



Neuroinflammation, metabolic dysfunction, and chronic stress converge on the insular cortex in chronic pain

José García-Cancela^a, Orlando Conde-Vázquez^{b,e,*}, Santiago Navarro-Ledesma^{c,d}, Leo Pruimboom^c

^a Clinical Medicine and Public Health PhD Program, Faculty of Health Sciences, University of Granada, Granada, Spain

^b Department of Functional Biology and Health Sciences, Faculty of Physiotherapy, University of Vigo, Isaiúde Research Group, Pontevedra, Spain

^c University Chair in Clinical Psychoneuroimmunology, University of Granada and PNI Europe, Granada, Spain

^d Department of Physical Therapy, Faculty of Health Sciences, Campus of Melilla, University of Granada, Granada, Spain

^e Fisiología Research Group, Galicia Sur Health Research Institute (IIS Galicia Sur), SERGAS-UVigo, Spain

ARTICLE INFO

Keywords:

Chronic pain
Interoception
Insular cortex
Allostatic load

ABSTRACT

Chronic pain is a prevalent cause of disability worldwide and is increasingly recognized as a complex condition involving alterations in neural processing, emotional regulation, and bodily awareness. Among the brain regions implicated in persistent pain states, the insular cortex has consistently been identified as the most frequently affected cortical region, playing a central role in the integration and interpretation of interoceptive signals. Interoception enables the brain to monitor and regulate internal bodily states, and disruptions in this system may contribute to the persistence of pain by altering how physiological signals are perceived and interpreted. This narrative review synthesizes current evidence linking chronic pain with impaired interoceptive processing and structural and functional alterations in the insular cortex. Particular attention is given to three biological mechanisms capable of affecting insular function and interoception: neuroinflammation and immune signaling, metabolic dysfunction, and chronic activation of stress-related neuroendocrine systems. We also summarize anthropogenic lifestyle exposures that may activate these mechanisms and discuss non-pharmacological strategies capable of modulating them. Integrating these findings within an interoceptive and allostatic framework suggests that chronic pain may partly reflect disturbances in the brain's capacity to accurately interpret and regulate internal bodily states. This perspective may help bridge biological mechanisms with behavioral and lifestyle interventions, opening new avenues for prevention and more comprehensive therapeutic strategies.

1. Introduction

Chronic pain is one of the leading causes of disability worldwide. It affects 18% of the population in developed countries and has profound personal, social and economic consequences (Sá et al., 2019; Stubhaug et al., 2024). Beyond its association with tissue injury, chronic pain is increasingly recognized as a complex, multidimensional condition involving persistent changes in neural processing, affective regulation, cognition, and bodily awareness (McCarberg and Peppin, 2019; Patel et al., 2025; Yang and Chang, 2019).

Contemporary pain science has made significant advances in identifying peripheral and central mechanisms implicated in chronification, including peripheral sensitization, central sensitization, maladaptive

neuroplasticity, and alterations in descending modulation (Lyndon, 2026). These advances have refined classification systems and led to the introduction of constructs such as central, nociplastic, or primary pain (Fitzcharles et al., 2021; Treede et al., 2019). Yet these conceptual developments have also generated substantial controversy. Critics argue that strict central-peripheral distinctions oversimplify a fundamentally distributed process and that some diagnostic labels function more as taxonomic placeholders than mechanistic explanations (Cohen et al., 2023; Párraga and Castellanos, 2023). They also claim that circular reasoning and gaps in translation between animal and human research continue to limit interpretability (Cohen et al., 2013; Leone et al., 2025). Meanwhile, mounting evidence indicates that chronic pain cannot be fully grasped through linear stimulus-response models, but rather

* Correspondence to: Department of Functional Biology and Health Sciences, Faculty of Physiotherapy, Pontevedra, University of Vigo. Campus da Xunqueira, s/n, Pontevedra 36005, Spain.

E-mail address: orlando.conde@uvigo.gal (O. Conde-Vázquez).

<https://doi.org/10.1016/j.neubiorev.2026.106791>

Received 25 March 2026; Received in revised form 20 May 2026; Accepted 31 May 2026

Available online 2 June 2026

0149-7634/© 2026 The Author(s). Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

emerges from the dynamic interplay of neural, immune, endocrine and contextual systems (Bijker et al., 2025; Lyndon, 2026; Pruijboom et al., 2024).

Within this evolving landscape, a recent meta-analysis has shown that the insular cortex (IC) plays a central role among all the affected brain areas associated with chronic pain (Zeng et al., 2025). Repeated structural imaging studies demonstrate alterations in insular grey matter volume and thickness, while functional investigations reveal abnormal activation and connectivity patterns. Neurochemical analyses also identify region-specific shifts in excitatory and modulatory signalling (Locatelli et al., 2025; Mandloi et al., 2023; Todd et al., 2024; Wang et al., 2018). Meanwhile, the insula is widely regarded as the primary cortical hub of interoception — the process by which the brain monitors, integrates and interprets signals arising from the internal environment (Gogolla, 2017; Locatelli et al., 2023). From this perspective, chronic pain is characterized by a paradoxical interoceptive profile: diminished objective accuracy in sensing internal signals coexisting with heightened subjective attention and reduced bodily trust (Horsburgh et al., 2024; Solcà et al., 2020). This imbalance suggests that chronic pain unfolds within an imprecise interoceptive landscape, where noisy or poorly integrated bodily inputs distort salience attribution and emotional appraisal. In this narrative review, we examine converging mechanistic pathways capable of reshaping insular structure and function, including neuroinflammation, metabolic dysfunction, and chronic stress-related neuroendocrine dysregulation. Despite their historical study in distinct domains, these processes converge on the insula and interconnected salience networks, resulting in alterations to excitability, connectivity, and predictive integration of bodily signals. The persistent involvement of the IC across inflammatory, metabolic, and stress-related conditions suggests that chronic pain may, at least in part, reflect a disorder of interoceptive integration, where altered internal signalling and maladaptive predictive processes stabilize pain as a dominant perceptual state.

Finally, the present study extends this perspective by discussing anthropogenic and lifestyle-related risk factors capable of activating these convergent mechanisms, and by considering whether interventions targeting metabolic health, stress regulation, and systemic inflammation may help restore insular integrity and recalibrate interoceptive processing.

2. Interoception, the insular cortex and chronic pain conditions

2.1. Impaired interoception and chronic pain

Interoception refers to the process by which the nervous system senses, integrates and interprets signals from within the body to create a real-time representation of the body's physiological state. This process transforms bodily signals (including pain) into conscious feelings and motivational states that guide behaviour and support homeostatic and allostatic regulation (Locatelli et al., 2023).

Interoceptive signals reach the insular cortex through vagal and spinal C and Aδ fibres that project to the nucleus tractus solitarius, parabrachial nucleus, and lamina I pathways of the spinal cord before relaying through specific thalamic nuclei toward the posterior insular cortex, particularly the dorsal granular fundus considered the primary interoceptive cortex. From these posterior sensory-interoceptive representations, information is progressively integrated within dysgranular and anterior agranular insular regions involved in autonomic regulation, motivational states, emotional salience, and behavioural responses (Berntson and Khalsa, 2021; Fermin et al., 2022). Preclinical data indicate that these pathways enable signals related to satiety, inflammation, cardiovascular activity, stress responses, and nociceptive input to converge within interconnected insular circuits (F. Li et al., 2025; Livneh et al., 2017; Z. Wang et al., 2025).

The cortical processing of interoceptive signals relies on a distributed network in which the IC plays a central integrative role (Shura et al., 2014). Accumulating evidence indicates that chronic pain is associated with a profound disruption of interoceptive processing and brain structural and functional alterations, mainly in the IC (Zeng et al., 2025). Across conditions, a paradoxical pattern consistently emerges: reduced objective interoceptive accuracy coexisting with heightened subjective attention to bodily sensations, reflecting a system that is simultaneously imprecise and hypervigilant (Horsburgh et al., 2024; Solcà et al., 2020).

Objective measures of interoceptive accuracy reveal a diminished capacity to detect internal physiological signals in multiple chronic pain conditions. Individuals with CRPS show impaired performance in heartbeat counting tasks and reduced cortical responses to cardiac signals, as indexed by attenuated heartbeat-evoked potentials (HEPs) (Solcà et al., 2020). Similar deficits in cardiac interoceptive accuracy have been reported in fibromyalgia (Duschek et al., 2017), where poorer performance correlates with greater negative affect and pain-related reactivity (Garfinkel and Eccleston, 2025). Importantly, interoceptive impairments may not be uniform across bodily domains. In endometriosis, deficits are more pronounced in visceral interoception—such as gastric or bladder signal discrimination—while cardiac accuracy may remain relatively preserved (Cantoni et al., 2025), suggesting modality-specific disruptions of interoceptive mapping. Comparable impairments have also been documented in musculoskeletal pain and migraine, where individuals exhibit reduced ability to discriminate levels of muscular tension (Blanchard et al., 1981; Di Lernia et al., 2016; Flor et al., 1992a). Beyond chronic pain, in people with chronic physical illnesses, poor symptom perception has recently been reported (Locatelli et al., 2025).

Alongside this loss of objective precision, there is a distinct and clinically relevant dissociation in subjective interoceptive sensitivity. Meta-analytic data suggest that individuals with chronic pain tend to score higher on measures of attentional focus towards bodily sensations, while scoring lower on dimensions related to bodily trust and self-regulation (Horsburgh et al., 2024). In other words, the results of the meta-analysis suggest that those with chronic pain display impaired interoceptive accuracy and enhanced interoceptive sensitivity. This pattern has been observed in various conditions, such as fibromyalgia, musculoskeletal pain, endometriosis and vulvodynia, where patients report difficulty in disengaging their attention from bodily sensations and experience their bodies as unsafe or unreliable (Cantoni et al., 2025; Horsburgh et al., 2024; Scarpina et al., 2025).

Systematic reviews together with theoretical models of interoceptive predictive processing suggest that reduced awareness or misinterpretation of bodily sensations—such as cardiac rhythms, fatigue, or visceral sensations—plays a critical role in the amplification of pain and its consolidation as the dominant bodily signal. When interoceptive precision is compromised, particularly in the perception of subtle physiological cues, the brain's capacity to predict and regulate internal states is diminished. Under these conditions, the salience system may become unstable, allowing pain to disproportionately capture attention, not necessarily because it is more intense, but because it remains the most coherent and reliably interpretable signal within an otherwise imprecise interoceptive landscape (Di Lernia et al., 2016; Garfinkel and Eccleston, 2025; Horsburgh et al., 2024). Furthermore, altered interoceptive processing may also interact with sensorimotor prediction mechanisms. Experimental induction of visuo-proprioceptive incongruence in frozen shoulder exacerbates pain and sensory discomfort, indicating that mismatches between predicted and actual bodily states are processed as signals of threat (Mertens et al., 2026). In chronic pain, such incongruence appears to be interpreted by interoceptive integration systems as evidence of compromised bodily integrity, further amplifying defensive responses and pain experience (Garfinkel and Eccleston, 2025; McCabe et al., 2009, 2007; McCabe and Blake, 2007).

Table 1

Anthropogenic risk factors capable of activating neuroinflammatory, metabolic, and stress-related mechanisms affecting interoceptive–insular function. BBB: blood brain barrier; GR: glucocorticoid resistance; HPA: hypothalamus-pituitary-adrenal; IR: insulin resistance; LGI: low grade inflammation; LR: leptin resistance.

Risk factor	Mechanisms affecting insular function and interoception		
	Neuroinflammation	Metabolic dysfunction	Chronic stress system activation
Western / ultra-processed diets	Microglial activation, BBB damage, accumulation of toxic amyloid (Więckowska-Gacek et al., 2021)	Hyperinsulinemia, IR, hyperleptinemia, LR, dyslipidaemia, LGI, gut dysbiosis, ectopic fat (Grinshpan et al., 2024; Mendoza-Herrera et al., 2021)	HPA axis hyperreactivity, central GR, sympathetic activation (Hryhorczuk et al., 2017; Shin et al., 2019)
Sedentary behaviour	Peripheral inflammation leading to microglia activation and progressive neurodegeneration (Burini et al., 2020; Wang et al., 2023)	IR, mitochondrial dysfunction, metabolic inflexibility, dyslipidaemia, LGI, ectopic fat (Pinto et al., 2023)	Sympathetic activation, decreased parasympathetic tone, HPA axis dysregulation (Chauntry et al., 2022; Daniela et al., 2022)
Sleep deprivation / circadian disruption	Astrocyte and microglial activation, aberrant synaptic pruning, glutamatergic excitotoxicity, BBB damage, altered glymphatic drainage (Herrero Babiloni et al., 2023; Ma et al., 2025; Xu et al., 2023)	IR, LR, dyslipidaemia, LGI, disrupt liver, muscle and adipose tissue metabolism (Briançon-Marjollet et al., 2015; Reutrakul and Van Cauter, 2018)	Central hyperarousal, sympathetic and HPA desynchronisation, decreased parasympathetic tone (Koch et al., 2017)
Social isolation / social defeat	Danger signals released in stress-responsive brain regions activating resident microglia (Al Omran et al., 2022; Weber et al., 2017)	IR, increase in hepatic gluconeogenesis, LGI (Baumer et al., 2023; Song et al., 2023)	Sympathetic and HPA desynchronisation, GR, decreased parasympathetic tone (Jung et al., 2015; Scatà et al., 2023)
Environmental pollutants	Oxidative stress, microglial activation, mitochondrial dysfunction, BBB damage (Campbell, 2004)	Oxidative stress, mitochondrial dysfunction, IR, LGI, adipogenesis, dyslipidaemia (Khalil et al., 2023; Mlynarska et al., 2025)	Sympathetic and HPA axis activation, GR (El Kouche et al., 2025; Thomson, 2019)
Smoking	Endothelial dysfunction, cerebral hypoperfusion, BBB damage, oxidative stress, microglial and astrocyte activation (Ewees et al., 2025; Khanna et al., 2013)	IR, dyslipidaemia, oxidative stress, LGI, lipotoxicity (Aslam et al., 2025; Mukharjee et al., 2020)	HPA axis and sympathetic dysregulation after chronic exposure (LaFond et al., 2024; Rohleder and Kirschbaum, 2006)

At the neural level, these perceptual and regulatory failures converge on dysfunction of the IC, a central hub for interoceptive integration (Quadt et al., 2018). Human neuroimaging and tractography studies indicate that the IC operates through a posterior-to-anterior hierarchy, transforming primary representations of bodily state into subjective feelings and motivational states (Shura et al., 2014). In people with chronic pain due to diabetic neuropathy, fibromyalgia, trigeminal neuralgia, spinal cord injury, psoriasis arthritis, and other chronic diseases, consistent reductions in insular grey matter volume, cortical thickness, and altered connectivity have been reported (Croosu et al., 2023a; Locatelli et al., 2025; Mandloi et al., 2023; Sunzini et al., 2025; Todd et al., 2024; Wang et al., 2018).

Converging evidence suggests that interoceptive processing and insular function may also differ according to sex. In humans, women generally report greater interoceptive sensibility and show stronger associations between subjective interoceptive measures and insular morphology (Alfano et al., 2023). Moreover, metanalytic data indicated that females demonstrated poor cardiac accuracy in counting and discrimination tasks in comparison with males (Prentice and Murphy, 2022). Experimental studies further indicate sex-dependent patterns of insular connectivity and pain-related processing. During acute visceral pain, female rodents show greater intra-insular functional connectivity reorganization and altered connectivity with the medial prefrontal cortex, thalamus, and brainstem compared with males (Wang et al., 2019). In a model combining temporomandibular disorder and irritable bowel syndrome, females exhibited increased and more persistent insular activity associated with visceral hypersensitivity, whereas males showed greater recruitment of descending inhibitory pathways and faster resolution of pain-related responses (Da Silva et al., 2024). Together, these findings suggest that sex-related differences in interoceptive processing and insular network organization may contribute to variability in chronic pain susceptibility and symptom expression.

A broad range of anthropogenic risk factors characteristic of modern environments may activate biological pathways capable of altering interoceptive processing and insular function through multiple behavioural and physiological routes. Among the most consistently implicated processes are neuroinflammatory signalling, metabolic dysfunction, and chronic activation of stress systems. Although these mechanisms have not yet been systematically integrated into dominant models of chronic

pain, they warrant consideration given their potential to bias insular structure and function. Table 1 summarises common risk factors that may contribute to the activation of these mechanisms.

2.2. Mechanisms affecting the structure and function of the insular cortex

2.2.1. Neuroinflammation and immune signalling

Neuroimmune and inflammatory signalling can influence interoceptive processing and IC function across peripheral, central, and systemic levels. It is a well-established fact that microglial activation disseminates throughout the brain parenchyma, including the IC, after peripheral insult (Labrakakis, 2023; Quadt et al., 2018). Experimental inflammatory challenges in humans provide direct evidence that peripheral immune activation rapidly alters insular physiology. For example, the administration of lipopolysaccharide or typhoid vaccine increases metabolic activity and blood-oxygen-level-dependent responses in the mid/posterior and anterior insula within hours, alongside microstructural changes detectable with quantitative magnetization transfer imaging (Hannestad et al., 2012; Harrison et al., 2015, 2009; Savitz and Harrison, 2018). These effects are biologically plausible given that circulating cytokines can access the brain through circumventricular organs (Dantzer et al., 2008) or endothelial pathways (Banks, 2016; Wohleb et al., 2015), while experimental animal studies demonstrate that vagal afferents relay immune information to the caudal nucleus of the solitary tract and subsequently to the insula (Goehler et al., 2000), establishing parallel humoral and neural routes of immune-to-brain communication.

In line with these experimental findings, peripheral inflammatory markers such as C-reactive protein (CRP) and interleukin-6 have been shown to correlate with reduced functional connectivity between the insula/frontal operculum and the posterior cingulate cortex, as well as broader dysconnectivity within large-scale networks involved in interoceptive and salience processing (Aruldass et al., 2021). In addition, cortical thinning of the IC was observed in patients with ankylosing spondylitis-induced low back pain (Wu et al., 2013). Human studies using voxel-based morphometry have shown that chronic neuropathic pain and inflammatory states result in a distinct pattern of decreased grey matter volume (GMV) in the anterior insula and increased GMV in the posterior insula (Gustin et al., 2011), and reductions in GMV across

the thalamus, primary somatosensory cortex, and nucleus accumbens are observed concurrently with insular changes in chronic pain individuals (Pan et al., 2015; Wang et al., 2021). In rats, in vivo microdialysis has demonstrated an increase in extracellular serotonin and its metabolite 5HIAA within the IC following carrageenan-induced inflammation (Coffeen et al., 2024), while synaptic remodelling involving the phosphorylation of GluA1 AMPA receptor subunits (Qiu et al., 2014) and increased NMDA receptor expression (Qiu et al., 2013) has been directly demonstrated in the IC of neuropathic mice. Longitudinal and treatment-monitoring studies reinforce a causal contribution of immune activity to these neural changes: anti-TNF α therapy in rheumatoid arthritis modifies insular responses within 24 h, preceding measurable peripheral clinical improvement (Hess et al., 2011), while effective surgical treatment of neuropathic pain can reverse insular cortical thinning (DeSouza et al., 2015), indicating that structural abnormalities remain plastic and dependent on ongoing nociceptive or inflammatory drive.

Beyond peripheral signalling, convergent evidence indicates that centrally generated neuroinflammation also contributes to insular dysfunction. Human TSPO-PET imaging demonstrates widespread microglial activation in inflammatory neuropsychiatric states (Setiawan et al., 2015), whereas FDG-PET, magnetic resonance spectroscopy, and quantitative magnetization transfer studies reveal, respectively, increased glucose metabolism (Hannestad et al., 2012), elevated posterior insular glutamate (Harris et al., 2009), and rapid microstructural alterations (Harrison et al., 2015) associated with fatigue, malaise, and reduced pain thresholds (Harrison et al., 2015; Labrakakis, 2023). However, it is important to note that much of this evidence emerges in the context of peripherally induced inflammation, and therefore does not unequivocally establish fully autonomous, primary neuroinflammation within the insula. Preclinical studies additionally suggest that the insula may encode prior inflammatory experiences through distributed neuronal ensembles capable of reinstating peripheral immune responses when reactivated, (Koren et al., 2021; Koren and Rolls, 2022; Rolls, 2023). However, for this neuroimmunological memory to be generated correctly, optimal recognition of neuroimmune inputs by the IC should be necessary, and experimental animal studies and lesion evidence reviewed by Gogolla demonstrated that when the IC is damaged, the recognition and valence of sensory input, as well as the regulation of emotion, are compromised (Gogolla, 2017).

In addition to the alterations that inflammation can cause in the IC, research has been conducted on the direct effects on interception. Evidence synthesized from experimental inflammatory challenge studies and contemporary interoceptive frameworks suggests that inflammation impairs the objective ability to accurately sense internal bodily signal (Aruldass et al., 2021; Quadt et al., 2018; Savitz and Harrison, 2018), while subjective interoceptive sensitivity may paradoxically increase, generating inaccurate or noisy metacognitive awareness (Savitz and Harrison, 2018). Within the Interoceptive Predictive Processing (IPP) framework, it has been proposed that inflammation causes a mismatch between descending predictions and actual afferent inputs, leading to persistent prediction errors that the brain may eventually ignore, resulting in the "locked-in" emotional numbness seen in depression (Barrett et al., 2016; Quadt et al., 2018). Inflammation-related dysconnectivity within salience-related networks further biases attention toward pain and bodily distress and has been associated with fatigue, malaise, anhedonia, and alexithymia (Quadt et al., 2018), shifts motivational priorities away from reward-directed behaviour and enhancing sensitivity to pain (Harrison et al., 2016; Savitz and Harrison, 2018). Finally, poor symptom perception has been recently linked to chronic diseases such as diabetes, cancer, and heart failure (Locatelli et al., 2025), all of which are associated with LGI (Bertero et al., 2024; Cifuentes et al., 2025). Together, these findings support a model in which immune activity reshapes sensory perception and emotional

interpretation of internal bodily states, which may explain, at least in part, the persistence of pain.

2.2.2. Metabolic dysfunction

Accumulating evidence suggests that metabolic dysfunction — encompassing insulin and leptin resistance, adipose tissue inflammation, and disrupted energy-balance signalling — can directly and indirectly alter interoceptive processing and insular function, thereby contributing to affective dysregulation and chronic pain vulnerability. Convergent findings from human neuroimaging studies, preclinical cellular studies, and theoretical interoceptive models suggest that the insula functions as a key neural interface through which metabolic signals shape bodily awareness, motivational states, and nociceptive sensitivity.

In humans, the insula has been shown to behave as a primary insulin-responsive cortical region (Cui et al., 2022; Kullmann et al., 2016). Following intranasal insulin administration in healthy individuals, increased cerebral blood flow has been observed (Schilling et al., 2014), a response that is markedly blunted in obesity and type 2 diabetes (T2D), consistent with central insulin resistance (Edwin Thanarajah et al., 2019; Kullmann et al., 2015; Tschritter et al., 2006). Functional neuroimaging studies have shown that the insula has also been demonstrated to dynamically track physiological satiation: its activity typically decreases following glucose ingestion or feeding (Frank et al., 2013; Kullmann et al., 2016; Zhao et al., 2025), whereas this inhibitory response is absent in diabetes (Ten Kulve et al., 2015), indicating impaired detection of bottom-up metabolic signals (Mehrfhof et al., 2025). Network-level alterations accompany these effects, including reduced functional connectivity within the default mode network and disrupted coupling between insular activity and reward-related circuitry, particularly in cases of hyperphagic depression (Simmons et al., 2020, 2016), T2D (Hoogenboom et al., 2014; Musen et al., 2012), and obesity (Kullmann et al., 2012). The presence of structural and functional abnormalities has been demonstrated to further support the hypothesis of insular involvement, with decreased mid-insular activation linked to impaired interoceptive awareness in obesity individuals (Brooks et al., 2013; Simmons et al., 2013), heightened anterior insula reactivity to food cues associated with body mass index and motivational drive (Aboushaar and Serrano, 2024; Bud Craig, 2009; Elenkov and Chrousos, 2002; Roekner et al., 2021; Uddin et al., 2017) and reduced anterior insular surface area has been observed in hyperphagic depressive phenotypes (Toenders et al., 2020).

Preclinical research provides mechanistic resolution for these observations. The insula contains leptin receptor-positive glutamatergic neurons whose excitability and firing increase in response to leptin, and direct intra-insular leptin manipulation alters feeding behaviour and body weight, demonstrating that long-term adiposity signals are encoded within insular circuitry. These neurons project toward reward-related regions such as the basolateral amygdala, linking metabolic state sensing with motivational behaviour (Zhao et al., 2025). Parallel evidence shows that insulin modulates synaptic plasticity, including hippocampal long-term potentiation, which becomes impaired in diabetic or high-fat diet models but can be restored by insulin signalling (Barber et al., 2021; Kullmann et al., 2016). Together, these findings indicate that metabolic hormones act as bottom-up interoceptive inputs shaping neural plasticity and behavioural regulation.

From an interoceptive systems perspective, metabolic dysfunction degrades the precision of bodily signalling. Obesity-related insulin and leptin resistance generate faulty afferent metabolic information, reducing the reliability of bottom-up interoceptive signals and forcing the brain to rely on inaccurate internal predictions of energy state (Alhadeff and Yapici, 2024; Mehrhof et al., 2025). This disturbance is consistent with theoretical models of interoceptive energy allostasis, in which disrupted hormonal calibration produces persistent prediction

errors, maladaptive top-down control, apathy, anhedonia, or hypersensitivity to food reward (Barrett et al., 2016; Kleckner et al., 2017; Mehrhof et al., 2025; Stephan et al., 2016). Diet-induced obesity may additionally impair vagal gut-brain communication, potentially disrupting the integration of short-term satiety signals within insular predictive models (Tellez et al., 2013; Van Galen et al., 2023).

These metabolic and interoceptive disturbances extend to chronic pain risk. Visceral adiposity and adipose-derived inflammation are strongly associated with persistent pain prevalence and severity, outperforming body mass index as predictors (Wright et al., 2010; Xu et al., 2025). Mechanistic and conceptual reviews suggest that pro-inflammatory cytokines released from dysfunctional adipose tissue sensitize peripheral and central nociceptive pathways and contribute to anhedonia and neurodegeneration (Kempuraj et al., 2017; Milaneschi et al., 2020), while experimental animal studies and translational reviews indicate that insulin and leptin resistance within mesolimbic dopamine circuits dampen reward responsiveness and promote depression-like behaviours (Bruijnzeel et al., 2011; Kleinridders and Pothos, 2019), frequently comorbid with chronic pain (Reis et al., 2024). Neuroimaging in painful diabetic neuropathy further demonstrates impaired activity in somatosensory, cognitive, and insula-related pain-processing regions (Zhang et al., 2019).

Importantly, interventional and longitudinal evidence suggests that these alterations are at least partially reversible. Weight loss following bariatric surgery normalizes insular responses to food cues and reverses obesity-related abnormalities in brain glucose metabolism (Frank et al., 2014; Tuulari et al., 2013). Exercise improves insulin sensitivity within reward circuitry linked to insular integration (Kullmann et al., 2022, 2016), whereas GLP-1 receptor agonists reduce food-related activation in the insula and associated limbic regions (Van Bloemendaal et al., 2014). Conversely, even brief exposure to high-calorie diets can rapidly impair central insulin action (Kullmann et al., 2025), underscoring the dynamic sensitivity of insular and interoceptive networks to metabolic state. Improvements in metabolic health—including caloric restriction, hormonal modulation, and inflammation reduction—are also associated with enhanced satiety signalling (Teeuwisse et al., 2012; Zhao et al., 2025), which represents an improvement in the brain's ability to restore interoceptive prediction, and such metabolic enhancements were proposed to alleviate chronic pain burden (Xu et al., 2025).

2.2.3. Chronic stress system activation

A growing body of evidence indicates that chronic activation of stress-related systems is closely associated with structural, functional, and perceptual alterations within the insular cortex and broader interoceptive networks. Prolonged activation of the hypothalamic-pituitary-adrenal (HPA) axis and the sympatho-adreno-medullary (SAM) system produces cumulative allostatic load, which can impair the brain's ability to monitor internal bodily states and regulate affective responses (Schulz and Vögele, 2015; Vachon-Presseau, 2018).

In humans, chronic stress exposure is consistently linked to reduced interoceptive accuracy—reflected in poorer heartbeat detection performance and diminished HEPs—as observed in conditions characterized by sustained sympathetic activation such as hypertension or early-life adversity (Schulz et al., 2022; Yoris et al., 2018). Structural neuroimaging further shows that greater stress severity in chronic pain populations is associated with reduced GMV in the right posterior insula (Quidé et al., 2025), a region central to sensory-discriminative pain processing (Bud Craig, 2009; Uddin et al., 2017), whereas larger volume in the left anterior insula has been interpreted as a potential marker of compensatory adaptation or resilience (Quidé et al., 2025; Roekner et al., 2021). At the network level, human neuroimaging evidence that chronic stress contributes to corticolimbic reorganization, shifting activity from primary sensory regions toward medial prefrontal and amygdalar circuits involved in emotional valuation and salience attribution (Vachon-Presseau, 2018), a transition that parallels the

chronification of pain and the emergence of maladaptive affective states such as catastrophizing and hypervigilance (Aboushaar and Serrano, 2024). Sustained HPA axis activation may also evolve into hypocortisolism (Elenkov and Chrousos, 2002), as well as into cortisol resistance and alterations in intracellular β 2-adrenergic signalling (Walsh et al., 2021), weakening immune regulation and promoting LGI that further perturbs brain structure and pain modulation (Marsland et al., 2015).

Experimental and longitudinal observations support a mechanistic role for stress-hormone signalling in shaping insular function. Basal cortisol levels show inverse associations with HEPs amplitudes, suggesting that chronic HPA axis activation may reduce the brain's sensitivity to internal bodily signals (Schulz et al., 2013; Schulz and Vögele, 2015), whereas pharmacological noradrenergic challenges disproportionately reduce interoceptive accuracy in individuals with histories of chronic adversity, suggesting enduring alterations in adrenergic sensitivity within interoceptive circuits (Schulz et al., 2022). Experimental data shows that acute elevations in cortisol can transiently enhance cortical representation of visceral signals (Flasbeck et al., 2025), while conceptual models propose that persistent dysregulation of stress systems may progressively reduce sensitivity to internal bodily information, contributing to a shift from adaptive to maladaptive interoceptive processing over time (Schulz and Vögele, 2015). Converging longitudinal data further demonstrate that as back pain becomes chronic, neural representation migrates from posterior insular sensory coding toward limbic-affective circuitry (Hashmi et al., 2013), highlighting stress-related network plasticity as a key feature of pain persistence.

Preclinical research offers complementary mechanistic insight, demonstrating that chronic stress directly alters insular excitability, synaptic plasticity, and gene expression. Chronic restraint stress in rodents induces visceral hypersensitivity and hyperalgesia through glucocorticoid-dependent activation of the IC, effects that are reversed by local glucocorticoid-receptor blockade (X. Li et al., 2025). Physiological stress exposure (e.g., foot shock) has been shown to produce a complete loss of long-term potentiation in the anterior insula, while psychological stress (witnessing a conspecific in fear) merely reduces it, suggesting that direct physiological trauma may damage the capacity of the IC for cognitive memory formation more severely than psychological stress (Shi et al., 2022). In adult rats, prenatal stress induces sex-specific transcriptomic vulnerability signatures involving inflammatory pathways in males and serotonergic dysregulation in females (Zonca et al., 2025), while corticotropin-releasing factor signalling suppresses local GABAergic inhibition and promotes excitatory information flow through insular circuits (Rieger et al., 2022). Furthermore, although chronic stress has been shown to produce CS, lesions of the bilateral insula markedly inhibit stress-induced visceral hypersensitivity (Yi et al., 2014), underscoring the necessity of this region for maintaining stress-related pain states.

A schematic representation of the proposed mechanisms is shown in Fig. 1.

Despite the IC being frequently conceptualised as a unified interoceptive hub (Craig, 2002), converging evidence from human and non-human primate studies indicates a more complex functional organisation than the classical posterior-interoceptive/anterior-awareness model. Neuroanatomical and stimulation studies indicates that the IC is organised along both anteroposterior and dorsoventral axes, with relatively specialised subregions that support distinct nociceptive, visceral, autonomic, motivational, and socio-emotional functions (Evrard, 2019; Kurth et al., 2010; Simone et al., 2025). In humans, direct electrical stimulation studies have shown that the posterior insula is critically implicated in nociceptive and somatosensory processing and can reliably evoke painful sensations. By contrast, stimulation of anterior and dysgranular regions more frequently elicits visceral sensations and autonomic responses (Kurth et al., 2010; Mazzola et al., 2019). Posterior regions also demonstrate a somatotopic organisation distributed along a spino-cranial axis (Simone et al., 2025), while anterior

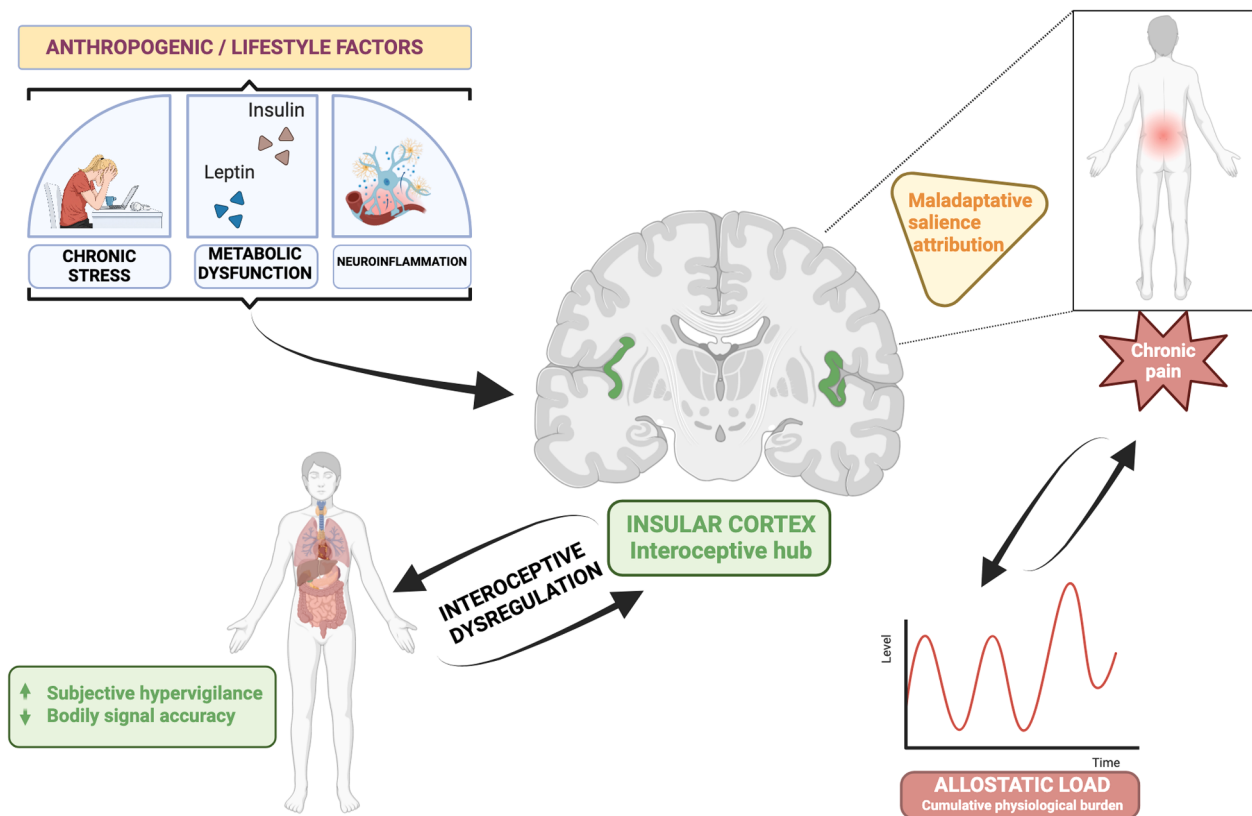


Fig. 1. Conceptual model of interoceptive dysregulation in chronic pain. Schematic overview of the proposed framework linking anthropogenic and lifestyle-related exposures with chronic pain. These factors converge on chronic stress, metabolic dysfunction, and neuroinflammatory processes, which collectively influence the insular cortex as a central hub of interoceptive processing. Alterations in insular function may disrupt the integration of internal bodily signals, leading to reduced interoceptive accuracy and increased hypervigilance. This imbalance may bias salience attribution, promoting pain as a dominant perceptual signal. Over time, these processes are embedded within a feedback loop involving cumulative physiological burden (allostatic load), contributing to the persistence of chronic pain. Created with BioRender.com.

regions exhibit a stronger association with salience detection, emotional processing, autonomic regulation, and feeding-related functions (Cai and Menon, 2025; Simone et al., 2025; Uddin, 2015). Complementary evidence from macaque studies further refines this organisation, showing that posterior dorsal sectors receive high-resolution interoceptive afferents and are preferentially linked to body-centred and skeletomotor functions, whereas ventral and anterior agranular regions are more involved in socio-emotional and affiliative behaviours and act as major visceromotor output areas involved in autonomic and behavioural regulation (Evrard, 2019). Collectively, these findings suggest that the mechanisms under discussion in this review may not affect the insula uniformly, but rather preferentially influence specialised sub-regions depending on the dominant physiological disturbance. Within this theoretical framework, metabolic dysfunction may predominantly affect anterior regions involved in feeding behaviour and energy regulation, chronic stress may preferentially alter ventral anterior insula-limbic connectivity, and inflammatory or nociceptive processes may more strongly impact posterior body-specific interoceptive representations.

3. Discussion

The results of the present review suggest that chronic pain may develop within a destabilized interoceptive system influenced by cumulative biological burden. Across diverse chronic pain conditions, the IC emerges as the most consistently altered cortical region, with converging evidence of reduced GMV and cortical thickness, micro-structural changes, metabolic alterations, neurochemical imbalance, and large-scale connectivity disruptions. This uniformity observed in

various pain conditions, in conjunction with other chronic pathologies, indicates that insular involvement is not merely coincidental but rather indicative of a shared neural substrate that underlies persistent pain (Briançon-Marjollet et al., 2015; Croosu et al., 2023b; Reutrakul and Van Cauter, 2018; Scatà et al., 2023; Sunzini et al., 2025; Więckowska-Gacek et al., 2021; Xu et al., 2023; Yokum et al., 2011; Zeng et al., 2025).

In chronic pain, objective interoceptive accuracy is reduced, while subjective attention towards bodily sensations is heightened and bodily trust diminished (Di Lernia et al., 2016; Duschek et al., 2017; Garfinkel and Eccleston, 2025; Horsburgh et al., 2024; Solcà et al., 2020). This dissociation is indicative of an imprecise yet hypervigilant system, whereby bodily signals are poorly discriminated but disproportionately prioritised. In such circumstances, pain could assume a privileged status not simply because it is stronger, but because it is clearer and more interpretable than other ambiguous internal signals. This opens the possibility that chronic pain may, at least in part, be a disorder of body perception. Rather than reflecting continuous peripheral injury that leads to central sensitisation, we hypothesised that pain may persist because the internal model of the body has become distorted. The insula, given its hierarchical organisation and role in transforming primary bodily signals into subjective feeling states (Quadt et al., 2018; Shura et al., 2014), is uniquely positioned to mediate this transformation. The structural reductions and altered functional organisation of the IC suggest that the integration of sensory, affective, and motivational information is reshaped over time. As pain becomes chronic, there appears to be a migration of representation from posterior sensory mapping to anterior affective and evaluative circuits (Hashmi et al., 2013; Vachon-Presseau, 2018), reinforcing the interpretation of bodily signals through emotional and salience-based filters. This aligns with

longitudinal and transversal findings showing that cognitive and affective factors predict pain chronification (Fillingim et al., 2025; Kelleher et al., 2025), and with evidence linking insular changes to somatic symptom severity (Quidé et al., 2025).

The concept of allostatic load provides a unifying framework for understanding how chronic pain becomes embedded within interoceptive circuits (Guidi et al., 2021). Repeated activation of the stress axis, chronic immune signalling and metabolic dysfunction generates a cumulative biological burden that reshapes neural architecture and function (Aruldass et al., 2021; Cui et al., 2022; Dantzer et al., 2008; Quidé et al., 2025). Rather than a chronification of a localized lesion or linear sensitization cascade, the aetiology of chronic pain may be better understood as reflecting instability within a bio-social regulatory ecosystem (Borsook, 2025) in which the insula functions as a central integrative node (Zeng et al., 2025). Prospective data lend further support to this interpretation. Large cohort studies demonstrate that a greater burden of CNS symptoms—sleep disturbance, affective dysregulation, neuroticism and stress exposure—in pain-free adults predicts the subsequent development of chronic primary pain, but not other pain categories over a 10-year period (Kelleher et al., 2025). These findings suggest that pre-existing central vulnerability may confer risk for certain pain phenotypes, while still leaving open the question of whether such alterations represent primary pathology or markers of systemic dysregulation. Furthermore, allostatic load indices have been shown to prospectively predict the development of chronic pain (Borsook, 2025). Longitudinal neuroimaging studies demonstrate that as back pain progresses to a chronic state, there is a shift in activity from sensory regions to corticolimbic circuits (Hashmi et al., 2013), and errors in prediction in reward circuitry have been shown to be a reliable predictor of transition to chronic pain (Büchel, 2023).

Within this framework, the insula functions as both a mediator and an amplifier. As primary interoceptive cortex (Gogolla, 2017; Shura et al., 2014), it integrates metabolic, immune, autonomic, and nociceptive signals into a unified representation of bodily state. Under sustained stress, inflammation, or metabolic dysfunction, this integrative process becomes biased. Chronic HPA-axis activation, sympathetic overdrive, and glucocorticoid dysregulation impair interoceptive accuracy (Schulz et al., 2013, 2022; Schulz and Vögele, 2015; Yoris et al., 2018), peripheral and central inflammatory signalling alters insular microstructure, metabolism, and connectivity (Aruldass et al., 2021; Hannestad et al., 2012; Harrison et al., 2009), and insulin and leptin resistance degrade the precision of metabolic afferent signalling and disrupt insular–reward coupling (Kullmann et al., 2015; Tschrirter et al., 2006; Zhao et al., 2025). In accordance with the latter, recent theoretical work has proposed that metabolic signals are embedded within a broader interoceptive system through which the brain predicts and regulates internal energetic states. Rather than acting in isolation, hormones such as insulin, leptin or ghrelin are integrated into hierarchical predictive models that guide motivation and reward processing. Disruptions in this interoceptive energy allostasis may therefore alter mesolimbic dopaminergic function, shifting effort allocation, reward sensitivity and behavioural engagement. Within this framework, cumulative allostatic load does not simply reflect peripheral wear and tear, but a progressive destabilization of predictive brain–body regulation, in which impaired metabolic signalling, inflammation and stress converge to bias internal models toward energy threat or scarcity. Such biased predictions may sustain motivational withdrawal, anhedonia and altered salience attribution, while simultaneously reinforcing metabolic dysfunction, generating a self-perpetuating loop between bodily dysregulation and affective symptoms (Mehrhof et al., 2025).

These observations are also consistent with the concept of “allo-sensitization”, whereby repeated physical, psychological, socioeconomic, or environmental stressors progressively reduce resilience and amplify pathological responses across interacting regulatory systems (Borsook, 2025). From this perspective, chronic pain may be better understood not solely as a disorder of nociceptive amplification, but as a

dysregulation of the broader brain–body ecosystem that shapes interoceptive inference and salience allocation. In this framework, allostatic load captures the cumulative burden imposed by interacting neural, endocrine, immune, metabolic, and social stressors, and chronic pain may reflect instability within such a bio-social ecosystem rather than dysfunction within a single pathway (Liang and Booker, 2024). This interpretation is also compatible with evolutionary and exposome accounts of chronic disease. Anthropogenic and lifestyle-related exposures, including poor diet quality, visceral adiposity, physical inactivity, sleep disruption, chronic psychosocial stress, loneliness, artificial light exposure, and environmentally adverse conditions, may act in concert to maintain prolonged activation of stress systems, low-grade inflammation, and metabolic dysregulation (Buntinx et al., 2025; Pruimboom et al., 2024). In that context, mismatch between phenotype and exposome may bias insular processing toward threat, bodily deficit, and maladaptive salience attribution, thereby lowering the threshold at which pain becomes a coherent and dominant perceptual state (Pruimboom et al., 2024).

Recent evidence further supports the integration of stress-system dysfunction into this model. A systematic review and meta-analysis in chronic primary pain found that greater pain sensitivity was associated with higher basal cortisol, lower high-frequency heart rate variability during recovery, and higher heart rate across different phases of the stress response, implicating both HPA-axis and autonomic dysregulation, although the certainty of evidence remained limited by methodological heterogeneity (Vyverman et al., 2026). These findings fit well with the present framework, in which repeated stress exposure does not simply accompany chronic pain, but may progressively destabilize interoceptive and salience-processing systems that converge on the insula and related networks (Vyverman et al., 2026). If so, therapeutic models may benefit from moving beyond analgesia alone toward multimodal strategies aimed at reducing allostatic load and restoring interoceptive precision. Such approaches may include improving sleep and circadian regularity, enhancing metabolic health, reducing excess adiposity and inflammatory burden, increasing physical activity, and targeting chronic stress and maladaptive threat-related appraisal through psychologically informed interventions (Hamed Hamed et al., 2023; Liang and Booker, 2024; Navarro-Ledesma et al., 2024b; Núñez-Cortés et al., 2025b; Runge et al., 2024). This does not imply that lifestyle factors fully explain chronic pain, nor that a single causal pathway operates across all phenotypes. However, prospective evidence indicates that allostatic load predicts future chronic pain burden, particularly through metabolic dysfunction, while systematic reviews support sleep disturbance as a risk factor for chronic musculoskeletal pain and identify physical activity as a central pillar of lifestyle-based management (Liang and Booker, 2024; Núñez-Cortés et al., 2025b; Runge et al., 2024). Together, these findings support the rationale for integrated interventions acting across metabolic, immune, autonomic, and affective domains (Borsook, 2025; Hamed Hamed et al., 2023; Liang and Booker, 2024; Runge et al., 2024).

If chronic pain is partly maintained by a dysregulated interoceptive system under conditions of elevated allostatic load, then treatment models may need to move beyond analgesia alone towards multimodal strategies aimed at restoring interoceptive precision and reducing cumulative biological burden. Importantly, not all non-pharmacological interventions are expected to act directly on the insula. Rather, they may influence the interoceptive system at different levels; by reducing systemic drivers such as inflammation, metabolic dysfunction, and chronic stress-axis activation, or by modulating peripheral, autonomic, nociceptive, and affective signalling that ultimately contributes to the bodily information integrated within insular-related networks.

3.1. Clinical implications

The interventions discussed below are included as representative non-pharmacological approaches that may interact, through different

mechanisms, with the interoceptive–allostatic processes considered in this review. Some may act primarily by reducing systemic inflammatory, metabolic, or stress-related burden, whereas others may modulate peripheral, autonomic, nociceptive, or affective signalling that ultimately contributes to the bodily information integrated within insular-related networks.

Based on the proposed mechanisms that directly affect interoception and in line with recent literature (Nijs et al., 2024), interventions for chronic pain should individually assess which risk factors present in the individual's life may be linked to the activation of the mechanisms investigated in this manuscript, in order to eliminate them where possible or minimise their impact when they cannot be completely eliminated. In addition, identifying risk factors (e.g., poor diet, sleep problems, social defeat, or sedentary lifestyle) helps to select and individualise interventions and to consider the person's context when planning treatment, something that the literature on chronic pain considers very important (McCracken, 2023; Sherriff et al., 2022). On the other hand, there are numerous non-pharmacological interventions to act on neuroinflammation, metabolic dysfunction, and chronic activity of the stress axes.

Diet affects the immune system, and systematic reviews have shown that a diet rich in anti-inflammatory nutrients reduces the severity of pain (Brain et al., 2019) and may even reduce the risk of neurodegeneration (Kurowska et al., 2023), while calorie restriction in animals has been shown to reduce microglial activity (Liu et al., 2018). In this regard, the type of dietary fats is vitally important, as diets rich in trans fatty acids, saturated fatty acids and omega-6 promote neuroinflammation, while diets higher in monounsaturated fatty acids, omega-3 and sphingolipids can reduce neuroinflammation (Custers et al., 2022). Likewise, diet improves metabolic dysfunction, especially by restoring insulin sensitivity, reducing lipotoxicity, and normalising nutrient signalling. The greatest benefits are seen with Mediterranean-type patterns, reduction of refined carbohydrates, and calorie restriction or intermittent fasting strategies tailored to the individual (Feng et al., 2025; Murillo-Cancho et al., 2025). In addition to their composition, meal times must be taken into account in order to optimise results (Mihaylova et al., 2023). Regarding the influence of diet on stress axes, animal studies show that diet regulates stress axes mainly by modulating basal activation and reactivity of the HPA axis, serotonergic signalling, and gut microbiota. Western diets rich in fat/sugar tend to hyperactivate or dysregulate these axes (Niu et al., 2019; Shin et al., 2010; Zhang et al., 2024), while certain patterns and nutrients (omega-3, tryptophan, better overall diet quality) can dampen the stress response and normalise neuroendocrine signalling (Peixoto et al., 2024; Shaikh et al., 2018). Finally, diet plays a fundamental role in modulating the microbiota (Beam et al., 2021). The microbiota has been demonstrated to act as a peripheral pain generator via the gut-brain axis (Cai et al., 2025; Meerschaert and Chiu, 2025), supported by the results of a recent systematic review suggesting that faecal microbiota transplantation improves pain in people with fibromyalgia and irritable bowel syndrome (Martín Pérez et al., 2025).

Physical exercise is proposed as a powerful immunomodulation strategy, as shown by a 20-year systematic review analysing its effects on autoimmune diseases (Luo et al., 2024). Numerous experimental studies show that exercise reduces neuroinflammation, glial activation and oxidative stress (Chen et al., 2025; Choi et al., 2024; De Miguel et al., 2021), while improving myelination (Hahn et al., 2025) and levels of anti-inflammatory cytokines (Zheng et al., 2024). The effects of exercise on metabolic dysfunction have been extensively researched. In individuals with type 2 diabetes or metabolic syndrome, structured exercise programs (aerobic, resistance, or combined) lasting 8–24 weeks reduce fasting glucose, insulin resistance, and HbA1c, even in the absence of major weight loss (Liang et al., 2021; Sampath Kumar et al., 2019; J. Wang et al., 2025). Exercise also has a modulating effect on the HPA axis, reducing chronic stress and increasing physiological and psychological resilience to stress (Franklin et al., 2021; Yilai et al.,

2025). It also improves mood, sleep, self-esteem, and provides distraction and social support, all of them key factors in alleviating chronic stress (Herbert, 2022; Hossain et al., 2024). The justification for physical exercise as a therapeutic strategy for chronic pain is even more important considering that a recent large-scale study showed that physical inactivity is the most important unhealthy lifestyle factor for pain severity in older adults (Núñez-Cortés et al., 2025a). Person-centred strategies, education, and accessible environments have been identified as key factors for effectively promoting physical activity in individuals living with chronic pain (Leese et al., 2024).

Sleep and circadian rhythm interventions have shown potential to reduce neuroinflammation by modulating microglia and astrocytes, decreasing systemic cytokine levels and increasing the clearance of brain metabolites (Camberos-Barraza et al., 2024; Müller and Di Benedetto, 2025; Zielinski and Gibbons, 2022). Just one night of poor sleep can affect the glymphatic drainage of the brain, impacting neuroimmune interactions (Ma et al., 2025). Interventions that increase sleep show consistent but generally moderate effects on weight, insulin sensitivity and cardiometabolic profile (Depner et al., 2014; Duan et al., 2023), although a meta-analysis has shown that the effects of sleep improvement on glucose metabolism are still inconclusive (Kothari et al., 2021). In terms of the chronic activity of stress axes, there is evidence that interventions targeting sleep and the circadian rhythm can reduce and synchronise the persistent activation of the HPA axis and autonomic nervous system, particularly when addressing issues of chrono-disruption and poor sleep quality over the medium to long term (Agorastos and Olf, 2021; Laufer et al., 2025; Van Dalfsen and Markus, 2018). It is important to note that sleep interventions for pain, including sleep hygiene (i.e. healthy sleep habits), mindfulness, relaxation training, and cognitive behavioural therapy, have been shown to improve sleep and alleviate chronic pain conditions (Abolhosseini et al., 2025).

Photobiomodulation (PBM) has also emerged as a potentially relevant non-pharmacological strategy within this framework (De Oliveira et al., 2022; González-Muñoz et al., 2023). Experimental and translational studies suggest that PBM may exert anti-inflammatory and immunomodulatory effects by reducing oxidative stress, modulating inflammatory signalling, and promoting tissue repair (Al Balah et al., 2025; Hamblin, 2017). With respect to metabolic dysfunction, PBM appears to influence mitochondrial function and cellular bioenergetics, mechanisms that may be relevant in conditions characterised by impaired energy regulation and persistent nociceptive or inflammatory drive (Al Balah et al., 2025; Hamblin, 2018). In relation to stress-related physiology, the available literature is more limited, but some authors have proposed that PBM may support cellular resilience and modulate autonomic or neurophysiological regulation, although these mechanisms remain less clearly established in chronic pain populations (Afhami et al., 2025; Hamblin, 2018). In chronic pain, these effects may be relevant insofar as reducing peripheral inflammatory and nociceptive input could alter the intensity or salience of bodily signals reaching higher-order interoceptive networks (De Oliveira et al., 2022; Ferreira et al., 2026; Navarro-Ledesma et al., 2024a). Emerging evidence also suggests that PBM may influence the gut microbiota and the gut–brain axis, potentially through effects on intestinal bioenergetics, epithelial barrier integrity, and immune–metabolic signalling (Da Silva et al., 2025; N. F. Guimarães et al., 2025). Recent reviews describe this as a plausible extension of PBM's systemic actions, while exploratory experimental studies report shifts in microbial composition and metabolites linked to inflammatory and neurobiological regulation (Cao et al., 2025). Although this literature remains preliminary and is still largely preclinical, these mechanisms are relevant to the present framework because microbiota-related changes could, in principle, modify inflammatory tone, visceral afferent signalling, and other bodily inputs that contribute to interoceptive processing (Liebert et al., 2019). However, although recent reviews suggest promising analgesic effects and a favourable safety profile in some chronic pain conditions, the

clinical literature remains heterogeneous in terms of protocols, populations, and outcomes (Ferreira et al., 2026; Son et al., 2025). Accordingly, PBM may currently be best considered as an adjunctive approach within a broader multimodal model rather than as a core strategy for restoring interoceptive–insular regulation.

Another promising strategy is intermittent hypoxia (IH) therapy. In preclinical models of neurodegeneration, moderate IH has been shown to exert neuroprotective and anti-inflammatory effects. In Alzheimer's disease models, it improves memory, reduces amyloid- β plaque burden, and lowers pro-inflammatory cytokines in the CNS (Serebrovska et al., 2025; Yue et al., 2021). In mice exposed to chronic hypoxia, intermittent hypoxic conditioning reverses neurological deficits and reduces microglial activation and inflammatory cytokine expression (Li et al., 2023). Similarly, in experimental multiple sclerosis, acute IH decreases inflammatory cell infiltration and promotes a pro-repair microglial/macrophage phenotype (Tokarska et al., 2023). Systematic reviews suggest that repeated exposure to IH may induce neuroprotective and anti-inflammatory adaptations when applied at low doses. Interestingly, positive results were found in 75% of human studies included (Damgaard et al., 2023). IH also has been studied for metabolic dysfunction in humans, showing enhancements in cardiometabolic parameters, including reductions in blood pressure, LDL cholesterol, and fasting glucose, although evidence remains limited and heterogeneous (Behrendt et al., 2022; Bestavashvili et al., 2022; Uzun et al., 2025). Regarding chronic stress, IH acts as a hormetic stressor that induce cross-adaptation, as it temporarily activates stress axes but promotes adaptation and a stress-buffering effect (Kurhaluk et al., 2024; Rybníková et al., 2022; Shamenko et al., 2019).

Whole-body hyperthermia in the febrile range has been shown to exert immunomodulatory and potentially neuroprotective effects. Experimental studies indicate that it enhances mitochondrial function and induces heat shock proteins, molecular chaperones with cytoprotective and immunoregulatory roles that may help modulate neuroinflammatory processes (Hunt et al., 2020; Smadja and Abreu, 2025). Febrile-range hyperthermia can also reshape immune responses by altering leukocyte populations and innate immune mediators, suggesting a controlled reprogramming of inflammatory signalling (Kozłowski et al., 2025). Observational studies report that frequent sauna use is associated with a substantially lower risk of dementia and Alzheimer's disease, effects partly attributed to anti-inflammatory, antioxidant, and vascular adaptations, including improved cerebral perfusion (Hunt et al., 2020; Laukkanen and Kunutsor, 2024; Reeder et al., 2023). Experimental models further suggest that sauna-like thermal exposure may reduce pathological tau phosphorylation and promote a more anti-inflammatory cytokine profile (Guisle et al., 2022). Passive heat exposure has been explored as a potential strategy to improve metabolic function. Some intervention studies report reductions in fasting glucose, insulin levels, body mass index, and lipid markers (Pallubinsky et al., 2020; Shiralkar et al., 2018; Yadav and Devi, 2023). However, evidence remains inconsistent, as recent meta-analytic findings indicate limited overall effects on glycaemic control and lipid profiles, with only modest improvements observed in some cardiovascular risk parameters (Hamaya et al., 2025). Although acute heat exposure activates physiological stress systems, when applied repeatedly under controlled conditions, it promotes hormetic adaptations characterized by attenuated cortisol responses and autonomic nervous system modulation consistent with improved stress regulation (Ahokas et al., 2025; Patrick and Johnson, 2021; Podstawski et al., 2021).

Manual therapy and other touch-based interventions appear to induce multisystem responses involving both neuroimmune and neuroendocrine regulation. Evidence suggests these approaches can shift inflammatory activity toward a more anti-inflammatory profile, with reductions in pro-inflammatory cytokines (e.g., IL-1 β , TNF- α) and increases in mediators such as IL-10, alongside changes in immune markers including NK cells, CD4 lymphocytes, and circulating immunoglobulins. Preclinical studies further suggest potential effects on

neuroinflammation, showing reduced glial activation and decreased expression of neuroinflammatory markers (Keter et al., 2025). In parallel, touch-based interventions influence stress-related neuroendocrine pathways, particularly the HPA axis, with several studies reporting moderate to large reductions in cortisol (Packheiser et al., 2024) and increases in oxytocin following tactile stimulation (Haavik et al., 2021; Kovanur-Sampath et al., 2017). Some evidence also indicates changes in the testosterone–cortisol ratio and that repeated sessions may enhance stress-regulatory effects (Kovanur Sampath et al., 2024), although results for other neuroendocrine mediators such as adrenalin and noradrenalin are generally inconsistent (Keter et al., 2025). Overall, while these findings support a potential role for tactile interventions in modulating inflammatory and stress-related physiology, the mechanistic evidence remains heterogeneous and of generally low certainty.

Importantly, the interventions proposed in this review require behavioural change, decision-making, and sustained effort from individuals. These processes depend partly on the proper functioning of the brain reward system, which plays a central role in motivation and reinforcement of adaptive behaviours (Lewis et al., 2021). Mesolimbic circuits, particularly the ventral tegmental area and nucleus accumbens, are closely linked to immune regulation through neuroendocrine and sympathetic pathways, while cytokines can directly influence reward-related neurotransmission (Wheeler and Quintana, 2025). Experimental evidence indicates that activation of dopaminergic reward circuits can enhance innate and adaptive immune responses (Ben-Shaanan et al., 2018, 2016), whereas chronic peripheral inflammation may impair central reward processing, contributing to anhedonia, reduced motivation, effort sensibility and maladaptive behaviours that can further sustain inflammatory states (Alloy et al., 2023; Miller et al., 2021; Nusslock et al., 2024; Zhu et al., 2025). Accordingly, addressing systemic inflammation may be important to restore reward sensitivity, effort tolerance, and facilitate engagement with therapeutic lifestyle interventions. Providing individuals with knowledge and meaningful explanations may enhance engagement, supporting informed decision-making and adherence to recommended behavioural changes. Moreover, acquiring relevant knowledge—particularly when it helps individuals understand previously unexplained symptoms—may itself activate reward-related processes (Cancela et al., 2025). Notably, the treatment strategies proposed are closely aligned with physiological and natural sources of reward, such optimal food, sleep, exercise, respiration practises, skin to skin contact, social interaction, and cognitive challenges, which appears to be the most consistent combination for optimal neuroimmune functioning and greater resilience to stress (Dresp-Langley, 2023; Fujiwara et al., 2022; Lewis et al., 2021). Therefore, beyond the specific biological effects of each intervention, an additional mechanism worth considering is the regulation of reward circuits, given their central role in coordinating behavioural motivation and systemic responses to challenges that impose allostatic load and may ultimately contribute to chronic pain.

An additional aspect warranting further investigation is the potential influence of sex-related differences on the neuroinflammatory, metabolic, and stress-related mechanisms discussed throughout this review. Preclinical evidence suggests sex-dependent differences in insular excitability, synaptic plasticity, inflammatory signalling, and stress-related molecular pathways. For example, posterior insular pyramidal neurons appear more excitable in male mice, whereas females show stronger synaptic transmission and region-specific long-term potentiation (Iezzi et al., 2024). Similarly, early-life stress models demonstrate distinct molecular signatures within the insula according to sex, with inflammatory and collagen-related pathways predominating in vulnerable males, whereas vulnerable females show reduced serotonergic signalling (Zonca et al., 2025). Reviews focusing on neuroimmune and stress-related mechanisms further suggest marked sex-dependent differences in glial activation, cytokine signalling, and inflammatory vulnerability that may contribute to the transition toward chronic pain states (Bekhat and Neigh, 2018; Gregus et al., 2021; Smith et al., 2025).

These findings raise the possibility that neuroinflammatory, metabolic, and stress-related disturbances may differentially influence insular processing and interoceptive regulation according to sex, potentially contributing to differences in chronic pain vulnerability and treatment responses.

3.2. Limitations

Despite converging evidence across inflammatory, metabolic, and stress-related pathways, several important limitations remain. First, much of the human literature is based on cross-sectional and correlational designs, providing only static snapshots of brain structure and function and preventing firm conclusions about causality—specifically whether insular alterations precede chronic pain or emerge because of prolonged allostatic load and systemic dysregulation (Aruldass et al., 2021; Mehrhof et al., 2025; Quidé et al., 2025; Rolls, 2023; Schulz et al., 2025). Second, substantial heterogeneity across clinical populations, symptom profiles, and insular subregions complicates interpretation of findings, as different conditions or phenotypes (e.g., hyperphagia, anhedonia, or distinct pain syndromes) may show divergent patterns of structural or functional alteration (Afhami et al., 2025; Ferreira et al., 2026). Third, methodological limitations further constrain current evidence, including variability in neuroimaging acquisition and analytical thresholds, indirect neuroimaging proxies of underlying biological processes, debated validity of some interoceptive tasks (e.g., heartbeat-based measures), and potential metabolic, pharmacological, or sampling confounders that may influence observed associations (Quidé et al., 2025; Walsh et al., 2021; Wang et al., 2021). In addition, mechanistic insights derived from animal models—such as layer-specific recordings, chemogenetic manipulations, or sex-specific molecular signatures—cannot be directly translated to humans, limiting the extent to which cellular or circuit-level findings can be extrapolated to clinical pain conditions. In addition, competing theoretical interpretations remain regarding the meaning of insular alterations, which may reflect immune sensing, persistent nociceptive input, maladaptive predictive processing, or broader system-level dysregulation, leaving the precise causal pathways linking metabolic dysfunction, stress, inflammation, and altered interoceptive processing to chronic pain incompletely defined (Koren et al., 2021; Quadt et al., 2018; Rolls, 2023). Finally, although several lifestyle and physiological interventions are discussed as potential modulators of the mechanisms reviewed in this manuscript, the clinical evidence supporting their effects on interoceptive–insular pathways and chronic pain remain heterogeneous and often indirect. Many findings derive from experimental or preclinical studies, and further longitudinal and mechanistically informed clinical trials are needed to determine their specific relevance for pain chronification.

3.3. Future directions

Future research should aim to clarify the causal relationships between interoceptive dysfunction, insular alterations, and the biological processes associated with chronic pain. The integration of immune, metabolic, and neuroimaging measures in longitudinal human studies will be of particular importance in determining whether these alterations precede the chronification of pain or emerge as its consequence. Moreover, enhancing the ecological validity of interoceptive assessment and formulating mechanistically informed interventions targeting brain–body regulation may facilitate the translation of these conceptual advances into more effective prevention and treatment strategies.

4. Conclusion

The evidence reviewed suggests that chronic pain may be understood not only as a disorder of nociceptive persistence, but also as a disturbance in the brain's capacity to accurately interpret and regulate internal bodily states. Within this framework, the insular cortex emerges

as a central hub integrating immune, metabolic, autonomic, and stress-related signals that shape interoceptive inference and behavioural responses to physiological challenge. Disruptions across these systems may progressively bias internal models of the body towards persistent threat and imbalance, reinforcing allostatic load and favouring pain persistence. Understanding chronic pain through this integrative lens may help bridge biological mechanisms with behavioural and lifestyle-related interventions, opening new avenues for prevention and more comprehensive therapeutic strategies.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

The authors declare that the research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

References

- Abolhosseini, S., Malatesta, A., Asmundson, A.J.N., Gilron, I., Salomons, T.V., 2025. Analgesic benefits of pharmacological and nonpharmacological sleep interventions for adults with fibromyalgia: a systematic review and meta-analysis. *Pain* 166, 2698–2720. <https://doi.org/10.1097/j.pain.0000000000003708>.
- Aboushaar, N., Serrano, N., 2024. The mutually reinforcing dynamics between pain and stress: mechanisms, impacts and management strategies. *Front. Pain. Res.* 5, 1445280. <https://doi.org/10.3389/fpain.2024.1445280>.
- Afhami, M., Hamblin, M.R., Hashemi, M., Azarshin, S.Z., Mohaghegh Shalmani, L., Razavi, M., Javani Jouni, F., Zafari, J., 2025. Effects of photobiomodulation on nervous system disorders: a narrative review. *J. Lasers Med. Sci.* 16, e37. <https://doi.org/10.34172/jlms.2025.37>.
- Agorastos, A., Olf, M., 2021. Sleep, circadian system and traumatic stress. *Eur. J. Psychotraumatology* 12, 1956746. <https://doi.org/10.1080/20088198.2021.1956746>.
- Ahokas, E.K., Kyröläinen, H., Ihalainen, J.K., Hanstock, H.G., 2025. Salivary cortisol response to post-exercise infrared sauna declines over time. *Temperature* 12, 281–295. <https://doi.org/10.1080/23328940.2025.2493460>.
- Al Balah, O.F., Rafie, M., Osama, A.-R., 2025. Immunomodulatory effects of photobiomodulation: a comprehensive review. *Lasers Med. Sci.* 40, 187. <https://doi.org/10.1007/s10103-025-04417-8>.
- Al Omran, A.J., Shao, A.S., Watanabe, S., Zhang, Z., Zhang, J., Xue, C., Watanabe, J., Davies, D.L., Shao, X.M., Liang, J., 2022. Social isolation induces neuroinflammation and microglia overactivation, while dihydromyricetin prevents and improves them. *J. Neuroinflammation* 19, 2. [doi:10.1186/s12974-021-02368-9](https://doi.org/10.1186/s12974-021-02368-9).
- Alfano, V., Cavaliere, C., Di Cecca, A., Ciccarelli, G., Salvatore, M., Aiello, M., Federico, G., 2023. Sex differences in functional brain networks involved in interoception: an fMRI study. *Front. Neurosci.* 17, 1130025. <https://doi.org/10.3389/fnins.2023.1130025>.
- Alhadeff, A.L., Yapici, N., 2024. Interoception and gut–brain communication. *Curr. Biol.* 34, R1125–R1130. <https://doi.org/10.1016/j.cub.2024.10.035>.
- Alloy, L.B., Chat, I.K.-Y., Grehl, M.M., Stephenson, A.R., Adogli, Z.V., Olino, T.M., Ellman, L.M., Miller, G.E., Nusslock, R., 2023. Reward and Immune Systems in Emotion (RISE) prospective longitudinal study: protocol overview of an integrative reward–inflammation model of first onset of major depression in adolescence. *Brain Behav. Immun. Health* 30, 100643. <https://doi.org/10.1016/j.bbih.2023.100643>.
- Aruldass, A.R., Kitzbichler, M.G., Morgan, S.E., Lim, S., Lynall, M.-E., Turner, L., Vertes, P., Cavanagh, J., Cowen, P., Pariante, C.M., Harrison, N.A., Bullmore, E.T., 2021. Dysconnectivity of a brain functional network was associated with blood inflammatory markers in depression. *Brain Behav. Immun.* 98, 299–309. <https://doi.org/10.1016/j.bbi.2021.08.226>.
- Büchel, C., 2023. The role of expectations, control and reward in the development of pain persistence based on a unified model. *eLife* 12, e81795. <https://doi.org/10.7554/eLife.81795>.
- Aslam, M.A., Iqbal, H., Ilyas, K., Rehman, K., Hussain, A., Akash, M.S.H., Shahid, M., Chen, S., 2025. Metabolomic Insights into Smoking-Induced Metabolic Dysfunctions: A Comprehensive Analysis of Lipid and Amino Acid Metabolomes. *Metabolites* 15, 96. [doi:10.3390/metabo15020096](https://doi.org/10.3390/metabo15020096).
- Banks, W.A., 2016. From blood–brain barrier to blood–brain interface: new opportunities for CNS drug delivery. *Nat. Rev. Drug. Discov.* 15, 275–292. <https://doi.org/10.1038/nrd.2015.21>.
- Barber, T.M., Kyrou, I., Randeva, H.S., Weickert, M.O., 2021. Mechanisms of insulin resistance at the crossroad of obesity with associated metabolic abnormalities and cognitive dysfunction. *IJMS* 22, 546. <https://doi.org/10.3390/ijms22020546>.
- Barrett, L.F., Quigley, K.S., Hamilton, P., 2016. An active inference theory of allostasis and interoception in depression. *Philos. Trans. R. Soc. B* 371, 20160011. <https://doi.org/10.1098/rstb.2016.0011>.

- Baumer, Y., Pita, M.A., Baez, A.S., Ortiz-Whittingham, L.R., Cintron, M.A., Rose, R.R., Gray, V.C., Osei Baah, F., Powell-Wiley, T.M., 2023. By what molecular mechanisms do social determinants impact cardiometabolic risk? *Clin. Sci.* 137, 469–494. doi:10.1042/CS20220304.
- Beam, A., Clinger, E., Hao, L., 2021. Effect of diet and dietary components on the composition of the gut microbiota. *Nutrients* 13, 2795. <https://doi.org/10.3390/nu13082795>.
- Behrendt, T., Bielitzki, R., Behrens, M., Herold, F., Schega, L., 2022. Effects of intermittent hypoxia-hyperoxia on performance- and health-related outcomes in humans: a systematic review. *Sports Med. - Open.* 8, 70. <https://doi.org/10.1186/s40798-022-00450-x>.
- Bekhat, M., Neigh, G.N., 2018. Sex differences in the neuro-immune consequences of stress: focus on depression and anxiety. *Brain Behav. Immun.* 67, 1–12. <https://doi.org/10.1016/j.bbi.2017.02.006>.
- Ben-Shaanan, T.L., Azulay-Deby, H., Dubovik, T., Starosvetsky, E., Korin, B., Schiller, M., Green, N.L., Admon, Y., Hakim, F., Shen-Orr, S.S., Rolls, A., 2016. Activation of the reward system boosts innate and adaptive immunity. *Nat. Med.* 22, 940–944. <https://doi.org/10.1038/nm.4133>.
- Ben-Shaanan, T.L., Schiller, M., Azulay-Deby, H., Korin, B., Boshnak, N., Koren, T., Krot, M., Shakyia, J., Rahat, M.A., Hakim, F., Rolls, A., 2018. Modulation of anti-tumor immunity by the brain's reward system. *Nat. Commun.* 9, 2723. <https://doi.org/10.1038/s41467-018-05283-5>.
- Berntson, G.G., Khalsa, S.S., 2021. Neural Circuits of Interoception. *Trends Neurosci.* 44, 17–28. <https://doi.org/10.1016/j.tins.2020.09.011>.
- Bertero, E., Carmisciano, L., Jonasson, C., Butler, J., Maack, C., Ameri, P., 2024. Association of inflammatory markers with incident heart failure or cancer in the HUNT3 and Health ABC population studies. *Eur. J. Prev. Cardiol.* 31, 1400–1407. <https://doi.org/10.1093/eurjpc/zwac089>.
- Bestavashvili, Afina, Glazachev, O., Bestavashvili, Alexander, Suvorov, A., Zhang, Y., Zhang, X., Rozhkov, A., Kuznetsova, N., Pavlov, C., Glushenkov, D., Kopylov, P., 2022. Intermittent hypoxic-hyperoxic exposures effects in patients with metabolic syndrome: correction of cardiovascular and metabolic profile. *Biomedicines* 10, 566. <https://doi.org/10.3390/biomedicines10030566>.
- Bijker, L., Ten Have, M., Scholten-Peeters, G.G.M., Coppeters, M.W., Cuijpers, P., De Wit, L.M., 2025. Associations between social factors and spinal pain-related disability in people with back pain and/or neck pain. *Ann. Med.* 57, 2577877. <https://doi.org/10.1080/07853890.2025.2577877>.
- Blanchard, E.B., Jurish, S.E., Andrasik, F., Epstein, L.H., 1981. The relationship between muscle discrimination ability and response to relaxation training in three kinds of headaches. *Biofeedback Self-Regul.* 6, 537–545. <https://doi.org/10.1007/BF00998738>.
- Borsook, D., 2025. Allostatic load and pain: instability of a bio-social ecosystem. *Pain* 166, S27–S32. <https://doi.org/10.1097/j.pain.0000000000003716>.
- Brain, K., Burrows, T.L., Rollo, M.E., Chai, L.K., Clarke, E.D., Hayes, C., Hodson, F.J., Collins, C.E., 2019. A systematic review and meta-analysis of nutrition interventions for chronic noncancer pain. *J. Human. Nutr. Diet.* 32, 198–225. <https://doi.org/10.1111/jhn.12601>.
- Briançon-Marjollet, A., Weissenstein, M., Henri, M., Thomas, A., Godin-Ribuot, D., Polak, J., 2015. The impact of sleep disorders on glucose metabolism: endocrine and molecular mechanisms. *Diabetol. Metab. Syndr.* 7, 25. <https://doi.org/10.1186/s13098-015-0018-3>.
- Brooks, S.J., Cedernaes, J., Schiöth, H.B., 2013. Increased prefrontal and parahippocampal activation with reduced dorsolateral prefrontal and insular cortex activation to food images in obesity: a meta-analysis of fMRI studies. *PLoS ONE* 8, e60393. <https://doi.org/10.1371/journal.pone.0060393>.
- Bruijnzeel, A.W., Corrie, L.W., Rogers, J.A., Yamada, H., 2011. Effects of insulin and leptin in the ventral tegmental area and arcuate hypothalamic nucleus on food intake and brain reward function in female rats. *Behav. Brain Res.* 219, 254–264. <https://doi.org/10.1016/j.bbr.2011.01.020>.
- Bud Craig, A.D., 2009. How do you feel – now? The anterior insula and human awareness. *Nat. Rev. Neurosci.* 10, 59–70. <https://doi.org/10.1038/nrn2555>.
- Buntinx, Y., Hendrix, J., Wyns, A., Van Campenhout, J., Xiong, H.-Y., Laeremans, T., Cuesta-Sanchez, S., Aerts, J.L., Nijls, J., Polli, A., 2025. Exploring chronic pain, immune dysfunction and lifestyle: a focus on t cell exhaustion and senescence. *Biomolecules* 15, 1601. <https://doi.org/10.3390/biom15111601>.
- Cai, W., Menon, V., 2025. Heterogeneity of human insular cortex: five principles of functional organization across multiple cognitive domains. *Brain Struct. Funct.* 230, 161. <https://doi.org/10.1007/s00429-025-03027-y>.
- Burini, R.C., Anderson, E., Durstine, J.L., Carson, J.A., 2020. Inflammation, physical activity, and chronic disease: An evolutionary perspective. *Sports Med. Health Sci.* 2, 1–6. doi:10.1016/j.smhs.2020.03.004.
- Cai, W., Haddad, M., Haddad, R., Kesten, I., Hoffman, T., Laan, R., Westfall, S., Defaye, M., Abdullah, N.S., Wong, C., Brown, N., Tansley, S., Lister, K.C., Hooshmandi, M., Wang, F., Lorenzo, L.-E., Hovhannissyan, V., Ho-Tieng, D., Kumar, V., Sharif, B., Thuraiarajah, B., Fan, J., Sahar, T., Clayton, C., Wu, N., Zhang, J., Bar-Yoseph, H., Pitashny, M., Krock, E., Mogil, J.S., Prager-Khoutorsky, M., Séguela, P., Altier, C., King, L.L., De Koninck, Y., Brereton, N.J.B., Gonzalez, E., Shir, Y., Minerbi, A., Khoutorsky, A., 2025. The gut microbiota promotes pain in fibromyalgia. *Neuron* 113, 2161–2175.e13. <https://doi.org/10.1016/j.neuron.2025.03.032>.
- Camberos-Barraza, J., Camacho-Zamora, A., Bátiz-Beltrán, J.C., Osuna-Ramos, J.F., Rábago-Monzón, Á.R., Valdez-Flores, M.A., Angulo-Rojo, C.E., Guadrón-Llanos, A. M., Picos-Cárdenas, V.J., Calderón-Zamora, L., Norzagaray-Valenzuela, C.D., Cárdenas-Torres, F.I., De La Herrán-Arita, A.K., 2024. Sleep, glial function, and the endocannabinoid system: implications for neuroinflammation and sleep disorders. *IJMS* 25, 3160. <https://doi.org/10.3390/ijms25063160>.
- Campbell, A., 2004. Inflammation, Neurodegenerative Diseases, and Environmental Exposures. *Ann. New. Y. Acad. Sci.* 1035, 117–132. doi:10.1196/annals.1332.008.
- Cancela, J.G., Vázquez, O.C., Ledesma, S.N., Prumboom, L., 2025. The effectiveness of pain neuroscience education in people with chronic non-specific low back pain: an umbrella review with meta-analysis. *Ann. Phys. Rehabil. Med.* 68, 102020. <https://doi.org/10.1016/j.rehab.2025.102020>.
- Cantoni, C., Ciccarone, S., Porpora, M.G., Aglioti, S.M., 2025. Impaired gastric and urinary but preserved cardiac interoception in women with endometriosis. *PLoS One* 20, e0322865. <https://doi.org/10.1371/journal.pone.0322865>.
- Cao, S., Shi, X., Chen, Y., Liu, T., Hu, J., Dong, X., Chen, H., Dai, J., Yin, H., 2025. Gut microbiota-targeted photobiomodulation ameliorates Alzheimer's pathology via the gut-brain axis: comparable efficacy to transcranial irradiation. *Microorganisms* 13, 2659. <https://doi.org/10.3390/microorganisms13122659>.
- Chantry, A.J., Bishop, N.C., Hamer, M., Paine, N.J., 2022. Sedentary behaviour, physical activity and psychobiological stress reactivity: A systematic review. *Biol. Psychol.* 172, 108374. doi:10.1016/j.biopsycho.2022.108374.
- Chen, Y., Chen, X., Luo, Z., Kang, X., Ge, Y., Wan, R., Wang, Q., Han, Z., Li, F., Fan, Z., Xie, Y., Qi, B., Zhang, X., Yang, Z., Zhang, J.H., Liu, D., Xu, Y., Wu, D., Chen, S., 2025. Exercise-induced reduction of IGF1R sumoylation attenuates neuroinflammation in APP/PS1 transgenic mice. *J. Adv. Res.* 69, 279–297. <https://doi.org/10.1016/j.jare.2024.03.025>.
- Choi, J.-W., Jo, S.-W., Kim, D.-E., Paik, I.-Y., Balakrishnan, R., 2024. Aerobic exercise attenuates LPS-induced cognitive dysfunction by reducing oxidative stress, glial activation, and neuroinflammation. *Redox Biol.* 71, 103101. <https://doi.org/10.1016/j.redox.2024.103101>.
- Cifuentes, M., Verdejo, H.E., Castro, P.F., Corvalan, A.H., Ferreccio, C., Quest, A.F.G., Kogan, M.J., Lavandero, S., 2025. Low-grade chronic inflammation: a shared mechanism for chronic diseases. *Physiology* 40, 4–25. <https://doi.org/10.1152/physiol.00021.2024>.
- Coffeen, U., Ramírez-Rodríguez, G.B., Simón-Arce, K., Mercado, F., Almanza, A., Jaimés, O., Parra-Vitela, D., Vázquez-Barreto, M., Pellicer, F., 2024. The role of the insular cortex and serotonergic system in the modulation of long-lasting nociception. *Cells* 13, 1718. <https://doi.org/10.3390/cells13201718>.
- Cohen, M., Quintner, J., Buchanan, D., 2013. Is chronic pain a disease? *Pain. Med.* 14, 1284–1288. <https://doi.org/10.1111/pme.12025>.
- Cohen, M., Quintner, J., Weisman, A., 2023. Nociceptive pain: a challenge to nosology and to nociception. *J. Pain.* 24, 2131–2139. <https://doi.org/10.1016/j.jpain.2023.07.019>.
- Craig, A.D., 2002. How do you feel? Interoception: the sense of the physiological condition of the body. *Nat. Rev. Neurosci.* 3, 655–666. <https://doi.org/10.1038/nrn894>.
- Croos, S.S., Røikjer, J., Mørch, C.D., Ejkskjær, N., Frøkjær, J.B., Hansen, T.M., 2023b. Alterations in functional connectivity of thalamus and primary somatosensory cortex in painful and painless diabetic peripheral neuropathy. *Diabetes Care* 46, 173–182. <https://doi.org/10.2337/dc22-0587>.
- Croos, S.S., Røikjer, J., Mørch, C.D., Ejkskjær, N., Frøkjær, J.B., Hansen, T.M., 2023a. Alterations in functional connectivity of thalamus and primary somatosensory cortex in painful and painless diabetic peripheral neuropathy. *Diabetes Care* 46, 173–182. <https://doi.org/10.2337/dc22-0587>.
- Cui, Y., Tang, T., Lu, C., Ju, S., 2022. Insulin resistance and cognitive impairment: evidence from neuroimaging. *Magn. Reson. Imaging* 56, 1621–1649. <https://doi.org/10.1002/jmri.28358>.
- Custers, Emma, E.M., Kilian, Amanda, J., 2022. Dietary lipids from body to brain. *Progress. Lipid Res.* 85, 101144. <https://doi.org/10.1016/j.plipres.2021.101144>.
- Da Silva, J.T., Hernandez-Rojas, L.G., Mekonen, H.K., Hanson, S., Melemedjian, O., Scott, A.J., Ernst, R.K., Seminowicz, D.A., Traub, R.J., 2024. Sex differences in visceral sensitivity and brain activity in a rat model of comorbid pain: a longitudinal study. *Pain* 165, 698–706. <https://doi.org/10.1097/j.pain.0000000000003074>.
- Da Silva, L.E., Martins, D.F., De Oliveira, M.P., Stenier, M.R., Fernandes, B.B., Willemann, S.D.S., De Souza, G., Vieira, W.F., Hewitson, A., Cidral-Filho, F.J., Rezin, G.T., 2025. Photobiomodulation of gut microbiota with low-level laser therapy: a light for treating neuroinflammation. *Lasers Med. Sci.* 40, 64. <https://doi.org/10.1007/s10103-025-04319-9>.
- Damgaard, V., Mariagaard, J., Lindhardsen, J.M., Ehrenreich, H., Miskowiak, K.W., 2023. Neuroprotective effects of moderate hypoxia: a systematic review. *Brain Sci.* 13, 1648. <https://doi.org/10.3390/brainsci13121648>.
- Daniela, M., Catalina, L., Ilie, O., Paula, M., Daniel-Andrei, I., Ioana, B., 2022. Effects of Exercise Training on the Autonomic Nervous System with a Focus on Anti-Inflammatory and Antioxidants Effects. *Antioxidants* 11, 350. doi:10.3390/antiox11020350.
- Dantzer, R., O'Connor, J.C., Freund, G.G., Johnson, R.W., Kelley, K.W., 2008. From inflammation to sickness and depression: when the immune system subjugates the brain. *Nat. Rev. Neurosci.* 9, 46–56. <https://doi.org/10.1038/nrn2297>.
- De Miguel, Z., Khoury, N., Betley, M.J., Lehallier, B., Willoughby, D., Olsson, N., Yang, A. C., Hahn, O., Lu, N., Vest, R.T., Bonanno, L.N., Yerra, L., Zhang, L., Saw, N.L., Fairchild, J.K., Lee, D., Zhang, H., McAlpine, P.L., Contrepas, K., Shamloo, M., Elias, J.E., Rando, T.A., Wyss-Coray, T., 2021. Exercise plasma boosts memory and dampens brain inflammation via clusterin. *Nature* 600, 494–499. <https://doi.org/10.1038/s41586-021-04183-x>.
- De Oliveira, M.F., Johnson, D.S., Demchak, T., Tomazoni, S.S., Leal-Junior, E.C., 2022. Low-intensity LASER and LED (photobiomodulation therapy) for pain control of the most common musculoskeletal conditions. *Eur. J. Phys. Rehabil. Med.* 58. <https://doi.org/10.23736/S1973-9087.21.07236-1>.
- Depner, C.M., Stothard, E.R., Wright, K.P., 2014. Metabolic consequences of sleep and circadian disorders. *Curr. Diab Rep.* 14, 507. <https://doi.org/10.1007/s11892-014-0507-z>.

- DeSouza, D.D., Davis, K.D., Hodaie, M., 2015. Reversal of insular and microstructural nerve abnormalities following effective surgical treatment for trigeminal neuralgia. *Pain* 156, 1112–1123. <https://doi.org/10.1097/j.pain.0000000000000156>.
- Di Lerna, D., Serino, S., Riva, G., 2016. Pain in the body. Altered interoception in chronic pain conditions: a systematic review. *Neurosci. Biobehav. Rev.* 71, 328–341. <https://doi.org/10.1016/j.neubiorev.2016.09.015>.
- Dresp-Langley, B., 2023. From reward to anhedonia-dopamine function in the global mental health context. *Biomedicine* 11, 2469. <https://doi.org/10.3390/biomedicine11092469>.
- Duan, D., Kim, L.J., Jun, J.C., Polotsky, V.Y., 2023. Connecting insufficient sleep and insomnia with metabolic dysfunction. *Ann. New. Y. Acad. Sci.* 1519, 94–117. <https://doi.org/10.1111/nyas.14926>.
- Duschek, S., Montoro, C.L., Reyes Del Paso, G.A., 2017. Diminished interoceptive awareness in fibromyalgia syndrome. *Behav. Med.* 43, 100–107. <https://doi.org/10.1080/08964289.2015.1094442>.
- Edwin Thanarajah, S., Iglesias, S., Kuzmanovic, B., Rigoux, L., Stephan, K.E., Brüning, J. C., Tittgemeyer, M., 2019. Modulation of midbrain neurocircuitry by intranasal insulin. *NeuroImage* 194, 120–127. <https://doi.org/10.1016/j.neuroimage.2019.03.050>.
- El Kouche, S., Halvick, S., Morel, C., Duca, R., Van Nieuwenhuysse, A., Turner, J.D., Grova, N., Meyre, D., 2025. Pollution, stress response, and obesity: A systematic review. *Obes. Rev.* 26, e13895. <https://doi.org/10.1111/obr.13895>.
- Elenkov, I.J., Chrousos, G.P., 2002. Stress hormones, proinflammatory and antiinflammatory cytokines, and autoimmunity. *Ann. New. Y. Acad. Sci.* 966, 290–303. <https://doi.org/10.1111/j.1749-6632.2002.tb04229.x>.
- Evrad, H.C., 2019. The organization of the primate insular cortex. *Front. Neuroanat.* 13, 43. <https://doi.org/10.3389/fnana.2019.00043>.
- Ewees, M.G., El-Mahdy, M.A., Hannawi, Y., Zweier, J.L., 2025. Tobacco cigarette smoking induces cerebrovascular dysfunction followed by oxidative neuronal injury with the onset of cognitive impairment. *J. Cereb. Blood Flow Metab.* 45, 48–65. <https://doi.org/10.1177/0271678X241270415>.
- Feng, S., Liu, R., Colwell, B., Chung, S., Barry, A., Wang, H., 2025. Carbohydrate-restricted diet types and macronutrient replacements for metabolic health in adults: a meta-analysis of randomized trials. *Clin. Nutr.* 54, 27–41. <https://doi.org/10.1016/j.clnu.2025.09.005>.
- Fermin, A.S.R., Friston, K., Yamawaki, S., 2022. An insula hierarchical network architecture for active interoceptive inference. *R. Soc. Open. Sci.* 9, 220226. <https://doi.org/10.1098/rsos.220226>.
- Ferreira, L.M.A., Oliveira, A.B.C., Mendes, J.J.B., Costa, G.V., Silva, I.R., Santos, G.N., Pereira, G.S., Silva, M.L., 2026. Photobiomodulation in chronic pain: a systematic review of randomized clinical trials. *Front. Integr. Neurosci.* 20, 1717372. <https://doi.org/10.3389/fnint.2026.1717372>.
- Fillingim, M., Tanguay-Sabourin, C., Parisien, M., Zare, A., Guglietti, G.V., Norman, J., Petre, B., Bortsov, A., Ware, M., Perez, J., Roy, M., Diatchenko, L., Vachon-Presseau, E., 2025. Biological markers and psychosocial factors predict chronic pain conditions. *Nat. Hum. Behav.* 9, 1710–1725. <https://doi.org/10.1038/s41562-025-02156-y>.
- Fitzcharles, M.-A., Cohen, S.P., Clauw, D.J., Littlejohn, G., Usui, C., Häuser, W., 2021. Nociceptive pain: towards an understanding of prevalent pain conditions. *Lancet* 397, 2098–2110. [https://doi.org/10.1016/S0140-6736\(21\)00392-5](https://doi.org/10.1016/S0140-6736(21)00392-5).
- Flasbeck, V., Schedlowski, M., Brüne, M., Engler, H., 2025. Impact of experimental inflammation on the neuronal processing of cardiac interoceptive signals and heart rate variability in humans. *NeuroImage* 314, 121257. <https://doi.org/10.1016/j.neuroimage.2025.121257>.
- Flor, H., Schugens, M.M., Birbaumer, N., 1992. Discrimination of muscle tension in chronic pain patients and healthy controls. *Biofeedback Self-Regul.* 17, 165–177. <https://doi.org/10.1007/BF01000401>.
- Frank, S., Kullmann, S., Veit, R., 2013. Food related processes in the insular cortex. *Front. Hum. Neurosci.* 7, <https://doi.org/10.3389/fnhum.2013.00499>.
- Frank, S., Wilms, B., Veit, R., Ernst, B., Thurnheer, M., Kullmann, S., Fritzsche, A., Birbaumer, N., Preissl, H., Schultes, B., 2014. Altered brain activity in severely obese women may recover after Roux-en-Y gastric bypass surgery. *Int. J. Obes.* 38, 341–348. <https://doi.org/10.1038/sj.ijo.2013.60>.
- Franklin, B.A., Rusia, A., Haskin-Popp, C., Tawney, A., 2021. Chronic stress, exercise and cardiovascular disease: placing the benefits and risks of physical activity into perspective. *IJERPH* 18, 9922. <https://doi.org/10.3390/ijerph18189922>.
- Fujiwara, H., Tsurumi, K., Shibata, M., Kobayashi, K., Miyagi, T., Ueno, T., Oishi, N., Murai, T., 2022. Life habits and mental health: behavioural addiction, health benefits of daily habits, and the reward system. *Front. Psychiatry* 13, 813507. <https://doi.org/10.3389/fpsy.2022.813507>.
- Garfinkel, S.N., Eccleston, C., 2025. Interoception and pain: body–mind integration, rupture, and repair. *Pain* 166, 1470–1474. <https://doi.org/10.1097/j.pain.0000000000003515>.
- Goehrl, L.E., Gaykema, R.P.A., Hansen, M.K., Anderson, K., Maier, S.F., Watkins, L.R., 2000. Vagal immune-to-brain communication: a visceral chemosensory pathway. *Auton. Neurosci.* 85, 49–59. [https://doi.org/10.1016/S1566-0702\(00\)00219-8](https://doi.org/10.1016/S1566-0702(00)00219-8).
- Gogolla, N., 2017. The insular cortex. *Curr. Biol.* 27, R580–R586. <https://doi.org/10.1016/j.cub.2017.05.010>.
- González-Muñoz, A., Cuevas-Cervera, M., Pérez-Montilla, J.J., Aguilar-Núñez, D., Hamed-Hamed, D., Aguilar-García, M., Pruimboom, L., Navarro-Ledesma, S., 2023. Efficacy of photobiomodulation therapy in the treatment of pain and inflammation: a literature review. *Healthcare* 11, 938. <https://doi.org/10.3390/healthcare11070938>.
- Gregus, A.M., Levine, L.S., Eddinger, K.A., Yaksh, T.L., Buczynski, M.W., 2021. Sex differences in neuroimmune and glial mechanisms of pain. *Pain* 162, 2186–2200. <https://doi.org/10.1097/j.pain.0000000000002215>.
- Grinshpan, L.S., Eilat-Adar, S., Ivancovsky-Wajcman, D., Kariv, R., Gillon-Keren, M., Zelber-Sagi, S., 2024. Ultra-processed food consumption and non-alcoholic fatty liver disease, metabolic syndrome and insulin resistance: A systematic review. *JHEP Reports* 6, 100964. <https://doi.org/10.1016/j.jhepr.2023.100964>.
- Guidi, J., Lucente, M., Sonino, N., Fava, G.A., 2021. Allostatic load and its impact on health: a systematic review. *Psychother. Psychosom.* 90, 11–27. <https://doi.org/10.1159/000510696>.
- Guisle, I., Canet, G., Pétry, S., Fereydouni-Forouzandeh, P., Morin, F., Kéraudon, R., Whittington, R.A., Calon, F., Hébert, S.S., Planel, E., 2022. Sauna-like conditions or menthol treatment reduce tau phosphorylation through mild hyperthermia. *Neurobiol. Aging* 113, 118–130. <https://doi.org/10.1016/j.neurobiolaging.2022.02.011>.
- Gustin, S.M., Peck, C.C., Wilcox, S.L., Nash, P.G., Murray, G.M., Henderson, L.A., 2011. Different pain, different brain: thalamic anatomy in neuropathic and non-neuropathic chronic pain syndromes. *J. Neurosci.* 31, 5956–5964. <https://doi.org/10.1523/JNEUROSCI.5980-10.2011>.
- Haavik, H., Niazi, I.K., Kumari, N., Amjad, I., Duehr, J., Holt, K., 2021. The potential mechanisms of high-velocity, low-amplitude, controlled vertebral thrusts on neuroimmune function: a narrative review. *Medicina* 57, 536. <https://doi.org/10.3390/medicina57060536>.
- Hahn, K.R., Hwang, I.K., Yoo, D.Y., 2025. Low-intensity physical exercise is associated with improved myelination and reduced microglial activation in a cuprizone-induced demyelination model. *Neurochem. Res.* 50, 182. <https://doi.org/10.1007/s11064-025-04441-8>.
- Hamaya, R., Joyama, Y., Miyata, T., Fuse, S., Yamane, N., Maruyama, N., Kanazawa, H., Morishita, K., Sesso, H.D., 2025. Non-acute effects of passive heating interventions on cardiometabolic risk and vascular health: systematic review and meta-analysis of randomized controlled trials. *Am. J. Prev. Cardiol.* 23, 101082. <https://doi.org/10.1016/j.ajpc.2025.101082>.
- Hamblin, M.R., 2017. Mechanisms and applications of the anti-inflammatory effects of photobiomodulation. *AIMS Biophys.* 4, 337–361. <https://doi.org/10.3934/biophys.2017.3.337>.
- Hamblin, M.R., 2018. Mechanisms and applications of mitochondrial redox signaling in photobiomodulation. *Photochem. Photobiol.* 94, 199–212. <https://doi.org/10.1111/php.12864>.
- Hamed Hamed, D., Struyf, F., Pruimboom, L., Navarro-Ledesma, S., 2023. Efficacy of combined strategies of physical activity, diet and sleep disorders as treatment in patients with chronic shoulder pain. A systematic review. *Front. Physiol.* 14, 1221807. <https://doi.org/10.3389/fphys.2023.1221807>.
- Hannestad, J., Subramanyam, K., DellaGioia, N., Planeta-Wilson, B., Weinzimmer, D., Pittman, B., Carson, R.E., 2012. Glucose metabolism in the insula and cingulate is affected by systemic inflammation in humans. *J. Nucl. Med.* 53, 601–607. <https://doi.org/10.2967/jnumed.111.097014>.
- Harris, R.E., Sundgren, P.C., Craig, A.D., Kirshenbaum, E., Sen, A., Napadow, V., Clauw, D.J., 2009. Elevated insular glutamate in fibromyalgia is associated with experimental pain. *Arthritis Rheum.* 60, 3146–3152. <https://doi.org/10.1002/art.24849>.
- Harrison, N.A., Brydon, L., Walker, C., Gray, M.A., Steptoe, A., Dolan, R.J., Critchley, H. D., 2009. Neural origins of human sickness in interoceptive responses to inflammation. *Biol. Psychiatry* 66, 415–422. <https://doi.org/10.1016/j.biopsych.2009.03.007>.
- Harrison, N.A., Cooper, E., Dowell, N.G., Keramida, G., Voon, V., Critchley, H.D., Cercignani, M., 2015. Quantitative magnetization transfer imaging as a biomarker for effects of systemic inflammation on the brain. *Biol. Psychiatry* 78, 49–57. <https://doi.org/10.1016/j.biopsych.2014.09.023>.
- Harrison, N.A., Voon, V., Cercignani, M., Cooper, E.A., Pessiglione, M., Critchley, H.D., 2016. A Neurocomputational account of how inflammation enhances sensitivity to punishments versus rewards. *Biol. Psychiatry* 80, 73–81. <https://doi.org/10.1016/j.biopsych.2015.07.018>.
- Hashmi, J.A., Baliki, M.N., Huang, L., Baria, A.T., Torbey, S., Hermann, K.M., Schnitzer, T.J., Apkarian, A.V., 2013. Shape shifting pain: chronification of back pain shifts brain representation from nociceptive to emotional circuits. *Brain* 136, 2751–2768. <https://doi.org/10.1093/brain/awt211>.
- Herbert, C., 2022. Enhancing mental health, well-being and active lifestyles of university students by means of physical activity and exercise research programs. *Front. Public Health* 10, 849093. <https://doi.org/10.3389/fpubh.2022.849093>.
- Herrero Babiloni, A., Baril, A.-A., Charlebois-Plante, C., Jodoin, M., Sanchez, E., De Baets, L., Arbour, C., Lavigne, G.J., Gosselin, N., De Beaumont, L., 2023. The Putative Role of Neuroinflammation in the Interaction between Traumatic Brain Injuries, Sleep, Pain and Other Neuropsychiatric Outcomes: A State-of-the-Art Review. *JCM* 12, 1793. <https://doi.org/10.3390/jcm12051793>.
- Hess, A., Axmann, R., Rech, J., Finzel, S., Heindl, C., Kreitz, S., Sergeeva, M., Saake, M., García, M., Kollias, G., Straub, R.H., Sporns, O., Doerfler, A., Brune, K., Schett, G., 2011. Blockade of TNF- α rapidly inhibits pain responses in the central nervous system. *Proc. Natl. Acad. Sci. U. S. A.* 108, 3731–3736. <https://doi.org/10.1073/pnas.1011774108>.
- Hoogenboom, W.S., Marder, T.J., Flores, V.L., Huisman, S., Eaton, H.P., Schneiderman, J.S., Bolo, N.R., Simonson, D.C., Jacobson, A.M., Kubicki, M., Shenton, M.E., Musen, G., 2014. Cerebral White Matter Integrity and Resting-State Functional Connectivity in Middle-aged Patients With Type 2 Diabetes. *Diabetes* 63, 728–738. <https://doi.org/10.2337/db13-1219>.
- Horsburgh, A., Summers, S.J., Lewis, A., Keegan, R.J., Flood, A., 2024. The relationship between pain and interoception: a systematic review and meta-analysis. *J. Pain* 25, 104476. <https://doi.org/10.1016/j.jpain.2024.01.341>.

- Hossain, M.N., Lee, J., Choi, H., Kwak, Y.-S., Kim, J., 2024. The impact of exercise on depression: how moving makes your brain and body feel better. *Phys. Act. Nutr.* 28, 43–51. <https://doi.org/10.20463/pan.2024.0015>.
- Hryhorczuk, C., Décarie-Spain, L., Sharma, S., Daneault, C., Rosiers, C.D., Alquier, T., Fulton, S., 2017. Saturated high-fat feeding independent of obesity alters hypothalamus-pituitary-adrenal axis function but not anxiety-like behaviour. *Psychoneuroendocrinology* 83, 142–149. [doi:10.1016/j.psyneuen.2017.06.002](https://doi.org/10.1016/j.psyneuen.2017.06.002).
- Hunt, A.P., Minett, G.M., Gibson, O.R., Kerr, G.K., Stewart, I.B., 2020. Could heat therapy be an effective treatment for Alzheimer's and Parkinson's diseases? A narrative review. *Front. Physiol.* 10, 1556. <https://doi.org/10.3389/fphys.2019.01556>.
- Iezzi, D., Cáceres-Rodríguez, A., Strauss, B., Chavis, P., Manzoni, O.J., 2024. Sexual differences in neuronal and synaptic properties across subregions of the mouse insular cortex. *Biol. Sex. Differ.* 15, 29. <https://doi.org/10.1186/s13293-024-00593-4>.
- Jung, S.H., Wang, Y., Kim, T., Tarr, A., Reader, B., Powell, N., Sheridan, J.F., 2015. Molecular mechanisms of repeated social defeat-induced glucocorticoid resistance: Role of microRNA. *Brain Behav. Immun.* 44, 195–206. [doi:10.1016/j.bbi.2014.09.015](https://doi.org/10.1016/j.bbi.2014.09.015).
- Kelleher, E., Kaplan, C.M., Kheirabadi, D., Schrepf, A., Tracey, I., Clauw, D.J., Irani, A., 2025. The number of central nervous system-driven symptoms predicts subsequent chronic primary pain: evidence from UK Biobank. *Br. J. Anaesth.* 134, 772–782. <https://doi.org/10.1016/j.bja.2024.12.009>.
- Kempuraj, D., Thangavel, R., Selvakumar, G.P., Zaheer, S., Ahmed, M.E., Raikwar, S.P., Zahoor, H., Saeed, D., Natteru, P.A., Iyer, S., Zaheer, A., 2017. Brain and peripheral atypical inflammatory mediators potentiate neuroinflammation and neurodegeneration. *Front. Cell. Neurosci.* 11, 216. <https://doi.org/10.3389/fncel.2017.00216>.
- Keter, D.L., Bialosky, J.E., Brochetti, K., Courtney, C.A., Funabashi, M., Karas, S., Learman, K., Cook, C.E., 2025. The mechanisms of manual therapy: a living review of systematic, narrative, and scoping reviews. *PLoS ONE* 20, e0319586. <https://doi.org/10.1371/journal.pone.0319586>.
- Khalil, W.J., Akeblersane, M., Khan, A.S., Moin, A.S.M., Butler, A.E., 2023. Environmental Pollution and the Risk of Developing Metabolic Disorders: Obesity and Diabetes. *IJMS* 24, 8870. [doi:10.3390/ijms24108870](https://doi.org/10.3390/ijms24108870).
- Khanna, A., Guo, M., Mehra, M., Royal, W., 2013. Inflammation and oxidative stress induced by cigarette smoke in Lewis rat brains. *J. Neuroimmunol.* 254, 69–75. [doi:10.1016/j.jneuroim.2012.09.006](https://doi.org/10.1016/j.jneuroim.2012.09.006).
- Kleckner, I.R., Zhang, J., Touroutoglou, A., Chanes, L., Xia, C., Simmons, W.K., Quigley, K.S., Dickerson, B.C., Feldman Barrett, L., 2017. Evidence for a large-scale brain system supporting allostasis and interoception in humans. *Nat. Hum. Behav.* 1, 0069. <https://doi.org/10.1038/s41562-017-0069-9>.
- Kleinridders, A., Pothos, E.N., 2019. Impact of brain insulin signaling on dopamine function, food intake, reward, and emotional behavior. *Curr. Nutr. Rep.* 8, 83–91. <https://doi.org/10.1007/s13668-019-0276-z>.
- Koch, C.E., Leinweber, B., Drengberg, B.C., Blaum, C., Oster, H., 2017. Interaction between circadian rhythms and stress. *Neurobiol. Stress* 6, 57–67. [doi:10.1016/j.ynstr.2016.09.001](https://doi.org/10.1016/j.ynstr.2016.09.001).
- Koren, T., Rolls, A., 2022. Immunoception: defining brain-regulated immunity. *Neuron* 110, 3425–3428. <https://doi.org/10.1016/j.neuron.2022.10.016>.
- Koren, T., Yifa, R., Amer, M., Krot, M., Boshnak, N., Ben-Shaanan, T.L., Azulay-Debbi, H., Zalayat, I., Avishai, E., Hajjo, H., Schiller, M., Haykin, H., Korin, B., Farfara, D., Hakim, F., Kobiler, O., Rosenblum, K., Krolls, A., 2021. Insular cortex neurons encode and retrieve specific immune responses. *Cell* 184, 5902–5915. [doi:10.1016/j.cell.2021.10.013](https://doi.org/10.1016/j.cell.2021.10.013).
- Kothari, V., Cardona, Z., Chirakalwasan, N., Anothaisintawee, T., Reutrakul, S., 2021. Sleep interventions and glucose metabolism: systematic review and meta-analysis. *Sleep. Med.* 78, 24–35. <https://doi.org/10.1016/j.sleep.2020.11.035>.
- Kovanur Sampath, K., Tumilty, S., Wooten, L., Belcher, S., Farrell, G., Gisselman, A.S., 2024. Effectiveness of spinal manipulation in influencing the autonomic nervous system - a systematic review and meta-analysis. *J. Man. Manip. Ther.* 32, 10–27. <https://doi.org/10.1080/10669817.2023.2285196>.
- Kovanur-Sampath, K., Mani, R., Cotter, J., Gisselman, A.S., Tumilty, S., 2017. Changes in biochemical markers following spinal manipulation-a systematic review and meta-analysis. *Musculoskelet. Sci. Pract.* 29, 120–131. <https://doi.org/10.1016/j.msksp.2017.04.004>.
- Kozłowski, H.M., Sobocińska, J., Jędrzejewski, T., Działuk, A., Wrotek, S., 2025. Unveiling the immunomodulatory mechanisms of fever-range whole-body hyperthermia in humans: insights from miRNA and protein mediators. *Int. Immunopharmacol.* 165, 115510. <https://doi.org/10.1016/j.intimp.2025.115510>.
- Kullmann, S., Heni, M., Veit, R., Ketterer, C., Schick, F., Häring, H., Fritsche, A., Preissl, H., 2012. The obese brain: association of body mass index and insulin sensitivity with resting state network functional connectivity. *Human. Brain Mapp.* 33, 1052–1061. <https://doi.org/10.1002/hbm.21268>.
- Kullmann, S., Heni, M., Veit, R., Scheffler, K., Machann, J., Häring, H.-U., Fritsche, A., Preissl, H., 2015. Selective insulin resistance in homeostatic and cognitive control brain areas in overweight and obese adults. *Diabetes Care* 38, 1044–1050. <https://doi.org/10.2337/dc14-2319>.
- Kullmann, S., Heni, M., Hallschmid, M., Fritsche, A., Preissl, H., Häring, H.-U., 2016. Brain insulin resistance at the crossroads of metabolic and cognitive disorders in humans. *Physiol. Rev.* 96, 1169–1209. <https://doi.org/10.1152/physrev.00032.2015>.
- Kullmann, S., Goj, T., Veit, R., Fritsche, L., Wagner, L., Schneeweiss, P., Hoene, M., Hoffmann, C., Machann, J., Niess, A., Preissl, H., Birkenfeld, A.L., Peter, A., Häring, H.-U., Fritsche, A., Moller, A., Weigert, C., Heni, M., 2022. Exercise restores brain insulin sensitivity in sedentary adults who are overweight and obese. *JCI Insight* 7, e161498. <https://doi.org/10.1172/jci.insight.161498>.
- Kullmann, S., Wagner, L., Hauffe, R., Kühnel, A., Sandforth, L., Veit, R., Dannecker, C., Machann, J., Fritsche, A., Stefan, N., Preissl, H., Kroemer, N.B., Heni, M., Kleinridders, A., Birkenfeld, A.L., 2025. A short-term, high-caloric diet has prolonged effects on brain insulin action in men. *Nat. Metab.* 7, 469–477. <https://doi.org/10.1038/s42255-025-01226-9>.
- Kurhaluk, N., Lukash, O., Kamiński, P., Tkaczko, H., 2024. L-Arginine and intermittent hypoxia are stress-limiting factors in male wistar rat models. *IJMS* 25, 12364. <https://doi.org/10.3390/ijms252212364>.
- Kurowska, A., Ziemichód, W., Herbet, M., Piątkowska-Chmiel, I., 2023. The role of diet as a modulator of the inflammatory process in the neurological diseases. *Nutrients* 15, 1436. <https://doi.org/10.3390/nu15061436>.
- Kurth, F., Zilles, K., Fox, P.T., Laird, A.R., Eickhoff, S.B., 2010. A link between the systems: functional differentiation and integration within the human insula revealed by meta-analysis. *Brain Struct. Funct.* 214, 519–534. <https://doi.org/10.1007/s00429-010-0255-z>.
- Labrakakis, C., 2023. The role of the insular cortex in pain. *IJMS* 24, 5736. <https://doi.org/10.3390/ijms24065736>.
- LaFond, M., DeAngelis, B., al'Absi, M., 2024. Hypothalamic pituitary adrenal and autonomic nervous system biomarkers of stress and tobacco relapse. Review of the research. *Biol. Psychol.* 192, 108854. [doi:10.1016/j.biopsycho.2024.108854](https://doi.org/10.1016/j.biopsycho.2024.108854).
- Laufer, S., Bohn, J., Engel, S., Klusmann, H., Skoluda, N., Nater, U.M., Knaevelsrud, C., Schumacher, S., 2025. Sleep quality and the biological stress system during an internet-based intervention for major depressive disorder. *Compr. Psychoneuroendocrinology* 24, 100314. <https://doi.org/10.1016/j.cpnec.2025.100314>.
- Laukkanen, J.A., Kunutsor, S.K., 2024. The multifaceted benefits of passive heat therapies for extending the healthspan: a comprehensive review with a focus on Finnish sauna. *Temperature* 11, 27–51. <https://doi.org/10.1080/23328940.2023.2300623>.
- Leese, C., Gupte, D., Christogianni, A., Higgins, C., Adair, P., Dall, P., Cameron, P., Smith, B.H., Colvin, L., 2024. Barriers and facilitators for physical activity in people living with chronic pain: a systematic review and combined analysis. *Pain* 165, 2721–2732. <https://doi.org/10.1097/j.pain.0000000000003314>.
- Leone, C.M., Lenoir, C., Van Den Broeke, E.N., 2025. Assessing signs of central sensitization: a critical review of physiological measures in experimentally induced secondary hyperalgesia. *Eur. J. Pain.* 29, e4733. <https://doi.org/10.1002/ejp.4733>.
- Lewis, R.G., Florio, E., Punzo, D., Borrelli, E., 2021. The Brain's Reward System in Health and Disease. In: Engmann, O., Brancaccio, M. (Eds.), *Circadian Clock in Brain Health and Disease, Advances in Experimental Medicine and Biology*. Springer International Publishing, Cham, pp. 57–69. https://doi.org/10.1007/978-3-030-81147-1_4.
- Li, F., Li, Z.-A., Li, J., Tian, H.-M., Li, D.-N., Liu, Z.-Y., Cheng, J., Zhao, T.-Y., Liu, L.-M., Liu, Y.-H., Tao, S.-S., Huang, F.-S., Sun, Y.-G., Liu, S.-B., Li, Y.-Q., 2025. Projection from the parafascicular nucleus of the thalamus to the insular cortex mediate analgesia and anti-anxiety behaviors in mice. *Neurobiol. Dis.* 216, 107107. <https://doi.org/10.1016/j.nbd.2025.107107>.
- Li, G., Guan, Y., Gu, Y., Guo, M., Ma, W., Shao, Q., Liu, J., Ji, X., 2023. Intermittent hypoxic conditioning restores neurological dysfunction of mice induced by long-term hypoxia. *CNS Neurosci. Ther.* 29, 202–215. <https://doi.org/10.1111/cns.13996>.
- Li, X., Ouyang, G., Li, Y., Qu, L., Hu, J., Gu, L., Deng, Q., Sun, G., Xing, J., 2025. Insular cortex mediates chronic restraint stress-induced irritable bowel syndrome-like behaviors via glucocorticoid signaling. *Neurobiol. Dis.* 217, 107180. <https://doi.org/10.1016/j.nbd.2025.107180>.
- Liang, M., Pan, Y., Zhong, T., Zeng, Y., Cheng, A.S.K., 2021. Effects of aerobic, resistance, and combined exercise on metabolic syndrome parameters and cardiovascular risk factors: a systematic review and network meta-analysis. *Rev. Cardiovasc. Med.* 22, 1523. <https://doi.org/10.31083/j.rcm2204156>.
- Liang, Y., Booker, C., 2024. Allostatic load and chronic pain: a prospective finding from the national survey of midlife development in the United States, 2004–2014. *BMC Public Health* 24, 416. <https://doi.org/10.1186/s12889-024-17888-1>.
- Liebert, A., Bicknell, B., Johnstone, D.M., Gordon, L.C., Kiat, H., Hamblin, M.R., 2019. Photobiomics: can light, including photobiomodulation, alter the microbiome? *Photo Photomed. Laser Surg.* 37, 681–693. <https://doi.org/10.1089/photob.2019.4628>.
- Liu, Y., Ni, Y., Zhang, W., Sun, Y.E., Jiang, M., Gu, W.J., Ma, Z.L., Gu, X.P., 2018. Antinociceptive effects of caloric restriction on neuropathic pain in rats involves silent information regulator 1. *Br. J. Anaesth.* 120, 807–817. <https://doi.org/10.1016/j.bja.2017.09.009>.
- Livneh, Y., Ramesh, R.N., Burgess, C.R., Levandowski, K.M., Madara, J.C., Fenselau, H., Goldey, G.J., Diaz, V.E., Jikomes, N., Resch, J.M., Lowell, B.B., Andermann, M.L., 2017. Homeostatic circuits selectively gate food cue responses in insular cortex. *Nature* 546, 611–616. <https://doi.org/10.1038/nature22375>.
- Locatelli, G., Matus, A., James, R., Salmoirago-Blotcher, E., Ausili, D., Vellone, E., Riegel, B., 2023. What is the role of interoception in the symptom experience of people with a chronic condition? A systematic review. *Neurosci. Biobehav. Rev.* 148, 105142. <https://doi.org/10.1016/j.neubiorev.2023.105142>.
- Locatelli, G., Matus, A., Lin, C.-Y., Vellone, E., Riegel, B., 2025. Symptom perception in adults with chronic physical disease: a systematic review of insular impairments. *Heart Lung* 70, 122–140. <https://doi.org/10.1016/j.hrtlng.2024.11.004>.
- Luo, B., Xiang, D., Ji, X., Chen, X., Li, R., Zhang, S., Meng, Y., Nieman, D.C., Chen, P., 2024. The anti-inflammatory effects of exercise on autoimmune diseases: a 20-year systematic review. *J. Sport. Health Sci.* 13, 353–367. <https://doi.org/10.1016/j.jshs.2024.02.002>.
- Lyndon, S., 2026. Pathophysiology of Chronic Pain. *Clin. J. Pain.* <https://doi.org/10.1097/AJP.0000000000001362>.

- Młynarska, E., Grabarczyk, M., Leszko, K., Luba, G., Motor, J., Sosińska, A., Rysz, J., Franczyk, B., 2025. Environmental Insults to Glucose Metabolism: The Role of Pollutants in Insulin Resistance. *IJMS* 26, 8979. [doi:10.3390/ijms26188979](https://doi.org/10.3390/ijms26188979).
- Mukharjee, S., Bank, S., Maiti, S., 2020. Chronic Tobacco Exposure by Smoking Develops Insulin Resistance. *EMIDDT* 20, 869–877. [doi:10.2174/1871530320666200217123901](https://doi.org/10.2174/1871530320666200217123901).
- Müller, L., Di Benedetto, S., 2025. Bridging the brain and gut: neuroimmune mechanisms of neuroinflammation and therapeutic insights. *Front. Cell. Neurosci.* 19, 1590002. <https://doi.org/10.3389/fncel.2025.1590002>.
- Ma, J., Chen, M., Liu, G.-H., Gao, M., Chen, N.-H., Toh, C.H., Hsu, J.-L., Wu, K.-Y., Huang, C.-M., Lin, C.-M., Fang, J.-T., Lee, S.-H., Lee, T.M.C., 2025. Effects of sleep on the glymphatic functioning and multimodal human brain network affecting memory in older adults. *Mol. Psychiatry* 30, 1717–1729. <https://doi.org/10.1038/s41380-024-02778-0>.
- Mandloi, S., Syed, M., Shoraka, O., Ailes, I., Kang, K.C., Sathe, A., Heller, J., Thalheimer, S., Mohamed, F.B., Sharan, A., Harrop, J., Krisa, L., Matias, C., Alizadeh, M., 2023. The role of the insula in chronic pain following spinal cord injury: a resting-state fMRI study. *J. Neuroimaging* 33, 781–791. <https://doi.org/10.1111/jon.13117>.
- Marsland, A.L., Gianaros, P.J., Kuan, D.C.-H., Sheu, L.K., Krajina, K., Manuck, S.B., 2015. Brain morphology links systemic inflammation to cognitive function in midlife adults. *Brain Behav. Immun.* 48, 195–204. <https://doi.org/10.1016/j.bbi.2015.03.015>.
- Martín Pérez, S.E., Abdel Lah, H.A.L., García, N.H., Reyes Carreño, U.A., Martín Pérez, I. M., 2025. Effectiveness of fecal microbiota transplantation in nociceptive pain management: a systematic review. *Gastrointest. Disord.* 7, 5. <https://doi.org/10.3390/gidisd7010005>.
- Mazzola, L., Mauguier, F., Isnard, J., 2019. Functional mapping of the human insula: Data from electrical stimulations. *Rev. Neurol.* 175, 150–156. <https://doi.org/10.1016/j.neurol.2018.12.003>.
- McCabe, C.S., Blake, D.R., 2007. Evidence for a mismatch between the brain's movement control system and sensory system as an explanation for some pain-related disorders. *Curr. Pain. Headache Rep.* 11, 104–108. <https://doi.org/10.1007/s11916-007-0006-x>.
- McCabe, C.S., Cohen, H., Blake, D.R., 2007. Somaesthetic disturbances in fibromyalgia are exaggerated by sensory motor conflict: implications for chronicity of the disease? *Rheumatology* 46, 1587–1592. <https://doi.org/10.1093/rheumatology/kem204>.
- McCabe, C.S., Cohen, H., Hall, J., Lewis, J., Rodham, K., Harris, N., 2009. Somatosensory conflicts in complex regional pain syndrome type 1 and fibromyalgia syndrome. *Curr. Rheumatol. Rep.* 11, 461–465. <https://doi.org/10.1007/s11926-009-0067-4>.
- McCarberg, B., Peppin, J., 2019. Pain pathways and nervous system plasticity: learning and memory in pain. *Pain. Med.* 20, 2421–2437. <https://doi.org/10.1093/pm/pnz017>.
- McCracken, L.M., 2023. Personalized pain management: is it time for process-based therapy for particular people with chronic pain? *Eur. J. Pain.* 27, 1044–1055. <https://doi.org/10.1002/ejp.2091>.
- Meerschaert, K.A., Chiu, I.M., 2025. The gut–brain axis and pain signalling mechanisms in the gastrointestinal tract. *Nat. Rev. Gastroenterol. Hepatol.* 22, 206–221. <https://doi.org/10.1038/s41575-024-01017-9>.
- Mehrf, S.Z., Fleming, H., Nord, C.L., 2025. An interoceptive model of energy allostasis linking metabolic and mental health. *Sci. Adv.* 11, eady4356. <https://doi.org/10.1126/sciadv.ady4356>.
- Mendoza-Herrera, K., Florio, A.A., Moore, M., Marrero, A., Tamez, B., Bhupathiraju, S. N., Mattei, J., 2021. The Leptin System and Diet: A Mini Review of the Current Evidence. *Front. Endocrinol.* 12, 749050. [doi:10.3389/fendo.2021.749050](https://doi.org/10.3389/fendo.2021.749050).
- Mertens, M.G., Núñez-Cortés, R., Lluch, E., Balasch-Bernat, M., Sanchis-Sánchez, E., Morcillo-Alcolea, M., Dueñas, L., 2026. Sensorimotor incongruence is associated with increased symptom severity in people with frozen shoulder: a cross-sectional study. *Musculoskelet. Sci. Pract.* 81, 103458. <https://doi.org/10.1016/j.msksp.2025.103458>.
- Mihaylova, M.M., Chaix, A., Delibegovic, M., Ramsey, J.J., Bass, J., Melkani, G., Singh, R., Chen, Z., Ja, W.W., Shirasu-Hiza, M., Latimer, M.N., Mattison, J.A., Thalacker-Mercer, A.E., Dixit, V.D., Panda, S., Lamming, D.W., 2023. When a calorie is not just a calorie: diet quality and timing as mediators of metabolism and healthy aging. *Cell. Metab.* 35, 1114–1131. <https://doi.org/10.1016/j.cmet.2023.06.008>.
- Milaneschi, Y., Lamers, F., Berk, M., Penninx, B.W.J.H., 2020. Depression heterogeneity and its biological underpinnings: toward immunometabolic depression. *Biol. Psychiatry* 88, 369–380. <https://doi.org/10.1016/j.biopsych.2020.01.014>.
- Miller, G.E., White, S.F., Chen, E., Nusslock, R., 2021. Association of inflammatory activity with larger neural responses to threat and reward among children living in Poverty. *AJP* 178, 313–320. <https://doi.org/10.1176/appi.ajp.2020.20050635>.
- Murillo-Cancho, A.F., Lozano-Paniagua, D., Nievas-Soriano, B.J., 2025. Alternative dietary strategies to modulate obesity and improve metabolic health in aging: a comparative narrative review. *Obesities* 5, 30. <https://doi.org/10.3390/obesities5020030>.
- Musen, G., Jacobson, A.M., Bolo, N.R., Simonson, D.C., Shenton, M.E., McCartney, R.L., Flores, V.L., Hoogenboom, W.S., 2012. Resting-state brain functional connectivity is altered in type 2 diabetes. *Diabetes* 61, 2375–2379. <https://doi.org/10.2337/db11-1669>.
- N. F. Guimarães, G., Dos Santos Cardoso, F., Gamboa, L., W. Barrett, D., Gonzalez-Lima, F., 2025. Abdominal photobiomodulation and the gut-brain axis: a systematic review of mechanistic and translational evidence. *Biomedicine* 13, 3042. <https://doi.org/10.3390/biomedicine13123042>.
- Núñez-Cortés, R., Cruz-Montecinos, C., López-Bueno, R., Andersen, L.L., Calatayud, J., 2025a. Physical inactivity is the most important unhealthy lifestyle factor for pain severity in older adults with pain: A SHARE-based analysis of 27,528 cases from 28 countries. *Musculoskelet. Sci. Pract.* 76, 103270. <https://doi.org/10.1016/j.msksp.2025.103270>.
- Núñez-Cortés, R., Salazar-Méndez, J., Nijs, J., 2025b. Physical activity as a central pillar of lifestyle modification in the management of chronic musculoskeletal pain: a narrative review. *JFMK* 10, 183. <https://doi.org/10.3390/jfmk10020183>.
- Navarro-Ledesma, S., Carroll, J.D., González-Muñoz, A., Burton, P., 2024a. Outcomes of whole-body photobiomodulation on pain, quality of life, leisure physical activity, pain catastrophizing, kinesophobia, and self-efficacy: a prospective randomized triple-blinded clinical trial with 6 months of follow-up. *Front. Neurosci.* 18, 1264821. <https://doi.org/10.3389/fnins.2024.1264821>.
- Navarro-Ledesma, S., Hamed-Hamed, D., Gonzalez-Muñoz, A., Pruimboom, L., 2024b. Impact of physical therapy techniques and common interventions on sleep quality in patients with chronic pain: A systematic review. *Sleep. Med. Rev.* 76, 101937. <https://doi.org/10.1016/j.smrv.2024.101937>.
- Nijs, J., Malfliet, A., Roose, E., Lahousse, A., Van Bogaert, W., Johansson, E., Runge, N., Goossens, Z., Labie, C., Bilterys, T., Van Campenhout, J., Polli, A., Wyns, A., Hendrix, J., Xiong, H.-Y., Ahmed, I., De Baets, L., Huysmans, E., 2024. Personalized multimodal lifestyle intervention as the best-evidenced treatment for chronic pain: state-of-the-art clinical perspective. *JCM* 13, 644. <https://doi.org/10.3390/jcm13030644>.
- Niu, X., Wu, X., Ying, A., Shao, B., Li, X., Zhang, W., Lin, C., Lin, Y., 2019. Maternal high fat diet programs hypothalamic-pituitary-adrenal function in adult rat offspring. *Psychoneuroendocrinology* 102, 128–138. <https://doi.org/10.1016/j.psyneuen.2018.12.003>.
- Nusslock, R., Alloy, L.B., Brody, G.H., Miller, G.E., 2024. Annual Research Review: Neuroimmune network model of depression: a developmental perspective. *Child. Psychol. Psychiatry* 65, 538–567. <https://doi.org/10.1111/jcpp.13961>.
- Packheiser, J., Hartmann, H., Fredriksen, K., Gazzola, V., Keyzers, C., Michon, F., 2024. A systematic review and multivariate meta-analysis of the physical and mental health benefits of touch interventions. *Nat. Hum. Behav.* 8, 1088–1107. <https://doi.org/10.1038/s41562-024-01841-8>.
- Pallubinsky, H., Phielix, E., Dautzenberg, B., Schaart, G., Connell, N.J., De Wit-Verheggen, V., Havekes, B., Van Baak, M.A., Schrauwen, P., Van Marken Lichtenbelt, W.D., 2020. Passive exposure to heat improves glucose metabolism in overweight humans. *Acta Physiol.* 229, e13488. <https://doi.org/10.1111/apha.13488>.
- Pan, P.L., Zhong, J.G., Shang, H.F., Zhu, Y.L., Xiao, P.R., Dai, Z.Y., Shi, H.C., 2015. Quantitative meta-analysis of grey matter anomalies in neuropathic pain. *Eur. J. Pain.* 19, 1224–1231. <https://doi.org/10.1002/ejp.670>.
- Párraga, J.P., Castellanos, A., 2023. A Manifesto in Defense of Pain Complexity: A Critical Review of Essential Insights in Pain Neuroscience. *JCM* 12, 7080. <https://doi.org/10.3390/jcm12227080>.
- Patel, M., Hasoon, J., Diez Tafur, R., Lo Bianco, G., Abd-Elseyed, A., 2025. The impact of chronic pain on cognitive function. *Brain Sci.* 15, 559. <https://doi.org/10.3390/brainsci15060559>.
- Patrick, R.P., Johnson, T.L., 2021. Sauna use as a lifestyle practice to extend healthspan. *Exp. Gerontol.* 154, 111509. <https://doi.org/10.1016/j.exger.2021.111509>.
- Peixoto, D., Carvalho, I., Machado, M., Aragão, C., Costas, B., Azeredo, R., 2024. Dietary tryptophan intervention counteracts stress-induced transcriptional changes in a teleost fish HPI axis during inflammation. *Sci. Rep.* 14, 7354. <https://doi.org/10.1038/s41598-024-57761-0>.
- Pinto, A.J., Bergougnan, A., Dempsey, P.C., Roschel, H., Owen, N., Gualano, B., Dunstan, D.W., 2023. Physiology of sedentary behavior. *Physiol. Rev.* 103, 2561–2622. <https://doi.org/10.1152/physrev.00022.2022>.
- Podstawski, R., Boryslawski, K., Pomianowski, A., Krystkiewicz, W., Żurek, P., 2021. Endocrine effects of repeated hot thermal stress and cold water immersion in young adult men. *Am. J. Mens. Health* 15, 15579883211008339. <https://doi.org/10.1177/15579883211008339>.
- Prentice, F., Murphy, J., 2022. Sex differences in interoceptive accuracy: a meta-analysis. *Neurosci. & Biobehav. Rev.* 132, 497–518. <https://doi.org/10.1016/j.neubiorev.2021.11.030>.
- Pruimboom, L., Rocio, F.A., Navarro-Ledesma, S., 2024. Psychoneuroimmunology in the Daily Clinic is Only Possible Within a Contextual Frame. In: Rezaei, N., Yazdanpanah, N. (Eds.), *PsychoNeuroImmunology, Integrated Science*. Springer Nature Switzerland, Cham, pp. 515–563. https://doi.org/10.1007/978-3-031-73061-0_16.
- Qiu, S., Chen, T., Koga, K., Guo, Y., Xu, H., Song, Q., Wang, J., Descalzi, G., Kaang, B.-K., Luo, J., Zhuo, M., Zhao, M., 2013. An increase in synaptic NMDA receptors in the insular cortex contributes to neuropathic pain. *Sci. Signal.* 6. <https://doi.org/10.1126/scisignal.2003778>.
- Qiu, S., Zhang, M., Liu, Y., Guo, Y., Zhao, H., Song, Q., Zhao, M., Haganir, R.L., Luo, J., Xu, H., Zhuo, M., 2014. GluA1 phosphorylation contributes to postsynaptic amplification of neuropathic pain in the insular cortex. *J. Neurosci.* 34, 13505–13515. <https://doi.org/10.1523/JNEUROSCI.1431-14.2014>.
- Quadt, L., Critchley, H.D., Garfinkel, S.N., 2018. The neurobiology of interoception in health and disease. *Ann. New. Y. Acad. Sci.* 1428, 112–128. <https://doi.org/10.1111/nyas.13915>.
- Quidé, Y., Hesam-Shariati, N., Norman-Nott, N., McAuley, J.H., Gustin, S.M., 2025. Stress-related brain alterations in chronic pain. *Eur. J. Pain.* 29, e70034. <https://doi.org/10.1002/ejp.70034>.
- Reeder, M., Anderson, T., Alumbaugh, B., Murray, S., 2023. Sauna bathing as an alternative adjunct therapy in the prevention and treatment of chronic health conditions including cardiovascular disease, neurodegenerative disease, metabolic disease, and mental health disorders. *MRAJ* 11. <https://doi.org/10.18103/mra.v11i6.3965>.

- Reis, J.T., Silva, I.G.G., Borges, A.C.R.L., Reis, A.P.T.D., Santos, W.A.D.M., Benevides, K. A.M.M., Abreu, S.A.N.D., Moreno, T., Almeida, J.Q., Manguiera, C.D.M., Vasconcelos, F.H., Mariano, W.D.S., Sampaio, A.C.M., 2024. The relationship between depression and chronic pain: a literature review. *J. Adv. Med. Med. Res.* 36, 301–312. <https://doi.org/10.9734/jammr/2024/v36i85548>.
- Reutrakul, S., Van Cauter, E., 2018. Sleep influences on obesity, insulin resistance, and risk of type 2 diabetes. *Metabolism* 84, 56–66. <https://doi.org/10.1016/j.metabol.2018.02.010>.
- Rieger, N.S., Varela, J.A., Ng, A.J., Granata, L., Djerdjaj, A., Brenhouse, H.C., Christianson, J.P., 2022. Insular cortex corticotropin-releasing factor integrates stress signaling with social affective behavior. *Neuropsychopharmacol* 47, 1156–1168. <https://doi.org/10.1038/s41386-022-01292-7>.
- Roekner, A.R., Oliver, K.L., Lebois, L.A.M., Van Rooij, S.J.H., Stevens, J.S., 2021. Neural contributors to trauma resilience: a review of longitudinal neuroimaging studies. *Transl. Psychiatry* 11, 508. <https://doi.org/10.1038/s41398-021-01633-y>.
- Rohleder, N., Kirschbaum, C., 2006. The hypothalamic–pituitary–adrenal (HPA) axis in habitual smokers. *Int. J. Psychophysiol.* 59, 236–243. [doi:10.1016/j.ijpsycho.2005.10.012](https://doi.org/10.1016/j.ijpsycho.2005.10.012).
- Rolls, A., 2023. Immunoception: the insular cortex perspective. *Cell. Mol. Immunol.* 20, 1270–1276. <https://doi.org/10.1038/s41423-023-01051-8>.
- Runge, N., Ahmed, I., Saueressig, T., Perea, J., Labie, C., Mairesse, O., Nijs, J., Malfliet, A., Verschueren, S., Van Assche, D., De Vlam, K., Van Waeyenberg, T., Van Haute, J., De Baets, L., 2024. The bidirectional relationship between sleep problems and chronic musculoskeletal pain: a systematic review with meta-analysis. *Pain* 165, 2455–2467. <https://doi.org/10.1097/j.pain.0000000000003279>.
- Rybnikova, E.A., Nalivaeva, N.N., Zenko, M.Y., Baranova, K.A., 2022. Intermittent hypoxic training as an effective tool for increasing the adaptive potential, endurance and working capacity of the brain. *Front. Neurosci.* 16, 941740. <https://doi.org/10.3389/fnins.2022.941740>.
- Sá, K.N., Moreira, L., Baptista, A.F., Yeng, L.T., Teixeira, M.J., Galhardoni, R., De Andrade, D.C., 2019. Prevalence of chronic pain in developing countries: systematic review and meta-analysis. *PR9* 4, e779. <https://doi.org/10.1097/PR9.0000000000000779>.
- Sampath Kumar, A., Maiya, A.G., Shastry, B.A., Vaishali, K., Ravishankar, N., Hazari, A., Gundmi, S., Jadhav, R., 2019. Exercise and insulin resistance in type 2 diabetes mellitus: A systematic review and meta-analysis. *Ann. Phys. Rehabil. Med.* 62, 98–103. <https://doi.org/10.1016/j.rehab.2018.11.001>.
- Savitz, J., Harrison, N.A., 2018. Interception and Inflammation in Psychiatric Disorders. *Biol. Psychiatry Cogn. Neurosci. Neuroimaging* 3, 514–524. <https://doi.org/10.1016/j.bpsc.2017.12.011>.
- Scarpina, F., Navarra, M.E., Varallo, G., Bernorio, R., 2025. The role of interoceptive sensibility on central sensitization to pain in vulvodynia. *J. Sex. Med.* 22, 491–499. <https://doi.org/10.1093/jsxmed/qdae203>.
- Scatà, C., Carandina, A., Della Torre, A., Arosio, B., Bellocchi, C., Dias Rodrigues, G., Furlan, L., Tobaldini, E., Montano, N., 2023. Social isolation: a narrative review on the dangerous liaison between the autonomic nervous system and inflammation. *Life* 13, 1229. <https://doi.org/10.3390/life13061229>.
- Schilling, T.M., Ferreira De Sá, D.S., Westerhausen, R., Strelzyk, F., Larra, M.F., Hallschmid, M., Savaskan, E., Oitzl, M.S., Busch, H., Naumann, E., Schächinger, H., 2014. Intranasal insulin increases regional cerebral blood flow in the insular cortex in men independently of cortisol manipulation. *Human. Brain Mapp.* 35, 1944–1956. <https://doi.org/10.1002/hbm.22304>.
- Schulz, A., Strelzyk, F., Ferreira De Sá, D.S., Naumann, E., Vögele, C., Schächinger, H., 2013. Cortisol rapidly affects amplitudes of heartbeat-evoked brain potentials—Implications for the contribution of stress to an altered perception of physical sensations. *Psychoneuroendocrinology* 38, 2686–2693. <https://doi.org/10.1016/j.psyneuen.2013.06.027>.
- Schulz, A., Deuter, C.E., Breden, I.-H., Vögele, C., Wingenfeld, K., Otte, C., Kuehl, L.K., 2022. Noradrenergic activation induced by yohimbine decreases interoceptive accuracy in healthy individuals with childhood adversity. *Dev. Psychopathol.* 34, 1013–1024. <https://doi.org/10.1017/S0954579420001613>.
- Schulz, A., Bellingrath, S., Lutz, A., Drost, L.M., Vögele, C., 2025. Acute stress enhances heartbeat-evoked potentials, but does not affect cardiac interoceptive accuracy. *Psychophysiology* 62, e70194. <https://doi.org/10.1111/psyp.70194>.
- Schulz, A., Vögele, C., 2015. Interoception and stress. *Front Psychol* 6, 993. <https://doi.org/10.3389/fpsyg.2015.00993>.
- Serebrovska, Z., Xi, L., Fedoriuk, M., Dosenko, V., Shysh, A., Khetsuriani, M., Porkhalo, D., Savchenko, A., Goncharov, S., Utiko, N., Virko, S., Kholin, V., Egorov, E., Koval, R., Maksymchuk, O., 2025. Intermittent hypoxia-hyperoxia training ameliorates cognitive impairment and neuroinflammation in a rat model of Alzheimer's disease. *Brain Res.* 1847, 149301. <https://doi.org/10.1016/j.brainres.2024.149301>.
- Setiawan, E., Wilson, A.A., Mizrahi, R., Rusjan, P.M., Miler, L., Rajkowska, G., Suridjan, I., Kennedy, J.L., Rekkas, P.V., Houle, S., Meyer, J.H., 2015. Role of translocator protein density, a marker of neuroinflammation, in the brain during major depressive episodes. *JAMA Psychiatry* 72, 268. <https://doi.org/10.1001/jamapsychiatry.2014.2427>.
- Shaikh, S.R., Shaver, P.R., Shewchuk, B.M., 2018. High fat diet dysregulates hypothalamic-pituitary axis gene expression levels which are differentially rescued by EPA and DHA ethyl esters. *Mol. Nutr. Food Res.* 62, 1800219. <https://doi.org/10.1002/mnfr.201800219>.
- Shamenko, V.O., Kadzharian, Ye.V., Abramov, A.V., 2019. Intermittent hypobaric hypoxia and neuroendocrine reaction of the parvocellular neurons of the paraventricular hypothalamic nucleus. *Pathologia* 16. <https://doi.org/10.14739/2310-1237.2019.3.188834>.
- Sherriff, B., Clark, C., Killingback, C., Newell, D., 2022. Impact of contextual factors on patient outcomes following conservative low back pain treatment: systematic review. *Chiropr. Man. Ther.* 30, 20. <https://doi.org/10.1186/s12998-022-00430-8>.
- Shi, W., Fu, Y., Shi, T., Zhou, W., 2022. Different synaptic plasticity after physiological and psychological stress in the anterior insular cortex in an observational fear mouse model. *Front. Synaptic Neurosci.* 14, 851015. <https://doi.org/10.3389/fnsyn.2022.851015>.
- Shin, A.C., MohanKumar, S.M.J., Balasubramanian, P., Sirivelu, M.P., Lanning, K., Woolcock, A., James, M., MohanKumar, P.S., 2019. Responsiveness of hypothalamo-pituitary-adrenal axis to leptin is impaired in diet-induced obese rats. *Nutr. Diabetes* 9, 10. <https://doi.org/10.1038/s41387-019-0076-y>.
- Shin, A.C., MohanKumar, S.M.J., Sirivelu, M.P., Claycombe, K.J., Haywood, J.R., Fink, G. D., MohanKumar, P.S., 2010. Chronic exposure to a high-fat diet affects stress axis function differentially in diet-induced obese and diet-resistant rats. *Int. J. Obes.* 34, 1218–1226. <https://doi.org/10.1038/ijo.2010.34>.
- Shiralkar, V.V., Jagtap, P.E., Belwalkar, G.J., Nagane, N.S., Dhonde, S.P., 2018. Effect of steam sauna bath on fasting blood glucose level in healthy adults. *Indian. J. Med. Biochem.* 22, 18–21. <https://doi.org/10.5005/jp-journals-10054-0047>.
- Shura, R.D., Hurley, R.A., Taber, K.H., 2014. Insular cortex: structural and functional neuroanatomy. *JNP* 26, iv–282. <https://doi.org/10.1176/appi.neuropsych.260401>.
- Simmons, W.K., Avery, J.A., Barcalow, J.C., Bodurka, J., Drevets, W.C., Bellgowan, P., 2013. Keeping the body in mind: Insula functional organization and functional connectivity integrate interoceptive, exteroceptive, and emotional awareness. *Human. Brain Mapp.* 34, 2944–2958. <https://doi.org/10.1002/hbm.22113>.
- Simmons, W.K., Burrows, K., Avery, J.A., Kerr, K.L., Bodurka, J., Savage, C.R., Drevets, W.C., 2016. Depression-related increases and decreases in appetite: dissociable patterns of aberrant activity in reward and interoceptive neurocircuitry. *AJP* 173, 418–428. <https://doi.org/10.1176/appi.ajp.2015.15020162>.
- Simmons, W.K., Burrows, K., Avery, J.A., Kerr, K.L., Taylor, A., Bodurka, J., Potter, W., Teague, T.K., Drevets, W.C., 2020. Appetite changes reveal depression subgroups with distinct endocrine, metabolic, and immune states. *Mol. Psychiatry* 25, 1457–1468. <https://doi.org/10.1038/s41380-018-0093-6>.
- Simone, L., Caruana, F., Borra, E., Del Sorbo, S., Jezzini, A., Rozzi, S., Luppino, G., Gerbella, M., 2025. Anatomical-functional organization of insular networks: from sensory integration to behavioral control. *Progress. Neurobiol.* 247, 102748. <https://doi.org/10.1016/j.pneurobio.2025.102748>.
- Smadja, D.M., Abreu, M.M., 2025. Hyperthermia and targeting heat shock proteins: innovative approaches for neurodegenerative disorders and Long COVID. *Front. Neurosci.* 19, 1475376. <https://doi.org/10.3389/fnins.2025.1475376>.
- Smith, A.F., Plumb, A.N., Berardi, G., Sluka, K.A., 2025. Sex differences in the transition to chronic pain. *J. Clin. Investig.* 135, e191931. <https://doi.org/10.1172/JCI191931>.
- Solcà, M., Park, H.-D., Bernasconi, F., Blanke, O., 2020. Behavioral and neurophysiological evidence for altered interoceptive bodily processing in chronic pain. *NeuroImage* 217, 116902. <https://doi.org/10.1016/j.neuroimage.2020.116902>.
- Son, Y., Lee, Hyeri, Yu, S., Kim, H.J., Park, J., Woo, S., Lee, Hayeon, Fond, G., Boyer, L., Rahmati, M., Smith, L., López Sánchez, G.F., Dragioti, E., Kang, J., Kim, T., Yon, D. K., 2025. Effects of photobiomodulation on multiple health outcomes: an umbrella review of randomized clinical trials. *Syst. Rev.* 14, 160. <https://doi.org/10.1186/s13643-025-02902-3>.
- Song, Y., Zhu, Chen, Shi, B., Song, C., Cui, K., Chang, Z., Gao, G., Jia, L., Fu, R., Dong, Q., Feng, L., Zhu, Chenggang, Yin, D., Manson, J.E., Dou, K., 2023. Social isolation, loneliness, and incident type 2 diabetes mellitus: results from two large prospective cohorts in Europe and East Asia and Mendelian randomization. *eClinicalMedicine* 64, 102236. <https://doi.org/10.1016/j.eclim.2023.102236>.
- Stephan, K.E., Manjaly, Z.M., Mathys, C.D., Weber, L.A.E., Paliwal, S., Gard, T., Tittgemeyer, M., Fleming, S.M., Haker, H., Seth, A.K., Petzschner, F.H., 2016. Allostatic self-efficacy: a metacognitive theory of dyshomeostasis-induced fatigue and depression. *Front. Hum. Neurosci.* 10. <https://doi.org/10.3389/fnhum.2016.00550>.
- Stubhaug, A., Hansen, J.L., Hallberg, S., Gustavsson, A., Eggen, A.E., Nielsen, C.S., 2024. The costs of chronic pain—Long-term estimates. *Eur. J. Pain.* 28, 960–977. <https://doi.org/10.1002/ejp.2234>.
- Sunzini, F., Stefanov, K., Al-Wasity, S., Kaplan, C., Schrepf, A., Waller, N., Harte, S., Harris, R., Clauw, D.J., McLean, J., Siebert, S., Groppa, C.S., Waiter, G.D., Basu, N., 2025. The insula represents a key neurobiological pain hub in psoriatic arthritis. *Arthritis Res. Ther.* 27, 70. <https://doi.org/10.1186/s13075-025-03526-7>.
- Teeuwisse, W.M., Widdya, R.L., Paulides, M., Lamb, H.J., Smit, J.W.A., De Roos, A., Van Buchem, M.A., Pijl, H., Van Der Grond, J., 2012. Short-term caloric restriction normalizes hypothalamic neuronal responsiveness to glucose ingestion in patients with type 2 diabetes. *Diabetes* 61, 3255–3259. <https://doi.org/10.2337/db11-1835>.
- Tellez, L.A., Medina, S., Han, W., Ferreira, J.G., Licona-Limón, P., Ren, X., Lam, T.T., Schwartz, G.J., De Araujo, I.E., 2013. A gut lipid messenger links excess dietary fat to dopamine deficiency. *Science* 341, 800–802. <https://doi.org/10.1126/science.1239275>.
- Ten Kulve, J.S., Veltman, D.J., Van Bloemendaal, L., Barkhof, F., Deacon, C.F., Holst, J.J., Konrad, R.J., Sloan, J.H., Drent, M.L., Diamant, M., IJzerman, R.G., 2015. Endogenous GLP-1 mediates postprandial reductions in activation in central reward and satiety areas in patients with type 2 diabetes. *Diabetologia* 58, 2688–2698. <https://doi.org/10.1007/s00125-015-3754-x>.
- Thomson, E.M., 2019. Air Pollution, Stress, and Allostatic Load: Linking Systemic and Central Nervous System Impacts. *J. Alzheimers Dis.* 69, 597–614. [doi:10.3233/JAD-190015](https://doi.org/10.3233/JAD-190015).
- Todd, J., Plans, D., Lee, M.C., Bird, J.M., Morelli, D., Cunningham, A., Ponzio, S., Murphy, J., Bird, G., Aspell, J.E., 2024. Heightened interoception in adults with

- fibromyalgia. *Biol. Psychol.* 186, 108761. <https://doi.org/10.1016/j.biopsycho.2024.108761>.
- Toenders, Y.J., Schmaal, B.J., Dinga, R., Berk, M., Davey, C.G., 2020. Neurovegetative symptom subtypes in young people with major depressive disorder and their structural brain correlates. *Transl. Psychiatry* 10, 108. <https://doi.org/10.1038/s41398-020-0787-9>.
- Tokarska, N., Nanioglu, J.M.A., Johnston, J.M., Salapa, H.E., Muir, G.D., Levin, M.C., Popescu, B.F., Verge, V.M.K., 2023. Acute intermittent hypoxia alters disease course and promotes CNS repair including resolution of inflammation and remyelination in the experimental autoimmune encephalomyelitis model of MS. *Glia* 71, 2045–2066. <https://doi.org/10.1002/glia.24381>.
- Treede, R.-D., Rief, W., Barke, A., Aziz, Q., Bennett, M.I., Benoliel, R., Cohen, M., Evers, S., Finnerup, N.B., First, M.B., Giamberardino, M.A., Kaasa, S., Korwisi, B., Kosek, E., Lavand'homme, P., Nicholas, M., Perrot, S., Scholz, J., Schug, S., Smith, B. H., Svensson, P., Vlaeyen, J.W.S., Wang, S.-J., 2019. Chronic pain as a symptom or a disease: the IASP classification of chronic pain for the international classification of diseases (ICD-11). *Pain* 160, 19–27. <https://doi.org/10.1097/j.pain.0000000000001384>.
- Tschritter, O., Preissl, H., Hennige, A.M., Stumvoll, M., Porubská, K., Frost, R., Marx, H., Klösel, B., Lutzenberger, W., Birbaumer, N., Häring, H.-U., Fritzsche, A., 2006. The cerebrocortical response to hyperinsulinemia is reduced in overweight humans: a magnetoencephalographic study. *Proc. Natl. Acad. Sci. U. S. A.* 103, 12103–12108. <https://doi.org/10.1073/pnas.0604404103>.
- Tuuluri, J.J., Karlsson, H.K., Hirvonen, J., Hannukainen, J.C., Bucci, M., Helmiö, M., Ovaska, J., Soinio, M., Salminen, P., Savisto, N., Nummenmaa, L., Nuutila, P., 2013. Weight loss after bariatric surgery reverses insulin-induced increases in brain glucose metabolism of the morbidly obese. *Diabetes* 62, 2747–2751. <https://doi.org/10.2337/db12-1460>.
- Uddin, L.Q., 2015. Salience processing and insular cortical function and dysfunction. *Nat. Rev. Neurosci.* 16, 55–61. <https://doi.org/10.1038/nrn3857>.
- Uddin, L.Q., Nomi, J.S., Hébert-Seropian, B., Ghaziri, J., Boucher, O., 2017. Structure and Function of the Human Insula. *J. Clin. Neurophysiol.* 34, 300–306. <https://doi.org/10.1097/WNP.0000000000000377>.
- Uzun, A.-B., Nedelcu, A.-D., Iliescu, M.-G., Stanciu, L.-E., Petcu, A., Petcu, L.C., Obada, B., Tofolean, D.-E., 2025. Intermittent hypoxia-hyperoxia therapy in medical rehabilitation: Effects on body composition in patients with metabolic syndrome. *Balneo PRM Res. J.* 16. <https://doi.org/10.12680/balneo.2025.780>.
- Vachon-Presseau, E., 2018. Effects of stress on the corticolimbic system: implications for chronic pain. *Progress. Neuro-Psychopharmacol. Biol. Psychiatry* 87, 216–223. <https://doi.org/10.1016/j.pnpbp.2017.10.014>.
- Van Bloemendaal, L., IJzerman, R.G., Ten Kulve, J.S., Barkhof, F., Konrad, R.J., Drent, M. L., Veltman, D.J., Diamant, M., 2014. GLP-1 receptor activation modulates appetite and reward-related brain areas in humans. *Diabetes* 63, 4186–4196. <https://doi.org/10.2337/db14-0849>.
- Van Dalfsen, J.H., Markus, C.R., 2018. The influence of sleep on human hypothalamic–pituitary–adrenal (HPA) axis reactivity: a systematic review. *Sleep. Med. Rev.* 39, 187–194. <https://doi.org/10.1016/j.smrv.2017.10.002>.
- Van Galen, K.A., Schrantz, A., Ter Horst, K.W., La Fleur, S.E., Booij, J., Constable, R.T., Schwartz, G.J., DiLeone, R.J., Serlie, M.J., 2023. Brain responses to nutrients are severely impaired and not reversed by weight loss in humans with obesity: a randomized crossover study. *Nat. Metab.* 5, 1059–1072. <https://doi.org/10.1038/s42255-023-00816-9>.
- Vyverman, J., De Baere, R., Timmers, I., Coppieters, I., Van Oosterwijck, J., Moerkerke, M., 2026. The stress–pain connection in chronic primary pain: a systematic review and meta-analysis of physiological stress markers in relation to experimental pain responses. *Neurosci. Biobehav. Rev.* 184, 106604. <https://doi.org/10.1016/j.neubiorev.2026.106604>.
- Walsh, C.P., Bovbjerg, D.H., Marsland, A.L., 2021. Glucocorticoid resistance and β 2-adrenergic receptor signaling pathways promote peripheral pro-inflammatory conditions associated with chronic psychological stress: a systematic review across species. *Neurosci. Biobehav. Rev.* 128, 117–135. <https://doi.org/10.1016/j.neubiorev.2021.06.013>.
- Wang, J., Fan, S., Wang, Jianshe, 2025. Resistance training enhances metabolic and muscular health and reduces systemic inflammation in middle-aged and older adults with type 2 diabetes: a meta-analysis. *Diabetes Res. Clin. Pract.* 229, 112941. <https://doi.org/10.1016/j.diabres.2025.112941>.
- Wang, N., Zhang, Y.-H., Wang, J.-Y., Luo, F., 2021. Current understanding of the involvement of the insular cortex in neuropathic pain: a narrative review. *IJMS* 22, 2648. <https://doi.org/10.3390/ijms22052648>.
- Wang, Y., Zhang, Y., Zhang, Jinlei, Wang, J., Xu, J., Li, J., Cui, G., Zhang, Jiuquan, 2018. Structural and functional abnormalities of the insular cortex in trigeminal neuralgia: a multimodal magnetic resonance imaging analysis. *Pain* 159, 507–514. <https://doi.org/10.1097/j.pain.0000000000001120>.
- Wang, Z., Guo, Y., Mayer, E.A., Holschneider, D.P., 2019. Sex differences in insular functional connectivity in response to noxious visceral stimulation in rats. *Brain Res.* 1717, 15–26. <https://doi.org/10.1016/j.brainres.2019.04.005>.
- Wang, Y., Han, Q., Han, X., Dong, Y., Mao, M., Wang, C., Wang, X., Tang, S., Liu, C., Li, Y., Hou, T., Cong, L., Du, Y., Qiu, C., 2023. Objectively-measured movement behaviors, systemic low-grade inflammation, and plasma neurofilament light chain in older adults: a population-based study. *Immun. Ageing* 20, 36. <https://doi.org/10.1186/s12979-023-00363-7>.
- Wang, Z., Li, X., Li, Y., Sun, X., Wang, Y., Lu, T., Zhao, D., Ma, X., Sun, H., 2025. The insular cortex–nucleus tractus solitarius glutamatergic pathway involved in acute stress-induced gastric mucosal damage in rats. *Neurobiol. Stress.* 36, 100723. <https://doi.org/10.1016/j.ynstr.2025.100723>.
- Weber, M.D., Godbout, J.P., Sheridan, J.F., 2017. Repeated Social Defeat, Neuroinflammation, and Behavior: Monocytes Carry the Signal. *Neuropsychopharmacol.* 42, 46–61. [doi:10.1038/npp.2016.102](https://doi.org/10.1038/npp.2016.102).
- Wheeler, M.A., Quintana, F.J., 2025. The neuroimmune connectome in health and disease. *Nature* 638, 333–342. <https://doi.org/10.1038/s41586-024-08474-x>.
- Więkowska-Gacek, A., Mietelska-Porowska, A., Wydrych, M., Wojda, U., 2021. Western diet as a trigger of Alzheimer's disease: from metabolic syndrome and systemic inflammation to neuroinflammation and neurodegeneration. *Ageing Res. Rev.* 70, 101397. <https://doi.org/10.1016/j.arr.2021.101397>.
- Wohleb, E.S., McKim, D.B., Sheridan, J.F., Godbout, J.P., 2015. Monocyte trafficking to the brain with stress and inflammation: a novel axis of immune-to-brain communication that influences mood and behavior. *Front. Neurosci.* 8. <https://doi.org/10.3389/fnins.2014.00447>.
- Wright, L.J., Schur, E., Noonan, C., Ahumada, S., Buchwald, D., Afari, N., 2010. Chronic pain, overweight, and obesity: findings from a community-based twin registry. *J. Pain.* 11, 628–635. <https://doi.org/10.1016/j.jpain.2009.10.004>.
- Wu, Q., Imman, R.D., Davis, K.D., 2013. Neuropathic pain in ankylosing spondylitis: a psychophysics and brain imaging study. *Arthritis & Rheum.* 65, 1494–1503. <https://doi.org/10.1002/art.37920>.
- Xu, W., Shi, R., Zhu, Y., Feng, W., 2025. Association of visceral adiposity index and chronic pain in US adults: a cross-sectional study. *Sci. Rep.* 15, 9135. <https://doi.org/10.1038/s41598-025-93041-1>.
- Xu, X., Wang, J., Chen, G., 2023. Circadian cycle and neuroinflammation. *Open. Life Sci.* 18, 20220712. <https://doi.org/10.1515/biol-2022-0712>.
- Yadav, M., Devi, D., 2023. Effect of kuti sweda (sauna bath) on cardiometabolic health: a randomized controlled study. *IAMJ* 11, 1232–1237. <https://doi.org/10.46607/iamj0211062023>.
- Yang, S., Chang, M.C., 2019. Chronic pain: structural and functional changes in brain structures and associated negative affective states. *IJMS* 20, 3130. <https://doi.org/10.3390/ijms20133130>.
- Yi, L., Sun, H., Ge, C., Chen, Y., Peng, H., Jiang, Y., Wu, P., Tang, Y., Meng, Q., Xu, S., 2014. Role of insular cortex in visceral hypersensitivity model in rats subjected to chronic stress. *Psychiatry Res.* 220, 1138–1143. <https://doi.org/10.1016/j.psychres.2014.09.019>.
- Yilai, Z., Kamaruzaman Syed Ali, S., Basar, A., 2025. The role of physical exercise in reducing stress. *IJSSMR* 08, 01–07. <https://doi.org/10.37602/IJSSMR.2025.8601>.
- Yokum, S., Ng, J., Stice, E., 2011. Attentional bias to food images associated with elevated weight and future weight gain: an fMRI study. *Obesity* 19, 1775–1783. <https://doi.org/10.1038/oby.2011.168>.
- Yoris, A., Abrevaya, S., Esteves, S., Salamone, P., Lori, N., Martorell, M., Legaz, A., Alifano, F., Petroni, A., Sánchez, R., Sedeño, L., García, A.M., Ibáñez, A., 2018. Multilevel convergence of interoceptive impairments in hypertension: new evidence of disrupted body–brain interactions. *Human. Brain Mapp.* 39, 1563–1581. <https://doi.org/10.1002/hbm.23933>.
- Yue, X., Zhou, Y., Qiao, M., Zhao, X., Huang, X., Zhao, T., Cheng, X., Fan, M., Zhao, Y., Chen, R., Zhu, L., 2021. Intermittent hypoxia treatment alleviates memory impairment in the 6-month-old APPswe/PS1dE9 mice and reduces amyloid beta accumulation and inflammation in the brain. *Alz Res. Ther.* 13, 194. <https://doi.org/10.1186/s13195-021-00935-z>.
- Zeng, X., Sun, Y., Zhiying, Z., Hua, L., Yuan, Z., 2025. Chronic pain-induced functional and structural alterations in the brain: A multi-modal meta-analysis. *J. Pain.* 28, 104740. <https://doi.org/10.1016/j.jpain.2024.104740>.
- Zhang, Q., Zhang, P., Yan, R., Xu, X., Mao, C., Liu, X., Li, F., Ma, J., Ye, L., Yao, Z., Wu, J., 2019. A Single-blinded trial using resting-state functional magnetic resonance imaging of brain activity in patients with type 2 diabetes and painful neuropathy. *Diabetes Ther.* 10, 135–147. <https://doi.org/10.1007/s13300-018-0534-x>.
- Zhang, Y., Luo, C., Huang, P., Chen, L., Ma, Y., Ding, H., 2024. Effects of chronic exposure to a high fat diet, nutritive or non-nutritive sweeteners on hypothalamic–pituitary–adrenal (HPA) and –gonadal (HPG) axes of male Sprague-Dawley rats. *Eur. J. Nutr.* 63, 2209–2220. <https://doi.org/10.1007/s00394-024-03427-6>.
- Zhao, Z., Xu, B., Anthony, S., Subramanian, S., Granger, B., Von-Walter, C., Mizrahi, E., Kidd, M., Srigiriraju, A., McKie, I., Li, Z., Bolton, M.M., Berto, S., Stern, S.A., 2025. Direct interoceptive input to the insular cortex shapes learned feeding behavior. *bioRxiv* [Preprint]. doi:10.1101/2025.05.13.653896.
- Zheng, Y.-N., Zheng, Y.-L., Wang, X.-Q., Chen, P.-J., 2024. Role of exercise on inflammation cytokines of neuropathic pain in animal models. *Mol. Neurobiol.* 61, 10288–10301. <https://doi.org/10.1007/s12035-024-04214-4>.
- Zhu, X.A., Starosta, S., Ferrer, M., Hou, J., Chevy, Q., Lucantonio, F., Muñoz-Castañeda, R., Zhang, F., Zang, K., Zhao, X., Flocchi, F.R., Bergstrom, M., Siebels, A. A., Upin, T., Wulf, M., Evans, S., Kravitz, A.V., Osten, P., Janowitz, T., Pignatelli, M., Kepecs, A., 2025. A neuroimmune circuit mediates cancer cachexia-associated anapathy. *Science* 388, eadm8857. <https://doi.org/10.1126/science.adm8857>.
- Zielinski, M.R., Gibbons, A.J., 2022. Neuroinflammation, sleep, and circadian rhythms. *Front. Cell. Infect. Microbiol.* 12, 853096. <https://doi.org/10.3389/fcimb.2022.853096>.
- Zonca, V., Marizzoni, M., Saleri, S., Mazzelli, M., Petrillo, G., Di Benedetto, M.G., De Cillis, F., Riva, M.A., Cattaneo, A., 2025. Exposure to early-life stress uncovers shared biological signatures underlying vulnerability in the habenula and insular cortex of male and female adult rats. *Neurobiol. Stress.* 39, 100761. <https://doi.org/10.1016/j.ynstr.2025.100761>.