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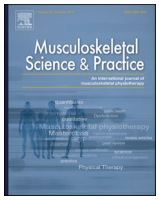

Neuroimmune interactions in musculoskeletal conditions. An introduction for clinicians

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ABSTRACT

Background: The immune system protects against invading pathogens and helps maintain homeostasis. Other pivotal roles include the regulation of tissue health through interactions with the nervous system. Understanding how these neuroimmune interactions may go awry in musculoskeletal conditions and how they can be targeted therapeutically may optimise patient care.
Methods: We conducted a clinically focused narrative review of the role of the immune and nervous systems in musculoskeletal health and conditions such as neck pain, back pain and osteoarthritis and how psychosocial and behavioural factors impact these conditions via interacting with neuroimmune functioning.
Results: The interplay between the immune and nervous system is involved in both the physiology and pathology of musculoskeletal tissues, including bone, joint, nerve, muscle and tendon. We describe this at the local tissue, whole nervous system, and systemic (blood) level and how psychosocial and behavioural factors impact immune activity and influence outcomes. We also highlight recent advances in medical imaging and multi-omics that shed new light on the interplay between the immune and nervous systems in musculoskeletal conditions. Advances in understanding these relationships provide promising new treatment avenues for musculoskeletal conditions and important insights into how psychosocial- and behavioural-based therapies such as exercise and cognitive behavioural therapy work and can be optimised to improve outcomes.
Conclusions: This review provides clinicians with a foundation in the neuroimmunology of musculoskeletal conditions. It also explores how the immune and nervous systems, and their interplay can be modulated to improve prevention and management strategies.

1. Introduction to immunology for musculoskeletal clinicians

Musculoskeletal conditions, such as back pain, neck pain and osteoarthritis, collectively make up the largest burden of all diseases (Cieza, Causey et al., 2021). Although breakthroughs in immunotherapies have revolutionised care for various diseases (e.g., cancer), gaps in understanding of the role of the immune system in musculoskeletal conditions have limited progress and may partly explain why outcomes are worsening (Bennett, Reeves et al., 2018). The immune system functions in close association with the nervous system in musculoskeletal health and disease. The crosstalk and often reciprocal interplay between immune cells, neurons and musculoskeletal tissues is

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extraordinarily complex and only beginning to be unravelled (Chapman, Tuckett et al., 2008). This complexity may pose a substantial challenge for clinicians who had limited training in neuroimmune biology required to adequately comprehend these intricate systems and their implications for clinical practice (Reezigt, Beetsma et al., 2022). Given the clinical nature and broad exploration of interactions across different systems required to present insights and hypotheses relevant to clinicians, a narrative review with the following search terms was conducted in Medline (via PubMed): musculoskeletal pain, immune, neuroimmune and inflammation. This review aims to provide a clinically relevant overview - comprehensible to musculoskeletal clinicians - of the interactions between the immune and nervous systems in musculoskeletal conditions.

2. Immunology fundamentals: organisation, cells and molecules

The immune system is a complex network of cells, tissues and organs that work together to protect the body against potential and actual harm. It consists of two main parts: the innate and adaptive immune systems (Nicholson, 2016). The innate immune system – from the Latin word *innatus*, meaning present from birth – is the host's first line of defence. It responds rapidly and in a generalised way to many pathogens and tissue damage that activate it (Parham, 2021). This response is mediated by pattern recognition receptors (PRR) that can recognise features of pathogens and/or damaged cells. Through PRRs, innate immune cells recognise structures called pathogen-associated molecular patterns and/or danger-associated molecular patterns, triggering innate immunity (Parham, 2021). The adaptive immune system – from the Latin verb *adaptare*, meaning to adjust – is a coordinated and slower response that builds upon the early rapid response of the innate immune system. The adaptive immune response is characterised by its specificity in targeting invading pathogens and mutated self (Spoel and Dong, 2012). This antigen specificity of the adaptive immune response contrasts that of the innate immune response. Where the innate immune system detects simple repeated patterns, the adaptive response refines and enhances its targeting of specific pieces of a pathogen and the transfer of this specificity to the development of immunological memory, enabling specific immune cells (lymphocytes) to react faster and more effectively to a previously encountered antigen upon a future re-exposure (Parham, 2021).

The immune system employs and coordinates various cells and molecules to mediate its functions. Among these, cytokines and the complement system play essential roles in regulating immune responses (Parham, 2021). Cytokines are signalling molecules secreted by diverse cell types, including those of both the innate and adaptive immune systems. These molecules facilitate communication between immune cells and help regulate immunity. Cytokines are classified into several groups, including interleukins (IL), tumour necrosis factors (TNF), chemokines (chemotactic cytokines), interferons (IFN) and growth factors (Vivier and Malissen, 2005). They can act on the cells that produce them (i.e., autocrine), on nearby cells (i.e., paracrine) or on distant cells (i.e., endocrine) or systemically once secreted into bloodstream (Parham, 2021). Their effects may be pro-inflammatory, anti-inflammatory, or context-dependent (pleiotropy) depending on their microenvironment (Saxton, Glassman et al., 2023).

The complement system is comprised of over 50 plasma proteins that work together to promote inflammation and facilitate the clearance of pathogens and damaged cells (Parham, 2021). Complement proteins are present in bodily fluids and tissues (e.g., blood, skin, bone) in an inactive form but become activated in response to danger signals, such as pathogen-associated molecular patterns (PAMPS, which are molecular structures commonly found on pathogens but not on human cells) or immune complexes (which are antigen and antibodies that bound together) (Sarma and Ward, 2011). A well-known biomarker that activates the complement system (specifically the 'classical pathway') is C-reactive protein (CRP) (Pearson, Mensah et al., 2003). CRP is an acute-phase reactant protein released by the liver in response to inflammatory cytokines, predominately IL-6, and decreases rapidly as inflammation subsides.

Other important inflammatory mediators include neuropeptides, reactive oxygen species, nucleotides, prostaglandins and neurotrophins (Mittal, Siddiqui et al., 2014; Xanthos and Sandkühler, 2014; Khan and Smith, 2015). Table 1 provides an overview of different immune cells and their main actions in inflammation. Table 2 lists cytokines and their role in inflammation in musculoskeletal conditions.

The immune system can be triggered by different stimuli associated with musculoskeletal conditions, including tissue damage, infection and autoimmunity, as can occur with conditions such as complex regional pain syndrome and fibromyalgia (Goebel and Blaes, 2013, Goebel, Krock et al., 2021). Following tissue damage, an inflammatory response typically occurs to heal and repair damaged tissues (Punchard, Whelan et al., 2004). This response typically manifests as the five cardinal signs of inflammation, namely pain, heat, redness, swelling and loss of function. Microorganisms (viral, bacterial, fungal and parasitic pathogens) also trigger immune responses that can lead to musculoskeletal conditions, such as septic arthritis and osteomyelitis (Jaramillo, 2011). During infection, signs of inflammation are typically pronounced and accompanied by a marked increase in circulating CRP (i.e., up to a 1000-fold increase at the site of infection) (Sproston and Ashworth, 2018). Autoimmunity can also occur when the immune system mistakenly attacks the host's own healthy cells, tissues and organs (Costenbader, Gay et al., 2012), causing unprovoked inflammation and damage. This immune dysregulation can result in numerous musculoskeletal conditions, such as rheumatoid arthritis and ankylosing spondylitis (Szekanecz, McInnes et al., 2021).

Chronic low-grade inflammation has received increasing attention for its role in musculoskeletal conditions over the last decade (Furman, Campisi et al., 2019). Chronic low-grade inflammation is characterised by a mild and persistent inflammatory state caused by elevation in systemic levels of inflammatory biomarkers (e.g., TNF, IL-6 and CRP) that often presents in the absence of the cardinal signs of inflammation (Furman, Campisi et al., 2019). This state can impair other physiological processes through immune system dysregulation and impacts broader systems like the nervous system, highlighting the importance of neuroimmune interactions in musculoskeletal conditions (Klyne, Barbe et al., 2021). Although chronic low-grade inflammation can be difficult to detect with conventional diagnostic methods, results from blood tests may provide clues, e.g., CRP levels between 3 and 10 mg/L (Pearson, Mensah et al., 2003). Although the cause is not entirely clear, various and interrelating biological (e.g., genetics (Farrell, Sterling et al., 2023)), psychosocial and behavioural factors likely contribute. The consequences of chronic low-grade inflammation are broad and can contribute to the development and persistence of numerous musculoskeletal conditions (e.g., back pain and knee osteoarthrosis (Williams, Kamper et al., 2018; Furman, Campisi et al., 2019)) and symptoms (e.g., fatigue (Lacourt, Vichaya et al., 2018) and poor cognitive performance (Dyer, McNulty et al., 2024)).

3. Neuroimmune interactions in musculoskeletal pain

It is becoming increasingly clear that the nervous and immune systems act in coordinated ways, influencing each other (Costa-Pinto and Palermo-Neto, 2010; Dantzer, 2018). The nervous system houses various non-neuronal cells (glial cells), such as microglia and astrocytes (Purves, Augustine et al., 2004). The roles of glial cells include maintaining local homeostasis and modulating synaptic function (Purves, Augustine et al., 2004). Immune cells, glial cells and neurons form an intimate and integrated network in which immune responses modulate

Table 1
Selected immune cells and their key actions in inflammation.

Immune cell	Key actions in inflammation	Examples of involvement in pro-inflammatory processes in musculoskeletal conditions	Examples of involvement in anti-inflammatory processes in musculoskeletal conditions
Leukocytes	General term for white blood cells involved in immune response; includes lymphocytes, monocytes, and granulocytes	Activated leukocytes (including neutrophils and monocytes) infiltrate inflamed tissues, releasing cytokines and enzymes that contribute to inflammation and joint damage in RA (Yap, Tee et al., 2018)	Regulatory T-cells (a subset of leukocytes) secrete anti-inflammatory cytokines and inhibit excessive immune responses in musculoskeletal conditions (Yap, Tee et al., 2018)
Granulocytes	Subtype of leukocytes including neutrophils, eosinophils, and basophils; involved in phagocytosis, degranulation, and release of inflammatory mediators	Granulocytes, such as neutrophils, release ROS and proteases that exacerbate inflammation and tissue damage (Gallo, Raska et al., 2017)	Neutrophils can switch to an anti-inflammatory role by clearing apoptotic cells and secreting anti-inflammatory cytokines to resolve inflammation in back pain (Ramos and Oehler, 2024)
Eosinophils	Combat parasitic infections and participate in allergic reactions by releasing cytotoxic granules and cytokines	Eosinophils release pro-inflammatory cytokines like IL-5 and granule proteins that contribute to inflammation and tissue damage in eosinophilic arthritis (Tay, 1999)	Eosinophils can release anti-inflammatory cytokines such as IL-4 and IL-10, which help in tissue repair and reducing inflammation in myositis
Basophils	Involved during allergic reactions; participate in immune responses to parasites	Basophils release histamine and other pro-inflammatory mediators	Basophils release IL-4, which can promote the differentiation of anti-inflammatory macrophages
Mast-cells	Contribute to vasodilation, increased vascular permeability, and recruitment of other immune cells	Mast-cells release histamine, TNF, and proteases that contribute to inflammation and tissue degradation in osteoarthritis (Wang, Lepus et al., 2019)	Mast-cells release IL-10 and other mediators that suppress inflammation and promote healing
Neutrophils	Act as first responders to infection; engage in phagocytosis of pathogens, release antimicrobial peptides, and form NETs	Neutrophils release ROS, proteases, and pro-inflammatory cytokines (e.g., IL-1β, TNF) that exacerbate inflammation and tissue damage in osteoarthritis (Herrero-Cervera, Soehnlein et al., 2022)	Neutrophils can transition to a pro-resolving phenotype by secreting lipid mediators like resolvins and protectins, aiding in the resolution of acute back pain (Parisien, Lima et al., 2022)
Monocytes	Circulate in the blood and migrate to tissues where they differentiate into macrophages or dendritic cells; involved in phagocytosis and cytokine production	Monocytes differentiate into pro-inflammatory macrophages that secrete cytokines like TNF and IL-1β, contributing to inflammation in RA	Monocytes can differentiate into anti-inflammatory macrophages that produce IL-10 and TGF-β, promoting resolution of inflammation in muscle repair
Macrophages	Phagocytosis of pathogens and debris, secretion of pro-inflammatory cytokines (e.g., TNF, IL-1β), antigen presentation to T-cells, and resolution of inflammation by secreting anti-inflammatory cytokines	Pro-inflammatory differentiated macrophages produce pro-inflammatory cytokines (e.g., TNF, IL-1β, IL-6) that may sustain chronic inflammation in people with back pain (Li, Liu et al., 2016)	Anti-inflammatory differentiated macrophages produce anti-inflammatory cytokines like IL-10 and TGF-β, aiding in tissue regeneration and reducing inflammation
Dendritic cells	Act as antigen-presenting cells; capture antigens and present them to T-cells to initiate adaptive immune response	Pro-inflammatory dendritic cells activate T-cells and produce cytokines (e.g., IL-12, IL-23) that contribute to inflammation in axial spondyloarthritis (Slobodin, Rosner et al., 2019)	Tolerogenic dendritic cells induce regulatory T-cells and produce anti-inflammatory cytokines, helping in maintaining immune tolerance
Lymphocytes	Include B-cells, T-cells, and natural killer cells; essential for adaptive immune response	Pro-inflammatory T-cells (e.g., Th1 and Th17 cells) produce cytokines (e.g., IFN-γ, IL-17) that drive inflammation	Regulatory T-cells secrete anti-inflammatory cytokines such as IL-10 and TGF-β, reducing inflammation and promoting tissue repair
Natural killer cells	Recognise and destroy infected or cancerous cells by releasing cytotoxic granules and cytokines; also involved in shaping adaptive immune responses	NK-cells produce pro-inflammatory cytokines like IFN-γ that can exacerbate inflammation and contribute to tissue damage in autoimmune conditions like RA.	NK-cells can produce anti-inflammatory cytokines like IL-10 and can kill pro-inflammatory cells, thus reducing inflammation in autoimmune diseases like RA
B-cells	Produce antibodies that neutralise pathogens; present antigens to T-cells; can differentiate into plasma cells that secrete large volumes of antibodies	B-cells produce auto-antibodies and pro-inflammatory cytokines (e.g., IL-6, TNF) that contribute to the autoimmune response	Regulatory B-cells produce IL-10, which helps in controlling inflammation and promoting immune tolerance
T-cells	Regulate and coordinate immune responses; cytotoxic T-cells kill infected cells, while helper T-cells activate other immune cells	Pro-inflammatory T-cells (e.g., Th1, Th17) produce cytokines (e.g., IFN-γ, IL-17) that sustain chronic inflammation and joint damage	T-helper 2 cells counterbalance the pro-inflammatory effects of Th1 cells by inhibiting IFN-γ production (a key cytokine produced by Th1 cells). This shift from a Th1-dominant response to a Th2-dominant response can reduce inflammation in certain contexts

ROS: reactive oxygen species; IL: interleukin; TNF: tumor necrosis factor; IFN: interferon-α; TGF: transforming growth factor; RA: rheumatoid arthritis; Th-cells: T helper cells; Th1: T helper cell type 1; Th17: T helper cell type 17; NK-cells: natural killer cells.

the excitability of the nervous system. In a manner equivalent to neurons, immune cells and glial cells show dynamic and activity-dependent plasticity (switching between pro and anti-inflammatory functioning). Nerve cells also directly modulate immune function. For example, neurogenic inflammation is triggered when C-fibres, are activated and release neuropeptides such as substance P, calcitonin gene-related peptide (CGRP) and prostanoids into innervated tissues (Fig. 1, panel A). Rapid plasma extravasation and edema follow, and these processes contribute to and sometimes maintain peripheral neuronal sensitisation (Matsuda, Huh et al., 2019). Similarly, when afferent nociceptor terminals are activated, they release neuropeptides in the spinal cord that trigger glial cells to, in turn, release inflammatory mediators within the central nervous system. This process, called neurogenic neuroinflammation, affects the excitability of spinal cord neurons (including local interneurons and spinothalamic tract neurons, which is considered an essential component of central sensitisation (Fig. 1, panel B) (Xanthos and Sandkühler, 2014). This form of inflammation is one of the mechanisms leading to nociplastic pain, which is present in conditions such as migraine and complex regional pain syndrome (Edvinsson, Haanes et al., 2019). Neurogenic neuroinflammation has been demonstrated in the spinal cord (Albrecht, Ahmed et al., 2018) brain (Albrecht, Kim et al., 2021) in people with lumbar radiculopathy and low back pain).

Direct interactions between the nervous and immune systems allow for efficient protective mechanisms against danger during appropriate healing times. However, inappropriate and prolonged responses from either system could lead to significant and widespread consequences. Persistent inflammation and neuronal sensitisation (peripherally and centrally) can occur and manifest as excessive and/or persistent pain and/or dysfunction that spreads beyond the originally affected area, sometimes affecting the entire body (Chapman, Tuckett et al., 2008). The following section will explore the immune system's role in various musculoskeletal conditions.

4. Examples of immune system involvement in musculoskeletal conditions

4.1. Role in the clinical presentation

Painful radiculopathy is often accompanied by symptoms that are not limited to the anatomical region innervated by the affected spinal nerve (e.g., dermatome) (Marco, Evans et al., 2023). Widespread symptoms can be explained by associated neuroimmune reactivity at the dorsal root ganglion (DRG), spinal cord and/or brain. Neuroimmune reactivity can be visualised *in vivo* using positron emission tomography (PET). In people with painful cervical and lumbar radiculopathy, this method has shown neuroimmune responses within the DRG (Albrecht, Ahmed et al., 2018; Alshelh, Brusaferri et al., 2022; Lutke Schipholt, Koop et al., 2025) and the spinal cord (Albrecht, Ahmed et al., 2018, Alshelh, Brusaferri et al., 2022) and brain. Disturbance of the homeostasis at the spinal nerve and/or nerve root can stimulate the recruitment of immune cells to the site of injury and DRG (Schmid, Coppieters et al., 2013). These immune cells release inflammatory mediators that lower the firing threshold and induce ectopic activity of mechanosensitive and nociceptive neurons. The DRG contains the cell bodies of primary sensory neurons from different peripheral nerves that lie adjacent to each other (Haberberger, Barry et al., 2019). Various other cell types, such as glial cells, form a layer around the affected/local neuronal cell bodies and further contribute to neuroimmune reactivity. At the DRG, neuroimmune responses of one or more nerve cells can induce responses in other previously unaffected adjacent nerve cells as neuroimmune reactivity spreads and affects nearby neurons and glial cells within the DRG. This immune signalling help explain, at least in part, the presence of widespread symptoms following localised peripheral nerve pathology. Another factor to consider is that sensory fibres from multiple levels can converge at a single spinal segment, as afferent fibres often ascend or descend several segments after entering the spinal cord before synapsing in the dorsal horn. Consequently, paracrine immune signalling at a specific spinal cord level may reduce the firing threshold of sensory fibres originating from multiple segments (Schmid, Nee et al., 2013). Finally, recent PET studies showed that glial reactivity in sensory-discriminative pain structures, such as the thalamus and

Table 2
Selected cytokines and their key actions in inflammation.

	Cytokine	Main cellular source	Key actions in inflammation
Pro-inflammatory	IL-1α/IL-1β	Macrophages, B-cells, dendritic cells	Stimulates various immune cells and pro-inflammatory cytokine synthesis, regulates growth factor activity, activates microglia, induces fever (pyrogenic) and acute phase response, haematopoiesis
	IL-2	T-cells, NK-cells	Stimulates proliferation of B-cells and activated T-cells, NK functions
	IL-6	Macrophages, Th-cells, fibroblasts	Induces acute phase response, stimulates growth and differentiation of T and B-cells, secretes antibodies, regulates pro-inflammatory factors (i.e., anti-inflammatory), thrombopoiesis
	IL-8	Macrophages	Chemoattractant (attracts) for neutrophils, basophils and T-cells
	IL-12	Macrophages, B-cells	Activates NK-cells, stimulates IFN-γ synthesis
	IL-18	Macrophages, dendritic cells	Stimulates maturation of T and NK-cells, stimulates IFN-γ synthesis
	TNF	Macrophages, Th-cells, NK-cells	Stimulates various immune cells and pro-inflammatory cytokine synthesis, activates microglia and phagocytic cells, tissue destruction/cell death, endotoxic shock
	IFN-α	T-cells, macrophages, NK-cells	Anti-viral effects, activates macrophages and NK-cells, induces class I MHC (MHC-I) expression on various cells
	IFN-γ	T-cells, Th-cells, macrophages, NK-cells	Anti-viral, activates microglia, macrophages and NK-cells, increases neutrophil and monocyte function, induces class I and II MHC (MHC-I/–II) expression on various cells
	CCL2/CCL3	Macrophages	Chemoattractant for various immune cells
Anti-inflammatory	IL-4	T-cells, Th-cells	Stimulates proliferation of B and cytotoxic T-cells, eosinophil and mast cell growth, enhances MHC-II expression, stimulates antibody (IgG, IgE) synthesis, inhibits Th1 cell synthesis
	IL-10	T-cells, B-cells, Th-cells, macrophages, monocytes	Inhibits pro-inflammatory cytokine synthesis (from macrophages and Th-cells), NK-cells, and mononuclear cell function, promotes B cell proliferation and antibody production
	IL-13	Th-cells	IL-4-like activities. As it affects B-lymphocytes and monocytes it inhibits the synthesis of various pro-inflammatory cytokines and substances
	TGF-β	T-cells, B-cells, monocytes	Inhibits T and B cell proliferation, inhibits haematopoiesis, inhibits pro-inflammatory cytokine synthesis, promotes wound healing

Cytokines are grouped based on whether they favour pro-inflammatory or anti-inflammatory activities, but most have capacity for both. IL: interleukin; TNF: tumor necrosis factor; IFN: interferon-α; CCL2 and CCL3: chemokine (C-C motif) ligand 2 and ligand 3; TGF: transforming growth factor; NK-cells: natural killer cells; Th-cells: T helper cells; Th1: T helper cell type 1; MHC: major histocompatibility complex.

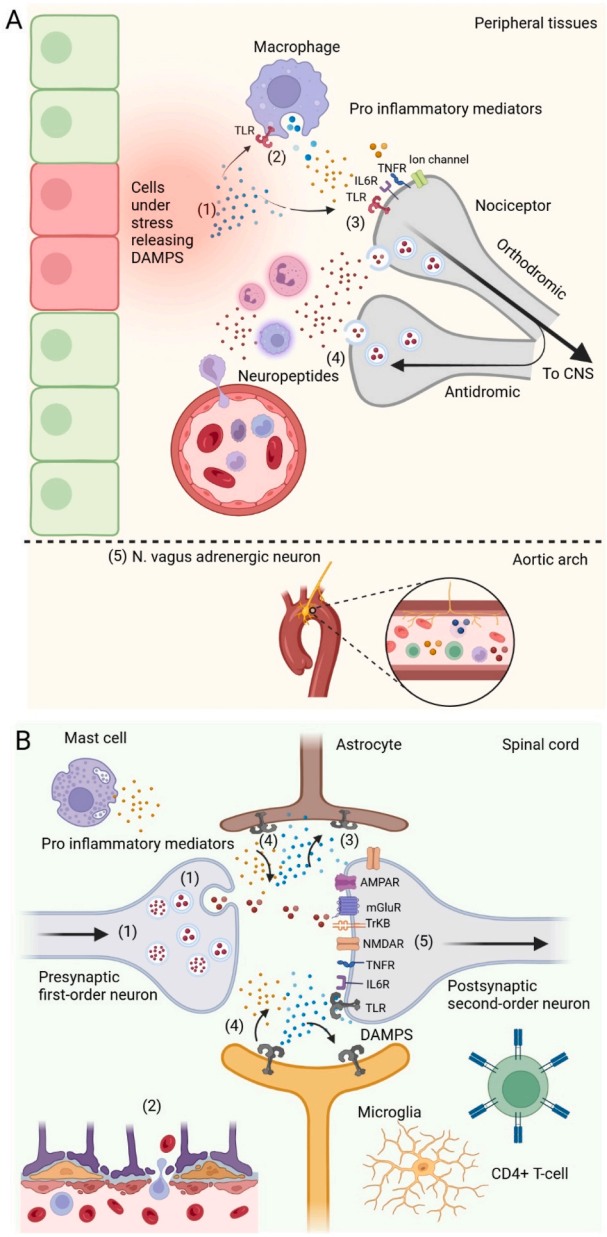

Fig. 1. Neuroimmune interactions within peripheral tissues and spinal cord. **Panel A:** Local neuroimmune interaction within peripheral tissues: (1) Cells such as myocytes, tenocytes and chondrocytes under stress (e.g., mechanical, chemical, thermal) release DAMPS (danger-associated molecular patterns). (2) These DAMPS can bind to toll like receptors (TLR) on immune cells such as macrophages, triggering the release of pro-inflammatory mediators. (3) DAMPS can also bind directly to nociceptors, which leads to the generation of an orthodromic action potential (i.e., for sensory nerves: from the terminal to the spinal cord). (4) In addition to travelling towards the central nervous system, action potentials also travel towards collateral peripheral nerve terminals in an antidromic manner, resulting in the release of neuropeptides (e.g., substance-P) that cause neurogenic inflammation in a larger area than the triggered nerve ending. Due to the release of chemokines, immune cells from the blood infiltrate the peripheral tissues. (5) Systemic inflammatory mediators can activate afferent neurons of the vagus nerve, which contribute to the resolution of inflammation via releasing pro-resolving mediators (e.g., noradrenaline, netrin, inflammatory reflex). The vagus nerve detects peripheral tissue inflammation indirectly, without directly innervating the e.g., the joint. Instead, it monitors systemic inflammation through sensors and immune signals, relaying this to the central nervous system. Afferent fibres of the vagus nerve track inflammatory signals in the blood at key sites like the aortic arch, liver, and gut, where receptors detect cytokines and immune activity. **Panel B:** Spinal cord neuroimmune interactions: (1) Action potentials generated by first-order neurons result in the release of neurotransmitters and neuropeptides from presynaptic neurons, which under normal circumstances lead to the activation (via action potential) of secondary post-synaptic neurons. However, if this process is uncontrolled and/or persists, it can contribute to neurogenic neuroinflammation in the spinal cord. (2) This neuronal activity can compromise the integrity of the blood-spinal cord barrier, allowing immune cells (such as mast cells and $CD4^+$ T-cells) to infiltrate the central nervous system. (3) Astrocytes play a neuroprotective role by absorbing excess glutamate and potassium, helping to maintain homeostasis. (4) However, in response to danger signals (e.g., excessive neural firing), astrocytes, along with microglia, can also contribute to neurogenic neuroinflammation by releasing inflammatory mediators. Given that a single astrocyte can interact with over 100 synapses, changes in the activation status of astrocytes can have widespread effects on synaptic excitability. (5) Neurogenic neuroinflammation can lead to amplified postsynaptic neuronal signalling along the neuraxis, a phenomenon known as central sensitisation.

Abbreviations: CNS: central nervous system; DAMPS: danger associated molecular pattern, TLR: toll like receptor, IL6R: interleukin 6 receptor, TNFR: tumor necrosis factor receptor, NMDAR: N-methyl-D-aspartate receptor, TrKB: Tropomyosin receptor kinase B, AMPAR: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor. Images created using Biorender.

somatosensory cortex, is associated with clinical presentation (Alshelh, Brusaferri et al., 2022). The PET-captured neuroimmune signals within the brain differed between patients with back-related leg pain versus those with only localised back pain, inferring that each condition is characterised by a glial reactivity-specific pattern (Alshelh, Brusaferri et al., 2022). Moreover, these reactivity 'patterns' might be further distinguishable between patients based on the pain descriptor: nociplastic versus nociceptive versus neuropathic (Shraim, Massé-Alarie et al., 2024). Neuroimmune signalling within the DRG, spinal cord and/or brain might also explain the lack of agreement between involved segmental levels derived from patient-reported body charts versus MRI (Marco, Evans et al., 2023).

4.2. Role in recovery and chronification

Systemic inflammatory responses appear to strongly influence recovery trajectories in people with musculoskeletal pain. For example, people who had developed persistent neck pain had elevated levels of hsCRP, TNF and IL-1β. Moreover, one in three of people with persistent neck pain had hsCRP levels indicative of chronic low-grade systemic inflammation (i.e., ≥3.0 mg/L) (Lutke Schipholt, Scholten-Peeters et al., 2022). Individuals with acute neck pain (i.e., within 2 weeks of onset) who recovered poorly maintained elevated systemic levels of hsCRP over a 6-month period (from onset), whereas levels resolved to baseline levels in individuals who recovered better (Lutke Schipholt et al., 2024a). Similarities have been observed in people with acute back pain, whose recovery was associated with systemic CRP and TNF trajectories over 12 months (Klyne, Barbe et al., 2022). It is important to recognise, however, that systemic inflammatory responses are not necessarily harmful and are, in fact, a normal adaptive response to initiate and facilitate repair following tissue injury. For instance, IL-6 and CRP levels are high early in the process of tissue healing, but resolve quickly after an acute episode of back pain (i.e., within 2 weeks of onset) in those who recover best (Klyne, Barbe et al., 2018). Likewise, transient rises in neutrophil activity have been linked to recovery in back pain patients over 3 months (Parisien, Lima et al., 2022). IL-6 and CRP possess both pro- and anti-inflammatory properties that facilitate the clearance of dead and damaged cells, and the regulation of inflammatory molecules important for repair (Sarma and Ward, 2011). This may partly explain why the use of anti-inflammatory medications in people with acute back pain is associated with an increased risk of developing ongoing, chronic pain (Parisien, Lima et al., 2022). In contrast, other medications with analgesic effects, like acetaminophen and antidepressants, not affecting inflammation, showed no link to chronic back pain development (Parisien, Lima et al., 2022). Further work is needed to establish the prognostic value and clinical utility of measuring various systemic inflammatory biomarkers in different musculoskeletal conditions.

4.3. Role in the affective dimensions of musculoskeletal pain

Glial reactivity in the brain is associated with sensory-discriminative but also affective disturbances in people with persistent back pain

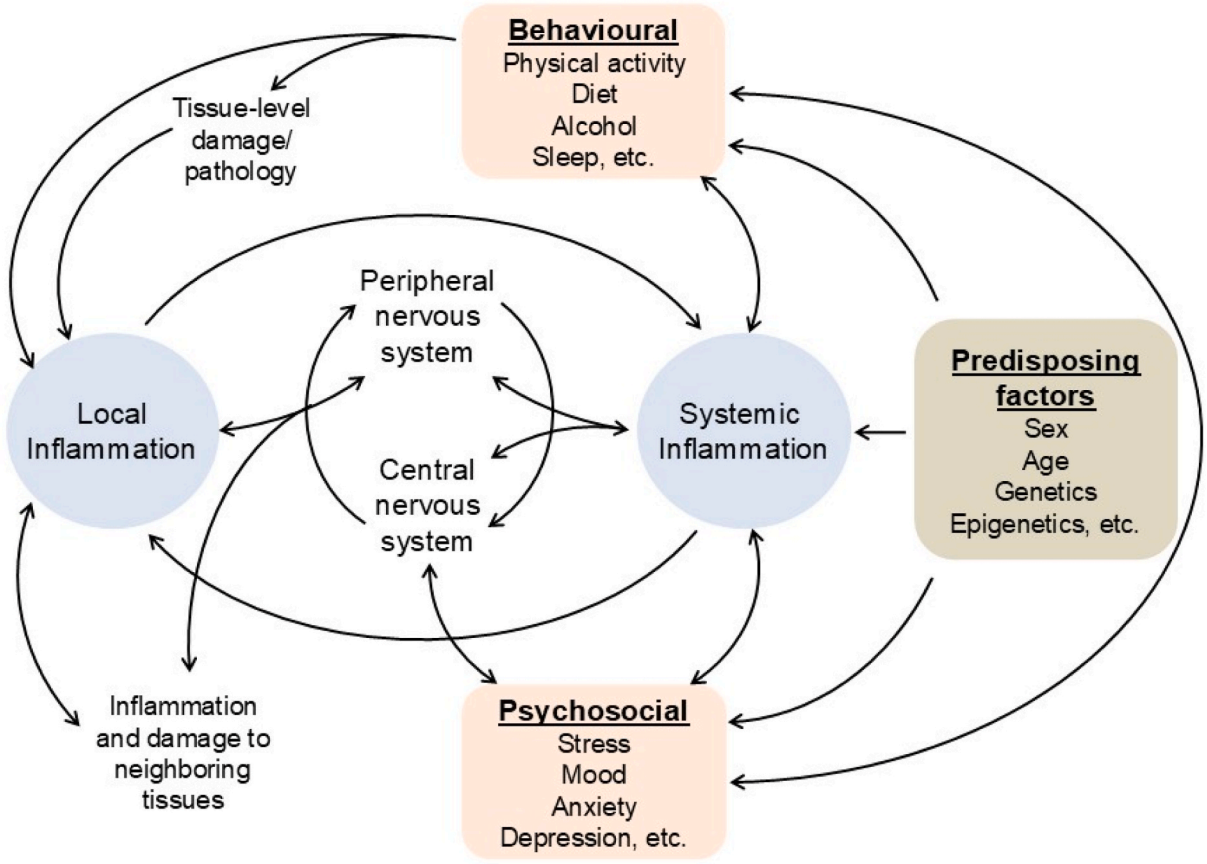

Fig. 2. Conceptual model of the factors that impact tissue health in musculoskeletal conditions. Modified from (Klyne, Barbe et al., 2021) (with permission from D.M. Klyne). Tissues can trigger an inflammatory response both locally and, in some cases, systemically (blue boxes). Various psychosocial factors (e.g., stress, anxiety) and behavioral factors (e.g., physical inactivity) can either increase or decrease systemic inflammation and in some cases local inflammation (orange boxes). Several predisposing factors (e.g., genetics) may influence an individual's susceptibility to these factors (green box). Local and systemic inflammation interact bidirectionally with the peripheral and central nervous systems. Excessive and persistent inflammation can significantly affect various cells, tissues, and organs, increasing the risk of developing numerous musculoskeletal conditions.

(Albrecht, Kim et al., 2021; Alshelh, Brusaferri et al., 2022). There is preclinical and clinical evidence that affective disturbances are related to supraspinal neuroimmune interactions (Fiore and Austin, 2016, Taylor, Mehrabani et al., 2017). Affective disturbances include impaired cognition, appetite and anhedonia (i.e., feeling numb or less interested in things that were once enjoyed) (Price, 2000). Preclinical studies have identified the presence of neuroimmune reactivity in different brain regions critical for regulating affective behaviour, such as the hippocampus, medial prefrontal cortex, striatum/nucleus accumbens, anterior cingulate cortex (ACC), hypothalamus, amygdala and periaqueductal grey (Fiore and Austin, 2016, Taylor, Mehrabani et al., 2017). In people with back pain and depressive symptoms, PET studies show higher neuroimmune reactivity in the anterior medial cingulate cortex and pregenual ACC compared to those without depressive symptoms and pain/depression-free individuals (Albrecht, Kim et al., 2021). Further, neuroimmune signals within the cingulate cortices are positively associated with back depression inventory scores (Albrecht, Kim et al., 2021). These data suggest that supraspinal neuroimmune interactions are linked not only to sensory-discriminative aspects of persistent pain but also to affective disturbances.

5. Bidirectional interactions between neuroimmune activity and psychosocial and behavioural factors

Illness or injury can provoke a number of metabolic and neuroendocrine changes that manifest as a constellation of behaviours known as 'sickness behaviours', such as sadness, anhedonia (i.e., lack of interest, enjoyment or pleasure), fatigue, altered sleep and social withdrawal (Dantzer, O'Connor et al., 2008). These 'sickness behaviours' are primarily triggered by pro-inflammatory cytokines as part of a highly organised strategy to fight infection and trauma by modifying behaviour (Dantzer, O'Connor et al., 2008). Conversely, various psychosocial and behavioural states can influence systemic and local inflammation (Fig. 2). Excessive and persistent inflammation can substantially alter various cells, tissues and organs, increasing the risk of developing various musculoskeletal conditions (Klyne, Barbe et al., 2021).

A key consideration in the association between musculoskeletal health and immunology is the bidirectional link between psychology (e.g., stress and depression) and immune activity (Klyne, Barbe et al., 2017; Klyne, Barbe et al., 2018; Lutke Schipholt, Scholten-Peeters et al., 2022). One can affect the other through shared pathways such as the hypothalamic-pituitary-adrenal axis and sympathetic nervous system (Joëls and Baram, 2009; Xanthos and Sandkühler, 2014). For example, preclinical studies have long shown that peripheral inflammatory events, such as those occurring after tissue injury, induce many of the same psychological symptoms of affective disturbances in the absence of prior stress or other psychological impact (Watkins and Maier, 2005, Dantzer, O'Connor et al., 2008). Similar immune responses to musculoskeletal injury and/or pain might partly account for the presence and/or exacerbation of psychosocial and/or behavioural disturbances in humans (Dantzer, 2018). Regardless of the direction of causality, persistent psychological disturbances and unmoderated inflammation could have a synergistic effect, amplifying the cycle of psychological distress, inflammation and pain.

Behavioural factors such as sleep disturbance are also powerful modulators of systemic inflammation and frequently co-occur with musculoskeletal pain (Meijer, Barbe et al., 2020; Klyne and Hall, 2024). Reduced sleep duration and/or quality can alter circadian rhythms and affect the expression levels of many inflammatory cytokines, amplifying pain via peripheral and central nervous system mechanisms (Möller-Levet, Archer et al., 2013; Irwin, 2019). Repeated or sustained periods of poor sleep could lead to persistently elevated inflammation, driving central nervous system changes that, in turn, contribute to the transition from acute to persistent pain (Cho, Seeman et al., 2015; Besedovsky, Lange et al., 2019). Like stress, these relationships are bidirectional and potentially cyclical — changes in peripheral inflammation, as occurs with tissue damage, can adversely affect sleep via various mechanisms (Krueger, 2008; Irwin, 2019).

Other relevant behavioural factors include physical activity and diet. Aerobic physical activity strongly suppresses pro-inflammatory processes and promotes anti-inflammatory processes (Gleeson, Bishop et al., 2011), whereas inactivity has the opposite effects (Fischer, Berntsen et al., 2007). Persistent physical inactivity leads to a cascade of changes (e.g., accumulation of abdominal adipose tissue, which is a potent source of inflammatory mediators) that further drive inflammation (Fantuzzi, 2005). Regarding diet, many foods and drinks modulate acute and chronic inflammation via various mechanisms, including those linked with increased adiposity and gut permeability (Minihane, Vinoy et al., 2015). Overall, many of these psychosocial and behavioural factors are reciprocally related via shared neuroimmune pathways, meaning that a disturbance to any could profoundly impact others, instigating a vicious cycle resulting in excessive inflammation with potential implications for musculoskeletal health.

6. Immunomodulatory and non-pharmacological therapies for musculoskeletal conditions

The fact that many biological, psychological and behavioural factors are reciprocally related via shared inflammatory mechanisms means that a disturbance to any could have pathological consequences on the other (Klyne, Barbe et al., 2021). On the flip side, this opens the possibility that interventions aimed at improving one aspect (e.g., stress, sleep, physical activity or inflammation) could positively affect the others.

Regular physical activity plays a vital role in modulating immune system activity in musculoskeletal conditions. Exercise, especially aerobic exercise, can enhance immune function by increasing anti-inflammatory mediators (e.g., IL-10, IL-4 and IL-1 receptor antagonist) and decreasing pro-inflammatory mediators (e.g., TNF) (Gleeson, Bishop et al., 2011; Sleijser-Koehorst, Koop et al., 2023). Additionally, exercise mobilises immune cells essential for tissue repair and remodelling and induces hormonal (e.g., oestrogen (Copeland, Consitt et al., 2002; Pang, Chen et al., 2023)) changes that regulate immune responses. One mechanism by which exercise induces long-term anti-inflammatory effects is by reducing body fat (i.e., adipose tissue, especially abdominal fat (Paley and Johnson, 2018)), which is a potent source of cytokines (known as adipokines) that activate a network of inflammatory pathways (Gleeson, Bishop et al., 2011). Although the pain-relieving and function-enhancing effects of exercise are thought to be partly mediated through changes in body weight and systemic inflammation, the latter two are not always dependent on each other (i.e., reduced body weight leading to reduced inflammation) (Runhaar, Beavers et al., 2019).

Another immunoregulatory effect of exercise is its regulation of the body's antioxidant defence mechanism through the modulation of nuclear factor erythroid 2-related factor 2 (Nrf2) (Petrikonis, Bernatoniene et al., 2024). During exercise, mechanical and oxidative stress activate Nrf2, which then translocates to the nucleus and triggers the expression of various antioxidant and cytoprotective genes (Powers, Lategan-Potgieter et al., 2024). Dysregulated oxidative stress responses can exacerbate inflammation and tissue damage in musculoskeletal conditions, and the antinociceptive effects of exercise are, in part, mediated by Nrf2 signalling. Moreover, the protective effects of exercise in preventing neuropathic pain are modulated in part through the activation of Nrf2-antioxidant signaling (Green-Fulgham, Harland et al., 2022; Koop, Sleijser-Koehorst et al., 2023).

Exercise also benefits psychological (e.g., stress) and behavioural (e.g., sleep) states, which in turn positively influence systemic inflammation (Klyne, Hilliard et al., 2024). These relationships are bidirectional and potentially cyclical as reduced inflammation positively influences mental health and sleep (Paolucci, Loukov et al., 2018). In contrast, over-exercising can have opposite (pro-inflammatory) effects (Docherty, Harley et al., 2022). The precise mode, intensity and duration of exercise

to optimally reduce inflammation is likely to differ widely between individuals. Research studies is needed to clarify the dose-response relationships for different exercise programs to optimally target neuro-immune responses when managing musculoskeletal conditions.

The tight relationship between sleep and immune functioning identifies sleep as a novel potential treatment target for managing and even preventing musculoskeletal conditions (Besedovsky, Lange et al., 2019). Poor sleep often co-occurs with musculoskeletal conditions and chronic pain (Herrero Babiloni, De Koninck et al., 2020), and 50 % of people living with insomnia also experience chronic pain (Herrero Babiloni, De Koninck et al., 2020; Klyne, Smith et al., 2024). One promising intervention is cognitive behavioural therapy for insomnia (CBT-I) (Klyne, Smith et al., 2024), which reduced systemic inflammation and improves sleep and pain in people with musculoskeletal conditions (Herrero Babiloni, De Koninck et al., 2020).

Psychological interventions can have profound immunomodulatory effects in people with musculoskeletal conditions (Andrés-Rodríguez, Borràs et al., 2019). For example, cognitive behavioural therapy and mindfulness-based stress reduction interventions aimed at reducing maladaptive stress responses can also substantially enhance immune cell activity and substantially reduce systemic inflammation (Shields, Spahr et al., 2020). Reduced concentrations of circulating cytokines are also associated with stress relief (Diez, Anitua et al., 2022). If the proper management of stress or other psychological conditions can reduce systemic inflammation, then it is plausible that these inflammatory changes will positively benefit musculoskeletal conditions. These interventions may also have an additive effect on lowering systemic inflammation and musculoskeletal symptoms when combined with other treatments, such as exercise and CBT-I. Whether this is true and to what extent this will have important clinical implications for musculoskeletal health is not yet understood.

Besides exercise and psychological interventions, joint and nerve mobilisation are frequently applied techniques by musculoskeletal clinicians for the treatment of musculoskeletal conditions. Preclinical evidence indicates that joint and nerve mobilisation have potent beneficial immunomodulatory effects (Lutke Schipholt, Coppieters et al., 2021). This is especially evident in animals with induced compression neuropathies where reversal of abnormal immune activation is shown in various parts of the nervous system in response to these treatments (Lutke Schipholt, Coppieters et al., 2021). A recent study in people with neck pain however found no short-term differences in systemic (blood) inflammatory markers between people who received spinal manual therapy or a placebo (Lutke Schipholt, Coppieters et al., 2023). An explanation for the discrepancy between the findings from human and animal studies may be that systemic measures may not be a refined enough proxy to investigate local neuro-immune changes at the spinal nerve, DRG or spinal cord. Indeed, there is preliminary evidence that these findings in animals may translate to humans if inflammation is measured locally. A case study using PET-imaging in a patient with cervical radiculopathy showed reductions in neuroimmune reactivity within the neuroforamina (i.e., spinal nerve and DRG) and but not at the spinal cord following 6 weeks of neural tissue management (i.e., neurodynamics and manual therapy) (Lutke Schipholt, 2024b). Interestingly, these neuroimmune changes correlated with decreased pain intensity (Lutke Schipholt, 2024b). However, further research is needed to clarify the impact of joint and nerve mobilisation versus natural course on inflammation in both local and remote (i.e., away from the body site being treated) tissues, as well as on clinical outcomes.

7. Precision medicine enabled by objective measures

Precision medicine advances treatment by moving beyond subjective assessments and embracing objective and individual biological data to tailor treatments (Grace, Tawfik et al., 2021). Precision medicine has been successful in various medical fields, but remains underdeveloped in musculoskeletal pain management (Lu, Terry et al., 2023). Achieving precision pain medicine requires objective measures that account for the complex, multidimensional nature of inflammation and neuroimmune interactions in people with musculoskeletal pain (Mustafa, Bajic et al., 2023).

Current approaches to treating musculoskeletal pain often involve linear, anti-inflammatory strategies. However, inflammation is a highly complex and dynamic process. The immune system interacts intricately with neural circuits through multifaceted signalling pathways, making a single-dimensional approach insufficient (Mustafa, Bajic et al., 2023). Precision medicine in musculoskeletal pain requires treatments that 'fine-tune' the immune system, addressing specific pathways and phases of inflammation rather than suppressing it indiscriminately. Such an approach has the potential to provide more effective, long-lasting relief by addressing the underlying neuroimmune interactions that contribute to chronic pain. Technological advances are now providing tools to enable this shift towards precision medicine for musculoskeletal pain (Yoon, Kogan et al., 2020).

One promising technology is PET-imaging, which allows the quantification of inflammation by measuring the extent of cellular, chemical and molecular changes that occur with inflammation. For example, using the tracer [C^{11}]D-Deprenyl during PET-imaging enables to quantify macrophage activity (the tracer binds on monoamine oxidase B (MOA-B) which is upregulated in activated astrocytes and microglia/macrophages during neuroinflammation). This method revealed elevated macrophage activity in neck muscles, cervical vertebrae and facet joints in people with traumatic neck pain and this activity was associated with pain, disability, and recovery at 6 months (Aarnio, Fredrikson et al., 2022). While PET imaging offers detailed insights, its high cost, complexity and the radio-activity of the current tracers prevent its widespread use in clinical settings.

Another ground-breaking technology is multi-omics (Parisien, Lima et al., 2022; Yao, Ren et al., 2022), which integrates multiple types of biological data to get a more comprehensive understanding of pathology than with a single omics-approach. Analysing genetic (genomics), epigenetics (epigenomics), protein (proteomics) and metabolic (metabolomics) profiles in people with musculoskeletal conditions enables the development of targeted and individualised treatments (Freidin, Lauc et al., 2016; Mobasheri, Kapoor et al., 2021). Multi-omics involves the generation and analysis of big data, which has enormous potential to prevent and improve the management of musculoskeletal conditions (Alyass, Turcotte et al., 2015).

Another technological innovation is hyperspectral imaging (Staikopoulos, Gosnell et al., 2016). This technology can capture detailed data about cellular changes, providing a window into the complex neuroimmune processes that underlie musculoskeletal conditions (Gosnell, Staikopoulos et al., 2021). By analysing the endogenous fluorescent signals (natural light signals) from cells and tissues, hyperspectral imaging can reveal complex physiological processes (Hutchinson, 2020). Moreover, the hyperspectral imaging analysis of biomarkers in the blood reflects both biological and environmental factors influencing musculoskeletal pain (Hutchinson and Terry, 2019). Combining hyperspectral imaging with biomarker analysis offers a deeper understanding of the biological processes contributing to each individual phenotype (Gosnell, Staikopoulos et al., 2021).

Advanced computational and mathematical methods, such as artificial intelligence, can assist in identifying biomarkers and biosignatures (i.e., a combination of individual biomarkers), cluster individuals with similar symptoms and characteristics, and predict how people will respond to specific treatments (Lötsch and Ultsch, 2018; Tack, 2019). The application of hybrid and interpretable artificial intelligence could improve care by making treatments better suited to each patient's unique needs.

8. Conclusions

This review provides a foundation for clinicians to understand the

interplay between the immune and nervous systems in musculoskeletal conditions. Insight into these "neuroimmune" interactions and the role of psychosocial and behavioural factors in shaping them will promote understanding of the connection between body and mind in musculoskeletal health. This is intended to guide personalized therapies to improve the prevention and management of musculoskeletal conditions.

CRediT authorship contribution statement

Ivo J. Lutke Schipholt: Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Michel W. Coppieters:** Writing – review & editing, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Gwendolyne G.M. Scholten-Peeters:** Writing – review & editing, Methodology, Investigation, Formal analysis, Conceptualization. **Mark R. Hutchinson:** Writing – review & editing, Investigation, Formal analysis, Data curation. **David M. Klyne:** Writing – review & editing, Investigation, Formal analysis, Data curation, Conceptualization.

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Declaration of competing interest

None.

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