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Spaceflight exposome/microgravity effects on the psychoimmunoneuroendocrine system

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Spaceflight missions represent a new exposome, unpredicted by evolution. Life-threatening agents activate non-specific stress responses involving the psycho-immune-neuroendocrine network. The main molecular pathways regulating this network and those affected by spaceflight exposome/microgravity are reported in various experimental setups. They include gut microbiota-derived metabolites, potentially valuable for countermeasure development. Meaningfully, the application of neuromodulation techniques, like the non-invasive transcutaneous vagal stimulation, for the prevention of pathophysiological alterations related to stress responses, is discussed.

The immune system (IS) oversees and regulates whole-body homeostasis at many levels. The most recognized function is coordinating the host defense against invading pathogens and, more broadly, against all types of stressors. The concept of the exposome¹ aptly encompasses the various agents/stressors, both internal and external to the body, to which the IS must respond in order to prevent or mitigate bodily injuries.

Spaceflight missions, however, present a novel type of exposome that evolution force did not face. These missions have to counteract numerous agents, including psychosocial and physical stressors: G-force variability, exposure to solar particle events and/or galactic cosmic rays, confinement, sleep deprivation, persistent circadian misalignment, and dietary factors, among others. When the organism faces this unique exposome^{2,3} attempts to cope with it to restore homeostasis^{4,5} with processes of adaptation or maladaptation⁶.

IS has a close molecular relationship with the neuroendocrine system, interacting with psychological and cognitive functions. Together, these systems form the Psycho-Immune-Neuro-Endocrine (PINE) network, in which each component can influence the others, ultimately affecting the entire organism. Figures 1 and 2 depict all molecular patterns and signaling able to mediate and regulate the four integrated systems, i.e., IS, Autonomic Nervous System, Psychological and Cognitive function and, Neuro-Endocrine System. In particular, Fig. 2 depicts the classical activation of the stress system, which is located in the central nervous system (amygdala,

limbic system), whose major effectors are the Hypothalamic-Pituitary-Adrenal (HPA) axis and the Autonomic Nervous System (ANS)⁷.

This review explores the emerging and recently identified effects of short- and long-term spaceflight exposome/microgravity (SEM). Specifically, studies on in vivo and in vitro models, both on ground and in Low Earth Orbit (LEO), which focus on the effects on PINE network, are considered, highlighting valuable convergences with gut microbiota-derived signaling.

The activation of the Psycho-ImmunoNeuroEndocrine (PINE) system

Spaceflight exposome represents life-threatening and synergic stressors that require new modalities of adaptation^{8–11}. Exposure to any stressor, irrespective of its nature, activates an undifferentiated physiological pattern to cope with the threat, the so-called “General Adaptation Syndrome”¹². In the first phase, the brain’s amygdala, which is involved in emotional processing, sends a distress signal to the hypothalamus, inducing a massive activation of the HPA axis and the sympathetic branch of the ANS, called the Sympathetic Nervous System (SNS)¹³ (Fig. 2). This activation is essential for survival, as it enables the mobilization of resources necessary to counteract the stressor through the corticosteroid release by the HPA axis. As a consequence, there is an acceleration of heart rate, increase in blood pressure, increase in breathing rate and pattern, and activation of the inflammatory response, via SNS activation¹⁴, that tightly depend on type, duration, and

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Fig. 1 | The PINE- psychoImmuneNeuroEndocrine network. All the involved molecular signaling is depicted to highlight the pathways that may be modulated to counteract or adapt the spaceflight exposome/microgravity effects. Red color for endogenous signaling with examples of mediators inside the parenthesis. HPA axis activation with Autonomic Nervous System interaction is described in the Fig. 2. HPA Hypothalamic-Pituitary-Adrenal axis, CRH corticotropin-releasing hormone, ACTH adrenocorticotropic hormone, VIP vasoactive intestinal peptide, NPY Neuropeptide Y, AEA anandamide, 2-AG 2-arachidonoylglycerol.

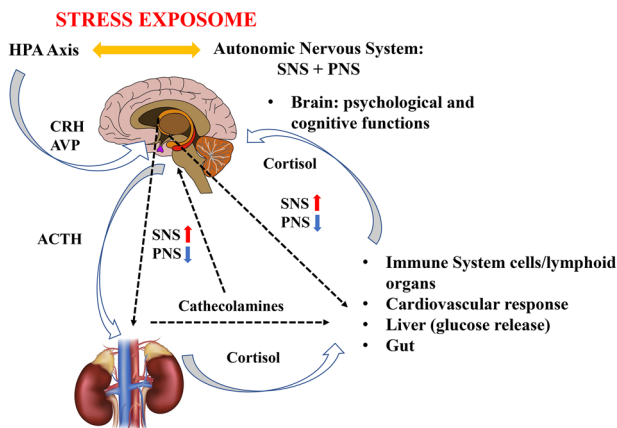
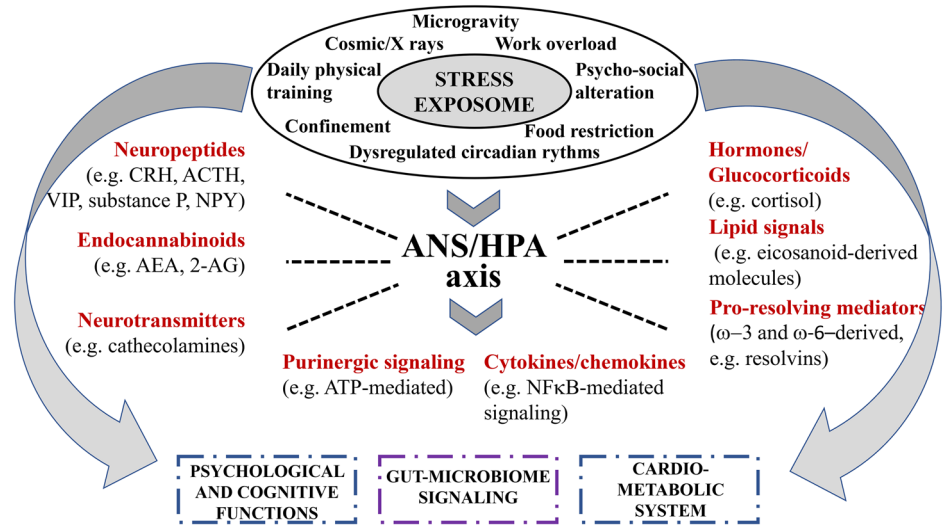


Fig. 2 | Hypothalamic-Pituitary-Adrenal (HPA) axis and Autonomic Nervous System interactions. HPA is activated in response to physical, emotional, or environmental stressors. The hypothalamus detects stress through sensory inputs and integrates signals from the limbic system (emotional processing). It releases CRH (corticotropin-releasing hormone) and AVP (arginine vasopressin) into the hypophyseal portal system. CRH and AVP stimulate the anterior pituitary to secrete ACTH (adrenocorticotropic hormone) into the bloodstream. ACTH targets the adrenal cortex, prompting the release of glucocorticoids (e.g., cortisol in humans). Cortisol helps mobilize energy by increasing glucose availability, suppressing non-essential functions (like digestion and immunity), and facilitating adaptation to stress. The ANS (Autonomic Nervous System), particularly the SNS (Sympathetic Nervous System), is the body's rapid-response system during stress. It closely interacts with the HPA axis. Stress triggers the hypothalamus to activate the SNS. The SNS stimulates the adrenal medulla to release catecholamines (e.g., adrenaline and noradrenaline). Catecholamines cause immediate physiological changes: increased heart rate, blood pressure, pupil dilation, and energy mobilization (the “fight or flight” response). Catecholamines can modulate hypothalamic activity, influencing CRH release. Similarly, glucocorticoids can enhance or suppress SNS activity depending on the context. The SNS provides a quick response, while the HPA axis sustains the stress response over minutes to hours. After the stressor is resolved, the PNS (Parasympathetic Nervous System) counteracts the SNS, promoting “rest and digest” functions. Glucocorticoid feedback to the hypothalamus and pituitary inhibits the HPA axis, facilitating recovery. The prefrontal cortex, involved in stress regulation, also responds to endocannabinoid signaling to modulate HPA axis activity, enhancing adaptive responses to stress.

intensity of stressors, with a different effect on PINE system and particularly immune system¹⁵. If the threat has been effectively counteracted, the body returns to a pre-stress condition. On the contrary, if the stressor is still present, this prolonged or repeated activation loses its biological value,

becoming pathological¹⁶ and inducing the so-called “resistance phase”: the body remains in a state of activation, eventually adapting to a higher-than-usual level of metabolic and physiological functioning. Thus, it sets a new level of homeostasis, which, however, is too costly to be maintained¹⁷, running out all the organism’s physical and mental resources¹². This dysregulation may lead to an increased risk of chronic, cardiovascular, or neuropsychiatric disease^{18–20}. In particular, a sustained activation of SNS, without an effective counteraction by the parasympathetic branch of the autonomic nervous system (called PNS), and a steadily increased cytokine production leads to increased cardiovascular morbidity and mortality²¹, anxiety and depression²², as well as to immune dysregulation^{17,23}.

The complexity of this integrated system places it at the center of homeostasis, allowing it to counteract stress responses of varying intensities and durations, whatever is the stressor. Recent data from animal models and human studies suggest a close relationship between this system and gut microbiota signaling²⁴. This relationship enhances the modulation of PINE activation and regulation, as discussed later in this review. In this context, part of the integrated system will be reviewed as a target of the spaceflight exposome.

Effects of spaceflight exposome/microgravity on the immune system signaling

Accumulated evidence has convincingly demonstrated that SEM significantly impacts on the immune response, by acting on both innate and adaptive immunity. SEM may affect all cells that participate in the inflammatory response, as it modulates the soluble mediators released by them, such as cytokines/chemokines and bioactive lipids⁶. Additionally, membrane molecules, such as MHC class I molecules, crucial for immune response, exhibited long-term suppression²⁵. Some alterations also became apparent upon acute exposure to SEM, and recovered afterwards, as suggested by investigations showing that reduced interferon (IFN)- γ production from T cells was associated only with short duration flights (i.e., on the Space shuttle), while being absent in long-term missions (i.e., on board the International Space Station, ISS)²⁶. Interestingly, a system biology-based meta-analysis of published data has shown that SEM acts on the different cells involved in inflammation, by acting on a core signature of roughly 100 conserved signaling pathways²⁷. In particular, repression of the tumor necrosis factor (TNF)- α /NF- κ B/Rel transduction axis, as well as of T-cell receptor (TCR)-mediated signals, was found in omics array datasets of various studies^{28,29}. Moreover, SEM impairs immune tolerance by significantly enhancing the production of inflammatory cytokines, such as IFN- γ and IL-17, the latter molecule being engaged in the pathogenesis of autoimmune conditions^{30,31}. This effect apparently depends on the depletion of T regulatory (Treg) cells through the repression of the IL-2/CD25 axis³¹.

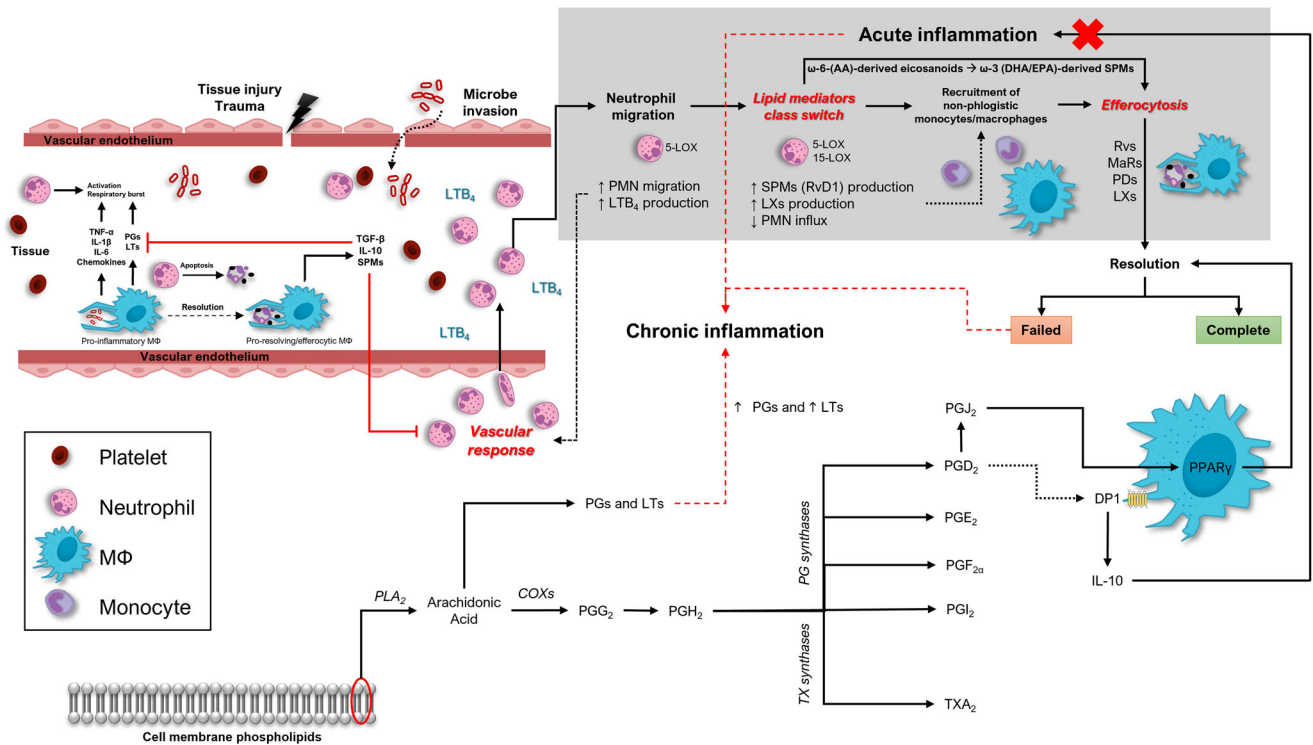


Fig. 3 | Resolution of inflammation and the lipid class switch. Upon tissue injury or trauma, pathogens penetrate the organism via the disrupted endothelium. LTB₄ and a number of specific PGs are first produced from arachidonic acid as part of the vascular response, and PMNs migrate towards the site of injury. During the acute inflammatory cascade, the production of lipid mediators shifts from LTs and PGs—made by neutrophils, platelets, and pro-inflammatory MΦ—to lipoxins—by neutrophils, platelets, and pro-resolving/efferocytic MΦ (a process called “lipid mediators class switch process”). As a consequence, non-inflammatory monocytes and MΦ are recruited, which produce SPMs and LXs as crucial lipid signals for efferocytosis, i.e., removal by MΦ of apoptotic cells - the key process for resolution of inflammation. Additionally, within the bloodstream, LXA₄ controls MCP-1 and prevents the LTB₄-dependent PMNs migration, thus creating an anti-inflammatory

milieu. Whenever the resolutive process fails and/or PGs and LTs production is excessive, chronic inflammation takes place. Thus, PGD₂ is synthesized in the attempt to transition from a chronic process to a resolutive one. PGD₂ has indeed the ability to bind to and activate the DP1 receptor, which causes the release of IL-10, a well-known cytokine with anti-inflammatory properties. Alternatively, PGD₂ can be converted into PGJ₂, which directly binds to PPAR_γ and prevents the synthesis of pro-inflammatory mediators, in order to restore homeostasis. LTB₄ leukotriene B₄, PG prostaglandin, PMN polymorphonuclear cell, MΦ macrophages, SPM pro-resolving mediator, LXA₄ lipoxin A₄, MCP-1 (or CCL2) monocyte chemoattractant protein-1, DP1 prostaglandin D₂ receptor 1, PPAR_γ peroxisome proliferator-activated receptor γ , TGF- α/β transforming growth factor α/β , IL-6 interleukin 6, TX thromboxane, PLA₂ phospholipase A₂, COX cyclooxygenase, RvD1 resolving D1.

Interestingly, the number of the latter cells has been recently found to be unaffected by confinement alone³². This evidence suggests that confinement is unlikely to trigger, per se, Treg cell number reduction observed in space³¹.

SEM can also act on the processes that orchestrate inflammation and its resolution, a rather complex series of events that are schematically depicted in Fig. 3. Indeed, SEM impairs macrophage differentiation and overall polarization³³ and alters complement system activation³⁴, while eliciting metabolic reprogramming and altering cytokine production³³. Recent studies have also reported a direct effect of SEM on endothelial cells, with a down-regulation of adhesion molecules responsible for the recruitment of immunocytes at the inflamed site³⁵, as well as the activation of iNOS/NO-NF- κ B/I κ B and the NLRP3 inflammasome signaling pathway in vitro cell model with simulated microgravity³⁶. In this context, SEM can also affect membrane fluidity³⁷, modifying membrane microdomain (e.g., lipid raft) distribution and signaling thereof, which in turn might lead to the production of pro-inflammatory mediators, most notably bioactive lipids and cytokines.

SEM can induce atrophy of both bone marrow and thymus, which control generation and maturation of T and B cells³⁸. Even though several groups have recently investigated the molecular mechanisms behind spaceflight-induced immune alterations, the full array of molecular actors behind them remains mostly elusive, with the biggest part of the published literature having focused on cytokines. Instead, the role of endogenous bioactive lipids, which are produced by the cells that orchestrate inflammation³⁹, has been poorly addressed⁴⁰. These molecules represent the

fulcrum of the immune response, governing the initiation, extent, and outcome of the inflammatory event^{40,41}.

In particular, endogenous bioactive lipids can be grouped into five main classes, which include widely investigated molecules like eicosanoids and endocannabinoids (eCBs), as well as other compounds such as specialized pro-resolving mediators (SPMs), sphingolipids, and glycerophospholipids^{41–44}. These substances are produced by virtually all the cells of the body as major pro-homeostatic factors and, during phlogistic events, they control recruitment, removal, and turnover of the immune cells (Fig. 3), thus attracting growing attention as main drivers of all inflammatory processes. In particular, while proper inflammation is governed by arachidonic acid (AA)-derived eicosanoids (i.e., prostaglandins, leukotrienes and thromboxanes), which control recruitment and activation of pro-inflammatory immune cells, resolution is organized in the aftermath of acute events to control and keep at bay the excessive inflammatory surge, and is mainly controlled by ω -6 polyunsaturated fatty acids (PUFA)-derived SPMs. As the tissue needs to return to physiological conditions, neutrophils, platelets, and non-phlogistic monocytes/macrophages undergo a lipid mediator class switch that leads to the production of SPMs, namely resolvins (Rvs), maresins (MaRs), protectins (PDs), and lipoxins (LXs). These lipid mediators are produced by innate immune cells through the concerted action of 5-, 12-, and 15-lipoxygenase (LOX) on docosahexaenoic, docosapentaenoic, eicosapentaenoic acid (DHA, DPA, EPA, respectively), as well as on AA. As they are produced, SPMs antagonize AA-derived autacoids and

Table 1 | Effects of spaceflight exposome/microgravity in lipid signaling of immune cells and cell lines

References	Experimental set up	Sample	Target	Effect
Maccarrone et al. ¹²²	RPM	K562 cells	COX-2	Enhanced activity
Maccarrone et al. ¹²³	Parabolic flight	Purified enzyme	15-LOX-1	Enhanced activity
Maccarrone et al. ¹²⁴	RPM	Lymphocytes, U937 cells	5-LOX	Enhanced activity
Choukèr et al. ¹²⁵ ; Strewe et al. ¹²⁶	Parabolic flight	Human blood	AEA	Enhanced production
Gasperi et al. ¹²⁷	RCCS	Jurkat T cells	5-LOX	Enhanced activity
Battista et al. ¹²⁸	ISS	PBMCs	5-LOX	Enhanced activity
			AEA	Enhanced production
			NAPE-PLD	Up-regulation (both mRNA and protein)
			FAAH	Down-regulation (both mRNA and protein)
Buchheim et al. ⁵⁴	ISS	Human Blood	AEA	Enhanced production
Kim et al. ²⁵ Leuti et al. ⁴⁶	RCCS	Primary Human Monocytes	RvD1	Reduced biosynthesis

AEA *N*-arachidonylethanolamine, COX-2 cyclooxygenase-2, FAAH fatty acid amide hydrolase, LOX lipoxygenase, NAPE-PLD *N*-acylphosphatidylethanolamines-specific phospholipase D, RPM random positioning machine, ISS International Space Station, RvD1 resolving D1, RCCS rotary cell-culture system bioreactor for simulated microgravity.

pro-inflammatory cytokines, stop the ingress of neutrophils and the activation of pro-inflammatory macrophages and lymphocytes, while inducing macrophage-mediated efferocytosis (i.e., the removal of apoptotic bodies and debris), which is crucial to both avoid aberrant inflammation and to favor trans-cellular biosynthesis of SPMs⁴⁵. On the other hand, eCBs have been shown to control immune functions both by acting directly on recruitment and activation of lymphocytes and monocytes/macrophages⁴¹, as well as by engaging SPM receptors (i.e., GPR18) and inducing SPM production⁴⁶. Despite the critical role of endogenous lipids in inflammatory homeostasis, the biggest part of SEM-related research has focused on eicosanoids and eCBs⁴⁰, and showed that microgravity increases leukotriene (LT) B₄ biosynthesis and 5-LOX activity. Furthermore, authentic microgravity upregulates the expression of the prominent eCB-biosynthetic enzyme *N*-acylphosphatidylethanolamines-specific phospholipase D (NAPE-PLD), while downregulating that of the prominent eCB-degrading enzyme fatty acid amide hydrolase (FAAH). Conversely, simulated microgravity during parabolic flights can depress the production of bona fide eCBs such as *N*-arachidonylethanolamine (AEA) and 2-arachidonoylglycerol (2-AG). To date, the effects of SEM on other signaling lipids have been largely neglected, except a recent study addressing such effects on SPMs⁴⁶. In particular, it was shown that simulated microgravity impairs RvD1 production, modulates LOX activity, and downregulates the expression of prominent SPM receptors GPR32 and GPR18⁴⁶.

The available data on SEM effects on eicosanoids, eCBs, and SPMs during the immune response are summarized in Table 1. Thus, molecular signals such as AEA, cyclooxygenase-2 (COX-2), LOXs, NAPE-PLD, FAAH, and more recently RvD1 were shown to be affected by SEM in different experimental setups. Overall, these findings are consistent with a SEM-induced increase of the pro-inflammatory response.

Spaceflight exposome/microgravity effects on the immune-neuroendocrine system

Both innate and adaptive immunity have a well-documented connection with neuroendocrine system involving adrenergic receptors⁴⁷, glucocorticoid receptors (GC)⁴⁸, and other relevant molecular signaling and pathways⁴⁹.

Beta-adrenergic and glucocorticoid receptors (GC) are expressed on NK cells and can inhibit their function⁵⁰. These receptors may be the cause of a compromised NK cell function during spaceflight⁵¹. In particular, the in-flight exposome decreases number and function of NK associated not only with virus reactivation, but also with excessive systemic release of glucocorticoids/cortisol due to persistent stress conditions. This finding was also reported after flight^{52–54}, suggesting a prolonged weakness of immune surveillance with potential health risk for astronauts.

The activity of neutrophils and monocytes/macrophages occurs through oxidative bursts, producing radical oxygen/nitrogen species. Taken together, astronauts exhibit elevated oxidants and reduced antioxidants⁵⁵. Consistently, animal models aboard the ISS demonstrated significant inhibition of gene-metabolite networks linked to oxidative stress, emphasizing mitochondrial dysfunction⁵⁶ and increased oxidative phosphorylation^{25,57}. Noteworthy, oxidative-stress balance is crucial not only as an immune activity marker but also as a potential pro-inflammatory marker with neuro-endocrine effects when disrupted⁵⁸.

Long-term spaceflight exposure increases the expression of PAMPs/DAMPs (Pathogen Associated Molecular Patterns/Danger Associated Molecular Patterns) receptors, such as Toll-Like Receptors (TLRs), in astronauts' peripheral blood granulocytes/monocytes and serum concentrations of their ligands. TLRs remain elevated post-flight but recover after seven days¹⁵. The rise in DAMP receptors may result from augmented self-alarmin molecules in stressed conditions, able to fuel inflammatory state. In this perspective, the increase of autophagic cell death has been shown in *in vitro* cell models, as cellular stress response after 28 days on board the ISS⁵⁹, suggesting a need for further *ex vivo* evaluation.

Spaceflight also reduces thymopoiesis and raises plasma/urinary cortisol levels, indicating a link between glucocorticoids and immune suppression^{60,61}. While T lymphocyte percentages are preserved post-flight, memory T lymphocytes increase⁵⁴, and delayed T cell activation occurs^{54,62}, thus reflecting immunosenescence effects observed in aging. This acceleration may affect neuroendocrine regulation of inflammation and increase the risk of disease onset.

B cell compartment appeared to be preserved during long-term spaceflight, even though B lymphocyte count was increased⁵⁴. Importantly, serum immunoglobulins A (sIgAs) increased in astronauts⁶³, in agreement with the single-cell expression data suggesting possible up-regulation of BCR signaling genes in B cells immediately post-flight²⁵. Since sIgAs mostly represent the mucosal humoral immune system, this finding may suggest an adaptive immune response in those districts and particularly in the Gut Associated Lymphoid Tissue (GALT), which tightly communicates with neuro-endocrine mediators⁶⁴.

Similarly, the brain may be involved in a systemic response to various stressors through different pathways, such as cytokine/chemokine signaling, p38 mitogen-activated protein kinase (MAPK) and NF- κ B signaling, indoleamine 2,3 dioxygenase and its downstream metabolites (kynurenine, quinolinic acid and kynurenic acid), and the neurotransmitters serotonin, dopamine and glutamate⁶⁵. In this perspective, some cytokines/chemokines are also produced at neuroglia level. Notably, plasma cytokine/chemokine level is affected by long-term spaceflight. Pro-inflammatory molecules such as IL-8 (or CXCL8) and troponins from muscle tissues were increased in

astronauts during long-duration missions onboard the ISS, even though both recovered on Earth⁶⁶. The NASA Twin Study reported changes in the 50-cytokine profile of a homozygous twin astronaut during a one-year spaceflight mission on the ISS compared with the other ground-based twin⁶⁷. However, different trends of cytokine levels may be different in other spaceflights. For instance, IL-6, a systemic pro-inflammatory cytokine that affects the hypothalamus as the central thermo-regulator, and Leptin, an adipokine mediator of the immune-neuroendocrine system, showed different trends comparing the NASA Twin Study with other astronauts/missions⁶⁸. This indicates a relevant inter-individual variability². Likewise, a decrease of regulatory/inhibitory cytokines after return to Earth⁵⁴ may support a systemic pro-inflammatory status after landing.

However, the overall impact on these different molecular patterns/signaling and their downstream protein deserves further investigation to better understand the systemic pro-inflammatory effect, the neuroendocrine system activation, and its recovery.

Spaceflight exposome/microgravity effects on PINE and gut microbiome (GM)

Molecules involved in the PINE network, not only have been studied in spaceflight exposome as reported in Table 2 (including GM in a few cases), but have also been investigated in the context of terrestrial analogs, such as isolation/confinement campaigns (Table 3), head-down bed rest (HDBR) studies (Table 4) and dry immersion studies (Table 5), that represent cheaper and logistically simpler settings, where the effects of single or multiple variables of the spaceflight exposome can be evaluated. On the whole, several studies have observed a predominance of sympathetic cardiac activity and elevated cortisol levels during spaceflight⁶⁹⁻⁷¹, in HDBR⁷²⁻⁷⁴, and in situations of prolonged confinement and isolation⁷⁵⁻⁷⁷. These modifications are acceptable for the body in the short term, as hypothesized by Selye¹². If prolonged, they give rise to a cascade of further multisystem alterations that impact the physical and mental health of the astronaut. Depressive symptoms and anxiety disorders,

Table 2 | Spaceflight exposome (Low Earth Orbit) effects on human PINE and Gut Microbiome (GM)

References	Source of data	Target	Effect
Mehta et al. ⁷⁰	Urine	CMV	Pre-flight shedding of CMV in seropositive astronauts. No significant changes in- and post-flight
		Cortisol, epinephrine, and norepinephrine	Post-flight increased levels
	Plasma	CMV antibody titer	Pre-flight increased production. No changes post-flight
		Cortisol	Post-flight decreased levels.
Stowe et al. ⁷¹	Blood	White blood cell counts	Short-duration missions: post-flight increased levels, except for a reduction in NK and T-cells Long-duration missions: post-flight increased levels, except for a reduction in eosinophils and no changes in NK cells, CD8 ⁺ T-cell, and monocytes
		Cortisol	Long-duration missions: increased levels at landing
	IL-10	Long-duration missions: post-flight increased levels	
	PBMCs	TNF- α and IFN- γ	Short-duration missions: decreased levels at landing Long-duration missions: only IFN- γ reduction
	Urine	Cortisol	Increased levels at landing (both short and long duration missions)
		Epinephrine and norepinephrine	Post-flight decreased levels (both short and long duration missions)
Jones et al. ⁷⁹	Reaction Self Test	Sleep (timing, duration, and quality), behavioral states, neurobehavioral performance	In flight, sleep deprivation and higher stress rating. Increased Psychomotor Vigilance Test response speed at the end of the mission
Barger et al. ⁸¹	Actigraphy	Sleep duration	In flight, sleep deprivation
Flynn-Evans et al. ⁸²	Actigraphy	Sleep (duration and efficiency) and circadian temperature minimum	In flight, sleep deprivation and circadian misalignment episodes depend on operational activities
Mehta et al. ⁵²	Urine	CMV virus	In flight CMV shedding
	Saliva	EBV, VZV, and HSV-1 viruses	In flight EBV and VZV shedding
		Cortisol	In flight changes in diurnal trajectory of salivary cortisol concentrations
Buchheim et al. ⁵⁴	Stress Questionnaire	Stress perception	In flight low individual stress levels
	Blood	White blood cell count	Increased number after landing
		Leukocyte distribution pattern	Neutrophils, monocytes, and B cells increased post-flight, whereas NK cells dropped CD14 ⁺ CD16 ⁺ monocytes and Treg cells decreased post-flight. Post-flight shift in CD8 ⁺ T cell repertoire toward CD8 ⁺ memory cells
		Surface adhesion markers	Post-flight increased shedding of L-selectin and strong activation of Polymorphonuclear Leukocytes.
	Endocannabinoids (AEA, 2-AG)	In flight increased levels	
	TGF-beta, IL-10 and IL-1Ra	In flight increased levels and post-flight decreased levels	
	Liu et al. ⁹⁷	Feces	GM composition
GM function			Genes related to environmental information processing and envelope biogenesis were increased. Antibiotic resistance genes and mobile genetic elements in the gut microbiota were affected by spaceflight. The total number of virulent genes in GM was increased

CMV cytomegalovirus, NK cells natural killer cells, IL-10 interleukin-10, TNF- α tumor necrosis factor- α , IFN- γ interferon- γ , PBMCs peripheral blood mononuclear cells, EBV Epstein-Barr virus, VZV varicella zoster virus, HSV-1 herpes simplex virus-1, AEA anandamide, 2-AG 2-arachidonoylglycerol, IL-1Ra interleukin-1 receptor antagonist.

Table 3 | Human PINE network in isolation/confinement studies

References	Experimental set up	Source of data	Target	Effect	Main Findings
Maggioli et al. ⁷⁵	Antarctica simulation study	Heart rate monitoring and ECG	Vagal modulation and sympathovagal balance	Decreased HF power during the mission (gradual reduction in vagal tone). LF/HF powers ratio shifted toward a sympathetic predominance in the last phase of the mission	The depression of cardio-vagal tone and the shift toward a sympathetic predominance observed during the mission suggest a long-term cardiac autonomic modulation in response to isolation and confinement
Yi et al. ⁷⁶	Mars520 simulation study	Saliva PBMCs	Cortisol Leukocyte distribution pattern	Increased levels during isolation Lymphocyte percentages increased (increased number of CD3 + T cells, CD19 + B cells, CD8+ cytotoxic T cells and CD4+ helper T cells), while neutrophils percentage decreased during the mission	Isolation/confinement may induce sensitization of the immune system (increased lymphocyte amount and leukocyte phenotype changes) to incoming virus and heightened immune response
Jacobowski et al. ⁷⁷	Mars520 simulation study	EEG	IFN- γ and TNF- α Alpha and beta global field power	Increased levels during the mission Decline during mission	Isolation/confinement may induce a decrease of global cortical activity, in both alpha- and beta-activity, and an increase of salivary cortisol. This impairment seems reversible by moderate exercise
Basner et al. ⁹	Mars520 simulation study	POMS Visual Analog Scales	Mood Psychological issues	Lower vigor-activity and higher confusion-bewilderment during the mission Higher feelings of sickness and tiredness, high workload perception, higher susceptibility to conflict during the mission	Isolation and confinement may induce, stress, fatigue, insomnia, poor sleep quality, mood and behavioral disturbances and psychological distress. Individual differences among crewmembers may be observed

EEG electrocardiogram, HF High frequency, LF/HF ratio of low to high frequency power, PBMCs peripheral blood mononuclear cells, IFN- γ Interferon- γ , EEG electroencephalogram, TNF- α tumor necrosis factor- α , POMS profile of mood states.

alteration of sleep, suppression of antiviral response, and establishment of a pro-inflammatory state are among the main maladaptive symptoms that may emerge^{78,79}.

All these alterations sustain each other in a detrimental loop, due to the tight relationship of the PINE network. The SNS innervates lymphoid organs including the spleen and lymph nodes and, its neurotransmitters epinephrine and norepinephrine, secreted by the adrenal gland and local sympathetic neurons, can be recognized by adrenergic receptors on immune cells and in particular by the β 2-adrenergic receptor⁴⁷. Depending on the cell type, adrenergic signaling regulates a variety of functions in immune cells ranging from cellular migration to cytokine secretion⁸⁰. Furthermore, due to the diurnal oscillation of systemic norepinephrine levels, various immune functions follow a circadian rhythmic pattern.

Sleep deficiency, common among astronauts due to circadian rhythm disruption during spaceflight^{81,82}, can activate the HPA axis and enhance SNS neurotransmitters, impacting the IS via neurotransmitter receptors and NF- κ B-mediated inflammatory signaling⁸³. Persistent sleep disturbances or deprivation may trigger norepinephrine release in lymphoid organs and adrenal epinephrine release, stimulating leukocyte adrenergic receptors (e.g. ADRB2) and activating NF- κ B-mediated inflammation, significantly affecting inflammatory status⁸³.

Psychological stress, also manifested as sleep disturbances and prolonged anxiety, can chronically activate the inflammatory response. This may lead to a chronic low-grade inflammation, known as inflammaging⁸⁴, which is associated with the aging process and age-related onset on Earth. Additionally, this process may be accelerated during long-term spaceflight missions^{2,85}.

Cortisol typically has anti-inflammatory effects and inhibits the immune response. However, chronic elevation of cortisol can lead to IS resistance. This results in an accumulation of stress hormones and increased production of inflammatory cytokines, which further compromise the immune response^{41,86,87}. It is well established that astronauts exhibit significantly increased salivary cortisol concentrations during spaceflight⁵² and cortisol spikes in plasma and urine after return to Earth. This response was more pronounced after long-term missions as compared to short-term missions⁷¹. A recent study also demonstrated an increased in-flight endocannabinoid blood levels as biological compensation of stress response⁵⁴. Thus, various IS components are secondary modified to prolonged psychological and physiological stressors which in turn may generate effects on the immune system.

In the neuroendocrine system great relevance has the gut/GALT and brain-gut axis. In particular, enterochromaffin (EC) cells are known as the major source of gut-derived serotonin (5-hydroxytryptamine, 5-HT). Lipid mediated engagement of invariant natural killer T cells with EC cells regulates peripheral 5-HT release via CD1d, indicating an immune-mediated selective neuroendocrine response to lipid antigens⁶⁴. This circuit is extremely important since connect gut microbiome (GM), lipid antigens and immune-neuroendocrine response. In this context, spaceflight is known to affect gut-microbiota^{67,88,89}, bacteria gene expression in an in vitro model⁹⁰, and recent evidence in animal model also suggests an effect on host-GM interaction⁹¹, thus the advancement of countermeasures for keeping GM homeostasis during spaceflight missions should be pursued for crew members' health. As well known, diet-derived tryptophan (TRP) and gut microbiota-host interaction significantly influence TRP availability and metabolism, which in turn may affect cognitive function⁹². TRP either crosses the blood-brain barrier for serotonin synthesis or undergoes metabolism in the gut or liver via the kynurenine pathway. Unbalance of this pathway can lead to neuroprotective kynurenic acid or neurotoxic quinolinic acid, thus potentially impairing cognitive function. Gut microbiota, not only metabolizes TRP, producing indoles that activate aryl hydrocarbon receptor (AhR) signaling, essential for the control of immune response and neuroinflammation⁹³⁻⁹⁵, but may also synthesizes TRP or convert it into serotonin. These processes can alter TRP availability for the host, with potential effects on the brain.

GM may lead to the acute activation of intestinal sensory neurons, in particular, it has been demonstrated through *Bacteroides fragilis*

Table 4 | Human PINE network in Head-Down Bed Rest (HDBR) studies

References	Source of data	Target	Effect	Main Findings
Hirayanagi et al. ⁷²	Blood	Hematocrit	Increased levels during HDBR	A reduction in the cardiac vagal nervous modulation on the sinus node and in the cardiac BRS may be observed within 24 h of both HDBR and post-HDBR
		Plasma volume	Decreased levels during HDBR	
	ECG and arterial tonometry device	Cardiovascular parameters	HR, total peripheral resistance, and systolic arterial pressure increased, while cardiac baroreceptor reflex response decrease, in the post-HDBR period	
Liang et al. ⁷³	Urine	Urine volume	Increased during HDBR; decreased after HDBR	A number of physiological variables may be modified, including hormone levels, urination and defecation frequencies
		Cortisol	Increased during and after HDBR	
		Melatonin	Increased during HDBR	
	Urination and defecation records	Urination and defecation frequency	Decreased rhythmicity of urinary and defecation frequency during HDBR	
Xu et al. ⁷⁴	PBMCs	IFN- γ and IL-17A	Increased levels during HDBR	Decreased cellular immune response and enhanced sterile inflammatory response occurred during HDBR
		IL-1 β and IL-18		
		IgE		
	Leukocyte distribution pattern	Increased percentages of memory T and B cells, Tregs and monocytes during HDBR		
	Serum	Cortisol	Increased levels during HDBR	
MCP-1		Decreased levels during HDBR		

ECG electrocardiogram, HR heart rate, BRS baroreceptor reflex sensitivity, PBMCs peripheral blood mononuclear cells, IFN- γ interferon- γ , IL-17A Interleukin-17A, IL-1 β Interleukin-1 β , IL-18 Interleukin-18, IgE immunoglobulin E, MCP-1 monocyte chemoattractant protein-1 (or CCL2).

polysaccharide A⁹⁶. Interestingly, *Bacteroides* species are among those affected by long-term spaceflight⁹⁷, thus suggesting an important GM-mediated effect potentially able to modify neuroendocrine response. In fact, recent studies confirm the central role not only of the brain-gut axis, but also of the GM in inter-organ communication with the involvement of neurotransmitters (catecholamines, serotonin, gamma-aminobutyric acid), intestinal peptides (cholecystokinin, peptide YY and glucagon-like peptide 1), and bacterial metabolites such as short-chain fatty acids⁹⁸. Main SCFAs include acetate, propionate, and butyrate. They have anti-inflammatory properties and influence immune cell function, being also able to modulate the brain-gut axis by acting on the vague nerve and influencing neurotransmitter production. GM and their lipid metabolites can affect the HPA axis, which is crucial for stress response and hormonal regulation. SCFAs and bile acids modified by microbiota strains can modulate the release of neurotransmitters like serotonin and dopamine, impacting mood and cognitive functions⁹⁹. It is noteworthy that changes in intestinal microbial abundance also alter the expression of neurotransmitter receptors within the brain in animal models^{100,101}, suggesting a strong potential for deeper investigation in humans and spaceflight countermeasures.

Holistic approach: countermeasures for PINE network modulation

Space is a hostile environment for humans. Altered gravity or circadian misalignment are just few of the factors that could challenge the maintenance of homeostasis. Indeed, psychological aspects are also involved¹⁰². In the context of future long-duration space missions, a holistic approach will be fundamental both to deepen our knowledge on the impact of these variables and to define appropriate countermeasures^{10,103}. The new approach has to overcome the strict distinction among different systems and between body and mind. To this aim, a trans-systemic approach is necessary that takes into account the potential integration of the pathways involved (Figs. 1 and 2). Moreover, there is an important and widely extended inter-individual variability in the perception and intensity of response to stimuli considered stress factors¹⁰⁴. A first approach to counteracting the adverse effects of spaceflight exposome could involve a systematic personalized retrospective analysis and the prospective identification of the most resilient psychophysiological profiles, as well as those that respond at the best to interventional countermeasures. Understanding how each astronaut or type of psychophysiological profile, including sex-related variables, copes with

spaceflight exposome would help to plan profile-related strategies to reduce or control stress-induced activation and its negative consequences on physical and mental health. On the other hand, a strong and high individual variability may reduce the efficacy of the identification of common psychophysiological profiles to be used as reference target. Recently, advanced strategies to improve mental training, such as mental imagery¹⁰⁵, have been developed that could be further implemented for a more personalized training application.

In this context, the ANS, through its multisystemic connections running from the central nervous system (CNS) to the entire organism, represents an important target to study¹⁰⁶. While the prolonged dominance of the SNS, a critical component of the stress response, can have harmful effects, the predominance of the PNS, especially vagal modulation, reflects a more adaptive autonomic state at rest. This is associated with greater resilience and faster recovery from stress¹⁰⁷. Future studies on terrestrial analogs or space missions will have to verify whether astronauts, who present an ANS modulated by a vagal predominance, are actually more resilient to the induced alterations. In addition, all the interventions aimed at maintaining or restoring the balance between sympathetic and parasympathetic modulation could represent effective countermeasures.

The possibility of vagal stimulation by GM-derived neurotransmitters, such as γ -aminobutyric acid (GABA), serotonin, and dopamine, paves the way for advanced countermeasures able to stimulate vagal afferent neurons and sending signals to the brain. For example, certain *Lactobacillus* and *Bifidobacterium* species produce GABA, which can interact with the vague nerve to influence mood and stress responses¹⁰⁸. Gut bacteria ferment dietary fibers and are able to produce short-chain fatty acids (SCFAs) like acetate, propionate, and butyrate. In turn, these SCFAs can stimulate the vague nerve either directly or indirectly through their anti-inflammatory effects¹⁰⁹. Furthermore, SCFAs can modulate the release of gut hormones such as neuropeptide Y (NPY), peptide YY (PYY), and glucagon-like peptide-1 (GLP-1), which can then activate vagal pathways⁹⁸. Supplementation with specific probiotics that enhance vagal stimulation may help to improve stress resilience. In this perspective, it should be recalled that both pre-/pro-biotics have been shown to efficiently promote the growth of beneficial gut bacteria producing SCFAs and neurotransmitters^{88,109}, and post-biotics, which supply beneficial bacterial metabolites¹¹⁰, can improve host-GM interaction, and hence human health.

Table 5 | Human PINE network in dry immersion studies

References	Source of data	Target	Effect	Main Findings
Bersenev et al. ¹²⁹	Polysomnographic Data	Sleep quality and REM phase duration	Day 3: Increased sleep latency, number of awakenings, and duration of wake after sleep onset. Decreased sleep efficiency, duration of REM, and duration of nonrapid eye movement stage 2 Day 10: Sleep architecture returned to the baseline values Day 19 and recovery: Increased REM duration	The most severe sleep disturbances occur on Day 3. An increased REM duration from Day 19 was found against a background of undisturbed sleep and was associated with changes in the cardiovascular parameters
	Saliva	Cortisol	No significant changes	
	ECG and BP monitoring	Cardiovascular parameters	Day 19: Increased night-time HR and decreased systolic and diastolic BP	
De Abreu et al. ¹³⁰	Urine	Cortisol and melatonin	Moderate increase	Increased plasma volume loss, orthostatic intolerance, pronounced autonomic changes, pronounced metabolic impairment, and influence on circadian rhythms are observed
	Blood	Insulin	Increased insulin levels	
	OT tests	Cardiovascular deconditioning	Decreased OT time	
Jollet et al. ¹³¹	Feces	GM composition	Significant increase in operational taxonomic units associated with the Clostridiales order and the Lachnospiraceae family. No effects on α and β diversity indices	Intestine bacteria are sensitive to hypoactivity
		SCFAs	Reduced propionate levels	
Lebedeva et al. ¹³² (study on women only)	Facial expression and speech acoustic analysis, STAI and POMS questionnaires	Psychological assessment	Increased anxiety and depression between Day 1 and Day 2	The acute period of adaptation in women under simulated microgravity began in the evening of the 1st day and ended in the morning of the 2nd day of dry immersion
	Cognitive and sensorimotor tests	Mental and sensorimotor functions	Decrease in error/labability values and time of mathematical computation	
Robin et al. ¹³³ (study on women only)	LBNP test	Cardiovascular deconditioning and OT	Decreased OT and increased HR	The study reports: - an 'ageing-like' cardiovascular deconditioning with loss of physical fitness and postural balance; - a sedentarily-like metabolism shift mimicking the beginning of a metabolic syndrome with a drop in glucose tolerance; - the absence of important endothelial inflammatory activation
	Oxycon Pro metabolic cart associate with cycle ergometer	Aerobic performance	Decreased $\dot{V}O_{2max}$ and maximum load	
	BP and HR continuous monitoring	Circadian variations of blood pressure	Dampened circadian variations of blood pressure with a decreased night dip for SBP, DBP, and HR	
	Posturography	Sensorimotor deconditioning	Decreased postural stability and balance control	
	Blood	Insulin and glucose	Decreased insulin sensitivity and glucose control	
	Blood	Soluble E-selectin	No changes in soluble E-selectin	

REM rapid eye movement, ECG electrocardiogram, BP blood pressure, HR heart rate, OT orthostatic tolerance, GM gut microbiota, SCFAs short chain fatty acids, STAI/Spielberger state-trait anxiety inventory, POMS Profile of Mood States, LBNP Lower Body Negative Pressure, $\dot{V}O_{2max}$ maximal volume of oxygen uptake per minute, SBP systolic blood pressure, DBP diastolic blood pressure.

Accordingly, physical personalized exercise, programs of stress management, or more direct intervention such as the vagus nerve stimulation (VNS) are all possible strategies to adopt. The first approach has already been introduced and studied, applying different protocols also in terrestrial analogs¹¹¹. However, it has been observed that subjects display markedly different responses to the same intervention, thus identifying “responders” and individuals that have “low sensitivity” to the physical activity¹⁰⁴. These aspects further emphasize the need for a more detailed profiling of the baseline psychophysiological states of the crew for the prediction of the future response both to the spaceflight exposome and to the adopted countermeasures. Furthermore, it is necessary to identify new strategies aiming to modify the perception of stimuli not foreseen by evolution (e.g., cognitive restructuring or positive psychology).

As for VNS, a growing literature data points to it as a powerful technique to normalize an altered sympathovagal balance¹¹², by reducing inflammation¹⁰⁶ and improving mood conditions¹¹³. A recent study in stress-susceptible mice has shown that chronic VNS restored behavior-relevant neuronal oscillations with the recovery of altered behavioral states, thus again suggesting that physiological vagal-brain communication underlies anxiety and mood disorders¹¹⁴.

It is known that transcutaneous VNS (tVNS) directly engages the nucleus tractus solitarius, which is the primary brainstem target of most afferent vagal projections, and significantly activates areas of the central vagal network, namely the locus caeruleus, amygdala, and nucleus

accumbens. Vagal afferent signaling to the nucleus tractus solitarius (NTS) may lead to an indirect reduction of sympathetic activity and a simultaneous increase in parasympathetic activity. Noteworthy, tVNS has recently been proposed as a new powerful non-invasive approach to dysautonomias, such as postural orthostatic tachycardia syndrome (POTS) and cyclic vomiting syndrome¹¹⁵.

Thus, targeting ANS as countermeasure by means of different techniques (from cognitive behavioral therapies and Gut microbiota-derived metabolites, to non-invasive tVNS) might represent a future holistic approach to modulate the PINE network in astronauts, as schematically depicted in Fig. 4.

Conclusions and perspectives

Recent studies on crew members involved in long-duration space missions have identified potential immune dysfunctions, including immune hyperactivity and hypo-reactivity^{25,52,54,66}. These dysfunctions may impact the PINE network through various molecular pathways, as illustrated in Figs. 1 and 2. Additionally, dysregulated psychophysiological features can negatively affect the integrated system and overall health, leading to arrhythmias, cardiovascular alterations, and depressive symptoms. Therefore, a comprehensive understanding of the role and regulation of molecular signaling within the PINE network is crucial. This knowledge could favor the development of targeted therapies and strategies to mitigate the effects of spaceflight on crew members, enhancing their resilience to threatening agents.

In this context, many ground-based findings suggest the significant role of GM-derived signaling as an exogenous contributor of molecules and mediators likely capable of modulating the PINE network. For instance, SCFAs can reduce the expression of pro-inflammatory cytokines and eicosanoids, which may subsequently decrease the induction of lipoxigenase (LOX) enzymes. Microbiota-induced changes in bile acid metabolites can affect lipid signaling and alter the activity of enzymes involved in lipid metabolism, including LOX. GM-derived signaling can also influence the endocannabinoid system through various mechanisms, such as the production of endocannabinoid-like substances. A research in animal models has shown that certain gut bacteria strains, such as *Akkermansia muciniphila*, can produce molecules similar to endocannabinoids, like 2-oleoylglycerol (2-OG), which can activate cannabinoid receptors¹¹⁶. GM can influence levels of endocannabinoids such as anandamide (AEA) and 2-arachidonoylglycerol (2-AG) by affecting their synthesis and degradation pathways in the gut and other tissues. This, in turn, may indirectly influence cannabinoid receptor expression and function, thus impacting the endocannabinoid signaling¹¹⁷.

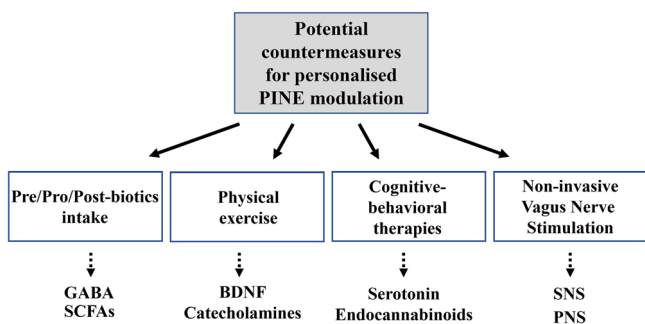
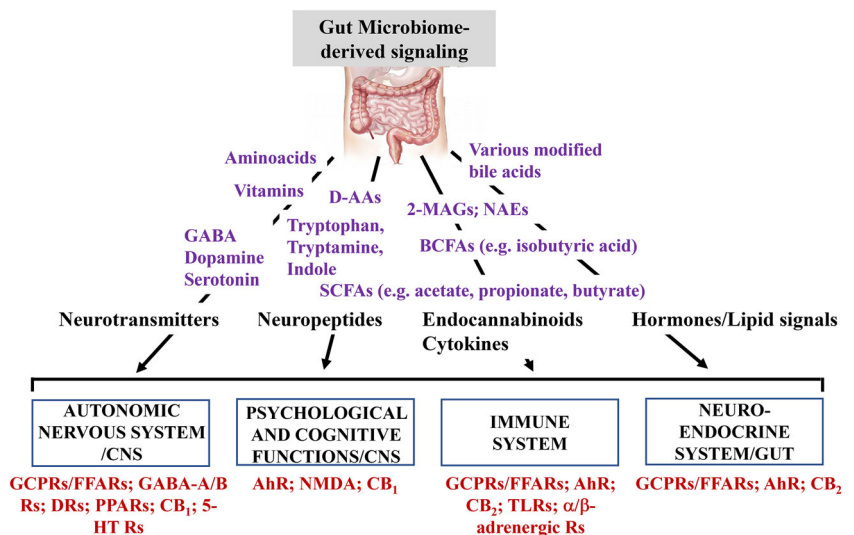


Fig. 4 | Potential countermeasures for PsychoImmuneNeuroEndocrine modulation. The main potential countermeasures targeting PINE system are summarized. Dotted arrows indicate potential induction of the specified molecules. BDNF brain -derived neurotrophic factor, GABA γ -aminobutyric acid, SCFAs short chain fatty acids, SNS sympathetic nervous system, PNS parasympathetic nervous system.

Fig. 5 | The potential molecular task-force of GM-derived metabolites for PINE network modulation.

The most important gut-derived metabolites are depicted with potential effect on molecular signaling for PINE network. The potential host receptors, which could be modulated, are highlighted in red. D-AAs Amino Acid with D configuration, NAEs *N*-acylethanolamines, 2-MAGs 2-monoacylglycerols, GABA, γ -aminobutyric acid, BCFAs Branched chain fatty acid, SCFAs short chain fatty acids, AhR aryl hydrocarbon receptor, NMDA *N*-methyl *D*-aspartate receptor, DRs Dopamine receptors, PPARs peroxisome proliferator-activated receptors, CB₁ cannabinoid receptors type 1, 5-HT_{1A} serotonin receptors, GCPRs/FFARs G-coupled Protein Receptors/Free Fatty Acid Receptors, CB₂ cannabinoid receptors type 2, TLRs toll-like receptors.



The potential molecular task-force behind GM-derived signaling is illustrated in Fig. 5, based on ground results independently of spaceflight^{118–121}. This issue deserves further investigations to be exploited for current and future countermeasures that could take into account the interactions of gut microbiota-derived metabolites, pre/pro/postbiotic valuable effects, and ad hoc physical exercise training with ASN interactions (Fig. 4).

The comprehensive role of GM-derived signaling and the involvement of specific bacterial strains seems crucial for developing countermeasures that influence PINE network regulation. Further investigation on the changes of GM composition/bacterial metabolites is deemed necessary to confirm the effects of spaceflight exposome and, approaching personalized medicine, to identify pre-/pro-/post-biotic and dietary supplements with a personalized approach for more effective countermeasures. Detecting the individual effects of the spaceflight exposome on PINE-associated molecular pathways and circulating blood mediators represents a new frontier for targeted, personalized therapies to counteract spaceflight exposome and preserve astronauts' health. Moreover, direct vagal activation, such as non-invasive tVNS, could be explored for preventing pathophysiological alterations related to physical and mental stress responses observed in astronauts during long-term space missions.

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Competing interests

The authors declare no competing interests.

Additional information

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