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Current Opinion in Neurobiology

The microbiome-gut-brain axis in acute and chronic brain diseases

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The gut microbiome — the largest reservoir of microorganisms of the human body — is emerging as an important player in neurodevelopment and ageing as well as in brain diseases including stroke, Alzheimer's disease and Parkinson's disease. The growing knowledge on mediators and triggered pathways has advanced our understanding of the interactions along the gut-brain axis. Gut bacteria produce neuroactive compounds and can modulate neuronal function, plasticity and behavior. Furthermore, intestinal microorganisms impact the host's metabolism and immune status which in turn affect neuronal pathways in the enteric and central nervous systems. Here, we discuss the recent insights from human studies and animal models on the bi-directional communication along the microbiome-gut-brain axis in both acute and chronic brain diseases.

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Current Opinion in Neurobiology 2020, **61**:1–9

This review comes from a themed issue on **Neurobiology of disease**

Edited by **Michel Goedert** and **Christian Haass**

For a complete overview see the Issue and the Editorial

Available online 6th December 2019

https://doi.org/10.1016/j.conb.2019.11.009

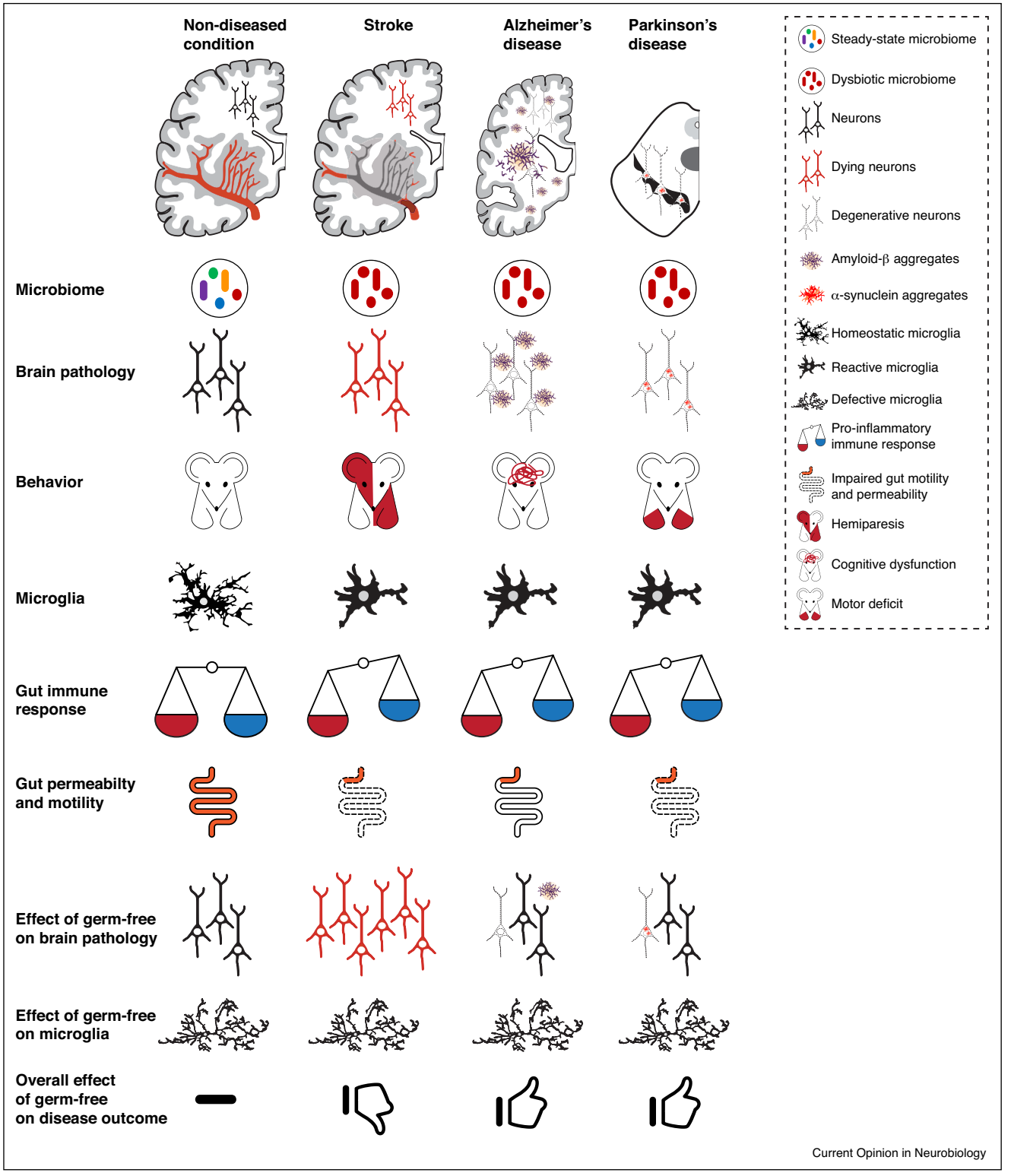
Introduction

A relatively small fraction of chronic human diseases can be explained by genetic factors alone. Exposure to environmental factors and the resulting gene-environment interactions have been postulated to play an important role in disease initiation and progression [1]. Highly diverse, complex communities of microorganisms comprising bacteria, archaea, microeukaryotes and viruses populate the human body whereby the gut represents the largest reservoir of microbial biomass [2]. Differences in the relative abundance, the composition and function of the gut microbiome between healthy individuals and patients have been described for a range of human diseases including autoimmune, metabolic and neurodegenerative diseases as well as cancer [3,4]. The importance of peripheral organs in the development of brain pathologies has long been considered marginal in the field of neurobiology. However, gut microbiota homeostasis and the associated host intestinal health not only impact the gastrointestinal tract (GIT) environment but also distant organs, including the brain [5]. The gut microbiome's early colonization is vital for brain function and behavior considering that its absence results in an impairment of the blood brain barrier (BBB), alteration of synapse plasticity and social behavior deficits [6••,7]. Germ-free (GF) mice also show an immature microglial phenotype leading to impaired immune responses [8•]. Bi-directional communication between the gut and the brain implies a key role for the gut microbiome via the regulation of the host metabolism, immune and vascular systems [9•]. Furthermore, the gut microbiota may also influence the central nervous system (CNS) via the vagus nerve (VN) by transmitting gut microbiome signals to the brain and *vice versa* in both health and disease [10]. In the present review, we focus on the role of the microbiome in a selection of major neurological disorders and discuss the current state of knowledge about the microbiome's impact on disease outcome and the potential mechanisms involved in these interactions. Specifically, we discuss the impact of the microbiome in stroke as a paradigm of acute brain injury as well as its role in two highly prevalent neurodegenerative disorders, namely Alzheimer's disease (AD) and Parkinson's disease (PD). This review of acute and chronic neurological disorders highlights common effects, as well as differences in the microbiome-brain axis between these diseases (Figure 1).

Gut microbiome alteration in acute and chronic brain diseases

Experimental and clinical studies indicate that stroke risk and outcome are substantially impacted by the gut microbiota composition [11••,12••,13]. It has been observed that significant changes of the microbial composition

Figure 1



Effect of GF on brain pathology.
Major neuronal and inflammatory mechanisms implicated in stroke, AD and PD in comparison to non-diseased condition as demonstrated in animal models. All of the three diseases lead to gut microbiome dybiosis, neuronal death, behavioral deficits, microglia activation, pro-inflammatory milieu in the gut, intestinal motility impairment and/or increased gut permeability. In a context of GF condition, microglia showed an

are apparent in the gut during the acute phase of stroke [12••,14,15] which has been correlated with the severity of brain lesions. Singh *et al.* showed that the bacterial diversity in stool is reduced in mice with a severe stroke, whereas the microbiome of mice subjected to a mild stroke was identical to controls. The overall changes were reflected in a reduction of the Firmicutes with a concomitant overgrowth of Bacteroidetes, representing the two main bacterial phyla in the gut. This shift was associated with reduced intestinal motility and an increased permeability of the intestinal wall [12••]. Shifts in the microbial populations were also observed in several portions along the GIT during the acute phase of stroke [14,15]. However, when analyzing microbiota changes at lower taxonomic ranks, some discrepancies regarding specific bacterial changes were observed across these studies. Houlden *et al.* found an increase in Peptococcaceae (Firmicutes phylum) and a decrease of Prevotellaceae (Bacteriodetes); Stanley *et al.* showed an increased abundance of *Akkermansia muciniphila* (Verrucomicrobia) and Clostridiales species (Firmicutes). Several differences in the experimental design could account for these differences, such as location of sampling (cecum versus small intestine), methods used for the extraction of genomic DNA and for 16S rRNA analysis, the severity of the stroke model and the baseline differences in the microbiota composition based on the provenance of the mice [16]. In turn, eradication of the microbiome in GF animals had a negative impact on stroke outcome (Figure 1) in comparison to control mice and GF mice colonized with a specific-pathogen-free (SPF) microbiome in early life (ex-GF mice) [12••]. In an attempt to resolve causal interdependencies, modification of the gut microbiome was performed using antibiotics before the induction of stroke. After two weeks of antibiotic treatment, there was a transient reduction in the bacterial density and an elimination of Clostridia and Bacteroidetes with a concomitant expansion in Proteobacteria. This shift was associated with an improved stroke outcome as shown by a significant reduction in the infarct volume and improvement of sensory and motor functions [11••]. To demonstrate causality, colonization with the microbiome from the antibiotic-treated mice — 'neuroprotective microbiome' — before the induction of stroke prevented the development of the infarct. Differences in the abundances of Ruminococcaceae, Verrucomicrobiaceae and Prevotellaceae can discriminate between the severity of brain damage - the larger the lesion volume the more pronounced the changes in the microbiota composition. Additionally, recent findings have identified that the microbiome from aged mice is associated with an imbalance of the ratio Firmicutes:Bacteroidetes in comparison to young mice. Interestingly, fecal matter transplantation from young mice into aged mice improved overall stroke outcome [17].

Clinical studies in stroke patients indicate an increase in diversity, a slight decrease in members of the phylum Bacteroidetes [18] and an increase in *Lactobacillus ruminis* (from the phylum Firmicutes) [13]. In contrast, analysis of fecal samples collected from AD patients has revealed a reduced diversity as well as an increased abundance in Bacteroidetes that was reproducible in animal models [19,20]. The composition of the PD microbiome in patients is characterized by increased abundances of *Akkermansia*, Bifidobacteriaceae, Enterobacteriaceae, Lactobacillaceae, and a dramatic decrease of Prevotellaceae which belongs to the phylum Bacteroidetes [21,22•]. However, these specific changes have not been recapitulated by all studies in PD [23] although some are already apparent at prodromal stages of the disease [22•]. Discrepancies in the shift of the microbiome between the different studies, and between patients and rodents, may be explained by confounding factors. Indeed, the observable shifts in the gut microbiome in PD might be linked to the gastrointestinal symptoms, for example, constipation, which are encountered in most patients [24]. In stroke patients, some of the identified shifts in the microbiota composition have been clearly associated with type-2 diabetes and the severity of the stroke [13], suggesting more complex interactions between the gut microbiome in patients with comorbidities and their impact on brain diseases. A disease-specific microbial 'fingerprint' has not yet been identified but might arise from future studies investigating larger patient cohorts and performing a more thorough characterization of the gut microbiome including functional analyses. Furthermore, consensus on molecular techniques, taxonomic levels, sample types and confounding factors should also be reached to allow comprehensive comparisons.

In contrast to stroke, in an AD mouse model, the lack or alteration of the gut microbiome in GF and antibiotic-treated mice, has been associated with a beneficial effect on AD pathology as shown by a reduced amyloid- β (Aβ) deposition (Figure 1) — according to the 'amyloid hypothesis' deposition Aβ plaques are the cause of neuronal degeneration and cognitive decline [25•,26]. Normalization of the antibiotics-induced changes using fecal transplants from control mice was able to at least partially restore AD pathology, indicating a causative role for the gut microbiome in some aspects of AD pathophysiology [27]. Interestingly, modification of the microbiome in AD mice was associated with a reduction in microglial activation [25•,26,28]. Similarly, using a severe mouse model of PD overexpressing the human α-synuclein

(Figure 1 Legend Continued) immature morphology suggesting a defective response to the brain damage. Indeed, GF mice subjected to stroke had a more severe brain pathology in comparison to SPF mice showed by an increase of the lesion volume. However, in a GF mouse model of AD and PD, aggregation of Aβ and SNCA was reduced, respectively and was associated with a better outcome.

(SNCA; aggregations of this protein in dopaminergic neurons are the major molecular hallmark of the pathology), Sampson *et al.* demonstrated that depletion of the gut microbiome reduced activation of microglia, motor deficits and GI defects, as well as SNCA aggregates in the brain, showing a better SNCA-associated brain pathology in mice depleted of gut microbiota (Figure 1) [29••]. Remarkably, colonization of these mice with a PD-derived gut microbiome from patients further enhanced motor dysfunction [29••]. However, following experimental stroke, microglia were less activated in the contralateral side of GF mice in comparison to ex-GF mice. In contrast to AD and PD, the lack of microglia response in GF mice was associated with a worsened stroke outcome [30]. This is particularly interesting, because the findings in AD and PD contrast with the common understanding that microglia are mainly involved in the phagocytosis of Aβ plaques and SNCA, respectively. Hence, an impaired activation is assumed to be associated with increased aggregates and reduced clearance. Together, the unexpected association of reduced microglial activation and lower pathological hallmarks of AD and PD with an altered microbial community needs to be further explored. In fact, the molecular mechanisms underlying microglia activation in relation to the gut microbiome and their effects in the development of acute and chronic brain disorders require further study. Additional immunological considerations about the involvement of alternative gut-immune pathways and gut metabolites in AD, PD and stroke beyond a putative role of microglia are further discussed below.

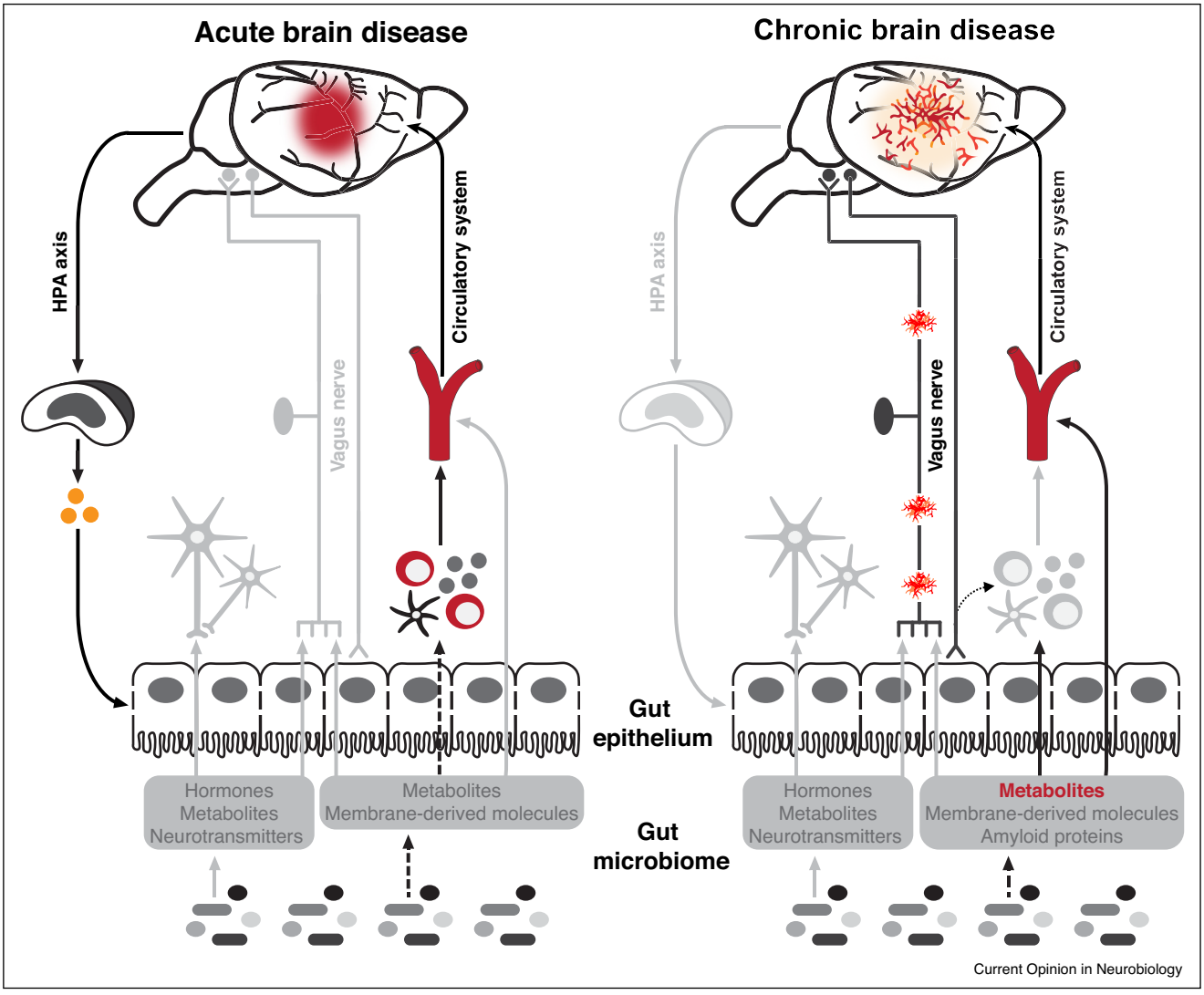
Microbiota-gut-brain axis mediators in acute and chronic diseases

Immune cells and the gut microbiome

The GIT is continuously exposed to millions of microbiome-derived molecules. Through constant contact with the microbial molecules, epithelial and immune cells in the gut have evolved a capacity to maintain a homeostatic state by defending host integrity while promoting tolerogenic responses to commensal microbes. Under healthy conditions, regulatory (T_{reg}) and effector T cells balance each other to preserve homeostasis [31•]. However, in diseases with inflammatory signatures, the fragile balance between protective function and immune modulation is dysregulated. In particular, T_{reg} cells play an important role in immune tolerance and the resolution of inflammation. An increase in inflammatory hyper-activation of effector lymphocytes or impaired T_{reg} functions represents common markers of chronic inflammation responsible for immunological tissue injury [32]. Consequently, it is important to consider the emergent functional properties of the gut microbiome in relation to the modulation of immune responses in relation to the gut-brain axis.

T lymphocytes play a crucial role in stroke progression. In particular the pro-inflammatory lymphocytic γδT-IL-17+ cells have been shown to promote lesion development, whereas anti-inflammatory T_{reg} cells are neuroprotective [33••,34]. A dysbiotic microbiome has been associated with an increase of CD4+-IL-17 cells in the gut and IL-17 expression in the brain [12••]. Additionally, colonization of GF mice with a microbiome from a SPF mouse has been found to be neuroprotective and showed a post-stroke mounted T cell-helper response in the gut and in the brain. These findings suggest that mice with a conventional microbiome generate an adequate lymphocyte-driven immune reaction in response to brain injury and trigger tissue protection. Importantly, the microbiome-mediated brain protection was absent in lymphocyte-deficient mice [30]. Interestingly, it has been highlighted that environmental factors modulating the gut microbiome are also important in mounting an inflammatory response in the gut. Indeed, mice from diverse commercial breeders exhibit a substantial variation in their microbiota composition and this influences the intestinal T cell response and the impact on stroke [16]. In another study, the key role of immune cells educated by the gut microbiome has been shown to have a considerable impact on stroke outcome (Figure 2). Bacterial priming of dendritic cells results in an expansion of T_{reg} in the gut, which secrete IL-10 to suppress pro-inflammatory IL-17+ γδT cells [11••]. Although this modulation of immune cells by the microbiota occurs in the gut, its effects are relayed to the brain, through T cell migration from the gut to the meninges [11••]. These findings highlight a direct connection along the gut-brain axis via intestinal T cells regulating the neuroinflammatory response to acute brain injury. In contrast, the direct link of the gut microbiome as an immunomodulator of AD and PD pathologies has not been fully explored yet. However, there is clear evidence which suggests that changes in the gut microbiome are associated with peripheral immune response in addition to the central neuroinflammation in AD and PD [29••,35,36]. Under physiological conditions the gut microbiome potently communicates with the peripheral immune system. Hence, gut microbiome shifts in AD patients can have a substantial impact on amyloidogenesis and disease progression not only by affecting cerebral immunity, but also by modulating the systemic immune response. In line with this hypothesis, previous studies have demonstrated that peripheral inflammation can modulate cerebral immunity in AD and that brain-invading T cells from the blood circulation also play a substantial role in AD-associated neuroinflammation [37]. The role of inflammation in PD [38•] is reinforced by the observation that patients with intestinal bowel disease taking anti-TNF-α therapy and individuals being treated with non-steroidal anti-inflammatory drugs are at a decreased risk for PD development [39]. Colonic biopsies and fecal markers evidence an elevated level of inflammatory cytokines in the gut and in the blood [36,40]. In addition, migration of peripheral, activated immunes cells to the brain has been described, directly linking systemic and encephalic inflammation [41]. A recent study reinforced the notion that PD may be an

Figure 2



Microbiome-gut-brain axis in acute and chronic brain diseases.
Summary of the current knowledge on the biological mechanisms implicated in the bidirectional microbiome-gut-brain interactions in acute (stroke) and chronic (AD and PD) brain disorders. Here is depicted the 3 main pathways of brain to gut communication: 1) immune cells via the blood circulation, 2) vagus nerve axis and 3) hypothalamo-pituitary-adrenal axis (HPA). Highlighted in black are the pathways with evidence from animal studies. In grey, are the un-investigated pathways. In particular, the role of the enteric nervous system and the possible bacteria-associated mediators: hormones, metabolites, neurotransmitters, have not been discussed here.

autoimmune disease, as approximately 40% of patients have auto-reactive T-cells activated by SNCA peptides [42]. Interestingly, both peripheral and neuroinflammation as well as increased gut permeability are augmented in PD [36]. Considering this complex interplay between peripheral immunity, the local immune response in the diseased brain and the impact of inflammation on AD and PD disease progression, it is conceivable that the microbiome could have a substantial impact on this well-balanced immunological network. Yet, the detailed mechanisms of peripheral-central immune interactions and the immune-active bacterial mediators involved herein are currently unexplored in chronic brain disorders and will require numerous future studies.

Vagus nerve and the gut microbiome

The VN provides bi-directional neuronal 'hardwiring' and is a mediator of the gut microbiome's effect in various brain diseases. This nerve regulates gut motility, secretions and inflammatory responses [43]. Studies in rodents demonstrate that following lipopolysaccharide (LPS) injection, the VN releases acetylcholine in the gut and suppresses secretion of TNF-α by gut resident macrophages. Regulation of inflammation by the efferent VN is

both local and systemic [44]. In PD patients, several studies have investigated the impact of vagotomy, yet due to the small number individuals, those studies have so far failed to demonstrate a clear involvement [45]. Braak *et al.* proposed the 'dual-hit hypothesis', postulating that a pathogen or a toxin may initiate PD pathogenesis by promoting SNCA aggregation [46]. This hypothesis is supported by animal studies where injection of fibrillar SNCA into the induces SNCA spreading along the VN toward the midbrain leading to neuronal damage [47,48]. Interestingly, SNCA aggregates are present in the patient's brain as well as along the gut-brain axis [49]. However, the role of the gut microbiome in affecting SNCA aggregation and further regulating the transport of SNCA to the CNS requires further study.

Despite these findings demonstrating a likely involvement of the VN in acute [50] and chronic brain diseases [51], its role in linking the gut microbiome to specific disease progression has so far not been comprehensively studied [45].

Microbial metabolites

Small molecules derived from the gut microbiome are the molecular basis for host-microbiome crosstalk. Among these molecules, a small fraction of bacterial metabolites have been shown to impact the host neurophysiology via multiple routes: blood circulation, humoral pathways, the immune system or neuronal pathways [52].

Short chain fatty acids

The degradation of dietary fiber by gut microbiota produces large amounts of SCFAs: acetate, propionate and butyrate in the gut. SCFAs enhance gut motility, lower inflammatory cytokines and modulate the adaptive immune tolerance as well as the level of gut hormones and neuropeptides [53]. SCFAs have been directly implicated in brain function, as for instance mono-colonization by a butyrate-producing bacterium restores the GF deficient BBB integrity and has a crucial role in the maturation of microglia [8•]. In a GF mouse model of PD, the oral gavage with SCFAs promotes microglia activation and motor dysfunction in comparison to GF vehicle-treated mice [29••]. Interestingly, the level of SCFAs in human feces has been linked to PD pathology [54]. Despite the key contribution of the gut microbiome to stroke outcome as well as AD and the identification of SCFAs as one of the microbiome's main bioactive mediators, the role of SCFA and their potential therapeutic use in stroke and AD has so far not been investigated (Figure 1).

Tryptophan metabolites

Tryptophan is an essential amino acid — sourced by the diet —, which is metabolized into the kynurenine pathway by the host or into indoles by the gut microbiota. Metabolites of tryptophan can modulate the intestinal immune cell function through the aryl hydrocarbon receptor (AHR) [55]. Several studies have shown that an increase in tryptophan catabolism is associated with the severity of stroke outcome in patients and might be related to the stroke-induced inflammatory response [56,57]. Stanley and colleagues found that the predicted metabolic KEGG pathway for xenobiotic biodegradation was regulated in the intestinal mucosal microbiota in a mouse model of stroke [15], suggesting that AHR ligands are regulated after stroke. In PD patients, CSF levels of tryptophan and kynurenic acid have been found to be significantly lower compared to healthy controls [58]. However, more work is required to decipher how tryptophan metabolites derived from microbes are linked to inflammation in brain disorders.

Membrane-derived molecules

Other gut microbiota-derived molecules have an important impact on host immunity and neurological diseases. A prominent example is the endotoxin lipopolysaccharide (LPS) which is a marker for chronic inflammatory diseases. Gut permeability facilitates LPS translocation and induces a strong inflammatory response which can disrupt the BBB and activate microglia [59]. In particular, gavage of wild-type mice with *Proteus mirabilis* reproduces PD-like symptoms and increased microglia activation via LPS [60•].

Aggregation of amyloid proteins is a key molecular hallmark of AD and PD. Functional amyloids represent a class of natively unfolded proteins produced by bacteria. They are involved in the composition of bacterial biofilms and are suggested to promote the aggregation of amyloid proteins involved in neurodegenerative diseases [61]. In the context of PD, one key study has revealed that gavage of rats with the functional amyloid-Curli-producing *Escherichia coli*, increases motors symptoms, SNCA aggregation and neuronal loss [62]. This study was the first showing a direct link between microbial amyloids, SNCA aggregation and neurological symptoms. However, further investigations are required to unravel the impact of gut microbial amyloids on brain diseases.

Conclusions

Here, we have described the emerging roles for the gut microbiome in affecting the pathological outcomes of acute and chronic brain disorders in animal models and human studies (Figure 2). Whereas it is well established that the microbiome influences numerous metabolic and immunologic aspects in health and disease, our understanding of how exactly the microbiota modulates brain function before and during disease progression is still limited. Studies implicating the microbiome-gut-brain axis have mainly involved associations between gut microbiome composition and disease symptomology. Detailed investigations of the mechanistic components —immune, neuronal, metabolic — of the complex bidirectional brain-gut interactions is required

to obtain a better understanding of the holistic aspects of brain diseases.

Financial support

This work was supported by the Luxembourg Fonds National de la Recherche (FNR) under grants CORE/BM/11333923 and AFR/Bilateral-RIKEN/11228553-4 and the Michael J. Fox Foundation under grant No. 14701 to PW; by the German Research Foundation (DFG, LI2534/2-1), the European Research Council (ERC-StG 802305) and the Munich Cluster for Systems Neurology (EXC 2145 SyNergy) to AL and by the European Marie Sklodowska-Curie grant agreement No 753893 to CB.

Conflict of interest statement

Nothing declared.

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- • of special interest
- •• of outstanding interest

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