Live Complexity Training

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Live Complexity Training Resources: Sickness Behavior (SBeh)

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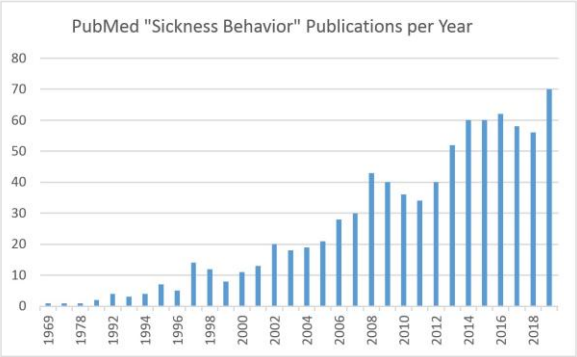
Theory: There exists a complexity-based transdiagnostic biomarker of sickness behavior and its remediation.

Introduction – The Sickness in the Signals



Canonical sickness behavior is a programmed response to stress, trauma, infection, inflammation, etc. The use of the technical term “sickness behavior” is increasingly common in the literature. You will find many examples in the Resources below.

Sickness behavior (SBeh) is a programmed organismal response and includes apoptosis of the cell and apoptosis of the self. The prototypical SBeh is the sequel of bacterial components in the gut called Lipopolysaccharides (LPS) that cross the gut-blood barrier and then the blood-brain barrier (BBB) and engender a complex immune and metabolic stress response.

The start of SBeh usually begins with a depression and anxiety and leads to anhedonia, fatigue, withdrawal, sleep disturbances, and dysregulation of body, feelings, and mind. This built-in response is influenced by environment as well as intergenerational epigenetic factors.

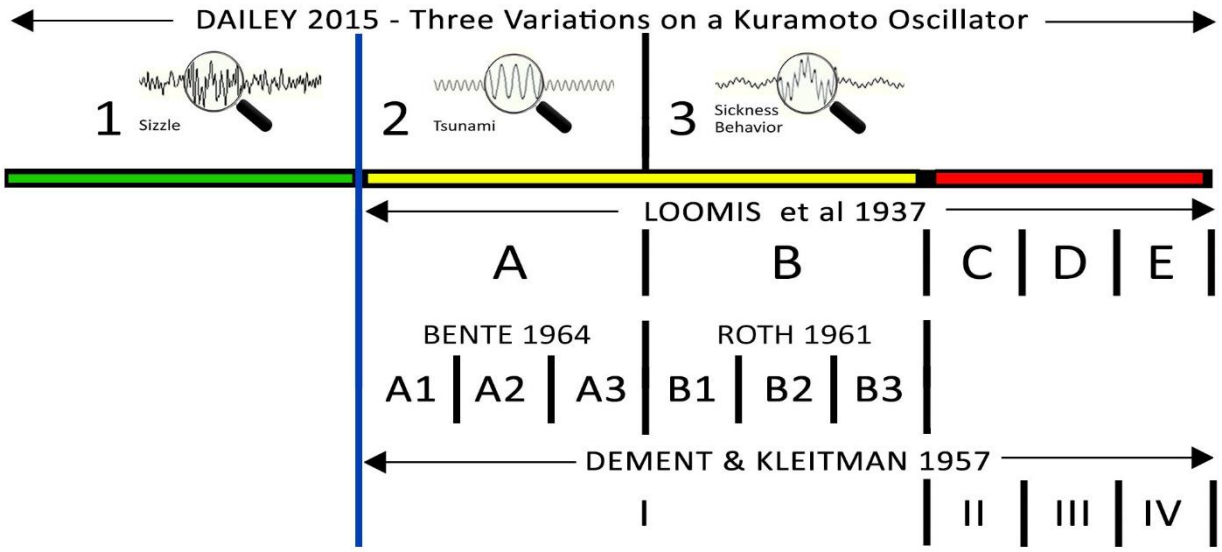
Each of the symptoms of SBeh listed above individually are transdiagnostic biomarkers (TDBMs). A TDBM is generally represented as a measurement that lies along a continuum. If measurements over time move in one direction along the continuum it is associated with decreased SBeh. If the measurements move in the opposite direction along the continuum it is associated with increased SBeh.

Diagnosis and treatment may be particularly difficult when consultation is remote, when diagnosis is uncertain or unavailable, and especially when there are multiple diagnoses and comorbidities. Such situations have prompted the National Institute of Health to launch its Research Domain Criteria project (NIMH RDoC) with its emphasis on transdiagnostic biomarkers – observations that indicate movement toward or away from sickness behavior regardless of diagnosis.

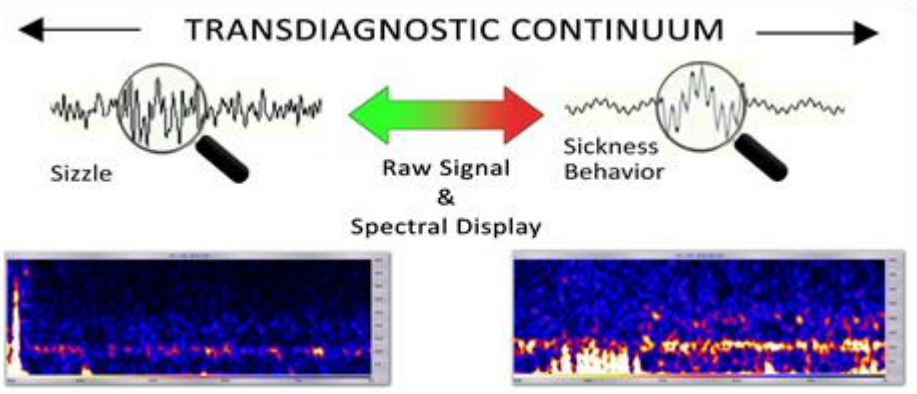
I have used a Kuramoto oscillator model to demonstrate the rise and fall of sickness behavior in physiological systems such as EEG, HRV, MRI, GSR. In general, SBeh in a signal such as EEG is seen as programmed redundancies - most commonly fast waves appearing to ride upon slow waves. This is also a classic EEG pattern called the “delta brush” that is characteristic of autoimmune encephalitis.

This model shows that movement away from SBeh and toward wellness behavior leads toward an EEG that looks like empty noise. This is complexity. Such complexity is required to carry “skillful means” over the networks. Such movements of the TDBM toward or away from SBeh are surprisingly easy to identify during Live Complexity Training even with minimal training.

Curiously the movement of the biomarker away from adaptive complexification and toward sickness behavior also follows the programmed stages in the loss of consciousness and sleep. There are 3 Kuramoto stages that illustrate this progression from awake adaptive consciousness toward loss of consciousness and sickness behavior. I have named them descriptively as sizzle, tsunami, and sickness behavior. See below how these 3 waveforms correspond to classical descriptions of sleep stages.



Movements of the TDBM toward or away from SBeh are surprisingly easy to identify during Live Complexity Training even with minimal training.



Resources

2021, 2020, 2019, 2018, 2017, 2016, 2015, 2014, 2013, 2012, 2011, 2010, 2009, 2008, 2007, 2006, 2005, 2004 & earlier

2021 ▲

Lopes PC, et al (2021) - **Sickness behaviors across vertebrate taxa: proximate and ultimate mechanisms**. J Exp Biol. 2021 May 1;224(9):jeb225847. [ABS]

> … behavioral changes associated with inflammatory responses (i.e. sickness behaviors) have important implications for disease spread by affecting contacts with others and with common resources, including water and/or sleeping sites. In this Review, we summarize the behavioral modifications, including changes to thermoregulatory behaviors, known to occur in vertebrates during infection, with an emphasis on non-mammalian taxa, which have historically received less attention.

McGarry N (2021) - **Double stranded RNA drives anti-viral innate immune responses, sickness behavior and cognitive dysfunction dependent on dsRNA length, IFNAR1 expression and age.** Brain Behav Immun. 2021 Apr 20:S0889-1591(21)00173-2. [ABS]

> Double stranded RNA is generated during viral replication. The synthetic analogue poly I:C is frequently used to mimic anti-viral innate immune responses in models of psychiatric and neurodegenerative disorders including schizophrenia, autism, Parkinson's disease and Alzheimer's disease. … The data have implications for CNS symptoms of acute systemic viral infection such as those with SARS-CoV-2 and for models of maternal immune activation.

Moreno KR, et al (2021) - **Sick bats stay home alone: fruit bats practice social distancing when faced with an immunological challenge.** Ann N Y Acad Sci. 2021 Apr 19. [ABS]

Navarro E, et al (2021) - **Central Activation of Alpha7 Nicotinic Signaling Attenuates LPS-Induced Neuroinflammation and Sickness Behavior in Adult but Not in Aged Animals.** Molecules. 2021 Apr 7;26(8):2107. [FULL TEXT]

> The alpha 7 nicotinic receptors bind acetylcholine and have effects that include promotion of neuroplasticity and neuroprotection and that limit programmed apoptosis.

Munk A, et al (2021) - **What Does CATS Have to Do with Cancer? The Cognitive Activation Theory of Stress (CATS) Forms the SURGE Model of Chronic Post-surgical Pain in Women with Breast Cancer.** Front Psychol. 2021 Mar 23;12:630422. [FULL TEXT]

> A sustained stress response may contribute to central sensitization, alterations in functional brain networks and excessive fear-based learning. This sets the stage for a prolonged state of inflammatory-induced **sickness behavior** - potentially driving and maintaining Chronic post-surgical pain.

Sharma R, et al (2021) - **A systemic immune challenge to model hospital-acquired infections independently regulates immune responses after pediatric traumatic brain injury.** J Neuroinflammation. 2021 Mar 17;18(1):72. [FULL TEXT]

> TBI patients are highly susceptible to nosocomial infections, which are mostly acquired within the first week of hospitalization, and such infections may modify TBI pathobiology and recovery. In this study, we hypothesized that a peripheral immune challenge such as lipopolysaccharide (LPS)-mimicking a hospital-acquired infection-would worsen outcomes after experimental pediatric TBI, by perpetuating the inflammatory immune response. …These findings provide novel insight into the potential influence of a secondary immune challenge to the injured pediatric brain, with future studies needed to elucidate the chronic effects of this two-hit insult.

Konsman JP (2021) - **So Many Faces, Phases, and Facets, Sickness Behavior Beyond Disciplines.** Front Psychiatry. 2021 Feb 25;12:630331. [FULL TEXT]

> Animals, including human beings, modify their behavior when they fall sick. Interestingly, sociology, biology, and psychology have at different times in their history developed constructs of illness or **sickness behavior**. The aims of the present paper are to consider sickness behavior in animals and humans and to evaluate to what extent the notions of sickness behavior would allow for interdisciplinary research.

Borniger JC, et al (2021) - **Peripheral Lipopolyssacharide Rapidly Silences REM-Active LH(GABA) Neurons.** Front Behav Neurosci. 2021 Feb 25;15:649428. [FULL TEXT]

> Immune factors (e.g., cytokines, chemokines) can alter the activity of neuronal circuits to promote "sickness behavior," a suite of adaptive actions that organisms exhibit in response to infection/injury in order to maximize their chances of recovery (i.e., return to homeostasis). This includes drastic alterations in sleep/wake states, locomotor activity, and food intake, among other behaviors.
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> Upon intraperitoneal LPS challenge, lateral hypothalamic GABA neurons rapidly decrease their activity in tandem with elimination of REM sleep behavior (characteristic of cytokine-induced sickness). Together, these data suggest that peripheral immune challenges can rapidly (in < 40 min) alter subcortical neuronal circuits controlling arousal states.

Smith CJ, et al (2021) - **Sickness and the Social Brain: Love in the Time of COVID.** Front Psychiatry. 2021 Feb 22;12:633664. [FULL TEXT]

> As a highly social species, inclusion in social networks and the presence of strong social bonds are critical to our health and well-being. Indeed, impaired social functioning is a component of numerous neuropsychiatric disorders including depression, anxiety, and substance use disorder. During the current COVID-19 pandemic, our social networks are at risk of fracture and many are vulnerable to the negative consequences of social isolation. Importantly, infection itself leads to changes in social behavior as a component of "sickness behavior." Furthermore, as in the case of COVID-19, males and females often differ in their immunological response to

infection, and, therefore, in their susceptibility to negative outcomes. In this review, we discuss the many ways in which infection changes social behavior-sometimes to the benefit of the host, and in some instances for the sake of the pathogen-in species ranging from eusocial insects to humans. We also explore the neuroimmune mechanisms by which these changes in social behavior occur. Finally, we touch upon the ways in which the social environment (group living, social isolation, etc.) shapes the immune system and its ability to respond to challenge. Throughout we emphasize how males and females differ in their response to immune activation, both behaviorally and physiologically.

Safadi JM, et al (2021) - **Gut dysbiosis in severe mental illness and chronic fatigue: a novel trans-diagnostic construct? A systematic review and meta-analysis.** Mol Psychiatry. 2021 Feb 8. [ABS]

Reduced gut-microbial diversity ("gut dysbiosis") has been associated with an anhedonic/amotivational syndrome ("sickness behavior") that manifests across severe mental disorders and represent the key clinical feature of chronic fatigue. …Elevated levels of gut dysbiosis markers positively correlated with severity of sickness behavior in patients with severe mental illness and chronic fatigue. Our findings suggest that gut dysbiosis may underlie symptoms of sickness behavior across traditional diagnostic boundaries. Future investigations should validate these findings comparing the performances of the trans-diagnostic vs. categorical approach. This will facilitate treatment breakthrough in an area of unmet clinical need.

Sumar AHS, et al (2021) - **Aerobic exercise ameliorates survival, clinical score, lung inflammation, DNA and protein damage in septic mice.** Cytokine. 2021 Apr;140:155401. [ABS]

Zefferino R, et al (2021) - **Molecular links between endocrine, nervous and immune system during chronic stress.** Brain Behav. 2021 Feb;11(2):e01960. [FULL TEXT]

…Particularly harmful conditions occur if the subject, instead to cope the stressful events, succumb to them, in this case, a cascade reaction happens that through different signaling causes a specific reaction named "sickness behaviour."

McFarland DC, et al (2020) - **The Sickness Behavior Inventory-Revised: Sickness behavior and its associations with depression and inflammation in patients with metastatic lung cancer.** Palliat Support Care. 2020 Nov 23:1-10. [ABS]

Roth S, et al (2021) - **Detection of cytokine-induced sickness behavior after ischemic stroke by an optimized behavioral assessment battery.** Brain Behav Immun. 2021 Jan;91:668-672. [ABS]

Stroke causes severe and long-lasting symptoms in patients. Besides focal deficits such as speech impairment and limb weakness, stroke also results in neuropsychiatric symptoms, including fatigue, anxiety, and depression, which are debilitating and often impair post-stroke rehabilitation. … Using this analysis tool, we detected that neutralizing systemic cytokines (TNF-α, IL-1β and IL-6) specifically ameliorated neuropsychiatric symptoms but did not affect focal deficits or lesion volume.

Lomba LA, et al (2021) - **Role of central endothelin-1 in hyperalgesia, anhedonia, and hypolocomotion induced by endotoxin in male rats.** Exp Brain Res. 2021 Jan;239(1):267-277. [ABS]

Béchade C, et al (2021) - **The serotonin 2B receptor is required in neonatal microglia to limit neuroinflammation and sickness behavior in adulthood.** Glia. 2021 Mar;69(3):638-654. [ABS]

2020 ▲

Smith CJ, et al (2020) - **Neonatal immune challenge induces female-specific changes in social behavior and somatostatin cell number.** Brain Behav Immun. 2020 Nov;90:332-345. [FULL TEXT]

> Decreases in social behavior are a hallmark aspect of acute "sickness behavior" in response to infection. However, immune insults that occur during the perinatal period may have long-lasting consequences for adult social behavior by impacting the developmental organization of underlying neural circuits. Microglia, the resident immune cells of the central nervous system, are sensitive to immune stimulation and play a critical role in the developmental sculpting of neural circuits, making them likely mediators of this process.

de Gomes MG, et al (2020) - **Curcumin-loaded lipid-core nanocapsules attenuates the immune challenge LPS-induced in rats: Neuroinflammatory and behavioral response in sickness behavior**. J Neuroimmunol. 2020 Aug 15;345:577270. [ABS]

Lasselin J, et al (2020) - **Immunological and behavioral responses to in vivo lipopolysaccharide administration in young and healthy obese and normal-weight humans**. Brain Behav Immun. 2020 Aug;88:283-293. [ABS]

> Obesity is associated with an increase prevalence of neuropsychiatric symptoms and diseases, such as depression. Based on the facts that pro-inflammatory cytokines are able to modulate behavior, and that obesity is characterized by a chronic low-grade inflammatory state, inflammation has been hypothesized to contribute to the neuropsychiatric comorbidity in obese individuals. There were little differences in the immune and behavioral responses to LPS between obese and normal-weight subjects, but the cortisol response to LPS was strongly attenuated in obese individuals. … Future studies will need to determine whether additional physiological and psychological factors interact with the state of obesity to increase the risk for inflammation-induced neuropsychiatric symptoms.

Kealy J, et al (2020) - **Acute Inflammation Alters Brain Energy Metabolism in Mice and Humans: Role in Suppressed Spontaneous Activity, Impaired Cognition, and Delirium.** J Neurosci. 2020 Jul 15;40(29):5681-5696. [FULL TEXT]

> Systemic infection triggers a spectrum of metabolic and behavioral changes, collectively termed sickness behavior, which while adaptive, can affect mood and cognition. In vulnerable individuals, acute illness can also produce profound, maladaptive, cognitive dysfunction including delirium, but our understanding of delirium pathophysiology remains limited. Here,

> we used bacterial lipopolysaccharide (LPS) in female C57BL/6J mice and acute hip fracture in humans to address whether disrupted energy metabolism contributes to inflammation-induced behavioral and cognitive changes. …These acute cognitive impairments were mimicked by insulin (11.5 IU/kg) and mitigated by glucose, demonstrating that acutely reduced glucose metabolism impairs cognition selectively in the vulnerable brain. …Hip fracture patients showed elevated CSF lactate and pyruvate during delirium, consistent with acutely altered brain energy metabolism. …Collectively, the data suggest that disruption of energy metabolism drives behavioral and cognitive consequences of acute systemic inflammation. .. Thus "bioenergetic stress" drives systemic inflammation-induced dysfunction.

van Eeden WA, et al (2020) - **Basal and LPS-stimulated inflammatory markers and the course of individual symptoms of depression.** Transl Psychiatry. 2020 Jul 15;10(1):235. [FULL TEXT]

> Multiple studies show an association between inflammatory markers and major depressive disorder (MDD). People with chronic low-grade inflammation may be at an increased risk of MDD, often in the form of sickness behaviors. We hypothesized that inflammation is predictive of the severity and the course of a subset of MDD symptoms, especially symptoms that overlap with sickness behavior, such as anhedonia, anorexia, low concentration, low energy, loss of libido, psychomotor slowness, irritability, and malaise.
>
> We found that basal and LPS-stimulated inflammatory markers were more strongly associated with sickness behavior symptoms at up to 9-year follow-up compared with non-sickness behavior symptoms of depression. However, we also found significant associations with some symptoms that are not typical of sickness behavior (e.g., sympathetic arousal among others). Inflammation was not related to depression as a unified syndrome but rather to the presence and the course of specific MDD symptoms, of which the majority were related to sickness behavior. Anti-inflammatory strategies should be tested in the subgroup of MDD patients who report depressive symptoms related to sickness behavior.

Yang L, et al (2020) - **Neuroprotection by dihydrotestosterone in LPS-induced neuroinflammation.** Neurobiol Dis. 2020 Jul;140:104814. [ABS]

> Microglia-induced neuroinflammation plays a vital role in the etiology and progression of neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease and multiple sclerosis. The neuroprotective role of androgens, including testosterone and its metabolite dihydrotestosterone (DHT), has been increasingly demonstrated in these diseases, but few studies investigated the effects of androgen on neuroinflammation. … Further behavioral tests revealed that DHT ameliorated LPS-induced spatial and learning impairment and motor incoordination, and partly improved the locomotor activity in LPS-injected mice. Therefore, this study suggests that DHT exerts anti-neuroinflammatory and neuroprotective effects; thus, androgen replacement therapy is a potential therapeutic strategy for improving cognitive and behavioral function in neuroinflammation-related diseases.

Harding CF, et al (2020) - **Mold inhalation causes innate immune activation, neural, cognitive and emotional dysfunction.** Brain Behav Immun. 2020 Jul;87:218-228. [FULL TEXT]

> Individuals living or working in moldy buildings complain of a variety of health problems including pain, fatigue, increased anxiety, depression, and cognitive deficits. …Patient symptoms following mold exposure are indistinguishable from those caused by innate immune activation following bacterial or viral exposure. …We intranasally administered either 1) intact, toxic Stachybotrys spores; 2) extracted, nontoxic Stachybotrys spores; or 3) saline vehicle to mice. As predicted, intact spores increased interleukin-1β immunoreactivity in the hippocampus. Both spore types decreased neurogenesis and caused striking contextual memory deficits in young mice, while decreasing pain thresholds and enhancing auditory-cued memory in older mice. Nontoxic spores also increased anxiety-like behavior. Levels of hippocampal immune activation correlated with decreased neurogenesis, contextual memory deficits, and/or enhanced auditory-cued fear memory. Innate-immune activation may explain how both toxic mold and nontoxic mold skeletal elements caused cognitive and emotional dysfunction.

Kirsten TB, et al (2020) - **Zinc, but not paracetamol, prevents depressive-like behavior and sickness behavior, and inhibits interferon-gamma and astrogliosis in rats.** Brain Behav Immun. 2020 Jul;87:489-497. [ABS]

> Considering all mental and addictive disorders, depression is the most responsible for years of life lost due to premature mortality and disability. Antidepressant drugs have limited effectiveness. Depression can be triggered by immune/inflammatory factors. Zinc and paracetamol interfere with immune system and have demonstrated beneficial effects on depression treatment when administered concomitant with antidepressant drugs. …In conclusion, zinc treatment was beneficial for sickness behavior and depressive-like behavior without concomitant administration of antidepressants. IFN-gamma and GFAP were linked with the expression of sickness behavior and depressive-like behavior and were also involved with the antidepressant effects. Therefore, zinc, IFN-gamma, and GFAP pathways should be considered for depression treatment.

Pereira de Souza Goldim M, et al (2020) - **Sickness Behavior Score Is Associated with Neuroinflammation and Late Behavioral Changes in Polymicrobial Sepsis Animal Model.** Inflammation. 2020 Jun;43(3):1019-1034. [ABS]

Fricke F, et al (2020) - **Proinflammatory Extracellular Vesicle-Mediated Signaling Contributes to the Induction of Neuroinflammation in Animal Models of Endotoxemia and Peripheral Surgical Stress.** Cell Mol Neurobiol. 2020 Jun 18. [ABS]

> Peripheral inflammation induced by endotoxemia or surgical stress induces neuroinflammation thereby causing neurological symptoms ranging from sickness behavior to delirium.
> … we tested whether nanometer-sized extracellular vesicles (EVs) that were produced during the peripheral inflammatory process have the capacity to induce neuroinflammation. … EVs were shown to pass the blood-brain barrier and induce … Preliminary results suggest that peripheral cholinergic signals might be involved in the control of proinflammatory EV-mediated signaling from the periphery to the brain.

Omdal R (2020) - **The biological basis of chronic fatigue: neuroinflammation and innate immunity.**

Curr Opin Neurol. 2020 Jun;33(3):391-396. [ABS]

> Chronic fatigue is common in cancer, neurodegenerative, and chronic inflammatory diseases and is regarded by many patients as their absolutely worst problem. …Biologically, fatigue occurs as part of the sickness behavior response, a complex and automated behavior triggered by the activation of innate immunity and neuroinflammation. IL-1β causes neuronal activation in the brain and subsequent fatigue. …Genetic studies indicate that fatigue may have evolved to enhance survival during infection and injury. Because fatigue is generated in the brain, … Studies on genetic variants, gene activation, and epigenetics are also required.

Bian H, et al (2020) - **Dihydrolipoic acid protects against lipopolysaccharide-induced behavioral deficits and neuroinflammation via regulation of Nrf2/HO-1/NLRP3 signaling in rat.** J Neuroinflammation. 2020 May 25;17(1):166. [FULL TEXT]

> Dihydrolipoic acid (DHLA) has been reported as a strong antioxidant and exhibits anti-inflammatory properties in various diseases… The DHLA and fluoxetine treatment exerted preventive effects in LPS-induced sickness behavior rats. … Thus, DHLA may serve as a potential therapeutic strategy for depression.

Böttcher M, et al (2020) - **NF-κB signaling in tanycytes mediates inflammation-induced anorexia.** Mol Metab. 2020 May 21;39:101022. [FULL TEXT]

> Infections, cancer, and systemic inflammation elicit anorexia. …Tanycytes form the brain barrier that mediates the anorexic effect of systemic inflammation in the hypothalamus.

Lasselin J, et al (2020) - **Comparison of bacterial lipopolysaccharide-induced sickness behavior in rodents and humans: Relevance for symptoms of anxiety and depression.** Neurosci Biobehav Rev. 2020 May 17;115:15-24. [ABS]

> Sickness behavior and emotional changes induced by experimental inflammatory stimuli have been extensively studied in humans and rodents to better understand the mechanisms underlying inflammation-driven mood alterations. …We also emphasize the differences between observable sickness behavior and subjective sickness reports, and advocate for the need to obtain both subjective reports and objective measurements of sickness behavior in humans. We aim to provide complementary insights for translational clinical and experimental research on inflammation-induced behavioral and emotional changes, and their relevance for mood disorders such as depression.

Stefanov K, et al (2020) - **Mild Inflammation in Healthy Males Induces Fatigue Mediated by Changes in Effective Connectivity Within the Insula.** Biol Psychiatry Cogn Neurosci Neuroimaging. 2020 Apr 22:S2451-9022(20)30098-7. [ABS]

> Systemic inflammation is associated with sickness behaviors such as low mood and fatigue. Activity patterns within the insula are suggested to coordinate these behaviors but have not been modeled. We hypothesized that mild systemic inflammation would result in changes in effective connectivity between the viscerosensory and the visceromotor regions of the

insula. … The vaccine condition was associated with greater interleukin-6 levels and greater fatigue 3 hours after the injection. Activity within the right mid/posterior insula increased the activity within the bilateral anterior insular regions. This connectivity was augmented by vaccination over a 99% posterior confidence threshold. …The right mid/posterior insula (viscerosensory)-to-left anterior insula (visceromotor) connectivity was significantly associated with fatigue and mediated the association between inflammation and increased fatigue scores.

Batista TH, et al (2020) - **Maternal protein malnutrition prolongs sickness behavior in male offspring.** J Neuroimmunol. 2020 Apr 15;341:577169. [ABS]

> Only the rats with maternal protein malnutrition expressed an increase in the plasma levels of TNF-α and corticosterone. Maternal protein malnutrition prolongs sickness behaviors in offspring.

Kuhlman KR, et al (2020) - **Early life stress sensitizes individuals to the psychological correlates of mild fluctuations in inflammation.** Dev Psychobiol. 2020 Apr;62(3):400-408. [ABS]

> Early life stress (ELS) has been linked to health disparities across the human lifespan, particularly increased risk for depression and its recurrence. …exposure to ELS moderated the association between change in IL-6 from pre- to post-vaccine and changes in both cognitive difficulty and depressed mood. Individuals exposed to greater ELS showed greater psychological sensitivity to increases in IL-6. CONCLUSIONS: Exposure to ELS may increase sensitivity to peripheral inflammation in the central nervous system.

Jonsjö MA, et al (2020) - **The role of low-grade inflammation in ME/CFS (Myalgic Encephalomyelitis/Chronic Fatigue Syndrome) - associations with symptoms.** Psychoneuroendocrinology. 2020 Mar;113:104578. [ABS]

> Patients with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) often present with a range of flu-like symptoms resembling sickness behavior as well as widespread pain and concentration deficits. …The aim of this study was to explore the association between inflammatory markers previously shown to be related to fatigue severity in ME/CFS and common ME/CFS symptoms post-exertional fatigue, impaired cognitive processing, musculoskeletal pain and recurrent flu-like symptoms, and the moderating effect of sex on these associations. … Only β-NGF was associated with the fatigue severity measure. However, higher levels of CCL11, CXCL10, IL-7, TNF-α and TGF-β-1 were significantly associated with higher levels of impaired cognitive processing and musculoskeletal pain, and sex was a significant moderator for CXCL10, IL-7 and TGF-β-1. Future studies should investigate the relationship between inflammatory markers and key symptoms in ME/CFS in a longitudinal design in order to explore if and for whom low-grade inflammation may contribute to illness development.

Hennessy MB, et al (2020) - **Presence of mother prompts dissociation of sickness behavior, fever, and hypothalamic gene expression in lipopolysaccharide-injected guinea pig pups.** Dev Psychobiol. 2020 Mar 1. [ABS]

During infection, sickness behaviors, such as a hunched stance with piloerection, can facilitate host resistance by supporting the generation and maintenance of fever. Fever, in turn, is mediated by hypothalamic neuroimmune signaling. Sickness behaviors, however, can also be influenced by social stimuli. In this study, guinea pig pups were injected with lipopolysaccharide to simulate a bacterial infection and then exposed to a novel, threatening environment while either with their mother or alone. We found that the presence of the mother suppressed sickness behavior, but enhanced fever, and had no measureable effect on gene expression of hypothalamic mediators of fever. …The results contribute to a growing literature linking immunological and social processes.

Da Ré C, et al (2020) - **Neuroinflammation induced by lipopolysaccharide leads to memory impairment and alterations in hippocampal leptin signaling.** Behav Brain Res. 2020 Feb 3;379:112360. [ABS]

Peripheral inflammation promotes immune-to-brain communication, mediated by cytokines that affect brain activity. Lipopolysaccharide (LPS) has been widely used to mimic systemic inflammation, and the adipokine leptin, released in this condition, modulates hypothalamic leptin receptors (ObR), contributing to sickness behavior. …Neuroinflammation was characterized in the LPS group by an increase in concentration of IL-1β, COX-2 and TLR4 in the hippocampus as well as glial fibrillary acidic protein (GFAP), indicating an astrocyte commitment. Cognitive damage was observed in the animals of the LPS group by an inability to increase the recognition index during the object recognition test. …we found a decrease in leptin concentration in the serum of the animals in the LPS group accompanied by an increase in TNF-α levels. Our results showed that neuroinflammation, even in an acute state, can lead to cognitive impairment and may be associated with leptin signaling disturbances in the hippocampus.

Shattuck EC, et al (2020) - **The Contribution of Sociocultural Factors in Shaping Self-Reported Sickness Behavior.** Front Behav Neurosci. 2020 Jan 24;14:4. [FULL TEXT]

Sickness behavior is an evolutionarily conserved phenomenon found across a diverse range of animals involving a change in motivational priorities to theoretically maximize energetic investment in immune function and recovery. Typical components of sickness behavior include reduced sociability and activity, changes in diet, and depressed affect. …Income below the national mean … stoic endurance of pain and discomfort, …and depressive symptomology …were each associated with greater sickness behavior scores. Familism …was positively associated with sickness behavior in men, but not women. Endurance of pain and discomfort was associated with greater sickness behavior in Whites only…These findings may reflect different social contexts of sickness across demographic groups, which may in turn have important implications for pathogen transmission and recovery times, potentially contributing to health disparities.

Kupferschmid BJ, et al (2020) - **Characterization of Spatial Learning and Sickness Responses in Aging Rats Following Recurrent Lipopolysaccharide Administration.** Biol Res Nurs. 2020 Jan;22(1):92-102. [ABS]

Infections in older individuals can result in cognitive function decline, yet research is limited on how recurrent infections affect cognitive responses. Activation of the immune system results in sickness responses mediated by cytokines. …Cognitive effects were dissociated from metabolic effects in aged rats, with recurring LPS exposure resulting in persistent cognitive impairment despite decreased sickness responses. Further research with older individuals is warranted.

2019

Savage JC, et al (2019) - **Microglial Ultrastructure in the Hippocampus of a Lipopolysaccharide-Induced Sickness** Mouse Model. Front Neurosci. 2019 Dec 20;13:1340. [FULL TEXT]

LPS treated mice displayed reduced activity in open-field tests 24 h post-injection, while social avoidance and weight gain/loss were not significantly different between treatment groups. …Microglial cell bodies and processes were investigated in the hippocampus CA1, a region responsible for learning and memory that is often impacted after peripheral LPS administration. …Microglia in LPS treated animals displayed larger cell bodies as well as less complex processes at the time point examined. Strikingly, microglial processes in LPS injected animals were also more likely to contact excitatory synapses and contained more phagocytic material compared with saline injected controls. We have identified at the ultrastructural level significant changes in microglia-synapse interactions shortly after LPS administration, which draws attention to studying the roles of microglia in synaptic rewiring after inflammatory stimuli.

van den Berg KS, et al (2019) - **Clinical characteristics of late-life depression predicting mortality.** Aging Ment Health. 2019 Dec 13:1-8. [ABS]

An explanation might be that minor depression in later life reflects depressive symptoms due to underlying aging-related processes, such as inflammation-based sickness behavior, frailty, and mild cognitive impairment, which have all been associated with increased mortality.

O'Callaghan J, et al (2019) - **Neuroinflammation disorders exacerbated by environmental stressors.** Metabolism. 2019 Nov;100S:153951. [FULL TEXT]

Neuroinflammation is a condition characterized by the elaboration of proinflammatory mediators within the central nervous system. Neuroinflammation has emerged as a dominant theme in contemporary neuroscience due to its association with neurodegenerative disease states such as Alzheimer's disease, Parkinson's disease and Huntington's disease. While neuroinflammation often is associated with damage to the CNS, it also can occur in the absence of neurodegeneration, e.g., in association with systemic infection. The "acute phase" inflammatory response to tissue injury or infections instigates neuroinflammation-driven "sickness behavior," i.e. a constellation of symptoms characterized by loss of appetite, fever, muscle pain, fatigue and cognitive problems. Typically, sickness behavior accompanies an inflammatory response that resolves quickly and serves to restore the body to homeostasis. However, recurring and sometimes chronic sickness behavior disorders can occur in the

absence of an underlying cause or attendant neuropathology. Here, we review myalgic enchepalomyelitis/chronic fatigue syndrome (ME/CFS), Gulf War Illness (GWI), and chemobrain as examples of such disorders and propose that they can be exacerbated and perhaps initiated by a variety of environmental stressors. Diverse environmental stressors may disrupt the hypothalamic pituitary adrenal (HPA) axis and contribute to the degree and duration of a variety of neuroinflammation-driven diseases.

Giménez-Llort L, et al (2019) - **Mortality of septic old and adult male mice correlates with individual differences in premorbid behavioral phenotype and acute-phase sickness behavior.** Exp Gerontol. 2019 Nov;127:110717. [ABS]

Walker AK, et al (2019) - **Leucine competes with kynurenine for blood-to-brain transport and prevents lipopolysaccharide-induced depression-like behavior in mice.** Mol Psychiatry. 2019 Oct;24(10):1523-1532. [FULL TEXT]

Inflammation activates indoleamine 2,3-dioxygenase (IDO) which metabolizes tryptophan into kynurenine. Circulating kynurenine is transported into the brain by the large amino transporter LAT1 at the level of the blood-brain barrier. We hypothesized that administration of leucine that has a high affinity for LAT1 should prevent the entry of kynurenine into the brain and attenuate the formation of neurotoxic kynurenine metabolites. …These findings demonstrate that leucine has antidepressant properties vis-à-vis inflammation-induced depression and one mechanism for this is by blocking the ability of kynurenine to enter the brain.

Munshi S, et al (2019) - **Peripheral anti-inflammatory cytokine Interleukin-10 treatment mitigates interleukin-1β - induced anxiety and sickness behaviors in adult male rats.** Behav Brain Res. 2019 Oct 17;372:112024. [FULL TEXT]

Pro-inflammatory cytokines produce manifestations of sickness during inflammation, such as malaise and lethargy. They also contribute to effects of inflammation on mood. Anti-inflammatory cytokines counteract damage caused by inflammatory processes and can limit the severity of inflammation. However, very little is known about the role of anti-inflammatory cytokines in sickness and mood changes during immune activation. … rats co-treated with both IL-10 and IL-1β showed locomotor activity, open field, social interaction and EPM behaviors very similar to control groups. This data demonstrate that IL-10 is capable of mitigating the sickness and anxiogenic effects caused by IL-1β, but that immune imbalance toward either a pro-inflammatory or an anti-inflammatory state can produce anxiety.

Zenz G, et al (2019) - **Intranasal Neuropeptide Y Blunts Lipopolysaccharide-Evoked Sickness Behavior but Not the Immune Response in Mice.** Neurotherapeutics. 2019 Oct;16(4):1335-1349. [FULL TEXT]

Neuropeptide Y (NPY) has been demonstrated to exert stress buffering effects and promote resilience. Non-invasive intranasal (IN) application of NPY to rodents is able to mitigate traumatic stress-induced behavioral changes as well as dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis. … We propose that IN NPY ablates sickness behavior at a site beyond the peripheral and cerebral cytokine response, an action that is associated with reduced activity of the HPA axis as determined by decreased plasma CORT. These results

indicate that IN NPY administration may be relevant to the management of neuropsychiatric disorders arising from immune-induced neuroendocrine dysfunction.

Dubois T, et al (2019) - **Role of gut microbiota in the interaction between immunity and psychiatry: a literature review.** Psychiatr Danub. 2019 Sep;31(Suppl 3):381-385. [ABS]

> BACKGROUND: Psychiatric disorders may be correlated with a low-grade systemic inflammation but the origin of this inflammatory response remains unclear and both genetics and environmental factors seems to be concerned. … Microbiota dysbiosis and increase gut permeability with subsequent immune challenges seems to be the source of the chronic mild inflammation associated with neuropsychiatric disorders. Repeated immune or stress events early in life may lead to neurodevelopmental disorders or sickness behavior later in life. CONCLUSIONS: Psychological stress impact gut microbiota with subsequent immune activation leading to neurodevelopmental disorders or sickness behavior and altering neurophysiology and reactivity to stress or lifestyle.

Oriolo G, et al (2019) - **Association of chronic inflammation and perceived stress with abnormal functional connectivity in brain areas involved with interoception in hepatitis C patients.** Brain Behav Immun. 2019 Aug;80:204-218. [ABS]

> Sickness behavioral changes elicited by inflammation may become prolonged and dysfunctional in patients with chronic disease, such as chronic hepatitis C (CHC). Neuroimaging studies show that the basal ganglia and insula are sensitive to systemic inflammation. …PSS (perceived stress scale) scores positively correlated with functional connectivity between the right anterior insula and right putamen, whereas PHQ-9 (depression) scores correlated with functional connectivity between most of the seeds and the right anterior insula. PGE2 (positively) and IL-6 (negatively) correlated with functional connectivity between the right anterior insula and right caudate nucleus and between the right ventral putamen and right putamen/globus pallidus. PGE2 and PSS scores accounted for 46% of the variance in functional connectivity between the anterior insula and putamen. CONCLUSIONS: CHC patients exhibited increased perceived stress and depressive symptoms, which were associated with changes in inflammatory marker levels and in functional connectivity between the insula and putamen, areas involved in interoceptive integration, emotional awareness, and orientation of motivational state.

Oliveira-Lima OC, et al (2019) - **Lipid dynamics in LPS-induced neuroinflammation by DESI-MS imaging.** Brain Behav Immun. 2019 Jul;79:186-194. [FULL TEXT]

> It is well-established that bacterial lipopolysaccharides (LPS) can promote neuroinflammation through receptor Toll-like 4 activation and induces sickness behavior in mice. This phenomenon triggers changes in membranes lipid dynamics to promote the intracellular cell signaling…. Desorption electrospray ionization mass spectrometry (DESI-MS) is a powerful technique that can be used to image the distribution of lipids in the brain tissue directly. …ions associated with phosphatidylethanolamine [PE(38:4)] and docosatetraenoic acid [FA (22:4)] could be used as biomarkers to distinguish samples from the control or LPS treated groups. Finally, our data demonstrated that monitoring cerebral lipids dynamics and its

neuroanatomical distribution can be helpful to understand sickness behavior and microglial activation after LPS administration.

Kobrzycka A, et al (2019) - **Peripheral and central compensatory mechanisms for impaired vagus nerve function during peripheral immune activation.** J Neuroinflammation. 2019 Jul 19;16(1):150. [FULL TEXT]

> We assessed biochemical and central neurotransmitter changes resulting from subdiaphragmatic vagotomy and whether they are modulated by intraperitoneal infection. …The lack of immunosensory signaling of the vagus nerve stimulated increased activity of discrete inflammatory marker signals, which we confirmed by quantifying biochemical changes in blood plasma. Behavioral results, although preliminary, support the observed biochemical alterations. Many of the neurotransmitter changes observed after vagotomy indicated that the vagus nerve influences the activity of many brain areas involved in control of immune response and sickness behavior

Rossetti AC, et al (2019) - **Differential Neuroinflammatory Response in Male and Female Mice: A Role for BDNF**. Front Mol Neurosci. 2019 Jul 17;12:166. [FULL TEXT]

> A growing body of evidence supports the close relationship between major depressive disorder (MDD), a severe psychiatric disease more common among women than men, and alterations of the immune/inflammatory system. …We found that the increased inflammatory response induced by LPS in the brain of male mice was independent of the genotype, whereas in the female, it was restricted to the heterozygous mice with no changes in the wild-type group, suggestive of a role for BDNF in the sex-dependent effect of the inflammatory challenge.

Sahu P, et al (2019) - **Cannabinoid receptor 2 activation mitigates lipopolysaccharide-induced neuroinflammation and sickness behavior in mice.** Psychopharmacology (Berl). 2019 Jun;236(6):1829-1838. [ABS]

> Cannabinoid receptor 2 (CB2R) signaling in the brain is associated with the pathophysiology of depression. Sickness behavior, characterized by lessened mobility, social interaction, and depressive behavior, is linked with neuroinflammation, oxidative stress, and immune system. The present study was aimed at evaluating 1-phenylisatin (PI), a CB2R agonist, in sickness behavior. … LPS elevated the brain TNF-α level, augmented oxidative stress, and induced the sickness behavior in mice. Acute and 7-day treatment of mice with PI significantly reduced the LPS-induced sickness behavior. In addition, PI inhibited the neuroinflammation evidenced by a reduction in brain TNF-α and oxidative stress. CONCLUSION: Our data propose that acute and long-term activation of CB2R might prevent neuroinflammation and oxidative stress-associated sickness behavior.

Shakhar K (2019) - **The Inclusive Behavioral Immune System.** Front Psychol. 2019 May 3;10:1004. [FULL TEXT]

> One widely-recognized example of the inclusive BIS is social immunity, which is prevalent

among eusocial organisms such as bees and ants. Their colonies engage in a collaborative protective behavior such as grooming and the removal of infected members from the nest. Another example may be sickness behavior, which includes the behavioral, cognitive and emotional symptoms that accompany infection, such as fatigue, and loss of appetite and social interest. My colleague and I recently suggested that sickness behavior has evolved because it reduces the direct and indirect contact between an infected host and its healthy kin - improving inclusive fitness. These additional behaviors are not carried out by the healthy individuals, but rather by whole communities in the first case, and by already infected individuals in the second. Since they step beyond the classical definition of BIS, it may be useful to broaden the term to the inclusive behavioral immune system.

Miller AL, et al (2019) - How many pigs within a group need to be sick to lead to a diagnostic change in the group's behavior? J Anim Sci. 2019 Apr 29;97(5):1956-1966. [FULL TEXT]

Zenz G, et al (2019) - Intermittent Fasting Exacerbates the Acute Immune and Behavioral Sickness Response to the Viral Mimic Poly(I:C) in Mice. Front Neurosci. 2019 Apr 17;13:359. [FULL TEXT]

Intermitted fasting and other forms of calorie restriction are increasingly demonstrated to exert potential health benefits. Interestingly, restricted feeding is also able to mitigate sickness in response to bacterial factors stimulating Toll-like receptor 4 (TLR4). However, little is known about how fasting modifies the activity of virus-associated molecular patterns. …Our data show that IF does not abate, but exaggerates the immune and sickness response to the viral mimic Poly(I:C). This adverse effect of IF occurs despite increased hypothalamic NPY expression and enhanced plasma corticosterone. We therefore propose that the effects of IF on the immune and behavioral responses to viral and bacterial factors are subject to different neuronal and neuroendocrine control mechanisms.

Weber MD, et al (2019) **- The Influence of Microglial Elimination and Repopulation on Stress Sensitization Induced by Repeated Social Defeat.** Biol Psychiatry. 2019 Apr 15;85(8):667-678. [FULL TEXT]

BACKGROUND: Stress is associated with an increased prevalence of anxiety and depression. Repeated social defeat (RSD) stress in mice increases the release of monocytes from the bone marrow that are recruited to the brain by microglia. These monocytes enhance inflammatory signaling and augment anxiety. Moreover, RSD promotes stress sensitization, in which exposure to acute stress 24 days after cessation of RSD causes anxiety recurrence.

Zhao J, et al (2019) - **Neuroinflammation induced by lipopolysaccharide causes cognitive impairment in mice.** Sci Rep. 2019 Apr 8;9(1):5790. [FULL TEXT]

We found that LPS treatment leads to sickness behavior and cognitive impairment in mice as shown in the Morris water maze and passive avoidance test, and these effects were accompanied by microglia activation (labeled by ionized calcium binding adaptor molecule-1, IBA-1) and neuronal cell loss (labeled by microtubule-associated protein 2, MAP-2) in the hippocampus. The levels of interleukin-4 (IL-4) and interleukin-10 (IL-10) in the serum and brain homogenates were reduced by the LPS treatment, while the levels of tumor necrosis

factor-α (TNF-α), interleukin-1β (IL-1β), prostaglandin E2 (PGE2) and nitric oxide (NO) were increased. In addition, LPS promoted the expression of cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) in the brain homogenates. The Western blot analysis showed that the nuclear factor kappa B (NF-κB) signaling pathway was activated in the LPS groups. Furthermore, VIPER, which is a TLR-4-specific inhibitory peptide, prevented the LPS-induced neuroinflammation and cognitive impairment.

Sharma R, et al (2019) - **Programming Effects of Pubertal Lipopolysaccharide Treatment in Male and Female CD-1 Mice**. J Immunol. 2019 Apr 1;202(7):2131-2140. [ABS]

The results of this study show that exposure to LPS during puberty programs the peripheral and central immune responses, resulting in an attenuated immune response following a subsequent homotypic stressor. Thus, exposure to an immune challenge during puberty affects immune function later in life, which could permanently affect brain function and have implications on mental health.

Ahmad Azam A, et al (2019) - **Effects of Clinacanthus nutans leaf extract on lipopolysaccharide - induced neuroinflammation in rats: A behavioral and (1)H NMR-based metabolomics study.** Avicenna J Phytomed. 2019 Mar-Apr;9(2):164-186. [FULL TEXT]

This research revealed the biochemical outcomes of metabolic dysregulation in serum associated with physiological sickness behavior following lipopolysaccharide (LPS)-induced neuroinflammation in rats, and treatment with Clinacanthus nutans (CN). …Treatment with the aqueous CN extract resulted in a statistically significant alteration in neuroinflammation metabolite biomarkers, including ethanol, choline, and acetate. … This result denotes that the metabolomics approach is a reliable tool to disclose the relationship between central neuroinflammation, and systemic metabolic and physiological disturbances which could be used for future ethno-pharmacological assessments.

Ajayi AM, et al (2019) - **Flavonoid-Rich Fraction of Ocimum gratissimum Attenuates Lipopolysaccharide-Induced Sickness Behavior, Inflammatory and Oxidative Stress in Mice.** Drug Res (Stuttg). 2019 Feb;69(3):151-158. [ABS]

PURPOSE: Ocimum gratissimum L. leaves has been traditionally used for management of febrile illnesses and symptoms typified of sickness behavior. In this work we investigated the modulatory effect of flavonoid-rich fraction of O. gratissimum leaves (EAFOg) on sickness behavior, inflammatory and oxidative stress responses in LPS-challenged mice.… Flavonoid-rich fraction of O. gratissimum leaf demonstrated significant modulation of LPS-induced sickness behavior, inflammatory and oxidative stress response in mice. This suggests an important therapeutic strategy in slowing down LPS-mediated hepatic and neuronal disease processes.

Lazo-Gomez R, et al (2019) - **Mechanisms of neurobehavioral abnormalities in multiple sclerosis: Contributions from neural and immune components.** Clin Neurophysiol Pract. 2019 Feb 21;4:39-46. [FULL TEXT]

Neuroinflammation and neurodegeneration are not isolated phenomena and various instances

of interaction between them have been described. This presents attractive targets for the development of therapeutic strategies for this neglected component of multiple sclerosis related disability.

Morita-Takemura S, et al (2019) - **Responses of perivascular macrophages to circulating lipopolysaccharides in the subfornical organ with special reference to endotoxin tolerance.** J Neuroinflammation. 2019 Feb 14;16(1):39. [FULL TEXT]

> Circulating endotoxins including lipopolysaccharides (LPS) cause brain responses such as fever and decrease of food and water intake, while pre-injection of endotoxins attenuates these responses. This phenomenon is called endotoxin tolerance, but the mechanisms underlying it remain unclear. The subfornical organ (SFO) rapidly produces proinflammatory cytokines including interleukin-1β (IL-1β) in response to peripherally injected LPS, and repeated LPS injection attenuates IL-1β production in the SFO, indicating that the SFO is involved in endotoxin tolerance. …The current data indicate that perivascular macrophages enable the SFO to produce IL-1β in response to circulating LPS and that its hyporesponsiveness may be the cause of endotoxin tolerance.

Tesoriero C, et al (2019) - **Sleep and brain infections.** Brain Res Bull. 2019 Feb;145:59-74. [ABS]

> Altogether the findings indicate that sleep-wake regulation is targeted by brain infections caused by different pathogens and, although the relevant pathogenetic mechanisms largely remain to be clarified, these alterations differ from hypersomnia occurring in sickness behavior. Thus, brain infections point to the vulnerability of the neural network of sleep-wake regulation as a highly relevant clinical and basic science challenge.

Korte-Bouws GAH, et al (2019) - **Juvenile Arthritis Patients Suffering from Chronic Inflammation Have Increased Activity of Both IDO and GTP-CH1 Pathways But Decreased BH4 Efficacy: Implications for Well-Being, Including Fatigue, Cognitive Impairment, Anxiety, and Depression.** Pharmaceuticals (Basel). 2019 Jan 8;12(1):9. [FULL TEXT]

2018

Toups M (2018) - **Inflammation and Depression: the Neuroimmune Connection.** Curr Treat Options Psychiatry. 2018 Dec;5(4):452-458. [FULL TEXT]

> Treatment of patients with depression should consider inflammatory status, as part of medical and psychiatric health. Recommendations for healthy diet and exercise are important for all patients but may be more important for patients who have clinical evidence of inflammation.

Lasselin J, et al (2018) - **Sickness behavior is not all about the immune response: Possible roles of expectations and prediction errors in the worry of being sick.** Brain Behav Immun. 2018 Nov;74:213-221. [ABS]

People react very differently when sick, and there are only poor correlations between the intensity of the immune response and sickness behavior. … The current findings suggest that the emotional component of sickness behavior is, at least partly, shaped by top-down expectations. Helping patients having a realistic expectation of symptoms during treatment of an illness may thus reduce aggravated emotional responses, and ultimately improve patients' quality of life and treatment compliance.

Stampanoni Bassi M, et al (2018) - **Exploiting the Multifaceted Effects of Cannabinoids on Mood to Boost Their Therapeutic Use Against Anxiety and Depression.** Front Mol Neurosci. 2018 Nov 20;11:424. [FULL TEXT]

The endocannabinoid system (ECS) has been recently recognized as a prominent promoter of the emotional homeostasis, mediating the effects of different environmental signals including rewarding and stressing stimuli. The ECS modulates the rewarding effects of environmental stimuli, influencing synaptic transmission in the dopaminergic projections to the limbic system, and mediates the neurophysiological and behavioral consequences of stress. Notably, the individual psychosocial context is another key element modulating the activity of the ECS. Finally, inflammation represents an additional factor that could alter the cannabinoid signaling in the CNS inducing a "sickness behavior," characterized by anxiety, anhedonia, and depressive symptoms. The complex influences of the ECS on both the environmental and internal stimuli processing, make the cannabinoid-based drugs an appealing option to treat different psychiatric conditions.

Craddock TJA, et al (2018) - **A Logic Model of Neuronal-Glial Interaction Suggests Altered Homeostatic Regulation in the Perpetuation of Neuroinflammation.** Front Cell Neurosci. 2018 Oct 15;12:336. [FULL TEXT]

Aberrant inflammatory signaling between neuronal and glial cells can develop into a persistent sickness behavior-related disorders, negatively impacting learning, memory, and neurogenesis. … The results support a role for the brain's own homeostatic drive in perpetuating the chronic neuroinflammation associated with exposure to the organophosphate DFP, with and without CORT priming. The deviation of illness profiles from exact model predictions suggests the presence of additional factors or of lasting changes to the brain's regulatory circuitry specific to each exposure.

Balter LJT, et al (2018) - **Low-grade inflammation decreases emotion recognition - Evidence from the vaccination model of inflammation.** Brain Behav Immun. 2018 Oct;73:216-221. [ABS]

The ability to adequately interpret the mental state of another person is key to complex human social interaction. Recent evidence suggests that this ability, considered a hallmark of 'theory of mind' (ToM), becomes impaired by inflammation… participants completed the Reading the Mind in the Eyes Test (RMET), a validated test for assessing how well the mental states of others can be inferred through observation of the eyes region of the face. Vaccination induced systemic inflammation, elevating IL-6 by +419% ($p < .001$), without fever, sickness symptoms (e.g., nausea, light-headedness), or mood changes (all p's > .21). Importantly, compared to placebo, vaccination significantly reduced RMET accuracy ($p < .05$). … the present study

provides further support for the hypothesis that immune activation impairs ToM. Such impairment may provide a mechanistic link explaining social-cognitive deficits in psychopathologies that exhibit low-grade inflammation, such as major depression.

de Gomes MG, et al (2018) - **Dietary hydrogenated vegetable fat exacerbates the activation of kynurenine pathway caused by peripheral lipopolysaccharide immune challenge in aged mice.** Chem Biol Interact. 2018 Sep 25;293:28-37. [ABS]

Sickness behavior is a normal immune response of body to fight infection, accompanied by endocrine and behavioral alterations. Lipopolysaccharide (LPS) causes sickness behavior in rodents through the increase of proinflammatory cytokines, generating peripheral inflammation and thus overactivation of kynurenine pathway (KP). …Overall, our study demonstrated that dietary hydrogenated vegetable fat (HVF) did not worsen the sickness behavioral induced by LPS administration. However, HVF aggravated the activation of KP and exacerbated the shift of KP metabolism towards the neurotoxic branch.

de Gomes MG, et al (2018) - **Fish oil ameliorates sickness behavior induced by lipopolysaccharide in aged mice through the modulation of kynurenine pathway.** J Nutr Biochem. 2018 Aug;58:37-48. [ABS]

We found that fish oil (FO) prevented the LPS-mediated body weight loss, anhedonic behavior, reduction of locomotor activity, up-regulation of the proinflammatory cytokines and serotoninergic alterations. We also found that FO was effective in modulating the KP biomarkers, inhibiting or attenuating KP dysregulation induced by LPS. Together, our results indicated that FO may have beneficial effects on LPS induced sickness-behavior in aged mice either by modulating central inflammation, KP and serotonergic signaling (indirectly effect) or by fatty acids incorporation into neuronal membranes (direct effect).

Lasselin J, et al (2018) - **Sex differences in how inflammation affects behavior: What we can learn from experimental inflammatory models in humans.** Front Neuroendocrinol. 2018 Jul;50:91-106. [ABS]

Human models demonstrate that experimental activation of the innate immune system has profound effects on brain activation and behavior, inducing fatigue, worsened mood and pain sensitivity. It has been proposed that inflammation is a mechanism involved in the etiology and maintenance of depression, chronic pain and long-term fatigue. … We suggest a model in which inflammation accentuates sex differences in brain networks and pre-existing vulnerability factors. This effect could render women more vulnerable to the detrimental effects of immune-to-brain communication over time.

Griton M, et al (2018) - **Neural pathways involved in infection-induced inflammation: recent insights and clinical implications.** Clin Auton Res. 2018 Jun;28(3):289-299. [ABS]

… sympathetic nerves do innervate these organs and modulate immune cell responses, production of inflammatory mediators and bacterial dissemination. Noradrenaline, which is both released by these fibers and often administered during sepsis, along with adrenaline, may

exert pro-inflammatory actions through the stimulation of β1 adrenergic receptors, as antagonists of this receptor have been shown to exert anti-inflammatory effects in experimental sepsis.

Fonken LK, et al (2018) - **Neuroinflammatory priming to stress is differentially regulated in male and female rats.** Brain Behav Immun. 2018 May;70:257-267. [FULL TEXT]

Exposure to stressors can enhance neuroinflammatory responses, and both stress and neuroinflammation are predisposing factors in the development of psychiatric disorders. Females suffer disproportionately more from several psychiatric disorders, …an immune challenge following either stress or CORT in females, but not males, increased peripheral inflammation (serum IL-1β). These novel data suggest that although males and females both enhance stress-induced neuroinflammatory and behavioral responses to an immune challenge, this priming may occur through distinct, sex-specific mechanisms.

Saxena S, et al (2018) - **Impact on the brain of the inflammatory response to surgery.** Presse Med. 2018 Apr;47(4 Pt 2):e73-e81. [FULL TEXT]

The brain is both the orchestrator as well as the target of the innate immune system's response to the aseptic trauma of surgery. When trauma-induced inflammation is not appropriately regulated persistent neuro-inflammation interferes with the synaptic plasticity that underlies the learning and memory aspects of cognition. The complications that ensue include postoperative delirium (POD) and postoperative cognitive dysfunction (POCD) at two poles of a constellation that is now termed perioperative neurocognitive disorders. …the innate immune system is vulnerable in clinical settings that include advanced age and lifestyle-induced diseases such as "unhealthy" obesity and the inevitable insulin resistance. Under these conditions, inflammation may become exaggerated and long-lived. Consideration is provided how to identify the high-risk surgical patient and both pharmacological (including biological compounds) and non-pharmacological strategies to customize care.

Draper A, et al (2018) - **Effort but not Reward Sensitivity is Altered by Acute Sickness Induced by Experimental Endotoxemia in Humans.** Neuropsychopharmacology. 2018 Apr;43(5):1107-1118. [ABS]

Sickness behavior in humans is characterized by low mood and fatigue, which have been suggested to reflect changes in motivation involving reorganization of priorities. …. We suggest that LPS-induced changes in motivation may be due to alterations to mesolimbic dopamine. Our behavioral paradigm could be used to further investigate effects of inflammation on motivational behavior in psychiatric and chronic illnesses.

Sorrenti V, et al (2018) - **Curcumin Prevents Acute Neuroinflammation and Long-Term Memory Impairment Induced by Systemic Lipopolysaccharide in Mice.** Front Pharmacol. 2018 Mar 5;9:183. [FULL TEXT]

Systemic lipopolysaccharide (LPS) induces an acute inflammatory response in the central nervous system (CNS) ("neuroinflammation") characterized by altered functions of microglial cells, the major resident immune cells of the CNS, and an increased inflammatory profile that

can result in long-term neuronal cell damage and severe behavioral and cognitive consequences. Curcumin, a natural compound, exerts CNS anti-inflammatory and neuroprotective functions mainly after chronic treatment. …these results suggest that the preventive effect of curcumin in inhibiting the acute effects of neuroinflammation could be of value in reducing the long-term consequences of brain inflammation, including cognitive deficits such as memory dysfunction.

Kuhlman KR, et al (2018) - **Within-subject associations between inflammation and features of depression: Using the flu vaccine as a mild inflammatory stimulus.** Brain Behav Immun. 2018 Mar;69:540-547. [FULL TEXT]

Greater increases in IL-6 were associated with greater mood disturbance on post-vaccine days, specifically depressed mood and cognitive symptoms. …Minor increases in inflammation were associated with corresponding increases in features of depression, and these associations occurred in the absence of any physical symptoms. The influenza vaccine could be used to probe causal relationships with a high degree of ecological validity, even in high-risk and vulnerable populations, to better understand the role of inflammation in the pathogenesis of depression.

McMillan LE, et al (2018) - **Eating when ill is risky: immune defense impairs food detoxification in the caterpillar Manduca sexta.** J Exp Biol. 2018 Feb 7;221(Pt 3):jeb173336. [ABS]

The results of this rescue experiment suggest that decreased glutathione availability, such as occurs during an immune response, impairs detoxification. We also found that the expression of some detoxification genes were not upregulated during a combined immune-toxin challenge, although they were when animals received a toxin challenge alone. These results suggest that immune defense reduces food detoxification capacity. Illness-induced anorexia may protect animals by decreasing exposure to food toxins when detoxification is impaired.

d'Avila JC, et al (2018) - **Age-related cognitive impairment is associated with long-term neuroinflammation and oxidative stress in a mouse model of episodic systemic inflammation.** J Neuroinflammation. 2018 Jan 30;15(1):28. [FULL TEXT]

Evidence shows that aged microglia are primed and show exaggerated response to acute inflammatory challenge….Episodic systemic inflammation induced systemic inflammation and sickness behavior mainly in aged mice. Systemic inflammation induced depressive-like behavior in both young and aged mice. Memory and learning were significantly affected in aged mice that presented lower exploratory activity and deficits in episodic and spatial memories, compared to aged controls and to young after episodic systemic inflammation. Systemic inflammation induced acute microglia activation in young mice that returned to base levels long term after episodic systemic inflammation. Aged mice presented dystrophic microglia in the hippocampus and entorhinal cortex at basal level and did not change morphology in the acute response to SI. Regardless of their dystrophic microglia, aged mice produced higher levels of pro-inflammatory (IL-1β and IL-6) as well as pro-resolution (IL-10 and IL-4) cytokines in the brain. Also, higher levels of Nox2 expression, oxidized proteins and lower antioxidant defenses were found in the aged brains compared to the young after episodic

systemic inflammation. CONCLUSIONS: Our data show that aged mice have increased susceptibility to episodic systemic inflammation. Aged mice that showed cognitive impairments also presented higher oxidative stress and abnormal production of cytokines in their brains. These results indicate that a neuroinflammation and oxidative stress are pathophysiological mechanisms of age-related cognitive impairments.

Kelly KA, et al (2018) - **Prior exposure to corticosterone markedly enhances and prolongs the neuroinflammatory response to systemic challenge with LPS.** PLoS One. 2018 Jan 5;13(1):e0190546. [FULL TEXT]

…it is well established that peripheral inflammation can affect the brain. Neuroinflammation, the elaboration of proinflammatory mediators in the CNS, commonly is associated with behavioral symptoms (e.g., lethargy, anhedonia, anorexia, depression, etc.) termed sickness behavior. Stressors have been shown to interact with and alter neuroinflammatory responses and associated behaviors. …a single week of CORT exposure maintained the potential for priming for 30 days, while intermittent exposure to CORT for up to 90 days synergistically primed the LPS-induced neuroinflammatory response. These findings highlight the possibility for an isolated inflammatory event to be exacerbated by a temporally distant stressful stimulus and demonstrates the potential for recurrent stress to greatly aggravate chronic inflammatory disorders.

Wen H, et al (2018) - **Inflammatory Signaling in Post-Stroke Fatigue and Depression.** Eur Neurol. 2018;80(3-4):138-148. [ABS]

In the United States, stroke continues to be the cause for long-term disability. … stroke induces a systemic inflammatory response that is the trigger for sickness behavior, of which fatigue and depression are predominant symptoms.

Pal M, et al (2018) - **Assessment of Pyrexia and Associated Sickness Behavior in Patients with Chronic Periodontitis.** Neuroimmunomodulation. 2018;25(3):138-145. [ABS]

The purpose of this study was to assess pyrexia and sickness behavior such as anxiety, depression, lethargy, and weight loss in subjects with chronic periodontitis, and evaluate inflammatory mediators such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) in the patients with fever. … The study demonstrated that there is a significant increase in the sublingual temperature amongst patients with severe chronic periodontitis. The subgingival temperature has a positive correlation with the sublingual temperature. There was a linear trend of an association of sickness behavior with the severity of chronic periodontitis. A significant increase in the circulating inflammatory mediators, CRP and ESR, were noticed in subjects with elevated body temperature.

Nascimento AF, et al (2018) - **Zinc Alleviates Lipopolysaccharide Interference with Both Body Temperature and Sickness Behavior in Virgin Female Rats.** Neuroimmunomodulation. 2018;25(2):89-95. [ABS]

Treatment with zinc attenuated LPS-increased temperature, decreased the body weight gain

and food consumption, and water consumption was increased.

Sorrenti V, et al (2018) - **A Model of Systemic Inflammation to Study Neuroinflammation.** Methods Mol Biol. 2018;1727:361-372. [ABS]

> Increasing evidence suggests that neurodegeneration occurs in part because the environment is affected during disease in a cascade of processes collectively termed neuroinflammation. This is a reactive response of the central nervous system against noxious elements that interfere with tissue homeostasis. Neuroinflammation is mediated by inflammatory molecules released by microglial cells. Understanding and controlling interactions between the immune system and microglial activation might represent the key to prevent or delay the onset of central nervous system diseases. This chapter details techniques to generate and characterize an in vivo model of neuroinflammation based on a single intraperitoneal injection of lipopolysaccharide, which can be used to understand the wide variety of cellular and molecular mechanisms of neuroinflammation, as well as to identify new therapies by testing the anti-inflammatory properties of synthetic and natural molecules.

Mansour HA, et al (2018) - **Neuroinflammatory reactions in sickness behavior induced by bacterial infection: Protective effect of minocycline.** J Biochem Mol Toxicol. 2018 Feb;32(2). [ABS]

> Rats infected with E. coli displayed reduced struggling time in forced swimming test, as well as, exploration and locomotion in open field test with reduction in neurotransmitters (norepinephrine, dopamine, and serotonin) versus elevation in the inflammatory (tumor necrosis factor-alpha, interferon-gamma) and oxidative stress (thiobarbituric acid reactive substance, reduced glutathione) biomarkers. Inflammatory infiltrates of nuclear cells were observed in brains of infected rats. MIN administration prevented the deleterious effects of E. coli infection, thus protects against sickness behavior possibly via defending from neuroinflammation.

Zager A, et al (2018) - **The wake-promoting drug Modafinil prevents motor impairment in sickness behavior induced by LPS in mice: Role for dopaminergic D1 receptor.** Prog Neuropsychopharmacol Biol Psychiatry. 2018 Feb 2;81:468-476. [ABS]

> The wake-promoting drug Modafinil has been used for many years for treatment of Narcolepsy and Excessive Daytime Sleepiness, due to a dopamine-related psychostimulant action. Recent studies have indicated that Modafinil prevents neuroinflammation in animal models. …This evidence suggests that Modafinil treatment might be useful to prevent inflammation-related behavioral alterations, possibly due to a neuroimmune mechanism.

Koo BB, et al (2018) - **Corticosterone potentiates DFP-induced neuroinflammation and affects high-order diffusion imaging in a rat model of Gulf War Illness.** Brain Behav Immun. 2018 Jan;67:42-46. [FULL TEXT]

> Veterans of the 1991 Gulf War were potentially exposed to a variety of toxic chemicals, including sarin nerve agent and pesticides, which have been suspected to be involved in the development of Gulf War Illness (GWI). Several of these exposures cause a neuroinflammatory

response in mice, which may serve as a basis for the sickness behavior-like symptoms seen in veterans with GWI. Furthermore, conditions mimicking the physiological stress experienced during the war can exacerbate this effect.

…applying our existing Gulf War illness (GWI) mouse model to rats, by exposing them to 4 days of corticosterone … to mimic high physiological stress, followed by a single injection of the sarin nerve agent surrogate, diisopropyl fluorophosphates (DFP). Then, we evaluated the neuroinflammatory responses using qPCR of cytokine mRNA and also examined brain structure with a novel high-order diffusion MRI. We found a CORT-enhancement of DFP-induced neuroinflammation, extending our mouse GWI model to the rat.

Particularly, while the CORT+DFP rats had more restricted spatial patterns in the hippocampus and the hypothalamus, the highest and most wide-spread differences were shown in DFP-treated rats compared to the controls in the thalamus, the amygdala, the piriform cortex and the ventral tegmental area. The association of these diffusion changes with neuroinflammatory cytokine expression indicates the potential for GW-relevant exposures to result in connectivity changes in the brain.

2017

Sylvia KE, et al (2017) - **A Return to Wisdom: Using Sickness Behaviors to Integrate Ecological and Translational Research.** Integr Comp Biol. 2017 Dec 1;57(6):1204-1213. [FULL TEXT]

Sickness is typically characterized by fever, anorexia, cachexia, and reductions in social, pleasurable, and sexual behaviors. These responses can be displayed at varying intensities both within and among individuals, and the adaptive nature of sickness responses can be demonstrated by the context-dependent nature of their expression. The study of sickness has become an important area of investigation for researchers in a wide range of areas, including psychoneuroimmunology (PNI) and ecoimmunology (EI). The general goal of PNI is to identify key interactions among the nervous, endocrine and immune systems and behavior, and how disruptions in these processes might contribute to disease states. EI, in turn, has been established more recently within the perspectives of ecology and evolutionary biology, and is aimed more at understanding natural variation in immune function and sickness responses within a broadly integrative, organismal, and evolutionary context. The goal of this review is to examine the literature on sickness from both basic and biomedical perspectives within PNI and EI and to demonstrate how the integrative study of sickness behavior can serve as an integrating agent to connect ecological and translational approaches to the study of disease. … By applying this integrative approach to sickness, we will be able to develop a more comprehensive view of sickness as a suite of adaptive responses rather than the simply deleterious consequences of illness.

Hamasato EK, et al (2017) - **Assessment of social behavior directed toward sick partners and its relation to central cytokine expression in rats.** Physiol Behav. 2017 Dec 1;182:128-136. [FULL TEXT]

> Acute illness not only reduces the expression of social behavior by sick rodents, but can also lead to avoidance responses when detected by healthy, would-be social partners. … Together, these data replicate and extend our prior work showing that healthy rats avoid sick conspecifics, and provide preliminary evidence for an anticipatory cytokine response when rats are exposed to a sick partner. These data also provide new evidence to suggest that recent housing history potently modulates cytokine responses evoked by LPS.

Harper JA, et al (2017) - **Pilot investigation into the sickness response to influenza vaccination in adults: Effect of depression and anxiety.** Gen Hosp Psychiatry. 2017 Sep;48:56-61. [FULL TEXT]

> These data suggest that influenza vaccine has a greater effect on affect in patients with depression and anxiety than in mentally healthy individuals. This effect was focused on positive affect, suggesting that influenza vaccine induced inflammation may be best suited to examine alterations in positive affect and positive valence systems.

Blank T, et al (2017) - **Type I interferon pathway in CNS homeostasis and neurological disorders.** Glia. 2017 Sep;65(9):1397-1406. [ABS]

> Type I interferons (IFNs), IFN-α and IFN-β, represent the major effector cytokines of the host immune response against viruses and other intracellular pathogens. … Whilst the contribution of type I IFNs to peripheral immunity is well documented, they can also be produced by almost every cell in the central nervous system (CNS). Furthermore, IFNs can reach the CNS from the periphery to modulate the function of not only microglia and astrocytes, but also neurons and oligodendrocytes, with major consequences for cognition and behavior. … In this review we will highlight the importance of a well-balanced level of type I IFNs for healthy brain physiology, and to what extent dysregulation of this cytokine system can result in brain 'interferonopathies'. … Given the pleiotropic nature of type I IFNs, it is critical to determine their exact cellular impact.

Miaskowski C, et al (2017) - **Cytokine Gene Polymorphisms Associated with Symptom Clusters in Oncology Patients Undergoing Radiation Therapy.** J Pain Symptom Manage. 2017 Aug 7. [ABS]

> Most of the reviews on the biological basis for symptom clusters suggest that inflammatory processes are involved in the development and maintenance of the symptom clusters. However, no studies have evaluated for associations between genetic polymorphisms and common symptom clusters (e.g., mood disturbance, sickness behavior).
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> Our findings support the hypotheses that symptoms that cluster together [(e.g., mood disturbance, sickness behavior)] have a common underlying mechanism and that the most common symptom clusters in oncology patients are associated polymorphisms in genes involved in a variety of inflammatory processes.

DeKorver NW, et al (2017) - **Toll-Like Receptor 2 Is a Regulator of Circadian Active and Inactive State Consolidation in C57BL-6 Mice.** Front Aging Neurosci. 2017; 9: 219. [FULL TEXT]

> We describe a previously unappreciated role that toll-like receptor 2 (Tlr2, a membrane bound

pattern recognition receptor that recognizes specific bacterial, viral, and fungal peptides), contributes toward regulation of behavioral arousal. …Prior studies have demonstrated that Tlr2 regulates sickness behaviors including hypophagia, hyperthermia, and decreased activity. Our work suggests that Tlr2 function also evokes behavioral fragmentation, another aspect of sickness behavior and a clinically significant problem of older adults.

Locker AR. et al (2017) - **Corticosterone primes the neuroinflammatory response to Gulf War Illness-relevant organophosphates independently of acetylcholinesterase inhibition.** J Neurochem. 2017 Aug;142(3):444-455. [FULL TEXT]

George DB, et al (2017) - **Carotenoids buffer the acute phase response on fever, sickness behavior and rapid bill color change in zebra finches.** J Exp Biol. 2017 Aug 15;220(Pt 16):2957-2964. [ABS]

Carotenoids are finite resources that animals can allocate to self-maintenance, attractiveness or reproduction. Here we test how carotenoids affect the acute phase response (APR), an intense rapid systemic response characterized by fever, sickness behavior and production of acute phase proteins, which serves to reduce pathogen persistence.

Among supplemented individuals, those with higher blood carotenoid levels exhibited a lower reduction in activity rate after 24 h. … immune activation may have caused birds to preferentially draw down carotenoids from the bloodstream, ostensibly for use in health. Rapid bill color changes over a 48-h period support growing evidence that bills may serve as short-term signals of health and condition.

Yang X, et al (2017) - **Resveratrol regulates microglia M1/M2 polarization via PGC-1α in conditions of neuroinflammatory injury.** Brain Behav Immun. 2017 Aug;64:162-172. [ABS]

Microglia are the primary cells that exert immune function in the central nervous system (CNS), and accumulating evidence suggests that microglia act as key players in the initiation of neurodegenerative diseases. It is now well recognized that microglia have functional plasticity and dual phenotypes, proinflammatory M1 and anti-inflammatory M2 phenotypes… Our study demonstrated that resveratrol reduced inflammatory damage and promoted microglia polarization to the M2 phenotype in LPS-induced neuroinflammation. In addition, resveratrol ameliorated LPS-induced sickness behavior in mice.

Avitsur R, et al (2017) - **Escitalopram or novel herbal treatments differentially alter cytokine and behavioral responses to immune challenge.** J Neuroimmunol. 2017 Aug 15;309:111-118. [ABS]

Studies suggest that inflammation is involved in the pathophysiology of depression. The present study examined the effects of the commonly used antidepressant escitalopram, in comparison with a novel herbal treatment (NHT) consisted of Crataegus pinnatifida, Triticum aestivum, Lilium brownii and Fructus Ziziphus jujuba, on cytokine and behavioral responses to an immune challenge. Escitalopram augmented lipopolysaccharide-induced tumor necrosis factor (TNF)-α peripheral secretion and induced a faster kinetics of interleukin-1β secretion, while marginally reducing sickness behavior. NHT (novel herbal treatment), on the other hand, completely abolished lipopolysaccharide-induced interleukin-1β and TNFα peripheral secretion

and diminished sickness behavior. These findings may have implications for the treatment of depressive symptoms associated with immune activation.

Wang N, et al (2017) - **Chronic unpredictable stress exacerbates surgery-induced sickness behavior and neuroinflammatory responses via glucocorticoids secretion in adult rats.** PLoS One. 2017 Aug 14;12(8):e0183077. [FULL TEXT]

D'Mello C, et al (2017) - **Interactions Between Platelets and Inflammatory Monocytes Affect Sickness Behavior in Mice With Liver Inflammation.** Gastroenterology. 2017 Aug 9. pii: S0016-5085(17)36022-5. [ABS]

> Patients with inflammatory liver disease commonly develop debilitating symptoms, called sickness behaviors, which arise via changes in brain function. Monocytes that produce tumor necrosis factor (TNF) interact with cerebral endothelial cells to activate microglial cells and promote sickness behavior. Platelets regulate inflammation, and aggregates of monocytes and platelets are increased in the circulation of patients with liver disease. We investigated the role of platelets in inducing inflammatory features of circulating monocytes and promoting sickness behaviors in mice with cholestatic liver injury.

Grissom NM, et al (2017) - **Suboptimal nutrition in early life affects the inflammatory gene expression profile and behavioral responses to stressors.** Brain Behav Immun. 2017 Jul;63:115-126. [ABS]

> Nutritional conditions in early life can have a lasting impact on health and disease risk, though the underlying mechanisms are incompletely understood. In the healthy individual, physiological and behavioral responses to stress are coordinated in such a way as to mobilize resources necessary to respond to the stressor and to terminate the stress response at the appropriate time. Induction of proinflammatory gene expression within the brain is one such example that is initiated in response to both physiological and psychological stressors, and is the focus of the current study. We tested the hypothesis that early life nutrition would impact the proinflammatory transcriptional response to a stressor. Pregnant and lactating dams were fed one of three diets; a low-protein diet, a high fat diet, or the control diet through pregnancy and lactation. Adult male offspring were then challenged with either a physiological stressor (acute lipopolysaccharide injection, IP) or a psychological stressor (15 min restraint). Expression of 20 proinflammatory and stress-related genes was evaluated in hypothalamus, prefrontal cortex, amygdala and ventral tegmental area. In a second cohort, behavioral responses (food intake, locomotor activity, metabolic rate) were evaluated. Offspring from low protein fed dams showed a generally reduced transcriptional response, particularly to LPS, and resistance to behavioral changes associated with restraint, while HF offspring showed an exacerbated transcriptional response within the PFC, a reduced transcriptional response in hypothalamus and amygdala, and an exacerbation of the LPS-induced reduction of locomotor activity. The present data identify differential proinflammatory transcriptional responses throughout the brain driven by perinatal diet as an important variable that may affect risk or resilience to stressors.

Tohidpour A, et al (2017) - **Neuroinflammation and Infection: Molecular Mechanisms Associated**

with Dysfunction of Neurovascular Unit. Front. Cell. Infect. Microbiol., 20 June 2017. [FULL TEXT]

Salvesen Ø, et al (2017) - **LPS-induced systemic inflammation reveals an immunomodulatory role for the prion protein at the blood-brain interface.** J Neuroinflammation. 2017 May 22;14(1):106. [FULL TEXT]

> BACKGROUND: The cellular prion protein (PrPC) is an evolutionary conserved protein abundantly expressed not only in the central nervous system but also peripherally including the immune system. …All LPS-treated goats displayed clinical signs of sickness behavior, which were of significantly ($p < 0.01$) longer duration in animals without PrPC. …Our data suggest that PrPC acts as a modulator of certain pathways of innate immunity signaling, particularly downstream of interferons, and probably contributes to protection of vulnerable tissues against inflammatory damage.

Schreuder L, et al (2017) - **Pathophysiological and behavioral effects of systemic inflammation in aged and diseased rodents with relevance to delirium: A systematic review.** Brain Behav Immun. 2017 May;62:362-381. [ABS]

> Delirium is a frequent outcome for aged and demented patients that suffer a systemic inflammatory insult. Animal models that reconstruct these etiological processes have potential to provide a better understanding of the pathophysiology of delirium. … This systematic review analyzed the impact of systemic inflammation on the production of inflammatory and neurotoxic mediators in peripheral blood, cerebrospinal fluid (CSF), and on the central nervous system (CNS). Moreover, concomitant behavioral and cognitive symptoms were also evaluated. Finally, outcomes of behavioral and cognitive tests from animal studies were compared to features and symptoms present in delirious patients.

Davis RL, et al (2017) - **The opioid antagonist, β-funaltrexamine, inhibits lipopolysaccharide-induced neuroinflammation and reduces sickness behavior in mice.** Physiol Behav. 2017 May 1;173:52-60. [ABS]

> Brain pathologies such as neurodegenerative diseases, infection, traumatic brain injury, and mood disorders produce enormous personal and economic burdens. It is well established that neuroinflammation plays an important role in the etiology and/or manifestation of such disorders. Previously, we discovered that beta-funaltrexamine (β-FNA) inhibits inflammatory signaling in human astrocytes in vitro, resulting in reduced expression of proinflammatory cytokines/chemokines. The present study examines the effects of peripherally administered β-FNA on lipopolysaccharide (LPS)-induced neuroinflammation and sickness behavior in vivo. …The reduction in sickness behavior may be in part due to decreased chemokine expression in the brain; further examination of the anti-inflammatory and neuroprotective effects of β-FNA is warranted.

Adelman JS, et al (2017) - **Infection reduces anti-predator behaviors in house finches.** J Avian Biol. 2017 Apr;48(4):519-528. [FULL TEXT]

> Infectious diseases can cause host mortality through direct or indirect mechanisms, including

altered behavior. Diminished anti-predator behavior is among the most-studied causes of indirect mortality during infection… Here we test whether the directly-transmitted bacterial pathogen, Mycoplasma gallisepticum (MG), reduces responses to predation-related stimuli in house finches (Haemorhous mexicanus). MG causes conjunctivitis and reduces survival among free-living finches, but rarely causes mortality in captivity, suggesting a role for indirect mechanisms. … MG infection reduced anti-predator responses during visual exposure to a mounted predator and simulated predator attack, even for birds without detectable visual obstruction from conjunctivitis. However, MG infection did not significantly alter responses during human approach or audio playback. These results are consistent with the hypothesis that predation plays a role in MG-induced mortality in the wild, with reduced locomotion, a common form of sickness behavior for many taxa, as a likely mechanism. Our results therefore suggest that additional research on the role of sickness behaviors in predation could prove illuminating.

Corrard F, et al (2017) - **Sickness behavior in feverish children is independent of the severity of fever. An observational, multicenter study**. PLoS One. 2017 Mar 9;12(3):e0171670. [FULL TEXT]

The 8 parameters suggested that SB and fever are two independent manifestations that are activated simultaneously during an infection. This independence is in harmony with recommendations to treat the discomfort of SB and not the fever.

Moraes MM, et al (2017) - **Propentofylline Prevents Sickness Behavior and Depressive-Like Behavior Induced by Lipopolysaccharide in Rats via Neuroinflammatory Pathway.** PLoS One. 2017 Jan 5;12(1):e0169446. [FULL TEXT]

Mendes-Lima T, et al (2017) - **Acute Lipopolysaccharide Switches the Selection of Maternal Behavior to Predatory Behavior in Female Rats.** Neuroimmunomodulation. 2017;24(1):1-10. [ABS]

A common problem during the postpartum period and during lactation is being affected by infection due to Gram-negative bacteria. In this situation, a sick mother needs to choose between caring for her pups or the need for survival. This study analyzed the effects of lipopolysaccharide (LPS)-induced sickness behavior on selection between maternal behavior (MB) and predatory behavior (PB) in lactating rats. To assess the LPS-induced sickness behavior, the plasma tumor necrosis factor-α (TNF-α) levels were measured. … LPS administration reduced the time and frequency of pup contact, grouping, grooming, and kyphosis, with an increase in the latency to first pup contact and grouping. With regard to PB, the time of foraging and eating insects increased, and the latencies to first insect contact, eating insects, and foraging decreased. With regard to general maternal activity, immobility time and TNF-α levels increased in the LPS-treated group. … LPS exposure switched MB to PB, prioritizing maternal survival. Thus, in more favorable situations, these rats may have new offspring and therefore her species would survive for long.

D'Mello C, et al (2017) - **Immune-to-Brain Communication Pathways in Inflammation-Associated Sickness and Depression.** Curr Top Behav Neurosci. 2017;31:73-94. [ABS]

A growing body of evidence now highlights a key role for inflammation in mediating sickness

behaviors and depression. Systemic inflammatory diseases such as rheumatoid arthritis, inflammatory bowel disease, and chronic liver disease have high comorbidity with depression. How the periphery communicates with the brain to mediate changes in neurotransmission and thereby behavior is not completely understood. Traditional routes of communication between the periphery and the brain involve neural and humoral pathways with TNFα, IL-1β, and IL-6 being the three main cytokines that have primarily been implicated in mediating signaling via these pathways. However, in recent years communication via peripheral immune-cell-to-brain and the gut-microbiota-to-brain routes have received increasing attention for their ability to modulate brain function. In this chapter we discuss periphery-to-brain communication pathways and their potential role in mediating inflammation-associated sickness behaviors and depression.

Harrison NA (2017) -**Brain Structures Implicated in Inflammation-Associated Depression.** Curr Top Behav Neurosci. 2017;31:221-248. [ABS]

Systemic inflammation rapidly impairs mood, motivation, and cognition inducing a stereotyped cluster of symptoms collectively known as "sickness behaviors." When inflammation is severe or chronic, these behavioral changes can appear indistinguishable from major depressive disorder (MDD). Human and rodent neuroimaging combined with experimental inflammatory challenges has clarified the neural circuitry associated with many of the key features of inflammation-induced-sickness behavior, and in so doing revealed often-remarkable commonalities with circuit abnormalities observed in MDD. This review aims to provide the first synthesis of this work illustrating areas of convergence and divergence with the MDD literature as well as highlighting areas for future study.

Dantzer R (2017) -**Role of the Kynurenine Metabolism Pathway in Inflammation-Induced Depression: Preclinical Approaches.** Curr Top Behav Neurosci. 2017;31:117-138. [FULL TEXT]

Physically ill patients with chronic inflammation often present with symptoms of depression. Our understanding of the pathophysiology of inflammation-associated depression has benefited from preclinical studies on the mechanisms of sickness and clinical studies on the symptoms of sickness and depression that develop in patients treated with immunotherapy. Sickness behavior develops when the immune system is activated by pathogen- or damage-associated molecular patterns. It is a normal biological response to infection and cell injury. It helps the organism to mobilize its immune and metabolic defenses to fight the danger. Depression emerges on the background of sickness when the inflammatory response is too intense and long lasting or the resolution process is deficient. The transition from sickness to depression is mediated by activation of the kynurenine metabolism pathway that leads to the formation of neurotoxic kynurenine metabolites including quinolinic acid, an agonist of N-methyl-D-aspartate receptors. The neuroimmune processes and molecular factors that have been identified in the studies of inflammation-associated depression represent potential new targets for the development of innovative therapies for the treatment of major depressive disorders.

Ashley NT, et al (2017) - **Neuroendocrine-immune circuits, phenotypes, and interactions.** Horm Behav. 2017 Jan;87:25-34. [FULL TEXT]

Multidirectional interactions among the immune, endocrine, and nervous systems have been demonstrated in humans and non-human animal models for many decades by the biomedical community, but ecological and evolutionary perspectives are lacking. Neuroendocrine-immune interactions can be conceptualized using a series of feedback loops, which culminate into distinct neuroendocrine-immune phenotypes. Behavior can exert profound influences on these phenotypes, which can in turn reciprocally modulate behavior. For example, the behavioral aspects of reproduction, including courtship, aggression, mate selection and parental behaviors can impinge upon neuroendocrine-immune interactions. One classic example is the immunocompetence handicap hypothesis (ICHH), which proposes that steroid hormones act as mediators of traits important for female choice while suppressing the immune system. Reciprocally, neuroendocrine-immune pathways can promote the development of altered behavioral states, such as sickness behavior. Understanding the energetic signals that mediate neuroendocrine-immune crosstalk is an active area of research. Although the field of psychoneuroimmunology (PNI) has begun to explore this crosstalk from a biomedical standpoint, the neuroendocrine-immune-behavior nexus has been relatively underappreciated in comparative species. The field of ecoimmunology, while traditionally emphasizing the study of non-model systems from an ecological evolutionary perspective, often under natural conditions, has focused less on the physiological mechanisms underlying behavioral responses. This review summarizes neuroendocrine-immune interactions using a comparative framework to understand the ecological and evolutionary forces that shape these complex physiological interactions.

Hennessy E, et al (2017) - **Systemic TNF-α produces acute cognitive dysfunction and exaggerated sickness behavior when superimposed upon progressive neurodegeneration.** Brain Behav Immun. 2017 Jan;59:233-244. [FULL TEXT]

Inflammation influences chronic neurodegeneration but its precise roles are not yet clear. Systemic inflammation caused by infection, trauma or co-morbidity can alter the brain's inflammatory status, produce acute cognitive impairments, such as delirium, and drive new pathology and accelerated decline. Consistent with this, elevated systemic TNF-α is associated with more rapid cognitive decline over 6 months in Alzheimer's disease patients. In the current study we challenged normal animals and those with existing progressive neurodegeneration (ME7 prion disease) with TNF-α (i.p.) to test the hypothesis that this cytokine has differential effects on cognitive function, sickness behavior and features of underlying pathology contingent on the animals' baseline condition. TNF-α (50μg/kg) had no impact on performance of normal animals (normal brain homogenate; NBH) on working memory (T-maze) but produced acute impairments in ME7 animals similarly challenged. Plasma TNF-α and CCL2 levels were equivalent in NBH and ME7 TNF-challenged animals but hippocampal and hypothalamic transcription of IL-1β, TNF-α and CCL2 and translation of IL-1β were higher in ME7+TNF-α than NBH+TNF-α animals. TNF-α produced an exaggerated sickness behavior response (hypothermia, weight loss, inactivity) in ME7 animals compared to that in NBH animals. However a single challenge with this dose was not sufficient to produce de novo neuronal death, synaptic loss or tau hyperphosphorylation that was distinguishable from that arising from ME7 alone. The data indicate that acutely elevated TNF-α has robust acute effects on brain function, selectively in the degenerating brain, but more sustained levels may be

required to significantly impact on underlying neurodegeneration.

Verburg-van Kemenade BML, et al (2017) - **Neuroendocrine-immune interaction: Evolutionarily conserved mechanisms that maintain allostasis in an ever-changing environment.** Dev Comp Immunol. 2017 Jan;66:2-23. [ABS]

> This review focuses on the principal mechanisms of bi-directional communication and the evidence for evolutionary conservation of the important physiological pathways involved.

Astiz M, et al (2017) - **Short-Term High-Fat Diet Feeding Provides Hypothalamic but Not Hippocampal Protection against Acute Infection in Male Mice.** Neuroendocrinology. 2017;104(1):40-50. [ABS]

Rich T, et al (2017) - **Association of fatigue and depression with circulating levels of proinflammatory cytokines and epidermal growth factor receptor ligands: a correlative study of a placebo-controlled fatigue trial.** Cancer Manag Res. 2017 Jan 31;9:1-10. [FULL TEXT]

> In this correlative analysis of a fatigue clinical trial, levels of fatigue were significantly associated with levels of IL-1 and IL-1Ra. Circadian-signaling pathways related to EGFR signaling were correlated with depression as were other cytokines. A major placebo effect was associated with a global decrease in cytokine and growth factors. These data provide further basis for testing hypotheses regarding the mechanisms of fatigue and depression in cancer patients.

2016

Le Thuc O, et al (2016) - **Central CCL2 signaling onto MCH neurons mediates metabolic and behavioral adaptation to inflammation.** EMBO Rep. 2016 Dec;17(12):1738-1752. [FULL TEXT]

Trammell RA, et al (2016) - **Effects of Chronic Diurnal Disruption and Acute Inflammatory Challenge on Mice with Latent Murine Gammaherpesvirus Infection.** Comp Med. 2016 Dec 1;66(6):445-454. [FULL TEXT]

> People who engage in shift work (SW) have increased risk of developing illnesses, including infectious diseases and various inflammatory conditions. …These findings suggest that exposure to repeated chronic diurnal disruption and an acute inflammatory challenge during latent murine gammaherpesvirus (MuGHV) infection, in the context of impaired host immune competence, contribute to enhanced viral reactivity and an increased viral load that might trigger 'sickness behavior' symptoms of infectious disease and perhaps contribute to chronic fatigue syndrome.

Stephan KE, et al (2016) - **Allostatic Self-efficacy: A Metacognitive Theory of Dyshomeostasis-Induced Fatigue and Depression.** Front Hum Neurosci. 2016 Nov 15;10:550. [FULL TEXT]

> This paper outlines a hierarchical Bayesian framework for interoception, homeostatic/allostatic

control, and meta-cognition that connects fatigue and depression to the experience of chronic dyshomeostasis. Specifically, viewing interoception as the inversion of a generative model of viscerosensory inputs allows for a formal definition of dyshomeostasis (as chronically enhanced surprise about bodily signals, or, equivalently, low evidence for the brain's model of bodily states) and allostasis (as a change in prior beliefs or predictions which define setpoints for homeostatic reflex arcs). Critically, we propose that the performance of interoceptive-allostatic circuitry is monitored by a metacognitive layer that updates beliefs about the brain's capacity to successfully regulate bodily states (allostatic self-efficacy). In this framework, fatigue and depression can be understood as sequential responses to the interoceptive experience of dyshomeostasis and the ensuing metacognitive diagnosis of low allostatic self-efficacy. While fatigue might represent an early response with adaptive value (cf. sickness behavior), the experience of chronic dyshomeostasis may trigger a generalized belief of low self-efficacy and lack of control (cf. learned helplessness), resulting in depression. This perspective implies alternative pathophysiological mechanisms that are reflected by differential abnormalities in the effective connectivity of circuits for interoception and allostasis. We discuss suitably extended models of effective connectivity that could distinguish these connectivity patterns in individual patients and may help inform differential diagnosis of fatigue and depression in the future.

Karshikoff B, et al (2016) - **Why sickness hurts: A central mechanism for pain induced by peripheral inflammation.** Brain Behav Immun. 2016 Oct;57:38-46. [ABS]

The subjects injected with LPS became more pain sensitive compared to the placebo group, and the heightened pain sensitivity was paralleled by decreased activity in the ventrolateral prefrontal cortex and the rostral anterior cingulate cortex (rACC) compared to placebo; areas involved in descending pain regulation. The LPS group also had higher activity in the anterior insular cortex, an area underpinning affective and interoceptive pain processing. Women displayed overall less pain-evoked rACC activity compared to men, which may have rendered women less resilient to immune provocation, possibly explaining sex differences in LPS-induced pain sensitivity. Our findings elucidate the pain-related brain circuits affected by experimental peripheral inflammation, strengthening the theoretical link between systemic inflammation and weakened pain regulation in chronic pain disorders. The results further suggest a possible mechanism underlying the female predominance in many chronic pain disorders.

van Niekerk G, et al (2016) - **Autophagy--A free meal in sickness-associated anorexia.** Autophagy. 2016;12(4):727-34. [FULL TEXT]

Lasselin J, et al (2016) - **Mood disturbance during experimental endotoxemia: Predictors of state anxiety as a psychological component of sickness behavior.** Brain Behav Immun. 2016 Oct;57:30-7. [ABS]

Reyes-Lagos JJ, 2016) - **Exogenous oxytocin reduces signs of sickness behavior and modifies heart rate fluctuations of endotoxemic rats.** Physiol Behav. 2016 Oct 15;165:223-30. [ABS]

Besides the well-known roles of oxytocin on birth, maternal bonding, and lactation, recent evidence shows that this hypothalamic hormone possesses cardioprotective, anti-

inflammatory and parasympathetic neuromodulation properties. In this study, we explore the heart rate fluctuations (HRF) in an endotoxemic rodent model that was accompanied by the administration of exogenous oxytocin. The assessment of HRF has been widely used as an indirect measure of the cardiac autonomic function. In this context, adult male Dark Agouti rats were equipped with a telemetric transmitter to continuously and remotely measure the electrocardiogram, temperature, and locomotion. In a between-subjects experimental design, rats received the following peripheral treatment: saline solution as a vehicle (V); lipopolysaccharide (LPS); oxytocin (Ox); lipopolysaccharide + oxytocin (LPS+Ox). Linear and non-linear parameters of HRF were estimated starting 3h before to 24h after treatments. Our results showed that exogenous oxytocin does not modify by itself the HRF of oxytocin-treated rats in comparison to vehicle-treated rats. However, in animals undergoing endotoxemia it: a) provokes a less anticorrelated pattern in HRF, b) decreased mean heart rate, c) moderated the magnitude and duration of the LPS-induced hyperthermia, and d) increased locomotion, up to 6h after the LPS injection. The less anticorrelated pattern in the HRF and decreased mean heart rate may reflect a cardiac pacemaker coupling with cholinergic influences mediated by oxytocin during LPS-induced endotoxemia. Finally, the anti-lethargic and long-term temperature moderating effects of the administration of oxytocin during endotoxemia could be a consequence of the systemic anti-inflammatory properties of oxytocin.

Campos AC, et al (2016) - **Absence of gut microbiota influences lipopolysaccharide-induced behavioral changes in mice.** Behav Brain Res. 2016 Oct 1;312:186-94. [ABS]

Changes in the microbiota composition of gastrointestinal tract are emerging as potential players in the physiopathology of neuropsychiatric disorders. In the present work we evaluated the relationship between the absence of gut microbiota and neuroinflammatory mechanisms in a murine model of LPS-induced behavioral alterations. Germ-free (GF) or conventional male mice received a single i.p. injection of lipopolysaccharide (LPS i.p.; 0.83mg/Kg) or PBS, and after 24h they were tested for depressive-like behaviors (forced swimming test, tail suspension test - TST, or sucrose preference test - SPT). After behavioral evaluation, animals were analyzed for possible changes in neuroplasticity by means of BDNF, NGF and cytokines levels in prefrontal cortex and hippocampus, and the expression of Iba-1 (microglial activation marker) in the hippocampus, and the cellular activity marker, ΔFosB, in the dorsal raphe nucleus. In conventional mice, LPS induced depressive-like behaviors. LPS-induced changes were followed by up-regulation of the expression of TNF and Iba-1 in the hippocampus. The same effects were not observed in GF mice. Behavioral effects of LPS were not observed in GF mice submitted to TST. GF mice present a lower response to the anhedonia-like effect induced by LPS when compared to conventional animals (SPT). There was up-regulation of ΔFosB in the dorsal raphe nucleus in the absence of gut microbiota, events not influenced by LPS treatment. Our results suggest that gut-microbiota interactions influence depressive-like behaviors, raphe nucleus activation and activation of pro-inflammatory mechanisms within the hippocampus.

Biesmans S, et al (2016) - **Systematic Analysis of the Cytokine and Anhedonia Response to Peripheral Lipopolysaccharide Administration in Rats.** Biomed Res Int. 2016;2016:9085273. [FULL TEXT]

Wang Y, et al (2016) - **Prior stressor exposure delays the recovery of surgery-induced cognitive impairment and prolongs neuroinflammation in aged rats.** Brain Res. 2016 Oct 1;1648(Pt A):380-6.

[FULL TEXT]

> Increasing evidence indicates that stress potentiates pro-inflammatory response to a subsequent peripheral immune challenge. The present study investigated if prior exposure to inescapable tail shock(IS) delayed the recovery of surgery-induced spatial learning and memory impairment and prolonged hippocampus interleukin(IL)-1β and IL-6expression.
>
> IS alone failed to induce cognitive deficits and increase pro-inflammatory cytokines expression. However, IS delayed the recovery of surgery-induced spatial learning and memory impairment and prolonged pro-inflammatory response to the subsequent surgery challenge.

Shattuck EC, et al (2016) - **Towards an integrative picture of human sickness behavior.** Brain Behav Immun. 2016 Oct;57:255-62. [ABS]

DiSabato DJ, et al (2016) - **Neuroinflammation: the devil is in the details.** J Neurochem. 2016 Oct;139 Suppl 2(Suppl 2):136-153. [FULL TEXT]

> In this review, we will use brain and spinal cord injury, stress, aging, and other inflammatory events to illustrate the potential harm and benefits inherent to neuroinflammation.

Gordon R, et al (2016) - **Protein kinase Cδ upregulation in microglia drives neuroinflammatory responses and dopaminergic neurodegeneration in experimental models of Parkinson's disease.** Neurobiol Dis. 2016 Sep;93:96-114. [FULL TEXT]

Berghman LR (2016) - **Immune responses to improving welfare**. Poult Sci. 2016 Sep 1;95(9):2216-8. [FULL TEXT]

Lekander M, et al (2016) - **Intrinsic functional connectivity of insular cortex and symptoms of sickness during acute experimental inflammation.** Brain Behav Immun. 2016 Aug;56:34-41. [ABS]

> In conclusion, the finding of increased functional connectivity between left anterior insula and middle cingulate cortex suggests a potential neurophysiological mechanism that can be further tested to understand the subjective feeling of malaise and discomfort during a sickness response.

Zhu X, et al (2016) - **A distinct brain pathway links viral RNA exposure to sickness behavior.** Sci Rep. 2016 Jul 20;6:29885. [FULL TEXT]

Jin S, et al (2016) - **Hypothalamic TLR2 triggers sickness behavior via a microglia-neuronal axis.** Sci Rep. 2016 Jul 12;6:29424. [FULL TEXT]

Santos LE, et al (2016) - **Microglial dysfunction connects depression and Alzheimer's disease.** Brain Behav Immun. 2016 Jul;55:151-165. [ABS]

> Alzheimer's disease (AD) and major depressive disorder (MDD) are highly prevalent neuropsychiatric conditions with intriguing epidemiological overlaps. Depressed patients are at

increased risk of developing late-onset AD, and around one in four AD patients are co-diagnosed with MDD. Microglia are the main cellular effectors of innate immunity in the brain, and their activation is central to neuroinflammation - a ubiquitous process in brain pathology, thought to be a causal factor of both AD and MDD.

Kazlauskas N, et al (2016) - **Sickness Behavior in Honey Bees.** Front Physiol. 2016 Jun 28;7:261. [FULL TEXT}

During an infection, animals suffer several changes in their normal physiology and behavior which may include lethargy, appetite loss, and reduction in grooming and general movements. This set of alterations is known as sickness behavior and although it has been extensively believed to be orchestrated primarily by the immune system, a relevant role for the central nervous system has also been established. The aim of the present work is to develop a simple animal model to allow studying how the immune and the nervous systems interact coordinately during an infection. We administered a bacterial lipopolysaccharide (LPS) into the thorax of honey bees to mimic a bacterial infection, and then we evaluated a set of stereotyped behaviors of the animals that might be indicative of sickness behavior. First, we show that this immune challenge reduces the locomotor activity of the animals in a narrow time window after LPS injection. Furthermore, bees exhibit a loss of appetite 60 and 90 min after injection, but not 15 h later. We also demonstrate that LPS injection reduces spontaneous antennal movements in harnessed animals, which suggests a reduction in the motivational state of the bees. Finally, we show that the LPS injection diminishes the interaction between animals, a crucial behavior in social insects. To our knowledge these results represent the first systematic description of sickness behavior in honey bees and provide important groundwork for the study of the interaction between the immune and the neural systems in an insect model.

Ma K, et al (2016) - **Pathogenetic and Therapeutic Applications of Tumor Necrosis Factor-α (TNF-α) in Major Depressive Disorder: A Systematic Review**. Int J Mol Sci. 2016 May 14;17(5):733. [FULL TEXT]

Major depressive disorder (MDD) is characterized by mood, vegetative, cognitive, and even psychotic symptoms and signs that can cause substantial impairments in quality of life and functioning. Up to now, the exact pathogenesis of MDD remains poorly understood. Recent research has begun to reveal that the pro-inflammatory cytokines, particularly, tumor necrosis factor-α (TNF-α), play an integral role in the pathophysiology of depressive disorders and the mechanism of antidepressant treatment. On the base of several observations: it is found that subsets of MDD patients have enhanced plasma levels TNF-α; antidepressant treatments had linked with the decline of TNF-α; central administration of TNF-α gives rise to sickness behavior which shares features with depression; and a blockade of it can ameliorate depressive symptomatology in animal models and clinical trials

Liu X, et al (2016) - **Euflammation attenuates peripheral inflammation-induced neuroinflammation and mitigates immune-to-brain signaling**. Brain Behav Immun. 2016 May;54:140-148. [FULL TEXT]

García Bueno B, et al (2016) - **Innate immune receptor Toll-like receptor 4 signalling in neuropsychiatric diseases**. Neurosci Biobehav Rev. 2016 May;64:134-47. [ABS]

The "leaky gut" hypothesis of neuropsychiatric diseases is based on the existence of an increase of the intestinal permeability which results in bacterial translocation able to activate TLR-4. Enhanced peripheral TLR-4 expression/activity has been described in subjects diagnosed with schizophrenia, bipolar disorder and in autistic children. A role for TLR-4 in drugs abuse has been also proposed.

Bueno BG, et al (2016) - **Innate immune receptor Toll-like receptor 4 signalling in neuropsychiatric diseases.** Neurosci Biobehav Rev. 2016 May;64:134-47. [ABS]

The "leaky gut" hypothesis of neuropsychiatric diseases is based on the existence of an increase of the intestinal permeability which results in bacterial translocation able to activate TLR-4. Enhanced peripheral TLR-4 expression/activity has been described in subjects diagnosed with schizophrenia, bipolar disorder and in autistic children. A role for TLR-4 in drugs abuse has been also proposed. The therapeutic potential of pharmacological/genetic modulation of TLRs signaling pathways in neuropsychiatry is promising, but a great preclinical/clinical scientific effort is still needed.

Labrenz F, et al (2016) - **Alterations in functional connectivity of resting state networks during experimental endotoxemia - An exploratory study in healthy men.** Brain Behav Immun. 2016 May;54:17-26. [ABS]

Seed based analysis revealed greater functional connectivity between the left thalamus and the cerebellum after LPS compared to placebo administration, while the functional coupling between seeds within the amygdala, insula, and cingulate cortex and various brain regions including parieto-frontal networks was significantly reduced. Within the LPS group, endotoxin-induced increases in Interleukin (IL)-6 were significantly associated with resting-state connectivity between the left thalamus and left precuneus as well as the right posterior cingulate cortex. In summary, this exploratory study provides first evidence that systemic inflammation affects the coupling and regulation of multiple networks within the human brain at rest.

Blank T, et al (2016) - **Brain Endothelial- and Epithelial-Specific Interferon Receptor Chain 1 Drives Virus-Induced Sickness Behavior and Cognitive Impairment.** Immunity. 2016 Apr 19;44(4):901-12. [FULL TEXT]

Herz J, et al (2016) - **Bugs and Brain: How Infection Makes You Feel Blue.** Immunity. 2016 Apr 19;44(4):718-20. [FULL TEXT]

Kalogiannis M, et al (2016) - **Serotonin as a putative scavenger of hypohalous acid in the brain.** Biochim Biophys Acta. 2016 Apr;1862(4):651-61. [FULL TEXT]

Patejdl R, et al (2016) - **Multiple sclerosis and fatigue: A review on the contribution of inflammation and immune-mediated neurodegeneration.** Autoimmun Rev. 2016 Mar;15(3):210-20. [ABS]

Multiple sclerosis (MS) is an immune mediated disease of the central nervous system (CNS) and the leading cause of non-traumatic disability among young and middle-aged adults in the western world. One of its most prevalent and debilitating symptoms is fatigue. …distinctive clusters of lesions and atrophy at different locations, mostly bifrontal or in subcortical structures, correlate specifically with fatigue. Regardless of the difficulties in pinpointing the immunogenesis of MS-fatigue, an important role of autoimmunity is strongly supported by an indirect route: A growing amount of data shows that the highly effective immunotherapeutics which have been introduced to MS-treatment over the last years effectively and sustainably stabilize and ameliorate fatigue in parallel to their dampening effects on the neuroinflammatory process

Buras A, et al (2016) - **Depression and inflammation in rheumatic diseases.** Postepy Hig Med Dosw (Online). 2016 Mar 4;70:162-8. [ABS]

It is known that the prevalence of depression in rheumatologic patients is higher than in the general population. Socioeconomic factors are not a sufficient explanation of mood disorder in these patients. Symptoms reported by patients with chronic inflammatory diseases resemble changes defined as "sickness behavior". Mood disorders among somatic patients could be explained by disturbances of the immune system according to the monoaminergic theory of depression. Inflammatory factors such as IL-1 (interleukin-1), IL-2 (interleukin-2), IL-6 (interleukin-6), TNF-α (tumor necrosis factor α), and IFN-γ (interferon-γ) act within the CNS (central nervous system). They get through from peripheral tissues as well as being synthesized de novo by neurons. This cytokine activity correlates positively with depression intensity as well as with genetic polymorphism of the serotonin (5-HT) transporter. The theory of glucocorticoid resistance-mediated depression (limbic-hypothalamic-pituitary-adrenal [LHPA] axis) is also connected with gained proinflammatory cytokines activity. It might assume the form of a vicious circle. Depressed mood is probably linked with depression in immune-mediated diseases. An elevated level of proinflammatory cytokines is able to activate IDO (indoleamine 2,3-dioxygenase)--an enzyme catabolizing tryptophan (5-HT precursor). Those reactions probably play the main role at the biochemical level. IDO metabolites extensively disturb neurotransmission. 3-Hydroxykynurenine (3OH-KYN), quinolinic acid (Quin) and kynurenic acid (KYNA) are neurotoxic by releasing oxidative stress mediators. Moreover, they activate MAO (monoamine oxidase), which degrades neurotransmitters responsible for stable mood. Bidirectional communication between the neuroendocrine and immune systems is significant for depression treatment, as well as CNS protection against incremental neurodegeneration among seemingly diverse diseases.

Rummel C, et al (2016) - **Obesity Impacts Fever and Sickness Behavior during Acute Systemic Inflammation**. Physiology (Bethesda). 2016 Mar;31(2):117-30. [ABS]

Obesity is reaching dramatic proportions in humans and is associated with a higher risk for cardiovascular disease, diabetes, and cognitive alterations, and a higher mortality during infection and inflammation. The focus of the present review is on the influence of obesity on the presentation of fever, sickness behavior, and inflammatory responses during acute systemic inflammation.

Araki R, et al (2016) - **Kamikihito Ameliorates Lipopolysaccharide-Induced Sickness Behavior via Attenuating Neural Activation, but Not Inflammation, in the Hypothalamic Paraventricular Nucleus and Central Nucleus of the Amygdala in Mice.** Biol Pharm Bull. 2016;39(2):289-94. [ABS]

> Kamikihito (KKT), a Kampo (traditional Japanese herbal) medicine composed of 14 herbs, has been used clinically to treat psychiatric dysfunction. These results suggest that KKT ameliorates sickness behavior via the suppression of neural activation without anti-inflammatory effects, and that KKT has the potential to treat sickness behavior.

Engler H, et al (2016) - **Men and women differ in inflammatory and neuroendocrine responses to endotoxin but not in the severity of sickness symptoms**. Brain Behav Immun. 2016 Feb;52:18-26. [ABS]

> Impaired mood and increased anxiety represent core symptoms of sickness behavior that are thought to be mediated by pro-inflammatory cytokines. Moreover, excessive inflammation seems to be implicated in the development of mood/affective disorders. Although women are known to mount stronger pro-inflammatory responses during infections and are at higher risk to develop depressive and anxiety disorders compared to men, experimental studies on sex differences in sickness symptoms are scarce.
>
> Women exhibited a more profound pro-inflammatory response with significantly higher increases in tumor necrosis factor (TNF)-α and interleukin (IL)-6. In contrast, the LPS-induced increase in anti-inflammatory IL-10 was significantly higher in men. The cytokine alterations were accompanied by changes in neuroendocrine factors known to be involved in inflammation regulation. Endotoxin injection induced a significant increase in noradrenaline, without evidence for sex differences. The LPS-induced increase in cortisol was significantly higher in woman, whereas changes in dehydroepiandrosterone were largely comparable. LPS administration also increased secretion of prolactin, but only in women. Despite these profound sex differences in inflammatory and neuroendocrine responses, men and women did not differ in endotoxin-induced alterations in mood and state anxiety or non-specific sickness symptoms. This suggests that compensatory mechanisms exist that counteract the more pronounced inflammatory response in women, preventing an exaggerated sickness response. Disturbance of these compensatory mechanisms by environmental factors such as stress may promote the development of affective disorders in women.

Konat G (2016) - **Cerebral Response to Peripheral Challenge with a Viral Mimetic.** Neurochem Res. 2016 Feb;41(1-2):144-55. [FULL TEXT]

> These inflammatory mediators modify the activity of neuronal networks leading to a constellation of behavioral traits collectively categorized as the sickness behavior. Sickness behavior is an important protective response of the host that has evolved to enhance survival and limit the spread of infections within a population. However, a growing body of clinical data indicates that the activation of inflammatory pathways in the brain may constitute a serious comorbidity factor for neuropathological conditions. Such comorbidity has been demonstrated using the PIC paradigm in experimental models of Alzheimer's disease, prion disease and seizures. Also, prenatal or perinatal PIC challenge has been shown to disrupt normal cerebral

development of the offspring resulting in phenotypes consistent with neuropsychiatric disorders, such as schizophrenia and autism.

Norouzi F, et al (2016) - **The effects of Nigella sativa on sickness behavior induced by lipopolysaccharide in male Wistar rats**. Avicenna J Phytomed. 2016 Jan-Feb;6(1):104-16. [FULL TEXT]

Straub RH, et al (2016) **- Chronic inflammatory systemic diseases: An evolutionary trade-off between acutely beneficial but chronically harmful programs**. Evol Med Public Health. 2016 Jan 27;2016(1):37-51. [FULL TEXT]

Vichaya EG, et al (2016) - **Sickness behavior induced by cisplatin chemotherapy and radiotherapy in a murine head and neck cancer model is associated with altered mitochondrial gene expression.** Behav Brain Res. 2016 Jan 15;297:241-50. [FULL TEXT]

Hanaa-Mansour A, et al (2016) - **Dexamethazone protects against Escherichia coli induced sickness behavior in rats.** Brain Res. 2016 Jan 1;1630:198-207. [ABS]

> Systemic bacterial infection results in systemic inflammatory response syndrome due to the release of lipopolysaccharide (LPS) in blood that can lead to multiple organ failure, shock, and potentially death. Other impact, LPS exposure produces robust increase in anxiety-like behavior, suppression of locomotor, exploratory activity, and reduced social behavior. The therapeutic use of glucocorticoids in septic shock remains one of the first-aid approaches for their anti-inflammatory properties. … The results revealed that DEX significantly protected animals against most E. coli-induced behavioral deficits, reduced signs of cognitive impairment. DEX also reduced the LPS-evoked rise in C-reactive protein (CRP), Interferon gamma (IFγ), as well as, expression of Caspase-3. In conclusion, DEX provides neuroprotection against E. coli-associated neurobehavioral and immunological changes via its anti-inflammatory and immunomodulatory effects.

2015

Orlandi L, et al (2015) - **Sickness behavior is accentuated in rats with metabolic disorders induced by a fructose diet**. J Neuroimmunol. 2015 Dec 15;289:75-83. [ABS]

Kongsui R, et al (2015) - **A combined cumulative threshold spectra and digital reconstruction analysis reveal structural alterations of microglia within the prefrontal cortex following low-dose LPS administration.** Neuroscience. 2015 Dec 3;310:629-40. [ABS]

Harden LM, et al (2015) - **Fever and sickness behavior: Friend or foe?** Brain Behav Immun. 2015 Nov;50:322-333. [ABS]

Fischer CW, et al (2015) - **Behavioral and systemic consequences of long-term inflammatory challenge.** J Neuroimmunol. 2015 Nov 15;288:40-6. [ABS]

Shakhar K, et al (2015) - **Why Do We Feel Sick When Infected--Can Altruism Play a Role?** PLoS Biol. 2015 Oct 16;13(10):e1002276. [FULL TEXT]

> Sickness syndrome is the generalized response of the host to infections. Its classical physiological signs include fever and anemia, but it also includes psychological symptoms—collectively termed "sickness behavior" (SB) [1–3]. These symptoms, familiar to anyone who has been sick, include fatigue, depression, irritability, discomfort, pain, nausea, and loss of interest in food, drink, social interactions, and sex. In animals, such changes can be quantified based on behavior and reflect reprioritization of motivations during disease [2].
>
> A common misconception is that pathogens directly produce these behavioral symptoms, but in fact SB is orchestrated by the host's immune and neuroendocrine systems; mammals have evolved several parallel pathways to alert the brain of inflammation and trigger symptomatic behaviors

Stieglitz J, et al (2015) - **Depression as sickness behavior? A test of the host defense hypothesis in a high pathogen population.** Brain Behav Immun. 2015 Oct;49:130-9. [FULL TEXT]

> Emotional, cognitive and somatic symptoms of depression are each associated with greater immune activation, both at baseline and in response to ex vivo stimulation.

Ying CJ, et al (2015) - **Anti-inflammatory Effect of Astaxanthin on the Sickness Behavior Induced by Diabetes Mellitus**. Cell Mol Neurobiol. 2015 Oct;35(7):1027-37. [ABS]

Doll DN, et al (2015) - **Lipopolysaccharide exacerbates infarct size and results in worsened post-stroke behavioral outcomes.** Behav Brain Funct. 2015 Oct 13;11(1):32. [FULL TEXT]

Sandiego CM, et al (2015) - **Imaging robust microglial activation after lipopolysaccharide administration in humans with PET.** Proc Natl Acad Sci U S A. 2015 Oct 6;112(40):12468-73. [FULL TEXT]

> Neuroinflammation is a brain immune response that is associated with neurodegenerative diseases and is primarily driven by activation of microglia, the brain's resident macrophages. Dysfunctional microglial activation may contribute to the behavioral changes observed in neurodegenerative diseases. Upon activation, microglia express translocator protein, which can be imaged with the radiotracer [11C]PBR28 and positron emission tomography (PET) in the living human brain.

Clouard C, et al (2015) - **Maternal Fish Oil Supplementation Affects the Social Behavior, Brain Fatty Acid Profile, and Sickness Response of Piglets.** J Nutr. 2015 Sep;145(9):2176-84. [FULL TEXT]

Tanaka S, et al (2015) - **Hypocretin/orexin prevents recovery from sickness.** Biomed Rep. 2015 Sep;3(5):648-650. [FULL TEXT]

> Sickness behavior is defined as states of lethargy, depression, anxiety, loss of appetite, hypersomnia, hyperalgesia, reduction of grooming and failure to concentrate that can be

induced by inflammatory diseases, such as infections and cancer. Recent findings revealed that the lipopolysaccharide (LPS) injection causes lethargy as a consequence of the inhibition of hypocretin signaling. The hypocretin system maintains the vigilance state in various physiological processes.

Wu MK, et al (2015) - **Association between toll-like receptor 4 expression and symptoms of major depressive disorder.** Neuropsychiatr Dis Treat. 2015 Jul 30;11:1853-7. [FULL TEXT]

Our results suggest a significant association between anxiety, body weight loss, and TLR4 mRNA levels in patients with MDD. Larger longitudinal studies combining both subjective and objective measures of depression are needed to clarify the link between TLR4 and symptoms of depression.

D'Mello C, et al (2015) - **Probiotics Improve Inflammation-Associated Sickness Behavior by Altering Communication between the Peripheral Immune System and the Brain.** J Neurosci. 2015 Jul 29;35(30):10821-30. [FULL TEXT]

Patients with systemic inflammatory diseases (e.g., rheumatoid arthritis, inflammatory bowel disease, chronic liver disease) commonly develop debilitating symptoms (i.e., sickness behaviors) that arise from changes in brain function. The microbiota-gut-brain axis alters brain function and probiotic ingestion can influence behavior. We have previously described a novel periphery-to-brain communication pathway in the setting of peripheral organ inflammation whereby monocytes are recruited to the brain in response to systemic TNF-α signaling, leading to microglial activation and subsequently driving sickness behavior development.

We now show that probiotic (VSL#3) treatment attenuates sickness behavior development in mice with liver inflammation without affecting disease severity, gut microbiota composition, or gut permeability. Attenuation of sickness behavior development was associated with reductions in microglial activation and cerebral monocyte infiltration. These events were paralleled by changes in markers of systemic immune activation, including decreased circulating TNF-α levels. Our observations highlight a novel pathway through which probiotics mediate cerebral changes and alter behavior. These findings allow for the potential development of novel therapeutic interventions targeted at the gut microbiome to treat inflammation-associated sickness behaviors in patients with systemic inflammatory diseases.

Stokes L, et al (2015) - **Understanding the role of P2X7 in affective disorders-are glial cells the major players?** Front Cell Neurosci. 2015 Jul 8;9:258. [FULL TEXT]

Avitsur R, et al (2015) - **Prenatal fluoxetine exposure affects cytokine and behavioral response to an immune challenge.** J Neuroimmunol. 2015 Jul 15;284:49-56. [ABS]

Fluoxetine (FLX), a selective serotonin reuptake inhibitor (SSRI) is a commonly prescribed antidepressant drug in pregnant women. FLX readily crosses the placenta, consequently altering serotonergic neurotransmission in the fetus and causing physiological and behavioral disturbances in the newborn.

Karrer M, et al (2015) - **Cytokine-induced sleep: Neurons respond to TNF with production of chemokines and increased expression of Homer1a in vitro.** Brain Behav Immun. 2015 Jul;47:186-92. [ABS]

> Interactions of neurons with microglia may play a dominant role in sleep regulation. TNF may exert its somnogeneic effects by promoting attraction of microglia and their processes to the vicinity of dendrites and synapses. We found TNF to stimulate neurons (i) to produce CCL2, CCL7 and CXCL10, chemokines acting on mononuclear phagocytes and (ii) to stimulate the expression of the macrophage colony stimulating factor (M-CSF/Csf1), which leads to elongation of microglia processes. TNF may also act on neurons by affecting the expression of genes essential in sleep-wake behavior. The neuronal expression of Homer1a mRNA, increases during spontaneous and enforced periods of wakefulness. Mice with a deletion of Homer1a show a reduced wakefulness with increased non-rapid eye movement (NREM) sleep during the dark period. Recently the TNF-dependent increase of NREM sleep in the dark period of mice with CD40-induced immune activation was found to be associated with decreased expression of Homer1a. In the present study we investigated the effects of TNF and IL-1β on gene expression in cultures of the neuronal cell line HT22 and cortical neurons. TNF slightly increased the expression of Homer1a and IL-1β profoundly enhanced the expression of Early growth response 2 (Egr2). The data presented here indicate that the decreased expression of Homer1a, which was found in the dark period of mice with CD40-induced increase of NREM sleep is not due to inhibitory effects of TNF and IL-1β on the expression of Homer1a in neurons.

Low CA, et al (2015) - **Neurocognitive Impairment as One Facet of Cancer-Related Sickness Behavior Symptoms.** J Natl Cancer Inst. 2015 Jun 22;107(8). [FULL TEXT]

O'Callaghan JP, et al (2015) - **Corticosterone primes the neuroinflammatory response to DFP in mice: potential animal model of Gulf War Illness**. J Neurochem. 2015 Jun;133(5):708-21. [FULL TEXT]

Shattuck EC, et al (2015) - **Human sickness behavior: Ultimate and proximate explanations**. Am J Phys Anthropol. 2015 May;157(1):1-18. [ABS]

> Sickness behavior, a coordinated set of behavioral changes in response to infection, lies at the intersection of immunology, endocrinology, and evolutionary biology. Sickness behavior is elicited by pro-inflammatory cytokines, is thought to be an adaptive means of redirecting energy away from disadvantageous behaviors and toward mounting an effective immune response, and may be modulated by hormones, including testosterone and oxytocin. Research on sickness behavior in humans has lagged behind non-human animal research due to methodological complexities. Here we review what is known about sickness behavior in humans, the effects of various hormones on sickness behavior, the possible role of cytokine gene variation in influencing sickness behavior responses, and the ways in which culture and gender norms could similarly influence these behavioral changes. We also propose methodologies for advancing further studies of sickness behavior in humans.

Nakagawasai O, et al (2015) - **Liver hydrolysate attenuates the sickness behavior induced by concanavalin A in mice.** J Pharmacol Sci. 2015 Apr;127(4):489-92. [ABS]

Ming Z, et al (2015) - **Acute systemic LPS-mediated inflammation induces lasting changes in mouse cortical neuromodulation and behavior.** Neurosci Lett. 2015 Mar 17;590:96-100. [ABS]

> Systemic lipopolysaccharide (LPS) is widely used to induce a neuroinflammatory response that is associated with short-term 'sickness'-behavior that can include fever, loss of activity, loss of appetite, impaired cognition, anxiety and depression. If large enough or left unchecked, this neuroinflammatory response can become self-perpetuating and lead to long-term neurodegenerative processes. In this study, we assess the longer-term effects of a single systemic LPS injection on electrophysiological neuromodulator effects and basic behavioral analysis in mice. Five months after LPS injection, we find a mild reduction in cortical inhibition and altered temporal dynamics of acetylcholine but not norepinephrine or serotonin neuromodulator effects. Consistent with electrophysiological findings, LPS treated mice showed a deficit in memory performance in the novel object recognition test with no effect on measures of anxiety or despair as measured in the open field test and tail suspension test, respectively. Furthermore, LPS-treated mice showed an increase in acetylcholinesterase activity. As increased acetylcholinesterase activity is associated with reduced acetylcholine signaling and impaired cognitive ability, these studies demonstrate the potential for a single inflammatory event to initiate processes that may lead to long-term neurodegeneration.

Kirsten TB, et al (2015) - **Zinc prevents sickness behavior induced by lipopolysaccharides after a stress challenge in rats.** PLoS One. 2015 Mar 16;10(3):e0120263. [FULL TEXT]

Silva VC, et al (2015) - **Sickness behavior is delayed in hypothyroid mice**. Brain Behav Immun. 2015 Mar;45:109-17. [ABS]

> Sickness behavior is an expression of a motivational state triggered by activation of the peripheral innate immune system, whereby an organism reprioritizes its functions to fight infection. The relationship between thyroid hormone and immune cells is complex, and additional insights are needed about the involvement of the cross-talk between thyroid hormone, the central nervous system and immune function, as demonstrated by the consequences to sickness behavior. The aim of this work was to evaluate sickness behavior in hypothyroid mice. Control mice and mice treated with propylthiouracil (PTU) for 30days (0.05%; added to drinking water) received a single dose of LPS (200μg/kg; i.p.) or saline, and the behavioral response was assessed for 24h. We provide evidence that thyroid status acts a modulator for the development of depressive-like and exploratory behaviors in mice that are subjected to an immunological challenge because the PTU pretreatment delayed the LPS-induced behavioral changes observed in an open field test and in a forced swimming test. This response was observed concomitantly with a lower thermal index until 4h after the LPS administration. This result demonstrates that thyroid status modifies behavioral responses to immune challenge and suggests that thyroid hormones are essential for the manifestation of sickness behavior during endotoxemia.

Sankowski R, et al (2015) - **Systemic inflammation and the brain: novel roles of genetic, molecular, and environmental cues as drivers of neurodegeneration.** Front Cell Neurosci. 2015 Feb 2;9:28. [FULL TEXT]

Shattuck EC, et al (2015) - **Mood, behavior, testosterone, cortisol, and interleukin-6 in adults during immune activation: a pilot study to assess sickness behaviors in humans.** Am J Hum Biol. 2015 Jan-Feb;27(1):133-5. [ABS]

> OBJECTIVES: Sickness behavior, a suite of behavioral changes subsequent to infection that includes depression, decreased social behaviors, and sleep disturbances, has been well described in model organisms. The phenomenon is relatively unexplored in humans due to methodological difficulties, and hormonal correlates of sickness behavior have not been studied. We therefore attempted to use a vaccine to elicit sickness behaviors outside of a clinical setting and uncover any correlations among testosterone, cortisol, and sickness behavior. METHODS: Eleven participants (five male, six female, mean age 22.8 years) naïve to the rabies vaccine were recruited from the School of Veterinary Medicine at Purdue University. Participants provided daily saliva and urine samples and completed questionnaires to assess mood and social behaviors for a period of 6 weeks. Saliva samples were assayed for cortisol and testosterone. Urine samples were assayed for interleukin-6 and creatinine. RESULTS: Analysis revealed an expected decrease in testosterone and an increase in cortisol. While mood did not differ, other behaviors, such as physical activity and hours slept, showed expected changes following vaccination. However, none of these results achieved statistical significance. CONCLUSION: Our results, while generally confirming previous research on sickness behavior and hormone changes during infection, are suggestive, but not statistically significant and so neither confirm nor contradict our hypotheses. We attribute this lack of significance to both the small sample size, as well as possible confounding factors, including the psychosocial stress of entering an intensive study program.

Nascimento AF, et al (2015) - **Lipopolysaccharide-induced sickness behavior in lactating rats decreases ultrasonic vocalizations and exacerbates immune system activity in male offspring.** Neuroimmunomodulation. 2015;22(4):213-21. [ABS]

> OBJECTIVE: The present study analyzed the effects of lipopolysaccharide (LPS) on maternal behavior during lactation and possible correlations with changes in emotional and immune responses in offspring. METHODS: Lactating rats received 100 μg/kg LPS, and the control group received saline solution on lactation day (LD) 3. Maternal general activity and maternal behavior were observed on LD5 (i.e. the day that the peak of fever occurred). In male pups, hematological parameters and ultrasonic vocalizations (USVs) were assessed on LD5. At weaning, an additional dose of LPS (50 μg/kg, i.p.) was administered in male pups, and open-field behavior, oxidative burst and phagocytosis were evaluated. RESULTS: A reduction in the time in which dams retrieved the pups was observed, whereas no effects on maternal aggressive behavior were found. On LD5, a reduction of the frequency of USVs was observed in pups, but no signs of inflammation were found. At weaning, an increase in immune system activity was observed, but no differences in open-field behavior were found. CONCLUSION: These results indicate that inflammation in lactating mothers disrupted mother/pup interactions and may have produced short- and long-term effects on pup behavior as well as biological pathways that modulate inflammatory responses to bacterial endotoxin challenge in pups.

Liesz A, et al (2015) - **DAMP signaling is a key pathway inducing immune modulation after brain injury.** J Neurosci. 2015 Jan 14;35(2):583-98. [FULL TEXT]

Johnson RW (2015) - **Feeding the beast: can microglia in the senescent brain be regulated by diet?** Brain Behav Immun. 2015 Jan;43:1-8. [FULL TEXT]

> Microglial cells, resident macrophages in the central nervous system (CNS), are relatively quiescent but can respond to signals from the peripheral immune system and induce neuroinflammation. In aging, microglia tend to transition to the M1 pro-inflammatory state and become hypersensitive to messages emerging from immune-to-brain signaling pathways. Thus, whereas in younger individuals where microglia respond to signals from the peripheral immune system and induce a well-controlled neuroinflammatory response that is adaptive (e.g., when well controlled, fever and sickness behavior facilitate recovery from infection), in older individuals with an infection, microglia overreact and produce excessive levels of inflammatory cytokines causing behavioral pathology including cognitive dysfunction. Importantly, recent studies indicate a number of naturally occurring bioactive compounds present in certain foods have anti-inflammatory properties and are capable of mitigating brain microglial cells. These include, e.g., flavonoid and non-flavonoid compounds in fruits and vegetables, and n-3 polyunsaturated fatty acids (PUFA) in oily fish. Thus, dietary bioactives have potential to restore the population of microglial cells in the senescent brain to a more quiescent state. The pragmatic concept to constrain microglia through dietary intervention is significant because neuroinflammation and cognitive deficits are co-morbid factors in many chronic inflammatory diseases. Controlling microglial cell reactivity has important consequences for preserving adult neurogenesis, neuronal structure and function, and cognition.

Hennessy MB, et al (2015) - **Selective social buffering of behavioral and endocrine responses and Fos induction in the prelimbic cortex of infants exposed to a novel environment.** Dev Psychobiol. 2015 Jan;57(1):50-62. [ABS]

> These results confirm the ability of the mother to reduce active behavioral and HPA responses and suggest a specific maternal buffering effect on the later developing passive behavioral responses. The findings also demonstrate an unexpected ability of adult males to reduce HPA responses and raise the possibility that different social partners buffer HPA activity through different underlying processes.

Tortorelli LS, et al (2015) - **Cocaine counteracts LPS-induced hypolocomotion and triggers locomotor sensitization expression.** Behav Brain Res. 2015;287:226-9. [ABS]

> Neuroimmune signalling underlies addiction and comorbid depression. Clinical observations indicate that infections and chronic lesions are more frequent in drug users and elevated inflammatory states are evident in cocaine dependents. Therefore, lipopolysaccharide (LPS) and inflammatory cytokines represent an important tool for the investigation of sickness, depressive illness and addiction behaviour. A major component of addiction is the progressive and persistent increase in locomotor activity after repeated drug administration and even prolonged periods of abstinence. The aim of this study was to investigate the response of

locomotor sensitization when a non-sensitizing dose of cocaine is paired with a systemic inflammatory stimulus. LPS and cocaine were administered intraperitonealy in young-adult male C57bl/6 mice during a 5-day acquisition phase. After a 48-h withdrawal period all groups were challenged with cocaine to evaluate locomotor expression. During the acquisition phase, the LPS-treated groups displayed characteristic hypolocomotion related to sickness behaviour. The low dose of cocaine did not increase the distance travelled, characterizing a non-sensitization dose. Groups that received both LPS and cocaine did not display hypolocomotion, indicating that cocaine might counteract hypolocomotion sickness behaviour. Moreover, during challenge, only these animals expressed locomotor sensitization. Our results indicate that LPS could facilitate the expression of locomotor sensitization in mice and that the immune system may modulate cocaine-induced sensitization.

Azizi-Malekabadi H, et al (2015) - **Deletion of ovarian hormones induces a sickness behavior in rats comparable to the effect of lipopolysaccharide.** Neurol Res Int. 2015;2015:627642. [FULL TEXT]

Neuroimmune factors have been proposed as the contributors to the pathogenesis of sickness behaviors. The effects of female gonadal hormones on both neuroinflammation and depression have also been well considered. In the present study, the capability of deletion of ovarian hormones to induce sickness-like behaviors in rats was compared with the effect lipopolysaccharide (LPS). The groups were including Sham, OVX, Sham-LPS, and OVX-LPS. The Sham-LPS and OVX-LPS groups were treated with LPS (250 μg/kg) two hours before conducting the behavioral tests. In the forced swimming (FST), the immobility times in both OVX and Sham-LPS groups were higher than that of Sham ($P < 0.001$). In open-field (OP) test, the central crossing number by OVX and Sham-LPS groups were lower than Sham ($P < 0.001$) while there were no significant differences between OVX-LPS and OVX groups. In elevated plus maze (EPM), the percent of entries to the open arm by both OVX and Sham-LPS groups was lower than that of Sham group ($P < 0.001$). The results of present study showed that deletion of ovarian hormones induced sickness behaviors in rats which were comparable to the effects of LPS. Moreover, further investigations are required in order to better understand the mechanism(s) involved.

2014

Hanken K, et al (2014) - **The representation of inflammatory signals in the brain - a model for subjective fatigue in multiple sclerosis.** Front Neurol. 2014 Dec 11;5:264. [FULL TEXT

Straub RH (2014) - **Insulin resistance, selfish brain, and selfish immune system: an evolutionarily positively selected program used in chronic inflammatory diseases**. Arthritis Res Ther. 2014 Nov 13;16 Suppl 2(Suppl 2):S4. [FULL TEXT]

Insulin resistance (IR) is a general phenomenon of many physiological states, disease states, and diseases. IR has been described in diabetes mellitus, obesity, infection, sepsis, trauma, painful states such as postoperative pain and migraine, schizophrenia, major depression, chronic mental stress, and others. In arthritis, abnormalities of glucose homeostasis were

described in 1920; and in 1950 combined glucose and insulin tests unmistakably demonstrated IR. The phenomenon is now described in rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, polymyalgia rheumatica, and others. In chronic inflammatory diseases, cytokine-neutralizing strategies normalize insulin sensitivity. This paper delineates that IR is either based on inflammatory factors (activation of the immune/ repair system) or on the brain (mental activation via stress axes). Due to the selfishness of the immune system and the selfishness of the brain, both can induce IR independent of each other. Consequently, the immune system can block the brain (for example, by sickness behavior) and the brain can block the immune system (for example, stress-induced immune system alterations). Based on considerations of evolutionary medicine, it is discussed that obesity per se is not a disease. Obesity-related IR depends on provoking factors from either the immune system or the brain. Chronic inflammation and/or stress axis activation are thus needed for obesity-related IR. Due to redundant pathways in stimulating IR, a simple one factor-neutralizing strategy might help in chronic inflammatory diseases (inflammation is the key), but not in obesity-related IR. The new considerations towards IR are interrelated to the published theories of IR (thrifty genotype, thrifty phenotype, and others).

Tarr AJ, et al (2014) - **Kinetic characteristics of euflammation: the induction of controlled inflammation without overt sickness behavior.** Brain Behav Immun. 2014 Nov;42:96-108. [FULL TEXT]

Townsend BE, et al (2014) - **Dietary broccoli mildly improves neuroinflammation in aged mice but does not reduce lipopolysaccharide-induced sickness behavior.** Nutr Res. 2014 Nov;34(11):990-9. [FULL TEXT]

Aging is associated with oxidative stress and heightened inflammatory response to infection. Dietary interventions to reduce these changes are therefore desirable. Broccoli contains glucoraphanin, which is converted to sulforaphane (SFN) by plant myrosinase during cooking preparation or digestion. Sulforaphane increases antioxidant enzymes including NAD(P)H quinone oxidoreductase and heme oxygenase I and inhibits inflammatory cytokines. We hypothesized that dietary broccoli would support an antioxidant response in brain and periphery of aged mice and inhibit lipopolysaccharide (LPS)-induced inflammation and sickness. Young adult and aged mice were fed control or 10% broccoli diet for 28 days before an intraperitoneal LPS injection. Social interactions were assessed 2, 4, 8, and 24 hours after LPS, and mRNA was quantified in liver and brain at 24 hours. Dietary broccoli did not ameliorate LPS-induced decrease in social interactions in young or aged mice. Interleukin-1β (IL-1β) expression was unaffected by broccoli consumption but was induced by LPS in brain and liver of adult and aged mice. In addition, IL-1β was elevated in brain of aged mice without LPS. Broccoli consumption decreased age-elevated cytochrome b-245 β, an oxidative stress marker, and reduced glial activation markers in aged mice. Collectively, these data suggest that 10% broccoli diet provides a modest reduction in age-related oxidative stress and glial reactivity, but is insufficient to inhibit LPS-induced inflammation. Thus, it is likely that SFN would need to be provided in supplement form to control the inflammatory response to LPS.

Araki R, et al (2014) - **Genipin attenuates lipopolysaccharide-induced persistent changes of emotional behaviors and neural activation in the hypothalamic paraventricular nucleus and the central amygdala nucleus.** Eur J Pharmacol. 2014 Oct 15;741:1-7. [ABS]

Sickness behavior is a series of behavioral and psychological changes that develop in inflammatory disease, including infections and cancers. Administration of the bacterial endotoxin lipopolysaccharide (LPS) induces sickness behavior in rodents. Genipin, an aglycon derived from an iridoid glycoside geniposide extracted from the fruit of Gardenia jasminoides, has anti-inflammatory and antidepressant activities. However, the effects of genipin on inflammation-induced changes in emotional behaviors are unknown. In this study, we examined the effects of genipin on LPS-induced inflammation in BV-2 cells and sickness behavior in mice. Pretreatment with genipin inhibited LPS-induced increases in NO production and reduced the mRNA levels of inflammation-related genes (iNOS, COX-2, IL-1β and IL-6) in BV-2 cells. Oral administration of genipin ameliorated LPS-induced depressive-like behavior in the forced swim test and social behavior deficits 24h after LPS administration in mice. LPS-induced expression of mRNAs for inflammation-related genes and the number of c-fos immunopositive cells decreased in the paraventricular nucleus (PVN) of the hypothalamus and the central nucleus of the amygdala (CeA), suggesting that genipin attenuates LPS-induced changes of emotional behaviors through inhibition of neural activation and inflammatory responses in the PVN and CeA. These novel pharmacological effects of genipin may be useful for treatment of patients with sickness behavior.

Jirkof P (2014) - **Burrowing and nest building behavior as indicators of well-being in mice.** J Neurosci Methods. 2014 Aug 30;234:139-46. [ABS]

The assessment of pain, distress and suffering, as well as evaluation of the efficacy of stress-reduction strategies, is crucial in animal experimentation but can be challenging in laboratory mice. Nest building and burrowing performance, observed in the home cage, have proved to be valuable and easy-to-use tools to assess brain damage or malfunction as well as neurodegenerative diseases. Both behaviors are used as parameters in models of psychiatric disorders or to monitor sickness behavior following infection. Their use has been proposed in more realistic and clinically relevant preclinical models of disease, and reduction of these behaviors seems to be especially useful as an early sign of dysfunction and to monitor disease progression. Finally, both behaviors are reduced by pain and stress. Therefore, in combination with specific disease markers, changes in nest building and burrowing performance may help provide a global picture of a mouse's state, and thus aid monitoring to ensure well-being in animal experimentation.

Blum E, et al (2014) - **Systemic inflammation alters satellite glial cell function and structure. A possible contribution to pain.** Neuroscience. 2014 Aug 22;274:209-17. [ABS]

Local peripheral injury activates satellite glial cells (SGCs) in sensory ganglia, which may contribute to chronic pain. We hypothesized that systemic inflammation affects sensory ganglia like local injury. We induced systemic inflammation in mice by injecting lipopolysaccharide (LPS) intraperitoneally, and characterized SGCs and neurons in dorsal root ganglia (DRG), using dye injection, calcium imaging, electron microscopy (EM), immunohistochemistry, and electrical recordings. Several days post-LPS, SGCs were activated, and dye coupling among SGCs increased 3-4.5-fold. EM showed abnormal growth of SGC processes and the formation of new gap junctions. Sensitivity of SGCs to ATP increased

twofold, and neuronal excitability was augmented. Blocking gap junctions reduced pain behavior in LPS-treated mice. Thus, changes in DRG due to systemic inflammation are similar to those due to local injury, which may explain the pain in sickness behavior and in other systemic diseases.

Rosenblat JD, et al (2014) - **Inflamed moods: a review of the interactions between inflammation and mood disorders.** Prog Neuropsychopharmacol Biol Psychiatry. 2014 Aug 4;53:23-34. [ABS]

Mood disorders have been recognized by the World Health Organization (WHO) as the leading cause of disability worldwide. Notwithstanding the established efficacy of conventional mood agents, many treated individuals continue to remain treatment refractory and/or exhibit clinically significant residual symptoms, cognitive dysfunction, and psychosocial impairment. Therefore, a priority research and clinical agenda is to identify pathophysiological mechanisms subserving mood disorders to improve therapeutic efficacy. During the past decade, inflammation has been revisited as an important etiologic factor of mood disorders. Therefore, the purpose of this synthetic review is threefold: 1) to review the evidence for an association between inflammation and mood disorders, 2) to discuss potential pathophysiologic mechanisms that may explain this association and 3) to present novel therapeutic options currently being investigated that target the inflammatory-mood pathway. Accumulating evidence implicates inflammation as a critical mediator in the pathophysiology of mood disorders. Indeed, elevated levels of pro-inflammatory cytokines have been repeatedly demonstrated in both major depressive disorder (MDD) and bipolar disorder (BD) patients. Further, the induction of a pro-inflammatory state in healthy or medically ill subjects induces 'sickness behavior' resembling depressive symptomatology. Potential mechanisms involved include, but are not limited to, direct effects of pro-inflammatory cytokines on monoamine levels, dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, pathologic microglial cell activation, impaired neuroplasticity and structural and functional brain changes. Anti-inflammatory agents, such as acetyl-salicylic acid (ASA), celecoxib, anti-TNF-α agents, minocycline, curcumin and omega-3 fatty acids, are being investigated for use in mood disorders. Current evidence shows improved outcomes in mood disorder patients when anti-inflammatory agents are used as an adjunct to conventional therapy; however, further research is needed to establish the therapeutic benefit and appropriate dosage.

Norden DM, et al (2014) - **TGFβ produced by IL-10 redirected astrocytes attenuates microglial activation.** Glia. 2014 Jun;62(6):881-95. [FULL TEXT]

While there clearly is an intimate relationship between astrocytes and microglia, few studies have examined these potentially dynamic interactions. In this study, cytokine-mediated communication between microglia and astrocytes under inflammatory conditions was investigated. We have previously shown that activated microglia produce Interleukin (IL)-10, a regulatory cytokine that plays an important role in resolving neuroinflammation. Nonetheless, the mechanism by which IL-10 attenuates pro-inflammatory cytokine expression in the brain is unclear. Here, we show that IL-10 redirected astrocytes regulate the activation of microglia in a transforming growth factor (TGF)-β dependent manner. In support of this concept, astrocytes in the brain maintained higher IL-10 receptor (IL-10R1) expression and primary astrocytes in culture were markedly more sensitive to the anti-inflammatory effects of IL-10 compared with

microglia. Moreover, studies using primary cultures and an astrocyte-microglia coculture system revealed that astrocytes mediated the anti-inflammatory effects of IL-10 on microglia through the production of TGFβ. For instance, only when astrocytes were present did IL-10 stimulation reduce the expression of IL-1β and increase expression of anti-inflammatory mediators fractalkine receptor (CX3 CR1) and interleukin 4 receptor-α (IL-4Rα) in microglia. Importantly, these IL-10-astrocyte dependent effects on microglia were blocked by a TGFβ inhibitor. Furthermore, inhibition of TGFβ signaling in the brain resulted in prolonged sickness behavior and amplified pro-inflammatory cytokine expression in mice challenged with lipopolysaccharide. Taken together, IL-10 stimulated the production of TGFβ by astrocytes, which in turn, attenuated microglial activation. Overall, these findings provide novel insight into the mechanisms by which astrocytes modulate microglia under inflammatory conditions.

Alt JA, et al (2014) - **Antisomnogenic cytokines, quality of life, and chronic rhinosinusitis: a pilot study.** Laryngoscope. 2014 Apr;124(4):E107-14. [FULL TEXT]

Sofroniew MV (2014) - Multiple roles for astrocytes as effectors of cytokines and inflammatory mediators. Neuroscientist. 2014 Apr;20(2):160-72. [ABS]

Astrocytes are increasingly recognized as exerting complex functions essential for normal neural activity in the healthy central nervous system (CNS). Because astrocytes also respond to all forms of CNS injury or disease, there is growing interest in how reactive astrogliosis might alter astrocyte functions and thereby affect neural functions. Reactive astrogliosis is heterogeneous and regulated in a context specific manner by different molecular signals. Prominent among astrocyte signaling mechanisms is the ability to respond to, as well as to produce, many different cytokines and inflammatory mediators. These signaling mechanisms enable astrocytes to interact with diverse cell types in ways that may contribute to crosstalk between immune/inflammatory and neural systems. Consistent with this notion is the increasing evidence that cytokines and inflammatory mediators modulate astrocyte signaling not only to influence immune and inflammatory activities in the CNS, but also to influence synaptic and neural functions in ways that may affect complex behaviors such as sickness behavior, pain, appetite, sleep, and mood.

Clark IA, et al (2014) - **Inflammation-sleep interface in brain disease: TNF, insulin, orexin.** J Neuroinflammation. 2014 Mar 21;11:51. [FULL TEXT]

Here we make the case that the cycles of unconsciousness that constitute normal sleep, as well as its aberrations, which range from sickness behavior through daytime sleepiness to the coma of inflammatory disease states, have common origins that involve increased inflammatory cytokines and consequent insulin resistance and loss of appetite due to reduction in orexigenic activity. Orexin reduction has broad implications, which are as yet little appreciated in the chronic inflammatory conditions listed, whether they be infectious or sterile in origin. Not only is reduction in orexin levels characterized by loss of appetite, it is associated with inappropriate and excessive sleep and, when dramatic and chronic, leads to coma. Moreover, such reduction is associated with impaired cognition and a reduction in motor control.

Hennessy MB, et al (2014) - **Sociality and sickness: have cytokines evolved to serve social functions**

beyond times of pathogen exposure? Brain Behav Immun. 2014 Mar;37:15-20. [FULL TEXT]

> During pathogen exposure or some forms of stress, proinflammatory processes induce an array of motivated and behavioral adjustments termed "sickness behaviors". Although withdrawal from social interactions is a commonly observed sickness behavior, the relation between social behavior and sickness is much more complex. Sickness can suppress or stimulate social behavior. Sickness can serve as a social cue. Stressors that are social in nature can induce sickness behaviors, and sickness behavior can be readily suppressed by meaningful social stimuli. The nature, context, and timing of these effects together suggest that cytokine-induced behavior may play a role in mediating social interactions in various non-pathological conditions.

Toyama RP, et al (2015) - **Dose-dependent sickness behavior, abortion and inflammation induced by systemic LPS injection in pregnant mice.** J Matern Fetal Neonatal Med. 2015 Mar;28(4):426-30. [ABS]

> OBJECTIVE: Clinical and experimental evidences indicate that intrauterine inflammation during pregnancy is associated to brain damage. The objective of this study is to determine the effects of lipopolysaccharide in temperature, cytokine production and sickness behavior of pregnant dams. METHODS: A single i.p. injection of lipopolysaccharide (LPS) (50, 150 or 300 μg/kg) was administered on E18. Controls received isotonic saline. Body temperature was controlled before and 3 h after injections. Animals' behavior was assessed by the OF test 3 h following treatment. Animals were sacrificed for leukocyte, IL-1β and TNF-α determination. Placental tissue and abortion were also examined. RESULTS: LPS administration elicited hypothermia. Abortion was observed in LPS 150 and 300 μg/kg. Leukocyte levels were significantly lower with LPS 300 μg/kg than in controls. LPS induced dose-dependent impairment in animals' locomotion. IL-1β serum and amniotic fluid were higher than the saline, and TNF-α serum and amniotic fluid increased when compared to controls. Placental histopathologic abnormality was not found. CONCLUSION: LPS induces dose-dependent sickness behavior and hypothermia in pregnant mice. Our findings suggest that the presence of inflammation may be a causative factor for premature labor and that Escherichia coli antigens modify the concentration of pro-inflammatory agents in circulatory system and intra-uterine environment.

Gaigé S, et al (2014) - **Modification of energy balance induced by the food contaminant T-2 toxin: a multimodal gut-to-brain connection.** Brain Behav Immun. 2014 Mar;37:54-72. [ABS]

> T-2 toxin is one of the most toxic Fusarium-derived trichothecenes found on cereals and constitutes a widespread contaminant of agricultural commodities as well as commercial foods. Low doses toxicity is characterized by reduced weight gain. To date, the mechanisms by which this mycotoxin profoundly modifies feeding behavior remain poorly understood and more broadly the effects of T-2 toxin on the central nervous system (CNS) have received limited attention. Through an extensive characterization of sickness-like behavior induced by T-2 toxin, we showed that its per os (p.o.) administration affects not only feeding behavior but also energy expenditure, glycaemia, body temperature and locomotor activity. Using c-Fos expression mapping, we identified the neuronal structures activated in response to T-2 toxin and observed that the pattern of neuronal populations activated by this toxin resembled that induced by inflammatory signals. Interestingly, part of neuronal pathways activated by the

toxin were NUCB-2/nesfatin-1 expressing neurons. Unexpectedly, while T-2 toxin induced a strong peripheral inflammation, the brain exhibited limited inflammatory response at a time point when anorexia was ongoing. Unilateral vagotomy partly reduced T-2 toxin-induced brainstem neuronal activation. On the other hand, intracerebroventricular (icv) T-2 toxin injection resulted in a rapid (<1h) reduction in food intake. Thus, we hypothesized that T-2 toxin could signal to the brain through neuronal and/or humoral pathways. The present work provides the first demonstration that T-2 toxin modifies feeding behavior by interfering with central neuronal networks devoted to central energy balance. Our results, with a particular attention to peripheral inflammation, strongly suggest that inflammatory mediators partake in the T-2 toxin-induced anorexia and other symptoms. In view of the broad human and breeding animal exposure to T-2 toxin, this new mechanism may lead to reconsider the impact of the consumption of this toxin on human health.

Maric T, et al (2014) - **The effects of dietary saturated fat on basal hypothalamic neuroinflammation in rats.** Brain Behav Immun. 2014 Feb;36:35-45. [ABS]

Bauman MD, et al (2014) - **Activation of the maternal immune system during pregnancy alters behavioral development of rhesus monkey offspring.** Biol Psychiatry. 2014 Feb 15;75(4):332-41. [ABS]

In this rhesus monkey model, MIA yields offspring with abnormal repetitive behaviors, communication, and social interactions. These results extended the findings in rodent MIA models to more human-like behaviors resembling those in both autism and schizophrenia.

Elmore MR, et al (2014) - **Respiratory viral infection in neonatal piglets causes marked microglia activation in the hippocampus and deficits in spatial learning.** J Neurosci. 2014 Feb 5;34(6):2120-9. [FULL TEXT]

Environmental insults during sensitive periods can affect hippocampal development and function, but little is known about peripheral infection, especially in humans and other animals whose brain is gyrencephalic and experiences major perinatal growth. Using a piglet model, the present study showed that inoculation on postnatal day 7 with the porcine reproductive and respiratory syndrome virus (PRRSV) caused microglial activation within the hippocampus with 82% and 43% of isolated microglia being MHC II(+) 13 and 20 d after inoculation, respectively. In control piglets, <5% of microglia isolated from the hippocampus were MHC II(+). PRRSV piglets were febrile ($p < 0.0001$), anorectic ($p < 0.0001$), and weighed less at the end of the study ($p = 0.002$) compared with control piglets. Increased inflammatory gene expression (e.g., IL-1β, IL-6, TNF-α, and IFN-γ) was seen across multiple brain regions, including the hippocampus, whereas reductions in CD200, NGF, and MBP were evident. In a test of spatial learning, PRRSV piglets took longer to acquire the task, had a longer latency to choice, and had a higher total distance moved. Overall, these data demonstrate that viral respiratory infection is associated with a marked increase in activated microglia in the hippocampus, neuroinflammation, and impaired performance in a spatial cognitive task. As respiratory infections are common in human neonates and infants, approaches to regulate microglial cell activity are likely to be important.

Dantoft TM, et al (2014) - **An elevated pro-inflammatory cytokine profile in multiple chemical**

sensitivity. Psychoneuroendocrinology. 2014 Feb;40:140-50. [ABS]

BACKGROUND: Multiple chemical sensitivity (MCS) is a medically unexplained condition characterized by reports of recurrent unspecific symptoms attributed to exposure to low levels of common volatile chemicals. The etiology of MCS is poorly understood, but dysregulation of the immune system has been proposed as part of the pathophysiology. OBJECTIVE: To compare plasma levels of cytokines in Danish MCS individuals with a healthy, sex- and age-matched control group. METHOD: Blood samples were obtained from 150 un-exposed MCS individuals and from 148 age- and sex-matched healthy controls. Plasma concentrations of 14 cytokines, chemokines and growth and allergen-specific IgE were measured. All participants completed a questionnaire including questions on MCS, psychological distress, morbidities and medication use at the time of the study. RESULTS: Plasma levels of interleukin-1β, -2, -4, and -6 were significantly ($P<0.001$) increased in the MCS group compared with controls, tumor necrosis factor-α was borderline significantly ($P=0.05$) increased and interleukin-13 was significantly decreased ($P<0.001$). CONCLUSION: MCS individuals displayed a distinct systemic immune mediator profile with increased levels of pro-inflammatory cytokines and interleukin-2 and inverse regulation of Th2 associated cytokines interleukin-4 and interleukin-13 suggestive of low-grade systemic inflammation, along with a deviating Th2-associated cytokine response not involving IgE-mediated mechanisms.

D'Mello C, et al (2014) - **Liver-brain interactions in inflammatory liver diseases: implications for fatigue and mood disorders.** Brain Behav Immun. 2014 Jan;35:9-20. [ABS]

Chronic inflammatory liver diseases are often accompanied by behavior alterations including fatigue, mood disorders, cognitive dysfunction and sleep disturbances. These altered behaviors can adversely affect patient quality of life. The communication pathways between the inflamed liver and the brain that mediate changes in central neural activity leading to behavior alterations during liver inflammation are poorly understood. Neural and humoral communication pathways have been most commonly implicated as driving peripheral inflammation to brain signaling. Classically, the cytokines TNFα, IL-1β and IL-6 have received the greatest scientific attention as potential mediators of this communication pathway. In mice with liver inflammation we have identified a novel immune-mediated liver-to-brain communication pathway whereby CCR2(+) monocytes found within the peripheral circulation transmigrate into the brain parenchyma in response to MCP-1/CCL2 expressing activated microglia. Inhibition of cerebral monocyte infiltration in these mice significantly improved liver inflammation associated sickness behaviors. Importantly, in recent work we have found that at an earlier time point, when cerebral monocyte infiltration is not evident in mice with liver inflammation, increased monocyte:cerebral endothelial cell adhesive interactions are observed using intravital microscopy of the brain. These monocyte:cerebral endothelial cell adhesive interactions are P-selectin mediated, and inhibition of these interactions attenuated microglial activation and sickness behavior development. Delineating the pathways that the periphery uses to communicate with the brain during inflammatory liver diseases, and the central neurotransmitter systems that are altered through these communication pathways (e.g., serotonin, corticotrophin releasing hormone) to give rise to liver inflammation-associated sickness behaviors, will allow for the identification of novel therapeutic targets to decrease the burden of debilitating symptoms in these patients.

Hildebrandt H, et al (2014) - **A longitudinal study on fatigue, depression, and their relation to neurocognition in multiple sclerosis.** J Clin Exp Neuropsychol. 2014;36(4):410-7. [ABS]

> AIMS: Fatigue and depression are two common syndromes in patients with multiple sclerosis (MS), but their inherent relation and causes are still under debate. METHOD: With a longitudinal design we analyzed their development over a period of one year and their relation to the clinical status, brain atrophy, and neurocognitive performance at the beginning of the study. Forty patients with relapsing-remitting MS were included and were assessed for fatigue and depressive mood, clinical status, neurocognitive performance, and brain parenchymal fraction. RESULTS: Regression analyses showed that changes in fatigue are predicted by fatigue status and gait performance at Visit 1. Changes in depressive mood are predicted by executive functioning, memory performance, and depressive mood at Visit 1. Additional evidence for a dissociation between fatigue and depression was found when patient groups suffering at Visit 2 from fatigue or not and having a depressed mood or not were contrasted. CONCLUSION: We conclude that although fatigue and depressive mood share many features, they do not behave similarly in the course of relapsing-remitting MS. Our results fit the proposal that fatigue is a reversible syndrome similar to sickness behavior, and that depressive mood is at least partially related to neurodegeneration.

2013

Alt JA, et al (2013) - **Chronic rhinosinusitis and sleep: a contemporary review.** Int Forum Allergy Rhinol. 2013 Nov;3(11):941-9. [FULL TEXT]

Fonken LK, et al (2013) - **Mice exposed to dim light at night exaggerate inflammatory responses to lipopolysaccharide**. Brain Behav Immun. 2013 Nov;34:159-63. [ABS]

> Mice exposed to dark or dimly lit nights had comparable sickness behavior directly following the LPS injection; however, dLAN mice showed greater reductions in locomotor activity, increased anorectic behavior, and increased weight loss than mice maintained in dark nights 24h post-LPS injection. Overall, these data suggest that chronic exposure to even very low levels of light pollution may alter inflammatory responses. These results may have important implications for humans and other urban dwelling species that commonly experience nighttime light exposure.

Trammell RA, et al (2013) - **Environmental perturbation, inflammation and behavior in healthy and virus-infected mice.** Brain Behav Immun. 2013 Oct;33:139-52. [ABS]

Hsuchou H, et al (2013) - **Saturable leptin transport across the BBB persists in EAE mice.** J Mol Neurosci. 2013 Oct;51(2):364-70. [FULL TEXT]

VanElzakker MB (2013) - **Chronic fatigue syndrome from vagus nerve infection: a psychoneuroimmunological hypothesis.** Med Hypotheses. 2013 Sep;81(3):414-23. [ABS]

Kelley KW, et al (2013) - **Aging leads to prolonged duration of inflammation-induced depression-like behavior caused by Bacillus Calmette-Guérin.** Brain Behav Immun. 2013 Aug;32:63-9. [FULL TEXT]

> In aged mice, greater tryptophan catabolism persisted longer and remained elevated at 21 days post-infection. This finding is consistent with the prolonged duration of depression-like behaviors in aged mice.

Guimarães HC, et al (2013) - **Serum levels of soluble TNF-α receptors but not BDNF are associated with apathy symptoms in mild Alzheimer's disease and amnestic mild cognitive impairment.** Dement Neuropsychol. 2013 Jul-Sep;7(3):298-303. [FULL TEXT]

Kullmann JS, et al (2013) - **Neural response to emotional stimuli during experimental human endotoxemia.** Hum Brain Mapp. 2013 Sep;34(9):2217-27. [ABS]

> Positive mood was decreased and state anxiety increased. In addition, activation of right inferior orbitofrontal cortex (OFC) in response to emotional visual stimuli was significantly increased in the LPS condition. Increased prefrontal activation during the presentation of emotional material may reflect enhanced cognitive regulation of emotions as an adaptive response during an acute inflammation.

Peters VA, et al (2013) - **IL-1 receptor 2 (IL-1R2) and its role in immune regulation.** Brain Behav Immun. 2013 Aug;32:1-8. [FULL TEXT]

Hines DJ, et al (2013) - **Prevention of LPS-induced microglia activation, cytokine production and sickness behavior with TLR4 receptor interfering peptides.** PLoS One. 2013;8(3):e60388. [FULL TEXT]

Biesmans S, et al (2013) - **Systemic immune activation leads to neuroinflammation and sickness behavior in mice.** Mediators Inflamm. 2013;2013:271359. [FULL TEXT]

Granger JI, et al (2013) - **Sepsis-induced morbidity in mice: effects on body temperature, body weight, cage activity, social behavior and cytokines in brain.** Psychoneuroendocrinology. 2013 Jul;38(7):1047-57. [FULL TEXT]

Chen Q, et al (2013) - **Controlled progressive innate immune stimulation regimen prevents the induction of sickness behavior in the open field test.** J Inflamm Res. 2013 Jul 4;6:91-8. [FULL TEXT]

Roman A, et al (2013) - **Macrophages and depression - a misalliance or well-arranged marriage?** Pharmacol Rep. 2013;65(6):1663-72. [ABS]

> Recent studies have shown that antidepressive therapies can affect the functional properties of peripheral and brain macrophages and skew them toward the anti-inflammatory M2 phenotype. Because macrophages can affect outcome of inflammatory diseases, alleviate sickness behavior and improve cognitive function, it is possible that the effects of antidepressive treatments may be, at least in part, mediated by changes in macrophage activity.

Linnman C, et al (2013) - **Inflaming the brain: CRPS a model disease to understand neuroimmune interactions in chronic pain.** J Neuroimmune Pharmacol. 2013 Jun;8(3):547-63. [FULL TEXT]

Burton MD, et al (2013) - **Central inhibition of interleukin-6 trans-signaling during peripheral infection reduced neuroinflammation and sickness in aged mice.** Brain Behav Immun. 2013 May;30:66-72. [FULL TEXT]

Avitsur R, et al (2013) - **Neonatal stress modulates sickness behavior: role for proinflammatory cytokines.** J Neuroimmunol. 2013 Apr 15;257(1-2):59-66. [ABS]

> Maternal separation increased sensitivity to the effects of proinflammatory cytokines on sickness behavior following an immune challenge.

Morris G, et al (2013) **- A narrative review on the similarities and dissimilarities between myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and sickness behavior.** BMC Med. 2013 Mar 8;11:64. [FULL TEXT]

Schieveld JN, et al (2013) - **The forthcoming DSM-5, critical care medicine, and pediatric neuropsychiatry: which new concepts do we need?** J Neuropsychiatry Clin Neurosci. 2013 Spring;25(2):111-4. [ABS]

> The first new concept described is “sickness behavior, as part of the organic reaction types of the brain”.

Harden LM, et al (2013) - **Interleukin-10 modulates the synthesis of inflammatory mediators in the sensory circumventricular organs: implications for the regulation of fever and sickness behaviors.** J Neuroinflammation. 2013 Feb 6;10:22. [FULL TEXT]

Stella J, et al (2013) - **Effects of stressors on the behavior and physiology of domestic cats.** Appl Anim Behav Sci. 2013 Jan 31;143(2-4):157-163. [FULL TEXT]

McCusker RH, et al (2013) - **Immune-neural connections: how the immune system's response to infectious agents influences behavior.** J Exp Biol. 2013 Jan 1;216(Pt 1):84-98. [FULL TEXT]

Ribeiro DE, et al (2013) - **Inhibition of nitric oxide synthase accentuates endotoxin-induced sickness behavior in mice.** Pharmacol Biochem Behav. 2013 Jan;103(3):535-40. [FULL TEXT]

Orr SK, et al (2013) - **n-3 Polyunsaturated fatty acids in animal models with neuroinflammation.** Prostaglandins Leukot Essent Fatty Acids. 2013 Jan;88(1):97-103. [ABS]

> Evidence by and large shows protective effects of n-3 PUFA in models of sickness behavior, stroke, aging, depression, Parkinson's disease, diabetes, and cytokine- and irradiation-induced cognitive impairments.t Fatty Acids.

Pimentel SP, et al (2013) - **Perinatal periodontal disease reduces social behavior in male offspring.**

Neuroimmunomodulation. 2013;20(1):29-38. [ABS]

> We conclude that pre- and postnatal periodontitis induces maternal sickness behavior and reduces the pups' play behavior without interference with frontal cortex reelin expression.

2012

Sukoff Rizzo SJ, et al (2012) - **Evidence for sustained elevation of IL-6 in the CNS as a key contributor of depressive-like phenotypes.** Transl Psychiatry. 2012 Dec 4;2(12):e199. [FULL TEXT]

Cohn DW, et al (2012) - **Lipopolysaccharide administration in the dominant mouse destabilizes social hierarchy.** Behav Processes. 2012 Sep;91(1):54-60. [ABS]

Smith KJ, et al (2012) - **An Exploration of Depressive Symptoms in Hepatitis C Patients Taking Interferon-alpha: Increase in Sickness Behaviors but not Negative Cognitions.** J Clin Exp Hepatol. 2012 Sep;2(3):218-23. [FULL TEXT]

Benson S, et al (2012) - **Experimental endotoxemia as a model to study neuroimmune mechanisms in human visceral pain.** Ann N Y Acad Sci. 2012 Jul;1262:108-17. [ABS]

Maes M, et al (2012) - **Depression and sickness behavior are Janus-faced responses to shared inflammatory pathways.** BMC Med. 2012 Jun 29;10:66. [FULL TEXT]

> Inflammation may provoke a Janus-faced response with a good, acute side, generating protective inflammation through sickness behavior and a bad, chronic side, for example, clinical depression, a lifelong disorder with positive feedback loops between (neuro)inflammation and (neuro)degenerative processes following less well defined triggers.

Illi J, et al (2012) - **Association between pro- and anti-inflammatory cytokine genes and a symptom cluster of pain, fatigue, sleep disturbance, and depression.** Cytokine. 2012 Jun;58(3):437-47. [FULL TEXT]

Straub RH (2012) - **Evolutionary medicine and chronic inflammatory state--known and new concepts in pathophysiology**. J Mol Med (Berl). 2012 May;90(5):523-34. [FULL TEXT]

2011

Moon ML, et al (2011) - **Macrophages make me sick: how macrophage activation states influence sickness behavior.** Psychoneuroendocrinology. 2011 Nov;36(10):1431-40. [FULL TEXT]

> Critically, the same cytokines which orchestrate immune defense and homeostasis dramatically impact sense of well being and cognition by eliciting sickness symptoms. Such behaviors are

the manifestation of pro/anti-inflammatory cytokine action in the brain and are a direct consequence of MΦ function.

Holmes C, et al (2011) - **Proinflammatory cytokines, sickness behavior, and Alzheimer disease.** Neurology. 2011 Jul 19;77(3):212-8. [FULL TEXT]

Increased serum proinflammatory cytokines are associated with the presence of symptoms characteristic of sickness behavior, which are common neuropsychiatric features found in AD. This association was independent of the presence of delirium.

MacDonald L, et al (2011) - **Calorie restriction attenuates LPS-induced sickness behavior and shifts hypothalamic signaling pathways to an anti-inflammatory bias**. Am J Physiol Regul Integr Comp Physiol. 2011 Jul;301(1):R172-84. [FULL TEXT]

It has been well established that CR can exert positive effects upon the life span and certain age-related diseases. This study demonstrated that a period of CR can attenuate sickness behavior following LPS administration. Regardless of the reason why CR animals do not display sickness behavior and the normal patterns of pro- and anti-inflammatory compounds after LPS, this finding could be significant in investigating mechanisms important in chronic illness, and possible avenues of treatment for these diseases.

Kelley KW, et al (2011) - **Alcoholism and inflammation: neuroimmunology of behavioral and mood disorders.** Brain Behav Immun. 2011 Jun;25 Suppl 1:S13-20. [FULL TEXT]

The remarkable conservation from mice to humans of the impact of inflammation on mood emphasizes the ever-expanding role for cross-talk among diverse physiological symptoms that are likely to be involved in the pathogenesis of alcohol abuse.

Maes M (2011) - **An intriguing and hitherto unexplained co-occurrence: Depression and chronic fatigue syndrome are manifestations of shared inflammatory, oxidative and nitrosative (IO&NS) pathways.** Prog Neuropsychopharmacol Biol Psychiatry. 2011 Apr 29;35(3):784-94. [ABS]

Maes M (2011) - **An intriguing and hitherto unexplained co-occurrence: Depression and chronic fatigue syndrome are manifestations of shared inflammatory, oxidative and nitrosative (IO&NS) pathways.** Prog Neuropsychopharmacol Biol Psychiatry. 2011 Apr 29;35(3):784-94. [ABS]

Wager-Smith K, et al (2011) - **Depression: a repair response to stress-induced neuronal microdamage that can grade into a chronic neuroinflammatory condition?** Neurosci Biobehav Rev. 2011 Jan;35(3):742-64. [FULL TEXT]

2010

Hanff TC, et al (2010) - **Biochemical and anatomical substrates of depression and sickness behavior.** Isr J Psychiatry Relat Sci. 2010;47(1):64-71. [FULL TEXT]

> Sickness behavior – the lethargy, hypoactivity, decreased libido, anorexia, anhedonia, and increased sleep that accompanies infectious disease (1, 2) was once thought to be a maladaptive consequence of an animal's immune response, damaging the animal's ability to successfully interact with its environment. However, two decades of research into the biological mechanism of sickness behavior have modified this view, demonstrating that sickness behavior is an adaptive central motivational state necessitated by the metabolic constraints for mounting a fever. The characterization of sickness behavior as a motivational state underscores similarities among mood disorders, the reaction to traumatic stress and recuperation from injury (4). Each of these conditions is associated with intense catabolic output (5) and is automatically and unconditionally followed by a compensatory shift to a behavioral state termed conservation-withdrawal (6). The sensory unresponsiveness, cognitive dullness and behavioral depression that characterize this state are adaptive mechanisms for husbanding limited resources and facilitating the recovery of energy homeostasis.

Sherry CL, et al (2010) - **Sickness behavior induced by endotoxin can be mitigated by the dietary soluble fiber, pectin, through up-regulation of IL-4 and Th2 polarization.** Brain Behav Immun. 2010 May;24(4):631-40. [FULL TEXT]

Eisenberger NI, et al (2010) - **Inflammation and social experience: an inflammatory challenge induces feelings of social disconnection in addition to depressed mood.** Brain Behav Immun. 2010 May;24(4):558-63. [FULL TEXT]

2009

Yariagadda A, et al (2009) - **The blood brain barrier and the role of cytokines in neuropsychiatry**. Psychiatry (Edgmont). 2009 Nov;6(11):18-22. [FULL TEXT]

> This article highlights the growing correlation of brain cytokine levels with corresponding psychiatric symptoms, known as cytokine-induced sickness behavior, comprising increased sleep, decreased appetite, decreased sexual drive, and overwhelming fatigue frequently combined with fever.

Bhatt S, et al (2009) **- Peripheral and central mediators of lipopolysaccharide induced suppression of defensive rage behavior in the cat.** Neuroscience. 2009 Nov 10;163(4):1002-11. [FULL TEXT]

Cremeans-Smith JK, et al (2009) - **In-hospital levels of C-reactive protein and IL-6 predict post-operative depressive symptoms among patients undergoing total knee replacement surgery.** Brain Behav Immun. 2009 Nov;23(8):1096-103. [ABS]

Avitsur R, et al (2009) - **Neonatal stress modulates sickness behavior.** Brain Behav Immun. 2009 Oct;23(7):977-85. [FULL TEXT]

> Together with previous studies, these findings suggest that neonatal stress disrupted the

regulation of innate resistance to an immune challenge resulting in enhanced immunological and behavioral responses to immune activation. Thus, long lasting effects of early stress events may be the basis for individual differences in health and susceptibility to disease.

Wynne AM, et al (2009) - **Immune and behavioral consequences of microglial reactivity in the aged brain.** Integr Comp Biol. 2009 Sep;49(3):254-66. [FULL TEXT]

Harrison NA, et al (2009) - **Neural origins of human sickness in interoceptive responses to inflammation.** Biol Psychiatry. 2009 Sep 1;66(5):415-22. [FULL TEXT]

> Performance of the Stroop task under inflammation activated brain regions encoding representations of internal bodily state. Spatial and temporal characteristics of this response are consistent with interoceptive information flow via afferent autonomic fibers. During performance of this task, activity within interoceptive brain regions also predicted individual differences in inflammation-associated but not placebo-associated fatigue and confusion. Maintenance of cognitive performance, despite inflammation-associated fatigue, led to recruitment of additional prefrontal cortical regions.
>
> These findings suggest that peripheral infection selectively influences central nervous system function to generate core symptoms of sickness and reorient basic motivational states.

Arakawa H, et al (2009) - **Central infusion of interleukin-1 receptor antagonist blocks the reduction in social behavior produced by prior stressor exposure**. Physiol Behav. 2009 Aug 4;98(1-2):139-46. [FULL TEXT]

Zager A, et al (2009) - **Modulation of sickness behavior by sleep: the role of neurochemical and neuroinflammatory pathways in mice**. Eur Neuropsychopharmacol. 2009 Aug;19(8):589-602. [ABS]

Dantzer R (2009) - **Cytokine, sickness behavior, and depression**. Immunol Allergy Clin North Am. 2009 May;29(2):247-64. [FULL TEXT]

Skinner GW, et al (2009) - **Avoidance of physical activity is a sensitive indicator of illness**. Physiol Behav. 2009 Mar 2;96(3):421-7. [ABS]

Kamath J, et al (2009) - **The thyrotropin-releasing hormone (TRH)-immune system homeostatic hypothesis.** Pharmacol Ther. 2009 Jan;121(1):20-8. [ABS]

2008

Dilger RN, et al (2008) - **Aging, microglial cell priming, and the discordant central inflammatory response to signals from the peripheral immune system**. J Leukoc Biol. 2008 Oct;84(4):932-9. [FULL TEXT]

Gibb J, et al (2008) - **Synergistic and additive actions of a psychosocial stressor and endotoxin**

challenge: Circulating and brain cytokines, plasma corticosterone and behavioral changes in mice. Brain Behav Immun. 2008 May;22(4):573-89. [ABS]

> In view of the combined actions of LPS challenge and a social stressor, these data are interpreted as suggesting that models of depression based on immune activation ought to consider the stressor backdrop upon which immune challenges are imposed.

2007

Goehler LE, et al (2007) - **Infection-induced viscerosensory signals from the gut enhance anxiety: implications for psychoneuroimmunology.** Brain Behav Immun. 2007 Aug;21(6):721-6. [FULL TEXT]

Willette AA, et al (2007) - **Environmental context differentially affects behavioral, leukocyte, cortisol, and interleukin-6 responses to low doses of endotoxin in the rhesus monkey.** Brain Behav Immun. 2007 Aug;21(6):807-15. [FULL TEXT]

Lowry CA, et al (2007) - **Identification of an immune-responsive mesolimbocortical serotonergic system: potential role in regulation of emotional behavior.** Neuroscience. 2007 May 11;146(2):756-72. [FULL TEXT]

Dantzer R, et al (2007) - **Twenty years of research on cytokine-induced sickness behavior.** Brain Behav Immun. 2007 Feb;21(2):153-60. [FULL TEXT]

Lemstra AW, et al (2007) - **Microglia activation in sepsis: a case-control study.** J Neuroinflammation. 2007 Jan 15;4:4. [FULL TEXT]

> This study shows for the first time in human brain tissue an association between a systemic infection and activation of microglia in the brain. Activated microglia during sepsis could play a role in behavioral changes associated with systemic infection.

2006

Godbout JP, et al (2006) - **Age and neuroinflammation: a lifetime of psychoneuroimmune consequences.** Neurol Clin. 2006 Aug;24(3):521-38. [ABS]

> This amplified or prolonged exposure to inflammatory cytokines in the brain may impair neuronal plasticity and underlie a heightened neuroinflammatory response in the aged that also may lead to other neurobehavioral impairments such as delirium, depression, and, potentially, the onset of neurologic disease.

Dantzer R (2006) - **Cytokine, sickness behavior, and depression.** Neurol Clin. 2006 Aug;24(3):441-60. [FULL TEXT]

Cohn DW, et al (2006) - **Differential effects of lipopolysaccharide in the social behavior of dominant and submissive mice.** Physiol Behav. 2006 May 30;87(5):932-7. [ABS]

> The use of a motivational perspective provides the assumption that, due to their high social ranking, dominant mice were able to prioritize recuperative behavior. Submissive mice, on the other hand, even though treated with LPS, seemed to essentially focus on social defensive behaviors since they remained in the presence of the dominant individuals.

2005

Godbout JP, et al (2005) - **Alpha-tocopherol attenuates NFkappaB activation and pro-inflammatory cytokine production in brain and improves recovery from lipopolysaccharide-induced sickness behavior.** J Neuroimmunol. 2005 Dec;169(1-2):97-105. [ABS]

Viljoen M, et al (2005) - **Non-termination of sickness behavior as precipitating factor for mental disorders.** Med Hypotheses. 2005;65(2):316-29. [ABS]

> In view of the similarities between the behavioral symptoms, the neuroendocrine and the cytokine profiles of sickness behavior and that of a number of mental disorders it is hypothesized that the inappropriate continuation of sickness behavior, (i.e., non-termination), after recovery from the initial disease, could form the basis for mental disturbances. This would be particularly relevant in individuals with alterations in stress vulnerability (altered activation threshold and impaired negative feedback), which may occur due to the combination of genetic disposition and priming by early life experiences.

Berg BM, et al (2005) - **Alpha-Tocopherol and selenium facilitate recovery from lipopolysaccharide-induced sickness in aged mice.** J Nutr. 2005 May;135(5):1157-63. [FULL TEXT]

Glaser R, et al (2005) - **How stress damages immune system and health.** Discov Med. 2005 Apr;5(26):165-9. [FULL TEXT]

2004 and earlier

Schwarz MJ (2003) - **Cytokines, neurophysiology, neuropsychology, and psychiatric symptoms.** Dialogues Clin Neurosci, 2003 Jun;5(2):139-53. [FULL TEXT]

Banks WA, et al (2002) - **Entry of blood-borne cytokines into the central nervous system: effects on cognitive processes.** Neuroimmunomodulation. 2002-2003;10(6):319-27. [ABS]

> Blood-borne cytokines affect many aspects of the central nervous system (CNS). One of the more dramatic effects is the induction of sickness behavior. Impairments in learning and

memory are an important component of sickness behavior and are largely mediated by IL-1.

Kronfol Z, et al (2000) - **Cytokines and the brain: implications for clinical psychiatry.** Am J Psychiatry. 2000 May;157(5):683-94. [ABS]

> Growing evidence suggests that, in addition to providing communication between immune cells, specific cytokines play a role in signaling the brain to produce neurochemical, neuroendocrine, neuroimmune, and behavioral changes. This signaling may be part of a generalized, comprehensive mechanism to mobilize resources in the face of physical and/or psychological stress and to maintain homeostasis. The clinical implications of these findings are far-reaching and include a possible role for cytokines in the pathophysiology of specific psychiatric disorders such as major depression, schizophrenia, and Alzheimer's disease.

Pollak Y, et al (2000) - **Behavioral aspects of experimental autoimmune encephalomyelitis.** J Neuroimmunol. 2000 Apr 3;104(1):31-6. [ABS]

Gaykema RP, et al (1998) - **Bacterial endotoxin induces fos immunoreactivity in primary afferent neurons of the vagus nerve.** Neuroimmunomodulation. 1998 Sep-Oct;5(5):234-40. [ABS]

Linthorst AC, et al (1998) - **Brain neurotransmission during peripheral inflammation.** Ann N Y Acad Sci. 1998 May 1;840:139-52. [ABS]

Yirmiya R, et al (1996) - **Effects of fetal alcohol exposure on fever, sickness behavior, and pituitary-adrenal activation induced by interleukin-1 beta in young adult rats.** Brain Behav Immun. 1996 Sep;10(3):205-20. [ABS]

Katz IR (1996) - **On the Inseparability of Mental and Physical Health in Aged Persons: Lessons from Depression and Medical Comorbidity.** Am J Geriatr Psychiatry. 1996 Winter;4(1):1-16. [ABS]

Aubert A, et al (1995) - **Pyrogens specifically disrupt the acquisition of a task involving cognitive processing in the rat.** Brain Behav Immun. 1995 Jun;9(2):129-48. [ABS]

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Select Articles for Group Discussion.

O'Callaghan J, et al (2019) - **Neuroinflammation disorders exacerbated by environmental stressors.** Metabolism. 2019 Nov;100S:153951. [FULL TEXT]

> Neuroinflammation is a condition characterized by the elaboration of proinflammatory mediators within the central nervous system. Neuroinflammation has emerged as a dominant theme in contemporary neuroscience due to its association with neurodegenerative disease states such as Alzheimer's disease, Parkinson's disease and Huntington's disease. While

neuroinflammation often is associated with damage to the CNS, it also can occur in the absence of neurodegeneration, e.g., in association with systemic infection. The "acute phase" inflammatory response to tissue injury or infections instigates neuroinflammation-driven "sickness behavior," i.e. a constellation of symptoms characterized by loss of appetite, fever, muscle pain, fatigue and cognitive problems. Typically, sickness behavior accompanies an inflammatory response that resolves quickly and serves to restore the body to homeostasis. However, recurring and sometimes chronic sickness behavior disorders can occur in the absence of an underlying cause or attendant neuropathology. Here, we review myalgic enchepalomyelitis/chronic fatigue syndrome (ME/CFS), Gulf War Illness (GWI), and chemobrain as examples of such disorders and propose that they can be exacerbated and perhaps initiated by a variety of environmental stressors. Diverse environmental stressors may disrupt the hypothalamic pituitary adrenal (HPA) axis and contribute to the degree and duration of a variety of neuroinflammation-driven diseases.

Stephan KE, et al (2016) - **Allostatic Self-efficacy: A Metacognitive Theory of Dyshomeostasis-Induced Fatigue and Depression.** Front Hum Neurosci. 2016 Nov 15;10:550. [FULL TEXT]

This paper outlines a hierarchical Bayesian framework for interoception, homeostatic/allostatic control, and meta-cognition that connects fatigue and depression to the experience of chronic dyshomeostasis. Specifically, viewing interoception as the inversion of a generative model of viscerosensory inputs allows for a formal definition of dyshomeostasis (as chronically enhanced surprise about bodily signals, or, equivalently, low evidence for the brain's model of bodily states) and allostasis (as a change in prior beliefs or predictions which define setpoints for homeostatic reflex arcs). Critically, we propose that the performance of interoceptive-allostatic circuitry is monitored by a metacognitive layer that updates beliefs about the brain's capacity to successfully regulate bodily states (allostatic self-efficacy). In this framework, fatigue and depression can be understood as sequential responses to the interoceptive experience of dyshomeostasis and the ensuing metacognitive diagnosis of low allostatic self-efficacy. While fatigue might represent an early response with adaptive value (cf. sickness behavior), the experience of chronic dyshomeostasis may trigger a generalized belief of low self-efficacy and lack of control (cf. learned helplessness), resulting in depression. This perspective implies alternative pathophysiological mechanisms that are reflected by differential abnormalities in the effective connectivity of circuits for interoception and allostasis. We discuss suitably extended models of effective connectivity that could distinguish these connectivity patterns in individual patients and may help inform differential diagnosis of fatigue and depression in the future.

Ashley NT, et al (2017) - **Neuroendocrine-immune circuits, phenotypes, and interactions.** Horm Behav. 2017 Jan;87:25-34. [FULL TEXT]

Multidirectional interactions among the immune, endocrine, and nervous systems have been demonstrated in humans and non-human animal models for many decades by the biomedical community, but ecological and evolutionary perspectives are lacking. Neuroendocrine-immune interactions can be conceptualized using a series of feedback loops, which culminate into distinct neuroendocrine-immune phenotypes. Behavior can exert profound influences on

these phenotypes, which can in turn reciprocally modulate behavior. For example, the behavioral aspects of reproduction, including courtship, aggression, mate selection and parental behaviors can impinge upon neuroendocrine-immune interactions. One classic example is the immunocompetence handicap hypothesis (ICHH), which proposes that steroid hormones act as mediators of traits important for female choice while suppressing the immune system. Reciprocally, neuroendocrine-immune pathways can promote the development of altered behavioral states, such as sickness behavior. Understanding the energetic signals that mediate neuroendocrine-immune crosstalk is an active area of research. Although the field of psychoneuroimmunology (PNI) has begun to explore this crosstalk from a biomedical standpoint, the neuroendocrine-immune-behavior nexus has been relatively underappreciated in comparative species. The field of ecoimmunology, while traditionally emphasizing the study of non-model systems from an ecological evolutionary perspective, often under natural conditions, has focused less on the physiological mechanisms underlying behavioral responses. This review summarizes neuroendocrine-immune interactions using a comparative framework to understand the ecological and evolutionary forces that shape these complex physiological interactions.

Grissom NM, et al (2017) - **Suboptimal nutrition in early life affects the inflammatory gene expression profile and behavioral responses to stressors.** Brain Behav Immun. 2017 Jul;63:115-126. [ABS]

Nutritional conditions in early life can have a lasting impact on health and disease risk, though the underlying mechanisms are incompletely understood. In the healthy individual, physiological and behavioral responses to stress are coordinated in such a way as to mobilize resources necessary to respond to the stressor and to terminate the stress response at the appropriate time. Induction of proinflammatory gene expression within the brain is one such example that is initiated in response to both physiological and psychological stressors, and is the focus of the current study. We tested the hypothesis that early life nutrition would impact the proinflammatory transcriptional response to a stressor. Pregnant and lactating dams were fed one of three diets; a low-protein diet, a high fat diet, or the control diet through pregnancy and lactation. Adult male offspring were then challenged with either a physiological stressor (acute lipopolysaccharide injection, IP) or a psychological stressor (15 min restraint). Expression of 20 proinflammatory and stress-related genes was evaluated in hypothalamus, prefrontal cortex, amygdala and ventral tegmental area. In a second cohort, behavioral responses (food intake, locomotor activity, metabolic rate) were evaluated. Offspring from low protein fed dams showed a generally reduced transcriptional response, particularly to LPS, and resistance to behavioral changes associated with restraint, while HF offspring showed an exacerbated transcriptional response within the PFC, a reduced transcriptional response in hypothalamus and amygdala, and an exacerbation of the LPS-induced reduction of locomotor activity. The present data identify differential proinflammatory transcriptional responses throughout the brain driven by perinatal diet as an important variable that may affect risk or resilience to stressors.

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