# How is aggression related to fatigue and neuro-immune mechanisms?

## Overview

Aggression and fatigue both occur in stress-related and medical conditions and are increasingly linked to shared **neuro-immune mechanisms**. The papers here connect social stress, inflammation, microglial activation, and cytokines to aggressive behavior, and separately show that similar immune changes drive fatigue and other "sickness" or physiosomatic symptoms.

## Neuro-Immune Basis of Aggression

- People with high trait aggression or disorders with pathological aggression show **elevated pro-inflammatory cytokines** (e.g., IL-6, TNF-α, CRP) and dysregulated immune responses, including slower wound healing (Takahashi et al., 2018; Gorlova et al., 2023; Couch et al., 2016).
- In schizophrenia, higher plasma Th17-related cytokines (IL-17, IL-23, TGF-β1) correlate with greater aggression scores (Ravi et al., 2021).
- Animal and human data indicate cytokines in both **periphery and brain** modulate offensive and defensive aggression; microglial activation and neuroinflammation influence intermale aggression and social behavior (Takahashi et al., 2018; Takahashi, 2024; Gorlova et al., 2023).

### Inflammation, Stress, and Behavior

| Stress / immune state | Main behavioral links | Citations |
|---|---|---|
| Social stress + immune dysregulation | Aggression, depression, anxiety, social withdrawal | (Takahashi et al., 2018; Tong et al., 2023; Nisha et al., 2025; Biltz et al., 2022) |
| Low-dose LPS + chronic stress | More depressive-like behavior, less aggression | (Couch et al., 2016) |
| Chronic stress–induced inflammation | Anhedonia, anxiety, fatigue, emotion dysregulation | (Tong et al., 2023; Hassamal, 2023) |

FIGURE 1 Stress–immune patterns connecting aggression and mood symptoms.

## Neuro-Immune Mechanisms in Fatigue

- In cancer and advanced cancer, **fatigue clusters** with pain and sleep disturbance and is partly related to higher TNF-α and other cytokines (Santos & Pyter, 2018; Kwekkeboom et al., 2018).
- Cancer-related fatigue is strongly tied to neuro-immune changes, including peripheral and brain cytokines and microglial activation; childhood adversity can prime neuroimmune responses and enhance later fatigue (Bower, 2019).
- In chronic fatigue syndrome/ME, poorer emotion regulation, interpersonal function, and sleep are associated with higher IL-1, IL-2, IL-6, and TNF-α (Raanes & Stiles, 2021).
- In major dysmood disorder and Long-COVID, chronic fatigue and fibromyalgia-like symptoms are driven by **immune activation, Th1/M1 polarization, oxidative and nitrosative stress, and neurotoxicity** (Maes et al., 2024; Al-Hakeim et al., 2022).

## Linking Aggression and Fatigue via Neuro-Immune Pathways

- Chronic stress and inflammation can produce **both aggression and fatigue**, often in the same individuals (e.g., depression with agitation/aggression and tiredness) (Takahashi et al., 2018; Tong et al., 2023; Gorlova et al., 2023; Hassamal, 2023).
- Pro-inflammatory cytokines and activated microglia alter neurotransmitter systems and brain circuits for motivation and emotion, underpinning **irritability/aggression on one hand and exhaustion, anhedonia, and psychomotor slowing on the other** (Takahashi et al., 2018; Tong et al., 2023; Gorlova et al., 2023; Hassamal, 2023).
- Experimental low-dose inflammation under chronic stress can **suppress aggression while intensifying depressive-like states**, showing that the balance of stress and immune activation shapes whether behavior skews toward aggressive arousal or fatigued withdrawal (Couch et al., 2016).

## Conclusion

Across conditions, aggression and fatigue are both linked to stress-related immune activation, with cytokines and microglia altering brain circuits that regulate arousal, mood, and social behavior. Differences in timing, context, and degree of neuro-immune activation help determine whether individuals exhibit more aggressive, activated responses or fatigued, withdrawn “sickness” behavior.



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