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The role of the microbiota–gut–brain axis in long-term neurodegenerative processes following traumatic brain injury

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Abstract

Traumatic brain injury (TBI) can be a devastating and debilitating disease to endure. Due to improvements in clinical practice, declining mortality rates have led to research into the long-term consequences of TBI. For example, the incidence and severity of TBI have been associated with an increased susceptibility of developing neurodegenerative disorders, such as Parkinson's or Alzheimer's disease. However, the mechanisms linking this alarming association are yet to be fully understood. Recently, there has been a groundswell of evidence implicating the microbiota–gut–brain axis in the pathogenesis of these diseases. Interestingly, survivors of TBI often report gastrointestinal complaints and animal studies have demonstrated gastrointestinal dysfunction and dysbiosis following injury. Autonomic dysregulation and chronic inflammation appear to be the main driver of these pathologies. Consequently, this review will explore the potential role of the microbiota–gut–brain axis in the development of neurodegenerative diseases following TBI.

KEYWORDS

inflammation, microbiota–gut–brain axis, neurodegeneration, Parkinson's disease, traumatic brain injury

1 | INTRODUCTION

As one of the most prevalent types of injury affecting modern society, traumatic brain injury (TBI) continues to burden large portions of the community and economy. Despite significant improvements in preventative, neurosurgical, and rehabilitative interventions, survivors experience changes that affect them for the remainder of their life (Corrigan & Hammond, 2013). Such changes range from physical health issues such as seizures and somatic

Abbreviations: AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; ATP, adenosine triphosphate; BBB, blood–brain barrier; CNS, central nervous system; CTE, chronic traumatic encephalopathy; EGC, enteric glial cells; ENS, enteric nervous system; GFAP, glial acidic fibrillary protein; GI, gastrointestinal; HPA, hypothalamic–pituitary axis; IL, interleukin; LPS, lipopolysaccharides; MGBA, microbiome–gut–brain axis; MND, motor neuron disease; MS, multiple sclerosis; NF-κB, nuclear factor kappa B; PD, Parkinson's disease; ROS, reactive oxygen species; SCFA, short chain fatty acids; sSIRS, systemic inflammatory response syndrome; TBI, traumatic brain injury; TLR, toll-like receptor; TNFα, tumour necrosis factor-α; αSyn, alpha-synuclein.

complaints to cognitive impairment, behavioural changes, and other mental health issues (Jagnoor & Cameron, 2014). Although TBI was once considered an acute injury, there is now wider acknowledgement that it should be re-defined as a chronic, neurodegenerative disease (Das et al., 2012; Masel & DeWitt, 2010). An abundance of literature has linked TBI to subsequent development of neurological disorders such as chronic traumatic encephalopathy (CTE), Alzheimer's disease (AD), Parkinson's disease (PD), motor neuron disease (MND), and psychiatric disorders such as depression and anxiety (Crane et al., 2016; Faden & Loane, 2015; Perry et al., 2016; Walker & Tesco, 2013). However, the mechanisms by which these neurodegenerative diseases could arise after TBI remain to be elucidated.

An emerging direction of research has started to uncover a potential association between gastrointestinal (GI) system changes and neurodegeneration. GI dysfunction and dysbiosis is often reported decades prior to diagnosis of PD and AD and may be implicated in other neurodegenerative diseases such as MND and multiple sclerosis (MS) (Kong et al., 2018; Ochoa-Repáraz et al., 2017; Zhang et al., 2017). Alterations in gut motility and the gut microbiome following TBI have been reported in animal models and patients (Hang et al., 2003; Royes & Gomez-Pinilla, 2019; Urban et al., 2020), with evidence to suggest that this could deleteriously feed back to the brain via the microbiota–gut–brain axis (MGBA). Therefore, this review will discuss the proposed mechanisms of TBI-induced GI changes and propose how such changes could be a trigger for sporadic cases of neurodegenerative disease following injury.

2 | TBI CONSEQUENCES WITHIN THE CNS AND BEYOND

The pathophysiological events following TBI are an amalgamation of highly complex processes. The initial mechanical force that induces trauma results in a closed head or penetrating TBI, both result in laceration of brain tissues primarily causing focal damages, intracranial haemorrhage, cerebral oedema, and ischaemia. The primary injury results in shearing, tearing, or stretching forces that damage the brain parenchyma (Loane & Faden, 2011). Diffuse axonal injury is a common pathology reported in all severities of TBI and has been associated with persistent cognitive impairment due to widespread damage across brain regions (Blumbergs et al., 1994; Poudel et al., 2020). Furthermore, it has been highlighted that damage to the subcortical white matter or the thalamic relay nuclei with minimal cortical damage often results in very poor patient outcomes (Adams et al., 2000). The secondary injury that follows includes biochemical, metabolic, and cellular changes that occur in response to the primary event (Loane & Faden, 2011; Werner & Engelhard, 2007). In addition, long-term secondary changes following TBI have far-reaching consequences outside the central nervous system (CNS) (Corrigan & Hammond, 2013; Das et al., 2012; Stocchetti & Zanier, 2016).

2.1 | TBI pathophysiology in the CNS

Excitotoxicity is a prominent event initiated in the acute stages of TBI, where there is excessive release of excitotoxic amino acids into the extracellular space and a toxic influx of ions such as sodium and calcium (Chiu, Anderton, Cross, et al., 2017; Chiu, Anderton, Knuckey, & Meloni, 2017). High intracellular calcium is detrimental to cellular bioenergetics, particularly when there is excessive uptake by mitochondria. Consequently, generation of reactive oxygen species (ROS) is increased, and ATP production is depleted, resulting in the loss of the mitochondrial membrane potential and increase in mitochondrial permeability (Brustovetsky et al., 2003; Dubinsky & Levi, 1998; MacDougall et al., 2019). The resultant oxidative stress from dysfunctional mitochondria can further negatively influence the inflammatory cascade by enhancing neutrophil infiltration and positively feeding back to ROS levels (Lozano et al., 2015; Vorobjeva et al., 2017), thus exacerbating the inflammatory response. Furthermore, ROS is implicated in altering BBB permeability to allow free passage of inflammatory molecules into and out of the brain (Das et al., 2012; Pun et al., 2009), complicating both central and peripheral inflammation.

These biochemical changes can contribute to further structural changes induced by the initial damaging mechanical force. Further, TBI can induce acute and long-term accumulation of protein aggregates such as the amyloid precursor protein (APP) and its cleavage products, neurofilament proteins, tau, and synuclein proteins (Edwards et al., 2020; Hawkins et al., 2013; Marmarou et al., 2005; Washington et al., 2014). The overexpression and accumulation of APP occur in swollen axons that undergo lysis and subsequent expulsion of Aβ and toxic tau proteins into the parenchyma to aggregate and cause plaque formation (Chen et al., 2004; Edwards et al., 2020). The presence of APP, Aβ, and toxic tau proteins causes molecular and cellular abnormalities, perturbing the overall environment of the CNS (Ikonomovic et al., 2017). This disrupts axonal transport, leading to its fracture, and subsequent Wallerian degeneration (Hill et al., 2016). Such changes in white matter

integrity are associated with reductions in volume of subcortical brain structures such as the hippocampus and amygdala (Zagorchev et al., 2016), thus negatively affecting patient outcome, particularly with earlier age of injury onset (Kinder et al., 2019; Tremblay et al., 2019).

2.2 | Peripheral effects of TBI

Some extracranial complications are believed to arise from damage to brain structures that communicate with peripheral organs. This leads to autonomic system dysfunction, to which the hypothalamic–pituitary–adrenal (HPA) axis is a crucial contributor (Catania et al., 2009; Khalid et al., 2019). The significant release of catecholamines from the adrenal medulla after sympathetic activation in response to a TBI (Tümer et al., 2013) can directly impact peripheral organs such as the lungs and heart, leading to neurogenic pulmonary oedema and cardiac dysfunction (Bahloul et al., 2006; Davison et al., 2012; Lu et al., 2017). The resulting vagal hyperactivity can also leave patients susceptible to nosocomial lung infections such as pneumonia (Hall et al., 2014; Hui et al., 2013), which is further exacerbated by pro-inflammatory molecules released from the compromised BBB (Weber et al., 2015). Circulating pro-inflammatory proteins from the brain can also elicit a cytotoxic response in the kidney (Civiletti et al., 2019) and liver (Schmidt et al., 2005), making them further susceptible to the effects of autonomic dysregulation (Nizamutdinov et al., 2017; Nongnuch et al., 2014). Consequently, TBI patients often develop comorbidities such as chronic pulmonary and kidney diseases, congestive heart failure, and diabetes (Lu et al., 2017), in addition to disorders related to the musculoskeletal, genitourinary, and gastrointestinal systems.

Patient immobilisation after TBI is a factor in skeletal muscular atrophy and reduced bone mineral density (McDonald et al., 2020). However, there are other contributors that have not been fully elucidated. Although TBI-induced mechanisms for skeletal muscular atrophy are not yet clear (Shahidi et al., 2018), peripheral inflammation may play a role in bone destruction. Increased levels of mediators such as interleukin (IL)-17, tumour necrosis factor-α (TNFα) (Ciucci et al., 2015), and ROS (Garrett et al., 1990) are known to promote bone resorption. HPA axis dysfunction further exacerbates this by the reduction of growth factors such as insulin-like growth factor-1 (Yu et al., 2014). Patient immobilisation is also thought to partly contribute to sexual dysfunction and incontinence. Furthermore, damage to the HPA axis can lead to hypogonadism, which negatively impacts long-term quality of life for 10–17% of the TBI population (Wagner et al., 2012). Hypogonadism has also been implicated in reduced muscle mass, strength, and osteoporosis (Agha & Thompson, 2005; Masel & DeWitt, 2010). Faecal and urinary incontinence is another commonly reported condition that is associated with injury to specific brain areas and poorer functional outcomes (Campagnolo et al., 1994; Giannantoni et al., 2011) and persists for some, even at 1-year post TBI (Foxx-Orenstein et al., 2003; Safaz et al., 2008). Similarly, decreased intestinal smooth muscle contractility, delayed gastrointestinal (GI) transit, faecal constipation, and difficulties with bladder emptying are also common (Giannantoni et al., 2011; Lim et al., 2012). Swallowing disorders occur in 61% of severely brain-injured patients (Mackay et al., 1999) and can persist for 8 years post-injury in paediatric cases (Morgan et al., 2010). Thus, the GI tract likely plays a key role in the long-lasting consequences of TBI that impact patient health and quality of life.

3 | THE GI TRACT AND GUT MICROBIOME

The human GI tract is inhabited by commensal microorganisms including bacteria, archaea, viruses, and other microorganisms that form part of an endosymbiotic relationship with the human body (Eloe-Fadrosh & Rasko, 2013). The human gut microbiome has coevolved within hosts and is extensively involved in digestion, maintaining function and integrity of the GI tract, detoxification, modulating inflammation, and immune defence (Grenham et al., 2011; Jandhyala et al., 2015; Valdes et al., 2018). Furthermore, these microorganisms can have direct effects on hormones, metabolites, short chain fatty acids (SCFAs), and neurotransmitter concentrations (Dave et al., 2012). The approximately 10^{13}–10^{14} microorganisms in a healthy gut primarily consist of the phyla *Firmicutes* and *Bacteroidetes*, with lower abundance of *Proteobacteria*, *Actinobacteria*, *Fusobacteria*, and *Verrucomicrobia* (Eckburg et al., 2005). The gut microbiome exhibits slight inter-individual diversity; however, each human contains a very similar consortium of microorganisms, often with varying relative abundance (Arumugam et al., 2011). Further, the composition of an individual's gut microbiome is dynamic but generally stable, except in ageing or a state of disease.

There appear to be stark differences in microbiota composition between infants, adults, and the elderly (Mariat et al., 2009), shifting at critical points that coincide with neurodevelopment and behaviour (Borre et al., 2014). The composition of microorganisms is less diverse during infancy and old age and is most diverse during adolescence and adulthood (Biagi et al., 2010;

Borre et al., 2014). This is influenced by nutrients present in the gut as a result of diet and lifestyle (Claesson et al., 2012; Odamaki et al., 2016). However, throughout adolescence and adulthood is also when individuals are most vulnerable to external stressors that have the ability to negatively impact the microbiota composition and be deleterious to health over time (Boehme et al., 2019; Borre et al., 2014). Medications such as non-steroidal anti-inflammatory drugs can also alter gut microbiome composition (Mäkivuokko et al., 2010) due to its adverse effect on the GI environment. However, ingestion of supplements such as probiotics and prebiotics can beneficially modify the environment to improve overall gut health (Björklund et al., 2012). Furthermore, it has been found that enrichment of potentially beneficial bacteria from *Ruminococcaceae*, *Akkermansia*, and *Christensenellaceae* promotes homeostasis, maintenance, and diversity of the gut microbiome, ultimately increasing longevity (Biagi et al., 2016; Kong et al., 2016). Thus, a balanced and diverse gut microbiome staves off harmful effects on overall health from dysbiosis (Bui & de Vos, 2021) by ensuring host metabolism, neurological development, immune defence, and energy homeostasis.

3.1 | The microbiota–gut–brain axis

The microbiota–gut–brain axis (MGBA) is a complex bidirectional communication system that integrates endocrine, immunological, and direct or indirect neural signalling pathways between the CNS, ENS, and the gut microbiota (Margolis et al., 2021). This axis can affect an organism at multiple levels, from modulating behaviour and influencing how and with whom, humans interact (Montiel-Castro et al., 2013), to regulating mood, cognition, pain, obesity, cancer, and inflammatory and autoimmune diseases (Burokas et al., 2015; Margolis et al., 2021; Moughnyeh et al., 2021; Ting-Ye et al., 2022). Thus, there is growing interest into the local and systemic effects this communication pathway has on host health and burden of disease.

It has been highlighted that both the HPA axis and inflammation appear to play a key role in diseases and disorders linked to the MGBA. HPA axis dysregulation is associated with altered gut microbiome composition, affecting the neuroendocrine system and manifesting as anxiety-like behaviour (Huo et al., 2017). Conversely, chronic exposure to stress can also activate the HPA axis, altering gut microbiota composition, and increasing peripheral inflammation (Moughnyeh et al., 2021). There is also evidence that neuroinflammation and neuroendocrine dysregulation may be involved in the pathogenesis of autism spectrum disorder, where patients present concomitantly with GI symptoms (Petra et al., 2015). This suggests that a dysbiotic microbiome increases the potential for microorganisms to disrupt the complex interactions directly or indirectly between the brain and the GI tract required for normal physiological function. Further understanding of the complex relationship between the gut microbiota, GI tract, and brain is required to elucidate the possibility of the MGBA as a therapeutic target to improve overall host health (Ting-Ye et al., 2022).

4 | TBI DISRUPTS MICROBIOTA–GUT–BRAIN HOMEOSTASIS

The recent accumulation of research highlighting the relationship between the gut microbiome and the brain has implicated that the MGBA plays a significant role in the development and progression of neurodegenerative diseases. GI dysfunction and associated microbial dysbiosis are thought to precede diagnosis of PD and AD during the prodromal and MCI stages respectively, thus presenting an opportunity for early intervention (Cersosimo et al., 2013; Li et al., 2019; Pietrucci et al., 2019). It has also long been noted that such symptoms are also reported in those with a history of TBI, though its significance and underlying mechanisms are unknown. Given the increasing recognition of TBI as a chronic disease and risk factor for the later development of neurodegenerative disease, GI dysfunction following TBI is being revisited to investigate its impact on patient outcomes. Studies in animals and humans have reported intestinal barrier permeability, chronic enteric inflammation, and gut dysbiosis after TBI which could contribute to and further exacerbate the injury profile.

4.1 | TBI induces intestinal barrier dysfunction

Blood–brain barrier disruption is a widely reported consequence of TBI. The structural integrity of the basement membranes is compromised and tight junction proteins between endothelial cells are lost, resulting in increased permeability (Chodobski et al., 2011). Interestingly, similar observations are found on the epithelial lining of the GI tract. This leads to intestinal barrier dysfunction which has been correlated with the probability of death in a *Drosophila* model of TBI, mediated by adrenergic signalling (Scharenbrock et al., 2021). Increased intestinal permeability after TBI is associated with alterations in the mucosal structure of the rodent gut such as decreased villous height, crypt depth, and surface area, epithelial cell death, and loss of tight-junction proteins such as

zonulin-1 and occludin (Bansal et al., 2009; Ma et al., 2017), creating a "leaky gut." These alterations are proposed to be due to multiple factors, including release of stress hormones from the HPA axis (Nicholson et al., 2019) and activation of inflammatory response molecules in the brain and gut (Bansal et al., 2009). However, more recent studies have not found similar decreases in tight-junction proteins, despite inducing intestinal inflammation (You et al., 2021).

4.2 | TBI induces enteric inflammation

Further, increasing awareness of the chronic and systemic nature of the inflammatory response following TBI is pivotal (Faden et al., 2021), particularly since TBI patients are at an increased risk of sepsis and fatal systemic inflammatory response syndrome (SIRS) (Marik & Flemmer, 2012). The neuroinflammatory response to TBI is the result of complex interactions between components from both the CNS and periphery; however, microglia are the principal cells involved. Once activated, these cells release cytokines, act as antigen-presenting cells, and remove debris. Although initially beneficial, a prolonged response can be deleterious (Morganti-Kossmann et al., 2002), contributing to BBB permeability and free passage of inflammatory response molecules between the systemic circulation and brain.

Enteric glial cells (EGC) are a major component of the ENS that regulate multiple GI functions, including inflammatory processes (Ochoa-Cortes et al., 2015). Much like their astrocytic counterparts in the brain, EGCs have demonstrated glial acidic fibrillary protein (GFAP)-reactivity in response to TBI, potentially contributing to the long-term sequelae in both the brain and gut (Hanscom et al., 2021; Ma et al., 2017). Pro-inflammatory pathways are also induced in the gut following TBI in animal models. The increase of Myd88 (Ling et al., 2013) in the gut is rapid and prolonged, whereas CD40 peaks within 12 h after injury (Hu et al., 2013). Both go on to activate NF-κB (Hu et al., 2013; Ling et al., 2013) via toll-like receptor signalling pathways (Shi et al., 2019) and thus mediates the intestinal inflammatory response with TNFα, IL-6, and IL-1β (Chen et al., 2008; Jin et al., 2009). Consequently, apoptosis of intestinal epithelial cells (Bansal et al., 2009; Chen et al., 2008; Hang et al., 2005) compromises barrier integrity and contributes to intestinal dysmotility (Royes & Gomez-Pinilla, 2019). Intestinal barrier dysfunction then allows these inflammatory response molecules to permeate, along with bacteria and their endotoxins (Mazarati et al., 2021), to elicit a systemic inflammatory response and peripherally influence the CNS (Sundman et al., 2017). The exacerbated inflammatory response can then lead to delayed SIRS and multiple organ dysfunction, increasing morbidity and mortality after TBI (Ma et al., 2017; Marik & Flemmer, 2012).

4.3 | TBI induces gut dysbiosis

Dysbiosis refers to the potential of the normal microbial balance between beneficial and pathogenic bacteria to become disrupted, resulting in an altered gut bacterial composition. A dysbiotic gut microbiome has potential for microorganisms to disrupt the complex interactions directly or indirectly between the brain and gut required for normal physiological function (Raval et al., 2020). Gut dysbiosis has been implicated in inflammatory diseases of the GI system, metabolic disorders, and neuropsychiatric conditions (Margolis et al., 2021; Torres-Fuentes et al., 2017). With increasing interest in its role in neurodegenerative disease development, TBI-induced gut dysbiosis is a phenomenon that has only very recently been explored. As such, not only are experimental data limited in number, TBI models and severity vary greatly between studies, making it difficult to draw generalisations (Table 1).

Faecal samples from moderately head-injured rodents found reduced abundance from beneficial anaerobic groups including species within the *Bacteroidetes* and *Firmicutes* phyla compared with uninjured controls and increases in facultative aerobes of the *Enterobacteriaceae* family (Nicholson et al., 2019; Waligora-Dupriet et al., 2018). Neurological deficits were further correlated with the *Bacteroidetes* family, *Porphyromonadaceae* in a milder model of injury (Houlden et al., 2016). In other studies, varying magnitudes of reduction in abundance was also found in species and/or genera of the *Firmicutes* phylum (Houlden et al., 2016; Nicholson et al., 2019; Treangen et al., 2018; Waligora-Dupriet et al., 2018). However, there does not appear to be a consensus between these studies below the phylum level on whether abundance of beneficial species are generally decreased after TBI. Furthermore, *Peptococcaceae* and *Eubacterium* genera of the *Firmicutes* phylum were also increased; however, their roles in determining TBI outcome were unclear (Houlden et al., 2016; Treangen et al., 2018). Interestingly, a clinical study in NCAA Football players with found a similar pattern of change in *Lachnospiraceae bacterium* A2 and *Lactobacillus johnsonii* after concussion (Soriano et al., 2022) as the preclinical study from Yanckello et al. (2022) modelling a milder injury. Conversely, a clinical study in patients with chronic moderate–severe TBI did not find similar microbiota changes (Urban et al., 2020) to those in more

TABLE 1 Summary of experimental studies on microbiome changes after injury to the central nervous system (CNS)

CNS injury	Animal model	Time-point sampled post-injury	Microbiome change	Reference
TBI – mild	CHI, mouse	72 h	Shifts in *Bacteroidetes*, the *Bacteroidetes* family *Porphyromonadaceae*, *Firmicutes*, and *α-Proteobacteria* correlated with neurological deficits	(Houlden et al., 2016)
	CHI (focal), mouse	24 h, 1.5 months	**24 h** + *Firmicutes bacterium* − *Akkermansia muciniphila* **24 h–1.5 months** + *Lachnospiraceae* family spp. − *Lactobacillus johnsonii*	(Yanckello et al., 2022)
TBI – moderate	FPI, rat	4 days	No change in overall bacterial load or *Clostridium* cluster IV + *E. coli* − *Clostridium* cluster XIVab, *Bacteroides/Prevotella* group, *Lactobacillus/Leuconostoc* group, *Enterococcus*, *Bifidobacterium*	(Waligora-Dupriet et al., 2018)
	CCI, rat	Prior to, then 2 h, and 1, 3, and 7 days	Larger brain lesions correlated with: + *Proteobacteria* − *Firmicutes* (*Peptococcaceae* and *Eubacterium* genera) Reduced alpha-diversity	(Nicholson et al., 2019)
TBI – moderate-severe	CCI, rat	0, 3, 30, and 60 days	− *Firmicutes* phyla, but no effect on *Bacteroidetes* or *Proteobacteria* − *Clostridia* class at 3 days only, no effect on *Bacilli, Erysipelotrichia* classes − *Clostridiales* order Microbiome shifts due to TBI were less robust after 3 days	(Frankot et al., 2022)
TBI – severe	CCI, mouse	24-h pre- and post-TBI	+ *Eubacterium sulci* and *Marvinbryantia formatexigens* − *Lactobacillus gasseri*, *Ruminococcus flavefaciens*, and *Eubacterium ventriosum*	(Treangen et al., 2018)
	Feeney weight-drop, rat	7 days	+ *Rikenellaceae* RC9 gut-group spp., *Lactobacillus*, *Turicibacter*, and *Helicobacter* spp., *Prevotellaceae* family (*Prevotella*) − *Agathobacter* spp., *Faecalibacterium* and *Paraprevotella* genera, *Eubacterium coprostanoligenes* Reduced alpha-diversity	(Taraskina et al., 2022)

(Continues)

TABLE 1 (Continued)

CNS injury	Animal model	Time-point sampled post-injury	Microbiome change	Reference
SCI – moderate-severe	Weight-drop impact at T10, rat	8 weeks	At the species level: + *Lactobacillus intestinalis*, *Clostridium disporicum*, and *Bifidobacterium choerinum* − *Clostridium saccharogumia*	(O'Connor et al., 2018)
SCI – severe	Partial laminectomy at T4 and T10, mouse	21 days	+ *Actinobacteria* phylum in T4 and T10 groups − *Firmicutes* phylum in T10 group, *Lactobacillus* genus (*L. johnsonii*) and *Turicibacter* in both T4 and T10 groups	(Du et al., 2021)
Stroke	tMCAO, mouse	24 h	+ *Akkermansia muciniphila*, *Parabacteriodes goldsteinii*, *Alistipes shahii*, *Anaerotruncus colihominis, Roseburia intestinalis*, *Bacteroides* genus	(Stanley et al., 2018)
	pMCAO, porcine	−1, 1, 3, and 5 days	**Phylum level** + *Proteobacteria*, *Actinobacteria* at 3 days but returned to pre-stroke level by 5 days, *Bacteroidetes* at 3 d and maintained to 5 days − *Firmicutes* at 3 days but returned to pre-stroke level by 5 days **Family level** + *Enterobacteriaceae*, *Erysipelotrichaceae*, *Prevotellaceae*, *Coriobacteriaceae*, *Desulfovibrionaceae, Peptostreptococcaceae*, and *Enterococcaceae* up to 3 days, decreased to pre-stroke levels by 5 days − *Lactobacillaceae* family at 3 days but returned to pre-stroke level by 5 days. **Genus level** + *Prevotella, Collinsella* up to 3 days but returned to pre-stoke levels by 5 days, *Parabacteroides* increased at 1 day after but fluctuated after. − *Lactobacillus* up to 3 days but returned to pre-stoke levels by day 5	(Jeon et al., 2020)

Abbreviations: +, increased abundance; −, decreased abundance; CCI, controlled cortical impact; CHI, closed head injury; FPI, fluid percussion injury; pMCAO, permanent middle cerebral artery occlusion; tMCAO, transient middle cerebral artery occlusion.

severe TBI animal models (Frankot et al., 2022; Treangen et al., 2018) except for the *Prevotellaceae* family (Taraskina et al., 2022).

There is an understanding that dysbiosis impairs recovery in spinal cord injury; however, studies that focus on the microbiota are similarly limited as TBI. Although

there has been some consensus on increased *Actinobacteria* species abundance, changes in *Lactobacillus* species are less clear (Du et al., 2021; O'Connor et al., 2018). In a porcine model of stroke, an increase in the *Actinobacteria* phylum was also observed (Jeon et al., 2020). However, this was no longer evident after 3 days post-injury. Furthermore, this study also found that microbiome changes tended to peak at 3 days but return to pre-injury levels by day 5 (Jeon et al., 2020), with the exception of *Parabacteroides* at 24 h post-injury (Jeon et al., 2020; Stanley et al., 2018) and fluctuating thereafter. The dynamic nature of the microbiome within the acute timeframe was also evident in a moderate–severe TBI model in rats (Frankot et al., 2022), persisting into sub-acute and chronic phases post-injury (Yanckello et al., 2022).

The mechanisms for how TBI drives dysbiosis are even less understood. Moderate TBI in rats has been shown to negatively impact GI motility in the ileum and, to a lesser extent, jejunum (Olsen et al., 2013), potentially via damage to the HPA axis (Yuen et al., 2020). Impaired GI motility coincided with an increase in inflammatory cytokines NF-κB, IL-1α, and IL-1β, though there was no substantial mucosal damage (Olsen et al., 2013). The inflammatory tissue environment within the gut could then drive gut dysbiosis by promoting aerobic respiration via the presence of ROS (Zeng et al., 2017), thus favouring facultative aerobes, which is seemingly evident in moderate TBI (Nicholson et al., 2019; Waligora-Dupriet et al., 2018). These findings highlight the complex relationship between gut microbiota and multiple disease outcomes, further revealing the notion that microbial populations can influence post-injury mediated neuro-pathophysiology and functional impairment through dysbiosis-dependent mechanisms.

5 | MICROBIOTA–GUT–BRAIN HOMEOSTASIS DISRUPTION IS IMPLICATED IN NEURODEGENERATIVE DISEASE DEVELOPMENT

Dysregulation in the MGBA stems from gut dysbiosis, enteric inflammation, and intestinal barrier dysfunction, resulting in altered communication between the gut and the brain. Given the role of the microbiota in maintaining homeostasis and wellbeing, MGBA dysregulation has been implicated in a range of GI, metabolic, developmental, and psychiatric disorders (Grenham et al., 2011). More recently, an emerging number of provocative studies have implicated MGBA homeostasis disruptions in the pathogenesis of neurodegenerative diseases such as PD (see Cheng et al., 2022, and Konjevod et al., 2021, for tables summarising MGBA and associated metabolite changes implicated in neurodegenerative diseases). Having long been defined by the cardinal motor symptoms related to asymmetric bradykinesia, resting tremor, rigidity, and postural instability, the multi-systemic nature of PD is gaining greater recognition.

A key feature of PD is alpha-synuclein (αSyn) aggregation, particularly within the substantia nigra, which has been implicated in the progressive degeneration and eventual death of dopaminergic neurons (Desplats et al., 2009; Periquet et al., 2007; Xu et al., 2002). Accumulation of the misfolded αSyn is a major component in toxic protein aggregates called Lewy bodies (Baba et al., 1998; Spillantini et al., 1997). The neurodegenerative accumulation of Lewy bodies develops over several years and has been hypothesised to originate in the periphery, with evidence of retrograde axonal and trans neuronal propagation to the CNS (Braak et al., 2003; Horsager et al., 2020; Liu et al., 2017). In 2003, Braak et al. hypothesised a pathological staging system that involved mapping the spread of Lewy bodies from the olfactory tract and ENS to the substantia nigra, resulting in the depletion of dopamine within the CNS and further suggesting a gut-brain link in the pathogenesis of PD (Hilton et al., 2014; Kupsky et al., 1987; Shannon et al., 2012).

5.1 | Intestinal barrier dysfunction is implicated in neurodegenerative disease development

"Leaky gut" syndrome has been proposed as a contributing factor to PD development and has been associated with intestinal inflammation, oxidative stress, and increased intestinal permeability (Forsyth et al., 2011). Preliminary studies in a mouse model of PD have demonstrated that permeability is more pronounced in the colon than the small intestine (Kelly et al., 2014), and this is similarly evident in humans (van IJzendoorn & Derkinderen, 2019). Colonic biopsy samples from patients with PD were found to have altered mucosal structure, with decreased expression of enteric tight junction proteins such as occludin and zonulin-1, and disorganised distribution of these proteins throughout the tissue, though there was not significant mucosal damage (Clairembault et al., 2015; Perez-Pardo et al., 2018). The compromised intestinal epithelial barrier exposes the individual to bacteria and their endotoxins, eliciting inflammation, and oxidative stress, and has been implicated in subsequent αSyn aggregation and neuroinflammation in the ENS (Forsyth et al., 2011).

5.2 | Enteric inflammation is implicated in neurodegenerative disease development

Intestinal barrier dysfunction is a potential trigger for enteric inflammation. However, if the trigger is not fully resolved, low-level inflammation develops, becoming chronic with deleterious effects over time (Houser & Tansey, 2017). Expression of pro-inflammatory cytokines such as TNFα, IL-6, and IL-1β are increased in the colon of PD patients (Devos et al., 2013), which is associated with increased expression of GFAP from colonic EGCs (Clairembault et al., 2014; Devos et al., 2013). Furthermore, other inflammatory cytokines released suggest increased activation of toll-like receptors (TLR) that are expressed in the ENS. Specifically, TLR4 has gained much interest due to its propensity for microbial interaction (Perez-Pardo et al., 2018). Microbial metabolites such as lipopolysaccharides (LPS) and short chain fatty acids (SCFAs) have the potential to modulate an inflammatory response via TLR4 pathways. Thus, dysbiosis of the gut microbiome and their metabolites can contribute to colonic pro-inflammatory cytokine production which may drive αSyn aggregation and influence PD progression and severity (Gorecki et al., 2020; Houser & Tansey, 2017; Rietdijk et al., 2017).

5.3 | Gut dysbiosis is implicated in neurodegenerative disease development

Evidence suggests that changes to the composition of the gut microbiome may be caused by aging, diet, lifestyle, medications, and/or injury. Individuals with PD have consistently shown lower diversity in gut bacteria (Gerhardt & Mohajeri, 2018; Gorecki et al., 2019; Petrov et al., 2017; Scheperjans et al., 2015), particularly when beta-diversity was analysed. Furthermore, the intestinal environment becomes dysbiotic due to a shift that favours deleterious populations of Gram-negative, LPS-producing bacteria, subsequently decreasing the abundance of Gram-positive bacteria and beneficial metabolites such as SCFA (Gorecki et al., 2019; Keshavarzian et al., 2015; Pietrucci et al., 2019; Scheperjans et al., 2015; Unger et al., 2016). The resulting increase in intestinal levels of certain LPS subtypes from dysbiosis may trigger enteric inflammation and intestinal barrier dysfunction (Houser & Tansey, 2017; Vatanen et al., 2016). Further, the impact of increased LPS subtypes in vitro and in vivo has been investigated and further instigated LPS as a catalyst for intestinal permeability and phenotypic change in Thy1-αSyn Mice compared to baseline and WT animals (Gorecki et al., 2019). Similarly, intrastriatal injection of LPS in a progressive PD related mouse model (C57/B6) revealed progressive and specific dopaminergic neurodegeneration, accompanied by dopamine depletion and behavioural impairment (Hunter et al., 2009). This shift in microbial population towards a pro-inflammatory environment has also been associated with hallmark motor and GI dysfunction via gut-brain signalling of metabolites that impact neuroinflammation and αSyn aggregation in mouse models (Thy1-αSyn) of PD (Sampson et al., 2016). Furthermore, dysbiotic microbial populations have also been associated with greater postural instability and gait difficulty (Scheperjans et al., 2015), and may negatively affect disease progression (Minato et al., 2017). Thus, highlighting the increasing evidence for microbial dysbiosis to act as a catalyst for αSyn pathophysiology and eventual neurodegeneration.

6 | TBI-INDUCED CHANGES IN THE MGBA COULD CONTRIBUTE TO THE DEVELOPMENT OF NEURODEGENERATIVE DISEASE

A TBI can have far-reaching consequences, both beyond the brain and years after the event. Survivors are widely considered to be at greater risk of developing neurodegenerative diseases such as PD (Delic et al., 2020; Goldman et al., 2006; Jafari et al., 2013). Although the mechanism for this is unknown, deleterious changes within the MGBA are commonly reported years after TBI and prior to PD diagnosis (Figure 1).

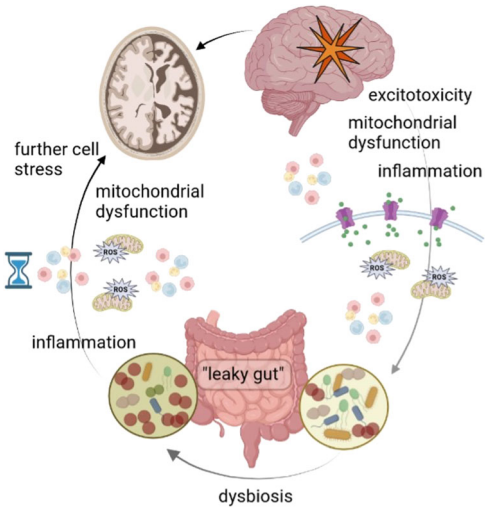

FIGURE 1 The biochemical injury cascade that occurs as a result of TBI may disrupt the gastrointestinal microbiome and contribute to a "leaky gut," thereby inducing low-level, chronic inflammation and exacerbating the peripheral effects of TBI. This, in turn, feeds back to the central nervous system, potentially leading to neurodegeneration.

In addition to neuroinflammation and compromised BBB induced by TBI, damage to the HPA axis can subsequently affect peripheral systems including the GI tract. Impaired GI motility is associated with a shift in relative microbial proportions and abundance, enteric inflammation, and barrier dysfunction, leading to a "leaky gut" through which inflammatory molecules and microbial metabolites permeate. The latency between a TBI and PD diagnosis may be characterised by unresolved, chronic, low-level inflammation, often termed "inflammaging" in the context of neurodegenerative disease (de Punder & Pruimboom, 2015; Perry & Teeling, 2013). This could lead to increased expression of αSyn in the gut and brain (Chen, Chia, et al., 2016; Houser & Tansey, 2017; Mondello et al., 2013), thus prompting aggregation and propagation, eventuating in hallmark PD pathologies in the brain (Braak et al., 2003; Rietdijk et al., 2017).

6.1 | Other neurodegenerative diseases

Aside from PD, deleterious changes to the GI environment after TBI may play a role in other neurodegenerative diseases. TBI-induced dysfunction to the MGBA could also increase a survivor's risk for AD, with similar mechanisms proposed which include enteric barrier compromise, inflammation, GI dysbiosis, and protein aggregate propagation (Kowalski & Mulak, 2019; MahmoudianDehkordi et al., 2019; Pistollato et al., 2016; Sochocka et al., 2019). Furthermore, a study of 60 MS patients determined that gut dysbiosis correlated with MS-specific immune responses (Jangi et al., 2016), concurring with other studies (Cantarel et al., 2015; Chen, Stribinskis, et al., 2016; Mirza et al., 2020; Miyake et al., 2015). Preclinical studies which transplant human faecal samples into germ-free mice associate dysbiosis with impaired regulatory T cell differentiation thereby weakening immunomodulation (Berer et al., 2017; Cekanaviciute et al., 2017). Investigations into the role MGBA dysfunction plays in ALS/MND are fewer. A small case study examined inflammatory markers and stool samples in five MND patients, associating their condition with gut inflammation and dysbiosis (Rowin et al., 2017). Another, larger study suggested that, while the faecal microbiome was significantly different to healthy controls, it may advance disease progression, thus increasing the risk of death (Ngo et al., 2020).

TBI has been demonstrated to cause gut microbiota dysbiosis in vivo and in vitro (Figure 1), contributing to gastrointestinal dysfunction, oxidative stress and neuroinflammation. Further investigation into the development of PD-related pathology within the context of an experimental model of TBI is necessary to highlight the possible causal relationship between TBI, dysbiotic microbiota, and neurodegeneration.

6.2 | Therapeutic implications

To date, pharmacological interventions for treating TBI have proven fruitless. Not only are they often invasive to administer, but they have also ultimately failed in the transition from bench to bedside despite preclinical promise. Should future studies support the idea that TBI-induced MGBA dysfunction contributes to the development of neurodegenerative diseases, gut dysbiosis thus presents a potential therapeutic target for personalised non-invasive dietary interventions and creates an avenue to develop a powerful diagnostic biomarker (Rice et al., 2019).

Literature on the efficacy of dietary interventions after TBI is scarce and none to date have examined its effects on the gut microbiota. Studies in rats with TBI have found that enteral nutrition supplemented with probiotics and glutamine improved mucosal architecture and GI function, and reduced bacterial translocation outside the GI system (Sun et al., 2015; Zhang & Jiang, 2015). Probiotic and glutamine supplementation in enteral feeding has also demonstrated benefits in patients with moderate–severe TBI, reducing nosocomial infection rate, systemic inflammation, and length of hospital stay, thus facilitating accelerated recovery (Falcao de Arruda & de Aguilar-Nascimento, 2004; Wan et al., 2019). Conversely, dietary interventions to alter the gut microbiome have been of considerable interest in modifying progression of PD (Gorecki et al., 2020), AD (Sochocka et al., 2019), and MS (Morshedi et al., 2019), demonstrating benefits particularly in PD.

7 | CONCLUSIONS

Alterations in gut microbiota composition and GI dysfunction are believed to play a significant role in the early stages of PD, with symptoms preceding diagnosis by up to 20 years. Separately, other studies have found that brain injuries induce similar changes in the gut and its microbiome.

The evidence explored in this review suggests that the cascade of events that follow TBI have the potential to influence MGBA signalling and result in changes within the gut, promoting the development of neurodegenerative pathologies, such as those found in PD. Importantly, the multifaceted nature of the microbiome, TBI, and neurodegenerative disease development and progression suggests that if TBI is not a key contributor to pathogenesis,

it has the potential to promote disease-modifying effects that hasten or exacerbate neurodegenerative processes. Therefore, providing a promising potential of the gut microbiome as an avenue worth exploring to elucidate the temporal relationship between TBI, the gut, and the development of neurodegenerative diseases such as PD. Moreover, this avenue of research has the power to contribute to improve preclinical identification, diagnosis, and non-invasive dietary interventions.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Li Shan Chiu: Conceptualization; writing-original draft; writing-review and editing. **Ryan S. Anderton:** Conceptualization; writing-original draft; writing-review and editing.

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