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Beyond the Symptom: The Biology of Fatigue

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Immunomodulators as Regulators of Sleep and Fatigue

Mark R. Opp, PhD

University of Colorado Boulder

Disclaimer and Disclosures

Disclaimer

This certifies that the views expressed in this presentation are those of the author and do not reflect the official policy of the NIH.

Disclosure

This certifies that I, Mark Opp, have no financial relationship that is relevant to the subject matter of this presentation.

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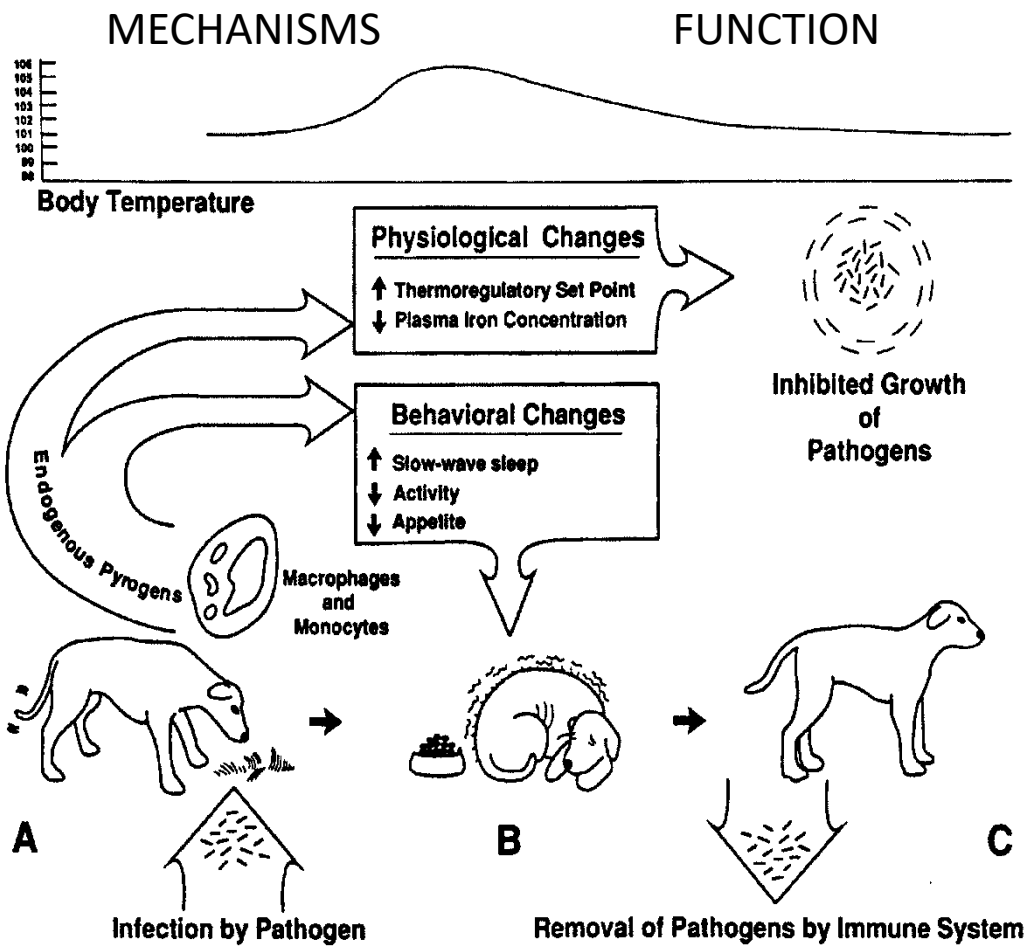
Biological Basis for the Behavior of Sick Animals



B. L. Hart. *Neurosci. Biobehav. Rev.* 12:123-137, 1988.

Cytokines are involved in the regulation of physiological and behavioral processes in health and sickness.

- arousal state
- thermoregulation
- appetite and feeding
- sexual behavior
- social exploration
- mood

Cytokines are involved in the regulation of physiological and behavioral processes in health and sickness.

- Interleukin-1β (IL-1)
- Interleukin-6 (IL-6)
- Tumor necrosis factor-α (TNF)

other cytokines, chemokines and growth factors

- IL-1α, IL-2, IL-4, IL-8, IL-10, IL-13, IL-15, IL-18, IL-36, IL-37, TNF-β
- γ-interferon
- MIP-1β
- GM-CSF, FGF, NGF, BDNF, GDNF, TGFβ

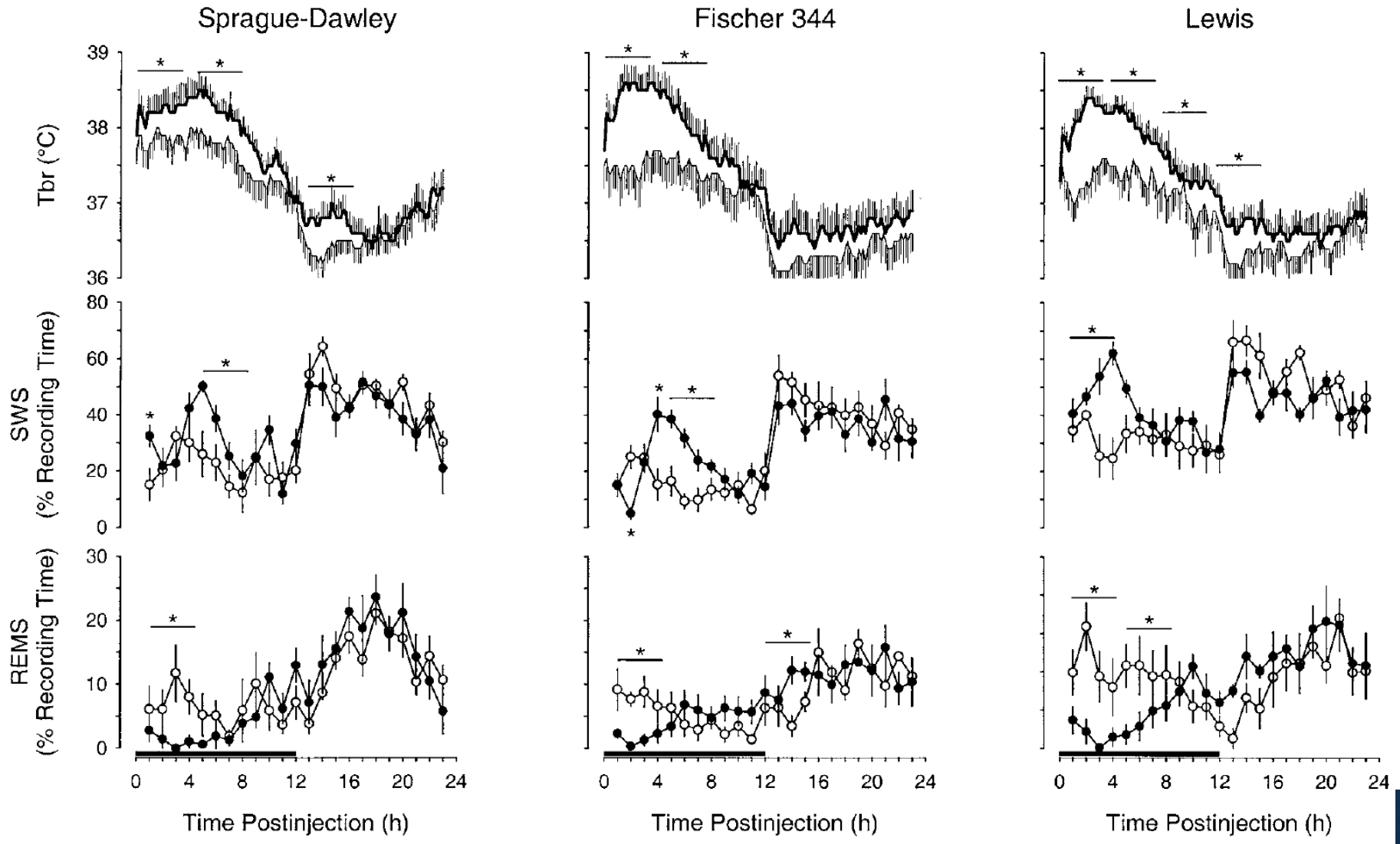
IL-1 and TNF are involved in the regulation of sleep.

- IL-1 concentrations in human plasma peak at sleep onset (*Moldofsky et al., 1986*).
- IL-1 concentrations in cat cerebrospinal fluid vary in phase with sleep-wake behavior (*Lue et al., 1988*).
- IL-1 and TNF mRNA and protein in brain exhibit diurnal variation (*Bredow et al., 1987; Floyd & Kreuger, 1997; Taishi et al., 1998*).
- IL-1 and TNF alter sleep in laboratory animals (*Kapás et al., 1992; Krueger et al., 1984; Opp et al., 1988; Shoham et al., 1987; Tobler et al., 1984*).

IL-1 and TNF are involved in the regulation of sleep.

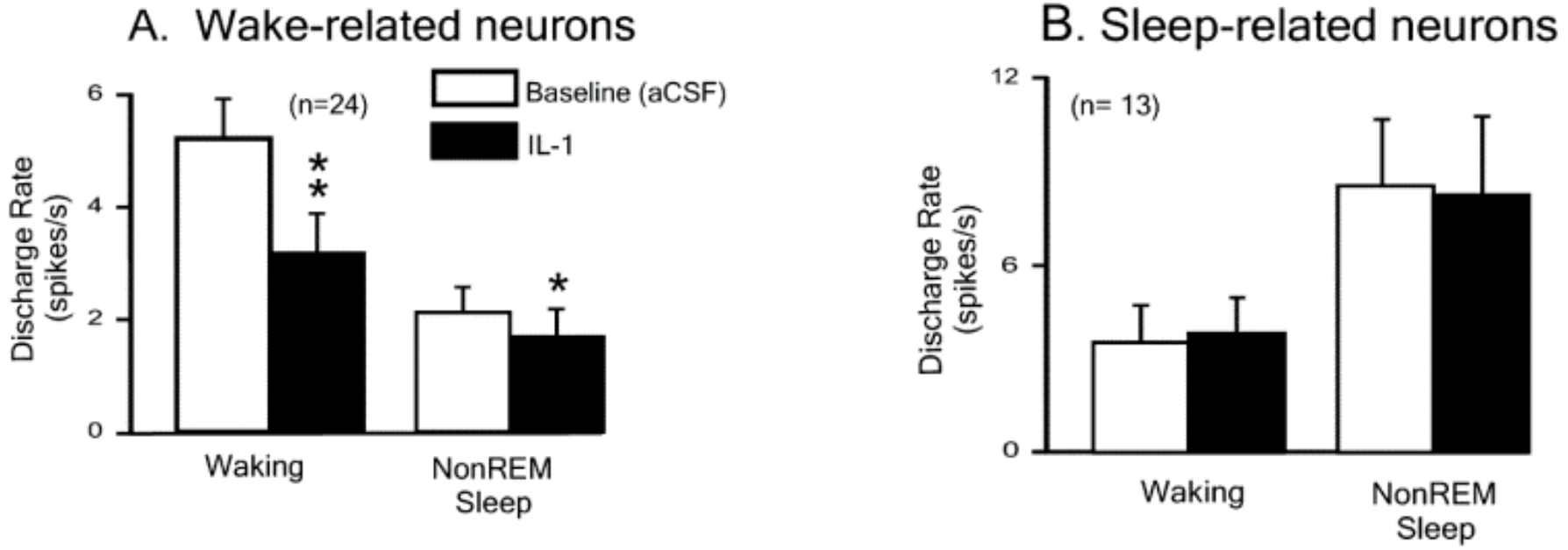
- Antagonizing the IL-1 or TNF systems reduces sleep (*Opp et al., 1991; Takahashi et al., 1994, 1995, 1996*).
- Mice lacking either IL-1R1 or TNF kDa55 receptors, or both, exhibit less NREM sleep than control mice (*Fang et al., 1997, 1998, Barrachi & Opp, 2008*).
- Interactions between cytokines and other neuromodulators are of functional significance to sleep regulation (*Opp & Chang, 2000; Opp & Imeri, 2001*).
- Mechanisms of action for IL-1 include direct effects on neurons in brain regions involved in the regulation of sleep (*Manfridi et al., 2003; Alam et al., 2004; Brambilla et al., 2010*).

IL-1 induces fever, increases NREMS, suppresses REMS of rats.



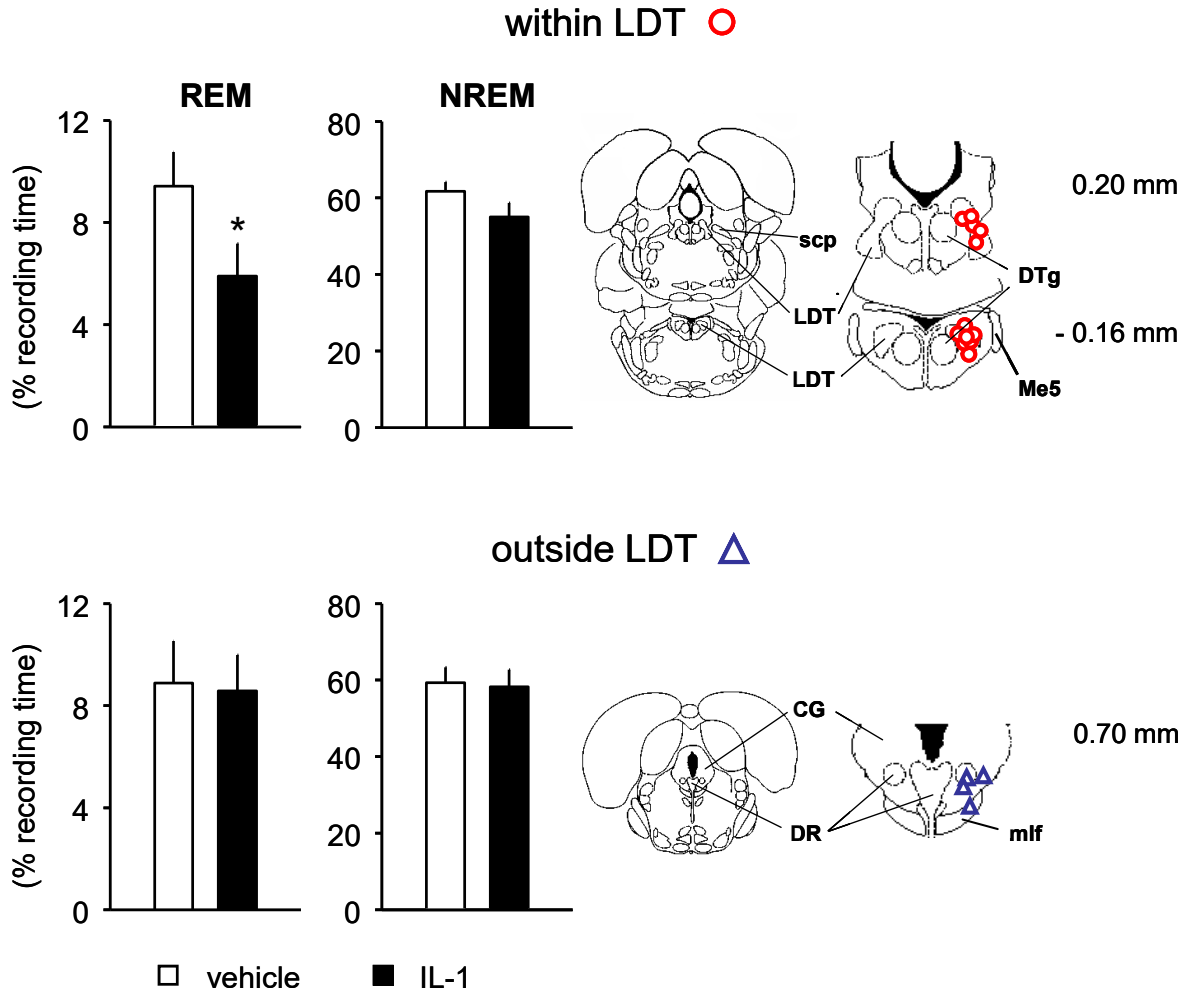
Opp, M.R. and L. Imeri. *Neuroendocrinology* 73: 272-284, 2001.

IL-1 reduces discharge rates of wake-active preoptic area neurons of rats.



Adapted from Alam, N., et al., *Eur. J. Neurosci.* 20: 207, 2004.

Microinjection of IL-1 into the LDT of the brainstem reduces REM sleep of rats.



Adapted from Brambilla, D. et al. SLEEP 33(7): 919, 2010.

Summary

- Acute changes in behavior and physiology during infectious disease is adaptive.
- Immunomodulators (cytokines, chemokines, growth factors) are involved in physiological sleep regulation in the absence of immune challenge.
- IL-1 and TNF act directly on neurons to alter membrane properties / discharge rates.
- IL-1 acts in the pre-optic area / basal forebrain (NREMS) and the brainstem (REMS) to alter sleep, in part, by suppressing activity of arousal-promoting systems.
- Any stimulus that alters normal cytokine patterns or concentrations may alter sleep.

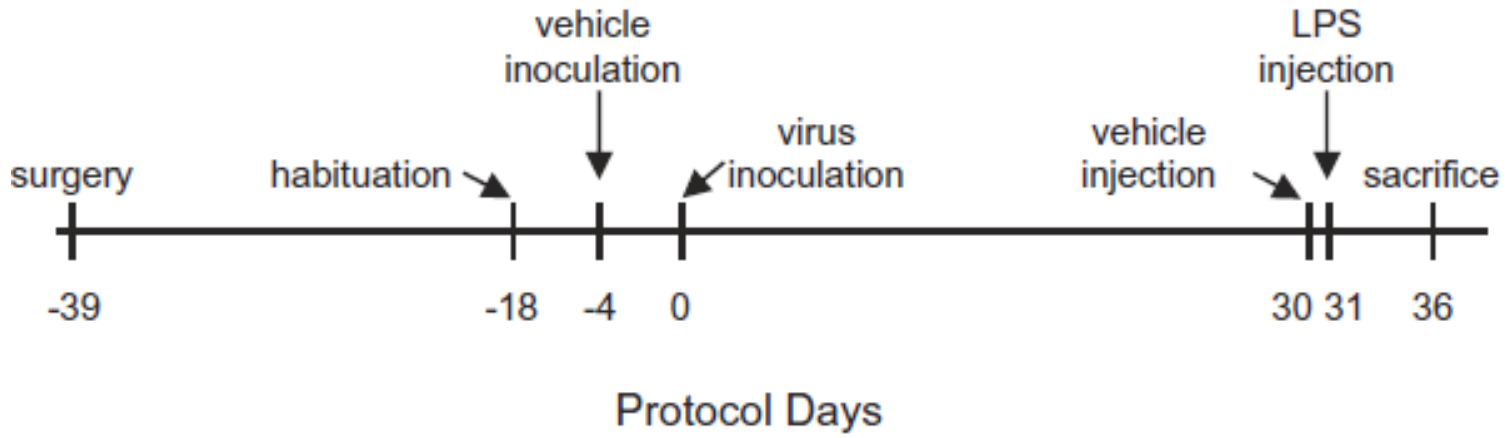
Sleep and Fatigue in Mice Infected with Murine gammaHerpesvirus 68 (γHV68)

- A subset of individuals infected with Epstein Barr virus develop symptoms that meet criteria for ME/CFS (*Jones et al., 1988; Natelson et al., 1994; Glaser and Kiecolt-Glaser, 1998; Kerr, 2019; Williams et al., 2019; Shikova et al., 2020*).

- Murine γHV68 is a natural mouse pathogen that shares similarities with human γHVs, including Epstein Barr virus.

- There are two phases in murine γHV68 infection, an active, *lytic* infection in lung and a subsequent *latent* infection in the spleen and other organs (*Doherty et al., 2001; Flano et al., 2005; Hwang et al., 2008*).

Sleep and Fatigue in Mice Infected with γHV68



Outcome measures included:

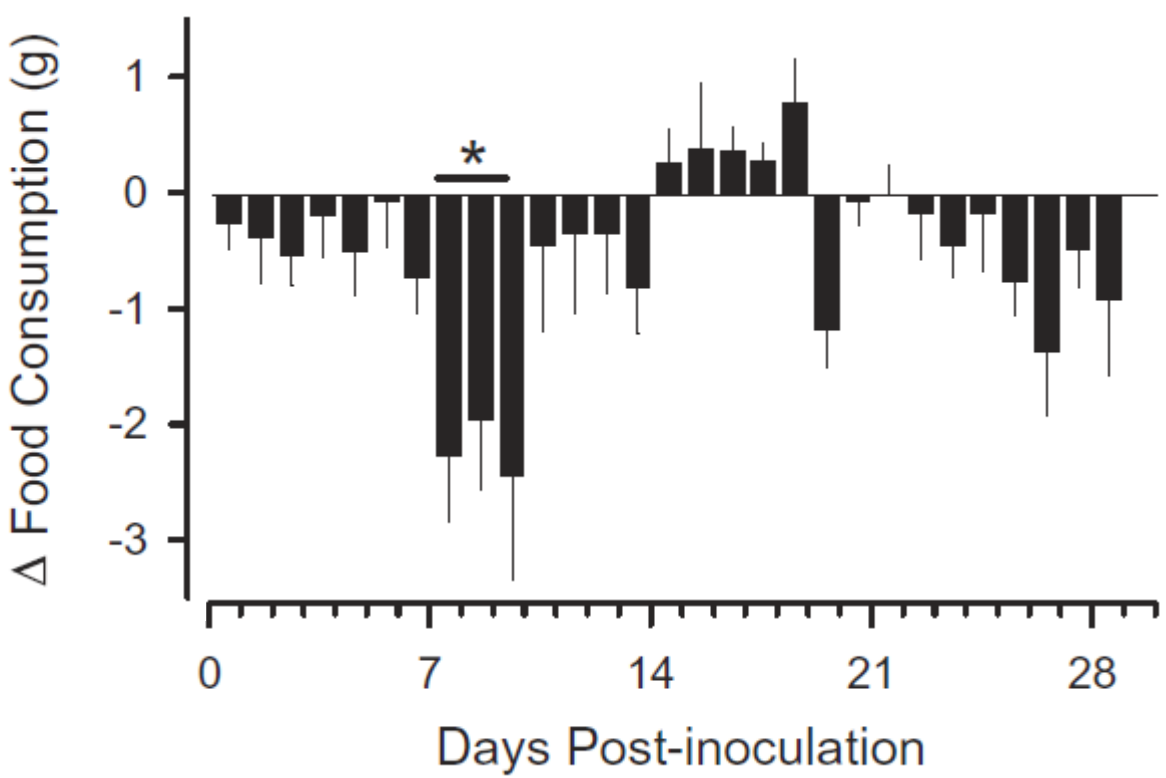
- food consumption, body weight, body temperature
- cage activity and wheel running
- sleep-wake behavior

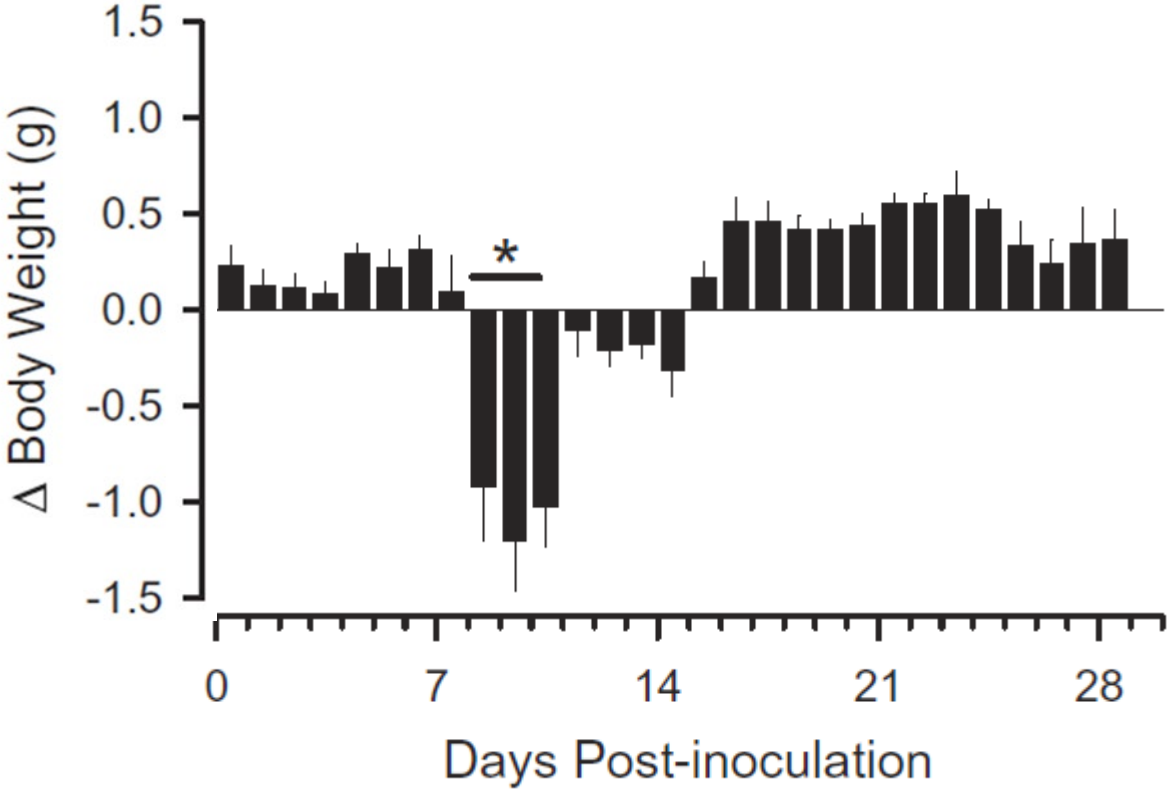
Operationally defined fatigue as a reduction in *voluntary activity*:

- essential (cage) activity: feeding, drinking
- voluntary activity: wheel running

Olivadoti, MD. et al. Brain. Behav. Immun. 25: 696, 2011.

Food consumption and body weights of mice are reduced during lytic infection with γHV68 *





* 40,000 pfu γHV68 intranasal inoculation

Adapted from Olivadoti, MD. et al. Brain. Behav. Immun. 25: 696, 2011

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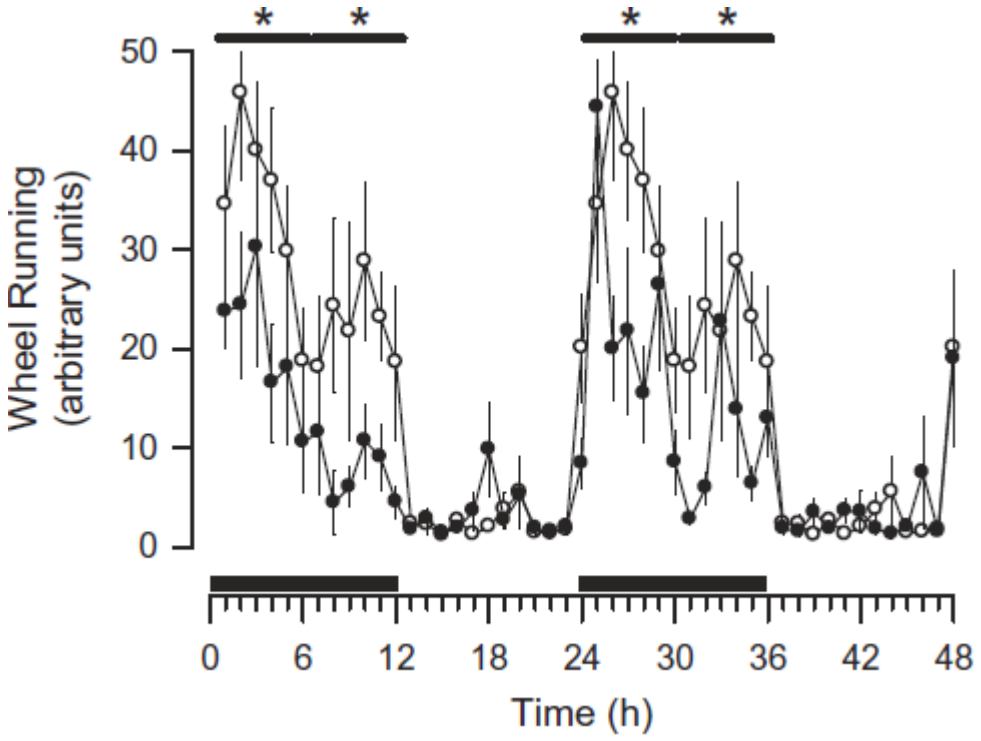
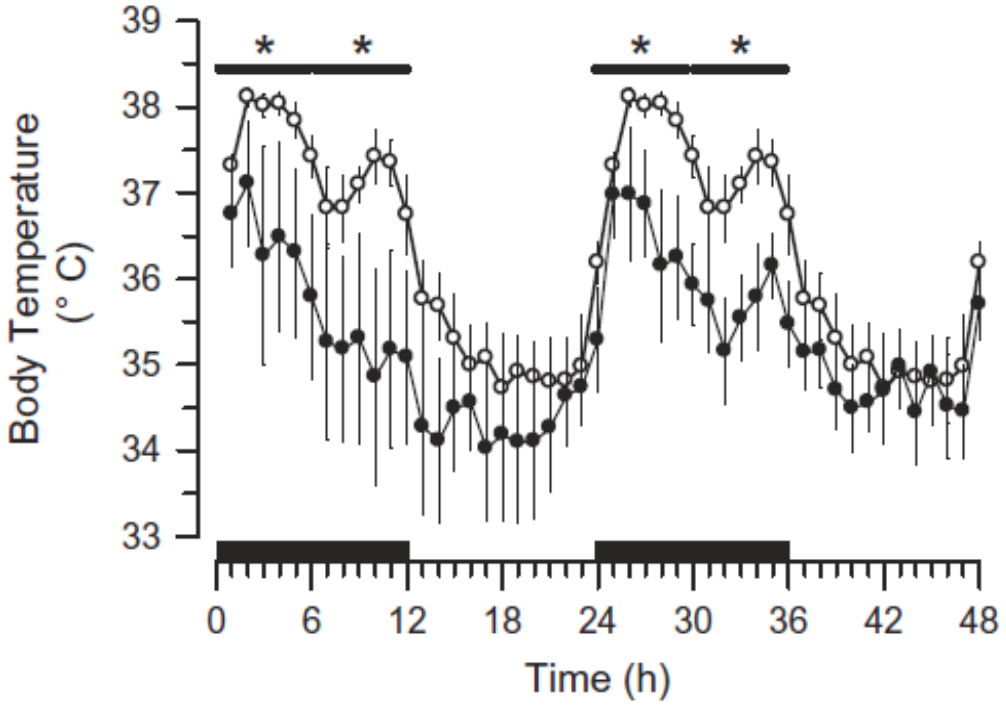
Wheel running and body temperatures of mice are reduced during lytic infection with γHV68 *





* 40,000 pfu γHV68 intranasal inoculation;
days 8 and 9 post-inoculation

Adapted from Olivadoti, MD. et al. Brain. Behav. Immun. 25: 696, 2011

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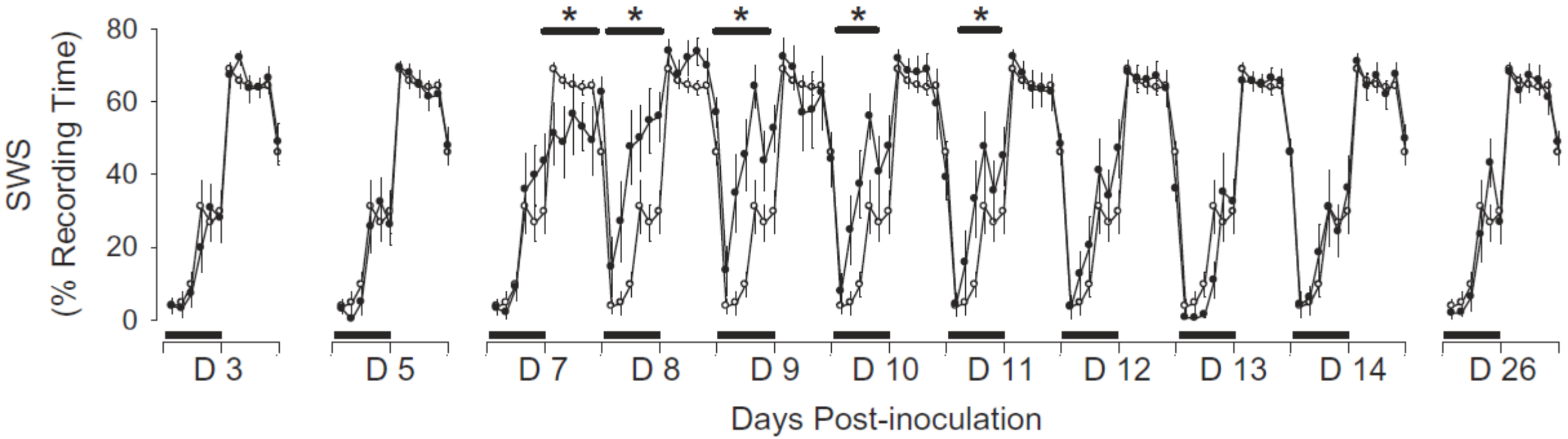
Sleep of mice is altered during lytic infection with γHV68 *



* 40,000 pfu γHV68 intranasal inoculation;
WAKE is reduced and **REMS** is not dramatically altered.

Adapted from Olivadoti, MD. et al. Brain. Behav. Immun. 25: 696, 2011

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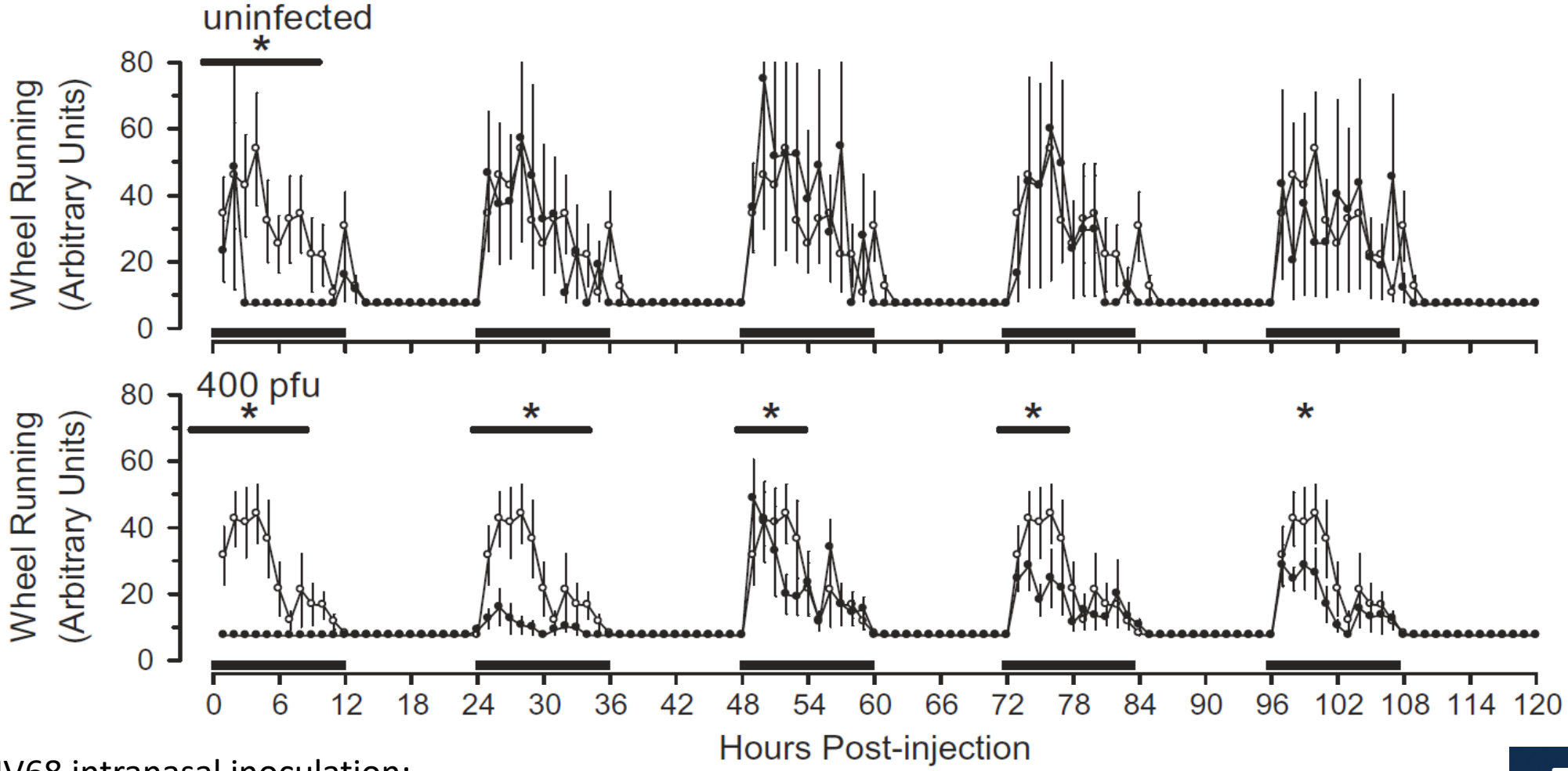
Responses to immune challenge * during latent infection with γHV68 are exacerbated: WHEEL RUNNING



* 400 pfu γHV68 intranasal inoculation;
Lipopolysaccharide 10 μg;
E. coli serotype O111:B4

Adapted from Olivadoti, MD. et al. Brain. Behav. Immun. 25: 696, 2011

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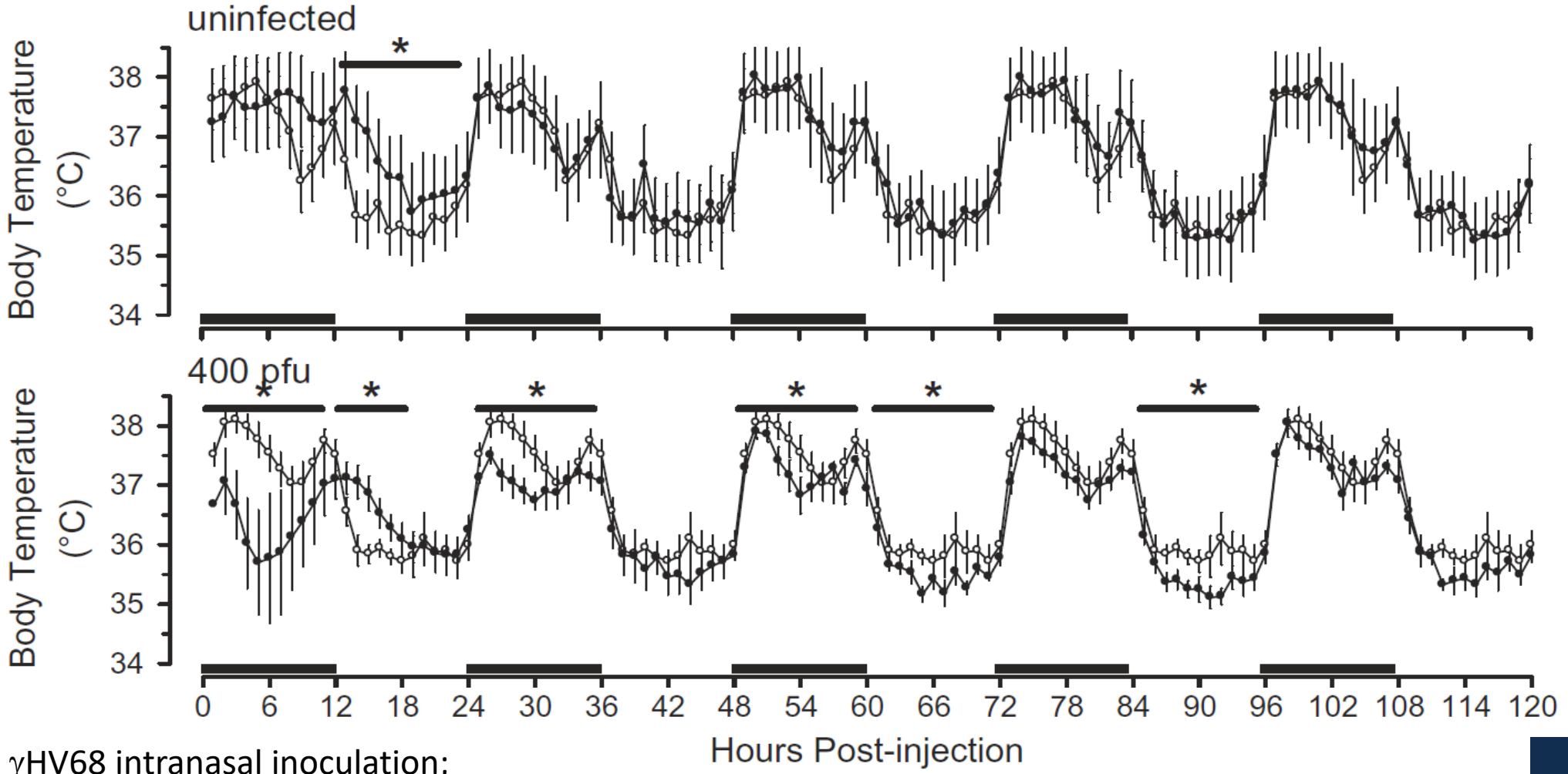
Responses to immune challenge * during latent infection with γHV68 are exacerbated: BODY TEMPERATURE



* 400 pfu γHV68 intranasal inoculation;
Lipopolysaccharide 10 μg;
E. coli serotype O111:B4

Adapted from Olivadoti, MD. et al. Brain. Behav. Immun. 25: 696, 2011

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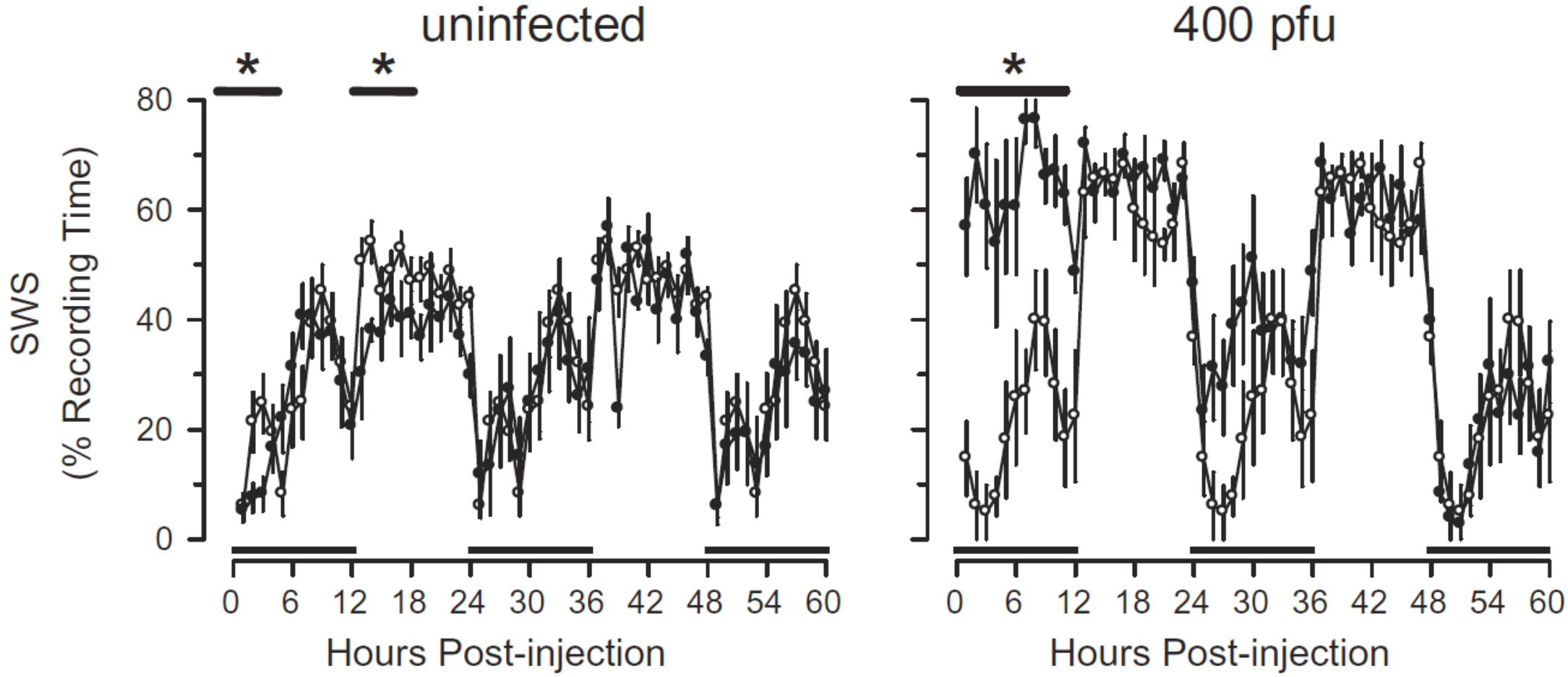
Responses to immune challenge * during latent infection with γHV68 are exacerbated: SLEEP



* 400 pfu γHV68 intranasal inoculation;
Lipopolysaccharide 10 μg;
E. coli serotype O111:B4

Adapted from Olivadoti, MD. et al. Brain. Behav. Immun. 25: 696, 2011

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Summary

- Viral infections have been implicated in the etiology of ME/CFS.
- Models using natural viral mouse pathogens mimic facets of ME/CFS.
- There are transient changes in mouse sleep and other physiologic / behavioral measures during lytic infection with γHV68.
- Responses of mice to immune challenge are exacerbated during latent infection with γHV68.

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