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ORIGINAL ARTICLE

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Hiding in Plain Sight: Factors Influencing the Neuroinflammatory Response to Sport-Related Concussion

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Abstract

Sport-related concussion (SRC) is a major concern among athletes and clinicians around the world. Research into fluid biomarkers of SRC has made significant progress in understanding the complex underlying pathophysiology of concussion. However, little headway has been made toward clinically validating any biomarkers to improve the clinical management of SRC. A major obstacle toward clinical translation of any fluid biomarker is the heterogeneity of SRC overlapping with multiple physiological systems involved in pathology and recovery. Neuroinflammation post-SRC is one such system that may confound fluid biomarker data on many fronts. Neuroinflammatory processes consist of cell mediators, both within the central nervous system and the periphery, that play vital roles in regulating the response to brain injury. Further, neuroinflammation is influenced by many biopsychosocial variables present in most athletic populations. In this commentary, we propose that future fluid biomarker research should take a systems biology approach in the context of the neuroinflammatory response to SRC. We highlight how biological variables, such as age, sex, immune challenges, and hypothalamic-pituitary-adrenal (HPA)-axis responses to stress, may alter neuroinflammation. Further, we underscore the importance of accounting for health and lifestyle variables, such as diet, exercise, sleep, and pre-morbid medical factors, when measuring inflammatory markers of SRC. To successfully move toward clinical translation, fluid biomarker research should take a more holistic approach in study design and data interpretation, collecting information on hidden variables that may be influencing the neuroinflammatory response to SRC.

Keywords: athletes; fluid biomarkers; hypothalamic-pituitary-adrenal axis; neuroinflammation; sport-related concussion

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Introduction

Considerable scientific progress has been made toward the discovery, optimization, and validation of fluid biomarkers of sport-related concussion (SRC). Leading candidate biomarkers include glial fibrillary acidic protein, ubiquitin-C-terminal hydrolase 1 (UCH-L1), Tau, neurofilament light (NF-L), and inflammatory cytokines (e.g., interleukin [IL]-1 β , IL-6, and tumor necrosis factor [TNF]- α).¹⁻⁶ Current SRC biomarker research strategies have focused on a handful of assays thought to be sensitive to various traumatic brain injury (TBI) pathologies. These biomarkers are then measured in their respective fluid mediums and assumed to be representative of the physiological state of the brain after injury. However, this approach ignores basic principles of systems biology, where multiple networks of physiological processes may influence levels of a particular biomarker or confound the relationship between biomarker and brain damage. For instance, ongoing secondary injury processes may alter the concentration of biomarkers that do not directly measure neuroinflammation (e.g., UCH-L1, Tau, and NF-L) over time, which are further compounded by fluctuating blood-brain barrier (BBB) permeability throughout recovery.^{7,8}

The neuroinflammatory response to TBI, including SRC, is highly complex, incorporating multiple biopsychosocial variables that should serve as a contextual framework for future SRC biomarker research. This commentary aims to highlight key variables that may confound much of the research currently being done on both brain injury and neuroinflammatory markers of SRC.

Discussion

Many factors influence neuroinflammation (both centrally and peripherally) that make it a difficult field to study in heterogeneous conditions like SRC. Age and sex are variables that must be considered for almost every aspect of SRC pathology and recovery in terms of immunological changes throughout development or sexually dimorphic inflammatory responses to injury. Moreover, many hormones exhibit regulatory functions over immunological processes. The effects of stress (physical and psychosocial) must also be considered given the bidirectional communication between the hypothalamic-pituitary-adrenal (HPA) axis and the immune system.⁹ Last, there are many lifestyle factors that can influence inflammatory processes like exercise, diet, sleep, and medications. All these confounding factors (see Fig. 1) contribute to the non-

specificity of neuroinflammation and its various effects on the release and peripheral measurement of fluid biomarkers of SRC.

Age

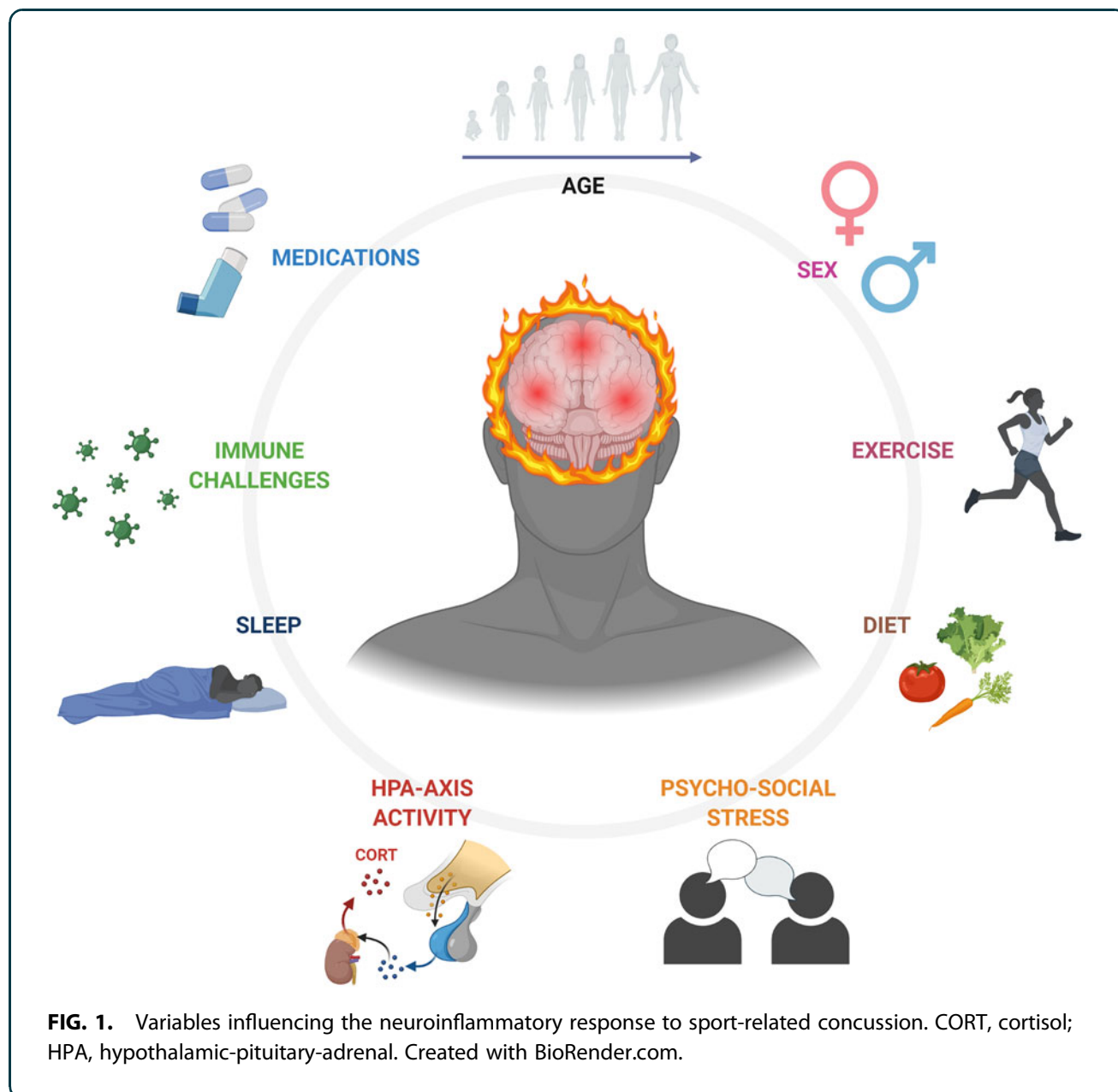
Age is an important variable in SRC and neuroinflammation, especially considering the physiological differences in the developing brain (e.g., ongoing synaptogenesis and myelination, higher brain water content, lower brain elasticity, and changes in cerebral blood flow and oxygen consumption)¹⁰⁻¹² and anatomical vulnerabilities (e.g., larger head-to-body size ratio).¹³ Various mediators of neuroinflammation (including resident cells in the central nervous system [CNS] and infiltrating peripheral immune cells) show age-related changes that could influence measures of inflammation and subsequent markers of brain damage. For example, microglia have shown age-dependent regional functional and morphological heterogeneity in addition to more dominant immune-vigilant phenotypes in the developing brain.¹⁴ Peripheral immune cell composition changes throughout development, too. For instance, healthy leukocyte counts have been shown to peak in children <9 years of age, whereas neutrophil counts were highest between the ages of 15 and 18 years.¹⁵

In addition, reduction in monocyte chemotaxis has been reported in children compared to adults.¹⁶ Inflammatory responses also change throughout adulthood given that both healthy aging and age-related diseases are associated with dysregulation of nuclear factor- κ B (NF- κ B) pathways and cytokine networks.¹⁷ These age-related differences in immune function likely result in altered contributions to the neuroinflammatory response to SRC that should be considered in all biomarker studies. In the context of adolescent athletes (and depending on clinical vs non-clinical research settings), investigators may consider measuring puberty status using physical exams, hormonal measures, picture-based interviews, or self-report tools (e.g., the Pubertal Development Scale) to examine associations between neurodevelopment and biomarker outcomes.¹⁸

Biological sex

Biological sex is another variable that has frequently been reported as a modifier of recovery post-TBI, but has been largely ignored in the literature concerning neuroinflammation post-SRC. Pre-clinical models are often used to study inflammatory responses to mild TBI given the ability to maintain homogenous





conditions in a model organism. To that effect, there has been a major bias toward the male sex given the layer of complexity added by the female menstrual cycle. The menstrual cycle introduces variations in circulating estrogen and progesterone, which can have many anti-inflammatory effects, both centrally and peripherally.¹⁹ Estradiol and progesterone also interact with cells of the CNS, mediating many effects through activation of estrogen and progesterone receptors and downregulation of inflammasome activity (a pro-inflammatory process driven by NF- κ B activation).^{20–22}

In animal TBI studies, estrogen and progesterone have been shown to suppress proinflammatory cytokine production (IL-1 β , IL-6, and TNF α) in microglia and overall astrogliosis, increase levels of anti-inflammatory cytokines (e.g., transforming growth factor- β and IL-10), and reduce levels of cerebral edema.¹⁹ In addition to female hormone cycles, testosterone levels also fluctuate in males²³; however, the influence of testosterone has not been taken into consideration in SRC biomarker studies to date. Peripheral immune cell composition may be partially regulated by



circulating hormone levels given the expression of estrogen, progesterone, and androgen receptors found on many immune cells and the sexually dimorphic responses to immune challenges (including brain injury).^{24–27} Whereas sampling sex hormone levels on all study participants would be ideal, a feasible alternative for females could be to implement self-reported menstrual cycle surveys to investigate associations between menstrual regularity and timing and the inflammatory variables in question.

Stress, hypothalamic-pituitary-adrenal axis, and glucocorticoid activity

Physical stress in the form of injury (e.g., associated peripheral injuries or central injury as in SRC) and psychological stress (e.g., anxiety, depression) activate the HPA axis, resulting in a release of glucocorticoids (GCs; i.e., cortisol in humans) throughout the body to restore homeostasis.^{28, 29} GCs regulate inflammation with both pro- and anti-inflammatory actions depending on the context and chronicity of the stressor. In response to acute stressors, GCs display anti-inflammatory actions mediated through binding of glucocorticoid receptors (GRs), which are then translocated to the nucleus where they interact with GC responsive elements to block transcription of proinflammatory factors (e.g., downregulate NF- κ B-mediated transcription of IL-1 β , TNF α , and IL-6).⁹ GRs are expressed all over the body, including many cell mediators of systemic and neuroinflammation. Microglia exhibit high GR expression and are prime targets for GC-induced immunosuppression.³⁰

Peripheral immune cells also express GRs, and T cells have even been reported to undergo GC-mediated apoptosis to help reduce inflammatory actions.³¹ GCs can also act on endothelial cells of the BBB to increase expression of tight junctions, thus decreasing permeability to peripheral immune cells and dampening neuroinflammation.^{32,33} In the context of SRC, potential HPA-axis dysfunction could lead to decreased GC secretion, unchecked neuroinflammation, and an impaired stress response.^{9,34,35} Additionally, animal TBI studies have shown how associated peripheral injuries may influence inflammation and recovery after brain injury, which may be relevant in clinical SRC studies.^{36,37}

The opposite effect can occur where the HPA axis is excessively activated, priming microglial reactivity in the presence of excessive GC levels, resulting in maladaptive inflammation and increased neuronal death.⁹

Similar events are thought to occur as a result of psychological stressors priming and increasing microglial reactivity.³⁸ Acute psychological stress has been shown to increase levels of circulating IL-1 β , TNF α , and IL-6 for up to 2 h in humans.³⁹ Chronic stress (i.e., sustained levels of GC in circulation) can influence systemic inflammation and the response to a traumatic event as well. For example, social determinants of health (e.g., socioeconomic status, educational and healthcare inequalities) have been associated with chronic inflammation.⁴⁰

Studies examining the consequences of chronic stress have also shown increased monocyte mobilization from bone marrow⁴¹ and elevated proinflammatory cytokines in circulation of those with chronic mental health disorders like post-traumatic stress disorders or major depression.^{42,43} Given the overlap of non-specific symptoms between mental health disorders and SRC, it is reasonable to assume that psychological distress influences neuroinflammation through HPA-axis activity, which may result in altered biomarker concentrations and clinical outcomes. Considering the complex biological response to stress, researchers may benefit from evaluating cortisol levels, asking questions pertaining to various social determinants of health, and implementing psychological screening tools in their assessments.

Lifestyle factors

Lifestyle factors that influence inflammation may be easily controlled in pre-clinical studies; however they are more difficult to account for in clinical SRC populations beyond self-reported measures. Examples of lifestyle variables include diet, exercise, and sleep quality. Many dietary variables have been shown to influence inflammation. For example, diets rich in trans-fats and high glycemic index carbohydrates lead to increased levels of proinflammatory cytokines in the general circulation.⁴⁴ High-calorie diets have also been linked to increased neuroinflammation, thought to be one of the main drivers of various cognitive and mood disorders.⁴⁵ Conversely, diets like the Mediterranean or ketogenic diet are associated with anti-inflammatory pathways, potentially attenuating neuroinflammation and positively influencing cognition.⁴⁶ Alcohol and caffeine consumption have also been shown to influence both peripheral and central levels of inflammation.^{47,48} A novel, yet highly understudied, field in SRC research is beginning to discover links between nutrition, metabolism, and SRC



outcomes, which might be partially attributable to changes in the gut microbiome and systemic inflammatory states.^{49–52}

Given the athletic context in which SRCs occur, the influence of exercise on measures of inflammation requires careful consideration. Exercise can produce both pro- and anti-inflammatory effects that stem from localized muscle tissue and peripheral immune cells.⁵³ For example, IL-6 levels are released from muscle tissue after acute exercise whereas levels of TNF α and IL-1 β are actively suppressed, all of which have been recently associated with SRC.^{4–6,54} Further, exercise has been shown to suppress microglial activation and downregulate the expression of many proinflammatory cytokines in the brain, mechanistically explaining (at least in part) the neuroprotective and therapeutic effects of aerobic exercise for SRC.^{55,56} Last, exercise influences regional macrophage function in: 1) skeletal muscle during physical activity; 2) adipose tissue during energy mobilization; and 3) circulation concerning the development/progression of atherosclerosis.⁵³ These influences of exercise on various immunological and cytokine networks may obscure the use of inflammatory molecules as potential diagnostic or prognostic biomarkers for SRC and need to be taken into consideration in these studies.

Sleep quality can also have a major impact on inflammation, especially given that sleep disturbance is a common symptom post-SRC.⁵⁷ Interestingly, sleep and immune function have their own bidirectional effects. Animal and human studies have shown sleep quality to change in response to infections, injury, and neurodegenerative disorders.⁵⁸ Sleep deprivation has also been reported to increase the expression of IL-1 β , IL-6, TNF α , and C-reactive protein.⁵⁹ A potential mechanistic explanation (particularly relevant for SRC) lies in the intimate relationship between sleep and the HPA axis given that regulation of sleep onset and completion depends on the circadian release of cortisol.⁹ Conversely, sleep disruption impacts HPA-axis function, which may lead to hyperactivity in the stress response, which as outlined above, could exacerbate inflammation. Overall, many lifestyle factors are insufficiently documented and incorporated into current biomarker analyses, which will continue to limit their clinical translation to wider athletic and general populations. Investigators may consider asking targeted questions toward recent diet habits, exercise activity, and sleep quality at the time of sample collection.

Health-related and pre-morbid host factors

Last, there are multiple health-related factors that can influence inflammation. The use of non-steroidal anti-inflammatory drugs (e.g., ibuprofen), exogenous corticosteroids (e.g., asthma medication), and even oral hormonal contraceptives may confound inflammatory data and must therefore be considered in clinical studies.^{27,60,61} Exposure to natural allergens (e.g., seasonal pollen, pet dander) may lead to increased inflammation and activated immune cells in persons with a predisposition to environmental allergies.⁶² Bacterial or viral infection would also activate a host immune response. Considering the current state of the COVID-19 pandemic and recent vaccination efforts, clinical SRC studies will need to document the type and recency of vaccine administration given that this will influence cytokine levels during data collection.^{63,64}

Conclusion

Despite enormous progress over the past decade, research into fluid biomarkers of SRC remains largely in its infancy given a large focus on a handful of biomarkers at single, variable time points post-injury. Studies in general for neurological disorders (including SRC) have yet to successfully identify candidate markers of underlying pathophysiology that are associated with standard clinical measures of recovery. This remains one of the largest barriers to the clinical translation and validation of the leading candidate biomarkers of SRC. However, we may not surpass this obstacle without fully understanding the complex interaction between the neuroinflammatory response to SRC and fluid biomarker measures. Many covariates, such as age, sex, stress, and lifestyle factors, may seem trivial at first glance; however, they each introduce an abundance of hidden physiological variation in different contexts, which must be considered when designing and interpreting biomarker studies. Many questions remain around how, when, and to what degree these factors may influence aspects of neuroinflammation. Further, the methods of capturing these data should be carefully selected when assessing their impact on biological outcomes, and SRC biomarker investigators may benefit from collaboration with experts across multiple domains of inflammation. A more holistic approach, rather than reductionist approach, to studying fluid biomarkers of SRC may be more optimal in moving the field toward clinical translation given that the neuroinflammatory response to SRC is consistently shown to be greater than the sum of its parts.



Authors' Contributions

All authors contributed to the writing and development of this manuscript. Authors J.T. and C.D. were involved in the original conception and writing of the initial draft. Authors M.M., T.M., and C.E. were involved in further developing ideas and finalizing the manuscript.

Funding Information

J.T. is funded by the Canadian Institute for Health Research (CIHR; award application #457525).

Author Disclosure Statement

No competing financial interests exist.

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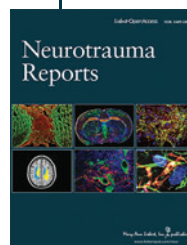
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Cite this article as: Tabor JB, McCrea MA, Meier TB, et al. Hiding in plain sight: factors influencing the neuroinflammatory response to sport-related concussion. *Neurotrauma Reports* 2022;3(1):200–206. doi: 10.1089/neur.2021.0081.

Abbreviations Used

- BBB = blood–brain barrier
- CNS = central nervous system
- GCs = glucocorticoids
- GRs = glucocorticoid receptors
- HPA = hypothalamic-pituitary-adrenal
- IL = interleukin
- NF- κ B = nuclear factor- κ B
- NF-L = neurofilament light
- SRC = sport-related concussion
- TBI = traumatic brain injury
- TNF = tumor necrosis factor
- UCH-L1 = ubiquitin-C-terminal hydrolase 1

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