76. Okumura, F., Okumura, A. J., Matsumoto, M., Nakayama, K. I. & Hatakeyama, S. TRIM8 regulates Nanog via Hsp90β-medicated nuclear translocation of STAT3 in embryonic stem cells. *Biochim. Biophys. Acta* 2 Jun 2011 (doi:10.1016/j.bbamcr.2011.05.013).
77. Ben-Zvi, I. & Livneh, A. Chronic inflammation in FMF: markers, risk factors, outcomes and therapy. *Nature Rev. Rheumatol.* **7**, 105–112 (2011).
78. Shaw, P. J., McDermott, M. F. & Kanneganti, T. D. Inflammasomes and autoimmunity. *Trends Mol. Med.* **17**, 57–64 (2011).
79. Richards, N. *et al.* Interaction between pyrin and the apoptotic speck protein (ASC) modulates ASC-induced apoptosis. *J. Biol. Chem.* **276**, 39320–39329 (2001).
80. Yu, J. W. *et al.* Pyrin activates the ASC pyroptosome in response to engagement by autoinflammatory PSTPIP1 mutants. *Mol. Cell* **28**, 214–227 (2007).
81. Papin, S. *et al.* The SPRY domain of Pyrin, mutated in familial Mediterranean fever patients, interacts with inflammasome components and inhibits proIL-1β processing. *Cell Death Differ.* **14**, 1457–1466 (2007).
82. Yu, J. W. *et al.* Cryopyrin and pyrin activate caspase-1, but not NF-κB, via ASC oligomerization. *Cell Death Differ.* **13**, 236–249 (2006).
83. Chae, J. J. *et al.* The familial Mediterranean fever protein, pyrin, is cleaved by caspase-1 and activates NF-κB through its N-terminal fragment. *Blood* **112**, 1794–1803 (2008).
84. Chae, J. J. *et al.* The B30.2 domain of pyrin, the familial Mediterranean fever protein, interacts directly with caspase-1 to modulate IL-1β production. *Proc. Natl Acad. Sci. USA* **103**, 9982–9987 (2006).
85. Unal, A., Dursun, A., Emre, U., Tascilar, N. F. & Ankarali, H. Evaluation of common mutations in the Mediterranean fever gene in multiple sclerosis patients: is it a susceptibility gene? *J. Neurol. Sci.* **294**, 38–42 (2010).
86. Yahalom, G. *et al.* Familial Mediterranean fever (FMF) and multiple sclerosis: an association study in one of the world's largest FMF cohorts. *Eur. J. Neurol.* 8 Feb 2011 (doi:10.1111/j.1468-1331.2011.03356.x).
87. Merrill, J. E. Proinflammatory and antiinflammatory cytokines in multiple sclerosis and central nervous system acquired immunodeficiency syndrome. *J. Immunother.* **12**, 167–170 (1992).
88. Shoham, N. G. *et al.* Pyrin binds the PSTPIP1/CD2BP1 protein, defining familial Mediterranean fever and PAPA syndrome as disorders in the same pathway. *Proc. Natl Acad. Sci. USA* **100**, 13501–13506 (2003).
89. Munding, C. *et al.* The estrogen-responsive B box protein: a novel enhancer of interleukin-1β secretion. *Cell Death Differ.* **13**, 1938–1949 (2006).
90. Hu, Y. *et al.* Tripartite-motif protein 30 negatively regulates NLRP3 inflammasome activation by modulating reactive oxygen species production. *J. Immunol.* **185**, 7699–7705 (2010).
91. Zhou, R., Yazdi, A. S., Menu, P. & Tschopp, J. A role for mitochondria in NLRP3 inflammasome activation. *Nature* **469**, 221–225 (2011).
92. Shi, M. *et al.* TRIM30α negatively regulates TLR-mediated NF-κB activation by targeting TAB2 and TAB3 for degradation. *Nature Immunol.* **9**, 369–377 (2008).
93. Tareen, S. U. & Emerman, M. Human Trim5α has additional activities that are uncoupled from retroviral capsid recognition. *Virology* **409**, 113–120 (2011).
94. Pertel, T. *et al.* TRIM5 is an innate immune sensor for the retrovirus capsid lattice. *Nature* **472**, 361–365 (2011).
95. Reymond, A. *et al.* The tripartite motif family identifies cell compartments. *EMBO J.* **20**, 2140–2151 (2001).
96. Asaoka, K. *et al.* A retrovirus restriction factor TRIM5α is transcriptionally regulated by interferons. *Biochem. Biophys. Res. Commun.* **338**, 1950–1956 (2005).
97. Chelbi-Alix, M. K. *et al.* Induction of the PML protein by interferons in normal and APL cells. *Leukemia* **9**, 2027–2033 (1995).
98. Strandberg, L. *et al.* Interferon-α induces up-regulation and nuclear translocation of the Ro52 autoantigen as detected by a panel of novel Ro52-specific monoclonal antibodies. *J. Clin. Immunol.* **28**, 220–231 (2008).
99. Casciola-Rosen, L. A., Anhalt, G. & Rosen, A. Autoantigens targeted in systemic lupus erythematosus are clustered in two populations of surface structures on apoptotic keratinocytes. *J. Exp. Med.* **179**, 1317–1330 (1994).
100. Ohlsson, M., Jonsson, R. & Brokstad, K. A. Subcellular redistribution and surface exposure of the Ro52, Ro60 and La48 autoantigens during apoptosis in human ductal epithelial cells: a possible mechanism in the pathogenesis of Sjogren's syndrome. *Scand. J. Immunol.* **56**, 456–469 (2002).
101. Chae, J. J. *et al.* Targeted disruption of pyrin, the FMF protein, causes heightened sensitivity to endotoxin and a defect in macrophage apoptosis. *Mol. Cell* **11**, 591–604 (2003).
102. Hoshino, K. *et al.* Anti-MDA5 and anti-TIF1-γ antibodies have clinical significance for patients with dermatomyositis. *Rheumatology* **49**, 726–1733 (2010).
103. Randrianarison-Huetz, V. *et al.* Gfi-1B controls human erythroid and megakaryocytic differentiation by regulating TGF-β signaling at the bipotent erythro-megakaryocytic progenitor stage. *Blood* **115**, 2784–2795 (2010).
104. Billaut-Mulot, O. *et al.* SS-56, a novel cellular target of autoantibody responses in Sjogren syndrome and systemic lupus erythematosus. *J. Clin. Invest.* **108**, 861–869 (2001).

Acknowledgements
The authors would like to acknowledge Science Foundation Ireland (grants 05/PICA/B815 and 08/IN.1/B2091) and the Health Research Board, Ireland (grant PHD/2007/11) for financial support associated with this work.

Competing interests statement
The authors declare no competing financial interests.

FURTHER INFORMATION
Caroline Jefferies's homepage:
http://research1.rcsi.ie/pi/cjefferies

SUPPLEMENTARY INFORMATION
See online article: S1 **(figure)** | S2 **(figure)**

ALL LINKS ARE ACTIVE IN THE ONLINE PDF

SCIENCE AND SOCIETY

Reciprocal regulation of the neural and innate immune systems

Michael R. Irwin and Steven W. Cole

Abstract | Innate immune responses are regulated by microorganisms and cell death, as well as by a third class of stress signal from the nervous and endocrine systems. The innate immune system also feeds back, through the production of cytokines, to regulate the function of the central nervous system (CNS), and this has effects on behaviour. These signals provide an extrinsic regulatory circuit that links physiological, social and environmental conditions, as perceived by the CNS, with transcriptional 'decision-making' in leukocytes. CNS-mediated regulation of innate immune responses optimizes total organism fitness and provides new opportunities for therapeutic control of chronic infectious, inflammatory and neuropsychiatric diseases.

Immune responses are mediated by the activation of immune response genes that encode regulatory and effector molecules, such as cytokines, antimicrobial peptides, antibodies and cytolytic molecules. Transcriptional activation in innate immune cells is triggered by two types of signal from the body's internal environment: pathogen-associated molecular patterns (PAMPs) and 'danger signals' derived from host cell stress or death[1]. A growing body of research shows that a third class of stimulus, in the form of neural and endocrine signals that result from macroenvironmental sensing, also plays a significant role in modulating immune responses[2]. In addition, immune mediators such as cytokines feed back to the brain to regulate neural and endocrine activity[3]. The resulting neuro–immune circuit coordinates immune responses with other physiological processes — such as fight-or-flight stress responses — to maximize the overall fitness of the organism within complex environments that bear multiple threats. Such threats can be microbial, physiological (such as trauma and sleep loss) or social–ecological (such as predation, conspecific violence and interpersonal loss) in nature[4].

The neuro–immune circuit was initially discovered in the context of adaptive immune responses[2], but recent findings suggest that this circuit originates with the innate immune system[5,6]. This article highlights emerging biological themes on the reciprocal regulation of immune response gene expression and central nervous system (CNS) function. We map the molecular signalling pathways involved in this reciprocal regulation, discuss their implications for social influences on disease[7] and highlight new therapeutic approaches for inflammatory diseases and psychiatric syndromes such as major depression, insomnia and fatigue[3]. In addition, we discuss the evolutionary basis for the emergence of a third, CNS-derived signal that controls immune responses[6].

Immune response gene regulation

Functional genomics studies have identified two broad gene expression programmes that can be induced in myeloid lineage cells by different types of microbial stimulus[8]. Extracellular pathogens, such as bacteria, activate a pro-inflammatory gene programme characterized by the expression of genes such as interleukin-1β (*IL1B*), *IL6* and tumour necrosis factor (*TNF*) via transcription factors including nuclear factor-κB (NF-κB) and activator protein 1 (AP1). Intracellular pathogens, such as viruses, elicit a distinct antiviral gene programme that involves the induction of type I interferon (IFN) genes via transcription factors such as interferon regulatory factors (IRFs). These two gene expression programmes mediate fundamentally different effector responses[8,9], but they have in common a substantial energetic cost and the potential for collateral damage (for example, septic shock, autoimmunity, fibrosis and the promotion of inflammation-associated diseases such as atherosclerosis, diabetes, neurodegeneration and neoplasia)[10]. To mitigate these autotoxic risks, an additional layer of regulation exists for the key genes mediating pro-inflammatory and antiviral responses. One type of licensing signal is mediated by 'danger' and requires the presence of signals that are induced by host cell stress, necrosis or apoptosis to generate high-level immune response gene transcription[1]. A second, macroenvironmental licensing signal allows the CNS to integrate information regarding general physiological conditions and the extra-organismal perceived environment to regulate immune response gene expression programmes via hormones and neurotransmitters[2] (FIG. 1).

The neural environment

The primary physiological role of the CNS is to perceive external physical and social conditions (the environment, broadly speaking), assess their implications for organismal well-being (fitness) and modulate the activity of internal physiological processes to optimally adapt to those external conditions[4]. In response to the perception of a threatening environment (for example, the appearance of a predator or hostile conspecifics), the CNS signals for adaptive changes in physiological function (for example, fight-or-flight stress responses). This signalling occurs via the release of neuroeffector molecules (such as noradrenaline) from nerves of the sympathetic nervous system (SNS) or of glucocorticoids from the hypothalamic–pituitary–adrenal (HPA) axis[4]. In addition to regulating virtually every other cell type in the body, these biochemical manifestations of CNS-perceived external conditions regulate the cells of the immune system (BOX 1).

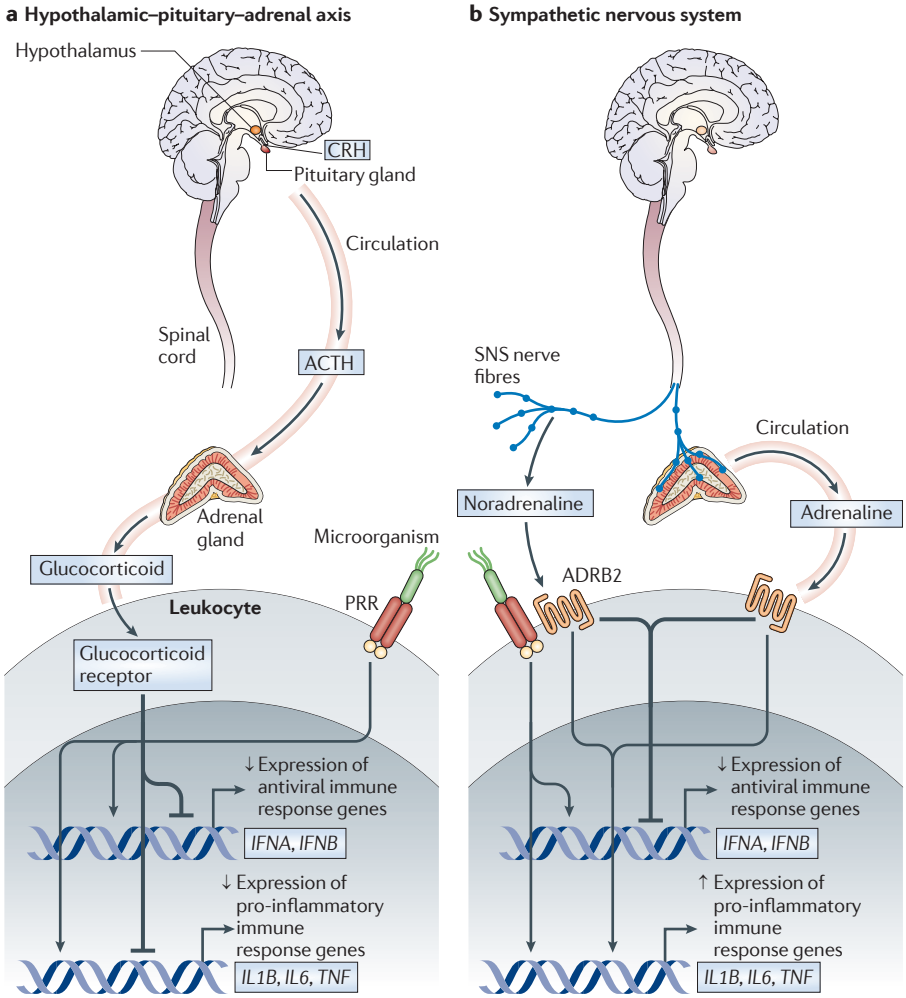

Figure 1 | **CNS regulation of innate immune response gene programmes. a** | The hypothalamic–pituitary–adrenal (HPA) axis distributes glucocorticoid hormones through the blood to regulate gene expression in virtually every cell of the body. Hormone activation of the glucocorticoid receptor in leukocytes results in profound suppression of both pro-inflammatory gene networks (for example, NF-κB-mediated transcription of pro-inflammatory cytokine genes, such as *IL1B*, *IL6* and *TNF*) and antiviral gene programmes (for example, IRF-mediated transcription of type I interferon (IFN) genes, such as *IFNA* and *IFNB*). Activation of cytokine receptors in the hypothalamus triggers the production of glucocorticoids by the HPA axis. This constitutes the body's primary systemic mechanism for negative feedback control of pro-inflammatory gene expression triggered by microbial pattern recognition receptors (PRRs). **b** | During fight-or-flight responses and acute injury, nerve fibres from the sympathetic nervous system (SNS) release the neurotransmitter noradrenaline into primary and secondary lymphoid organs, all other major organ systems (including the vasculature and perivascular tissues) and many peripheral tissues in which pro-inflammatory reactions occur. SNS nerve fibres can also stimulate the adrenal glands to release stored adrenaline into the systemic circulation. Both of these neuromediators regulate vascular function and stimulate leukocyte adrenergic receptors (for example, ADRB2) to activate transcription factors such as CREB and GATA family factors. SNS-induced transcriptional alterations can modulate haematopoiesis, redeploy leukocytes between tissue and blood, and repress IRF-mediated antiviral immune response gene programmes while enhancing many NF-κB-mediated pro-inflammatory programmes. ACTH, adrenocorticotropic hormone; ADRB2, β2-adrenergic receptor; CRH, corticotropin-releasing hormone; IL, interleukin; IRF, interferon regulatory factor; NF-κB, nuclear factor-κB; TNF, tumour necrosis factor.

The hypothalamic–pituitary–adrenal axis. The earliest identified CNS-mediated immunoregulatory function involved the brain's ability to suppress the transcription of both pro-inflammatory and antiviral gene programmes by stimulating

glucocorticoid release from the HPA axis[11–13]. Activation of the glucocorticoid receptor inhibits the transcription of many immune response genes. This effect is mediated by three mechanisms, namely: suppressive binding of the glucocorticoid receptor to gene promoter sequences; glucocorticoid receptor-mediated transcriptional induction of anti-inflammatory genes (such as *NFKBIA*, which encodes IκBα); and non-genomic antagonism of pro-inflammatory transcription factors (such as NF-κB and AP1) via protein–protein interactions[14].

The brain detects peripheral pro-inflammatory and antiviral cytokines via multiple pathways (BOX 2) and stimulates glucocorticoid release from the HPA axis to systemically inhibit immune response gene transcription when inflammation levels become damagingly high or energetic resources need to be shifted elsewhere[3,15]. Glucocorticoid-mediated feedback inhibition of immune response gene transcription is now recognized as the most fundamental physiological mechanism for protection against hyper-inflammatory disease and as a prototype of our most effective anti-inflammatory drugs[14,15].

The sympathetic nervous system. In addition to the global anti-inflammatory effect of glucocorticoids, a second neural pathway mediated by the SNS allows the CNS to 'steer' innate immune responses between pro-inflammatory and antiviral programmes[16,17]. The neural fibres of the SNS distribute the neurotransmitter noradrenaline into tissue microenvironments in which immune response gene transcription occurs, including all primary and secondary lymphoid organs, the vasculature and perivascular tissues, and most visceral organs and musculoskeletal structures[18]. Noradrenaline modulates leukocyte gene expression via stimulation of β-adrenergic receptors, which are associated with the signalling cascade that involves $G\alpha_s$, adenylyl cyclase, cyclic AMP and protein kinase A[18]. β-adrenergic signalling was initially found to modulate adaptive immune responses by stimulating the transcription of T helper 2 (T_H2)-type cytokine genes (such as *IL4* and *IL5*) and suppressing the expression of T_H1-type genes (such as *IFNG* and *IL12B*)[19–21]. Recent studies have discovered a similar SNS-mediated steering of innate immune response programmes, which involves suppression of type I IFN-mediated antiviral responses[17] and upregulated transcription of pro-inflammatory cytokine genes (such as *IL1B*, *IL6* and *TNF*)[16,22].

Box 1 | **Neural regulation of the innate immune response**

Several molecular pathways allow the central nervous system (CNS) to regulate the transcription of immune response genes in peripheral tissues[3]. These mechanisms include:

- Hypothalamic–pituitary–adrenal axis production of glucocorticoids, which circulate throughout the body to alter a variety of metabolic and developmental processes, in addition to suppressing both pro-inflammatory and antiviral immune response gene programmes;
- Sympathetic nervous system (SNS) innervation of primary and secondary lymphoid organs. This delivers the neurotransmitter noradrenaline directly into parenchymal tissues involved in haematopoiesis and interactions between antigen-presenting cells and lymphocytes[18];
- SNS innervation of the vasculature and peripheral organs and tissues. This releases noradrenaline into the local microenvironment of many acute and chronic inflammatory responses;
- SNS innervation of the adrenal gland. This releases the hormone adrenaline into systemic circulation, which suppresses type I interferon-mediated antiviral responses[17] and upregulates transcription of pro-inflammatory cytokines[23];
- Efferent neural distribution into peripheral tissues of pain-related neuropeptides, enteric system-regulating neuropeptides and a diverse array of other physiologically specialized neuromodulators that can stimulate receptors present on cells of the innate and adaptive immune systems;
- CNS-mediated release of circulating mediators, such as growth hormone, insulin-like growth factor, endogenous opioids and a diverse range of other hormones that can affect cells of the innate and adaptive immune systems.

Activation of the SNS has also been found to alter the production and trafficking of innate immune cells, for example through the upregulation of myelopoiesis and the mobilization of haematopoietic stem cells, natural killer cells and splenic neutrophils and monocytes[18]. Collectively, these studies of neuro–immune regulation have provided new insights into the mechanistic relationships between the cellular and microbial microenvironment in which immune responses have traditionally been analysed and the broader macroenvironment of the host body and its surrounding social and physical ecology, as perceived by the CNS[6,23,24] (BOX 1).

Neural influences on disease. Epidemiological studies have long identified a link between adverse social and environmental conditions — such as the death of a spouse, low socio-economic status or social isolation — and an increased risk of infectious disease (presumably owing to insufficient expression of immune response genes). The risk of inflammation-associated cardiovascular, autoimmune, neurodegenerative and neoplastic diseases is also increased (presumably owing to excessive expression of immune response genes)[7,16,25,26]. Efforts to account for this pattern of infectious versus inflammation-associated disease risk based on glucocorticoid-mediated suppression of an immune response were obviously unsuccessful, but the discovery that the SNS could simultaneously inhibit antiviral genes and activate pro-inflammatory genes has provided a more plausible mechanistic explanation.

Laboratory animal and human studies have confirmed that experimental induction of acute psychological stress can increase circulating levels of IL-6 and IL-1β[27], activate NF-κB in peripheral blood mononuclear cells[27,28] and prime leukocytes for increased *ex vivo* production of pro-inflammatory cytokines in response to stimulation by the PAMP lipopolysaccharide (LPS) and other Toll-like receptor ligands[5,29,30]. Some of these effects may be mediated by mobilization of specific leukocyte subsets[31], but their net effect is to acutely increase the pro-inflammatory potential of the circulating innate immune system.

Additional insights into the immunological effects of long-term social stress have come from transcriptional profiling of circulating leukocytes in human populations[6,23,26,32] and experimental analyses of repeated social threat in animal models (such as encountering an aggressive intruder)[5,33,34]. People confronting long-term social adversities — such as the mortal illness of a spouse, low socio-economic status, post-traumatic stress disorder or long-term social isolation — have repeatedly been found to show increased expression of pro-inflammatory immune response genes, despite the presence of stable or elevated glucocorticoid levels[6,23,26,32,35].

Promoter-based bioinformatic analysis of the transcription factors involved in these responses suggests a genome-wide reduction in glucocorticoid-mediated transcription (not just among immune response genes) as a mechanistic explanation for this apparent paradox. Reduced levels of

Box 2 | **Inflammatory regulation of brain function**

Several molecular pathways allow peripherally generated pro-inflammatory signals to alter neural activity in the central nervous system (CNS). These mechanisms include:

- Interaction of circulating cytokines with brain cytokine receptors in circumventricular organs that lack a functional blood–brain barrier;
- Stimulation of brain vascular endothelial cells to release second messengers that stimulate subsequent cytokine production within the brain;
- Active transport of cytokines across the blood–brain barrier via carrier molecules;
- Peripheral inflammatory stimulation of afferent nerves that subsequently stimulate CNS tissues to produce cytokines.

Brain structures that show functional alterations in response to cytokine signalling include:

- The hypothalamus, which has a key role in the regulation of systemic physiological function and organism-level biobehavioural dynamics (such as metabolism, sleep and feeding);
- The amygdala, which mediates fear- or threat-related responses and processes social information;
- The hippocampus, which has a key role in learning and short-term memory, general information processing, spatial information processing, and navigation and mobility;
- The pre-frontal cortex, which is involved in complex information processing and planning;
- The anterior cingulate cortex, which is involved in a diverse array of cognitive–emotional interactions;
- The ventral striatum, which is involved in positive motivation and reward.

In many cases, cytokines directly interact with receptors in one brain structure (for example, the brainstem), which subsequently influences the functional activity of other brain structures (for example, the hypothalamus) via distant neural projections[80].

glucocorticoid-mediated gene transcription despite elevated circulating glucocorticoid levels have also been observed in animal models of chronic social threat[5,33,34] and appear to reflect a functional desensitization of the glucocorticoid receptor[15]. As a result of reduced glucocorticoid-mediated feedback inhibition, gene transcription shifts towards increased NF-κB- and AP1-mediated pro-inflammatory gene expression both under basal conditions and in response to stimulation by PAMPs. Recent analyses suggest that chronic threat-induced glucocorticoid receptor desensitization may stem from increased myelopoietic generation of immature LY6C^{hi} monocytes (CD16^{-} monocytes in humans) that express constitutively high levels of mitogen-activated protein kinases[33,34], which constitutively inhibit glucocorticoid receptor function[15]. A similar desensitization of glucocorticoid receptor genomic signalling has been observed in monocytes from humans confronting extended social adversity[26].

Transcriptome analyses of leukocytes from humans undergoing chronic social adversity have also begun to identify some of the specific neurobehavioural pathways through which stressful life circumstances affect innate immune responses. Wake–sleep cycles have emerged as prominent regulators of inflammatory biology, with experimental sleep restriction studies showing upregulated leukocyte expression of pro-inflammatory cytokine genes and increased NF-κB activity[36,37]. Observational studies have also identified elevated levels of C-reactive protein and other inflammation-related biomarkers in night-shift workers, insomniacs and people suffering poor sleep duration or quality[38]. Experimentally induced sleep loss (whole night) or restriction (partial reduction over several days) has also been found to increase circulating pro-inflammatory biomarkers[39]. These effects are especially pronounced in females[37,40], possibly owing to sex difference in SNS upregulation of IL-6 production[41], and this might contribute to sex differences in the incidence of inflammation-related behavioural and autoimmune diseases.

In sum, the CNS orchestrates the perception of the external physical and social environment and the evaluation of environmental conditions as threatening versus salutary. In cases of threat, the CNS activates stress signalling pathways (such as the HPA axis and the SNS) to regulate multiple internal physiological processes, including broad patterns of transcriptional activity in innate immune cells. Activation of the HPA axis inhibits both antiviral and pro-inflammatory gene modules, whereas SNS activation suppresses antiviral responses while stimulating pro-inflammatory genes. In turn, circulating pro-inflammatory cytokines evoke a glucocorticoid-mediated negative feedback response from the CNS, raising the possibility that other brain-mediated processes might also be altered.

Inflammatory regulation of behaviour

Several molecular signalling pathways have been identified to convey peripheral pro-inflammatory and antiviral signals into the brain[3,42] (BOX 2). Within the brain, pro-inflammatory cytokines decrease the activity of key behaviour-modulating neurotransmitters, including noradrenaline, dopamine and serotonin[43]. Moreover, these cytokines activate physiological and behavioural responses, such as fever and social withdrawal, which function together with leukocyte activation dynamics to limit the spread of infectious disease both within and between individuals[3,44,81].

Sickness. Prostaglandin E2 released from brain endothelial cells is well known to trigger CNS-mediated febrile and metabolic responses to infection[3]. Recent studies also show that pro-inflammatory cytokines can activate the CNS to produce a broader array of 'sickness behaviours', which include emotional alterations (anhedonia, fatigue and dysphoria), reductions in exploratory and reward-seeking motivation, altered cognitive and motor function, sleep alterations and reduced social and reproductive motivation[3,44]. These behaviours are triggered in part via IL-1 receptors in the hypothalamus and hippocampus[3,44]. Experimental administration of type I IFNs or pro-inflammatory cytokines in mice has been found to activate sickness behaviour syndromes[3,44], although the exact behavioural dynamics vary somewhat with the specific triggering cytokine.

Functional neuroimaging studies in humans have begun to map the specific neural circuits associated with cytokine-induced sickness behaviours. The findings have shown altered connectivity between the subgenual anterior cingulate cortex, amygdala and medial prefrontal cortex[45,46], and a reduced ventral striatum response to reward cues[47]. The functions of these areas of the brain are described in BOX 2. Given the strong evolutionary conservation of cytokine-induced sickness behaviour[3,44], these dynamics appear to play a key role in coordinating the overall mammalian response to acute infection by regulating systemic physiological processes and altering behaviour. Such physiological or behavioural modifications include redirecting energy resources to the immune response, reducing circulating iron levels, raising the body temperature above the optimal levels for some pathogens, immobilization to conserve energy and avoid predation, and reducing social and/or reproductive contact to limit the spread of infection[3,44,81].

Depression. Sickness behaviours are highly reminiscent of some common adverse behavioural syndromes with poorly understood aetiology, suggesting that dysregulated activation of cytokine-mediated sickness behaviours might underlie some cases of medically unexplained fatigue, sleep impairment or major depressive disorder (MDD)[43]. Consistent with this hypothesis, epidemiological studies have linked IL-6 and TNF levels with the risk of developing MDD[48], and documented increased rates of MDD in clinical conditions involving high levels of inflammation (for example, in patients with cancer)[43,49].

Pharmacological administration of IFNα to patients with cancer induces an array of MDD symptoms, including anhedonia and sadness, disturbed sleep, fatigue and loss of appetite[43,50,51]. Conversely, pharmacological antagonism of TNF has been shown to reduce depressive symptoms[52]. Gene polymorphisms that result in the increased expression of *IL1B* and *TNF* are associated with increased MDD risk and reduced clinical response to antidepressant medication[43,53]. Elevated circulating pro-inflammatory biomarkers such IL-6 and TNF also predict poor clinical response to antidepressant medications[43,54].

These results suggest that blockade of pro-inflammatory cytokines might diminish the risk and improve the treatment response of depression. In addition, they raise the possibility that circulating pro-inflammatory biomarkers and inflammation-related genetic polymorphisms could be used to help guide targeted therapies for specific MDD subtypes that are thought to have an inflammatory component (such as depression in older adults or in those with inflammation-associated disease). Links between inflammation and depressive symptoms have also led to the hypothesis that contemporary increases in the prevalence of MDD may stem from dysregulated pro-inflammatory signalling that is due to the decreased exposure to tolerogenic microorganisms in modern industrialized societies (a psychiatric version of the 'hygiene hypothesis')[55].

Sleep. Pro-inflammatory cytokines and type I IFNs also have a role in the homeostatic regulation of sleep[56]. Animal genetic studies and LPS administration studies in humans[56,57] have linked changes in non-rapid eye movement sleep (NREM sleep) to elevated levels of circulating type I IFNs and pro-inflammatory cytokines. Moreover, pharmacological administration of IL-6 and IFNα in humans results in decreases in NREM slow-wave sleep and complementary increases in REM sleep[56,58], although animals studies show that other cytokines (such as TNF) increase NREM sleep and decrease REM sleep[56]. Elevated daytime levels of TNF have also been linked with sleepiness, fatigue and altered sleep architecture, and pharmacological antagonism of TNF can reduce these effects[59,60]. TNF antagonism can also normalize REM sleep levels (for example, in abstinent alcohol-dependent individuals, who have elevated amounts of REM sleep)[61].

Given the substantial fraction of time we spend asleep and the general immunological activation that occurs during sleep[38], as well as the epidemiological links between abnormally high levels of REM sleep and mortality[62], regulation of sleep architecture by the innate immune system may play a substantial role in structuring overall inflammatory homeostasis[38,56].

Fatigue. Pro-inflammatory gene expression can induce profound fatigue during waking hours[63] — one of the most debilitating burdens of chronic inflammatory disease. Clinical studies have documented links between inflammation-related biomarkers and the development of fatigue both in healthy older adults[64] and in individuals with inflammatory diseases such as multiple sclerosis[65], Sjogren's syndrome[66], rheumatoid arthritis[67] and cancer[68]. Patients with cancer often experience substantial increases in NF-κB inflammatory signalling owing to tumour-derived cytokines, the effects of cancer treatment (for example, radiation and chemotherapy) on tissue[69] and therapeutic administration of type I IFNs[49].

Even when chemotherapy and/or radiation treatments are completed, approximately one-third of breast cancer survivors suffer from persistent, medically unexplained fatigue. This fatigue is associated with increased circulating biomarkers of IL-1β and IL-6 activity[70], increased NF-κB-mediated gene transcription[71] and enhanced IL-6 and TNF production in response to *ex vivo* LPS-mediated stimulation of circulating leukocytes[70]. Fatigue in breast cancer survivors is also particularly elevated among patients with *IL1B*, *IL6* or *TNF* polymorphisms that cause high-level expression of the respective cytokines[72]. Pharmacological antagonism of TNF can reduce chemotherapy-related fatigue[60], confirming a key functional role for pro-inflammatory cytokines in the aetiology of cancer-associated fatigue.

In sum, peripheral innate immune responses can influence CNS functions (including neurotransmitter metabolism, regional brain activity and sleep–wake cycles) and behavioural processes (including depression, sleep and fatigue), and this has implications for neuropsychiatric disease.

Glossary

Conspecific
Belonging to the same species.

Glucocorticoids
A class of steroid hormones that are involved in carbohydrate, protein and fat metabolism. These hormones are anti-inflammatory and immunosuppressive.

Hypothalamic–pituitary–adrenal
(HPA). This term refers to a complex set of direct influences and feedback interactions between the hypothalamus, the pituitary gland (a pea-shaped structure located below the hypothalamus) and the adrenal glands (small, conical organs on top of the kidneys).

Non-rapid eye movement sleep
(NREM sleep). The sleep stages 1–3 (previously known as stages 1–4) are collectively referred to as NREM sleep. Rapid eye movement (REM) sleep is not included. There are distinct electroencephalographic and other characteristics seen in each stage, and there is usually little or no eye movement during NREM sleep. Dreaming is rare during NREM sleep, and muscles are not paralyzed as in REM sleep.

Social ecology
A broad range of complex physical and symbolic features of the environment that are created by the presence of conspecifics (including social structures such as cultural systems or socio-economic status), as well as physical processes, such as transmission of communicable diseases, provision of medical care or physical aggression.

Sympathetic nervous system
(SNS). One of three parts of the autonomic nervous system (along with the enteric and parasympathetic systems). The SNS serves to mobilize the body's resources during flight-or-flight stress responses.

The neuro–immune circuit

Understanding and controlling innate immune responses is complicated by the fact that immune response genes are regulated by both external influences (through neural activity) and internal factors (such as pathogens and cell damage)[16] (FIG. 2). Furthermore, the reciprocal regulation of neural activity by immune response genes would seem to hopelessly complicate matters. However, such reciprocal regulation provides exactly the feedback required by dynamic systems theory to stabilize the circuit as a whole, particularly given the fact that CNS function is itself regulated by both the internal (inflammatory) and external (ecological) environments simultaneously.

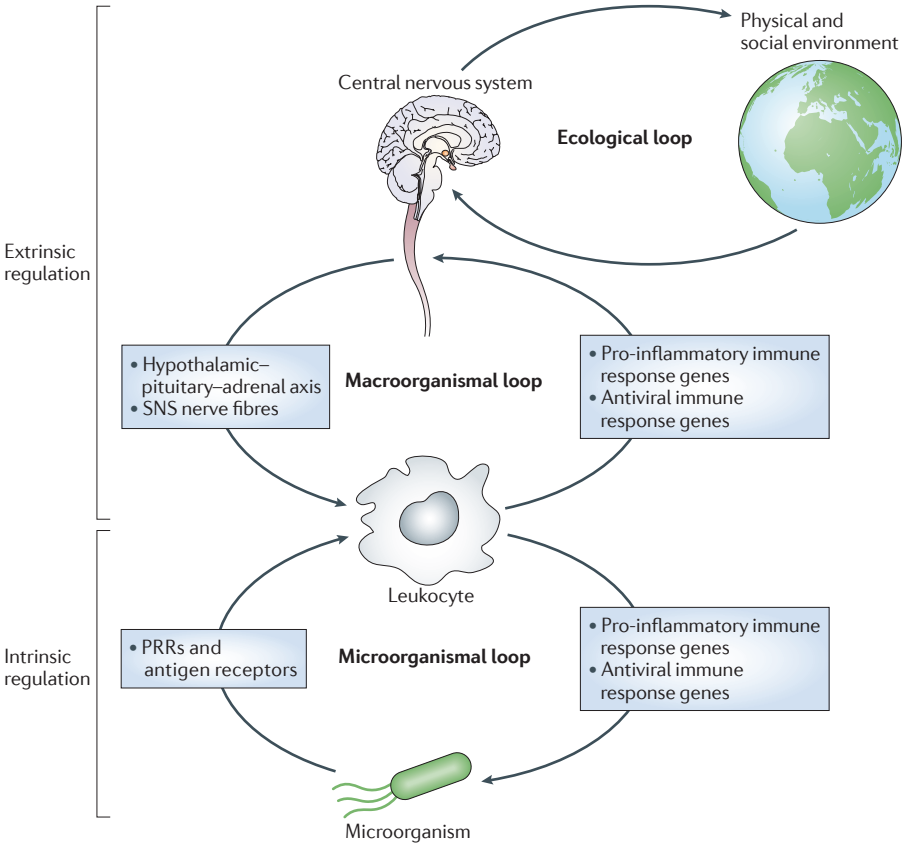

Figure 2 | **Multi-circuit control of the innate immune transcriptome.** Leukocyte transcription of immune response gene programmes is regulated by both intrinsic immunological signals representing local tissue and microbial conditions and extrinsic neural and endocrine signals representing global physiological and environmental conditions. Intrinsic circuits detect microorganisms via pattern recognition receptors (PRRs) and stimulate pro-inflammatory and antiviral immune response gene programmes via transcription factors such as nuclear factor-κB (NF-κB) and interferon regulatory factors (IRFs). The resulting production of innate immune effector molecules reduces microbial burden, and thereby feeds back to reduce PRR and antigen receptor signalling and immune response gene transcription. Extrinsic regulation of immune response gene transcription is mediated by central nervous system (CNS) integration of information regarding general physiological and ecological conditions. This can either globally suppress immune response gene transcription via the hypothalamic–pituitary–adrenal axis or steer immune response gene transcriptional profiles away from antiviral programmes and towards more robust pro-inflammatory gene expression. CNS-mediated transduction of information from the social and physical ecology allows extra-organismal environmental conditions to indirectly regulate the immune response gene transcriptional profiles of immune cells. SNS, sympathetic nervous system.

What the organism as a whole gains by superimposing the 'extrinsic' CNS–leukocyte–CNS regulatory circuit on the more immunologically fundamental 'intrinsic' microorganism–leukocyte–microorganism circuit is the opportunity to coordinate the microbiological battle between pathogen and immune response within the context of the broader macrobiological conditions that affect overall survival and natural selection. For example, this crosstalk allows the organism to suppress the immobilizing effects of inflammation and sickness behaviour to facilitate fight-or-flight responses to predation or conspecific aggression. There are lots of other ways to die or fail to reproduce besides infection, and an optimal immune response needs to be adapted to the total array of conditions that confront the organism rather than blindly pursuing its microbial antagonists. The fitness advantage of innate immune regulation by the extrinsic circuit is demonstrated by the reduced survival of organisms that are challenged with pathogens following blockade of CNS signalling to leukocytes, as well as by the reduced individual and population-level resistance to infectious disease in the absence of leukocyte signalling to the CNS[44,81]. These whole-organism fitness implications provide a teleological rationale for the evolution of CNS–immune interactions, as well as new opportunities for therapeutic intervention.

Biobehavioural control of inflammation

Several behavioural interventions have been applied to modulate pro-inflammatory signalling in the innate immune system. Randomized controlled trials have documented reductions in pro-inflammatory cytokine activity following several types of behavioural intervention (BOX 3), including cognitive behavioural therapy[73], aerobic exercise[74], meditation[75] and Tai Chi[76,77]. The regulation of leukocytes by the CNS may also contribute to the neurobiological impact of behavioural interventions if, for example, CNS-mediated reductions in peripheral inflammation feed back to reciprocally reduce sickness behaviour. SNS-mediated regulation of pro-inflammatory and antiviral genes also suggests potential neuropharmacological strategies for mitigating the long-observed effects of environmental adversity on disease risk[4]. For example, β-adrenergic receptor blockade has been shown in animal models to reverse several stress-induced alterations in immune response gene transcription[22,34,78]. Therefore, it may provide a strategy for redirecting the leukocyte transcriptome via the induction of multiple *trans*-acting transcription factors by β-adrenergic receptors.

Teleological considerations

Perhaps the most striking implication of neuro–immune circuitry is the possibility that the innate immune response may be controlled in part by an anticipation of future environmental conditions by the CNS, in addition to its regulation by the present microbial and host cell environment. Allostatic theories of physiology[4] propose that natural selection favours 'prepared' physiological systems that actively anticipate homeostatic challenges and proactively alter their function to mitigate these challenges. Given that the HPA axis and the SNS both regulate leukocyte gene transcription, and both show CNS-mediated anticipatory activation[4], CNS-mediated perceptions of potential threat may be sufficient to alter the basal leukocyte transcriptome in ways that subsequently affect responses to pathogens (for example, by altering inflammatory responses in myeloid lineage cells)[5,6,16,26,78]. This 'forward-looking' view of the immune system represents a significant departure from traditional pathogen- or damage-reactive models of immune regulation. But it does provide a parsimonious account of epidemiological data that link social–ecological conditions to immune response gene expression and disease resistance, as well as a plausible evolutionary rationale for the specific pattern of transcriptional alterations observed.

Box 3 | **Behavioural interventions that modulate inflammation**

Several types of behavioural intervention have been found to reduce cellular and plasma biomarkers of inflammation.

Cognitive behavioural therapy (CBT)
CBT uses a programme of specific verbal and/or written protocols that guide participants through exercises designed to change specific targeted thoughts, feelings and behavioural patterns. As an example, CBT for depression involves a restructuring of dysfunctional thoughts and ruminations that contribute to negative perceptions of self and the environment. Benefits on the cellular expression of pro-inflammatory cytokines were found after 16 weeks in individuals whose depression was improved[73].

Aerobic exercise
This involves moderate-intensity physical activities, such as walking for 20–30 minutes per day, which provides aerobic training without activating anaerobic respiration. Benefits on inflammatory markers were found after 12 months[74].

Meditation
Meditation involves thought-focusing and relaxation exercises that calm cognitive and emotional processes and reduce sympathetic nervous system activity and related peripheral physiological processes. The practices found to alter inflammatory responses to stress used concentrative and mindfulness exercises to establish focus and awareness, followed by analytical exercises designed to challenge unexamined assumptions regarding feelings and actions towards others, with a focus on generating spontaneous empathy and compassion for themselves and others. Benefits on inflammatory markers were found after 6 weeks[75].

Tai Chi Chih
Tai Chi Chih is a westernized form of the Chinese martial art Tai Chi, which involves slow movement and meditation. It combines the practice of 20 aerobic exercises with relaxed breathing, attentional focus and body awareness. Benefits on inflammatory markers were found after 25 weeks[76].

Biomarkers affected by such interventions include indicators of pro-inflammatory cytokine activity (for example, C-reactive protein) and *ex vivo* cellular production of tumour necrosis factor and interleukin-1β in response to lipopolysaccharide stimulation.

Social ecology of immune responses. Specific patterns of neural and endocrine activity are associated with distinctive social or ecological conditions, and these conditions affect the nature of the injuries and pathogens we confront. Thus, a natural selective pressure arises for immune response genes to develop a sensitivity to these neural and endocrine signals[6]. Such sensitivity could explain why, for example, the SNS has evolved the capacity to steer the innate immune transcriptome away from antiviral responses and towards pro-inflammatory responses. As threat-induced SNS signalling has historically been associated with a near-term increase in the likelihood of wound-mediated bacterial infection (for example, via predation of isolated organisms or conspecific hostility), SNS priming of the pro-inflammatory gene programme would seem to be highly adaptive.

By contrast, viral infections disseminate predominately through close social contact. Therefore, there would be little need for antiviral priming under hostile or isolated social conditions, but a much greater value in priming an antiviral transcriptional bias under long-term salutary social conditions (when SNS activity levels are generally low). Similarly, in response to more profound threats — such as trauma, starvation or exhaustion — that markedly activate the HPA axis, it makes good evolutionary sense for the body to redirect resources away from both types of long-term antimicrobial defence (antiviral and pro-inflammatory) in favour of more immediate physiological survival needs.

Conclusion

The whole-organism fitness advantages of a forward-looking, neurally regulated and neurally regulating innate immune response have clarified a variety of previously puzzling phenomena. These include: environmentally dependent variations in the basal transcriptome of unstimulated immune cells[6,16,23,26,32,35,36,79]; the striking co-morbidity of neuropsychiatric symptoms and inflammatory disease; the biological rationale for specific HPA- and SNS-related patterns of immune response gene transcription; and the distinctive impact of effector systems of the CNS (the HPA axis and the SNS) on peripheral myeloid lineage cells. As the relationship between environmental conditions and infectious disease has changed over the past century[10], the historically beneficial crosstalk between the CNS and the immune system has become misaligned with our current ecology. Now, this crosstalk may allow abstract non-physical threats to induce inflammation-related cardiovascular, neurodegenerative and neoplastic diseases, while undermining our innate antiviral defences. Nevertheless, it may still be possible to harness reciprocal neural–immune regulation through pharmacological or behavioural interventions to redirect the basic transcriptional stance of the innate immune system and more effectively accommodate the health ecology that we now inhabit.

Michael R. Irwin and Steven W. Cole are at the Cousins Center for Psychoneuroimmunology, Semel Institute for Neuroscience, 300 UCLA Medical Plaza, University of California, Los Angeles, California 90095-7076, USA.

Steven W. Cole is also at the Department of Medicine, Division of Haematology-Oncology, Jonsson Comprehensive Cancer Center, and the UCLA Molecular Biology Institute, University of California, Los Angeles, California, USA.

Correspondence to M.R.I.
e-mail: mirwin1@ucla.edu

doi:10.1038/nri3042
Published online 5 August 2011

1. Matzinger, P. Friendly and dangerous signals: is the tissue in control? *Nature Immunol.* **8**, 11–13 (2007).
2. Glaser, R. & Kiecolt-Glaser, J. K. Stress-induced immune dysfunction: implications for health. *Nature Rev. Immunol.* **5**, 243–251 (2005).
3. Dantzer, R., O'Connor, J. C., Freund, G. G., Johnson, R. W. & Kelley, K. W. From inflammation to sickness and depression: when the immune system subjugates the brain. *Nature Rev. Neurosci.* **9**, 46–56 (2008).
4. McEwen, B. S. Physiology and neurobiology of stress and adaptation: central role of the brain. *Physiol. Rev.* **87**, 873–904 (2007).
5. Powell, N. D., Mays, J. W., Bailey, M. T., Hanke, M. L. & Sheridan, J. F. Immunogenic dendritic cells primed by social defeat enhance adaptive immunity to influenza A virus. *Brain Behav. Immun.* **25**, 46–52 (2011).
6. Cole, S. W., Hawkley, L. C., Arevalo, J. M. & Cacioppo, J. T. Transcript origin analysis identifies antigen-presenting cells as primary targets of socially regulated gene expression in leukocytes. *Proc. Natl Acad. Sci. USA* **108**, 3080–3085 (2011).
7. Cohen, S., Janicki-Deverts, D. & Miller, G. E. Psychological stress and disease. *JAMA* **298**, 1685–1687 (2007).
8. Amit, I. *et al.* Unbiased reconstruction of a mammalian transcriptional network mediating pathogen responses. *Science* **326**, 257–263 (2009).
9. Decker, T., Muller, M. & Stockinger, S. The yin and yang of type I interferon activity in bacterial infection. *Nature Rev. Immunol.* **5**, 675–687 (2005).
10. Finch, C. E. Evolution in health and medicine Sackler colloquium. Evolution of the human lifespan and diseases of aging: roles of infection, inflammation, and nutrition. *Proc. Natl Acad. Sci. USA* **1**, 1718–1724 (2010).
11. Sapolsky, R., Rivier, C., Yamamoto, G., Plotsky, P. & Vale, W. Interleukin-1 stimulates the secretion of hypothalamic corticotropin-releasing factor. *Science* **238**, 522–524 (1987).
12. Berkenbosch, F., VanOers, J., DelRey, A., Tilders, F. & Besedovsky, H. Corticotropin-releasing factor-producing neurons in the rat activated by interleukin-1. *Science* **238**, 524–526 (1987).
13. Besedovsky, H., del Rey, A., Sorkin, E. & Dinarello, C. A. Immunoregulatory feedback between interleukin-1 and glucocorticoid hormones. *Science* **233**, 652–654 (1986).
14. Rhen, T. & Cidlowski, J. A. Antiinflammatory action of glucocorticoids — new mechanisms for old drugs. *N. Engl. J. Med.* **353**, 1711–1723 (2005).
15. Pace, T. W., Hu, F. & Miller, A. H. Cytokine-effects on glucocorticoid receptor function: relevance to glucocorticoid resistance and the pathophysiology and treatment of major depression. *Brain Behav. Immun.* **21**, 9–19 (2007).
16. Cole, S. *et al.* Computational identification of gene–social environment interaction at the human *IL6* locus. *Proc. Natl Acad. Sci. USA* **107**, 5681–5686 (2010).

17. Collado-Hidalgo, A., Sung, C. & Cole, S. Adrenergic inhibition of innate anti-viral response: PKA blockade of type I interferon gene transcription mediates catecholamine support for HIV-1 replication. *Brain Behav. Immun.* **20**, 552–563 (2006).
18. Nance, D. M. & Sanders, V. M. Autonomic innervation and regulation of the immune system (1987–2007). *Brain Behav. Immun.* **21**, 736–745 (2007).
19. Lee, H. J. *et al.* GATA-3 induces T helper cell type 2 (Th2) cytokine expression and chromatin remodeling in committed Th1 cells. *J. Exp. Med.* **192**, 105–115 (2000).
20. Panina-Bordignon, P. *et al.* β_2-agonists prevent Th1 development by selective inhibition of interleukin 12. *J. Clin. Invest.* **100**, 1513–1519 (1997).
21. Cole, S. W., Korin, Y. D., Fahey, J. L. & Zack, J. A. Norepinephrine accelerates HIV replication via protein kinase A-dependent effect on cytokine production. *J. Immunol.* **161**, 610–616 (1998).
22. Grebe, K. M. *et al.* Cutting edge: sympathetic nervous system increases proinflammatory cytokines and exacerbates influenza A virus pathogenesis. *J. Immunol.* **184**, 540–544 (2009).
23. Cole, S. W. *et al.* Social regulation of gene expression in human leukocytes. *Genome Biol.* **8**, 1–13 (2007).
24. Sloan, E. K. *et al.* Social stress enhances sympathetic innervation of primate lymph nodes: mechanisms and implications for viral pathogenesis. *J. Neurosci.* **27**, 8857–8865 (2007).
25. Kiecolt-Glaser, J. K. *et al.* Chronic stress and age-related increases in the proinflammatory cytokine IL-6. *Proc. Natl Acad. Sci. USA* **100**, 9090–9095 (2003).
26. Miller, G. E. *et al.* A functional genomic fingerprint of chronic stress in humans: blunted glucocorticoid and increased NF-κB signaling. *Biol. Psychiatry* **64**, 266–272 (2008).
27. Pace, T. W. *et al.* Increased stress-induced inflammatory responses in male patients with major depression and increased early life stress. *Am. J. Psychiatry* **163**, 1630–1633 (2006).
28. Bierhaus, A. *et al.* A mechanism converting psychosocial stress into mononuclear cell activation. *Proc. Natl Acad. Sci. USA* **100**, 1920–1925 (2003).
29. Goebel, M. U., Mills, P. J., Irwin, M. R. & Ziegler, M. G. Interleukin-6 and tumor necrosis factor-α production after acute psychological stress, exercise, and infused isoproterenol: differential effects and pathways. *Psychosom. Med.* **62**, 591–598 (2000).
30. Bower, J. E. *et al.* Inflammatory responses to psychological stress in fatigued breast cancer survivors: relationship to glucocorticoids. *Brain Behav. Immun.* **21**, 251–258 (2007).
31. Richlin, V. A., Arevalo, J. M., Zack, J. A. & Cole, S. W. Stress-induced enhancement of NF-κB DNA-binding in the peripheral blood leukocyte pool: effects of lymphocyte redistribution. *Brain Behav. Immun.* **18**, 231–237 (2004).
32. Miller, G. E. *et al.* Low early-life social class leaves a biological residue manifested by decreased glucocorticoid and increased proinflammatory signaling. *Proc. Natl Acad. Sci. USA* **106**, 14716–14721 (2009).
33. Engler, H., Bailey, M. T., Engler, A. & Sheridan, J. F. Effects of repeated social stress on leukocyte distribution in bone marrow, peripheral blood and spleen. *J. Neuroimmunol.* **148**, 106–115 (2004).
34. Wohleb, E. S. *et al.* β-adrenergic receptor antagonism prevents anxiety-like behavior and microglial reactivity induced by repeated social defeat. *J. Neurosci.* **31**, 6277–6288 (2011).
35. Chen, E. *et al.* Genome-wide transcriptional profiling linked to social class in asthma. *Thorax* **64**, 38–43 (2009).
36. Irwin, M. R., Wang, M., Campomayor, C. O., Collado-Hidalgo, A. & Cole, S. Sleep deprivation and activation of morning levels of cellular and genomic markers of inflammation. *Arch. Intern. Med.* **166**, 1756–1762 (2006).
37. Irwin, M. R. *et al.* Sleep loss activates cellular inflammatory signaling. *Biol. Psychiatry* **64**, 538–540 (2008).
38. Motivala, S. & Irwin, M. R. Sleep and immunity: cytokine pathways linking sleep and health outcomes. *Curr. Dir. Psychol. Sci.* **16**, 21–25 (2007).
39. Meier-Ewert, H. K. *et al.* Effect of sleep loss on C-reactive protein, an inflammatory marker of cardiovascular risk. *J. Am. Coll. Cardiol.* **43**, 678–683 (2004).
40. Irwin, M. R., Carrillo, C. & Olmstead, R. Sleep loss activates cellular markers of inflammation: sex differences. *Brain Behav. Immun.* **24**, 54–57 (2010).
41. O'Connor, M. F., Motivala, S. J., Valladares, E. M., Olmstead, R. & Irwin, M. R. Sex differences in monocyte expression of IL-6: role of autonomic mechanisms. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **293**, R145–R151 (2007).
42. Watkins, L. R. & Maier, S. F. Implications of immune-to-brain communication for sickness and pain. *Proc. Natl Acad. Sci. USA* **96**, 7710–7713 (1999).
43. Miller, A. H., Maletic, V. & Raison, C. L. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. *Biol. Psychiatry* **65**, 732–741 (2009).
44. Hart, B. L. Biological basis of the behavior of sick animals. *Neurosci. Biobehav. Rev.* **12**, 123–137 (1988).
45. Harrison, N. A. *et al.* Inflammation causes mood changes through alterations in subgenual cingulate activity and mesolimbic connectivity. *Biol. Psychiatry* **66**, 407–414 (2009).
46. Eisenberger, N. I., Inagaki, T. K., Rameson, L. T., Mashal, N. M. & Irwin, M. R. An fMRI study of cytokine-induced depressed mood and social pain: the role of sex differences. *Neuroimage* **47**, 881–890 (2009).
47. Eisenberger, N. I. *et al.* Inflammation-induced anhedonia: endotoxin reduces ventral striatum responses to reward. *Biol. Psychiatry* **68**, 748–754 (2010).
48. Gimeno, D. *et al.* Associations of C-reactive protein and interleukin-6 with cognitive symptoms of depression: 12-year follow-up of the Whitehall II study. *Psychol. Med.* **39**, 413–423 (2009).
49. Miller, A. H., Ancoli-Israel, S., Bower, J. E., Capuron, L. & Irwin, M. R. Neuroendocrine–immune mechanisms of behavioral comorbidities in patients with cancer. *J. Clin. Oncol.* **26**, 971–982 (2008).
50. Capuron, L. *et al.* Neurobehavioral effects of interferon-α in cancer patients: phenomenology and paroxetine responsiveness of symptom dimensions. *Neuropsychopharmacology* **26**, 643–652 (2002).
51. Capuron, L., Ravaud, A. & Dantzer, R. Early depressive symptoms in cancer patients receiving interleukin 2 and/or interferon α-2b therapy. *J. Clin. Oncol.* **18**, 2143–2151 (2000).
52. Tyring, S. *et al.* Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomised phase III trial. *Lancet* **367**, 29–35 (2006).
53. Wong, M. L., Dong, C., Maestre-Mesa, J. & Licinio, J. Polymorphisms in inflammation-related genes are associated with susceptibility to major depression and antidepressant response. *Mol. Psychiatry* **13**, 800–812 (2008).
54. Benedetti, F., Lucca, A., Brambilla, F., Colombo, C. & Smeraldi, E. Interleukin-6 serum levels correlate with response to antidepressant sleep deprivation and sleep phase advance. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **26**, 1167–1170 (2002).
55. Raison, C. L., Lowry, C. A. & Rook, G. A. Inflammation, sanitation, and consternation: loss of contact with coevolved, tolerogenic microorganisms and the pathophysiology and treatment of major depression. *Arch. Gen. Psychiatry* **67**, 1211–1224 (2010).
56. Imeri, L. & Opp, M. R. How (and why) the immune system makes us sleep. *Nature Rev. Neurosci.* **10**, 199–210 (2009).
57. Mullington, J. *et al.* Dose-dependent effects of endotoxin on human sleep. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **278**, R947–R955 (2000).
58. Raison, C. L. *et al.* Chronic interferon-α administration disrupts sleep continuity and depth in patients with hepatitis C: association with fatigue, motor slowing, and increased evening cortisol. *Biol. Psychiatry* **68**, 942–949 (2010).
59. Vgontzas, A. N. *et al.* Marked decrease in sleepiness in patients with sleep apnea by etanercept, a tumor necrosis factor-α antagonist. *J. Clin. Endocrinol. Metab.* **89**, 4409–4413 (2004).
60. Monk, J. P. *et al.* Assessment of tumor necrosis factor α blockade as an intervention to improve tolerability of dose-intensive chemotherapy in cancer patients. *J. Clin. Oncol.* **24**, 1852–1859 (2006).
61. Irwin, M. R., Olmstead, R., Valladares, E. M., Breen, E. C. & Ehlers, C. L. Tumor necrosis factor antagonism normalizes rapid eye movement sleep in alcohol dependence. *Biol. Psychiatry* **66**, 191–195 (2009).
62. Dew, M. A. *et al.* Healthy older adults' sleep predicts all-cause mortality at 4 to 19 years of follow-up. *Psychosom. Med.* **65**, 63–73 (2003).
63. Thomas, K. S., Motivala, S., Olmstead, R. & Irwin, M. R. Sleep depth and fatigue: role of cellular inflammatory activation. *Brain Behav. Immun.* **25**, 53–58 (2011).
64. Cho, H. J., Seeman, T. E., Bower, J. E., Kiefe, C. I. & Irwin, M. R. Prospective association between C-reactive protein and fatigue in the coronary artery risk development in young adults study. *Biol. Psychiatry* **66**, 871–878 (2009).
65. Heesen, C. *et al.* Fatigue in multiple sclerosis: an example of cytokine mediated sickness behaviour? *J. Neurol. Neurosurg. Psychiatry* **77**, 34–39 (2006).
66. Harboe, E. *et al.* Fatigue in primary Sjogren's syndrome — a link to sickness behaviour in animals? *Brain Behav. Immun.* **23**, 1104–1108 (2009).
67. Davis, M. C. *et al.* Chronic stress and regulation of cellular markers of inflammation in rheumatoid arthritis: implications for fatigue. *Brain Behav. Immun.* **22**, 24–32 (2008).
68. Schubert, C., Hong, S., Natarajan, L., Mills, P. J. & Dimsdale, J. E. The association between fatigue and inflammatory marker levels in cancer patients: a quantitative review. *Brain Behav. Immun.* **21**, 413–427 (2007).
69. Bower, J. E. *et al.* Inflammatory biomarkers and fatigue during radiation therapy for breast and prostate cancer. *Clin. Cancer Res.* **15**, 5534–5540 (2009).
70. Collado-Hidalgo, A., Bower, J. E., Ganz, P. A., Cole, S. W. & Irwin, M. R. Inflammatory biomarkers for persistent fatigue in breast cancer survivors. *Clin. Cancer Res.* **12**, 2759–2766 (2006).
71. Bower, J. E., Ganz, P. A., Irwin, M. R., Arevalo, J. M. & Cole, S. W. Fatigue and gene expression in human leukocytes: increased NF-κB and decreased glucocorticoid signaling in breast cancer survivors with persistent fatigue. *Brain Behav. Immun.* **25**, 147–150 (2011).
72. Collado-Hidalgo, A., Bower, J. E., Ganz, P. A., Irwin, M. R. & Cole, S. W. Cytokine gene polymorphisms and fatigue in breast cancer survivors: early findings. *Brain Behav. Immun.* **22**, 1197–1200 (2008).
73. Zautra, A. J. *et al.* Comparison of cognitive behavioral and mindfulness meditation interventions on adaptation to rheumatoid arthritis for patients with and without history of recurrent depression. *J. Consult. Clin. Psychol.* **76**, 408–421 (2008).
74. Nicklas, B. J. *et al.* Exercise training and plasma C-reactive protein and interleukin-6 in elderly people. *J. Am. Geriatr. Soc.* **56**, 2045–2052 (2008).
75. Pace, T. W. *et al.* Effect of compassion meditation on neuroendocrine, innate immune and behavioral responses to psychosocial stress. *Psychoneuroendocrinology* **34**, 87–98 (2009).
76. Irwin, M. R. & Olmstead, R. Mitigating cellular inflammation in older adults. *Am. J. Geriatr. Psychiatry* (in the press).
77. Lavretsky, H. *et al.* Complementary use of Tai Chi Chih augments escitalopram treatment of geriatric depression: a randomized controlled trial. *Am. J. Geriatr. Psychiatry* 6 Mar 2011 (doi:10.1097/JGP.0b013e31820ee9ef).
78. Sloan, E. K. *et al.* The sympathetic nervous system induces a metastatic switch in primary breast cancer. *Cancer Res.* **70**, 7042–7052 (2010).
79. Idaghdour, Y. *et al.* Geographical genomics of human leukocyte gene expression variation in southern Morocco. *Nature Genet.* **42**, 62–67 (2010).
80. Ericsson, A., Kovacs, K. J. & Sawchenko, P. E. A functional anatomical analysis of central pathways subserving the effects of interleukin-1 on stress-related neuroendocrine neurons. *J. Neurosci.* **14**, 897–913 (1994).
81. Cole, S. W. in *Complex Systems Science in Biomedicine* (eds Deisboeck, T. S. & Kresh, J. Y.) 605–629 (Springer, New York, 2006).

Acknowledgements
The authors are supported by grants R01-AG034588, R01-AG026364, R01-CA119159, R01-HL079955, P30-AG028748 and R01-MH091352 (to M.R.I.); grants R01-CA116778, R01-AG033590, R21-CA138687 and P30-AG028748 (to S.W.C.); and the Cousins Center for Psychoneuroimmunology.

Competing interests statement
The authors declare no competing financial interests.

FURTHER INFORMATION
Michael R. Irwin and Steven W. Cole's homepage:
http://www.semel.ucla.edu/cousins

ALL LINKS ARE ACTIVE IN THE ONLINE PDF