Traumatic Brain Injury Rehabilitation: An Exercise Immunology Perspective

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ABSTRACT

Traumatic brain injury (TBI) is the largest cause of death and disability globally. The physical and psychosocial consequences after TBI can persist for prolonged periods, and lead to increased health care and economic burden. Exercise has shown promise over recent years as a mode of rehabilitation that alleviates multiple TBI symptoms; but there is a lack of controlled large-scale studies and limited research into the underlying mechanisms. This critical review draws from animal and human studies on exercise immunology to speculate on possible mechanisms that could underlie beneficial outcomes of exercise after TBI. The anti-inflammatory role of exercise, protective role offered by pre-injury exercise, and the need for more objective studies on biomarker analysis are expected to be useful considerations to develop optimal post-TBI exercise rehabilitation programs. Future studies can consider investigating the specific immunological processes induced by exercise in consideration of individual differences and non-aerobic exercise modalities.

Keywords: traumatic brain injury, exercise immunology, neuroinflammation

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INTRODUCTION

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Traumatic brain injury (TBI) is the largest cause of worldwide death and disability around the world. Each year, it is estimated that up to 69 million people will experience a TBI globally (1), leading to healthcare costs and economic burden to patients and caregivers. The consequences of TBI can include a wide range of physical, cognitive, and emotional problems that require personalised care. Many patients take a long time to recover, with a majority never fully returning to pre-injury functioning (2, 3).

Currently, multimodal approaches are favoured to treat post-TBI symptoms. These approaches can include psychological therapy and education on TBI; however, more evidence is needed to identify an approach that can consistently demonstrate positive outcomes. Emerging evidence indicates that an exercise component could be beneficial in such programs because it can influence symptoms across multiple domains, but we lack clear rehabilitation guidelines about critical matters such as the timing, intensity, and frequency of exercise bouts. The underlying mechanisms of exercise that could offer benefits after a TBI are also not clearly understood. It is expected that drawing from literature on exercise immunology could offer some answers. This review will draw from existing literature on TBI pathophysiology and exercise rehabilitation to establish inferences about how exercise could influence post-TBI outcomes. While previous literature has explored these component topics separately, there is value in considering the connections between them. If exercise immunology can account for the apparent benefits of exercise for TBI rehabilitation, this could support program refinements and further development of much needed treatment programs.

Traumatic Brain Injury

Traumatic brain injury (TBI) is defined as "physical damage to, or impairment of brain function, or other evidence of brain pathology, caused by an external force", usually applied to the head (4). Clinically, the effects on brain structure and function are inferred from any period of loss of consciousness (LOC), post-traumatic amnesia (PTA), any neurological deficits (e.g., weakness, loss of balance, vision problems), or any alteration in mental state (e.g., confusion, disorientation) (4). TBIs are mostly caused by falls, motor-vehicle accidents, and sports-related injuries. While it is common to classify TBI as mild, moderate, and severe based on the duration of key

clinical indicators, such as LOC and PTA (5), these indicators do not always predict the magnitude of clinical and functional outcomes in individuals. Most TBIs are mild injuries (mTBI), also referred to as concussion in the literature (5-7), but the term concussion is less used, because it lacks diagnostic utility (8). In general, TBIs of all severities can cause physical and psychosocial consequences (5), resulting in increased healthcare burden and economic costs. A minority of people with mTBI can also suffer from a range of physical, cognitive, and emotional problems called post-concussion symptoms that can be persistent for months or years (9, 10). A history of mTBIs or sub-concussive injuries over prolonged periods is also thought to increase the risk for neurodegenerative conditions such as chronic traumatic encephalopathy (CTE) and Alzheimer's disease (AD) (8, 11).

TBIs pose considerable prognostic challenges. The diagnosis of moderate or severe TBIs can be aided by techniques such as neuroimaging and injury modelling from animal/human studies due to more measurable tissue damage (8). Along with physical symptoms resulting from primary trauma, the heterogeneity in factors across individuals (e.g., pre-existing psychological problems, history of injury) can result in varying levels of immune system activation and modulation, changing the clinical and functional course of outcomes post-TBI (12). This can plausibly explain why symptomology and recovery trajectories can be different in people after TBI. For those with mTBI, including the small proportion of whom experience persistent post-concussion symptoms, the pathology is less clear, given the lack of overt contusions or haemorrhage (8). The use of different clinical definitions and indicators (13), the lack of sufficient systematic evaluation of the impact of TBIs across the lifespan (14, 15), the fact that people with milder injuries might also require dedicated treatment from healthcare professionals (16) and the absence of reliable prognostic biomarkers especially for milder injuries (17) further affect the understanding of TBI outcomes. Notwithstanding such complexities, a review to better understand how rehabilitation efforts such as exercise work to improve outcomes can provide a neurobiological rationale and advance the field.

CURRENT REHABILITATION FOR TBI

Existing rehabilitation for TBI focuses on interdisciplinary, goal-oriented approaches to reduce disability and improve functioning in people. Neurocognitive therapies have shown promise in identifying and treating attention and memory problems (18, 19). Visual scanning techniques can assist people with visuospatial deficits (20), while more targeted approaches such as physical therapy and vestibular therapy are often used to aid motor recovery, vertigo, or balance problems (21-23). While such individualised approaches are ideal, the heterogeneity in clinical and functional outcomes (24), taken together with the difficulty of reliably predicting prognosis (25) make the provision of comprehensive care challenging and resource intensive. Individualised approaches are expected to address specific clinical outcomes post-TBI, but the underlying mechanisms behind one or more treatment modalities have not been clearly established. Exploring the rationale behind why a mode of rehabilitation might be effective through a neurobiological lens can be useful to make informed and objective decisions for TBI patients.

Exercise has shown promise with TBI rehabilitation in recent years. Studies have demonstrated that exercise can increase cerebral growth factor levels (26-29), reduce apoptosis (30-32), promote neurogenesis, neuronal survival, and regeneration (33-36), reduce lesion size (37, 38) , modulate inflammatory responses (39), reduce astrocytosis (40, 41) , and improve cerebral blood flow (42, 43). Findings from animal studies have contributed towards exercise being considered as a potential non-pharmacological approach to aid recovery after TBI. Given that symptoms from mTBIs are less incapacitating, and there can be a heightened risk of mobility in severe TBI patients, exercise rehabilitation research has largely focused on people with milder injuries (i.e., mTBIs or concussion). Most of the exercise studies have also focused on sports-related concussions (44), as athletes are expected to be more conditioned and less susceptible to adverse risks from exercise post-injury.

The efficacy of exercise rehabilitation for TBI is mixed in the literature. A lack of controlled studies with large samples tempers any general conclusions that exercise could be an effective treatment option. Nonetheless, several reviews on exercise rehabilitation after mTBI have demonstrated moderate support of exercise over and above a natural course of recovery (45-51). Owing to the salutary effects of exercise on positive physical and psychological health outcomes, exercise is often put forward as a non-pharmacological treatment option that can address one or more symptoms across physical, psychological, and cognitive domains after TBI (i.e., 'pan-domain') (52). However, ambiguity remains around exercise variables that are optimal, and that can be replicated in larger studies. As with other TBI rehabilitative modalities, physiological mechanisms underpinning exercise and its effect on symptoms are also not well understood. It is expected that exercise immunology may hold some answers in relation to restoring some of the deficits arising from TBI pathophysiology. While existing exercise literature predominantly focuses on mTBI, the generic pathophysiology after a brain injury can be understood from injuries of all severities (8). If inferences about exercise immunology can be made from currently available exercise studies, it may set forth the further exploration of how exercise affects recovery from more severe TBIs in future.

PATHOPHYSIOLOGY OF TBI

TBI pathophysiology has been investigated using animal models to better understand neuronal death, blood-brain barrier breakdown, oxidative stress, the influence of neurobiological forces that disrupt cell architecture, as well as the role of neuroinflammation (8, 53). Neuroinflammation, which is a key characteristic of the immune system and of interest to this review, is a protective process in central nervous system (CNS) injury (e.g., TBI, stroke); but if this inflammation is too intense and continues for prolonged periods, it can be detrimental, and cause secondary injury after TBI (54). While there is yet to be conclusive evidence on direct causal effects, there is emerging literature that has associated the cascade of processes in secondary injury with cognitive and emotional symptoms post-TBI (8, 55). Secondary injury is also considered a risk factor for neurodegenerative diseases, and there is increasing focus on this in recent literature (8, 11). In TBI,

the primary injury occurs immediately after cerebral trauma resulting in contusion of brain tissue, damage to blood vessels, and axonal shearing, all leading to disruptions in brain function (56-58). Secondary injury can ensue through a complex cascade of neurobiological processes such as ischemic and hypoxic damage, cerebral oedema, elevated intracranial pressure, and infection (56-58). This cascade of neurological and metabolic activity is thought to be induced by an interplay of several factors, including glutamate excitotoxicity, perturbation of cellular calcium homeostasis, membrane depolarisation, mitochondrial dysfunction, inflammation, apoptosis, and diffuse axonal injury (59, 60).

Specific to mTBI, while the general cascade of events is similar to that observed in more severe TBI, increased attention is placed on less observable neurometabolic activity. Immediately after an mTBI, disruption of neuronal membranes, diffuse axonal injury and cellular responses are expected to demand significant energy. In efforts to restore homeostasis, cellular membranes shift into a state of overdrive; but disruptions to cerebral blood flow cause a metabolic crisis (55, 61). This "vulnerability" phase is proposed as a possible explanation for post-concussive vulnerability, persistent symptomology, as well as considerable risks for consecutive injuries (i.e., second impact syndrome).

POST-TBI NEUROINFLAMMATION

In research on post-TBI neuroinflammation, both animal and human studies provide evidence of both central and peripheral inflammatory responses (62-64). These responses include, but are not limited to, activation of resident microglia (e.g., central response) and recruitment of macrophages, dendritic cells, neutrophils, B and T lymphocytes, and meningeal inflammation (e.g., peripheral responses) (8, 57, 65-68). Animal studies have consistently demonstrated an upregulation of proteins such as glial fibrillary acidic protein (GFAP) and ionised calcium-binding adaptor molecule (Iba1), as well as increased levels of proinflammatory cytokines and chemokines after a TBI (66, 67, 69). Exacerbation of neuroinflammation in repeated injuries in quick succession has also been observed (70, 71), lending further support for the potential ramifications of excessive neuroinflammatory processes in such circumstances.

The clinical indicators of moderate/severe TBI can be very different to mTBI, but as with the general pathophysiology, the neuroinflammatory processes that set in after an injury are thought to be similar (8). More importantly, the prolonged state of proinflammatory processes can affect neurobiological recovery because of the influx of infiltrating cells from peripheral systems (72), which in turn influence resident microglia activity and lead to persistent clinical outcomes (73-76). mTBI studies primarily show central inflammatory responses and activation of resident immune cells; but there is no substantial evidence of infiltration of peripheral immune cells, and its role in persistent symptomology. Meningeal inflammation, microglial activation, and some monocyte/macrophage recruitment to the cerebrovasculature has been noted in mild injuries (8). The magnitude and duration of inflammatory responses can be expected to increase in proportion to the severity of the injury and persist for prolonged periods (54, 77-79) — especially in the presence of parenchymal bleeding, haemorrhage or structural injury. A recent study revealed traces of neuroinflammation up to 1 year after an mTBI (80). This suggests that inflammatory processes can persist (even if injuries are mild) and highlights the need for more research into better identification and prediction of such post-TBI neuroinflammatory processes for different injury severities.

To summarise, neuroinflammation in the brain is a key immune response to CNS injury. It involves the activation of resident glia (microglia and astrocytes) and the recruitment of immune cells in the peripheral system (68). In TBI, microglia play a critical role as the first line of defence, producing anti-inflammatory mediators, clearing cellular debris, and orchestrating neurorestorative mechanisms for recovery (81). However, microglia can be a double-edged sword, because excessive amounts for prolonged periods can produce proinflammatory mediators that can exacerbate brain damage, hinder restorative activity and functional recovery (57, 81). Figure 1 summarises the physiological and neuroinflammatory processes that are thought to contribute towards clinical consequences post-TBI.

Studies on neuroinflammation suggest that interventions targeted to modulate inflammation may potentially reduce secondary injury cascades and improve recovery (53, 57). Yet, the clinical efficacy of measures to regulate inflammation after TBI remains questionable, possibly due to the considerable variations in study protocols, individual differences in immune responses, and the heterogeneity of TBI (53, 65). For these reasons, and established evidence that exercise can alter pro-inflammatory processes and also elicit neuroprotective actions, it is a rehabilitation option worth exploring in greater detail (82-85).

Before proceeding to applications of such models to better understand the potential effects of exercise on post-TBI outcomes, it is important to acknowledge that any generalisations being made to humans through predominantly animal models in this area of work need to take a cautionary approach. The closed and open head models used in animal studies to simulate TBI cannot replicate the representation of the injury in humans because of the much higher pathogenetic heterogeneity (25, 53). Injury severity in animal studies is often classified according to how the injury was induced (e.g., fluid percussion injury vs controlled cortical impact injury), rather than by the severity of clinical indicators observed in humans (53). While efforts are made to ensure some uniformity in animal studies, TBI studies in humans need to consider pre-existing factors, concurrent stressors, and individual differences in physiological make-up, that can all affect immune responses (53). Finally, the neuroinflammatory and immune system responses described in this review are specific to further the understanding of exercise immunology after TBIs. For a more comprehensive review of immunological processes post-TBI, see Postolache et al. (53), McKee and Lukens (78) and Simons et al. (11).

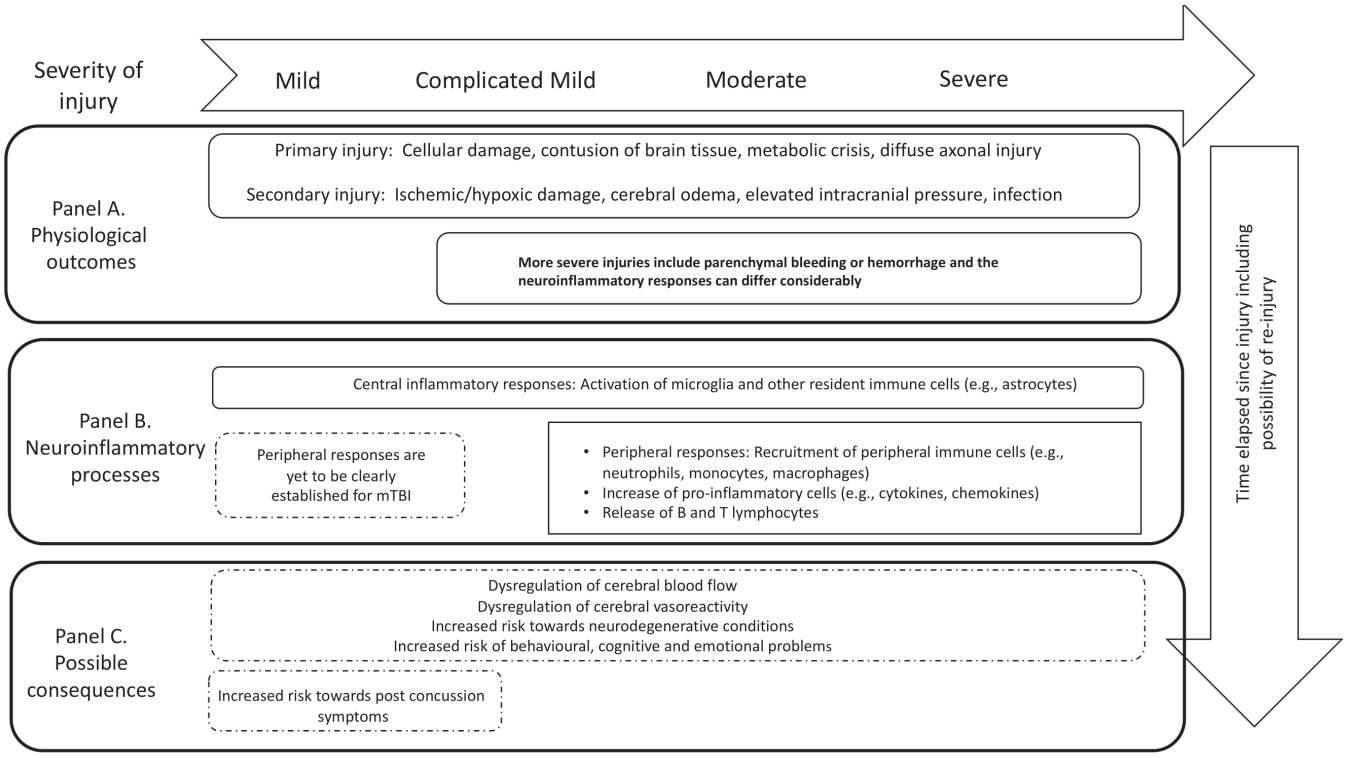

Figure 1. Summary of Physiological and Neuroinflammatory Processes Resulting in Possible Consequences After a TBI From Time of Injury

Note. Panel A briefly describes both the immediate primary and secondary injury outcomes that are part of the neurometabolic cascade of events post-TBI. Panel B outlines the key neuroinflammatory processes that take effect as part of the CNS immune response. Panel C describes some of the possible outcomes and risks that arise due to prolonged neuroinflammation processes. Dotted lines denote the need for further research to establish more conclusive evidence in these areas.

EXERCISE IMMUNOLOGY

Exercise immunology is a relatively new area of study that examines how the immune system responds to exercise (86-88). Progressing from research on acute changes in immune cell function, exercise immunology has now evolved to studying specific clinical outcomes and personalised approaches for various diseases (89). Animal studies on exercise immunology have contributed to the understanding that exercise (i) facilitates endogenous repair mechanisms (90), (ii) elicits neuroprotective actions evidenced in molecular system associated with control of cellular metabolism and synaptic plasticity (91, 92), and (iii) exerts prophylactic effects on acute hyperglycaemia and cerebral inflammatory response induced by TBI (93). Exercise can also alter systematic inflammatory states by reducing pro-inflammatory cytokines and neutrophils in the blood (85, 94, 95). These properties of exercise seem favourable to counteract some of the maladaptive processes after TBI. A closer examination of exercise studies on animals and humans post-TBI follows to draw any useful inferences about exercise immunology.

Animal Studies on Post-TBI exercise

Current animal models examining the effects of exercise have reported positive effects, such as increased levels of neurotrophic factors and increased anti-inflammatory responses. Crane and colleagues (96) compared the effects of voluntary exercise on TBI in rats with bilateral cortical contusions to the medial frontal cortex, or sham surgery. The authors reported greater neuroinflammatory responses in the animals that received the lesion through an increase in GFAB and Iba1 cells, but exercise did not lead to improved cognitive performance. Piao et al. (39) investigated time-dependent effects and the underlying mechanisms of exercise post-TBI using a cortical impact model involving mice. The mice that were exercised 5 weeks after the injury, as opposed to 1-week post-injury, showed significantly reduced memory impairments. Cognitive recovery was associated with attenuation of inflammatory pathways, activation of alternative inflammatory responses, and enhancement of neurogenesis. More importantly, the study concluded that the improved cognitive performance resulting from later exercise could have been due to more optimal balance of microglia expression and increased growth factor levels.

A protective aspect of exercise in the neuroinflammatory process is also a significant consideration. Mota et al. (97) investigated whether previous exercise (i.e., aerobic training) could act as a protective factor post-TBI using a fluid percussion induced (FPI) injury in rats. Rats that underwent 4 weeks of training were compared with sedentary rats after an FPI. The findings suggested that pre-injury exercise could exert protective effects by delaying or preventing secondary cascades post-TBI that led to long-term cell damage and neurobehavioral deficits. An important finding in this study was that regularly performed exercise appeared to have an anti-inflammatory effect, which supports other findings (98, 99). Similarly, de Castro et al. (93) induced neuroinflammation and oxidative stress in rats using an FPI. The study found that prior exercise modulated oxidative-inflammatory functions, putting forward the idea that exercise could be a preventive measure to minimise adverse consequences of TBI.

A series of rodent studies by Griesbach and colleagues (100, 101) further highlighted that voluntary exercise could upregulate brain derived neurotrophic factors (BDNF) and enhance recovery, but only after a period of delay post-injury. It was observed that the time window for resting before exercise could be beneficial increased with the severity of injury (102) and commencing exercising too early impacted growth factors levels and neuroplasticity negatively (103-105). These findings have important implications for exercise rehabilitation and immunology. The later administration of exercise, but not in the acute phase post-TBI, demonstrated benefits in some of these animal studies, suggesting that exercise may be optimal after allowing natural immune responses, including neuroinflammation, to take effect and resolve. Thus, commencing exercise too early post-TBI could disrupt the restorative immunity mechanisms such as cleaning of impacted tissue, protection of infections and increasing brain oxygen demand (95). The optimal time for commencing exercise in humans is yet to be determined, but these animal studies provide some groundwork to expand upon.

Human Studies on Post-TBI exercise

Over the past decade, there has been an increase in studies investigating the effects of exercise on post-TBI outcomes. As pointed out previously, most exercise studies has focused on athletes with mTBI/concussion, in view of the risk and ambulatory concerns for those with more severe TBIs. Early approaches to post-concussion rehabilitation involved prolonged rest or a "cocooning" model of care, emphasising sensory deprivation (106). The effectiveness of such sedentary methods was questioned and promising evidence from animal studies led to controlled studies on exercise in humans. Leddy and colleagues (107) were one of the first research groups to establish the safety of exercise rehabilitation in the post-acute stages after mTBI. Subsequent studies led to the establishment of graded sub-symptom threshold exercise, an aerobic exercise protocol that entailed progressive exercising to an intensity just below that which could trigger symptoms, demonstrating moderate benefits in symptom outcome (108-112). Derivatives of this hallmark feature have been adopted in various exercise studies in post-concussion rehabilitation research (113-117), but participants have been mostly athletes and adolescents, with a focus on post-intervention symptomology.

Most of the human exercise studies have not drawn direct relationships associating mechanisms of exercise immunology, but some parallels can be drawn between exercise immunology literature and post-concussion exercise rehabilitation. Leddy et al. (108) used an fMRI study to demonstrate restored patterns of hemodynamic response to pre-injury levels after an aerobic exercise intervention. Clausen and colleagues (118) pointed out that exercise intolerance after a concussion was attributed to abnormal cerebral blood flow (CBF) regulation as a result of altered sensitivity to carbon dioxide in the brain and/or circulatory system. The hemodynamic responses and restoration of cardiopulmonary processes observed in these studies can all be plausibly explained as a broader outcome of exercise immunology in effect (85, 89). While these studies did not specifically examine the anti-inflammatory effects of exercise, the outcomes could be indicative of potential by-products of the top-down anti-inflammatory mechanisms of exercise. More specifically, the energy crisis after a TBI, the metabolic demands and the neuroinflammatory responses that follow can potentially disrupt neurovascular coupling (i.e., glia, neurons and blood vessels acting as an integrated unit to distribute CBF), cerebral vasoreactivity (i.e., CBF responses to changes in carbon dioxide that is a vital homeostatic function) and cerebral autoregulation (i.e., regulatory mechanisms that counteract effects of arterial pressure fluctuations). The regulatory effects of exercise on such profound immune responses through hemodynamics (87), metabolic and cell function (88) have been noted in both exercise and post-concussion literature (119, 120).

The sub-symptom threshold exercise paradigm, distinctive to post-concussion rehabilitation, and the window of time to allow before exercise commencement in post-concussion literature are other areas that may also be linked with exercise immunology. There is evidence from exercise immunology literature, albeit contentious, that unaccustomed high-intensity exercise (i.e., practised by some elite athletes and the military) can be counterproductive to the immune system (86, 121). The current consensus is for exercising at a moderate intensity to be most conducive for optimal immunology processes to take effect (89). This appears to mirror the advice for post-concussion exercise rehabilitation, which recommends 80-90% of the sub-symptom threshold heart rate (HR) on a systematic assessment of exercise tolerance (i.e., a treadmill test) or 50-60% of the age-predicted maximum HR. Similarly, it is a common recommendation for sports-related concussion rehabilitation to allow an initial period of rest after a concussion before attempting any progressive return to activity. It is possible to draw a link here to previously observed findings in exercise immunology, whereby exercising too soon post-injury was found to impede the natural immune response. Interestingly, some post-concussion exercise studies have administered exercise in very acute stages (i.e., 2-5 days post injury) with encouraging findings (110, 122, 123). While it is difficult to interpret meaningful findings from these studies (given the small sample sizes), a possible explanation could be that mild injuries may not necessitate a prolonged period of natural immune responses as compared to more severe TBIs.

Implication of Findings

Taken together, despite the challenges in translating findings from animal models to humans, the promising findings from exercise studies have established some congruence. Both animal (124) and human studies (125) have demonstrated positive effects of aerobic exercise on cognitive and motor performance after TBI. Studies on TBI patients have also reported improvements in depression and anxiety after post-injury exercise (126, 127). As the exploration of exercise immunology specific to post-TBI rehabilitation can be considered to be in its nascent stages, any inferences drawn are speculative at this stage. Nevertheless, this review aims to integrate findings from both animal and human studies for the specific context of exercise rehabilitation for TBI. The findings have cast some light on the broad and specific mechanisms underlying exercise immunology, the role of prior exercise towards immune responses and the need to consider exercise variables for optimal effects. Figure 2 shows a summary of the possible effects exercise can exert on neurobiological mechanisms to regulate neuroinflammatory responses and potentially improve neurobiological recovery.

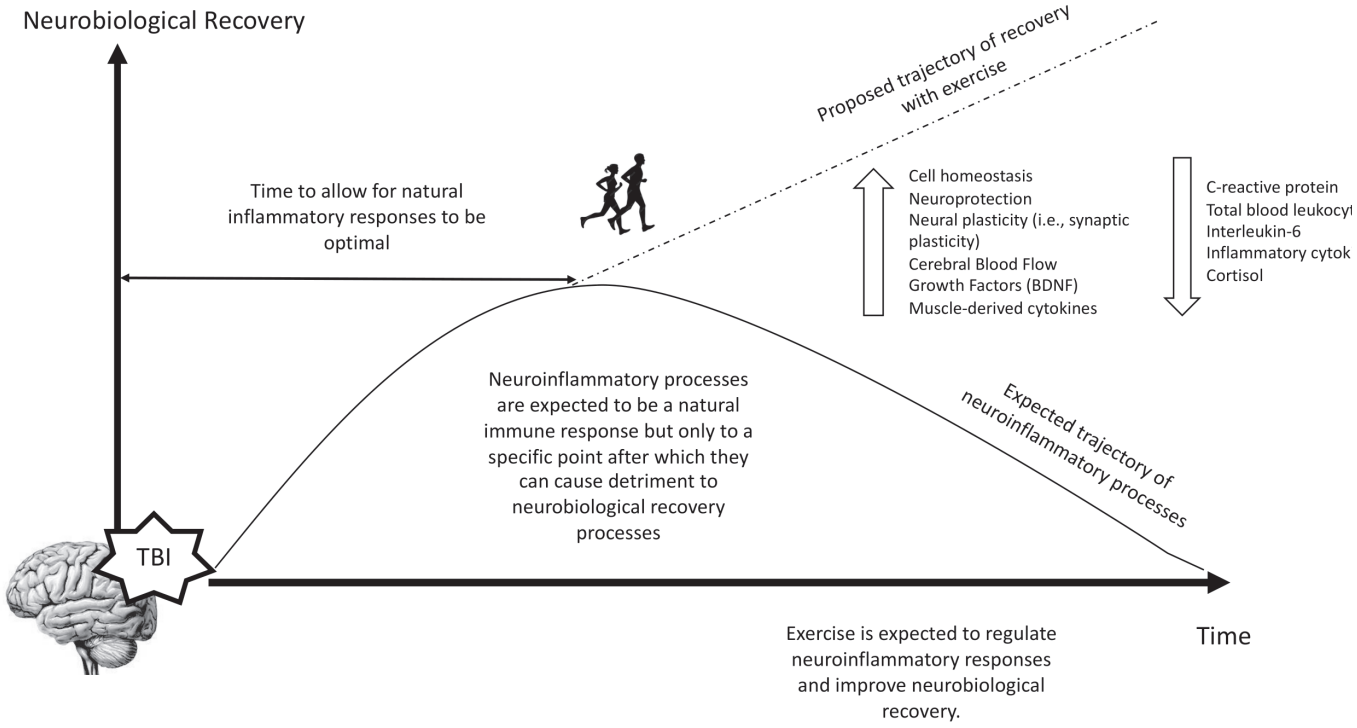

Figure 2. Summary of Proposed Effects of Exercise Modulating Neuroinflammatory Processes Post-TBI
Note. TBI: traumatic brain injury; The figure is a schematic of neuroinflammatory processes that are a key natural immune response to injury in the central nervous system (e.g., traumatic brain injury). The inverted-U curve denotes the dual role of the neuroinflammatory process, where it is beneficial to neurobiological recovery, but only up to a point after which pro-inflammatory processes can be detrimental for recovery. The dotted line indicates the proposed trajectory of recovery that can possibly be exerted through exercise. Exercise is expected to modulate neuroinflammation and facilitate recovery through a wide range of complex neurobiological processes. Some examples of these enhancing (i.e., upward arrow) and attenuating (i.e., downward arrow) processes are included under the dotted line.

FUTURE DIRECTIONS

Future exercise research for post-TBI rehabilitation can consider more specific and objective measures of exercise immunology. There is considerable interest in biomarkers in TBI studies, and exercise studies on TBI patients can examine the various anti- and pro-inflammatory processes resulting from various exercise protocols from start to end of an intervention program. This will significantly enhance TBI rehabilitation efforts to date, allow researchers to better understand immunological processes induced by exercise and perhaps identify exercise prescription guidelines for best effects. Including participants with a history of injury and other pre-existing issues in such studies can also help to clarify differences in the immune responses and the influence of exercise in the different profiles of people at risk of TBI. Notably, the use of biomarkers to identify inflammatory processes is not without problems. For example, some inflammatory cytokines are non-specific to central inflammatory responses, because peripheral injuries can also influence these markers. While cerebrospinal fluid levels may reveal biomarkers more specific to central inflammation, blood-brain barrier dysfunction after TBI can further confound any findings. A potential solution could be to identify both blood and cerebrospinal fluid biomarkers, especially in more severe injuries. For mild injuries, the use of MRI and near-infrared spectroscopy could be useful to determine a more indicative index (57).

More specific studies with larger, diverse samples are required to provide a clearer understanding of how the immune response induced by exercise can be different across demographics such as age and gender. Older age is considered to be a risk factor for TBI (128), and trauma-induced inflammatory processes have shown to increase with age (129, 130). A better understanding of such "immunosenescence" is particularly important, given the increased incidence of TBIs in older people. Exploring how exercise immunology affects this population can help to determine if the benefits of exercise can outweigh any risks for more vulnerable demographics. While the immune response may not be as reactive in older age, further research in this population can help to better understand if there are wider effects of exercise that extend beyond the expected capabilities to modulate inflammatory processes. Gender differences in immune responses also warrant further investigation, considering evidence of neuroprotection from female hormones (131). Most of the animal models studying inflammatory responses post-TBI have been conducted in male animals; how females respond to TBI is still relatively unknown (57). This is particularly important, given that males have an elevated risk of TBI, whereas females have an increased risk of prolonged symptoms after mTBI (7, 132).

The literature on exercise immunology and exercise post-TBI, respectively, has focused on cardiorespiratory exercise (86), and there is a lack of research on other exercise paradigms such as resistance training, or combined aerobic and resistance training. Future studies exploring different exercise paradigms and the potential effects of exercise immunology can be useful to offer more variety in TBI rehabilitation options and could reveal new models of care. There are emerging findings highlighting the potential for resistance training to induce neural adaptations beneficial for synaptic plasticity (133), suggesting that such exercises could be further ex-

plored for those with more severe disabilities after TBI. Resistance training programs that include seated exercise could also be considered to determine if this form of exercise can benefit people with post-TBI ambulatory or vestibular issues, and if such benefits correlate with immunological factors.

While this review emphasised neuroinflammation and the potential anti-inflammatory properties of exercise on post-TBI outcomes, it is important to acknowledge that the benefits of exercise can extend to reduction of apoptosis, increased neurogenesis, enhanced neuroplasticity and increased cerebral blood flow. It is difficult to decouple just the anti-inflammatory characteristics of exercise, as this can be impossible. Any benefits observed could be the outcome of a cascade of neurobiological activity. Additionally, psychological benefits from exercise such as mood improvements can also be a result of complex neurotransmission and hormonal activity, which cannot be entirely explained from an immunological perspective. Nevertheless, the promise of exercise still holds for its ability to potentially influence post-TBI symptoms across multiple domains, and possibly from a profound system-wide process.

CONCLUSIONS

TBI is complex and can affect people from all walks of life. A multi-factorial approach to understand and develop effective rehabilitation is necessary. Exercise has shown promise over recent years as a pan-domain option to alleviate multiple symptoms across physical and psychological domains. However, specific mechanisms underlying the potential benefits of exercise are not well understood. Both animal and human studies on exercise immunology are useful to cast some light on the anti-inflammatory role and the neuroprotective benefits offered by exercise. While post-TBI exercise studies have yet to explore exercise immunology in detail, current findings from post-concussion exercise rehabilitation studies allow some parallels to be drawn. Speculation that exercise immunology is at work to alleviate post-TBI symptoms should serve as a useful springboard for more objective studies in this area.

Author contributions:

The concept for the article was developed by KSJ and KS. The first author led the drafting of all sections. The second author provided advice on the drafts. Both authors approved the final version of the article.

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