Psychoneuroimmunology

TABLE 1-3 Comparison of innate and adaptive immunity

	Innate	Adaptive
Response time	Hours	Days
Specificity	Limited and fixed	Highly diverse; improves during the course of immune response
Response to repeat infection	Identical to primary response	Much more rapid than primary response
Major components	Barriers (e.g., skin); phagocytes; pattern recognition molecules	Lymphocytes; antigen-specific receptors; antibodies

Table 1-3
Kuby IMMUNOLOGY, Sixth Edition

Cytokine Actions in the Brain: From Sickness Behavior to Depression

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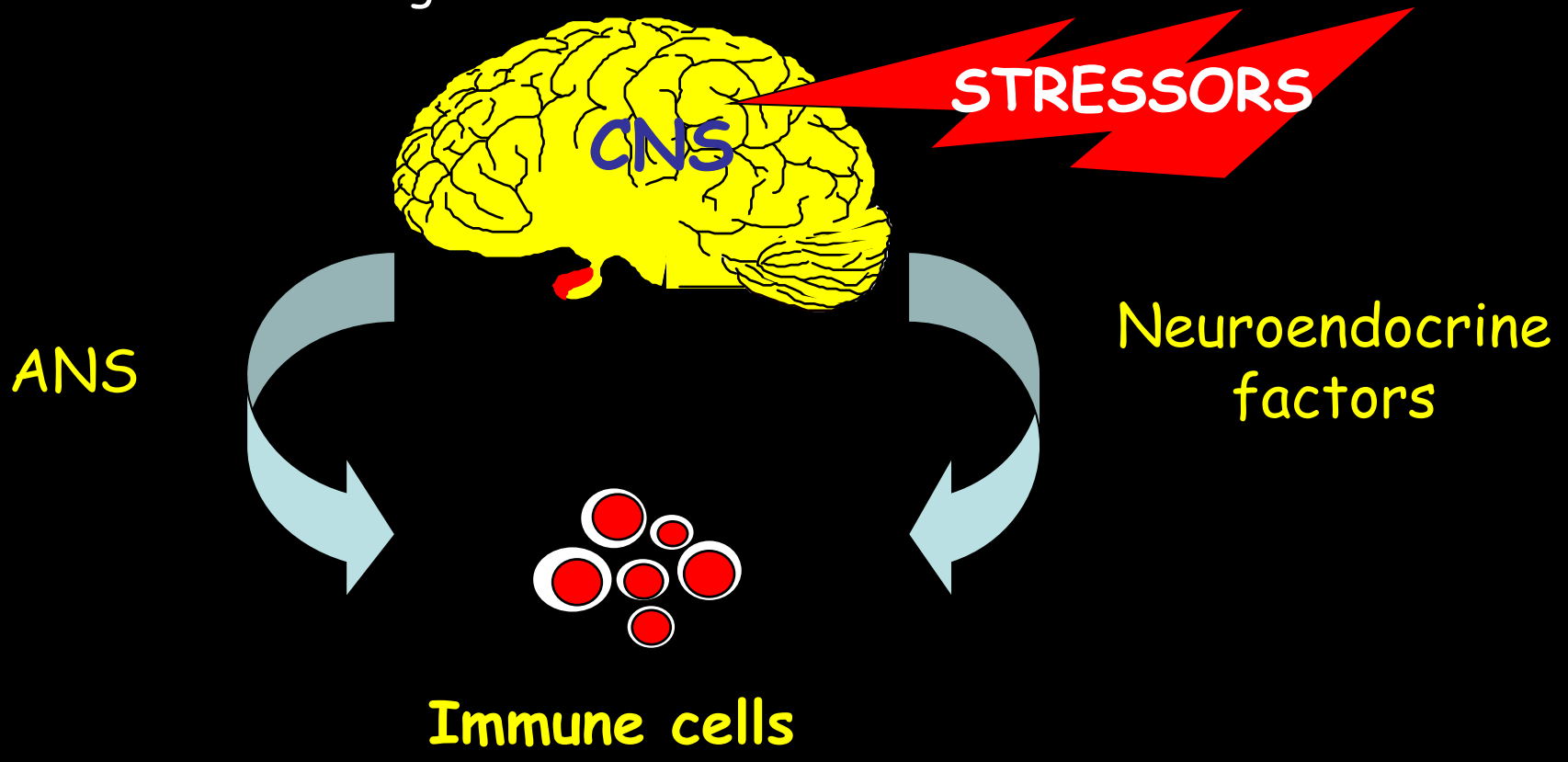
The Golden Age of Psychoneuroimmunology in the 1970s: Immune Responses are Modulated by Brain Events

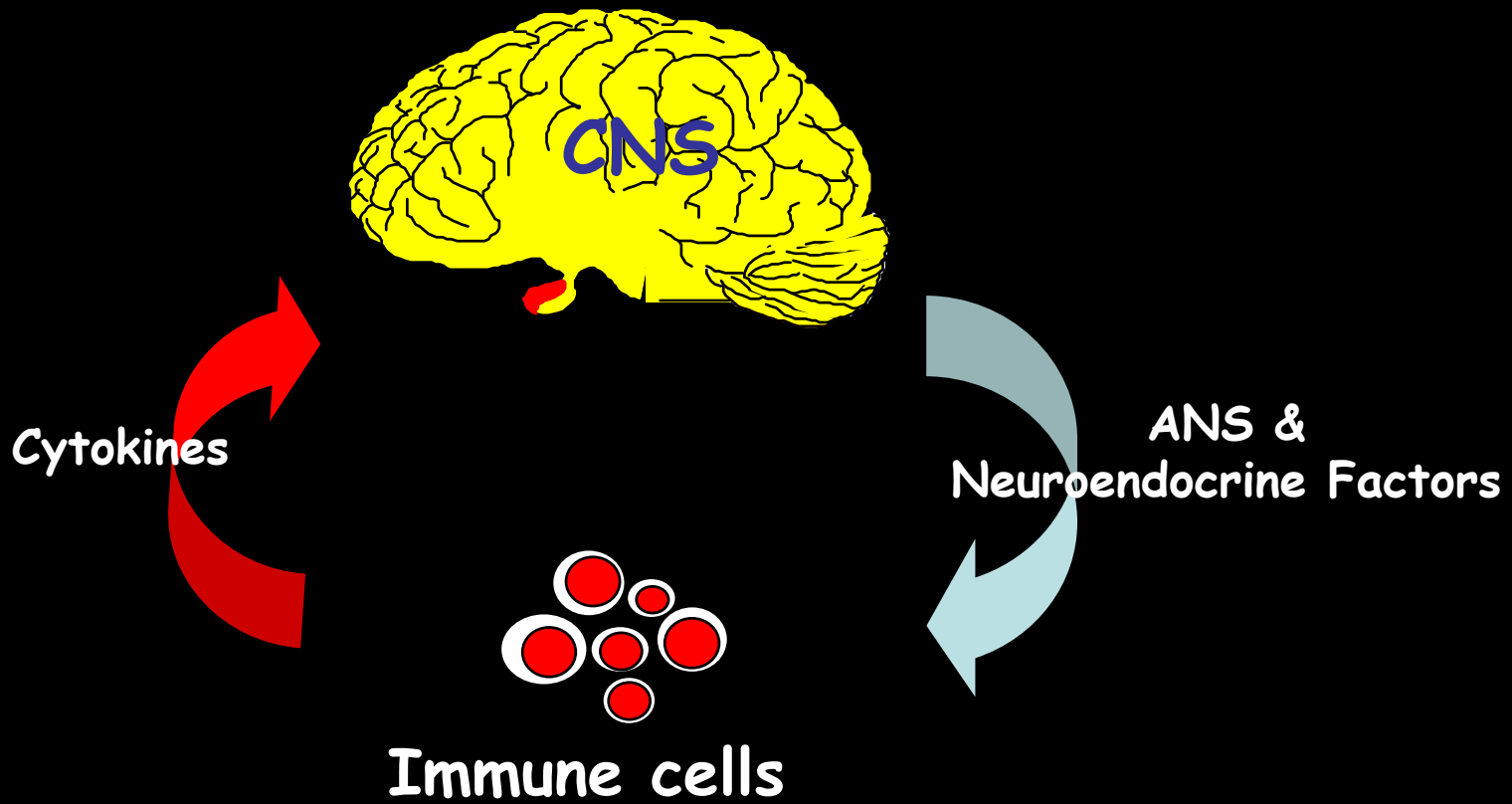
- What is processed by the brain has an impact on the functioning of the immune system (e.g., psychosocial events, emotions…).
- This is possible because the immune system is connected to the brain via autonomic nerves and neuroendocrine factors and shares common cellular communication messengers.

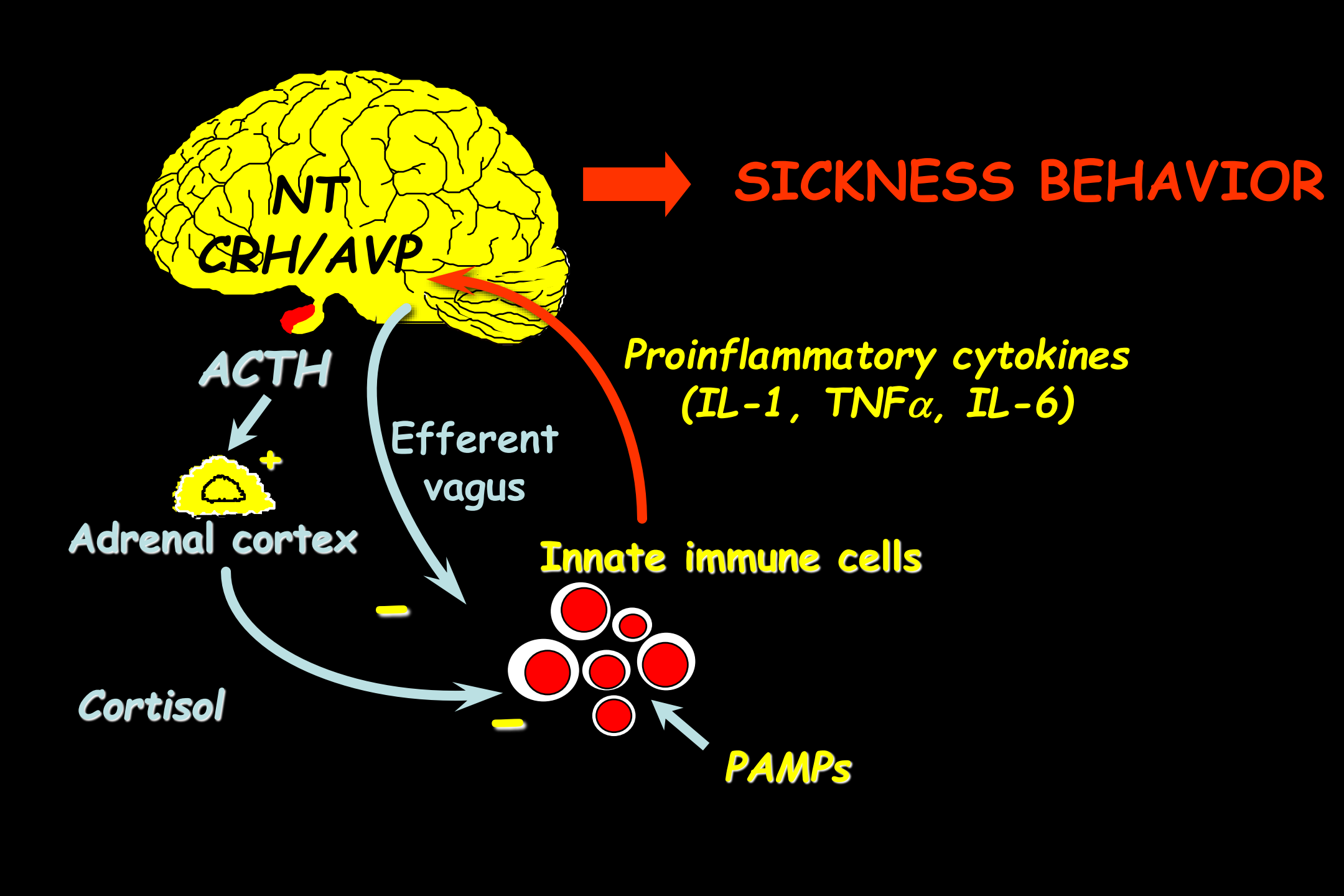


An Emerging Concept in the late 1980s: The Immune System Needs to Talk to the Brain

- Like any other physiological system in the body, the immune system needs the brain to do what it has to do and to be regulated

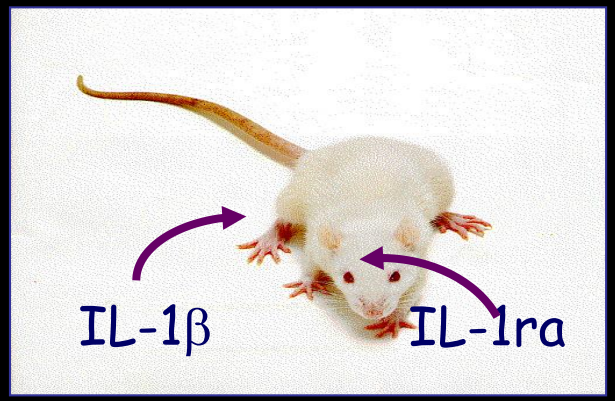
- If it is the case, the brain has an « immunostat » that enables it to perceive and represent what is going on in the immune system, using immune cell communication molecules **(cytokines)**

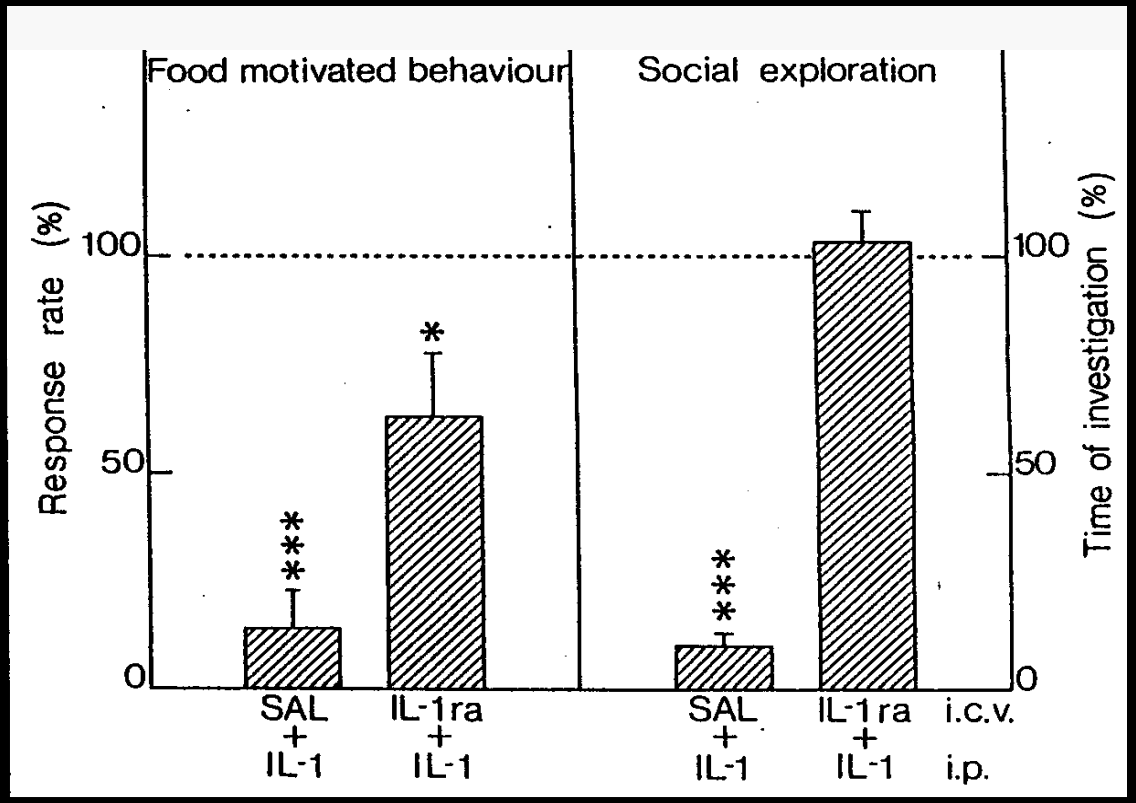



NT
CRH/AVP
SICKNESS BEHAVIOR
ACTH
Proinflammatory cytokines
(IL-1, TNFα, IL-6)
Efferent
vagus
+
Adrenal cortex
Innate immune cells
−
Cortisol
−
PAMPs

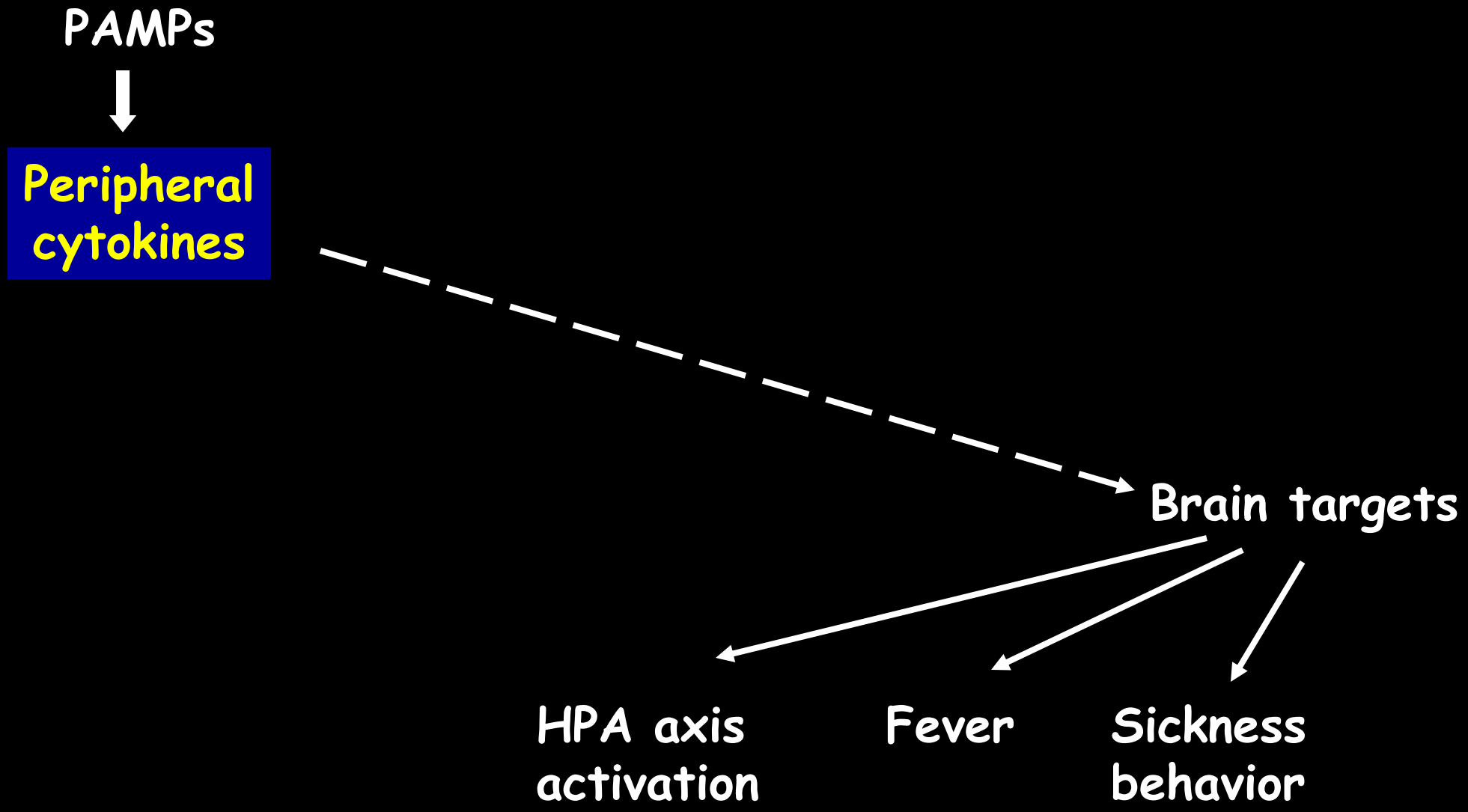
1. **What are the mechanisms of action of cytokines on the brain?**
2. How is organized the sickness response to cytokines?
3. How does sickness behavior translate into pathology?

The sickness inducing effects of peripheral IL-1 are mediated centrally (from Kent et al, 1992)

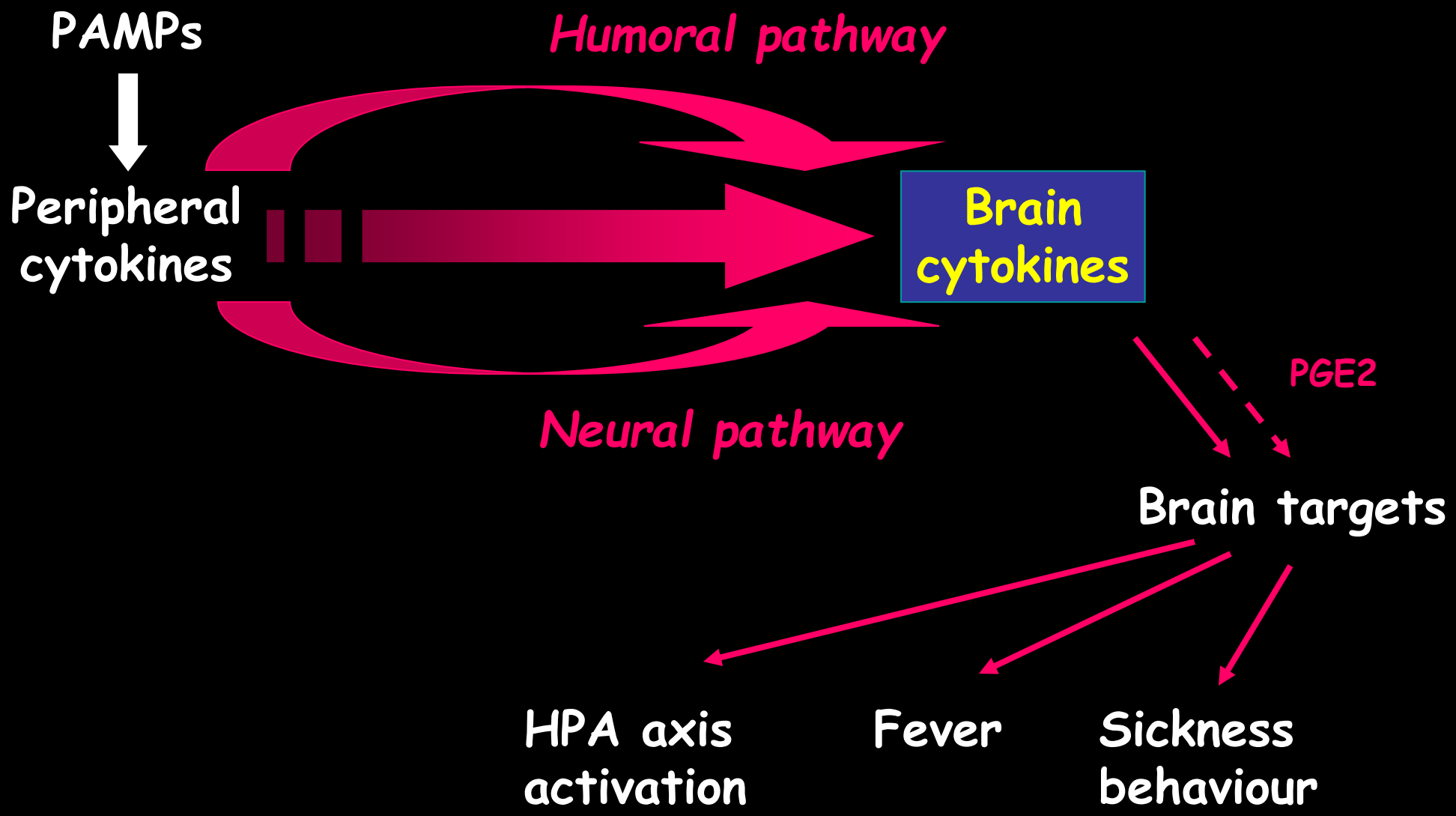




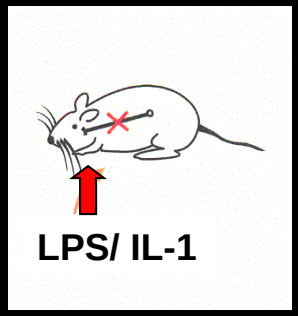
How can peripherally produced cytokines act in the brain?



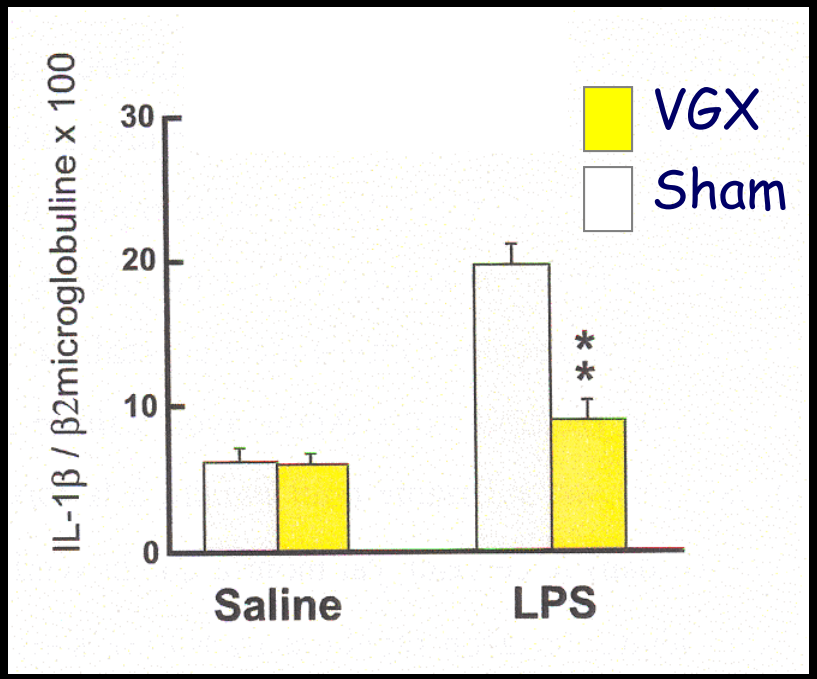
Peripheral cytokines do not need to get into the brain because they are produced in the brain



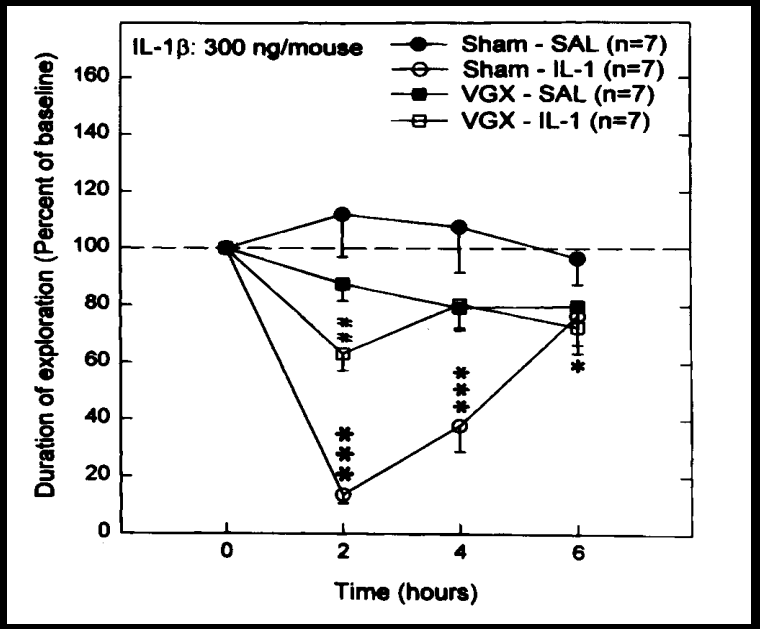
Vagotomy abrogates the induction of hypothalamic IL-1β expression and sickness behavior



Hypothalamic expression of IL-1β



Social exploration



From Layé, Bluthe et al, 1995

Conclusions

- By their actions on the brain, proinflammatory cytokines produced by activated macrophages and monocytes induce sickness behavior
- The brain forms a molecular and cellular representation of the peripheral immune response
- This representation is mediated by several immune-to-brain communication pathways including a neural pathway that is critical for sickness behavior

1. Why do we feel and behave in a sick way when we are ill?
2. **How is organized the sickness response to cytokines?**
3. How does sickness behavior translate into pathology?

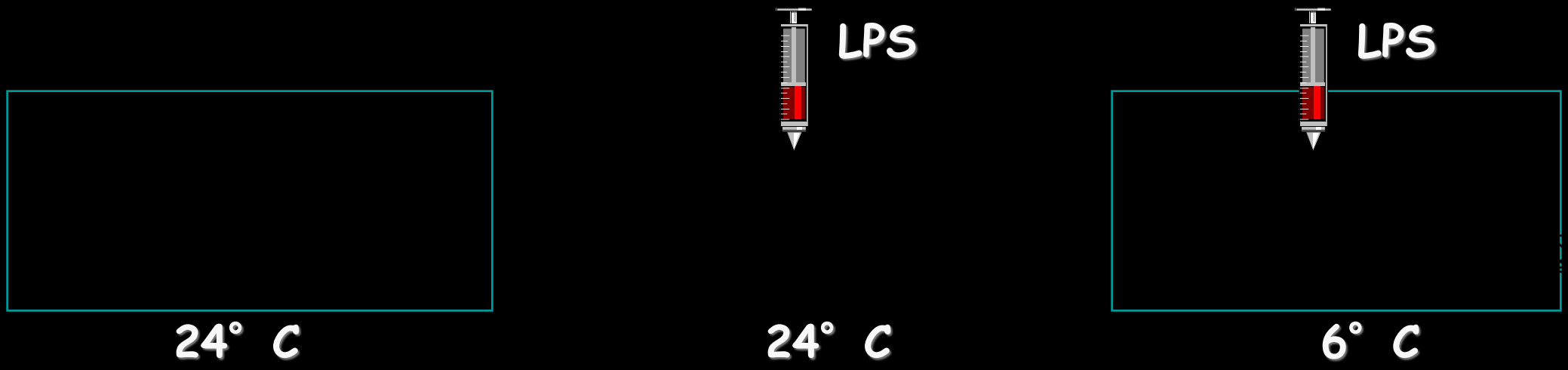
The behavioral effects of cytokines correspond to a reorganization of the host's priorities (Aubert et al., 1997)

Medical interpretation

Cytokines → Internal state (weakness) → Behavioral alterations

Motivational interpretation

Cytokines → Internal state → Environmental contingencies → Behavioral alterations



MOTIVATIONAL INTERPRETATION OF FEAR

Threat → **Fear** →

- Fear feelings
- Fear behavior
- Visceral arousal

MOTIVATIONAL INTERPRETATION OF SICKNESS

Threat → **Fear** →

- Fear feelings
- Fear behavior
- Visceral arousal

Pathogenic micro-organisms → **Sickness** →

- Malaise
- Sickness behavior
- Visceral arousal

- The brain forms a representation of the peripheral innate immune response. This representation is at the origin of sickness behavior

- Sickness behavior corresponds to a reorganization of the host's priorities.

- Sickness behavior is normally fully reversible

Georges Canguilhem: « être en bonne santé, c'est pouvoir tomber malade et s'en relever » (To be healthy is to be able to become ill and recover from it…)

1. Why do we feel and behave in a sick way when we are ill?
2. How is organized the sickness response to cytokines?
3. **How does sickness behavior translate into pathology?**

What does happen when the innate immune system remains activated?

Examples :

- Chronic inflammatory disorders
- Chronic administration of exogenous cytokines
- Cancer
- Aging
- Viral pathologies

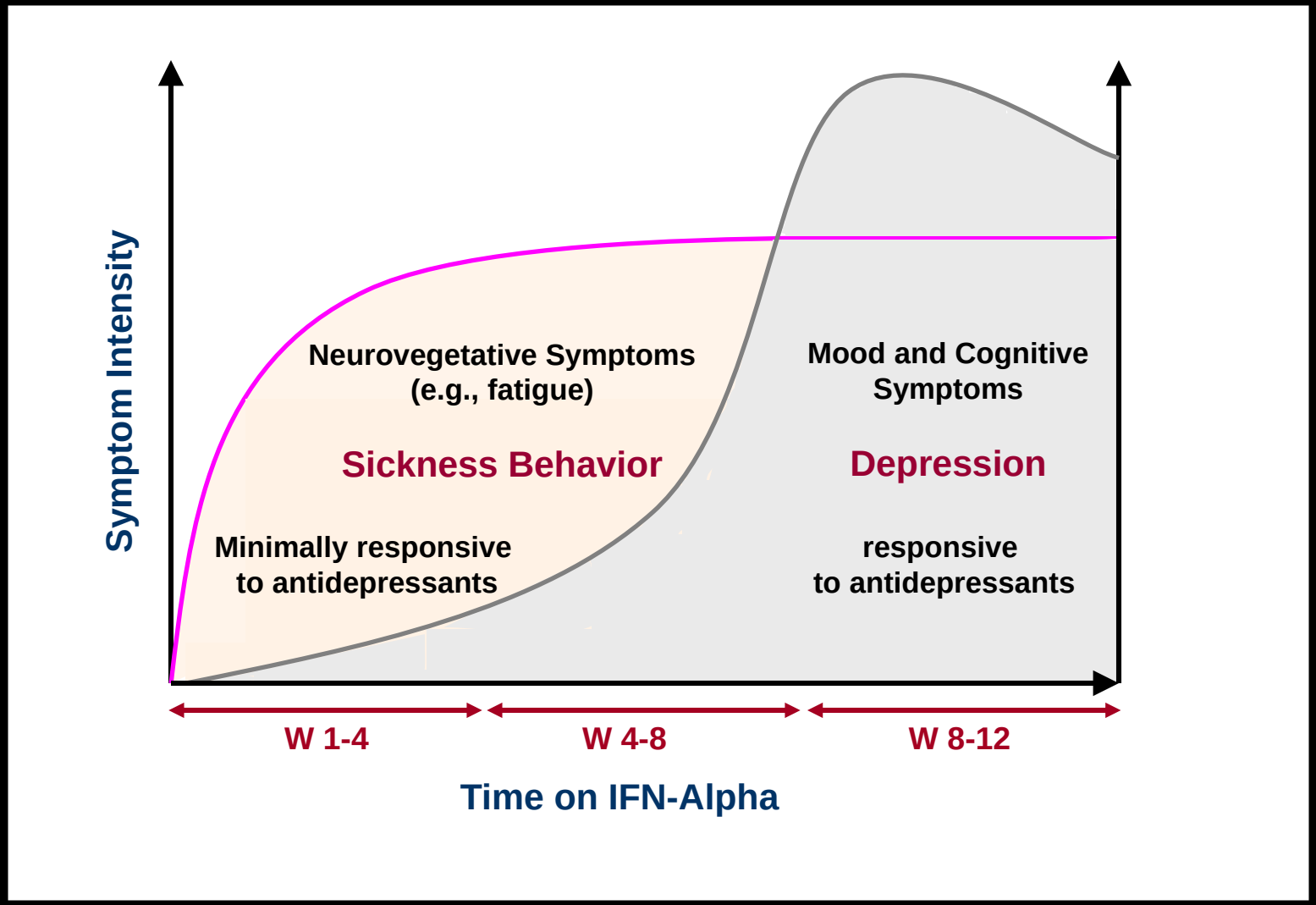
Each of these conditions is associated not only with specific signs of the disease but also with non specific symptoms of an exaggerated sickness response such as fatigue and an increased incidence of affective and cognitive disorders.

Prevalence of Depression in Patients with Immune-based Disorders

Condition	Prevalence
✧ General Population	5-10%
✧ Cancer	18-39%
✧ Autoimmune Disorders	15-40%
✧ Cardiovascular Disease	15-40%
✧ Chronic illnesses (e.g. irritable bowel syndrome, chronic fatigue syndrome)	15-60%
✧ Obesity / Metabolic Syndrome	20-30%

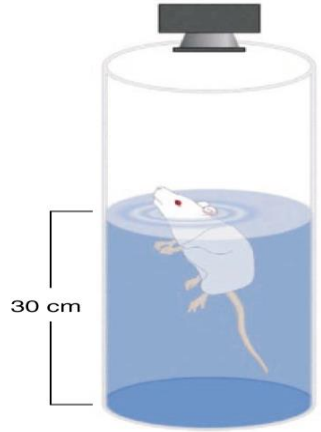
See for review, Evans et al., *Biological Psychiatry*, 58, 2005

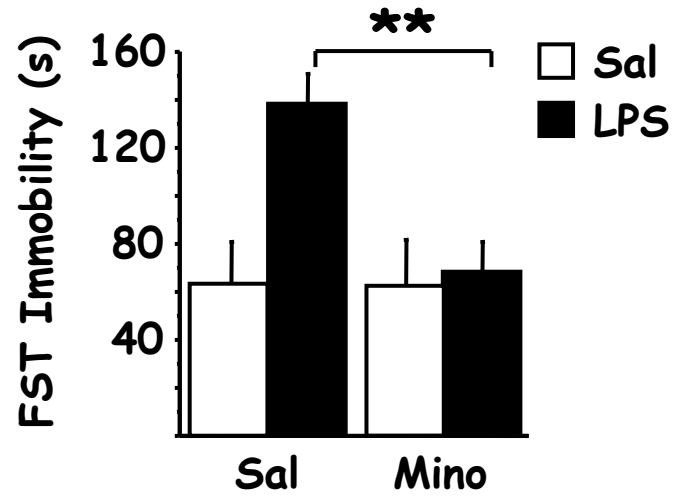
Temporal Evolution of the Behavioral Symptoms Induced by Chronic Cytokine Therapy



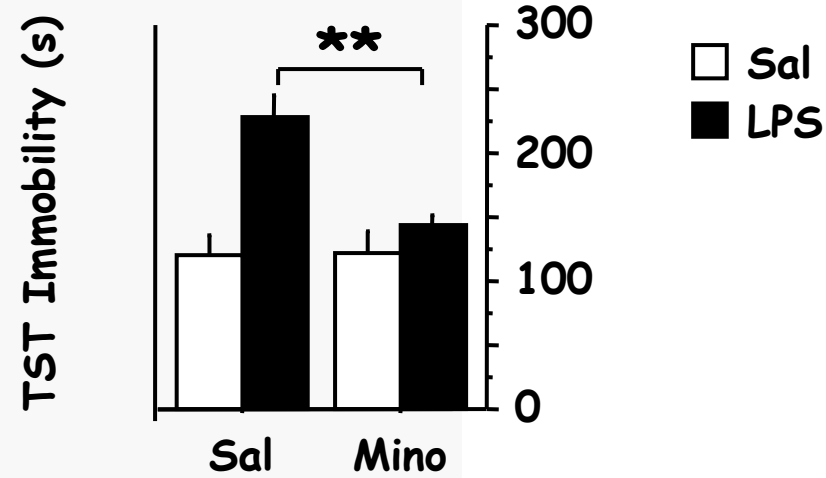
BLOCKADE OF PROINFLAMMATORY CYTOKINE EXPRESSION BY MINOCYCLINE ABROGATES LPS-INDUCED DEPRESSIVE-LIKE BEHAVIOR

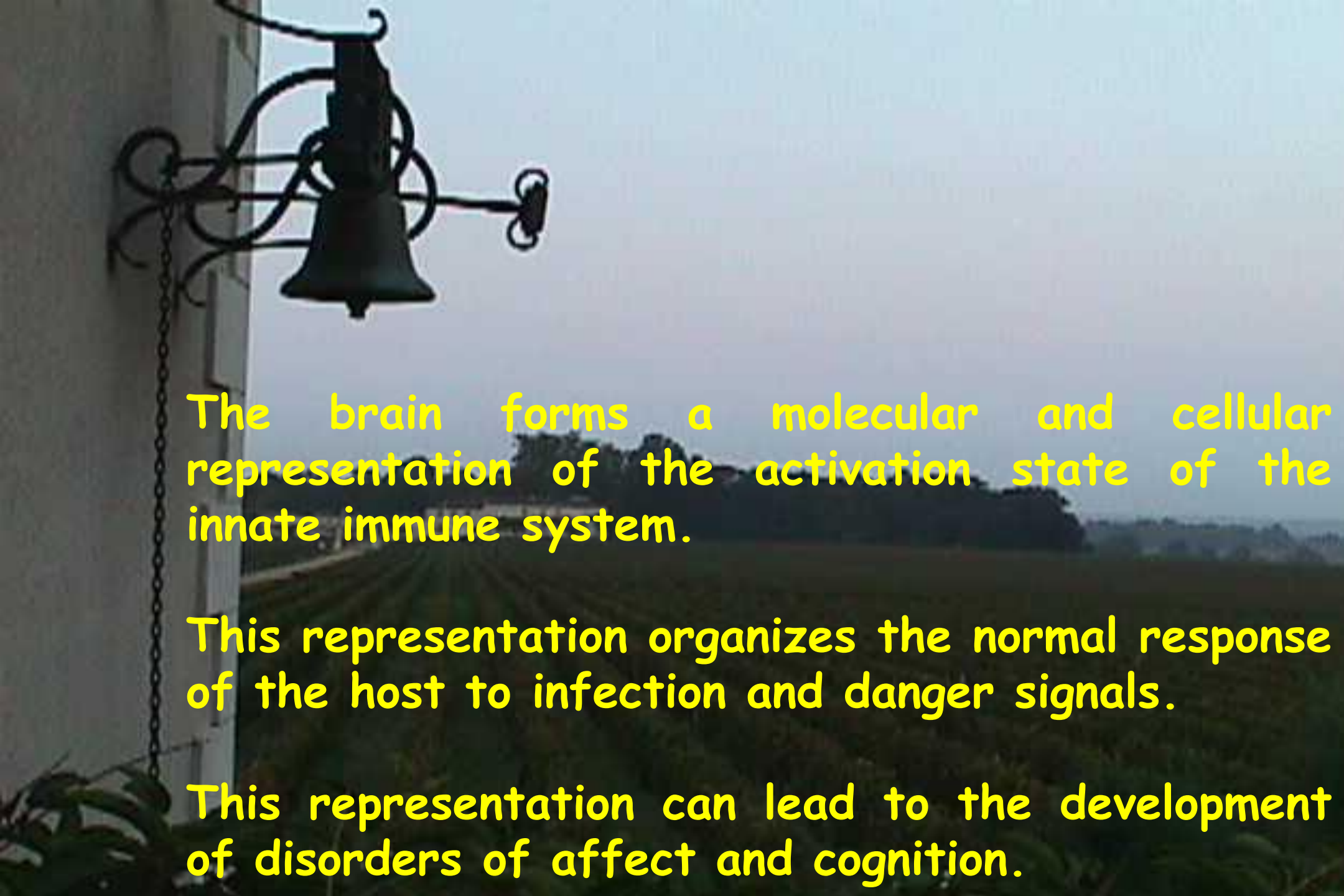
Forced Swim Test





Tail Suspension Test





The brain forms a molecular and cellular representation of the activation state of the innate immune system.

This representation organizes the normal response of the host to infection and danger signals.

This representation can lead to the development of disorders of affect and cognition.

Review of sickness behavior evidence

- increased prevalence of clinical depression in physically ill people
- peripheral or central administration of lipopolysaccharide (LPS) or cytokines directly, induces sickness behaviour
- major depressive disorders develop in roughly a third of patients who are treated with the recombinant human cytokines
- some depressed patients have increased peripheral inflammatory markers