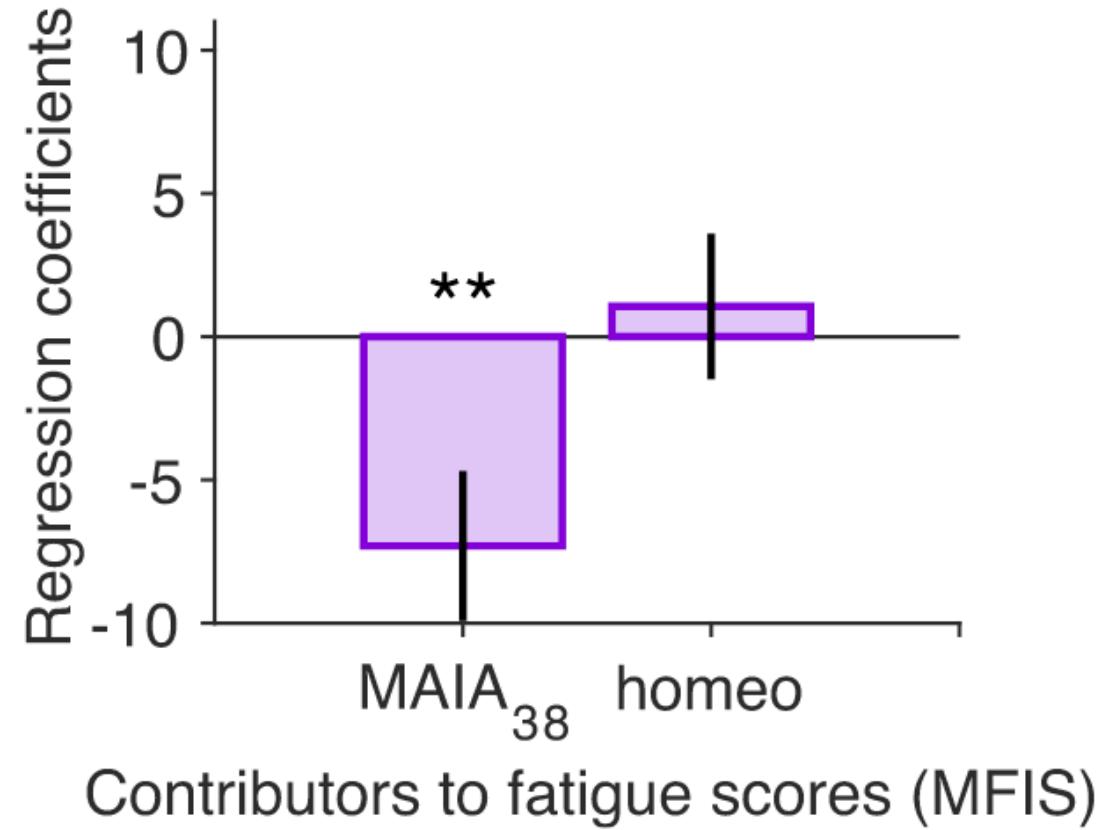
5) *Trusting Body Sensations*

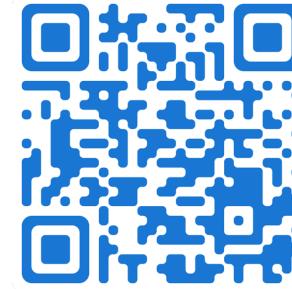
Trusting: Experiences one's body as safe and trustworthy

NOTE: Numbered, italicized concepts are overall dimensions; scale names are bolded.

doi:10.1371/journal.pone.0048230.t004

Results





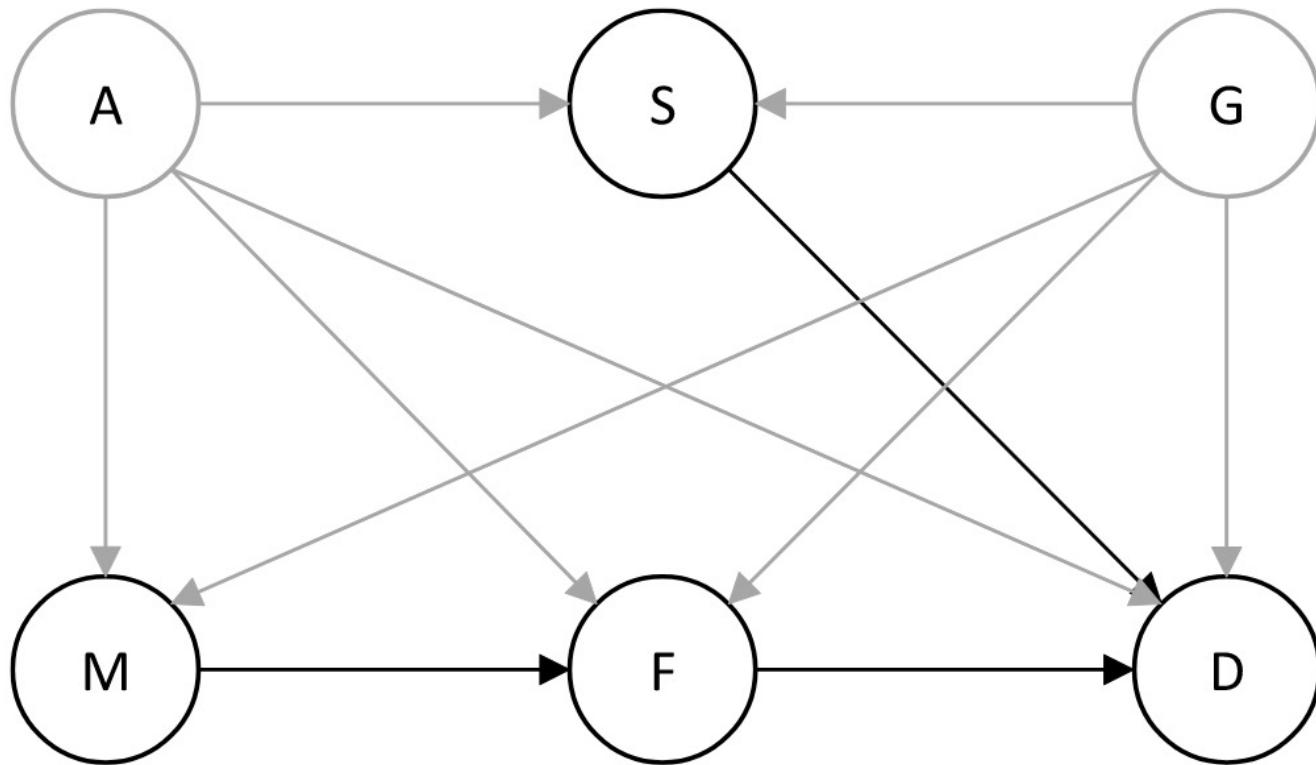
Analysis plan



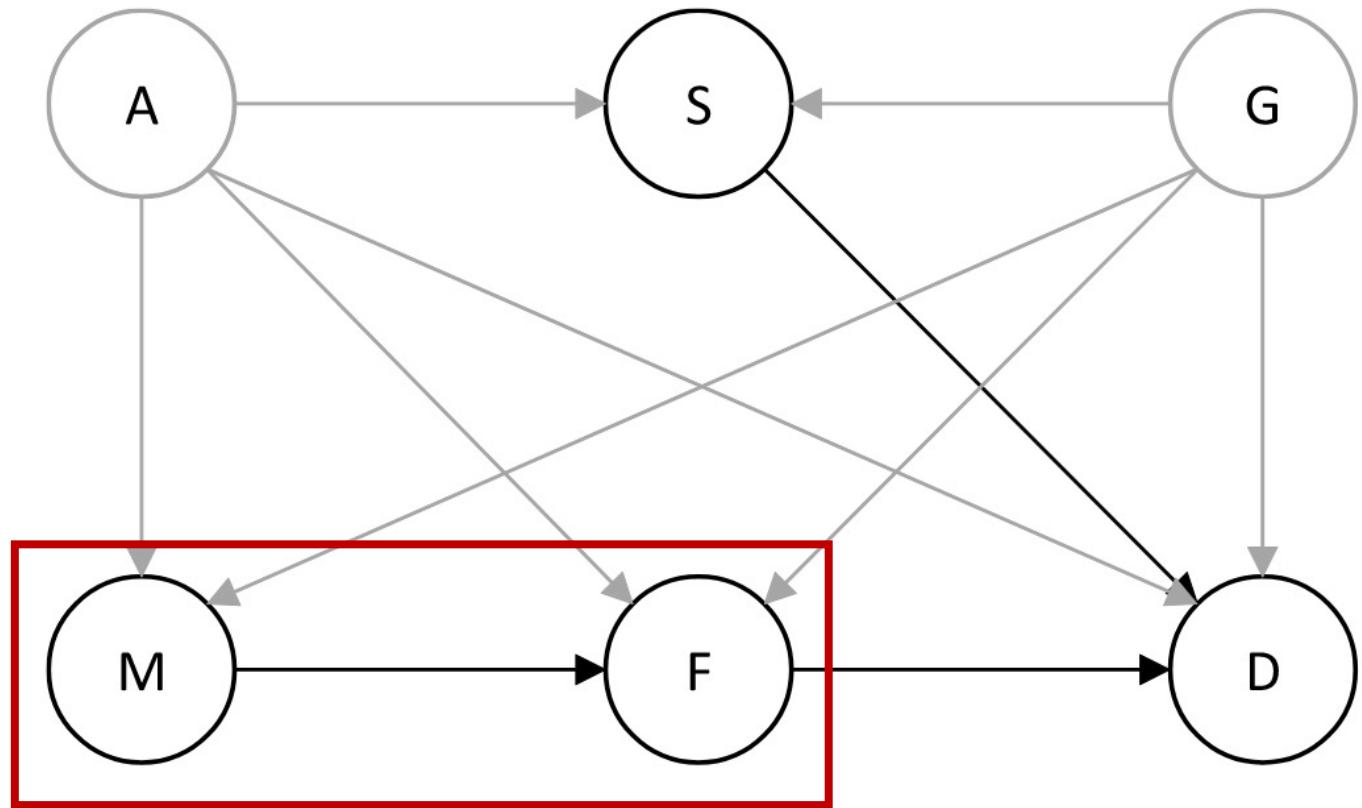
Article

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

Alexander J. Hess ^{1,*}, Dina von Werder ^{1,2,3}, Olivia K. Harrison ^{1,4}, Jakob Heinzle ¹ and Klaas Enno Stephan ^{1,5}



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



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



Zina-Mary
Manjaly



Réka Enz



Delania Meng



Stefania Mare



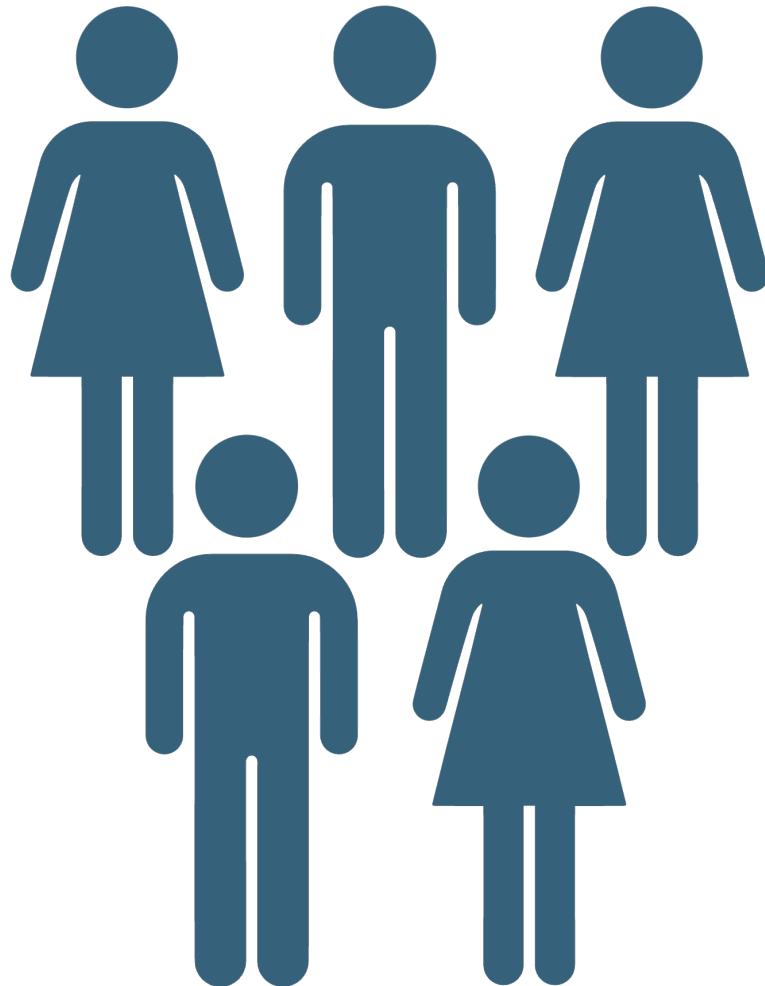
Laura Köchli

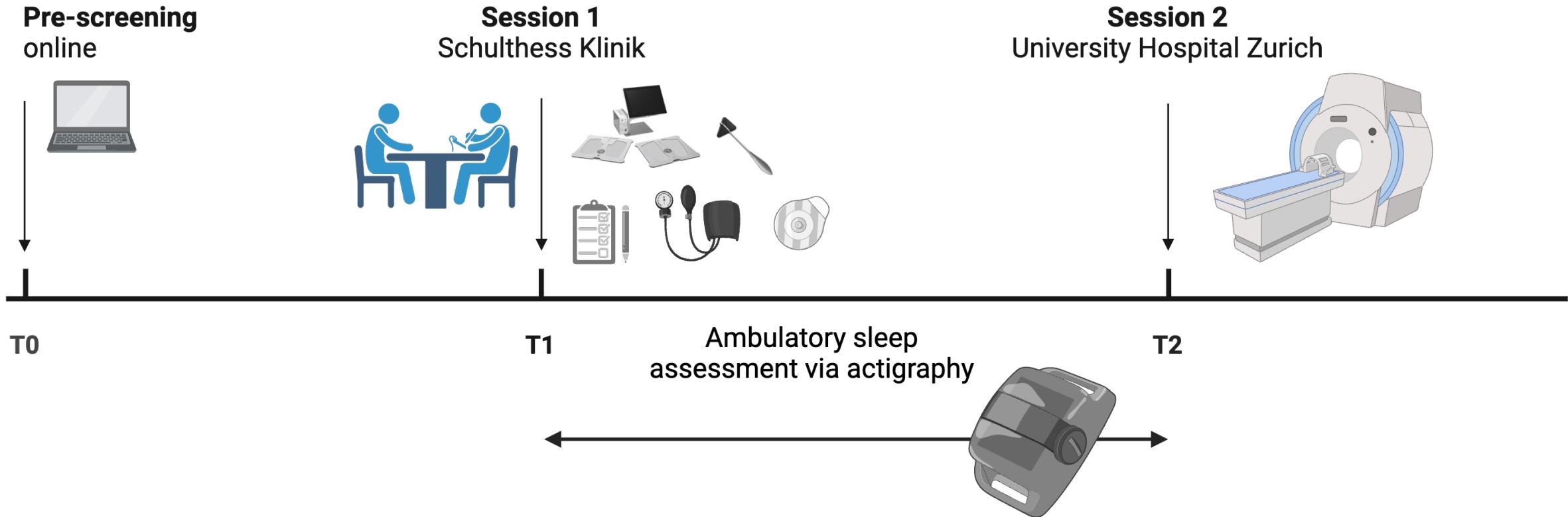


Inês Pereira

Participants

- N=75
- Age: 18-50 years
- All MS subtypes
- Different levels of fatigue
(FSS and FSMC Scores)

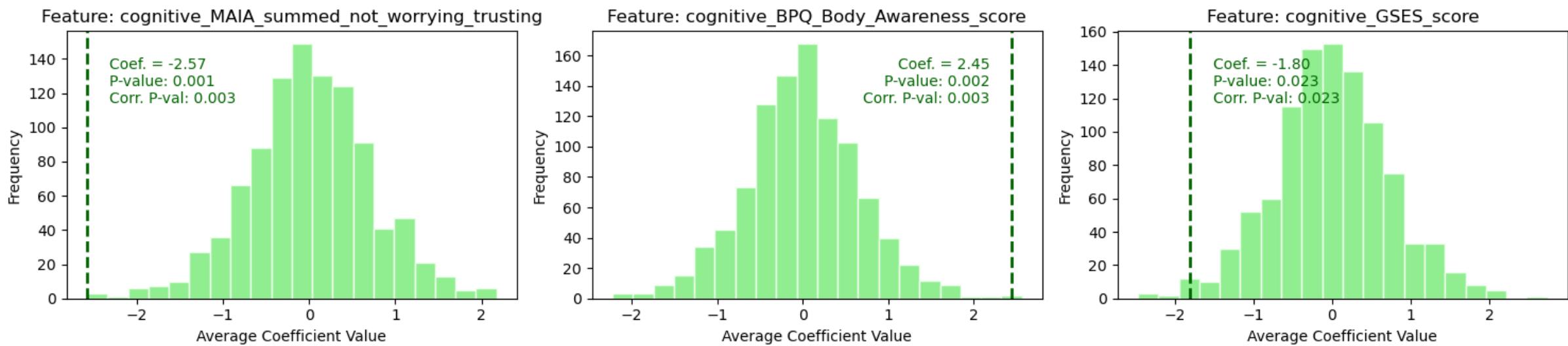




Category	Feature
qT2 imaging features	Median T2-rt for each ROI (22 ROIs in total)
fMRI features	rDCM connectivity estimates (484 connections)
Physiological features	Heart rate variability (RMSSD) Average skin conductance of upper extremities Average skin conductance of lower extremities Systolic blood pressure difference (lying versus standing) Diastolic blood pressure difference (lying versus standing) Heart rate difference (lying versus standing)
Sleep features	PSQI score (0-21) ESS score (0-24) ISI score (0-28) Sleep onset latency in minutes (mean) Sleep onset latency in minutes (SD) Total sleep time in hours (mean) Total sleep time in hours (SD) Sleep efficiency in % (mean) Sleep efficiency in % (SD)
Clinical features	Age (years) Sex (binary 0/1) Relapsing-remitting MS (binary 0/1) EDSS score (0-10) Disease duration (years) Disease-modifying therapy (binary 0/1) Sedative medication (binary 0/1) Urge symptoms (binary 0/1) Complete bladder emptying (binary 0/1) Incontinence (binary 0/1) Sexual dysfunction (binary 0/1) PHQ-2 score (0-6)
Cognitive features	BPQ Body Awareness subscale (1-5) GSES score (10-40) MAIA subscales 3+8 (0-10)

	MAE	p-value (corrected)
FSS		
<i>1st-level models</i>		
Sleep model	7.13	0.003
Clinical model	8.39	0.003
Cognitive model	10.92	0.108
fMRI model	11.35	0.312
qT2 model	10.92	0.108
Physiological model	13.33	0.980
<i>2nd-level model</i>	7.67	0.001
FSMC		
<i>1st-level models</i>		
Sleep model	9.13	0.006
Clinical model	14.95	0.009
Cognitive model	16.30	0.040
fMRI model	16.06	0.044
qT2 model	18.32	0.754
Physiological model	19.38	0.986
<i>2nd-level model</i>	13.98	0.001

Average Coefficient Distributions for First-level Model: cognitive_



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!



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 - Klaas Enno Stephan
 - Zina-Mary Manjaly
 - ... for all their input!
- Figures made with Biorender.com

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

Questions?

Thank you for your attention!



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