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# *Brain-Organ Axis: How Stress Regulates Peripheral Immunity Through Neural Signaling*

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***Abstract.*** The immune effects of psychological stress differ across cell populations and peripheral organs. Classical endocrine and sympathetic models explain major stress responses, but the contribution of individual brain circuits to specific immune outcomes is less clear. This focused literature review compares neuroendocrine, autonomic and circuit-specific regulation of peripheral immunity through a mouse neural-circuit study and a controlled human viral-challenge study. Glucocorticoid signalling and autonomic relays affect leukocyte trafficking and inflammatory activity. In mice, motor circuits mobilise neutrophils through skeletal-muscle signals while hypothalamic circuits direct monocytes and lymphocytes towards bone marrow; in humans, greater psychological stress before controlled viral exposure is associated with higher susceptibility to respiratory infection. Location and timing affect the outcome. Stress can therefore change both the distribution of immune cells and their functional responses, with the signalling pathway involved, target tissue and timing of the response helping to explain the different consequences of acute and chronic stress and offering measurable targets for studies of neuromodulation and behavioural interventions to improve immune health.

***Keywords:*** brain-organ axis, psychological stress, peripheral immunity, neuroimmune signalling

## 1. Introduction

Psychological stress can change the distribution of immune cells, their responses and host resistance to infection, with effects that vary across organs and cell populations [1]. A synthesis of human studies associated brief laboratory stressors, short natural stressors and persistent stress with different immune response patterns [2]. In the controlled viral-challenge study by Cohen and colleagues, psychological stress measured before exposure was associated with subsequent infection and clinical colds [3]. Stress is therefore part of the biological context of an immune response, with implications for host defence. The hypothalamic-pituitary-adrenal (HPA) axis and autonomic nervous system are established routes between stress processing and the body [4], and their mediators help organisms meet immediate demands, although prolonged or repeated activation can carry physiological costs [5]. Because neural and immune communication also involves local interactions and feedback from peripheral tissues, a circulating hormone concentration captures only

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part of the response [6]. The target organ, the responding cell and the interval between stress exposure and immune measurement also matter.

Endocrine, autonomic and circuit studies describe different parts of the stress response, leaving central sources, peripheral targets and time courses difficult to compare within a single account. Drawing on ten publications, this focused review compares a mouse circuit study with a human viral-challenge study to examine how stress reaches peripheral immunity. Experimental control, stress duration and immune endpoints provide the basis for comparing pathway-specific effects and their relevance to human health, with particular attention to how timing changes their interpretation. A circuit-level explanation identifies which immune processes are under neural control, including the movement of cells between the blood and bone marrow and changes in cytokine release. These processes offer candidate readouts for intervention studies. This review contributes a comparison of central pathways, peripheral targets and response timing, distinguishing evidence for cell redistribution from evidence for immune function.

## 2. Literature review

### 2.1. HPA axis and glucocorticoid signalling

The HPA axis is an endocrine route from stress-responsive brain activity to the circulation. Neurons in the hypothalamic paraventricular nucleus release corticotropin-releasing hormone (CRH), which promotes pituitary secretion of adrenocorticotropic hormone (ACTH) and, through ACTH action on the adrenal cortex, the release of glucocorticoids. Cortisol is the principal glucocorticoid in humans, whereas corticosterone is prominent in rodent stress models. Limbic and brainstem inputs help determine recruitment of this pathway according to the nature and intensity of a stressor, and glucocorticoid feedback helps regulate its duration [4]. Central processing can therefore affect many tissues at once through glucocorticoid actions on immune-cell trafficking, inflammatory gene expression and cellular responsiveness [1, 6]. These processes require different measurements. A lower blood lymphocyte count can arise because cells have moved to another compartment, whereas reduced cytokine production reflects a change in activity and altered resistance to a pathogen is a functional outcome. Although cell distribution, cytokine production and pathogen resistance can change after the same endocrine response, each reflects a different property of peripheral immunity and therefore requires a measurement suited to that process when relating it to brain activity. These measurements cannot be treated as interchangeable indices of immune strength. Exposure duration also matters for glucocorticoids. In McEwen's account of allostasis, mediators that support adaptation can become damaging when activation is repeated, prolonged or poorly terminated, so interpreting brain-organ regulation requires attention to the exposure pattern as well as the responsiveness of the target tissue [5]. Hormone measurements after a brief challenge and during persistent stress reflect different conditions, because a shared endocrine route can act on cells with different signalling histories and response states.

### 2.2. Autonomic regulation

Sympathetic nerves provide anatomically distributed access to immune organs and their supporting tissues, where noradrenaline released at peripheral terminals can influence both leukocytes and the stromal or vascular environment through which these cells move. Thus, sympathetic output can change immune behaviour through local tissue conditions as well as through receptors on immune cells [1, 6]. Although sympathetic signalling follows a defined neural route, its immune effect

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depends on the organ and receptors involved; comparisons between studies therefore need to account for both.

The vagal inflammatory reflex is another route of neural control. Borovikova and colleagues found that electrical stimulation of the peripheral vagus reduced tumour necrosis factor (TNF) responses and attenuated shock in rats exposed to endotoxin [7]. Sensory detection and neural control of inflammation are linked in Tracey's inflammatory-reflex framework [8]. Rosas-Ballina and colleagues then identified acetylcholine-producing T cells as a relay required for suppression of TNF during vagus nerve stimulation in mice [9]. In this splenic pathway, noradrenaline from adrenergic nerves engages acetylcholine-producing T cells, and their acetylcholine acts on macrophage alpha7 nicotinic receptors; the effect on macrophage cytokine release thus depends on a sequence involving different transmitters and cell types. The experiments in endotoxin models and the inflammatory-reflex framework identify a neural route with a measurable inflammatory output; Figure 1 places this route alongside the endocrine and sympathetic mechanisms relevant to stress research. Interventions directed at a circulating hormone, an organ's nerve supply or a neural-immune relay act at different points in the response, so the immune measurement must be appropriate to the route being tested [7-9].

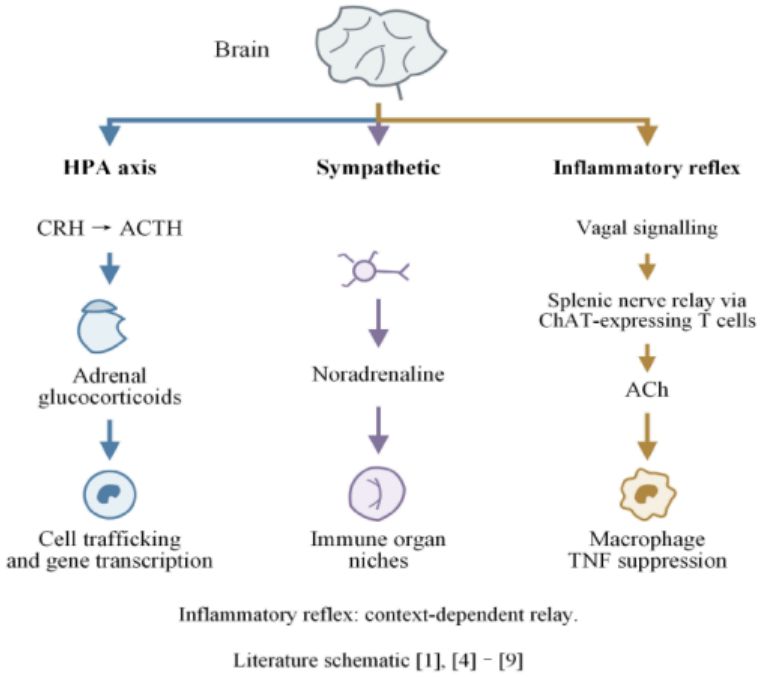


Figure 1. Endocrine and autonomic routes linking central regulation to peripheral immunity. The inflammatory-reflex branch includes a splenic adrenergic and acetylcholine-producing T-cell relay. Arrows summarise signalling sequences established in the cited experimental settings [1, 4-9]

## 2.3. Defined neural circuits

Circuit studies add anatomical resolution to these broad routes. Chan and colleagues review hypothalamic, motor, insular and reward-related contributions to peripheral immune regulation [1]. While hypothalamic populations link central activity to endocrine output, insular studies connect representations of bodily state with later immune responses, and reward-related studies link central motivational systems to peripheral regulation. The insular and reward findings provide context for the range of central influences on immunity, while the hypothalamic and motor pathways are

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examined in detail below because their responding cells and peripheral routes have been resolved experimentally. Poller and colleagues showed that acute stress in mice recruits separable circuits with different leukocyte effects [10]. The mixed blood response is consistent with these opposing movements: motor activity drives a skeletal-muscle signal associated with neutrophil mobilisation, whereas CRH neurons in the paraventricular hypothalamus (PVH) engage adrenal glucocorticoid and direct monocytes and lymphocytes towards the bone marrow. A blood sample records only one moment: cell populations with different destinations and functions may be entering or leaving the circulation at the time of collection, so a total leukocyte count can conceal the differences between them. When the brain population, peripheral mediator and responding cell have been identified, successive steps between a central event and a measurable peripheral process can be tested. An account that links stress to inflammation alone leaves those intermediate steps unresolved.

## 3. Case analysis

### 3.1. Poller et al. 2022

Poller and colleagues combined acute stress paradigms with neural and peripheral interventions to determine how the brain changes leukocyte distribution in mice [10], tracking several cell populations across the blood and tissues and testing the routes responsible for their movement. Neutrophil mobilisation followed a different route from monocyte and lymphocyte relocation; Figure 2 shows the two pathways and their destinations. In the motor pathway, strong skeletal-muscle activity increased CXCL1, which promoted CXCR2-dependent neutrophil mobilisation from bone marrow into blood and peripheral tissues through a motor-muscle response that was independent of sympathetic signalling. In the endocrine pathway, PVH CRH neurons engaged the HPA axis, and glucocorticoid signalling within leukocytes promoted the movement of B cells, T cells and monocytes from blood and secondary lymphoid organs towards bone marrow [10]. The opposing changes in circulating cell populations were therefore components of the same stress response. The mechanism also involved skeletal muscle as an intermediate organ, so it was not restricted to direct communication between the brain and immune cells.

Redistribution also affected disease outcomes. The PVH-CRH-glucocorticoid pathway altered monocyte and lymphocyte distribution and had contrasting effects across the mouse models, including reduced susceptibility to experimental autoimmunity and impaired antiviral defence [10]. A fall in circulating cell count must therefore be interpreted in relation to where the cells move and which tissue gains or loses access to them during the immune response. In this review, these experimentally resolved routes provide a mechanistic reference for interpreting the human infection outcomes without assuming that the same circuits were demonstrated in people.

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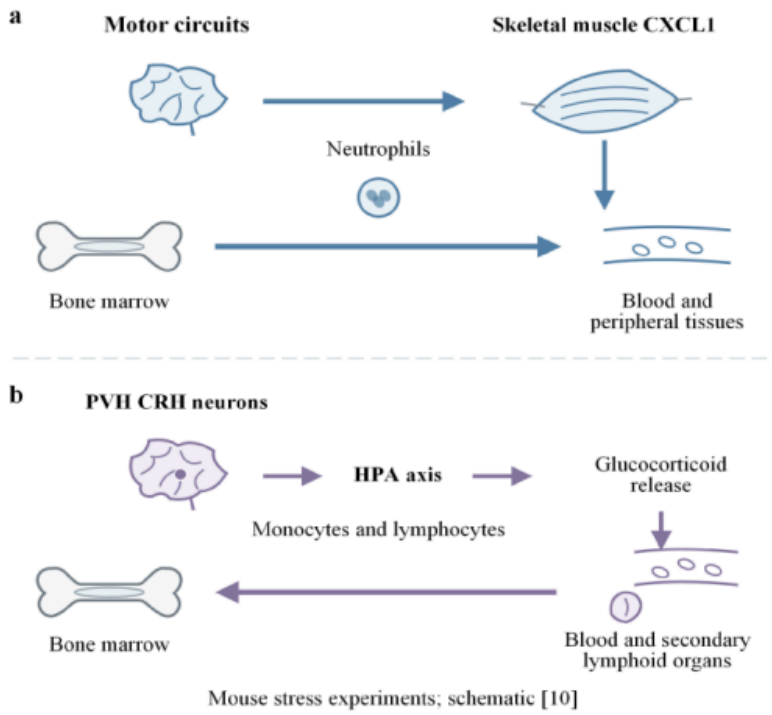


Figure 2. Opposing leukocyte movements during acute stress in mice. Motor circuits act through skeletal-muscle signals to mobilise neutrophils from marrow, while PVH CRH neurons engage glucocorticoid signalling to direct monocytes and lymphocytes towards marrow [10]

### 3.2. Cohen et al. 1991

Cohen and colleagues studied whether psychological stress before viral exposure predicted subsequent illness in healthy adults [3]. A total of 394 volunteers received nasal drops containing one of five respiratory viruses, and 26 received saline; psychological stress had been measured before inoculation, and participants were then monitored under controlled conditions. Documented infection required virus isolation or a rise in virus-specific antibody titres, while a clinical cold required both symptoms and documented infection. Infection and symptomatic illness were therefore separate outcomes. Across increasing stress levels, infection rates rose from approximately 74% to 90%, and clinical cold rates rose from approximately 27% to 47% [3], with the graded associations reported at $P < 0.005$ for infection and $P < 0.02$ for clinical colds. Recording symptoms distinguishes clinical illness from infection alone, although both outcomes concern host defence. Figure 3 places these outcomes in the study sequence, after measurement of stress and the controlled viral challenge.

Pathogen exposure was controlled and illness was followed prospectively, but stress was measured rather than randomly assigned; residual confounding therefore cannot be excluded. The human study is directly relevant to host defence because it measured infection and illness after a defined exposure, providing a reason to investigate the cellular and neural mechanisms tested experimentally in mice. The healthy-adult sample and controlled viral exposure also limit generalisation to other populations and immune challenges. No neural circuits were directly measured.

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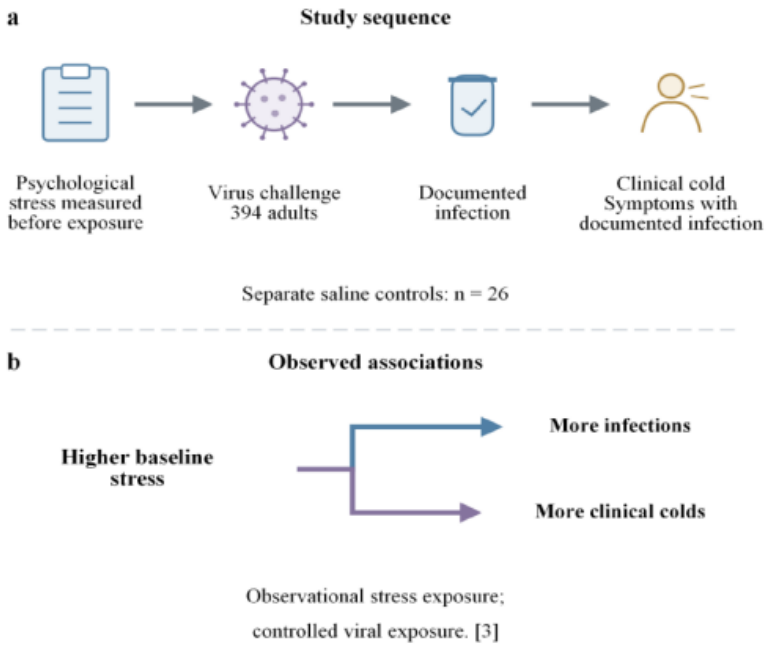


Figure 3. Design of the human viral-challenge study. Psychological stress was measured before inoculation; 394 adults received virus and 26 received saline. Documented infection and clinical colds were assessed after exposure. Higher stress was associated with both outcomes [3]

### 3.3. Cross-case comparison

The two cases address different levels of the same research question: Poller et al. manipulate neural and peripheral components to explain cell movement during acute stress, while Cohen et al. measure psychological stress before a controlled viral exposure and then assess infection and illness [3, 10]. The designs therefore complement one another in mechanistic depth and relevance to human illness. Their stress exposures also differ. Acute experimental stress has a defined onset and permits a specified interval before cell sampling, whereas the questionnaire before viral exposure covers a person's experience over its measurement window, a period that is not equivalent to a brief experimental stressor. The difference in biological scale also matters: movement between marrow and blood is a cellular process, whereas a clinical cold develops through several processes over time. Translation between these outcomes therefore requires identifying which stress-responsive pathways change the availability or activity of immune cells at the time of pathogen exposure.

## 4. Discussion

### 4.1. An integrated directional model

The brain-organ model supported by this evidence relates the direction and target of a signal to its immune effect. Endocrine, autonomic or somatic outputs recruited by stress-responsive central activity act through peripheral mediators on particular tissues and cell populations, where they change cell distribution, cytokine release or cellular responsiveness. Whether these changes meet the demands of infection, injury or inflammation determines their functional consequences [1, 6, 10], so immune regulation is understood as a change in a defined biological process rather than as a general increase or decrease in immunity. Redistribution changes where cells are available, whereas

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functional reprogramming changes how they respond through altered inflammatory signalling or gene expression, for example. Separating these processes allows both cell destination and subsequent activity to be considered. Comparisons between experiments are more informative when the stressor, recruited pathway, responding cell, tissue compartment and sampling interval are specified, because agreement at one step need not extend to the whole sequence. Two studies might report lower blood lymphocyte counts even though the cells move to different destinations or function differently afterwards. Recording destination and subsequent function can help explain apparently inconsistent findings and guide the choice of measurements in later work.

### 4.2. Acute and chronic stress

Duration affects the developing immune response. Segerstrom and Miller's synthesis associated brief stressors with potentially adaptive changes in some innate measures, while persistent stress was associated with broader impairment across cellular and humoral measures [2]. The pattern depended on the endpoint. Acute and chronic stress are therefore useful categories only in relation to a specific measurement and time course. McEwen's distinction between adaptation and accumulated physiological cost helps explain this temporal pattern [5]. A response that meets an immediate demand can still have costs when repeatedly recruited or poorly terminated, with immune consequences that may include prolonged inflammatory activity, altered tissue responsiveness or weakened defence. The acute mouse findings show that even a brief response can have different consequences across disease settings [10]; whether a response is adaptive therefore depends on its timing and the immune task as well as its duration. The sampling schedule must capture the response over time. Measurements during stress, shortly after its end and after repeated exposure answer different questions, and serial sampling across several compartments is therefore needed to distinguish rapid cell movement from persistent changes in cell state and to track differences between acute and chronic stress. A functional endpoint, such as pathogen control or tissue inflammation, then indicates whether those changes in cell location and activity serve the host in the setting being studied.

### 4.3. Implications for neuromodulation and behaviour

Several points in the brain-organ pathway are potential targets for intervention. Vagus nerve stimulation is one example: experimental findings and the inflammatory-reflex framework together identify a neural input and an immune output that can be measured [7-9]. Future studies can test how stimulation settings affect engagement of the relevant relay and whether this engagement is related to a disease-specific outcome. A cytokine change indicates biological activity, whereas improvement in a clinical endpoint provides evidence of a clinical benefit. Measuring both links the proposed mechanism to the intervention's therapeutic purpose. Behavioural approaches act further upstream by changing exposure to stress or the way a stressor is processed. The human challenge findings identify pre-exposure stress as a relevant variable in studies of host defence [3], suggesting a behavioural intervention design in which both the psychological response and the proposed mechanism are tested. Such a design would therefore examine whether changes in perceived stress precede changes in endocrine or autonomic activity and whether an immune outcome follows.

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## 5. Conclusion

Stress reaches peripheral immunity through endocrine signals, autonomic relays and specific neural circuits, whose effects become interpretable when the responding cell and organ are considered together. Glucocorticoids influence trafficking and inflammatory activity, autonomic relays regulate local responses, and the mouse circuit study distinguishes neutrophil mobilisation from monocyte and lymphocyte movement towards the bone marrow. The human viral-challenge study provides evidence that psychological stress before exposure is associated with susceptibility to infection and clinical illness. Interpretation therefore depends on the pathway involved, the tissue affected and the timing of measurement. Relating neural control to these measurable peripheral processes explains how stress can redistribute immune resources and change cellular activity, with different consequences for host defence and inflammation. This review draws on a focused literature set, and its detailed circuit evidence comes mainly from acute-stress experiments in rodents. The human viral-challenge study links stress to infection risk without directly measuring the neural pathways involved. How the specific circuits discussed here operate in humans and under sustained or repeated stress therefore remains incompletely resolved. Future work can address these gaps by combining human neural imaging with immune profiling, tracking the transition from acute to persistent stress and testing targeted neuromodulation or behavioural interventions to examine how pathway engagement relates to immune function in the relevant organ.

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