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THEMED ISSUE REVIEW

# The role of gut microbiota in cerebrovascular disease and related dementia

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## Abstract

In recent years, increasing evidence suggests that commensal microbiota may play an important role not only in health but also in disease including cerebrovascular disease. Gut microbes impact physiology, at least in part, by metabolizing dietary factors and host-derived substrates and then generating active compounds including toxins. The purpose of this current review is to highlight the complex interplay between microbiota, their metabolites. and essential functions for human health, ranging from regulation of the metabolism and the immune system to modulation of brain development and function. We discuss the role of gut dysbiosis in cerebrovascular disease, specifically in acute and chronic stroke phases, and the possible implication of intestinal microbiota in post-stroke cognitive impairment and dementia, and we identify potential therapeutic opportunities of targeting microbiota in this context.

KEYWORDS
dementia, gut, microbiota, post-stroke cognitive impairment, stroke

**Abbreviations:** AhR, aryl hydrocarbon receptor; BAs, bile acids; DAM, disease-associated microglia; FMT, faecal microbiota transplantation; GF, germ-free; GM, gut microbiota; HPA, hypothalamic–pituitary–adrenal; MCAO, middle cerebral artery occlusion; mRS, modified Rankin Scale; PAMPs, pathogen-associated molecular patterns; PSCID, post-stroke cognitive impairment and dementia; TMAO, trimethylamine N-oxide.

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## 1 | INTRODUCTION

Dementia is characterized by a deterioration in cognitive function, beyond what might be expected from the usual consequences of biological ageing. This impairment in mental capacity causes a dramatic reduction in quality of life and clearly compromises everyday tasks and independent living. Most dementias occur in individuals of advanced age. By 2050, this older age group is expected to increase by around 21% (World Health Organization [WHO], 2017). Because of this population ageing and absence of efficient treatments for dementia, the number of affected individuals is estimated to rise from 50 million in 2018 to approximately 150 million in 2050 (Alzheimer's Disease International, 2018; WHO, 2017). This alarming scenario anticipates that dementia will become one of the major threats to public healthcare systems, with a high socioeconomic impact worldwide. Therefore, there is a critical need for the development of therapies and strategies to achieve optimal brain health during the ageing process, including preventing dementia and cognitive decline. Among the different types of dementia, vascular dementia (VaD) is the second leading type of dementia after the most prevalent, Alzheimer's disease (AD) (Alzheimer's Association, 2022; Alzheimer's Disease International, 2018). Importantly, cerebrovascular lesions are commonly found in the pathophysiology of AD patients (Iadecola, 2017; Iadecola et al., 2019; Loeb, 1993), up to the point that mixed VaD/AD pathology accounts for more than 50% of demented subjects, reinforcing the role of vascular dysfunction as a critical component in the development of dementia (Azarpazhooh et al., 2018). Common vascular risk factors such as hypertension, atherosclerosis and cerebrovascular disease play key roles in the occurrence of dementia and cognitive decline (Iadecola, 2013; Iadecola et al., 2019). In this sense, stroke, a leading cause of death and disability worldwide (World Stroke Organization [WSO], 2022), is a major risk factor for VaD and AD (Rost et al., 2022). In the past few decades, advances in prevention, management and exhaustive healthcare have resulted in reduced stroke mortality (Tsao et al., 2023); consequently, stroke is considered a chronically disabling disease with many stroke survivors displaying poor long-term functional outcome with motor, cognitive and psychiatric impairments. Cognitive deficits are present in around 70% of stroke survivors, depending on stroke type, definition, and time point of assessment. Additionally, more than one third of patients may develop post-stroke cognitive impairment and dementia (PSCID) after stroke (Mijajlović et al., 2017; Rost et al., 2022). PSCID is defined by the presence of cognitive impairments manifesting in the 3 to 6 months after both ischaemic or haemorrhagic stroke, and includes deficits specific to the lesion site, such as those due to strategic infarcts in brain structures like the hippocampi, thalami and key cortical regions, deficits that may have preceded the stroke and deficits due to secondary process or neurodegeneration. The development of PSCID is likely caused by the combination of primary infarct size and location and the interplay of multiple factors that contribute to brain repair, against those that may promote a secondary neurodegeneration (Mijajlović et al., 2017; Rost et al., 2022). Of note, accumulating evidence has revealed that microbiota–gut–brain axis plays an important role in the development and progression of different human pathologies affecting the central nervous system (CNS), including late-life cognitive impairment and AD (Cryan et al., 2020; Morais et al., 2021). Changes in the gut microbiota (GM) are seen in response to stroke, which may worsen stroke severity and impair recovery after injury. Therefore, it is tempting to speculate that intestinal microbiota can play role in the development of vascular cognitive decline especially in the development of PSCID as suggested for another types of dementias.

The main objective of the current review is to provide the most recent insights regarding the existing associations between gut microbes and brain functioning after stroke, and to expand our discussion to other aspects of stroke pathophysiology such as the possible implication of intestinal microbiota in the development of long-term vascular cognitive impairment after stroke. We first highlight the complex interplay between GM, their metabolites, and essential functions for human health, describing the most important evidence that supports a direct role of GM in modulating brain functioning. We next summarize the bidirectional communication that exists between the brain and the gut, including microbial metabolites. We analyse the role of gut dysbiosis during acute and chronic stroke phases and its implication in the development of PSCID. Finally, we evaluate how modulation of GM composition, microbial-derived metabolites and even targeting their receptors might provide a new promising and fascinating avenue to modulate cerebrovascular disease in both acute and chronic phases.

## 2 | THE MICROBIOTA–GUT–BRAIN AXIS IN PHYSIOLOGY

The microbiota–gut–brain axis represents a system that allows bidirectional communication between the brain and gut microbes. The GM includes trillions of symbiotic microorganisms such as bacteria, archaea, viruses and fungi (Knight & Girling, 2003; Quigley, 2013), most of them commensal or mutualistic organisms, that colonize the digestive tract after birth.

At the individual level, the microbiome varies over time as a result of a combination of factors such as host genotype, physiological or pathological status, environment exposure and lifestyle. Certain species and strains may be present in the body for years and they remain stable in part owing to the presence of a core microbiome (Chen et al., 2021; Stewart et al., 2018; Valles-Colomer et al., 2023). Its relevance for the host is clearly reflected if we consider that microbiome, that is, all intestinal microbial genes, comprises more than 1 order of magnitude higher in genes than the human genome (Cryan et al., 2019; Quigley, 2013). Thus, the host microbiome not only influences the physiology of the gastrointestinal tract (GIT), such as mucosal immunity and protection against outside pathogens, but also modulates the function of remote organs such as the immune system and CNS (Cryan et al., 2020; Fan & Pedersen, 2021; McCarville et al., 2020; Morais et al., 2021; Needham et al., 2020; Zheng et al., 2020). GM displays multiple metabolic actions, metabolizing essential substances like amino acids (AAs), vitamins, bile acids (BAs) and different dietary compounds into a variety of metabolites, some of them with neuroactive properties, which are absorbed into the systemic circulation and serve as mediators of GM actions on distant tissues such as the brain (Quigley, 2013). All these microbiota functions depend on the fine balance between the relative abundance, diversity and composition of microorganisms that colonize the intestine. In humans, GM is mainly composed of four categories of microbes, the most prevalent being *Firmicutes*, *Bacteroidetes*, *Proteobacteria* and *Actinobacteria* (The Human Microbiome Project Consortium, 2012). Gut microorganisms show host specificity in their composition and function, so that the relative distribution of gut bacteria and archaea is unique to an individual and is influenced by factors such as age or genetics and by environmental factors such as diet, drugs, stress and lifestyle (Asnicar et al., 2021; Falony et al., 2016; Ghosh et al., 2022; Valles-Colomer et al., 2023). In addition, bacterial load and diversity vary along the GIT, so intra-individual differences are found between the upper and lower GIT in both abundance and composition (The Human Microbiome Project Consortium, 2012; Vuik et al., 2019). Given this heterogeneity, it is difficult to define a standard reference for GM in healthy people but it is believed that a healthy GM is characterized by a high taxa diversity, microbial gene richness and stable microbiome functional cores (Chen et al., 2021; Valles-Colomer et al., 2023). This is fundamental for claiming *dysbiosis*, a term used to define a pathological dysregulation in the intestinal microbiome and is associated with a variety of chronic diseases, ranging from gastrointestinal disorders such as the irritable bowel syndrome (IBS) to cardiovascular and CNS diseases, making the condition of dysbiosis a very attractive therapeutic target in pathological situations. The altered composition of the microbiome determines the concentration of microbial metabolites, as well as neurotransmitters/neuromodulators, which are released into circulation (Fan & Pedersen, 2021; Honarpisheh et al., 2022; Peh et al., 2022; Tang et al., 2017; The Human Microbiome Project Consortium, 2012; Vogt et al., 2017). Thus, the microbiota represent a contributing factor to different diseases implicating, in some circumstances, the absence of normal metabolites generated by the healthy microbiota and, in others, the gain of high levels of metabolites with pathological actions that are generated by damage-associated microbiota.

In parallel to dysbiosis, a *leaky gut* (i.e., a reduction of intestinal barrier integrity or increased permeability) can be observed in different pathological contexts. The mammalian intestine has a single epithelial layer that physically separates the microbiota, which are located in the lumen, from the rest of the body (Figure 1). The intestinal barrier is composed not only of an epithelial layer but also a mucus layer characterized by a network of entangled and cross-linked mucins secreted by goblet cells, together with an abundance of different antibodies secreted by the immune system, including IgG and the secretory IgA. These physical gut barriers are fundamental for maintaining gastrointestinal health, because they prevent gut microbes from entering the circulation. An increase in gut permeability may lead to *bacterial translocation*, promoting the passage of bacteria and excessive microbial metabolites into the blood, which may reach peripheral tissues such as the liver, spleen, kidney and lung. In fact, bacterial translocation has been observed after stroke and is believed to contribute to post-stroke infections (Caso et al., 2009; Stanley et al., 2016; Tuz et al., 2022; Wen et al., 2019). But even in the absence of translocation, the leaky gut may result in an increase of microbial metabolites in the blood such as **trimethylamine N-oxide** (TMAO), short-chain fatty acids (SCFAs), indoles, kynurenines and different neurotransmitters, which cannot be removed efficiently by the liver and may directly affect the CNS. Most of these metabolites cannot cross the blood–brain barrier (BBB) and will accumulate in the blood, whereas others increase BBB permeability, facilitating the entrance of neuroactive microbial compounds. In addition, this accumulation of neuroactive microbial metabolites in the blood is especially relevant in those situations wherein alterations in the BBB function occur, such as in ageing and PSCID, mixed dementia and even AD (Connell et al., 2022; Honarpisheh et al., 2022; Mijajlović et al., 2017; Morais et al., 2021; Rost et al., 2022). A dysfunctional BBB facilitates that microbial metabolites reach the CNS and act on different neural substrates, mediating both beneficial and pathological responses.

## 3 | A ROLE FOR GM ON BRAIN FUNCTION

Different animal models and interventions are commonly used to interrogate the role of the GM in physiological host functions. Among these, germ-free (GF) mice, antibiotic usage, faecal microbiota transplantation (FMT) and probiotic/prebiotic administration are the more common. These strategies are especially relevant for manipulating GM under CNS pathological contexts, and have been also widely used for exploring the role of gut microbes on cognition. In this regard, the use of *GF mice*, that is, mice that have not been exposed to microorganisms since birth, demonstrate that the CNS is altered at multiple levels in the absence of microbiota, supporting the existence of a functional microbiota–gut–brain axis. GF mice display deficits in different cognitive domains (including anxiety, locomotion, exploratory

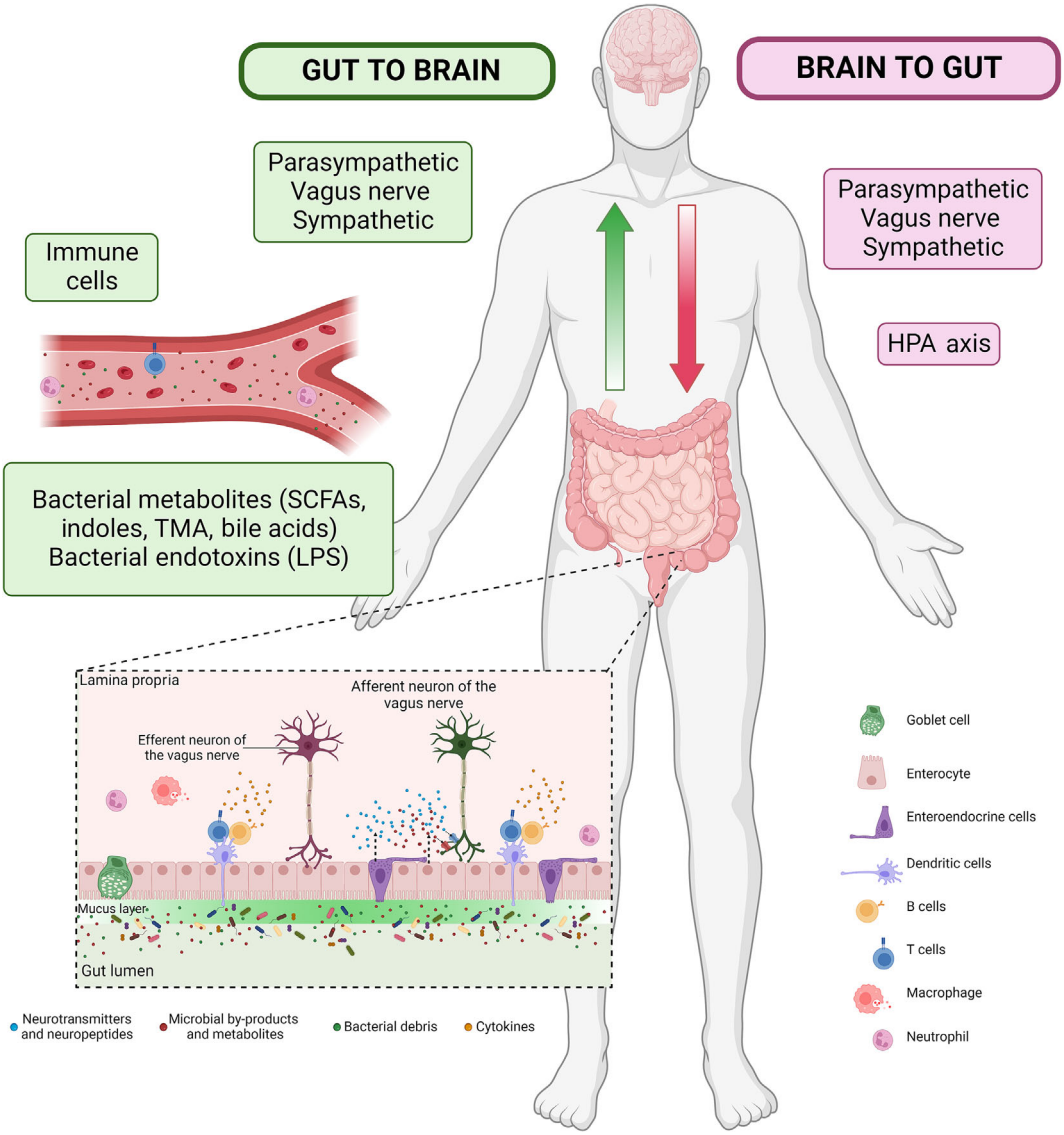


**FIGURE 1** Routes of bidirectional communication in the microbiota–gut–brain axis. The routes of communication involve the autonomic nervous system, the neuroendocrine system, the hypothalamic–pituitary–adrenal (HPA) axis, the immune system and metabolic pathways. The right side (in purple) represents pathways through which the brain controls the gut. The left side (in green) represents the main pathways for gut-to-brain signalling including neuronal, immunological and microbial metabolites-induced pathways. Inset reflects the intestinal gut barrier including both the epithelial and mucus layers, with gut bacteria located in the lumen and with the main cell types implicated in controlling gut function, intestinal mucosal immunity and, subsequently, gut homeostasis. Created with BioRender.com.

and social behaviour, learning and memory) by affecting mainly, although not exclusively, the hippocampus, the amygdala and the striatum (Connell et al., 2022; Cryan et al., 2019, 2020). This selectivity for specific regions suggests that microbial influence may differ among brain regions. The neurochemistry also is different in GF mice, with changes in neurotransmitters such as **serotonin** (5-HT), **noradrenaline** (NA) and **dopamine** (DA) (Bercik et al., 2011) and in synaptic plasticity proteins such as postsynaptic density protein-95 (PSD-95), synaptophysin, **5-hydroxytryptamine receptor 1** (5-$HT_1$), **brain-derived neurotrophic factor** (BDNF) and c-Fos (Bercik et al., 2011; Clarke et al., 2013). In addition, animals lacking microbiota show important alterations in physiological processes including neurogenesis, myelination, dendritic growth, BBB permeability, and even display a reduced microglial response compared with animals hosting commensal bacteria (Gareau et al., 2011; Heijtz et al., 2011; Morais et al., 2021). A great advantage of GF mice is that they allow for specific bacterial colonization, making them a commonly used strategy for studying whether one or more known bacteria can alter brain functioning. In addition, GF mice are used for the generation of humanized microbiota mice, that is, a GF mouse transplanted with human microbiota, to investigate in mice the contribution of the specific human GM to brain diseases (Park & Im, 2020). A second

common approach used for investigating how GM modulates cognition is *the use of antibiotics* (Cryan et al., 2019; Desbonnet et al., 2015; Fröhlich et al., 2016; Winek et al., 2016). A critical aspect when using antibiotics is whether they are absorbable or not. If they are, they may enter into the circulation, cross the BBB, and exert direct effects on CNS function and behaviour (as do **metronidazole** and **minocycline** when acting on microglial cells). In contrast, non-absorbable antibiotics such as **vancomycin** do not cross the BBB and become concentrated in the GIT, excluding direct effects of antibiotics on the brain or other distant tissues (Cryan et al., 2019). Chronic antibiotic administration for depleting microbiota has been shown to exert effects on different paradigms such as sociability, memory and anxiety-like behaviours in mice (Cryan et al., 2020; Desbonnet et al., 2015; Fröhlich et al., 2016). Importantly, microbiota elimination produces changes in some **tryptophan** (Trp)-derived metabolites with neuroactive properties, such as serotonin and L-kynurenine (L-Kyn). Again, as previously shown for GF mice, antibiotics also alter some synaptic proteins like BDNF, **serotonin transporter** (SERT) and **neuropeptide Y** (NPY) (Cryan et al., 2019, 2020; Desbonnet et al., 2015). A great advantage of antibiotics is that they are the perfect tool to mimic the clinical scenario in humans. In fact, antibiotic administration has been demonstrated to promote behavioural changes not only in animals but also in humans (Morais et al., 2021). A third strategy, used in clinics for treating *Clostridium difficile* infection (van Nood et al., 2013), is gut bacterial colonization with FMT, which basically consists of the transfer of the GM from one subject to another. This procedure can be done in rodents by oral administration of faecal material, where the donor microbiome colonizes the recipient GIT. This colonization process is facilitated by using as recipient a GF mouse or antibiotic-treated mouse, although, in some cases, a passive GM transfer is used. As a result, different studies have demonstrated that behaviours like depression and anxiety can be transferred from the host to the recipient of faecal microbiota (Bruce-Keller et al., 2015; Kelly et al., 2016). For instance, the study of Bercik et al. (2011) took advantage of the well-documented differences in both behaviour and GM composition of two common laboratory mice strains. They observed that when BALB/C mice, a strain that displays high anxiety-like behaviour, were colonized with gut microbes from Swiss mice (a very calm mice strain), colonized BALB/C mice exhibited a decreased anxiety, supporting the role of microbiota in brain functions (Bercik et al., 2011). Finally, administration of *prebiotics*, *probiotics* and *dietary substrates* has provided important cues about the existence of microbiota–gut–brain axis. Administering prebiotics such as some dietary fibres and resistant starches as well as probiotics modulates behaviour in both rodents and humans and promotes changes in learning, depression, anxiety, general hypothalamic neuronal activity and stress, alongside changes in immune markers, hippocampal synaptic efficacy and Trp metabolism (Cryan et al., 2019; Koh et al., 2016; Markowiak & Śliżewska, 2017; Quigley, 2013). In addition, probiotics, that is, live bacteria that are beneficial for the host health when ingested in adequate amounts, have a been employed in humans demonstrating that administration of specific strains has beneficial effects on cognitive performance. In this regard, the administration of *Lactobacillus*, the most widely used strain, was capable of preventing memory deficits in GF mice (Hsiao et al., 2013; Markowiak & Śliżewska, 2017; Quigley, 2013). Finally, diet contents and quantity have a major role in shaping the GM composition, microbial-derived metabolites and thereby how gut microbes modulate host functions and hence brain and behaviour. As they say, 'we are what we eat', linking dietary signals with the microbiota–gut–brain axis.

## 4 | PATHWAYS OF COMMUNICATION BETWEEN GM AND CNS

All previous evidence widely supports that the resident intestinal microbiota can exert considerable influence over host behaviour by modulating brain function through different pathways. Of course, this communication system is bidirectional; that is, the brain can influence basic gastrointestinal and immune-related functions. A clear example of this complex interaction between the gut and the brain is how the prognosis of different chronic gastrointestinal illnesses is directly influenced by factors such as stress and depressive behaviour. These emotional factors may modify the microbiota composition by influencing the integrity of the gut epithelial barrier and altering gut motility, then potentially contributing to dysbiosis, which highlights the intricate mechanisms that control this bidirectional modulation. This may explain, for instance, that patients with IBS, an intestinal disease characterized by low gut bacterial diversity, are frequently comorbid with different psychiatric illnesses like depression (Cryan et al., 2020; Morais et al., 2021; Needham et al., 2020). Gastrointestinal dysfunction such as nausea, dysphagia and defecatory problems also are common symptoms in different neurodegenerative disorders like Parkinson's disease (PD) and multiple sclerosis (MS) (Morais et al., 2021). Post-stroke intestinal ileus is one of the complications observed in stroke patients (Tuz et al., 2022). A recent study provided genetic insight into the gut–brain relationship, implicating shared but non-causal genetic susceptibility of disorders affecting GIT with AD's risk (Adewuyi et al., 2022). Therefore, there is a clear pattern of co-occurrence of neurological diseases including dementia, with GIT disorders or dysfunction probably suggesting that shared genetics and common biological pathways may explain the association. The microbiota–gut–brain axis allows intestinal microbiota to communicate with the brain, and the brain with the gut and involves the autonomic nervous system (ANS), specifically the enteric nervous system (ENS) and the vagus nerve (VN), the neuroendocrine system, the hypothalamic–pituitary–adrenal (HPA) axis, the immune system and, finally, metabolic pathways and microbial metabolites (Bonaz et al., 2018; Carabotti et al., 2015; Cryan et al., 2019) (see Figure 1).

### 4.1 | How the brain controls gut function

The CNS may directly modulate gut function through the innervation of the gut wall by the ANS (both sympathetic and parasympathetic) and the ENS, a specialized independent nervous system of the GIT

that is structured into the submucosal and myenteric plexus. The ENS is responsible for the coordination of different gut functions, for instance, gut motility. Different factors such as brain neurotransmitters, hormones and cytokines may activate the ENS, as well the efferent fibres of the VN and also some sympathetic innervation that, in turn, may influence gut motility and permeability, microbiota composition and mucosal immune response (Bonaz et al., 2018; Carabotti et al., 2015; Cryan et al., 2019; Mayer et al., 2015). Neurotransmitters can act directly on gut bacteria influencing bacterial metabolism, proliferation and virulence. In addition, the HPA is implicated in controlling gut barrier integrity. Stress responses activate the HPA axis by acting on hypothalamic neurons, making them secrete **corticotrophin receptor hormone** (CRH), which causes the release of **adrenocorticotrophic hormone** (ACTH). The adrenal gland is then stimulated for the synthesis and release of cortisol, which acts, for instance, on neuroimmune signalling responses affecting intestinal barrier integrity (Bonaz et al., 2018; Carabotti et al., 2015; Cryan et al., 2019; Mayer et al., 2015).

## 4.2 | How the gut and microbiome control the CNS

In the other direction, that is, the gut controlling the CNS, three main pathways have been described: (1) direct neural mechanisms, (2) cellular immune function and (3) systemic circulatory factors and microbial metabolites.

### 4.2.1 | Communication through direct neural mechanisms

One of the main neuronal communication pathways by which the gut controls the CNS involves the afferent fibres of VN. The VN is able to sense GM, to transfer this information to the CNS where it is integrated and then to generate an adapted or inappropriate response in the gut (Bonaz et al., 2018; Cryan et al., 2019, 2020). The VN is the most important component of the parasympathetic nervous system and is composed of both afferent (80%; from the gut to the CNS) and efferent (20%; from the CNS to the gut) fibres (Bonaz et al., 2018). Vagal afferent fibres are located along the gut wall innervating the muscle and mucosa layers, but they are not in direct contact with the microbiota, located in the lumen. Therefore, vagal fibres can only sense microbiota signals indirectly, either through the diffusion of bacterial compounds or metabolites or by other cells located in the epithelium that relay luminal signals. The afferent fibres can be stimulated directly by microbiota metabolites and/or components: for example, vagal activation mediated by the metabolite **butyrate** or even by bacterial components such as **lipopolysaccharide** (LPS), which is sensed by **toll-like receptor 4** (TLR4) located on vagal nerves (Bonaz et al., 2018; Carabotti et al., 2015; Cryan et al., 2019; Mayer et al., 2015). In addition, vagal afferents can be stimulated indirectly by hormones released by the enteroendocrine cells (EECs) (which, in turn, are stimulated directly by microbiota) such as serotonin, **glucagon-like peptide-1** (GLP-1), **cholecystokinin**, **ghrelin** and NPY. These afferent vagal projections act mainly through the activation of the *nucleus tractus solitarius* (NTS) located in the *medulla oblongata*. Projections from the NTS to the hypothalamus are clearly involved in regulating hormone release through the hypothalamic neurons of the HPA axis (Bonaz et al., 2018; Bravo et al., 2011; Cryan et al., 2019). In addition, NTS projections can reach the hypothalamus and the limbic forebrain (mainly the hippocampus, amygdala and limbic cortex) and affect the way in which these regions influence appetite and food intake behaviour. This communication may provide the neural network underlying the link between behaviour and gut function in health (the so-called 'stomach butterflies', for instance) and in disease (like IBS and depression). Vagal communication has been demonstrated to play a key role in modulating host behaviour in different studies. In this sense, administration of *Lactobacillus rhamnosus* modulates anxiety-like behaviour in mice and changes the expression of **γ-aminobutyric acid (GABA)** and its receptors in the brain areas associated with fear and emotions, such as the amygdala and hippocampus (Bravo et al., 2011). Importantly, most effects of *L. rhamnosus* were abrogated in vagotomized mice, suggesting that the effects of the bacteria depend on intact neuronal communication to the brain. Moreover, the VN is critical for mediating the beneficial effects of *Lactobacillus reuteri* in promoting social behaviour in animal models with autism spectrum disorder (ASD) (Sgritta et al., 2019). In addition to the communication through the VN, a recent study using neuronal tracing techniques demonstrated that GF mice display increased activation of gut extrinsic neurons connecting the brainstem sensory nuclei and in gut sympathetic neurons when compared with conventional mice (Muller et al., 2020), suggesting that microbiota may have an inhibitory effect on pathways implicated in the regulation of gut motility. In agreement with this proposal, administration of SCFA-synthetizing bacteria inhibits this neuronal pathway, supporting that GM can modulate neuronal pathways of the gut–brain axis through the production of specific microbial metabolites.

### 4.2.2 | Immunological mechanisms for gut–brain communication

The GM is a critical factor for the development and function of the peripheral immune system and for the maturation of the intestinal mucosal immune system (Zheng et al., 2020). Signals from the GM also play important roles in modulating the proper maturation and activity of microglia, the primary innate immune cells in the CNS. GM contributes to microglia homeostasis, probably through SCFA actions. In fact, as commented before, GF and antibiotic-treated mice displayed important defects in microglial maturation, which led to impaired innate immune responses, showing increased numbers of immature microglial cells (determined by both transcriptional signature and morphological features of microglia) (Erny et al., 2015;

Matcovitch-Natan et al., 2016). This study provided a link for GM-mediated microglial control, which might be of special relevance in dementias such as AD, wherein dramatic changes in the molecular signatures of microglia have been described (the so-called 'disease-associated microglia' [DAM] phenotype) (Butovsky & Weiner, 2018). Another important immune pathway, especially under pathological circumstances, involves either the activation of peripheral immune cells or the interaction of host mucosal surface cells with different microbiota products such as LPS and **peptidoglycans**. **Pattern recognition receptors** (PRRs) present in host cells such as **toll-like receptors** (TLRs) (Bryant & Monie, 2019) recognize pathogen-associated molecular patterns (PAMPs), which then may stimulate and instruct the host immune response, promoting the release of circulating cytokines and chemokines (Hsiao et al., 2013). Changes to systemic immunity drive altered immune signalling, either directly inducing neuroinflammation or promoting the migration from the periphery into the brain of different types of immune cells such as T cells, monocytes and neutrophils (Benakis et al., 2016; Singh et al., 2016, 2018).

### 4.2.3 | Communication through microbial-synthesized metabolites

Many GM-mediated effects in the CNS depend on hundreds of metabolites and bioactive molecules such as neurotransmitters, SCFAs, indoles and secondary BAs that are produced by gut microbes and derived from the transformation of host or dietary products (Connell et al., 2022; McCarville et al., 2020; Peh et al., 2022). These metabolites may enter the systemic circulation, travel to the brain and influence the function of most parts of the neural populations including neurons, microglia and astrocytes or even different cellular components of the BBB (Figure 2).

### 4.2.4 | Products of bacterial fermentation

SCFAs are the most studied GM metabolites (Connell et al., 2022; McCarville et al., 2020; Peh et al., 2022). The most common SCFAs are **acetate**, **propionate** and butyrate, which are produced by the fermentation of digestion-resistant starch and dietary fibres. Because mammals are not able to generate enzymes that digest these polysaccharides, they pass undigested through the gut and into the colon, where microbiota use them as an energy source and generate SCFAs as end products (Koh et al., 2016). SCFAs mediate the control of both mucosal and systemic immunity and exert important vasoactive actions (Corrêa-Oliveira et al., 2016). In addition, SCFAs influence host cells through a variety of mechanisms such as activation of G protein-coupled receptors, histone acetylation and cell proliferation. Loss of SCFA-producing bacteria has been described in several pathological models, including stroke, hypertension, obesity and diabetes mellitus wherein SCFAs supplementation seems to exert a beneficial effect (Connell et al., 2022; McCarville et al., 2020; Peh et al., 2022; Roager, 2018).

### 4.2.5 | AA metabolism

The best studied AAs in the context of host–microbe interactions are **Trp** and **L-carnitine** (Connell et al., 2022; McCarville et al., 2020; Peh et al., 2022). Trp is an essential AA that cannot be synthesized by animal cells, and is abundant in high-protein content foods, such as meats, nuts, fish, and eggs (Agus et al., 2018). Trp is metabolized in the gut by three main pathways. The first is the direct transformation of Trp by gut bacteria into several molecules including indoles and its derivatives. These microbial-derived metabolites directly produced by dietary Trp include different indoles such as indole-3-sulfate, indole-3-acetate, indole-3-aldehyde, indolepropionic acid, **tryptamine** and 3-methyl-indole (Agus et al., 2018; Hubbard et al., 2015). Interestingly, all these microbial metabolites activate the **aryl hydrocarbon receptor** (AhR) (Alexander et al., 2021) (see Section 6). The metabolism of Trp by microbes, by limiting the availability of host Trp, can indirectly modulate the other two major Trp metabolic pathways, that is, the serotonin pathway and the kynurenine pathway (KP). Thus, gut microbes may affect the levels of various neuroactive metabolites and neurotransmitters, including L-Kyn, which has been demonstrated to activate AhR, again reinforcing the fundamental role of AhR in the gut–brain axis. The GM is a major actor in intestinal serotonin production. Hence, GF mice exhibited impaired serotonin production in the gut and low concentrations in the blood (Agus et al., 2018). Trp metabolism is therefore critical for proper cognition. Indeed, numerous studies have identified abnormal Trp metabolism, with alterations either in Trp-derived microbial metabolites or in the serotonin and KP products, in patients with cognitive decline (Connell et al., 2022; Cryan et al., 2020; Cuartero et al., 2016; Morais et al., 2021; Sun et al., 2022). The other AA metabolized by GM is L-carnitine. This AA is mainly present in red meat and, once in the gut, is converted to trimethylamine (TMA) by intestinal bacteria. Thereafter, TMA is oxidized in the liver by hepatic flavin monooxygenases to form TMAO, an indirect product of bacteria metabolism that has been demonstrated to contribute in atherosclerosis pathogenesis (Koeth et al., 2013), modulating platelet hyperresponsiveness and thrombosis potential (Zhu et al., 2016). Due to TMAO's high association with atherosclerosis and cardiovascular disease, TMAO has been considered a risk factor of VaD and PSCID (Koeth et al., 2013; Morais et al., 2021; Needham et al., 2020; Tang et al., 2017).

### 4.2.6 | BA metabolism

BAs are compounds produced by the host that upon modification by gut bacteria form bile salts. The primary BAs **cholate** (CA) and **chenodeoxycholate** (CDCA) are produced from **cholesterol** in the liver through oxidation of cholesterol and then are conjugated to either **taurine** or **glycine**, forming bile salts. Conjugated bile salts that reach the intestinal tract are metabolized by gut bacteria into secondary BAs. Secondary BAs can further be manipulated by the GM by dihydroxylation,n producing **deoxycholate** (DCA) from CA and **lithocholate** and **ursodeoxycholate** (UDCA) from the primary CDCA.

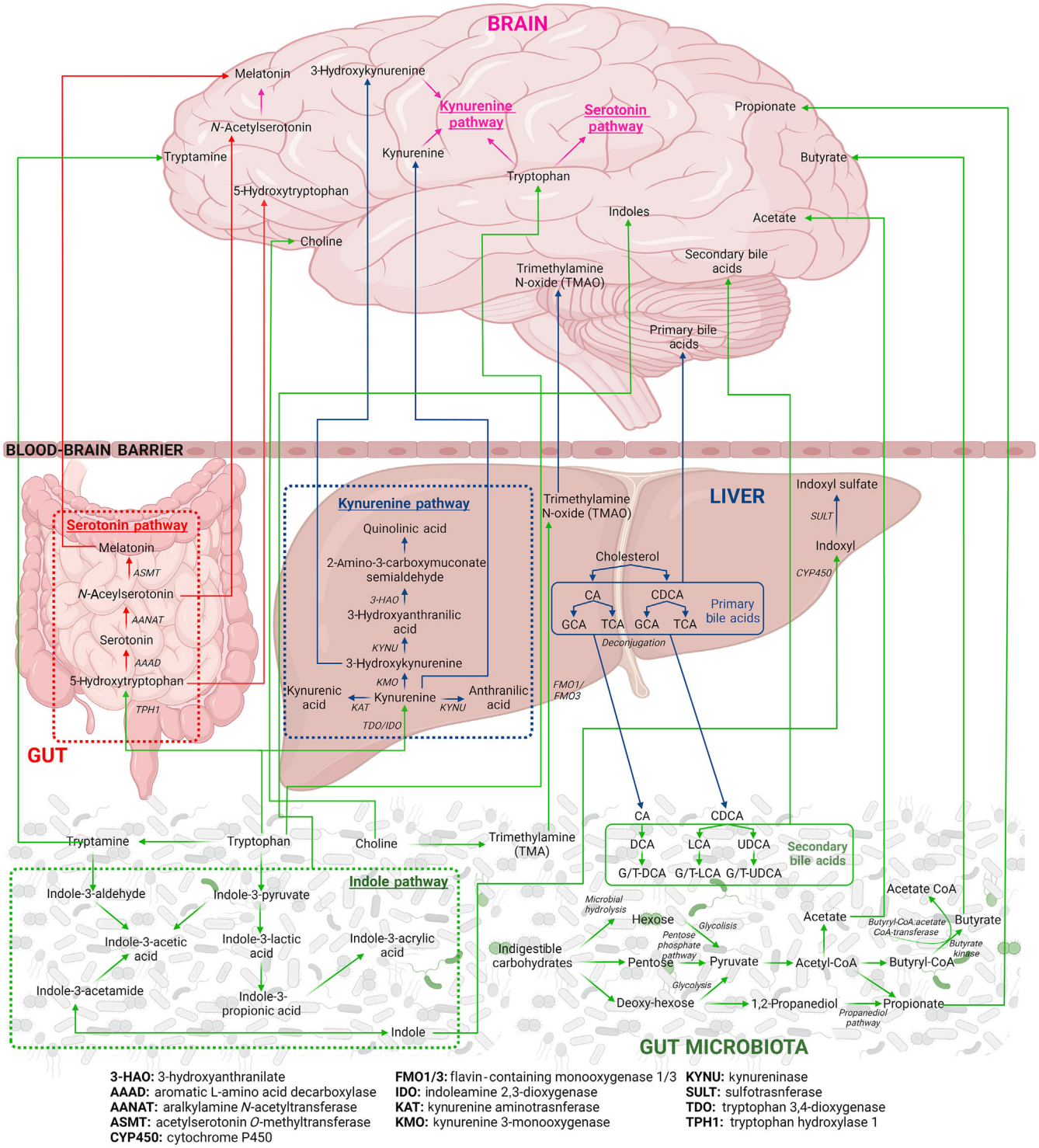


**FIGURE 2** Main microbial-derived metabolites implicated in gut microbiota signalling and their synthesis pathways. Metabolic pathways implicated directly or indirectly in the microbiota–gut–brain axis. Microbial-derived metabolites include indoles derived from Trp metabolism, bile acids (BAs), TMAO and SCFAs. Notice that some of these compounds can reach the brain. In addition, the serotonin and kynurenine pathways are also shown. Created with BioRender.com.

One of the most important functions of BAs is their major role in the clearance of cholesterol. In addition, they are important regulators in maintaining energy homeostasis through binding to nuclear receptors such as **FXR** and **LXR**. Very little is known about their function in the brain. Of note, several primary and secondary BAs and their receptors are found in the brain, supporting the notion that BAs may exert some direct physiological actions on the cerebral tissue. Some of these BA functions include the capacity to suppress the HPA axis (McNeilly

et al., 2010), to exert a modulatory influence on neurotransmission by acting on receptors for *N*-methyl-D-aspartate (**NMDA**) and GABA (Schubring et al., 2012), to increase the BBB permeability, and even to act as modulators of the neurogenesis process (Connell et al., 2022; Morais et al., 2021). Importantly, whereas some BAs may exert beneficial or neuroprotective effects such as tanti-inflammatory actions in microglia mediated by **tauroursodeoxycholate** (TUDCA) in an acute model of neuroinflammation (Yanguas-Casás et al., 2017), others are known to be cytotoxic. For instance, DCA has been demonstrated to promote apoptosis in different tissues and cell types, including neurons (MahmoudianDehkordi et al., 2019). Therefore, it is not strange that BAs have been associated with different cerebral pathological states and cognitive decline. One example is the altered BA profile observed in patients with hepatic encephalopathy, a cognitive dysfunction caused by liver disease (McMillin et al., 2016). In addition, in the context of AD, an increased ratio of DCA/CA, which reflects the activity of gut bacteria, was strongly associated with cognitive impairment (Connell et al., 2022; MahmoudianDehkordi et al., 2019; Morais et al., 2021; Needham et al., 2020), therefore suggesting a possible role of microbiota–gut–liver–brain axis in the pathogenesis of AD.

#### 4.2.7 | GM-dependent synthesis of neurotransmitters

Gut microbes can synthesize different neurotransmitters by themselves and even may promote the generation of neurotransmitters by the hosts. One of the most representative examples is the neurotransmitter GABA, which is produced by *Bacteroides*, *Bifidobacterium*, *Parabacteroides* and *Escherichia* (Lyte, 2013; Strandwitz et al., 2019). In fact, mice treated with antibiotics displayed altered faecal GABA levels, suggesting that microbiota is contributing to circulating levels of GABA. This is of interest because multiple diseases are associated with an altered GABAergic profile, such as depression, stroke and even PSCID (Strandwitz et al., 2019; Torres-López et al., 2022). In the context of major depressive disorder (MDD) (Strandwitz et al., 2019), by coupling microbiome sequencing with functional magnetic resonance imaging in patients with MDD and altered GABA pattern, a recent study found that the relative abundance of faecal *Bacteroides* negatively correlates with brain signatures of depression (Strandwitz et al., 2019). Bacteria also are important in the production of other types of neurotransmitters such as serotonin, NA, DA and **acetylcholine** (Lyte, 2013). In the case of serotonin, *Bifidobacterium infantis* has been shown to increase the circulating levels of Trp and thus influence central serotonin transmission. In physiological conditions, although these microbial-synthesized neurotransmitters can cross the intestinal barriers, their influence on the brain is likely to be indirect, probably acting on the ENS because they cannot cross the BBB and reach the brain. However, under pathological contexts wherein the BBB is compromised, microbial-synthesized neurotransmitters might exert direct brain effects.

## 5 | THE MICROBIOTA–GUT–BRAIN AXIS IN THE ACUTE AND CHRONIC STROKE PHASES

In cerebrovascular disease and specifically in stroke, increasing evidence indicates that targeting GM might be considered a therapeutic strategy. The relationship between microbiota and stroke is very complex and involves vascular predisposing factors such as atherosclerosis and the stroke phase, ranging from the acute stroke to the most chronic phase wherein the development PSCID takes place (Benakis et al., 2016; Durgan et al., 2019; Honarpisheh et al., 2022; Lee, d'Aigle, et al., 2020; Lee, Venna, et al., 2020; Peh et al., 2022; Singh et al., 2018; Spychala et al., 2018). The different changes related to the microbiota–gut–brain axis in stroke are summarized in Figure 3 and will be described in the following sections.

### 5.1 | Risk factors and GM

*Atherosclerosis* is one the major vascular risk factors for stroke, dementia and PSCID (Iadecola, 2013; Iadecola et al., 2019). Recent studies have found that bacterial DNA is found around atherosclerotic plaques, probably altering plaque stability. Importantly, the bacterial taxa observed in atherosclerotic plaques also were present in the gut of the same subjects (Koren et al., 2011). These results might indicate a bacterial translocation process wherein the origin of bacteria located in the plaque would be the gut. In addition, the metabolite TMAO has been implicated in atherosclerosis (Koeth et al., 2013; Yin et al., 2015). Indeed, by using GF mice, antibiotic treatment, and $ApoE^{-/-}$ mice, TMA/TMAO generated from metabolism of dietary nutrients has been demonstrated to have a pro-atherogenic effect contributing to the development of atherosclerotic plaques (Koeth et al., 2013). TMAO is linked to a reduction in cholesterol transport, alteration in tissue cholesterol and sterol metabolism, and changes in the composition and transport of BAs in both the liver and the gut, altering lipid levels and producing dyslipidaemia (Peh et al., 2022; Tang et al., 2017). Indeed, patients with *hyperlipidaemia* showed abnormal GM composition, which, in turn, would aggravate dyslipidaemia, whereas regulating GM can alleviate the abnormality of serum lipid in animal models (Peh et al., 2022; Tang et al., 2017). These findings demonstrate that GM might be an important regulator of the prognosis of hyperlipidaemic stroke and its consequences. In this sense, a recent study demonstrated that the GM signature of hyperlipidaemic patients is a predictor of adverse outcomes after acute ischaemic stroke, as determined by modified Rankin Scale (mRS) scores at 3 months after admission (Chen, Chi, et al., 2022). *Hypertension* is the most prevalent modifiable risk factor for stroke and dementia (van der Flier et al., 2018). Gut dysbiosis has been associated with hypertension in both animals and humans. In this context, dysbiosis has been found in models of hypertension in rats, including the genetic spontaneously hypertensive rat (SHR) model and the hypertension generated by **angiotensin-II** (Ang-II) infusion. Hypertensive rats displayed a decrease in microbial diversity and increased

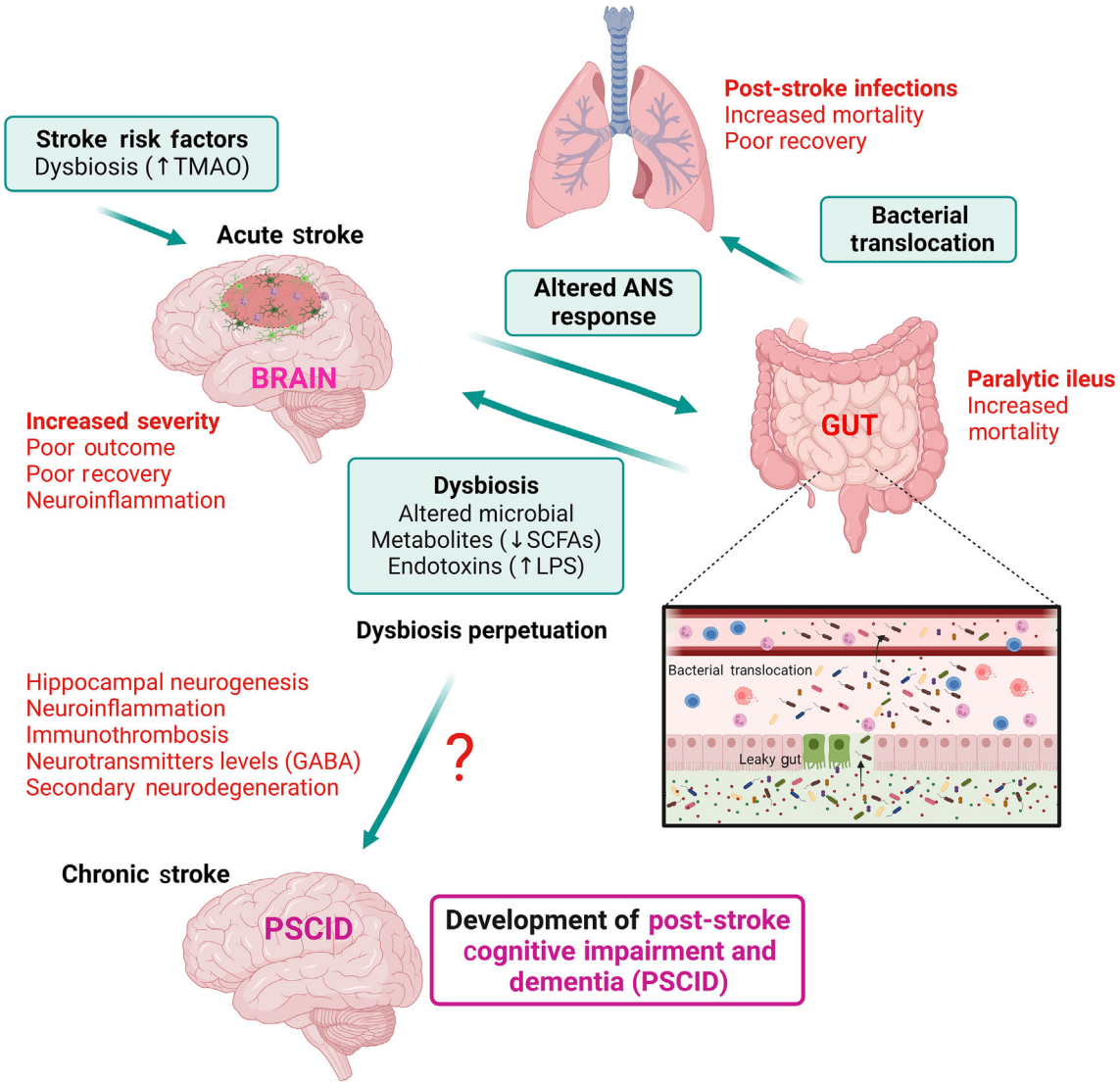


**FIGURE 3** Association of the gut microbiota–brain axis with stroke. Different vascular risk factors, like hypertension and atherosclerosis, and age are associated with dysbiosis and changes in microbiota composition and microbial metabolites like SCFAs or increased TMAO. In this sense, changes in microbiota composition prior to stroke are associated with increased stroke severity and poor stroke outcome. After stroke, the injured brain causes an alteration in the communication pathways that control the gut, promoting epithelial barrier breakdown, a leaky gut, translocation of bacteria and bacterial toxins, gut dysbiosis and paralytic ileus. Dysbiotic gut bacteria after stroke further exacerbate ischaemic damage and impair post-stroke recovery by mechanisms that included reduced SCFA production and increased neuroinflammation. Bacterial translocation contributes to post-stroke infection impairing recovery and increasing mortality after stroke. Finally, persistent dysbiosis is observed long term after stroke and likely contributes to the development of post-stroke cognitive impairment and dementia. Created with BioRender.com.

*Firmicutes/Bacteroidetes* ratio. The Ang-II model also has been used in GF mice, which do not show any sign of hypertension, indicating that microbiota is necessary for Ang-II-induced hypertension (Lau et al., 2017; Li et al., 2017; Tang et al., 2017). Furthermore, by using FMT wherein normotensive rats were colonized with microbiota of hypertensive rats, GM transfer was enough to elevate blood pressure in normotensive rats (Lau et al., 2017; Li et al., 2017; Tang et al., 2017). In humans, the composition of GM found in pre-hypertensive patients is the same as that observed in hypertensive patients and is quite different to control patients, suggesting that dysbiosis precedes hypertension rather than being a consequence of it (Lau et al., 2017; Li et al., 2017). In hypertensive patients, dysbiosis is reflected by a decreased diversity of the intestinal microbiota and a higher *Firmicutes/Bacteroidetes* ratio, as observed in animal models of hypertension (Li et al., 2017). Age is the predominant risk factor for cognitive decline, dementia and stroke. Microbiota composition, richness and function change with ageing (Connell et al., 2022; Ghosh et al., 2022; Honarpisheh et al., 2022; Lee, d'Aigle, et al., 2020). In humans, these changes have been associated with a decrease in species diversity, with a reduction in *Clostridiales* and *Bifidobacterium* and an increase in *Proteobacteria* and pathobionts (Odamaki et al., 2016; O'Toole & Jeffery, 2015). Importantly, these changes have been

suggested to play a role in low-grade inflammation, which is commonly observed in ageing, the so-called 'inflammageing'. The microbial metabolite profile has been demonstrated to be completely different with ageing (Odamaki et al., 2016; O'Toole & Jeffery, 2015). This, together with the alteration in the BBB as we age, may facilitate the ability of microbial metabolites to penetrate the brain, having a direct impact on cognition. In this sense, different bacterial metabolites, such as SCFAs, nitrites, TMAO and indoles, exert direct effects on BBB permeability, integrity and vascular function (Connell et al., 2022; Ghosh et al., 2022; Lee, d'Aigle, et al., 2020; Lee, Venna, et al., 2020). The GM also varies among stroke patients in different age groups. In experimental stroke in mice, age-related changes in the GM were shown to influence stroke outcome (Spychala et al., 2018). First, authors corroborated that microbiota is altered after stroke in young mice and is similar to microbiota found in control aged mice (with an increase *Firmicutes/Bacteroidetes* ratio). Accordingly, FMT from aged donor to young recipient increased mortality following middle cerebral artery occlusion (MCAO) and decreased performance in behavioural testing. Conversely, young microbiota colonization of aged mice increased survival and improved recovery following MCAO.

## 5.2 | GM composition prior ischaemia predisposes for stroke and determines its severity

The composition of GM prior to ischaemia influences stroke severity and is associated with stroke outcome and primary lesion size. As commented in the previous section, predisposing and risk factors wherein GM composition is altered are good examples. In addition, multiple studies have shown that the absence of microbiota in GF mice promotes a higher infarct size after stroke compared with conventional mice (Benakis et al., 2016, 2020; Singh et al., 2016, 2018). Importantly, infarct volume in GF mice is completely normal in size when mice are colonized with a healthy GM, indicating therefore that gut microbes have a profound impact on stroke outcome and in the primary lesion size. Furthermore, Singh et al. (2016), by using the proximal MCAO model, demonstrated that GF mice receiving faecal microbes from ischaemic donor mice had larger infarct volumes and displayed functional deficits compared with recipients of FMT from sham mice. Among the mechanisms that mediate microbiota-dependent changes in stroke lesion, these authors demonstrated the implication of a pro-inflammatory T-cell polarization (Th1 and Th17 cells) in Peyer patches and the ischaemic brain. The study of Benakis et al. (2016) also reflected that GM can be manipulated to either improve or worsen stroke outcomes. By administering antibiotics in mice prior stroke, they showed that antibiotic-induced alterations in commensal microbiota reduce ischaemic brain injury and, remarkably, that this neuroprotective effect can be transferred by FMT. Changes in bacterial gut composition alter immune homeostasis in the small intestine, leading to an increase in the neuroprotective/anti-inflammatory regulatory T (Treg) cells and a reduction in **IL-17**$^{+}$ γδ T cells that by opposite contribute to ischaemic damage and exert a pro-inflammatory effect, suggesting that GM might be a key regulator in priming the neuroinflammatory response to brain injury (Benakis et al., 2016). In addition, as commented previously, colonization of young mice by aged control microbiota did not promote higher infarct volumes, yet had a profound negative effect by increasing stroke mortality and impairing recovery (Singh et al., 2016).

## 5.3 | Stroke alters GM composition

Analysis of GM composition in ischaemic and haemorrhagic stroke patients has revealed that stroke promotes gut dysbiosis and, in the most cases, the degree of GM changes correlates with stroke severity. So far, several clinical studies have explored changes in GM composition in patients with stroke compared to control. Overall, these studies identified 62 up-regulated and 29 down-regulated microbial taxa (Peh et al., 2022). From all these studies, just a few tried to associate microbiome to stroke severity. Among these, one of the first clinical studies demonstrating dysbiosis after stroke showed that the GM of stroke and transient ischaemic attack patients was clearly different from that of control group (Yin et al., 2015), with more opportunistic pathogens, such as *Enterobacter*, *Megasphaera*, *Oscillibacter* and *Desulfovibrio*, and fewer commensal or beneficial genera including *Bacteroides*, *Prevotella* and *Faecalibacterium*. Importantly, this dysbiosis correlated with the severity of the disease. Consistently, Xu, Gao, et al. (2021) performed two clinical cohort studies in stroke patients and brain ischaemia in mice to capture the gut dysbiosis dynamics after stroke and their relationship with stroke prognosis. They demonstrated that ischaemic stroke rapidly triggers GM dysbiosis with *Enterobacteriaceae* overgrowth that, in turn, exacerbates brain infarction, demonstrating therefore a bidirectional interaction between stroke and GM. Chang et al. (2021) also detected an apparent dysbiosis of blood microbiota in patients with acute ischaemic stroke compared to healthy people, showing that *Ruminococcaceae* and *Prevotella* were elevated in blood samples of stroke patients with poor functional outcome. The study by Yamashiro et al. (2017) analysed faecal GM and metabolites in a Japanese cohort of stroke and control subjects. They found that the abundance of *Lactobacillus ruminis* was higher in stroke patients and correlated with inflammatory markers such as **interleukin-6** (IL-6). In addition, a decrease in microbial metabolites such as SCFAs, acetic and **valeric acids** was detected, supporting multiple alterations in GM after stroke. The study by Tan et al. (2021), with a cohort of 40 acute ischaemic patients and 92 controls, showed that the intestinal microbiota was different in stroke patients compared with healthy controls, especially those with increased stroke severity, in which SCFA levels, especially acetate, were associated with an increased risk of 90-day poor functional outcomes. A recent clinical study also demonstrated that gut dysbiosis takes place after haemorrhagic stroke (Chen, Wang, et al., 2022): By using 16S RNA sequencing, macrogenomics sequencing and untargeted metabolomics to explore the differences in gut microbial–metabolome interactions between patients with intracerebral haemorrhage and healthy control populations, they found a significant decrease in the phylum of *Firmicutes* and a significant increase of *Bacteroidetes* in haemorrhagic

stroke patients, which is accompanied by changes in serum microbial metabolites and correlates with the severity of intracerebral haemorrhage (Chen, Wang, et al., 2022). In addition, a role of GM in post-stroke prognosis and early stroke outcome has been demonstrated in a study including 104 patients with acute ischaemic stroke and 90 healthy individual showing that the stroke dysbiosis index (SDI) correlated not only with brain injury but also with early unfavourable outcome (Xia et al., 2019). These authors also performed experimental stroke models where they corroborated that mice receiving faecal transplants from patients with higher SDI (i.e., higher dysbiosis) developed a more severe brain injury than mice receiving transplants from low SDI patients, therefore reinforcing the causal relationship between gut dysbiosis and stroke outcome and severity (Xia et al., 2019).

The impact of stroke on the GM composition, dysbiosis and the mechanisms through which stroke affects the gut have been evaluated in experimental cerebral ischaemia models (Houlden et al., 2016; Singh et al., 2016, 2018; Xu, Gao, et al., 2021). In this sense, a study in cynomolgus monkeys found intestinal dysbiosis after stroke with an increase in *Bacteroidetes* and a reduction in *Firmicutes* and *Faecalibacterium* (Chen, Liang, et al., 2019). An interesting finding in the study of Singh et al. (2016) is that gut dysbiosis after stroke in mice may depend on lesion size. By using the proximal MCAO filament model that produces large hemispheric lesions, sequencing of GM composition revealed that ischaemic mice displayed gut dysbiosis reflected by a reduction in bacterial diversity and an increase in bacterial *Firmicutes*, *Bacteroidetes* and *Actinobacteria*; on the contrary, when stroke was induced by distal MCAO with the permanent electrocoagulation model, which causes smaller lesions, no significant change in the microbiota composition and species diversity was observed, suggesting that infarct size has a role in stroke-induced dysbiosis. This outcome also was observed in the study by Houlden et al. (2016) wherein intestinal dysbiosis correlated with the extent of injury in both experimental stroke and traumatic brain injury. Finally, the study by Spychala et al. (2018) provided evidence of dysbiosis after experimental stroke, although, in this case, major changes were detected in two main bacterial phyla in GM *Firmicutes* and *Bacteroidetes*, with an increased ratio of *Firmicutes* to *Bacteroidetes* (Spychala et al., 2018). The gut virome also has been demonstrated to change after experimental stroke, where it might play a crucial role in disease progression and recovery (Chelluboina et al., 2022).

Apart from gut dysbiosis, some clinical studies support for alterations on microbial metabolites. For instance, the studies in humans by Yamashiro et al. (2017) and by Tan et al. (2021) showed a reduction in faecal SCFAs. In agreement, SCFAs also are reduced in different experimental stroke models (Benakis et al., 2020; Chen, Xu, et al., 2019; Lee, d'Aigle, et al., 2020). Of note, Sadler et al. (2020) demonstrated that SCFA supplementation in the drinking water of mice significantly improved recovery of affected limb motor function after stroke, promoting synaptic plasticity processes at different levels, and systemic and brain resident immune cells were demonstrated as the main effectors (Sadler et al., 2020). While SCFAs seem to play a beneficial and protective role after stroke, some exceptions have been reported (Henry et al., 2021). In this sense, the recent study by Zhu et al. (2021) in experimental stroke model showed that gut microbes, through dietary **choline** and TMAO generation, directly impact cerebral infarct size resulting in adverse outcomes following stroke. In addition, they demonstrated that either dietary choline supplementation, which raises plasma TMAO, or direct TMAO feeding prior stroke ischaemia, impacted negatively stroke severity.

## 5.4 | GM and post-stroke complications

### 5.4.1 | Extensive brain injury impairs gastrointestinal function

Several studies have demonstrated gastrointestinal disturbances in stroke patients such as dysphagia, gastrointestinal bleeding or constipation (Tuz et al., 2022). A common post-stroke complication affecting the gut, which is a major contributor to stroke outcome, disability and mortality, is the so-called paralytic intestinal ileus or post-stroke ileus, which is characterized by abdominal distension and absent bowel sounds causing a reduced gastrointestinal motility, associated with overgrowth of intestinal bacteria and subsequent dysbiosis. As we commented above, microbiota gut function is under the control of CNS by innervation of the gut wall with both the ANS and the ENS. In addition, the HPA axis may play a role after stress responses. In this sense, previous reports have identified that brain impairment by stroke promotes a dysregulation of the ANS and a pronounced stress response that participates in the inflammatory post-stroke response (Chamorro et al., 2012; Dorrance & Fink, 2015; Meisel et al., 2005; Mracsko et al., 2014). In fact, post-stroke intestinal dysfunction and associated dysbiosis are probably a consequence of the catecholaminergic stress response generated after stroke (Houlden et al., 2016; Singh et al., 2016), although additional altered signalling through the ANS (for instance, the loss of cholinergic signalling in the ileum in favour of adrenergic one) or circulating factors may also contribute to this stroke complication.

### 5.4.2 | Bacterial translocation and post-stroke infection

Post-stroke infections are the most common problems of stroke patients, affecting around 30% of stroke survivals and associated with higher mortality and poor stroke outcome. Urinary tract infection and pneumonia are the most common types of infection, but pneumonia has a greater impact on clinical outcomes (Elkind et al., 2020). As we previously delineated, the integrity of the epithelial gut barrier is fundamental for maintaining intestinal homeostasis, avoiding gut microbe access to the circulation or distant organs. In this regard, it has been proposed that post-stroke infections may be due to the loss of integrity of the gut epithelial barrier after stroke (Crapser et al., 2016). Consequently, GM can translocate into the circulation and, from there,

disseminate to inappropriate tissues (for instance, the lung), being therefore potentially pathogenic and contributing to post-stroke pneumonia, as demonstrated by Stanley et al. (2016).

In fact, the analysis of stroke human samples demonstrated that more than 70% of bacteria found in the lungs were bacteria commonly found in the gut (and in the oral cavity) such as *Enterococcus* spp., *Escherichia coli* and *Morganella morganii*. Haak et al. (2021) also demonstrated that alterations in gut bacteria producing TMA and butyrate are associated with stroke-associated infections. In addition, alteration of GM in the aged mice increased the risk and severity of post-stroke lung infection (Crapser et al., 2016; Stanley et al., 2016; Wen et al., 2019). In agreement with bacterial translocation to the lungs contributing to post-stroke infection, GF mice did not develop spontaneous pneumonia after stroke (Stanley et al., 2016). Although gut microbes can be found in the lungs after stroke, the source of these gut bacteria could be different from bacterial translocation. Of note, post-stroke bacterial pneumonia may originate from aspiration of colonized oropharyngeal material into the lungs (Kumar et al., 2010). Because mice display coprophagic activities, the presence of intestinal bacteria in the lungs of mice after stroke could just reflect the inhalation of microbial mouth content from faecal origin. Although mice have a very low capacity for aspiration (Stanley et al., 2016), it should be noted that stroke increases the risk of pneumonia after aspiration. Indeed, nasal inoculation of only 200 colony-forming units (CFUs) of *Streptococcus pneumoniae* was enough to cause a severe pneumonia in stroke mice, whereas 200,000 CFUs was needed to induce comparable bacteraemia in sham animals (Prass et al., 2006). Therefore, in mice, due to coprophagic behaviour, stroke-facilitated aspiration of intestinal bacteria from the mouth may be, in addition to bacterial translocation, a possible source of gut bacteria found in the lungs.

## 5.5 | The vicious circle of injured brain and dysbiotic GM in post-stroke recovery

Stroke alters gut motility, increases gut permeability, activates resident immune cells and changes the gut microbiome to a dysbiotic GM. Subsequently, this dysbiotic GM in turn communicates to the brain having detrimental effects after stroke, by increasing lesion size and stroke severity. The mechanisms by which dysbiosis further exacerbates stroke damage probably involve local neuroinflammation, migration of immune cells into the brain, bacterial endotoxins and/or metabolites that can cross the disrupted BBB exerting neurotoxic actions. Therefore, the brain participates in gut dysbiosis and, subsequently, the gut dysbiosis feeds back to promote neuroinflammation following cerebral ischaemia. This vicious circle hinders the recovery during the sub-acute stroke phase. As commented before, different studies have demonstrated that FMT, antibiotics or specific supplementation with microbial metabolites (like SCFAs) prior and/or at the time of ischaemia may have a positive or a negative impact in stroke recovery (Sadler et al., 2020; Singh et al., 2016; Spychala et al., 2018). However, for being considered as a viable therapy for stroke treatment, the GM should be amenable to manipulation after stroke onset in order to contribute to post-stroke recovery. In this sense, it has been demonstrated that 'bacteriotherapy' is a viable post-stroke treatment option in the aged (Lee, d'Aigle, et al., 2020): FMT from young donor mice to recipient ischaemic aged mice 3 days after stroke improved behavioural recovery and gut integrity and conferred a protective phenotype in both gut and brain T cells. In addition, it was demonstrated that a reduction of microbial SCFAs is implicated in dysbiosis-mediated injury and showed that restoring SCFAs levels after stroke through probiotics and prebiotics was enough to improve outcomes in stroke aged mice (Lee, d'Aigle, et al., 2020).

A plethora of research studies show that dietary modifications influence the GM and that these modifications are associated with pro-inflammatory or anti-inflammatory responses. In this sense, a recent study demonstrated that changes in the diet after stroke can be used for restoring GM: Specifically, they observed that faecal dysbiosis after stroke in mice was reversed by protein restriction and improved influenced stroke outcome. Therefore, the modification of dietary protein content may represent an efficient and easy strategy for promoting stroke recovery and targeting the microbiota (Silva de Carvalho et al., 2022) once stroke has occurred.

## 5.6 | Association of GM with PSCID

Despite the immense differences in neuropathology of the most common dementias, that is, AD or those vascular-driven dementias including PSCID, they are associated with shared and disease-specific abnormalities in the composition and function of the GM (Alzheimer's Association, 2022; Connell et al., 2022; Cryan et al., 2019, 2020; Honarpisheh et al., 2022; Jung et al., 2022; Zhu et al., 2022). However, whether aberrant microbiota in this context is causal (i.e., implicated in predisposition, initiation or progression) or, on the contrary, a secondary epiphenomenon of the disease is still under debate. Of note, GM composition is known to be significantly altered in patients with mild cognitive impairment, that is, a preclinical stage that precedes dementia in AD, suggesting therefore that changes in microbial composition may occur during the early period of cognitive deterioration (Zhu et al., 2022).

Most evidence on the implication of GM in dementia arise from studies in demented patients in general or from studies focused in AD. Gut dysbiosis and alterations in microbiota composition in both AD patients and animal models are very well documented. In this context, changes in GM composition in AD patients include a decrease in the relative abundance of *Firmicutes* and *Bifidobacterium* spp. and an increase in *Bacteroidetes*, *Shigella* and *Escherichia* spp., which have been correlated with inflammation and amyloid aggregates (Cattaneo et al., 2017; Verhaar et al., 2021; Vogt et al., 2017; Zhuang et al., 2018). The role of the microbiota in AD has been studied in different AD animal models, including 5XFAD transgenic mice and the APP/PS1 line, which display important changes in the GM and microbial metabolites. In these mice, microbiota depletion by using antibiotics reduced brain amyloid deposition and inflammatory profile,

suggesting that the GM exacerbates the AD pathology (Colombo et al., 2021; Dodiya et al., 2022; Minter et al., 2016; Wang et al., 2019; Zhuang et al., 2018); however, the exact roles and the molecular mechanisms through GM mediate neurodegeneration in AD are still unknown.

PSCID, which develops in the months following stroke, is likely caused by a combination of stroke lesion size and location combined with a plethora of molecular mechanisms that may include a prolonged inflammatory response and immunothrombosis, a secondary neurodegeneration in remote areas, defects in myelin removal and phagocytosis, changes in neurotransmitters like GABA, alterations in physiological process like neurogenesis and malfunctioning of the glymphatic system (Cuartero et al., 2019; Doyle & Buckwalter, 2020; Rost et al., 2022). Interestingly, a great deal of these endogenous processes may be modulated by the GM and their metabolites, making gut microbes a very attractive target for chronic stroke. So far, most evidence that associate GM with the development of PSCID arise from very recent clinical studies. In this regard, the study by Xia et al. (2019) demonstrated not only that the GM plays a role in post-stroke prognosis and early outcome but also that dysbiosis persists long term after stroke. This persistent dysbiosis was confirmed by a recent study including 12 stroke patients, 18 control participants with stroke risk factors for stroke and 12 healthy participants (Hammond et al., 2022), where GM and its association with leaky gut markers, dietary intake and functional recovery measures were evaluated the first 3 weeks after stroke. Although sample size is limited, data support that dysbiosis is still observed 3 weeks after stroke, with significantly lower abundance of butyrate producers, secondary BA producers, and sulfate reducers in the stroke group. It is plausible that this persistent dysbiosis that is detected in patients long term after stroke onset contributes to the development of PSCID. Indeed, first associations between microbiota and PSCID arise from the studies carried out by Ling, Gong, et al. (2020) and Ling, Gu, et al. (2020) who characterized GM in faecal samples from ischaemic stroke patients. Patients were divided into two different groups, a PSCID group and the non-impaired, non-PSCID group, according to their Montreal Cognitive Assessment (MoCA) scores 3 months after stroke onset. In both studies, quite similar results were found regarding bacterial composition. At the phylum level, *Proteobacteria* was highly increased in the PSCID group compared with the non-impaired. In addition, after age adjusting, a decrease in the abundance of *Firmicutes* was observed in the impaired stroke group. The study of Liu et al. (2020) tried to find an association between of PSCID and GM metabolites. Again, stroke patients were classified in PSCID and non-PSCID based on their MoCA scores. The main findings of this study show that PSCID patients displayed a decrease in alpha diversity and disturbed microbial composition compared with non-PSCID patients. In addition, increased *Fusobacterium* and deficiency of microbial metabolized SCFAs were significantly associated with PSCID. A recent study by Wang et al. (2022) analysed the role of microbiota in the development of PSCID in both stroke patients and experimental stroke models in mice. The study includes a cohort of 83 stroke patients that were classified as PSCID and non-PSCID (34 and 49 stroke patients, respectively) by MoCA scores 3 months after stroke. By analysing GM composition, microbial metabolites and peripheral inflammatory factor levels, PSCID patients showed significantly higher levels of *Enterobacteriaceae*, LPS and peripheral inflammatory markers. To corroborate these data, ischaemic mice were colonized by FMT with GM from PSCID and non-PSCID patients. Consistently with data from stroke patients, ischaemic mice that received microbiota from PSCID patients displayed a higher level of *Enterobacteriaceae*, an increased expression of intestinal TLR4, increased levels of circulating LPS and inflammatory cytokines, and a reduction in faecal SCFA butyrate. Finally, authors demonstrated that supplementation with sodium butyrate via drinking water rescued detrimental changes caused by colonization of ischaemic mice with microbiota from PSCID patients.

In summary, although further studies are necessary for establishing the role of GM in the development of PSCID, the studies so far are consistent, revealing differences in the relative abundance of several taxa such as *Gammaproteobacteria*, *Proteobacteria* and *Enterobacteriaceae* between PSCID and non-impaired patients, therefore suggesting that a persistent gut dysbiosis may contribute to cognitive decline and dementia long term after stroke.

## 6 | POTENTIAL THERAPEUTIC OPTIONS FOR TARGETING GM IN CEREBROVASCULAR DISEASE

So far, different therapeutic approaches have been tested in pathological diseases affecting the CNS such as PD, epilepsy, MS and AD (Connell et al., 2022; Cryan et al., 2019, 2020; Morais et al., 2021). Owing to the exponentially growing knowledge gained from clinical and experimental studies about the impact of the GM in cerebrovascular disease including acute stroke and PSCID, there is an increased interest in testing the effect of microbiome interventions specifically in stroke patients. These include trials testing, among others, probiotics/prebiotics, dietary interventions, antibiotics, heterologous and autologous FMT and others such as vagal stimulation or modulation of different receptors like AhR (Figure 4).

### 6.1 | Probiotics/prebiotics and dietary interventions

So far, most common probiotics include *Bifidobacterium*, *Lactobacillus* and *Saccharomyces* spp., which have a long history as safe probiotics. In addition, potential next-generation probiotics include *Faecalibacterium prausnitzii* 185, *Akkermansia muciniphila* and several *Clostridia* spp. (Fan & Pedersen, 2021). Different studies carried out in stroke animal models have shown that treatment with probiotics reduces brain damage and cognitive decline after stroke (Akhoundzadeh et al., 2018; Sun et al., 2016). Consistently, clinical studies also demonstrated some positive effects (Chen, Hu, et al., 2022). This beneficial effect of probiotics has been observed in a hypoperfusion model caused by the

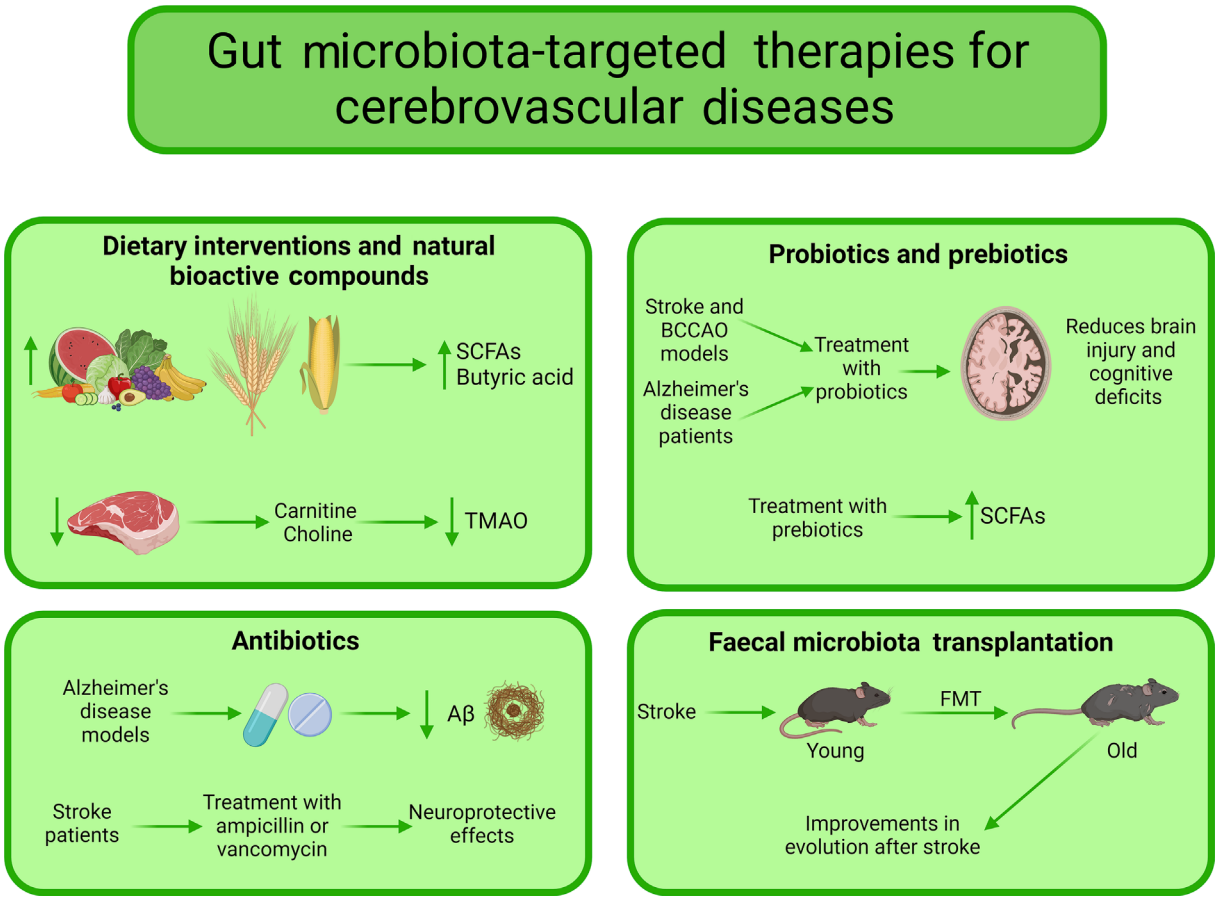


**FIGURE 4** Therapeutic options for gut microbiota targeting. Gut microbiota-targeted strategies for ischaemic stroke may include dietary interventions, probiotic and prebiotic supplementation, faecal microbiota transplantation and rationalization of antibiotic use. Created with BioRender.com.

occlusion of bilateral common carotid artery, where probiotic treatment reduced hippocampal injury and vascular cognitive impairment (Rahmati et al., 2019). Treatment with probiotics has been beneficial not only in cerebrovascular diseases but also in AD patients wherein probiotic administration resulted in some favourable effects (Leblhuber et al., 2018; Tamtaji et al., 2019).

Prebiotics are components of food that cannot be digested by the digestive tract enzymatically (Markowiak & Śliżewska, 2017). Thus, they are fermented by microbiota to generate metabolites such as SCFAs that, as commented above, have a beneficial effect in the ischaemic stroke (Sadler et al., 2020). Thus, increasing the endogenous production of SCFAs is an amenable strategy that can be achieved either by prebiotic administration or by dietary modifications. In this sense, a diet rich in fruits and vegetables and in resistant starches (such as whole grains and legumes) might promote an increase in the levels of SCFAs, the neuroprotective microbial metabolites reduced after stroke (Lee, d'Aigle, et al., 2020; Markowiak & Śliżewska, 2017; Sadler et al., 2020; Tan et al., 2021). In addition, treatment with prebiotics/probiotics reduced the incidence and severity of pneumonia in hospitalized patients, one of the main complications after stroke (Barraud et al., 2013). While increasing, for instance, dietary fibre consumption may be helpful for recovery after stroke, the consumption of red meat is not recommended because it increases the levels of the pro-thrombotic TMAO, a detrimental factor associated with poor prognosis and stroke severity (Rexidamu et al., 2019; Yin et al., 2015; Zhai et al., 2019).

### 6.2 | Antibiotics

The use of antibiotics for the treatment of stroke and dementias is so far controversial. Although it has been demonstrated to be beneficial in animal models of AD (Colombo et al., 2021; Dodiya et al., 2022; Minter et al., 2016) results from clinical trials with AD patients either had no effect on AD progression or even caused some neuropsychiatric side effects (Bravo et al., 2011; Molloy et al., 2013). Similar results were observed in stroke patients (Westendorp et al., 2021) and in animal stroke models (Benakis et al., 2016; Winek et al., 2016; Xia et al., 2019). In the current clinical practice, stroke patients are often treated with antibiotics due to post-stroke infections. However, not only bacteria in the target organ (like the lungs or the urinary tract) but also the gut bacterial populations are influenced by antibiotics treatment. Therefore, although antibiotics are a useful tool to manipulate the GM, antibiotic administration can have off-target effects and even promote microbiota independent changes in host metabolites that makes difficult their use as therapeutic tool.

### 6.3 | FMT

Transplantation with healthy bacteria may be a potential approach for restoring microbiota in stroke patients. Colonization with GM by FMT from healthy donors has been established in the treatment of patients with *C. difficile* colitis and has proved to be safe and successful in patients with inflammatory bowel disease (IBD), refractory bronchiolitis, and pseudomembranous colitis (van Nood et al., 2013). FMT therapy has already been tested in CNS diseases such as PD and ASD, reducing the symptoms in both cases (Morais et al., 2021; Xu, Huang, et al., 2021). Normalization of brain lesion-induced dysbiosis via FMT improved stroke outcome in experimental stroke models (Lee, d'Aigle, et al., 2020; Lee, Venna, et al., 2020; Spychala et al., 2018; Yamashiro et al., 2017). Although beneficial effects have been observed in animal stroke models, FMT trials conducted in patients who suffered stroke so far do not provide evidence of a beneficial effect (Wang et al., 2022; Xu, Huang, et al., 2021). Further studies are necessary to establish the effects of microbial colonization for stroke treatment.

### 6.4 | Other strategies for targeting stroke dysbiosis

Vagotomy, which is a surgical procedure that divides the VN and disrupts signalling from various peripheral organs to the brain, has been used to establish a casual role between the VN and the GM in different disorders affecting the CNS like PD, epilepsy and depression. For example, VN stimulation is an approved therapy for resistant epilepsy and depression (Aaronson et al., 2013; Morais et al., 2021). The role of the VN in stroke has been widely studied and involves both afferent and efferent fibres (Dorrance & Fink, 2015), pointing to the possibility that *activating the VN is a method of treating stroke*. In fact, stimulation of the VN has been shown to improve motor function in stroke patients. However, the function of the VN in stroke, which might involve other mechanisms beyond targeting GM, still requires further investigation.

Many GM-mediated effects in the brain depend on hundreds of metabolites and bioactive molecules that are produced by gut microbes. In the brain, as previously commented for some metabolites like BAs, part of these microbial-derived compounds exert their actions by acting on specific host receptors. Therefore, targeting these receptors by specific activators or inhibitors, or downstream targets of these microbial metabolites, could be also a future alternative approach for mitigating detrimental effects of dysbiosis after stroke.

In this sense, AhR (Alexander et al., 2021) is a nuclear receptor implicated in sensing a variety of Trp microbial-derived metabolites such as different indoles, like indole-3-acetate or indole-3-aldehyde. But not only that, AhR is activated by L-Kyn, another Trp-derived metabolite that is indirectly modulated by GM, partly by modulating circulating Trp availability, reinforcing the fundamental role of AhR in the gut–brain axis. AhR is a ligand-activated transcription factor mainly known for mediating the toxic and carcinogenic effects of xenobiotic compounds such as **Dioxin** (Agus et al., 2018; Barroso et al., 2021; Hubbard et al., 2015; Rothhammer & Quintana, 2019). In addition, many AhR ligands are processed and inactivated by cytochrome P450 family proteins, such as **Cyp1A1**, which is a direct AhR transcriptional target constituting a feedback loop for AhR signalling (Schiering et al., 2017). Apart from its functions as a xenobiotic sensor protein, AhR is a key modulator of important physiological functions, including the regulation of the immune system, metabolism, behaviour and lifespan. In addition, AhR has been implicated in pathological disorders affecting the CNS such as stroke, AD and MS (Cuartero et al., 2014; Rothhammer et al., 2016; Sun et al., 2022).

Mounting evidence indicates that reduced blood and faecal levels of GM-derived AhR ligands are associated with many human diseases, such as IBD, obesity, hypertension, and even AD. The ability of AhR to interact with multiple microbial metabolites, and its ubiquitous expression in the immune system, the gut and CNS enables AhR to regulate a variety of physiological processes that range from intestinal barrier integrity to different brain functions in response to microbial and metabolic signals. In this sense, targeting AhR could be a therapeutic strategy not only for modulating the effects of microbial-derived metabolites in the brain and the immune system but also for preventing dysbiosis and bacterial translocation after stroke. Indeed, different studies have demonstrated that AhR is a key component of GIT homeostasis by acting on epithelial renewal, barrier integrity and permeability and by affecting the maintenance of intestinal immune cells, including innate lymphoid cells (ILCs), Th17 and Treg cells. In addition, AhR activation may regulate gut motility through direct effects on neurons from the ENS (Agus et al., 2018; Barroso et al., 2021; Hubbard et al., 2015; Schiering et al., 2017). Finally, different studies have demonstrated that AhR activation by different dietary or exogenous ligands like 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD, or Dioxin) plays a critical role in shaping the composition and proper functioning of GM (Brawner et al., 2019; Neamah et al., 2020). Therefore, it is tempting to speculate that an unbalance in the AhR signalling during acute stroke might contribute to promote dysbiosis, to disrupt GIT barrier and, therefore, to cause bacterial translocation.

In the brain, AhR participates in the regulation of physiological processes like hippocampal neurogenesis and ageing (Bravo-Ferrer et al., 2019; de la Parra et al., 2018; Wei et al., 2021). Furthermore, AhR activation by directly or indirectly gut-derived metabolites was shown to modulate neuroinflammation in both AD and MS (Barroso et al., 2021; Hubbard et al., 2015; Rothhammer et al., 2016; Sun et al., 2022). In the ischaemic brain, alterations in the levels of Trp and Trp-derived metabolites and, also, changes in the expression of AhR and some of its target genes have been found during acute stroke phase, supporting a detrimental role of this receptor in the stroke context (Chen, Chang, et al., 2019; Cuartero et al., 2014), which may exert modulatory effects on different cell population such as neurons, microglia or astrocytes.

Therefore, the AhR pathway interacts with the microbiota–gut–brain axis at multiple levels, altering for instance microbiota composition by modulating GIT barrier, integrity and motility and also acting as an effector of microbial metabolites in the brain. Accordingly, AhR might be an amenable receptor for modulating the gut–brain axis in

stroke wherein potential therapeutic strategies might include, for instance, the blockade of AhR signalling by specific inhibitors or antagonists. In addition, we propose that depending on the stroke phase and even on the targeted cell or tissue (the gut vs. the brain, for instance), AhR activation would be an alternative therapeutic option after stroke.

The supplementation with Trp or Trp-derived metabolites could be beneficial in those situations where decreased GIT Trp availability may contribute to a lower production of AhR ligands by the GM. In addition, another possibility is the use of probiotics with capacity to generate AhR agonists that specifically activate the AhR (Figure 5). For example, the administration of *Lactobacillus*, which naturally produces AhR ligands, has been demonstrated to decrease colitis severity in a genetic IBD mouse model (Lamas et al., 2016). Similarly, *L. reuteri*, through the production of indole-3-lactic acid, an AhR agonist, is able to change intraepithelial T cells into an immunoregulatory phenotype (Cervantes-Barragan et al., 2017). Although promising, AhR targeting to modulate the microbiota–gut–brain axis in the stroke context still poses an important challenge that requires further investigation. In this sense, ligand promiscuity and diversity of AhR in a context-

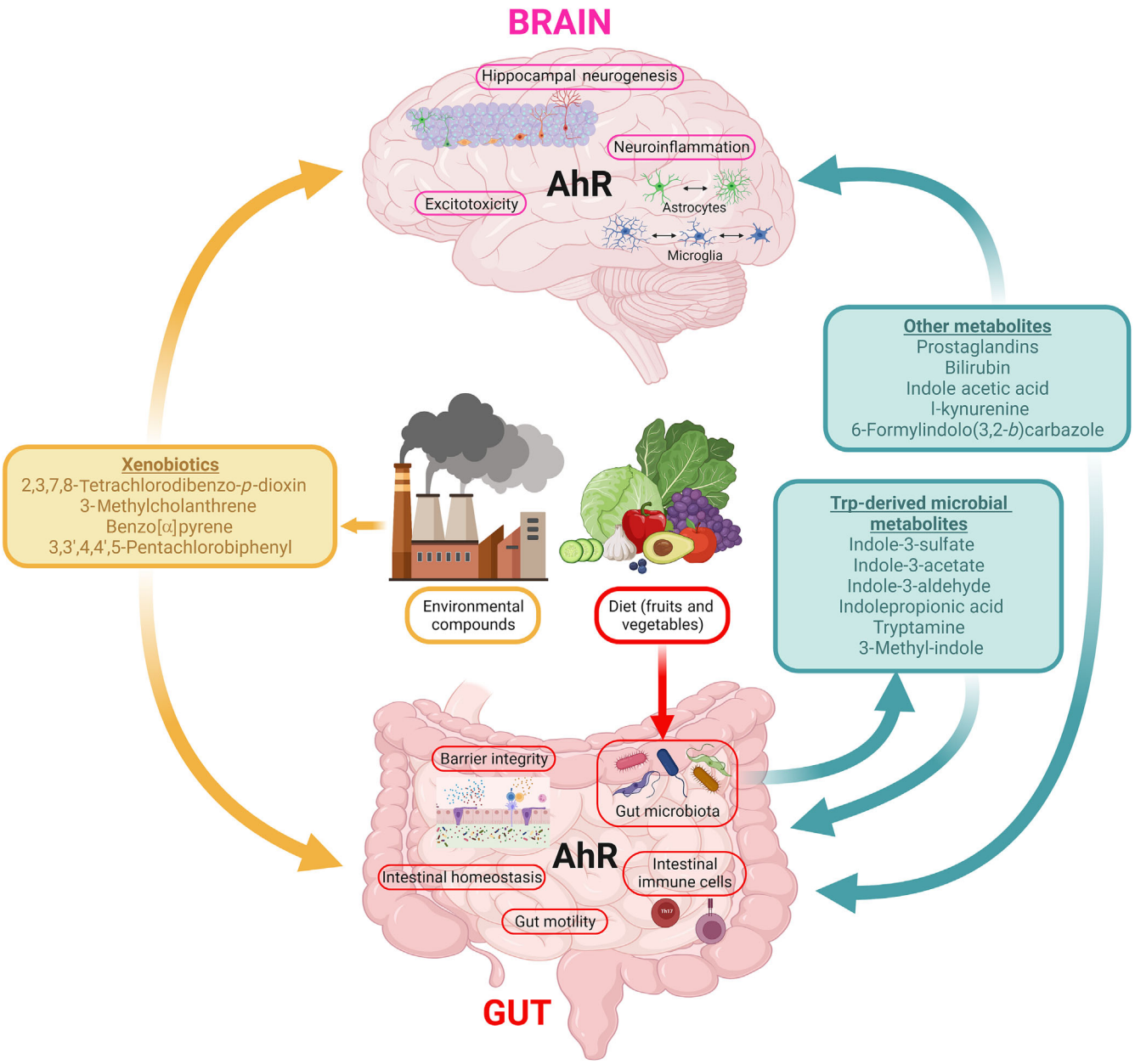


**FIGURE 5** The aryl hydrocarbon receptor (AhR) and its relation to the microbiota–gut–brain axis. AhR is a ligand-activated transcription factor that is activated for multiple environmental ligand,s such as dioxins, and also by microbial Trp-derived metabolites. The ability of AhR to interact with multiple microbial metabolites and even with some metabolites of the kynurenine pathway and its ubiquitous expression in the gut and the CNS enable this receptor to regulate physiological processes in brain function and also to maintain proper gut function. Created with BioRender.com.

specific manner together with the fact that a specific AhR ligand might promote different biological responses depending of the tissue are still the most intriguing gaps for targeting the AhR signalling.

## 7 | CONCLUSION AND PERSPECTIVES

Mounting information from humans and animals indicates that GM is fundamental in controlling cognition and brain function. Therefore, GM dysregulation is implicated in the development and progression of multiple pathologies and neurodegenerative disorders affecting the CNS such as PD, MS, ASD, and AD. There is no doubt that GM is associated with cerebrovascular disease and stroke at multiple levels, clearly participating in the acute stroke aetiopathogenesis and having important effects in stroke severity, outcome and recovery. Importantly, persistent dysbiotic microbiota is observed long-term affecter stroke onset, suggesting the implication of GM in the development of cognitive decline and dementia after stroke. Because VaD is the second cause of dementia after the most prevalent one AD, to establish a causal relationship between specific bacteria and PSCID pathology might have important repercussions and would be particularly relevant for the development of therapeutic strategies directed just to target disease-associated microbiota while maintaining intact the good one. This fascinating perspective that of course requires further investigation might combine dietary and lifestyles interventions with for instance directed probiotics or prebiotics and even pharmacological targeting of different receptors as suggested for AhR. Therefore, GM provides a new promising avenue to modulate cerebrovascular disease and, specifically, stroke outcome in both acute and chronic stroke.

### 7.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org and are permanently archived in the Concise Guide to PHARMACOLOGY 2021/22 (Alexander et al., 2021).

### AUTHOR CONTRIBUTIONS

**María Isabel Cuartero:** Conceptualization (lead); supervision (lead); writing—original draft (lead); writing—review and editing (lead). **Alicia García-Culebras:** Writing—original draft (equal); writing—review and editing (equal). **Carmen Nieto-Vaquero:** Writing—original draft (equal); writing—review and editing (equal). **Enrique Fraga:** Writing—review and editing (equal). **Cristina Torres-López:** Writing—review and editing (equal). **Jesús Pradillo:** Writing—review and editing (equal). **Ignacio Lizasoain:** Writing—review and editing (equal). **María Ángeles Moro:** Conceptualization (lead); writing—original draft (lead); writing—review and editing (lead).

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### CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

### DATA AVAILABILITY STATEMENT

N/A-Review.

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