Open Access

OBM Integrative and Complementary Medicine

LIDSEN Publishing Inc.

Hypothesis

Allostatic Mechanism of Mind-Body Medicine for Neuroinflammation

Poppy L.A. Schoenberg [1,*], Katlyn M. Gonzalez [2]

1. Physical Medicine & Rehabilitation, Vanderbilt University Medical Center, 3401 West End Ave., Suite 380:22, Nashville, TN, USA; E-Mail: poppy.schoenberg@vumc.org
2. Medicine, Health, & Society, Vanderbilt University, 300 Calhoun Hall, Nashville, TN, USA; E-Mail: Katlyn.m.gonzalez@vanderbilt.edu

* **Correspondence:** Poppy Schoenberg; E-Mail: poppy.schoenberg@vumc.org

Academic Editor: Gerhard Litscher

Special Issue: Mind-Body Approaches that are Revolutionizing the Health Field

OBM Integrative and Complementary Medicine
2023, volume 8, issue 1
doi:10.21926/obm.icm.2301005

Received: October 13, 2022
Accepted: January 02, 2023
Published: January 12, 2023

Abstract

Chronic inflammatory diseases are the most significant cause of death in the world and entail severe impairment to quality of life. The World Health Organization (WHO) ranks chronic inflammatory diseases as the greatest threat to human health and wellbeing. Inflammation is epicentral to many clinical conditions and symptoms, and it is anticipated that the health, economic, and mortality burdens associated with chronic inflammation will steadily increase in the United States over the next 30 years. An inflammatory model of disease premises that peripheral injury/trauma/toxins release signaling mediators that activate glial components of peripheral and central cellular circuitry which if prolonged causes toxification of the central nervous system, or neuroinflammation. This inflammatory process is associated with an array of systemic symptomatology affecting somatic, neurocognitive, and affective domains, that can often be misdiagnosed and/or ineffectively treated in the clinic. Centralized neuroinflammation determines a range of conditions and their clinical trajectories, from autoimmune diseases, cancers, cardiovascular diseases, chronic pain, to neurological and psychiatric disorders. It is coming to light that mind-body medicine, defined here as mindfulness- and yoga-based interventions, appear to modulate peripheral cell signaling

involved with inflammatory response. Translational mechanism nor intervention specificity of this early data is currently clearly delineated, posing an exciting and highly beneficial frontier for further empirical exploration in the field of integrative mind-body medicine. Here we initiate an allostasis model of working mechanism that aims to inform methodological design and ensuing empirical perspectives.

Keywords
Allostasis; homeostasis; meditation; mindfulness; mind-body medicine; neuroinflammation; systems biology; yoga

1. Inflammatory Hypothesis of Disease

Chronic inflammatory diseases are the greatest threat to human health and wellbeing, and most significant cause of death in the world according to the World Health Organization (WHO) [1]. Chronic inflammation and associated health, economic, and mortality burdens have been steadily increasing at a global scale, with this trend anticipated to continue over the next ~30 years [1, 2]. The mechanism of inflammatory response can be helpful to ensure homeostasis of the biological system and timely healing. Most infections/traumatic injuries are repaired swiftly, and homeostasis is restored. However, when this mechanism becomes over-exuberant or protracted, the adaptive inflammatory process is replaced by a chronic systemic inflammation that is the cause and exacerbation of biological fragility and many disease states [3]. Autoimmune, bone and joint, all cancer stages, cardiovascular, diabetes, metabolic, neurological, and pulmonary, medical conditions are universally associated with significant chronic inflammation [4]. Even psychiatric conditions that were previously not considered inflammatory disorders, such as mood disorders and psychosis, are now known to have a bidirectional relationship with inflammation, displaying elevated levels of circulating inflammatory cells and mediators [5]. The molecular connection between chronic (low grade) inflammation and “non-communicable” diseases is well established [6]. When one part of the inflammatory chain becomes dysregulated, continued inflammatory response ensues in the absence of acute stimulation causing inflammation of the central nervous system, also defined as neuroinflammation [7]. This peripheral-to-central neuroinflammatory process [8], is multicellular and mediated by neuroglial cells of the central nervous system. Chronic neuroglial and cytokine activation of the central nervous system (neuroinflammation) is present in neurodegeneration, neuronal dysfunction, injury, and disease progression across diverse clinical populations [9, 10].

2. Inflammation and Systemic Disease Sequelae

To simplify, inflammation activates the immune system and proinflammatory cytokine production via ‘Protection-Associated Molecular Patterns’ (PAMPs), such as release of neutrophil/monocytes, interleukins (i.e. IL-1, IL-6), and tumor necrosis factor/TNF by neuroglial macrophages during early innate immune response [11]. In acute stages, termination of pathogenic factors, i.e. infection, tissue/cell damage, toxic compounds, eliminates the harmful stimulus towards resolution and restoration of homeostasis. This process becomes chronic if the inflammatory response is not resolved and/or a new trigger of secondary inflammation ensues such

that a non-immune pathophysiologic process, which mirrors the normal immune response, continues through 'Damage-Associated Molecular Patterns' (DAMPs). Figure 1 (below) demonstrates the differentiated progression of resolving/adaptive versus cyclical non-resolving/maladaptive inflammation at the molecular level [12]. A non-resolving cycle of inflammatory response can initiate from direct primary insult/injury to the central nervous system, although in most instances, reflects a peripheral-to-centralized secondary neuroinflammatory process (brain-to-periphery inflammatory communication is also possible, albeit less researched [13]). This is where 'unmanageable' levels of inflammatory cells and mediators in non-central nervous systems/structures (peripheral inflammation) may progress to toxicity of the entire central nervous system, or centralized neuroinflammation. For example, chronic inflammation increases prolonged cytokine expression within the central nervous system that is recognized by the brain as a molecular signal of "sickness". In turn, this can have knock-on effects to the blood-brain barrier, brain-spinal barrier, blood-cerebrospinal fluid barrier, and/or neuro-axonal structures [14, 15].

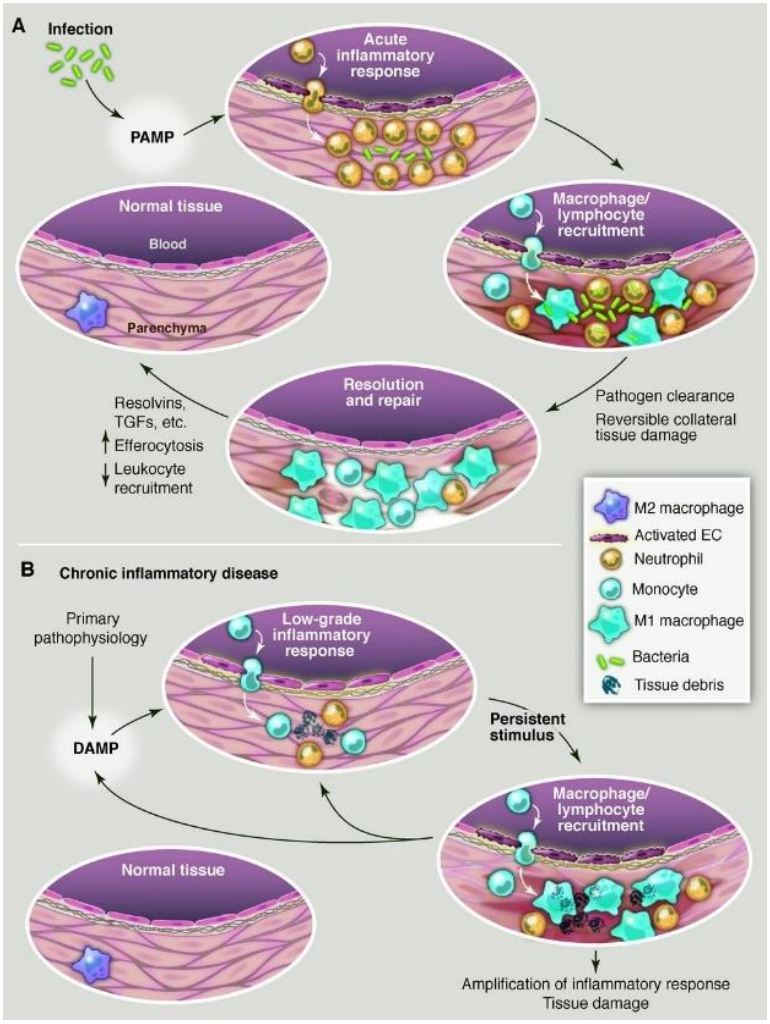

Figure 1 Illustration of adaptive (A) and maladaptive (B) inflammatory process. Reprinted with permission [12].

Other connective pathways also form part of this systemic signalling network. Central nervous system modulation associated with the peripheral-to-centralized process of systemic inflammation has bidirectional dynamics with the neuroimmune, neuroendocrine, and peripheral autonomic and

enteric nervous systems [16]. The hypothalamic-pituitary-adrenal axis is a complex system of neuroendocrine pathways that is primarily involved in the biologic regulation to stressors [17]. Disproportionate stress response through exuberant activation of the hypothalamic-pituitary-adrenal axis is associated with increased inflammation [18]. The central and enteric nervous systems share various structures, neurotransmitters and signalling pathways to form the brain-gut-microbiome axis [19], which primarily modulates the central nervous system via a bottom-up pathway through neuroimmune and neuroendocrine mechanisms and the vagus nerve [20]. Emerging evidence is highlighting the priority of targeting the vagus nerve as one of the main connective pathways between the brain and the periphery through the gastrointestinal tract in the treatment of various inflammatory conditions [21]. Changes in the microbiome can be beneficial for acute inflammatory stages and immunoregulatory function. Albeit, chronic microbiome changes and associated proinflammatory divisions of microbiota also appear to underline many chronic inflammatory diseases [16]. In sum, maladaptation to all or part of these regulatory pathways can contribute to the overall toxicity to the central nervous system, or neuroinflammation.

Patients with neuroinflammation (either from direct insult to centralized systems, or more commonly progression of abundant peripheral chronic inflammation that ultimately toxifies the central nervous system) will present in the clinic with nonspecific symptoms of sickness that are systemic in nature and often manifest in clusters [16, 22]. These include perceptual changes to temperature, sensitivity to pain, fatigue, cognitive dysfunction, altered appetite and mood, that result in diminished activity and mood disorder [23-25]. This can be difficult for the clinician to identify and address since the original medical problem that facilitated the neuroinflammation in the first instance may no longer be attributed to the symptoms and/or may no longer be present/observable. More broadly, depressogenic symptoms and sickness behaviors have been linked to common inflammatory pathways [26], which due to similarities in their clinical presentation, some clinicians might misdiagnose depression/low mood and prescribe anti-depressants that will target only one facet of the clinical issue. Another topical example is the Coronavirus Disease 2019 (COVID-19), originally understood as a highly contagious local respiratory virus. As clinical understanding of this virus unfolds, many cases continue to develop systemic symptomatology affecting almost all organ systems (cardiovascular, endocrine, gastrointestinal, hepatic, renal, and nervous systems). COVID-19 has shown to induce chronic inflammation in patients with and without pre-existing conditions [27]. Those known to have been infected while not showing signs of specific acute infection, in some cases are suffering prolonged systemic disease symptomatology, termed post-acute COVID-19 syndrome [28], akin to centralized inflammation caused by the original infectious pathogen. The prolonged trajectory of COVID-19 related systemic inflammatory symptoms is under continued study, with disease diagnostic definitions, outcomes, and treatment options remaining an area of urgent need since post-acute sequelae could become a significant global health burden [29].

3. Re-thinking Treatment of Neuroinflammation Through the Lens of Mind-body Interventions

Neuroinflammation may represent a form of neuroplasticity that can theoretically be reversed by neuroplastic interventions. For example, accruing evidence suggests significant cross-correlation between the neuroimmune system and neuroplastic mechanisms in responsiveness to chronic pain [30, 31], neuronal adaptation in mood disorders [32], neuroimmune plasticity factors involved in

central nervous system injury such as traumatic brain injury, spinal cord injury, and/or stroke [14, 33], and immune macroenvironment plasticity in cancer models [34], to name a few. Neuroinflammation manifested by prolonged cytokine signalling amplified through the central nervous system cytokine network, causes detrimental effects to neurotransmitter activity, synaptic plasticity, neuroendocrine function, and resultant behaviors/symptoms [31]. Moreover, central nervous system-specific neuroimmune cells that serve as tissue-resident macrophage are unlike peripheral macrophages. They have unique immunological properties through the ability to shift function based on a process of polarization [35]. In their non-pathological – or homeostatic – state they regulate neuronal activity, synaptic plasticity, and maintain brain homeostasis. However, in their pathological -or activated – state (the DAMP-PAMP process outlined above), they serve critical neuro-immunological functions by recruiting large scale cytokine and peripheral immune cell production towards pathogen destruction, debris clearance, and tissue repair [36]. This highly complex dynamic process is bidirectional and involves many neuroimmune cells and mediators that serve different roles depending on cues in the surrounding microenvironment. The "pro-inflammatory" phenotype is the classic first responder to toxin/injury/insult by releasing pro-inflammatory cytokines and neurotoxic molecules that promote inflammation and cytotoxic reactions. The "anti-inflammatory" phenotype once activated secretes cytokines and nutrient factors that promote the function of repair, regeneration, ultimately restoring homeostasis [35, 37].

Many contemporary treatments for "systems diseases", i.e. those underlined by chronic neuroinflammation (albeit inflammatory processes, peripherally and/or centrally, can be traced to practically all medical conditions), offer a 'piece-meal' interventional approach by treating singular symptoms, rather than whole systems or the central pathway that connects systems. For the patient, this can entail complicated treatment regimens comprising a gamut of different medications targeting specific symptoms that increase risk for further toxicity to the central nervous system, contraindications, and anti-neuroplastic effects. Such a treatment strategy ultimately serves to decrease treatment optimization, adherence, and potentially exacerbate further centralized inflammation, causing a potential symptom <--> treatment 'catch-22' scenario. Mind-body interventions, such as yoga and meditation, present compelling integrated therapeutic alternatives to this piecemeal approach. While mind-body medicine is often used as an adjunctive approach, structured mindfulness programs have been designed as stand-alone interventions, and show comparable efficacy as usual treatments when well-adapted for specific conditions [38]. For example, a combined nine randomized clinical trials totaling 1258 depression patients compared Mindfulness-Based Cognitive Therapy (developed in 2002 for depressive relapse prevention), with placebo, treatment-as-usual (psychotherapy), and antidepressant medications. Compared with antidepressants, MBCT showed to provide protection on-par with upto 3-years of continued medication use [39], and no MBCT-related side effects were reported in these studies.

Whilst mechanistic research for the clinical success of such interventions remains an early and exciting frontier, extant understanding of possible mechanism/s by which mind-body interventions work suggests the potential to target various systems, sub-systems, and clinical outcomes. Some regard this present evidence base indicative of non-specificity in the working mechanism/s of mind-body medicine. However, it may be that mind-body interventions, such as meditation and yoga, target central systems and/or connective biological pathways, explaining the wide scope in clinical action. Further investigation is warranted, although this premise seems a promising unifying theoretical perspective to understanding the seeming lack of clinical specificity. Another perspective

is that mind-body interventions have multi-levelled clinical action mechanisms. Since inflammation is central to many disease states and processes, this would have explanatory value for the wide-reaching clinical impact being reported. Examining the multi-levelled mechanistic interplays connected to the wide clinical scope may also require sophisticated multi-dimensional and encompassing approaches to identification/measurement in terms of mechanistic research and understanding complex therapeutic processes of mind-body interventions that appear to affect multiple systems simultaneously.

Mindfulness interventions appear to enact neuroplastic effects. For example, a seminal longitudinal study reported that mindfulness-based intervention (versus waitlist control) was associated with increases in regional brain gray matter density [40], albeit to date these findings have not been replicated. A review of 20 randomized controlled trials involving 1602 mixed patients, demonstrated promising effects of mindfulness interventions upon biomarkers of immune system activity. Findings included (i) reduction in the cellular transcription factor NF-κB, (ii) reduced circulating levels of blood-based C-reactive protein (CRP) a marker of inflammation, (iii) enhanced T lymphocyte cell counts (CD4+T), and (iv) increased telomerase activity [41]. Further research has demonstrated that mindfulness meditation (compared to a relaxation condition) increases default mode network resting state functional brain activity with regions involved in top-down executive modulation (i.e. dorsolateral prefrontal cortex) that also correlated with decreased circulating cytokinetic IL-6 at 4-month follow-up in a high stress sample [42]. These cytokine effects extend to oncologic populations, as a study in 322 recovering breast cancer survivors showed increased IL-6 and TNF-α levels at 4-month follow up in those exposed to mindfulness intervention compared with usual care [43]. While IL-6 can exert both pro- and anti-inflammatory properties, TNF-α is a pro-inflammatory cytokine, adding complexity to the result interpretation. The authors surmised because cytokine levels didn't increase during the mindfulness intervention trial, that the increased IL-6 and TNF-α levels may have reflected a mindfulness-related immune restoration process post-exposure [43]. Since the study did not include any other measures that would inform clinical status, it is difficult to interpret these findings. Other studies provide support that mindfulness interventions significantly modulate cytokine marker levels in breast and prostate cancers [44-47]. Other studies provide preliminary support for anti-inflammatory effects of mindfulness in healthy populations, such as the down-regulation of pro-inflammatory NF-κB transcription in isolated older adults. Although the n = 16 Mindfulness-Based Stress Reduction/MBSR (versus n = 19 wait-list control) sample was on the low side for RNA bioinformatics, and the examined sample had significantly up-regulated expression of pro-inflammatory genes in circulating leukocytes at baseline prior to mindfulness exposure [48]. Interestingly, perceptions of loneliness, assessed to be a risk factor for morbidity and mortality in an aged population by the authors and their primary aim of the study, [48] did improve and were associated with gene expression changes, despite peripheral markers of inflammatory proteins (CRP, IL-6) showing no change. These complex findings further support our centralized mechanistic proposal introduced above. Larger sample randomized controlled trials in healthy populations suffering "high-stress" found no differences in peripheral markers such as IL-6 and CRP [49, 50], with the contrary in a healthy sample during a brief 3-day mindfulness retreat (versus vacation control) reporting reduced cytokines IL-6* and IL-8 and increased anti-inflammatory cytokine IL-10 [51] (*the authors concluded IL-6 as reduced pro-inflammatory action, although IL-6 can be classified as both pro-and anti-inflammatory cytokine). These inconsistent patterns in healthy populations may be down to (i) investigation of peripheral

versus central markers of inflammation, (ii) data collection methods (i.e. salivary versus plasma assays, schedule and number of biosample collection), (iii) individual differences in mindfulness application/learning (i.e. duration and dose, scope of mindfulness practice, novice versus experienced practitioners), (iv) individual differences in stress-levels and coping even if not to clinical/pathological levels, and/or, (v) levels of the examined markers need to be differentiated at baseline in order for mindfulness to have any significant observable effects. Targeted applications of mind-body medicine for otherwise healthy populations might be in the form of whether 'predisposed' centralized maladaptation can be determined, elucidated by genes and transcription factors, and altered/modulated prior to culmination into maladapted/diseased peripheral endpoints (see more in Section 4.1 below). In sum, peripheral neuroimmune marker findings in clinically diagnosed populations are more consistent. Yoga interventions also appear to show neuroplastic modulation, such as replicated neuroprotective effects against whole-brain gray matter degradation in age-related neurocognitive decline [52], suggesting prolonged neuron density and health. Moreover, long-term yoga practitioners measure greater gray matter volume, compared with matched controls, in several brain regions; anterior cingulate cortex, cerebellum, hippocampus, insula, (inferior and superior) parietal cortices, posterior cingulate cortex, (primary and secondary) somatosensory cortices [53]. Similar plasticity in gray matter volume regions have also been reported in meditation studies [54], suggesting wide-spread neurovascular preservation from mind-body interventions.

To note, the above molecular measures pertain to the investigation of peripheral biomarkers of inflammation in mind-body interventions, not centralized inflammatory outcomes. Furthermore, molecular biomarkers of the pro-inflammatory phenotype appear to be modulated with mind-body interventions. For example, TNF-α is a pro-inflammatory cytokine, and NF-κB induces the expression of various pro-inflammatory genes such as those that encode pro-inflammatory cytokines and chemokines [55] (in simple terms since NF-κB transcription signaling associated with inflammation is quite convoluted). The remaining molecular markers have dual pro- and anti-inflammatory roles, thus without additional dimensions of data, it is difficult to translate which inflammatory phenotype is targeted by mind-body interventions. The extant scope of molecular biomarkers to investigate their mechanistic impact has been very narrow; more data is needed to generate/test hypotheses and frameworks. Principally, we hypothesize that due to the wide-ranging clinical effects of mind-body interventions, it is highly probable that mindfulness interventions enact through a centralized mechanism that then has knock-on modulatory effects on germane peripheral outcomes reported.

4. Mainstream Treatments and the Homeostatic "Status-quo"

As alluded to previously, mind-body interventions involving meditation and/or yoga appear to have far-reaching clinical potential that has been interpreted by some as a lack of treatment specificity. While clinical efficacy trials are accruing, less focus has been directed to mechanistic research. Some debate that solely understanding *whether* a treatment works is important, opposed to *why* it works. However, we reason it is vital to understand the underlying mechanism/s of effective treatments for various factors; (1) explaining how a treatment works has intrinsic value and is important in its own right [56], (2) very often mechanistic understanding of a treatment can add further insights to the disease/condition being treated, (3) not all patients respond the same to any given treatment. Thus, understanding treatment mechanism is important for developing

precision medicine models and ensuring patients are referred to the most useful treatment based on their (very often) complex clinical presentation, (4) the aforementioned point is particularly germane to mind-body approaches since the field is relatively diverse. For example, the umbrella term "mindfulness-based interventions", include an array of diverging approaches emanating from central concepts and practices of "mindfulness", i.e. Mindfulness-Based Stress Reduction/MBSR, Mindfulness-Based Cognitive Therapy/MBCT, Mindfulness-Based Pain Management/MBPM, Mindfulness-Based Cancer Recovery/MBCR, Cognitively-Based Compassion Training/CBCT, etc. Most however, are built upon the programmatic structure and practices of Mindfulness-Based Stress Reduction/MBSR, with alterations around psychoeducation and tailored exercises for specific clinical conditions, i.e. depressogenic mechanisms, pain processing and physiology, and so on. Furthermore, such interventions include mindful practise during movement, that have been built upon the core elements of yoga practices. This can potentially lead to a lack of elucidation in terms of mechanistic nuances between different mind-body interventions that have been specifically adapted for certain disorders/symptoms and might have subtle enacting pathways. Presently, the predominant empirical approach is to assume that all mindfulness and/or yoga-based interventions enact the same mechanisms to explain clinical efficacy, albeit it may be that this mechanistic purview is uni-levelled and lacking sophistication. Further research, particularly in the molecular domains, is warranted to explicitly unpack this.

The core goal of many mainstream pharmacological treatments and psychotherapies is driven by the concept of homeostasis; the process of maintaining metabolic stability within an organisms' internal environment, regardless of changes in the external environment. This process is achieved by anticipatory regulators and sensors located in the brain, spinal cord, carotid bodies, and internal organs (among others), that monitor various systems and subsystems so to maintain ongoing physiological stability. Because homeostasis requires that the parameters of the system must remain within relatively narrow limits for survival and wellbeing (such as body temperature), any deviation from the homeostatic range is a biological problem that needs to be treated or reset. In this vein, disorder/disease represents a perturbation within the biological system that causes physiological parameters to move away from a critical baseline that is needed to maintain the wellbeing of the organism. Homeostatic regulation responds such to coordinate physiological subsystems, and/or behaviors, back to this set baseline, i.e. stability through constancy. Translated within the context of traditional psychological treatments such as Cognitive-Behavioral Therapy/CBT, talking psychotherapies, progressive relaxation, and so on; it could be reasoned that such treatments enable patients' to implement psychological processes (i.e. mind processes, psychological responses), and/or behavior modification, in order to *maintain* a psychological homeostasis within a range where psychological stability does not become 'maladaptive' or overly radical. However, therapeutic models (biological and psychological) operating within homeostatic frameworks remain bound within conditioned limits of the system and/or multiple sub-systems such that they are not necessarily adaptive nor physiologically/psychologically transformative.

4.1 Homeostasis to Allostasis: Mechanistic Hypothesis for Mind-body Medicine

A related concept is "allostasis", the process by which physiological (or psychological) equilibrium is maintained via the adjustment of the system/s' parameters and set points to meet challenge. Thus, system stability is redefined through change, opposed to constancy, via imposed demands.

Afterall, health, wellbeing, and successful aging could be considered as the ability to modulate and effectively respond to the dynamic challenges of essentially being alive [57]. Allostasis represents a process in which homeostasis is restored *and* recalibrated by significant load to the system as a state of responsiveness and optimized predictive adaptation. It is differentiated from a traditional concept of homeostasis in that it ensues flexible/dynamic biological set-points, opposed to fixed/static ones, with emphasis on neural regulatory feedback and health as a whole-body adaptation to contextual demands [57]. In a biologically based example, this process is regulated by the immune, endocrine, and autonomic nervous systems, in response to significant stress conditions, or 'allostatic load'. These processes in turn have psychological implications, due to the mind-body connection. For example, within an allostatic load framework, the brain is central to processing perceived interpreted threat, that in turn activates stress-related physiology, i.e. HPA-axis, autonomic nervous system, associated neurotransmitters and neurohormones. Reactivity to real-world threat does have transient advantages for survival, albeit prolonged stress-related physiology, such as abundant immuno-stress-related neurotransmitter and neurohormone release, can represent primary mediators that cause dysregulation in brain-body (i.e. central-to-peripheral) protective mechanisms. Naturally, if biological systems do not adapt and remain overburdened by allostatic load, then the organism remains in a chronic maladaptive state with risk of suboptimal response and decline. This prodromal stage gives rise to secondary outcomes affecting metabolic, immune, and cardiovascular function/levels. If physiological allostatic maladaptation persists, advanced dysregulation culminates into disordered, diseased, and deceased health endpoints, considered as tertiary outcomes [57].

Another factor to consider is that chronic hyperactive immunity and associated inflammatory response consumes vast amounts of energy within a bio-psycho-social system. Energy is a limited resource for biological systems where storage and consumption are critically regulated by homeostasis [16]. In most instances high energy consumption must be acute, rather than chronic, because permanent damage can occur when energy output exceeds energy input. This is akin to a system shut-down or "survival mode" in an effort to diminish energy consumption and decrease allostatic load [58], defined as allostatic overload type 1. Parallels can be seen in the symptomatology associated with systemic inflammatory "sickness behaviors" and/or depressive disorder. Furthermore, a type 2 allostatic overload pertains to environmental factors within this stressor-energy demand dynamic. Low socioeconomic status, traumatic life events, social disadvantage and discrimination, represent psychosocial stressors that lead to inefficient energy allocation/expenditure and increased burden on the neuroimmune system. In both instances there is a deficit in the energy supply compared with demand that contributes to system disease trajectory. Accumulating data suggests that certain mechanisms can be targeted to facilitate individuals to respond to environmental stressors in an adaptive manner that bypasses the above-mentioned detrimental effects of disadvantage and adversity [58].

The link between perceived stressors, chronic stress exposure, inflammation, and disease, is widely supported [59, 60]. We refer to the common mechanism of inflammation as an underlying component of most disease development/expression, since what critical mass is required for adaptive to maladaptive transition, or why some individuals develop particular inflammation-associated disorders remains a complex dynamic interaction between specific genetic, transcriptional, proteomic, metabolomic, psychosocial, and environmental factors. Disentangling these dynamics is beyond the scope of this report and remains a richly complex domain of empirical

inquiry still in development. However, if a process of allostatic adaptation can be facilitated prior to (i) primary meditators activating secondary outcomes, (ii) secondary outcomes developing into tertiary ones, or even (iii) reversing the tertiary stage back to an adaptive state, this would potentially present an optimal and transformative treatment that could ultimately be achieved by transmuting homeostatic set-points more in accord with contextual demands/challenges. It may be that mind-body interventions built upon meditation and/or yoga, represent such capacity, providing explanatory value to their systemic influences upon multiple biologic, psychological, and social endpoints (see Figure 2). Rather than lacking specifity, meditation and/or yoga-associated mind-body interventions do not target the specific endpoint markers (outlined above and in more depth here [61]) per se, but may target the central mechanisms and/or intriniscally connective ones critical to allostatic adaptation. Such adaptive networks could involve germane pathways of peripheral-to-central inflammatory signalling, hypothalamic-pituitary-adrenal axis and neuroendocrine system, and/or brain-gut-microbiome axis and vagus nerve, in correspondence to specific epigenetic and psychosocial outcomes.

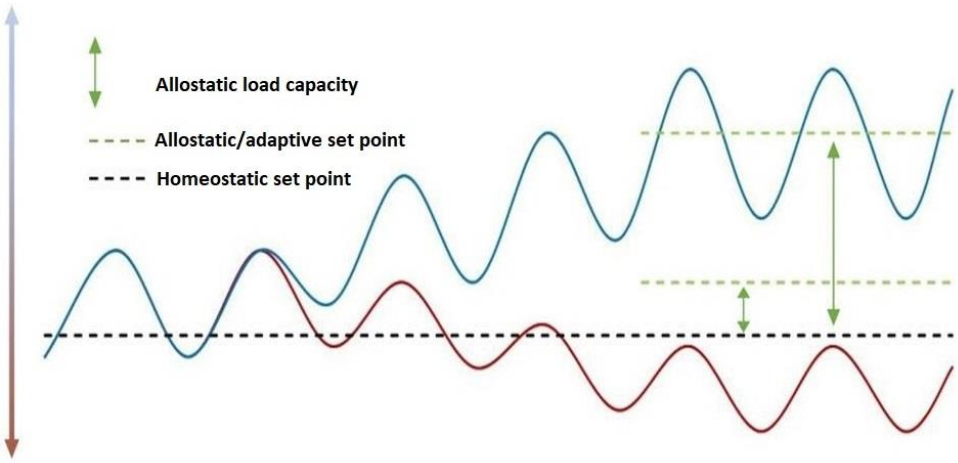

Figure 2 Potential allostatic mechanism of mind-body interventions. Based on a chronic stress allostatic biological systems framework [57, 62]: X-axis represents exposure across time; red line = exposure to stressors, blue line = exposure to stressors + mind-body intervention practice/s. Y-axis represents adjustment in 1°, 2°, 3° mediators/outcomes (see below); blue continuum = adaptive, red continuum = maladaptive. In sum, the potential multi-dimensional therapeutic action of mind-body interventions across primary mediators (stress-related physiology, such as immune-stress-related neurotransmission/neurohormone release), secondary outcomes (metabolic, immune, cardiovascular function/levels), and tertiary outcomes (disordered, diseased, deceased health endpoints). Moreover, increased allostatic load capacity would be efficient for both type 1 and 2 allostatic overload disease trajectories.

Clinically based data examining mind-body interventions yields promising modulation across the many related markers/endpoints that are connected to these central/connective molecular pathways, albeit largely peripheral outcomes have been measured. Moreover, such a framework emphasizes the role of the brain and central nervous system in allostatic adaptation, that may account for the accruing modulation of neurophysiological, neurochemical, and neurohormonal

markers associated with such treatments. It would also suggest that mind-body interventions, based in meditation and/or yoga, are not primarily 'relaxation' techniques, i.e. moving stress physiology back to a static set point by down-regulating the system. Relaxation may be a by-product outcome, although the therapeutic action mechanism/s is reasonably an allostatic one, that is recalibrating and adapting the entire physiological-psychological (body-mind) system for extended (and potentially new) contextual challenge/s.

5. Synthesis

We introduce the proposal that the therapeutic pathways of mind-body interventions may enact via an allostatic mechanism upon centralized and connective systems. This is where genomic, transcriptomic, proteomic, and metabolomic "set-points" fundamentally adaptively modify and may also be accompanied by an increase in the capacity of "allostatic load". Modification in allostatic load capacity would facilitate respective systems to adapt to greater stress and efficient energy allocation/dispersion, opposed to overburden, energy depletion, and decline. Homeostatic recovery may enact more rapidly for some parameters, although the potential allostatic mechanism of mind-body interventions essentially serves to change/modify adaptive range of stress-related physiology, such as immune-stress-related neurotransmission/neurohormone release (primary mediators), and/or metabolic, immune, cardiovascular function/levels (secondary outcomes). In turn, entailing beneficial effect upon tertiary outcomes, i.e. disordered, diseased, deceased health endpoints. We suggest that mind-body interventions, based in yoga and meditation, may not necessarily specifically target inflammatory biomarkers, rather modulate the centralized and connective pathways associated with chronic systemic inflammation.

Acknowledgments

The authors would like to thank the peer-reviewers who provided insightful feedback.

Author Contributions

Conceptualization: PLAS. Review: PLAS, KMG. Visualization: PLAS, KMG. Writing: PLAS.

Competing Interests

The authors have declared that no competing interests exist.

References

1. Pahwa R, Goyal A, Bansal P, Jialal I. Chronic inflammation. Treasure Island: StatPearls Publishing; 2021.
2. Bloom DE, Cafiero E, Jané-Llopis E, Abrahams-Gessel S, Bloom LR, Fathima S, et al. The global economic burden of noncommunicable diseases. Geneva: World Economic Forum; 2011.
3. Furman D, Campisi J, Verdin E, Carrera-Bastos P, Targ S, Franceschi C, et al. Chronic inflammation in the etiology of disease across the life span. Nat Med. 2019; 25: 1822-1832.
4. Camps J, García-Heredia A. Introduction: Oxidation and inflammation, a molecular link between non-communicable diseases. In: Oxidative stress and inflammation in non-communicable

diseases-molecular mechanisms and perspectives in therapeutics. Cham: Springer; 2014. pp. 1-4.
5. Bauer ME, Teixeira AL. Inflammation in psychiatric disorders: What comes first? Ann N Y Acad Sci. 2019; 1437: 57-67.
6. Phillips CM, Chen LW, Heude B, Bernard JY, Harvey NC, Duijts L, et al. Dietary inflammatory index and non-communicable disease risk: A narrative review. Nutrients. 2019; 11: 1873.
7. Disabato D, Quan N, Godbout JP. Neuroinflammation: The devil is in the details. J Neurochem. 2016; 139: 136-153.
8. Litvin DG, Denstaedt SJ, Borkowski LF, Nichols NL, Dick TE, Smith CB, et al. Peripheral-to-central immune communication at the area postrema glial-barrier following bleomycin-induced sterile lung injury in adult rats. Brain Behav Immun. 2020; 87: 610-633.
9. Bachiller S, Jiménez-Ferrer I, Paulus A, Yang Y, Swanberg M, Deierborg T, et al. Microglia in neurological diseases: A road map to brain-disease dependent-inflammatory response. Front Cell Neurosci. 2018; 12: 488.
10. Lull ME, Block ML. Microglial activation and chronic neurodegeneration. Neurotherapeutics. 2010; 7: 354-365.
11. Müller N. Anti-inflammatory and immune-modulatory therapeutic approaches in major depression. In: Systems neuroscience in depression. Cambridge: Academic Press; 2016. pp. 115-141.
12. Tabas I, Glass CK. Anti-inflammatory therapy in chronic disease: Challenges and opportunities. Science. 2013; 339: 166-172.
13. Filipov NM. Chapter six-Overview of peripheral and central inflammatory responses and their contribution to neurotoxicity. Adv Neurotoxicol. 2019; 3: 169-193.
14. O'Reilly ML, Tom VJ. Neuroimmune system as a driving force for plasticity following CNS injury. Front Cell Neurosci. 2020; 14: 187.
15. Raison CL, Capuron L, Miller AH. Cytokines sing the blues: Inflammation and the pathogenesis of depression. Trends Immunol. 2006; 27: 24-31.
16. Straub RH, Schradin C. Chronic inflammatory systemic diseases. An evolutionary trade-off between acutely beneficial but chronically harmful programs. Evol Med Public Health. 2016; 2016: 37-51.
17. Sheng JA, Bales NJ, Myers SA, Bautista AI, Roueinfar M, Hale TM, et al. The hypothalamic-pituitary-adrenal axis: Development, programming actions of hormones, and maternal-fetal interactions. Front Behav Neurosci. 2020; 14: 601939.
18. Tapp ZM, Godbout JP, Kokiko-Cochran ON. A tilted axis: Maladaptive inflammation and HPA axis dysfunction contribute to consequences of TBI. Front Neurol. 2019; 10: 345.
19. Carabotti M, Scirocco A, Maselli MA, Severi C. The gut-brain axis: Interactions between enteric microbiota, central and enteric nervous systems. Ann Gastroenterol. 2015; 28: 203-209.
20. Martin CR, Osadchiy V, Kalani A, Mayer EA. The brain-gut-microbiome axis. CMGH Cell Mol Gastroenterol Hepatol. 2018; 6: 133-148.
21. Breit S, Kuperberg A, Rogler G, Hasler G. Vagus nerve as modulator of the brain-gut axis in psychiatric and inflammatory disorders. Front Psychiatry. 2018; 9: 44.
22. Hockenberry MJ, Hooke MC, McCarthy K, Gregurich MA. Sickness behavior clustering in children with cancer. J Pediatr Oncol Nurs. 2011; 28: 263-272.

23. Konsman JP, Parnet P, Dantzer R. Cytokine-induced sickness behaviour: Mechanisms and implications. Trends Neurosci. 2022; 25: 154-159.
24. Dantzer R. Cytokine, sickness behavior, and depression. Immunol Allergy Clin North Am. 2009; 29: 247-264.
25. Murphy BA, Epstein J. Chronic systemic symptoms in cancer patients. In: Translational systems medicine and oral disease. Cambridge: Academic Press; 2020. pp. 353-369.
26. Maes M, Berk M, Goehler L, Song C, Anderson G, Galecki P, et al. Depression and sickness behavior are janus-faced responses to shared inflammatory pathways. BMC Med. 2012; 10: 66.
27. Ramos-Casals M, Brito-Zerón P, Mariette X. Systemic and organ-specific immune-related manifestations of COVID-19. Nat Rev Rheumatol. 2021; 17: 315-332.
28. Nalbandian A, Sehgal K, Gupta A, Madhavan MV, McGroder C, Stevens JS, et al. Post-acute COVID-19 syndrome. Nat Med. 2021; 27: 601-615.
29. Munblit D, Nicholson TR, Needham DM, Seylanova N, Parr C, Chen J, et al. Studying the post-COVID-19 condition: Research challenges, strategies, and importance of core outcome set development. BMC Med. 2022; 20: 50.
30. Pratscher S, Mickle AM, Marks JG, Rocha H, Bartsch F, Schmidt J, et al. Optimizing chronic pain treatment with enhanced neuroplastic responsiveness: A pilot randomized controlled trial. Nutrients. 2021; 13: 1556.
31. Sibille KT, Bartsch F, Reddy D, Fillingim RB, Keil A. Increasing neuroplasticity to bolster chronic pain treatment: A role for intermittent fasting and glucose administration? J Pain. 2016; 17: 275-281.
32. Pittenger C, Duman RS. Stress, depression, and neuroplasticity: A convergence of mechanisms. Neuropsychopharmacology. 2007; 33: 88-109.
33. Tian L, Kaarela T, Zhillin L. Neuroimmune crosstalk in the central nervous system and its significance for neurological diseases. J Neuroinflammation. 2012; 9: 155.
34. Allen BM, Hiam KJ, Burnett CE, Venida A, DeBarge R, Tenvooren I, et al. Systemic dysfunction and plasticity of the immune macroenvironment in cancer models. Nat Med. 2020; 26: 1125-1134.
35. Orihuela R, McPherson CA, Harry GJ. Microglial M1/M2 polarization and metabolic states. Br J Pharmacol. 2016; 173: 649-665.
36. Woodburn SC, Bollinger JL, Wohleb ES. The semantics of microglia activation: Neuroinflammation, homeostasis, and stress. J Neuroinflammation. 2021; 18: 258.
37. Tu H, Chu H, Guan S, Hao F, Xu N, Zhao Z, et al. The role of the M1/M2 microglia in the process from cancer pain to morphine tolerance. Tissue Cell. 2021; 68: 101438.
38. Blanck P, Perleth S, Hedenreich T, Kröger P, Ditzen B, Bents H, et al. Effects of mindfulness exercises as stand-alone intervention on symptoms of anxiety and depression: Systematic review and meta-analysis. Behav Res Ther. 2018; 102: 25-35.
39. Kuyken W, Warren FC, Taylor RS, Whalley B, Crane C, Bondolfi G, et al. Efficacy of mindfulness-based cognitive therapy in prevention of depressive relapse: An individual patient data meta-analysis from randomized trials. JAMA Psychiatry. 2016; 73: 565-574.
40. Hölzel B, Carmody J, Vangel M, Congleton C, Yerramsetti SM, Gard T, et al. Mindfulness practice leads to increases in regional brain gray matter density. Psychiatry Res. 2011; 191: 36-43.
41. Black DS, Slavich GM. Mindfulness meditation and the immune system: A systematic review of randomized controlled trials. Ann N Y Acad Sci. 2017; 1373: 13-24.

42. Creswell JD, Taren AA, Lindsay EK, Greco CM, Gianaros PJ, Fairgrieve A, et al. Alterations in resting-state functional connectivity link mindfulness meditation with reduced interleukin-6: A randomized controlled trial. Biol Psychiatry. 2016; 80: 53-61.
43. Reich RR, Lengacher CA, Klein TW, Newton C, Shivers S, Ramesar S, et al. A randomized controlled trial of the effects of mindfulness-based stress reduction (MBSR [BC]) on levels of inflammatory biomarkers among recovering breast cancer survivors. Biol Res Nurs. 2017; 19: 456-464.
44. Carlson LE, Speca M, Faris P, Patel KD. One year pre-post intervention follow up of psychological, immune, endocrine and blood pressure outcomes of mindfulness-based stress reduction (MBSR) in breast and prostate cancer outpatients. Brain Behav Immun. 2007; 21: 1038-1049.
45. Witek-Janusek L, Albuquerque K, Chroniak KR, Chroniak C, Durazo-Arvizu R, Mathews HL. Effect of mindfulness based stress reduction on immune function, quality of life and coping in women newly diagnosed with early stage breast cancer. Brain Behav Immun. 2008; 22: 969-981.
46. Bower JE, Crosswell AD, Stanton AL, Crespi CM, Winston D, Arevalo J, et al. Mindfulness meditation for younger breast cancer survivors: A randomized controlled trial. Cancer. 2015; 121: 1231-1240.
47. Lengacher CA, Reich RR, Paterson CL, Shelton M, Shivers S, Ramesar S, et al. A large randomized trial: Effects of mindfulness-based stress reduction (MBSR) for breast cancer (BC) survivors on salivary cortisol and IL-6. Biol Res Nurs. 2019; 21: 39-49.
48. Creswell JD, Irwin MR, Burklund LJ, Lieberman MD, Arevalo JM, Ma J, et al. Mindfulness-based stress reduction training reduces loneliness and pro-inflammatory gene expression in older adults: A small randomized controlled trial. Brain Behav Immun. 2012; 26: 1095-1101.
49. Villalba DK, Lindsay EK, Marsland AL, Greco CM, Young S, Brown KW, et al. Mindfulness training and systemic low-grade inflammation in stressed community adults: Evidence from two randomized controlled trials. PloS One. 2019; 14: e0219120.
50. Malarkey WB, Jarjoura D, Klatt M. Workplace based mindfulness practice and inflammation: A randomized trial. Brain Behav Immun. 2013; 27: 145-154.
51. Gardi C, Fazia T, Stringa B, Giommi F. A short Mindfulness retreat can improve biological markers of stress and inflammation. Psychoneuroendocrinology. 2022; 135: 105579.
52. Froeliger B, Garland EL, McClernon FJ. Yoga meditation practitioners exhibit greater gray matter volume and fewer reported cognitive failures: Results of a preliminary voxel-based morphometric analysis. Evid Based Complementary Altern Med. 2012; 2012: 821307.
53. Villemure C, Čeko M, Cotton VA, Bushnell MC. Neuroprotective effects of yoga practice: Age-, experience-, and frequency-dependent plasticity. Front Hum Neurosci. 2015; 9: 281.
54. Fox KC, Nijeboer S, Dixon ML, Floman JL, Ellamil M, Rumak SP, et al. Is meditation associated with altered brain structure? A systematic review and meta-analysis of morphometric neuroimaging in meditation practitioners. Neurosci Biobehav Rev. 2014; 43: 48-73.
55. Liu T, Zhang L, Joo D, Sun SC. NF-κB signaling in inflammation. Signal Transduct Target Ther. 2017; 2: 17023.
56. Parkkinen VP, Wallmann C, Wilde M, Clarke B, Illari P, Kelly MP, et al. Chapter 2, an introduction to mechanisms. In: Evaluating evidence of mechanisms in medicine: Principles and procedures. Cham: Springer Nature; 2018.
57. Juster RP, McEwen BS, Lupien SJ. Allostatic load biomarkers of chronic stress and impact on health and cognition. Neurosci Biobehav Rev. 2010; 35: 2-16.

58. McEwen BS, Wingfield JC. The concept of allostasis in biology and biomedicine. Horm Behav. 2003; 43: 2-15.
59. Salleh MR. Life event, stress and illness. Malays J Med Sci. 2008; 15: 9-18.
60. Shields GS, Slavich GM. Lifetime stress exposure and health: A review of contemporary assessment methods and biological mechanisms. Soc Personal Psychol Compass. 2017; 11: e12335.
61. Schoenberg PL, Gonzalez KM. Systematic review of high-dimensional omics in mind-body medicine. OBM Integr Complement Med. 2022; 7: 34.
62. Lee DY, Kim E, Choi MH. Technical and clinical aspects of cortisol as a biochemical marker of chronic stress. BMB Rep. 2015; 48: 275.