Motivational aspects of inflammation-induced fatigue
Cytokine actions in the brain account for why we feel sick and behave in a sick way when we are ill.

Pathogen-/damage-associated molecular patterns
Toll-like receptors
Inflammosome

Activation of innate immunity

Peripheral proinflammatory cytokines
NF-kappaB
MAP kinase pathways

Immune-to-brain communication pathways

Endothelial activation
Microglial activation
Brain proinflammatory cytokines

Sickness behavior with its metabolic and neuroendocrine accompaniment
What does it mean to feel sick and behave in a sick way?
Animals that are acutely ill with systemic protozoan, bacterial or viral infections are typically described as depressed and lethargic, with little interest in eating food and drinking water. A little later in the course of a disease they commonly show signs of dehydration along with indications that they have lost interest in grooming since they develop rough hair coats...
Re-allocation of energy during inflammation

NORMAL

Immune system

Thermoregulation

Metabolic energy

Muscles

Brain

INFLAMMATION

Immune system

Thermoregulation

Metabolic energy

Muscles

Brain
Sickness behavior is the expression of a motivational state
(Miller NE, Some psychophysiological studies of the motivation and of the behavioral effects of illness, Bull British Psychol Soc, 1964, 17, 1-20)

Forced exercise in a motorized wheel: rats injected with endotoxin work more than controls to stop running

Operant responding for food, water or intracranial rewarding electrical stimulation: rats injected with endotoxin work less than controls

Endotoxin-induced sickness is a motivational state
Sickness behavior is associated with a reorganization of host priorities (Aubert et al., Brain Behav Immun 1997, 11:229-238)

**Motivational interpretation of sickness behavior**

Cytokines → Internal state → Environmental contingencies → Behavioral alterations

In a situation of motivational competition, the resulting behavior will depend on the relative strength of the incentives for each motivation

**Example**: sickness behavior vs. maternal behavior

24°C  

![24°C sick behavior](image)

24°C  

![24°C maternal behavior](image)

6°C  

![6°C sick behavior](image)
What is the relationship between sickness and depression? Symptoms of depression develop on a background of sickness.
Major depressive disorders are associated with biomarkers of inflammation

<table>
<thead>
<tr>
<th>Study name</th>
<th>Subgroup within study</th>
<th>Cumulative statistics</th>
<th>Cumulative std diff in means (95% CI)</th>
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</thead>
<tbody>
<tr>
<td></td>
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<td>Standard error</td>
<td>Lower limit</td>
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<td>Joyce PR et al., 2002</td>
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<td>Hughes et al., 2012</td>
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<td>Rudolf S et al., 2014</td>
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<td>0.496</td>
<td>0.096</td>
</tr>
</tbody>
</table>

**CRP**

(d=0.47 (0.28-0.65))

**IL-6**

(d=0.54 (0.40-0.69))

Haapakoski et al., Cumulative meta-analysis of interleukins 6 and 1β, tumour necrosis factor α and C-reactive protein in patients with major depressive disorder, Brain Behav Immun, 2015
What are the symptoms that are characteristic of inflammation-induced depression?

Symptoms of depression

**Mood**
- Sadness
- Pessimism
- Suicidal thoughts
- Crying
- Agitation
- Irritability

**Neurovegetative**
- Fatigue
- Loss of energy
- Sleep alterations
- Changes in appetite
- Anhedonia/loss of interest
- Indecisiveness
- Concentration difficulties

**Affective-cognitive**
- Failure
- Guilty feelings
- Punishment feelings
- Self-dislike
- Self-criticism
- Worthlessness

BDI Factor Analysis
Population studies show that inflammation-associated depression is characterized by somatic symptoms.

ELSA cohort initiated in 2002 in subjects >=50 years of age, data collected in 2012-13 on 10,601 participants. Only 5,909 participants with all data. Depression assessed with 8-item version of CES-D.

CRP associated positively with fatigue, restless sleep, low energy but not with sadness and anhedonia.
**Inflammation and specific symptoms of depression**  
*(Jokela et al., 2016, JAMA Psychiatry)*

Based on 3 cross-sectional studies (the US National Health and Nutrition Surveys (2005-6; 2007-8; 2009-10)

<table>
<thead>
<tr>
<th>Depression Symptom</th>
<th>Mutually Adjusted OR (95% CI) for Higher C-Reactive Protein</th>
<th>Single OR (95% CI)</th>
<th>Symptomatic, No.</th>
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</thead>
<tbody>
<tr>
<td>Little interest in doing things</td>
<td>1.08 (1.00-1.17)</td>
<td>1.29 (1.19-1.40)</td>
<td>1097</td>
</tr>
<tr>
<td>Feeling down, depressed, or hopeless</td>
<td>0.94 (0.85-1.04)</td>
<td>1.22 (1.10-1.34)</td>
<td>1098</td>
</tr>
<tr>
<td>Trouble sleeping or sleeping too much</td>
<td>1.14 (1.07-1.21)</td>
<td>1.27 (1.19-1.36)</td>
<td>2353</td>
</tr>
<tr>
<td>Feeling tired or having little energy</td>
<td>1.22 (1.15-1.30)</td>
<td>1.32 (1.25-1.40)</td>
<td>2418</td>
</tr>
<tr>
<td>Poor appetite or overeating</td>
<td>1.17 (1.09-1.27)</td>
<td>1.32 (1.23-1.43)</td>
<td>1281</td>
</tr>
<tr>
<td>Feeling bad about yourself</td>
<td>0.91 (0.83-1.01)</td>
<td>1.20 (1.10-1.32)</td>
<td>783</td>
</tr>
<tr>
<td>Trouble concentrating on things</td>
<td>1.04 (0.92-1.16)</td>
<td>1.27 (1.16-1.39)</td>
<td>824</td>
</tr>
<tr>
<td>Moving or speaking slowly or too fast</td>
<td>0.97 (0.87-1.08)</td>
<td>1.20 (1.08-1.34)</td>
<td>525</td>
</tr>
<tr>
<td>Thought you would be better off dead</td>
<td>1.04 (0.84-1.28)</td>
<td>1.33 (1.09-1.61)</td>
<td>167</td>
</tr>
</tbody>
</table>

Filled squares: p<0.05, single association with depression symptoms in the table, mutually adjusted associations adjusted for the sum of all other symptoms than the outcome symptom in the figure.
Preclinical study of inflammation-induced depression

Acute: Lipopolysaccharide IP
What does it mean to be less motivated when inflamed?

Mouse operant conditioning cage
(progressive ratio for food reinforcement)
LPS decreases food-motivated behavior 24 h after treatment without altering motor activity

(Grossberg et al., in preparation)
LPS decreases food-motivated behavior 24 h after treatment without altering motor activity

(Grossberg et al., in preparation)
LPS reduces the motivation to engage in exercise.

Time to fatigue measured in mice that run on a motorized treadmill until volitional exhaustion (LPS 0.33 mg/kg 24 h before, n=8/group, Krzyszton et al., Am J Physiol, 2008, 295, R1109-14).

Number of rotations/hour in mice having a running wheel in their cage (LPS, 0.33 mg/kg, n=8/group, Vichaya et al., in preparation).
What does it mean to be less motivated when inflamed?

Effort-based decision making paradigm (J. Salamone)

Incentive motivation $\Rightarrow$ Number of operant responses
Sensitivity to reward $\Rightarrow$ Discrimination between reinforcers
As expected, LPS decreases the total number of nose pokes.

*Vichaya et al., Neuropsychopharmacology, 2014*
However, LPS boosts responding for the preferred reward (not compatible with a decrease in incentive motivation)
From mice to humans: Effort Expenditure for Reward Task (EEfRT) (Treadway)

Probability of win: 88%

Easy task $1.00

Hard task $2.37

Reward probability (12%, 50%, 88%)

Reward magnitude

Time left:

You won! $2.37
LPS increases effort for the high effort/high reward response modality and this effect is modulated by sleepiness

Effort expenditure for reward task (M. Treadway)

Healthy volunteers, n = 21
LPS (2.0 ng/kg bw) vs. Placebo

(Lasselin et al., Neuropsychopharmacology 2016)
From mice to humans: LPS increases effort for the high effort/high reward response modality and this effect is modulated by sleepiness.

Effort expenditure for reward task (M. Treadway)

Healthy volunteers, n = 21
LPS (2.0 ng/kg bw) vs. Placebo

Placebo

LPS

Sleepiness: Karolinska Sleepiness Scale
Low sleepiness: < 1st tertile (KSS < 5)
High sleepiness: ≥ 2nd tertile (KSS ≥ 7)

(Lasselin et al., Neuropsychopharmacology 2016)
Fatigued cancer survivors choose more frequently the high effort/high reward mode of responding despite their high level of fatigue.

Effort expenditure for reward task (M. Treadway)

Average number of high effort choices independently of reward probability

Average number of high effort choices according to reward probability

<table>
<thead>
<tr>
<th>Probability level (%)</th>
<th>Low fatigue</th>
<th>High fatigue</th>
</tr>
</thead>
<tbody>
<tr>
<td>% high effort choices</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low Fatigue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High fatigue</td>
<td></td>
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</tr>
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</table>

(Lacourt et al., in preparation)
Inflammation-induced depression is characterized by the predominance of somatic symptoms of depression including anergia/fatigue.
Conclusion and Perspectives

- Inflammation-induced depression is characterized by the predominance of somatic symptoms of depression including anergia/fatigue
- Inflammation does not decrease sensitivity to reward
- Inflammation does not uniformly reduce motivation or the willingness to expend effort in order to obtain a reward
- Inflammation reorganizes priorities and increases effort for rewards that are deemed worthwhile
Conclusion and Perspectives

- Inflammation-induced depression is characterized by the predominance of somatic symptoms of depression including anergia/fatigue.
- Inflammation does not decrease sensitivity to reward.
- Inflammation does not uniformly reduce motivation or the willingness to expend effort in order to obtain a reward.
- Inflammation reorganizes priorities and increases effort for rewards that are deemed worthwhile.
- This feature could be used as a behavioral marker of inflammation-associated brain dysfunction.
- Inflammation-induced alterations in reward-motivated behavior are mediated by mitochondrial dysfunction.
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