Psychoneuroimmunology
<table>
<thead>
<tr>
<th></th>
<th>Innate</th>
<th>Adaptive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response time</td>
<td>Hours</td>
<td>Days</td>
</tr>
<tr>
<td>Specificity</td>
<td>Limited and fixed</td>
<td>Highly diverse; improves during the course of immune response</td>
</tr>
<tr>
<td>Response to repeat infection</td>
<td>Identical to primary response</td>
<td>Much more rapid than primary response</td>
</tr>
<tr>
<td>Major components</td>
<td>Barriers (e.g., skin); phagocytes; pattern recognition molecules</td>
<td>Lymphocytes; antigen-specific receptors; antibodies</td>
</tr>
</tbody>
</table>
Cytokine Actions in the Brain: From Sickness Behavior to Depression

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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).
PAMPs + ACTH

Innate immune cells

Cortisol

NT

CRH/AVP

Adrenal cortex

Proinflammatory cytokines
(IL-1, TNFα, IL-6)

SICKNESS BEHAVIOR

Efferent vagus

Innate immune cells

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?

PAMPs

Peripheral cytokines

Brain targets

HPA axis activation

Fever

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

PAMPs → Peripheral cytokines

**Humoral pathway**

<table>
<thead>
<tr>
<th>Brain cytokines</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPA axis activation</td>
</tr>
<tr>
<td>Fever</td>
</tr>
<tr>
<td>Sickness behaviour</td>
</tr>
</tbody>
</table>

**Neural pathway**

Brain targets

PGE2
Vagotomy abrogates the induction of hypothalamic IL-1β expression and sickness behavior

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 \(\rightarrow\) Internal state (weakness) \(\rightarrow\) Behavioral alterations

**Motivational interpretation**

Cytokines \(\rightarrow\) Internal state \(\rightarrow\) Environmental contingencies \(\rightarrow\) Behavioral alterations

Environmental contingencies

- LPS
- LPS

Temperature conditions:
- 24°C
- 24°C
- 6°C
MOTIVATIONAL INTERPRETATION OF FEAR

- Threat
- Fear
- Fear feelings
- Fear behavior
- Visceral arousal

The image shows a diagram illustrating the motivational interpretation of fear, with "Fear" as the response to a threat.
MOTIVATIONAL INTERPRETATION OF SICKNESS

Pathogenic microorganisms → Sickness

Threat → Fear

Fear feelings
Fear behavior
Visceral arousal

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

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

See for review, Evans et al., *Biological Psychiatry*, 58, 2005
Temporal Evolution of the Behavioral Symptoms Induced by Chronic Cytokine Therapy

- Neurovegetative Symptoms (e.g., fatigue)
- Mood and Cognitive Symptoms
  - Minimally responsive to antidepressants
  - Responsive to antidepressants

Symptom Intensity over Time on IFN-Alpa:
- W 1-4: Sickness Behavior
- W 4-8: Transition from Sickness Behavior to Mood and Cognitive Symptoms
- W 8-12: Peak Depression
BLOCKADE OF PROINFLAMMATORY CYTOKINE EXPRESSION BY MINOCYCLINE ABROGATES LPS-INDUCED DEPRESSIVE-LIKE BEHAVIOR

Forced Swim Test

Tail Suspension Test

![Forced Swim Test Image](image1.png)

![Tail Suspension Test Image](image2.png)

**Graph 1:**
- Sal
- LPS

**Graph 2:**
- Sal
- Mino

**Graph 3:**
- Sal
- LPS

**Graph 4:**
- Sal
- Mino

**Graph 5:**
- Sal
- LPS
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