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Human Gut Microbiome and its Association with Neurodegenerative Diseases: an Integrative Evidence Synthesis

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ABSTRACT

Background: Recent evidence has converged to indicate that the gut microbiome is involved in neurodegeneration via immune, metabolic, and neural mechanisms, but these reports are spread across diseases, designs and levels of certainty. RQ1: What are the gut microbial signatures in Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and Huntington's disease (HD)? and RQ2: Is there compelling evidence that the microbiome plays a causal role in disease and has therapeutic potential? The method used was purposive selection of 50 human observational studies, meta-analyses, preclinical experiments, intervention studies and reviews from peer-reviewed sources relevant to this study (2015-2024) and coding by disease and design and appraising using a five-stage evidence ladder. Results: Evidence focused on PD (40%) and AD (34%) with only moderate evidence coverage for ALS (10%) and HD (4%). A convergent functional signature was supported in PD and plausible in AD, but not in ALS or HD, and there was a significant difference in taxa between diseases. The causal evidence in animals was most convincing in the transfer, germ-free, and colonization experiments, while in humans, the causal evidence was preliminary, limited, and somewhat uncontrolled. Conclusions: H1 was somewhat supported and H2 was supported. In order to implement microbiome-based diagnostics and therapies in clinical practice, there is a need for large longitudinal metagenomic cohorts, medication adjusted designs, and sufficiently powered randomized trials.

Introduction

Neurodegenerative diseases like Alzheimer's (AD), Parkinson's (PD), amyotrophic lateral sclerosis (ALS) and Huntington's (HD) are marked by the gradual deterioration of the structure and function of neurons, and there are few effective disease-modifying treatments available (Loh et al., 2024; Sorboni et al., 2022). Over the past few decades, study has focused on mechanisms within the brain itself, such as protein misfolding, mitochondrial dysfunction and chronic neuroinflammation. Recently, however, interest has broadened to other peripheral systems that influence the health of the brain throughout the lifespan, with the

gastrointestinal tract, and its resident microflora, among the most studied of these systems (Cryan et al., 2019; Morais et al., 2021).

The human gut is home to a rich, metabolically active and complex flora, which not only breaks down food substrates, but also educates the immune system, supports epithelial barrier function and generates a diversity of bioactive molecules. These functions are connected to the central nervous system via immune-signaling, neural connections (e.g., vagus nerve and enteric nervous system) and circulating microbial metabolites (Cryan et al., 2019; Dalile et al., 2019), all of which have been described as the microbiota–gut–brain axis. Disturbance of this ecosystem, commonly referred to as dysbiosis, has thus been suggested to be a modifiable factor that is not the innocent bystander in neurological disease.

This idea became prominent as a result of several key experiments. Erny et al. (2015) showed that mice lacking a microbiota have immature and functionally impaired microglia, the brain's resident immune cells. The germ-free mice overexpressing α-synuclein exhibited fewer motor deficits and less neuroinflammation than conventionally colonized mice, while the germ-free mice were more susceptible to increase their motor impairments when colonized with microbiota from PD patients (Sampson et al., 2016). Harach et al. (2017) have reported that the colonization of germ-free transgenic AD mice resulted in significantly more cerebral amyloid-β (Aβ) accumulation than did the germ-free condition. These studies put the field on a mechanism trail, if only in a rodent.

But translating these findings to humans is no easy task. Studies of the human microbiome differ in sequencing methods, geographic and dietary background, sample size, and the way confounders are addressed, and disease-related medications can, in turn, change the makeup of the microbiome (Boertien et al., 2019; Hill-Burns et al., 2017). There is also some debate regarding the direction of causality: changes in gut motility, diet, and behavior could lead to a change in the gut microbiota and not the other way around (Heintz-Buschart et al., 2018; Sorboni et al., 2022). Current reviews usually focus on a specific disease or on mechanisms, making it hard to assess whether microbial signatures are common across diseases and the level of evidence that they are valid targets for therapeutic interventions.

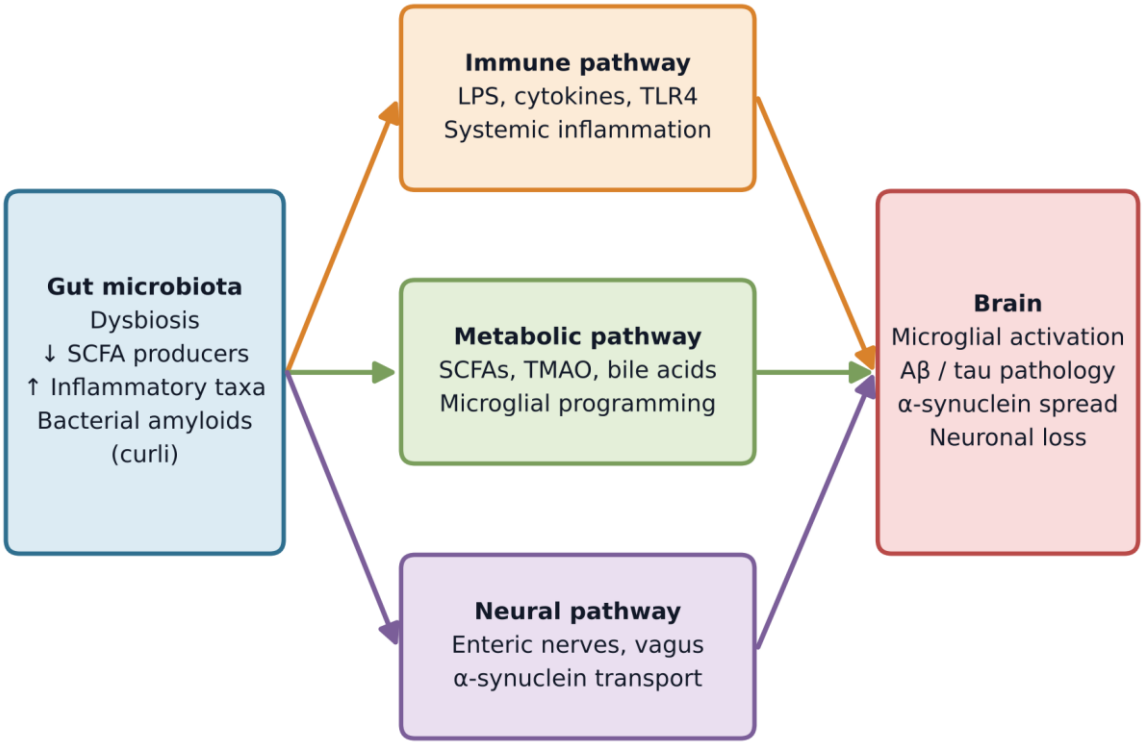
The present paper tackles these gaps by looking at an integrative evidence synthesis that covers AD, PD, ALS, and HD. It makes a contribution in three ways. First, it presents the distribution of evidence across disease, design and publication time, revealing areas of knowledge where it is concentrated, and where it is thin. Second, it uses an explicit coding scheme to compare microbial signatures between diseases. Third, it evaluates causal and therapeutic evidence via a graded hierarchy that separates association from mechanism, causal transfer, human intervention and clinical validation. The analysis is presented in relation to two research questions and two hypotheses outlined below.

Literature Review

The Microbiota – Gut – Brain axis: Architecture and signaling routes.

Communication between gut and brain is a two-way street and along at least three overlapping pathways, as summarized in Figure 1. The first is immune signaling. Bacterial elements like LPS bind to pattern-recognition receptors, driving systemic inflammation and disrupting the barrier in the intestine and blood–brain barrier, thus enhancing exposure of the brain to inflammatory mediators (Cryan et al., 2019; Sochocka et al., 2019). The second one is metabolic. Dietary fiber fermentation produces SCFAs, the main ones being acetate, propionate, and butyrate, which influence the epithelial barrier, immune cell differentiation, and maturation and activation of microglia (Dalile et al., 2019; Erny et al., 2015). Other microbial products such as trimethylamine N-oxide (TMAO) and secondary bile acids have been found to correlate with neurodegenerative biomarkers (Vogt et al., 2018). The third way is neural. Enteric neurons and vagal afferents can respond to microbial signals and misfolded proteins can be transported by these pathways (Kim et al., 2019).

Figure 1: Principal Signaling Routes of the Microbiota–Gut–Brain Axis in Neurodegeneration



Note. Schematic synthesized by the author from the cited literature. LPS = lipopolysaccharide; SCFA = short-chain fatty acid; TMAO = trimethylamine N-oxide.

Proteins also can have direct effects on aggregation due to the action of microbes. The amyloid protein curli from Escherichia coli has been shown by Chen et al (2016) to increase the aggregation of α-synuclein in aged rats and in the worm Caenorhabditis elegans. Subsequent studies by Sampson et al. (2020) demonstrated that gut bacteria that secrete curli were able to promote α-synuclein aggregation and motor impairment in mice, suggesting that bacterial amyloids may cross-seed host proteins. The literature suggests that the microbiome is a multi-channel modulator rather than a single causal factor and that the contribution of each channel likely varies from disease to disease (Cryan et al., 2019; Morais et al., 2021).

Barrier Function, Inflammation, and Microglial Programming

One common feature of all diseases is that the microbiota has an effect on immune status of the brain. Microglia are very responsive to microbial signals. Erny et al. (2015) noted that germ-free mice have immature microglia, and impaired responses to challenge; and that supplementation with SCFAs partially restored the phenotype, establishing a direct metabolic link between gut bacteria and brain immune cells. In a model of PD, Sampson et al. (2016) observed that SCFAs could actually cause microglial activation and motor deficits in mice that overexpressed α-synuclein, a finding that demonstrates how a gut metabolite that is thought to be beneficial, could be detrimental in a neurodegenerative context. Similarly, Colombo et al (2021) reported a double-edged effect of amyloid pathology, suggesting that the overall effect of SCFA is concentration, time, and stage dependent.

A second shared mechanism is the integrity of barriers. Some bacterial products, including LPS, can enter the circulation when the intestinal epithelium is permeable and activate innate immune cells and, both AD and PD are characterized by chronic low-grade inflammation (Bairamian et al., 2022; Sochocka et al., 2019). Human data support this possibility, as Marizzoni et al. (2020) found relationship between circulating LPS and SCFAs, and mucosal data in PD have demonstrated the enrichment of bacterial pro-inflammatory species (Keshavarzian et al., 2015). In animal models of ALS, increased intestinal permeability and abnormal function of Paneth cells have been noted in the disease model (Wu et al., 2015). Further evidence for the role of innate immune pathways comes from reduced inflammation and neuroprotection after microbiota-directed treatment in a toxin-induced PD model, which was associated with decreased TLR4 and tumor necrosis factor signaling (Sun et al., 2018). However, the question of whether barrier failure precedes or follows the downstream effects has yet to be determined..

Methodological Considerations in Human Microbiome Research

There are a number of methodological concerns in interpreting the human literature that can affect the conclusions that can be drawn. The first one is measurement. Shotgun metagenomics provides species and strain level resolution of communities as well as direct insight into functional genes, while early studies were based on 16S ribosomal RNA gene sequencing, which is only able to resolve communities at the genus or family level and is sensitive to primer choice and bioinformatic pipeline (Bedarf et al., 2017; Wallen et al., 2022). Thus, studies conducted on various platforms cannot directly be compared, and a systematic review of PD studies by Boertien et al. (2019) found that method variability was a key challenge for the reproducibility of such studies. Relative abundance data are also compositional data, that is, an apparent rise in abundance of one taxon may be due to a decrease in a second taxon.

Confounding is the second issue. Several factors like diet, age, body mass, bowel habit, geography and antibiotic exposure affect microbial composition and people with neurodegenerative disease tend to be different from the controls in a number of these aspects. Constipation is a frequent symptom in PD, and this is related to reducing the movements of the colon, and community changes. Particular concern is also around medications: Hill-Burns et al. (2017) demonstrated that PD medications have unique microbiome signatures, meaning that some of the apparent PD signal may be due to treatment. In part, this problem has been addressed in studies of drug-naive and early-stage patients, such as those of Bedarf et al., 2017; and meta-analytic studies have started revealing robust features from study-specific artifacts (Nishiwaki et al., 2020; Romano et al., 2021).

The third is temporal inference. Most studies only sample the microbiome once, and do not determine whether dysbiosis causes disease or is a consequence of disease. Thus, especially valuable are studies with longitudinal sampling, as done by Aho et al. (2019), and studies of the prodromal or preclinical populations, as in Ferreiro et al. (2023) and Heintz-Buschart et al. (2018). Finally, while animal models are key for causal inference, they cannot incorporate the full range of microbial composition, dietary exposures, or the genetic architecture of disease found in humans, and transgenic overexpression models only reflect certain facets of the disease (Cryan et al., 2019; Sorboni et al., 2022). Such factors encourage the staged process of evidence appraisals adopted in the present synthesis.

Alzheimer's Disease

Changes in gut community structure are consistently reported in human studies of AD, but different taxa are reported in different studies. Vogt et al. (2017) noted a decreased diversity of microbes in AD patients as well as lower levels of Firmicutes and Bifidobacterium and higher levels of Bacteroidetes, which were associated with cerebrospinal fluid markers of AD pathology. Interestingly, Zhuang et al. (2018) also reported that the fecal microbiota composition changed in a Chinese population, which suggests that dysbiosis is not limited to a particular population. Haran et al. (2019) linked the dementia associated microbiome to the dysregulated anti-inflammatory P-glycoprotein pathway, suggesting more of a functional disturbance than just a taxonomic change.

More importantly, there can be differences between the microbes and clinical symptoms. Ferreiro et al. (2023) found that among cognitively normal older adults, microbiome characteristics were linked to preclinical amyloid and tau pathology, indicating that gut alterations may occur early in the disease process. Metabolite studies provide additional information. Marizzoni et al. (2020) correlated circulating SCFAs and LPS with brain amyloid burden, and Vogt et al. (2018) observed elevated levels of TMAO in the CSF of individuals with mild cognitive impairment and AD which correlated with known disease markers. These results warn that the effects of microbial metabolites are not necessarily always beneficial or detrimental.

Animal experiments provide the best causal arguments. Harach et al. (2017) showed that the absence of a microbiota lowered Aβ pathology in transgenic mice. Kim et al. (2020) showed that transplanting microbiota from healthy donor mice led to a decrease in amyloid and tau pathology, and an improvement in cognition in a transgenic AD model. To add nuance, Colombo et al. (2021) reported the modulation of microglia by SCFAs and, in their model, the promotion of amyloid plaque deposition, indicating that the same metabolite can have different effects in different contexts. The microbiome was shown to interact with the ApoE genotype as a pathway to tau-mediated neurodegeneration, the effects of which varied by sex (Seo et al., 2023). There exists a model, which the narrative syntheses presented in this body of work converge on, whereby dysbiosis and barrier dysfunction are reinforcing each other as is microglial priming. (Bairamian et al., 2022; Kowalski & Mulak, 2019; Sochocka et al., 2019).

Parkinson's Disease

The human evidence base is the richest in the case of PD, partly because gastrointestinal symptoms (such as constipation) can precede motor signs. Prevotellaceae were found to be lower in individuals with PD and associated Enterobacteriaceae abundance and were associated with postural instability and gait difficulty, as reported by Scheperjans et al. (2015).

Keshavarzian et al. (2015) observed less anti-inflammatory, SCFA-producing bacteria and higher levels of pro-inflammatory taxa in the colonic mucosa and stool, and Unger et al. (2016) reported lower levels of fecal SCFAs and fewer Bacteroidetes and Prevotellaceae. Fecal microbiota alterations were also reproduced in a Chinese sample (Qian et al., 2018), and functional and taxonomic alterations were even observed in early-stage, levodopa-naive patients (Bedarf et al., 2017), suggesting that these changes were not due to medication alone.

Longitudinal and prodromal designs enhance the interpretation. Aho et al. (2019) determined that the PD associated microbiota was relatively stable over 2 years and some taxa correlated with disease progression. The authors of the study reported by Heintz-Buschart et al. (2018) indicated that gut changes occurred in people with idiopathic REM sleep behaviour disorder, a prodromal state, before motor onset, suggesting that dysbiosis may be a precursor to motor onset. In a large cohort, Wallen et al. (2022) used shotgun metagenomics to identify differences in a large number of species and pathways associated with disease, including reduction in SCFA-producing species and increased populations of opportunistic pathogens.

Meta-analyses can help to distinguish reproducible signals from noise. Nishiwaki et al. (2020), Romano et al. (2021) and Shen et al. (2021) all found depletion of SCFA-producing Lachnospiraceae-type bacteria, while others were enriched, but the idea of enriching taxa remains controversial as some bacteria are increased by medication use and constipation (Boertien et al., 2019; Hill-Burns et al., 2017). Mechanistic work suggests a gut-first pathway in at least some patients. Kim et al., 2019 reported that α-synuclein fibrils injected in the gut wall of mice spread to the brain through the vagus nerve and Sun et al., 2018 reported that fecal microbiota transplantation (FMT) improved gut dysbiosis, glial activation and neurodegeneration in a toxin-induced PD model.

Amyotrophic Lateral Sclerosis and Huntington's Disease

In ALS and HD the evidence is much less significant. Wu et al. (2015) reported intestinal permeability, impaired function of Paneth cells, and decreased butyrate-producing bacteria in a mouse model of ALS. Later, Zhang et al. (2017) demonstrated that the use of butyrate as a supplement was effective in protecting the gut and slowing disease progression in a similar model. Blacher et al. (2019) identified specific commensals that influenced disease course in the mouse and found that the microbial metabolite nicotinamide was beneficial for motor function, as well as lower levels of nicotinamide in the CSF of patients.

There is less consistency in human ALS data. Di Gioia et al. 2020 have studied the changes in microbiota over time in patients, while Nicholson et al. 2021 found some but inconsistent taxonomic changes between people with ALS and controls. In HD, Kong et al. (2020) reported dysbiosis in the gut of a transgenic mouse model and Wasser et al. (2020) demonstrated that gut dysbiosis occurred in HD patients was linked to cognitive performance and clinical parameters. Small, promising studies have been conducted, but it is not known if there is a human signature that is reproducible in either disease.

Microbiome-Targeted Interventions

Interventions can be dietary, probiotic, and transplantation. There are 2 randomized trials reporting improvement in cognitive and metabolic parameters after taking probiotics (Akbari et al., 2016) and after the combined probiotic and selenium supplementation (Tamtaji et al., 2019) in AD. A dietary intervention study using a modified Mediterranean-ketogenic diet in patients with mild cognitive impairment showed that it also modified the microbiome and SCFA profile, which was associated with CSF markers of AD (Nagpal et al., 2019) and a single case report showed cognitive improvement after FMT (Hazan, 2020). A single report of an open-label FMT trial in constipated patients showed positive outcomes for gastrointestinal and motor-related outcomes (Kuai et al., 2021), and another case series showed mixed results (Segal et al., 2021). The potential and the immaturity of therapeutic avenues are highlighted in reviews (Loh et al., 2024; Sorboni et al., 2022).

Research Questions and Hypotheses

The literature reviewed above shows mixed evidence that is promising. In order to organize the synthesis, two research questions and related hypotheses were created, and they are related to the evidence ladder as presented in Figure 2.

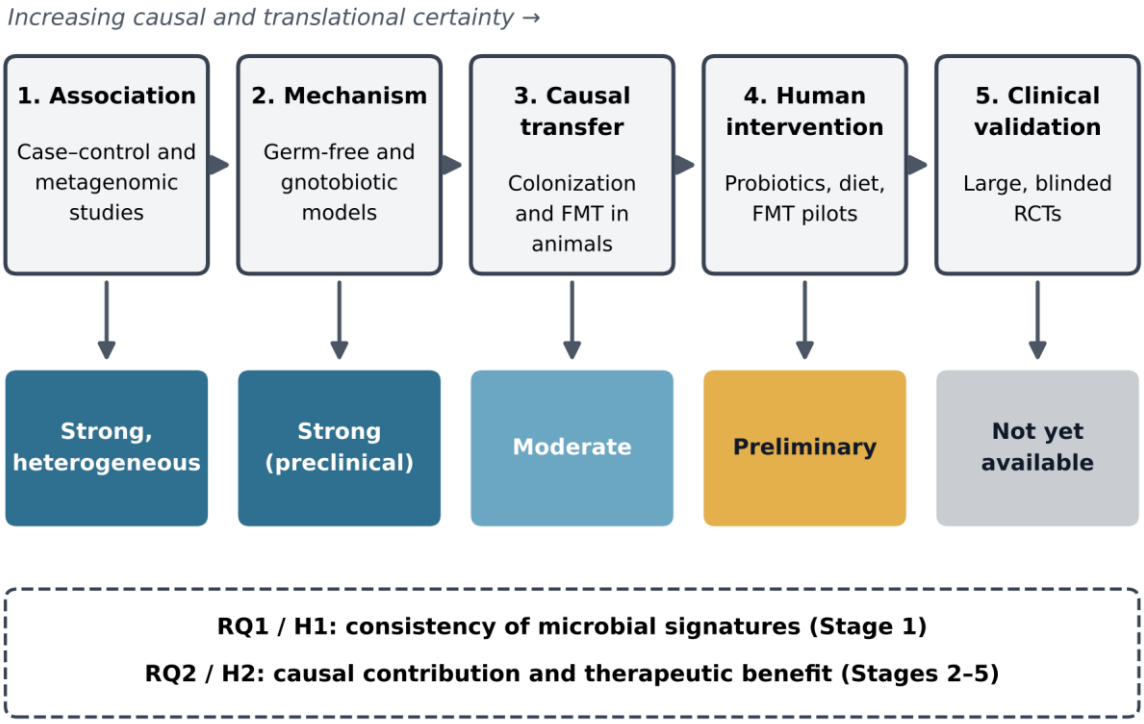
RQ1. Are there similar or distinct microbial signatures in AD, PD, ALS and HD, and, if so, are there common functional features?

H1. By disease there will be a convergence in functional pattern, i.e. depletion of taxa that produce SCFA and an enrichment of pro-inflammatory or mucosa-associated taxa, while specific taxa will vary by disease. The consistency of this pattern will be highest in PD, medium in AD and lowest in ALS and HD, due to the disparity of the amount and quality of available evidence.

RQ2. What is the evidence for the causal link between gut microbiome and neurodegeneration and what is the clinical impact of gut-targeted interventions?

H2. Causal evidence will be more evident in preclinical experiments than in human experiments, and human intervention evidence will be preliminary with small sample sizes, short follow-up, and limited blinding, and there will be no adequately powered confirmatory trials.

Figure 2: Evidence Ladder for Causal and Translational Appraisal and Its Link to the Research Questions



Note. Certainty ratings reflect the author's qualitative appraisal. FMT = fecal microbiota transplantation; RCT = randomized controlled trial; RQ = research question; H = hypothesis.

Method

Design and Rationale

An integrative evidence synthesis was selected due to the question crossing a variety of designs including case–control cohorts, metagenomic studies, gnotobiotic experiments, and small clinical trials, which make it impossible to directly compare and combine their results statistically. Integrative approaches enable the systematic and systematic comparison of different types of evidence while maintaining each type's strengths and weaknesses. The synthesis was descriptive and interpretive and an overall effect size was not calculated. It is, thus, more of an evidence map with structured narrative appraisal than a formal meta-analysis.

Source Selection

To represent the main lines of evidence linking the gut microbiome with neurodegeneration, 50 peer-reviewed publications from 2015 to 2024 were purposefully chosen. The criteria for selection were: (a) the article analyzed gut microbial composition, metabolites, or interventions that targeted the microbiome in relation to AD, PD, ALS, or HD, or included mechanisms that were shared across the different neurodegenerative diseases; (b) the article was published in a peer-reviewed journal with high visibility in neuroscience, microbiology, gastroenterology, or movement disorders; and (c) the article provided primary data, a quantitative synthesis, or an authoritative review. Studies using shotgun metagenomics or longitudinal designs were given priority, as were highly cited foundational studies, and studies reporting interventions. As the sample was not exhaustive but rather purposive, the sample represents the major evidence base but cannot claim to have identified all relevant publications.

Coding and Evidence Appraisal

The sources were all coded for disease (AD, PD, ALS, HD, or cross-disease), design (human observational, meta-analysis or systematic review, preclinical animal study, human intervention, or narrative review), and year of publication. The direction

of change for five microbial features (SCFA-producing taxa, Akkermansia, Bifidobacterium and Lactobacillus, Bacteroidetes, and pro-inflammatory Proteobacteria) was reported as an increase or decrease, or mixed or not established, for each disease, according to the directions reported in the cited human studies and meta-analyses for RQ1. A feature was only considered to be lower or higher if the available human evidence suggested the feature was clearly more likely to be lower or higher, respectively. Sources were sorted into five categories along an evidence ladder for RQ2: association, mechanism, causal transfer, human intervention, and clinical validation (Figure 2). Confounding, replication, sample size and design were assessed qualitatively at each step with certainty ranging from strong to not yet available, and intermediate levels.

Data Synthesis

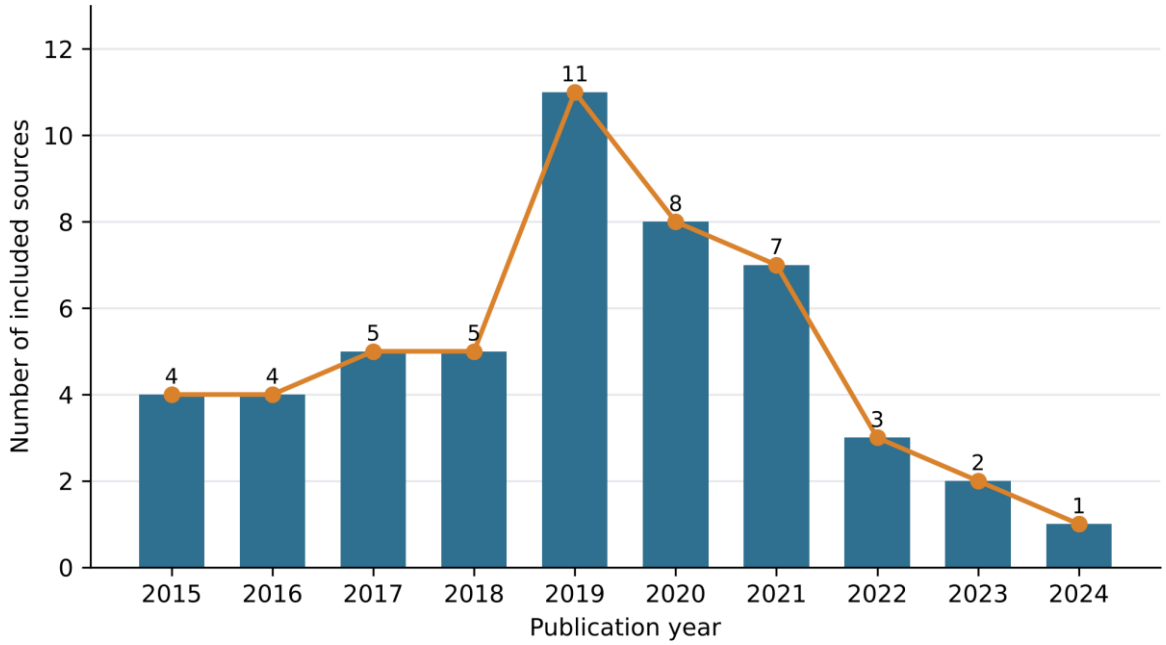
The evidence base was summarized using descriptive frequencies. Results were then compiled for human observational studies (Table 1), mechanistic pathways (Table 2) and interventions (Table 3). The hypotheses were tested by comparing coded evidence with the hypotheses predictions from H1 and H2, supported, partially supported and not supported. Since the coding was a judgment, the direction of change scheme should not be interpreted as an estimation of the statistical profile.

Results

Characteristics of the Evidence Base

The 50 sources spanned 2015 to 2024. Forty-two (84%) were published from 2017 onward and 32 (64%) from 2019 onward, with a peak of 11 sources in 2019 (Figure 3). Within this sample, fewer items were produced after 2021, not a decrease in research output, but a selection of foundational and high impact work.

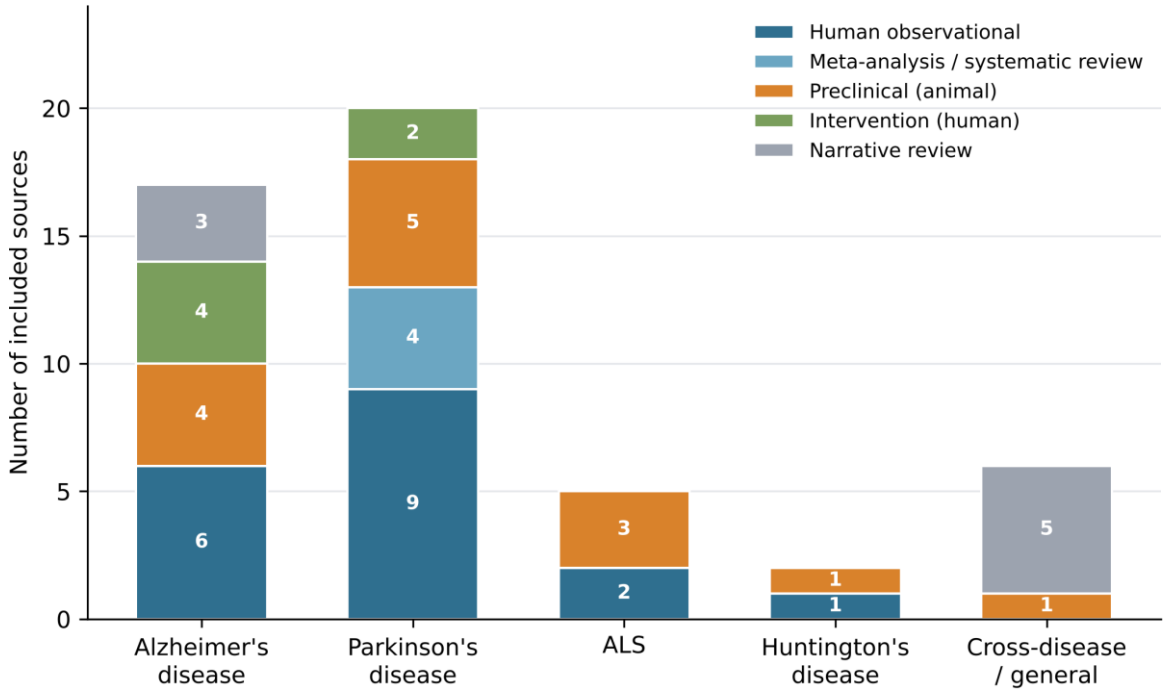
Figure 3: Number of Included Sources by Publication Year



Note. N = 50 sources. Counts are derived from the reference list of this synthesis and reflect purposive selection.

Studies included human observational studies (n = 18, 36%); preclinical animal studies (n = 14, 28%); narrative reviews (n = 8, 16%); human intervention studies (n = 6, 12%); and meta-analysis (n = 4, 12%). The 20 sources with PD represented 40%, and the 17 sources with AD represented 34% of all sources, while the five sources with ALS accounted for 10%, the two with HD accounted for 4%, and the six sources with cross-disease accounted for 12% of total sources. None of the meta-analyses included the microbiome of the AD, ALS, or HD; all were for the PD. No human intervention studies were conducted in ALS and HD (Figure 4), but were conducted in AD (n = 4) and PD (n = 2). This distribution is of importance in itself, since it is clear that the conclusions for ALS and HD are based on very limited studies, whereas for PD a quantitative synthesis is possible.

Figure 4: Included Sources by Disease and Study Design



Note. N = 50 sources. AD = Alzheimer's disease; PD = Parkinson's disease; ALS = amyotrophic lateral sclerosis; HD = Huntington's disease.

Microbial Signatures Across Diseases (RQ1)

A summary of representative human observation studies is provided in Table 1. The results of independent cohorts, a longitudinal study, a prodromal comparison and three meta-analyses were similar in PD: decreased abundance of SCFA-producing bacteria and increased abundance of Akkermansia, Lactobacillus, and Bifidobacterium (Nishiwaki et al., 2020; Romano et al., 2021; Shen et al., 2021). The results of the fecal SCFA measurements confirmed the taxonomic signal (Unger et al., 2016), and early involvement and functional breadth were provided by Heintz-Buschart et al. (2018) and Wallen et al. (2022). However, there was some lack of reproducibility within individual taxa. For instance, Prevotellaceae was relatively abundant in some cohorts but did not always appear, hence it is not included as a consensus feature.

Table 1: Representative Human Observational Studies of the Gut Microbiome in Neurodegenerative Disease

Disease	Study	Population and design	Principal finding
PD	Scheperjans et al. (2015)	PD vs. controls; fecal microbiota	Lower Prevotellaceae; Enterobacteriaceae linked to postural instability and gait difficulty
PD	Keshavarzian et al. (2015)	PD vs. controls; stool and colonic mucosa	Fewer anti-inflammatory, SCFA-producing bacteria; more pro-inflammatory taxa
PD	Unger et al. (2016)	PD vs. age-matched controls	Lower fecal SCFAs; reduced Bacteroidetes and Prevotellaceae; more Enterobacteriaceae
PD	Heintz-Buschart et al. (2018)	PD, iRBD, and controls; nasal and gut samples	Gut alterations also present in iRBD, consistent with changes before motor onset
PD	Wallen et al. (2022)	Large shotgun metagenomic cohort	Many species and pathways altered; SCFA producers depleted, opportunistic pathogens enriched
AD	Vogt et al. (2017)	AD vs. controls; fecal microbiota and CSF markers	Reduced diversity; lower Firmicutes and Bifidobacterium; higher Bacteroidetes; correlation with CSF markers

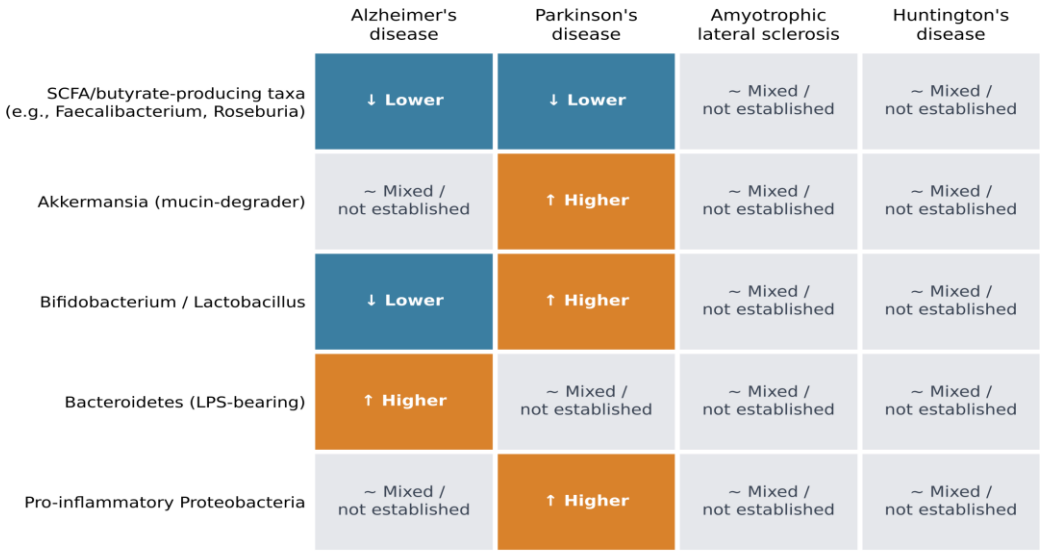
Disease	Study	Population and design	Principal finding
AD	Haran et al. (2019)	Dementia-associated microbiome; functional analysis	Altered microbiome linked to dysregulated anti-inflammatory P-glycoprotein pathway
AD	Ferreiro et al. (2023)	Cognitively normal older adults with and without preclinical AD	Microbiome features associated with preclinical amyloid and tau pathology
ALS	Nicholson et al. (2021)	People with ALS vs. controls	Limited and inconsistent taxonomic differences
HD	Wasser et al. (2020)	HD gene carriers vs. controls	Dysbiosis associated with cognitive performance and clinical outcomes

Note. AD = Alzheimer's disease; ALS = amyotrophic lateral sclerosis; CSF = cerebrospinal fluid; HD = Huntington's disease; iRBD = idiopathic rapid eye movement sleep behavior disorder; PD = Parkinson's disease; SCFA = short-chain fatty acid.

Another human study showed loss of beneficial taxa, such as lower levels of Bifidobacterium, Firmicutes, and higher levels of Bacteroidetes (Vogt et al., 2017), along with functional signals in relation to anti-inflammatory signaling and metabolite profiles (Haran et al., 2019; Marizzoni et al., 2020; Vogt et al., 2018). Evidence from animal models, in contrast, was more detailed than evidence from humans (Harach et al., 2017; Kim et al., 2020; Seo et al., 2023). While mouse studies revealed that butyrate-producing bacteria were decreased and barrier function was impaired in ALS, human studies showed inconsistent and limited differences. (Wu et al., 2015; Zhang et al., 2017; Di Gioia et al., 2020; Nicholson et al., 2021). Microbial changes were recorded in a mouse model and in humans, but were available from only two sources in HD (Kong et al., 2020; Wasser et al., 2020).

The coded directions are gathered together in Fig. 5. SCFA-producing bacteria were assigned lower scores in both AD and PD, while pro-inflammatory Proteobacteria, one of the genera in the group, were assigned higher scores in PD.Pro-inflammatory Proteobacteria, one of the genera of the group, was coded as higher in PD, and SCFA-producing taxa were coded as lower in both AD and PD. Taxa-level patterns differed between the two major diseases, with Bacteroidetes being coded as higher in AD, while Bifidobacterium and Lactobacillus were coded as lower in AD and higher in PD. None of the features could be coded with confidence in ALS or HD. Thus, the common factor in both AD and PD was not taxonomic, but instead focused on the loss of the ability to produce SCFA.

Figure 5: Coded Direction of Change in Key Gut Microbial Features by Disease



Note. Direction of change reflects the predominant direction reported across the cited human studies and meta-analyses and is a qualitative summary, not a pooled effect size. SCFA = short-chain fatty acid.

Strength and Consistency of Evidence by Disease

When design and signature are combined, a disease level appraisal of evidence maturity is achievable. The most advanced field was PD, which was investigated by independent cohorts, longitudinal and prodromal designs, metagenomic analyses, three meta-analyses, mechanistic animal study, and early clinical studies (Aho et al., 2019; Nishiwaki et al., 2020; Wallen et al., 2022). This finding is more credible than any one of the cohorts, because it is consistent across such different designs of lower taxa that produce the lower SCFA. However, the enrichment of Akkermansia, Lactobacillus, and Bifidobacterium has a somewhat mixed message as, these taxa could also be influenced by constipation, by drug therapy, and are generally regarded as beneficial (Boertien et al., 2019; Hill-Burns et al., 2017).

AD was intermediate. It had an adequate number of human observational studies (including cohorts from the United States and China), as well as very good preclinical evidence and the two randomized trials in the sample (Akbari et al., 2016; Tamtaji et al., 2019; Vogt et al., 2017; Zhuang et al., 2018). No meta-analysis was available, however, some taxa results varied between studies and metabolite results were not consistent in direction (Colombo et al., 2021; Marizzoni et al., 2020). The least developed were the ALS and HD. Mechanistic stories, such as those in mice where barrier dysfunction and butyrate and nicotinamide play a role (Blacher et al., 2019; Wu et al., 2015; Zhang et al., 2017) were not supported by consistent findings in humans using taxonomic analysis (Di Gioia et al., 2020; Nicholson et al., 2021). There were no studies in humans or animals in HD, so no judgement on consistency could be made. Across all these groups, the level of evidence became less mature from PD to AD to ALS to HD, with a decreasing level of evidence ranking similar to that predicted in H1.

Mechanistic Pathways (RQ2)

There are seven mechanistic pathways summarized in Table 2. Microbiological regulation of microglia via SCFAs was the most well established pathway in preclinical studies, albeit with disease model and context specific outcomes (Colombo et al. 2021; Erny et al. 2015; Sampson et al. 2016). There are animal models of gut-to-brain transmission of misfolded α-synuclein via the vagus nerve (Kim et al., 2019) and microbial amyloid cross-seeding (Chen et al., 2016; Sampson et al., 2020) which do not have an obvious human equivalent. Most of the human evidence was of an associative nature, such as the measurement of TMAO and SCFA in humans with AD (Marizzoni et al., 2020; Vogt et al., 2018). Barrier dysfunction, butyrate and nicotinamide were proposed as candidate pathways in ALS, based on mouse studies (Blacher et al., 2019; Wu et al., 2015; Zhang et al., 2017). Any mechanistic model is complicated by the fact that microbiome effects are genotype and sex specific, as shown by Seo et al. (2023).

Table 2: Candidate Mechanistic Pathways Linking the Gut Microbiome to Neurodegeneration

Pathway	Key mediators	Representative evidence	Evidence level
Microglial programming	SCFAs (acetate, propionate, butyrate)	Immature microglia in germ-free mice (Erny et al., 2015); SCFAs promote microglial activation in PD model (Sampson et al., 2016) and amyloid deposition in AD model (Colombo et al., 2021)	Preclinical, strong; human, indirect
Innate immune activation and barrier dysfunction	LPS, TLR4, cytokines	FMT attenuates TLR4/TNF-α signaling in PD model (Sun et al., 2018); LPS and SCFAs relate to amyloid burden (Marizzoni et al., 2020)	Mixed (preclinical and human association)
Bacterial amyloid cross-seeding	Curli, α-synuclein	Curli enhances α-synuclein aggregation (Chen et al., 2016; Sampson et al., 2020)	Preclinical
Vagal and enteric propagation	Misfolded α-synuclein	Gut-to-brain spread via the vagus nerve (Kim et al., 2019)	Preclinical
Microbial metabolites in the CNS	TMAO	Higher CSF TMAO in MCI and AD (Vogt et al., 2018)	Human association
Host genotype–microbiome interaction	ApoE, sex	Microbiome and ApoE isoform influence tau pathology (Seo et al., 2023)	Preclinical
Gut barrier and neuroprotective metabolites in ALS	Butyrate, nicotinamide	Leaky intestine (Wu et al., 2015); butyrate benefit (Zhang et al., 2017); nicotinamide benefit (Blacher et al., 2019)	Preclinical

Note. AD = Alzheimer's disease; ALS = amyotrophic lateral sclerosis; CNS = central nervous system; CSF = cerebrospinal fluid; FMT = fecal microbiota transplantation; LPS = lipopolysaccharide; MCI = mild cognitive impairment; PD = Parkinson's disease; SCFA = short-chain fatty acid; TMAO = trimethylamine N-oxide.

Causal and Therapeutic Evidence (RQ2)

Figure 2 shows that there was a clear gradient with placement on the evidence ladder. Association evidence (Stage 1) was of mixed intensity, mechanistic evidence from germ-free and gnotobiotic models (Stage 2) was strong in rodents, and causal transfer (Stage 3) through colonization or FMT was moderate, and is largely restricted to models of AD and PD (Kim et al., 2020; Sampson et al., 2016; Sun et al., 2018). No adequately powered and blinded confirmatory trial (Stage 5) was identified and preliminary human interventions (Stage 4) were limited.

The evidence for the interventions is presented in Table 3. The results from the two AD randomized trials were also obtained from cognitive scales of measurement and metabolic markers were used (Akbari et al., 2016; Tamtaji et al., 2019), and were small and of limited duration. In humans, there was one case report of transplantation in AD (Hazan, 2020), one open-label study of transplantation in PD with constipation (Kuai et al., 2021), and a case series with mixed outcomes (Segal et al., 2021). In contrast, FMT in animal models of AD and PD consistently reduced the pathology (Kim et al., 2020; Sun et al., 2018). These two levels of evidence make up the main empirical result of RQ2.

Table 3: Summary of Microbiome-Targeted Interventions and Certainty of Evidence

Intervention	Disease or model	Design	Reported outcome	Certainty
Multispecies probiotic (Akbari et al., 2016)	AD	Randomized, double-blind, controlled trial	Improved cognitive scores and some metabolic markers	Low to moderate (small trial)
Probiotic plus selenium (Tamtaji et al., 2019)	AD	Randomized, double-blind, controlled trial	Improved cognitive and metabolic measures	Low to moderate (small trial)
Modified Mediterranean-ketogenic diet (Nagpal et al., 2019)	MCI	Pilot dietary trial	Microbiome and SCFA changes related to CSF markers of AD	Low (pilot)
FMT (Hazan, 2020)	AD	Single case report	Reported cognitive improvement	Very low
FMT (Kuai et al., 2021)	PD with constipation	Open-label clinical study	Improved gastrointestinal and motor measures	Low (uncontrolled)
FMT (Segal et al., 2021)	PD	Case series	Variable benefit across patients	Very low
FMT (Sun et al., 2018; Kim et al., 2020)	PD and AD mouse models	Preclinical experiments	Reduced neurodegeneration, glial activation, and amyloid and tau pathology	Preclinical, consistent

Note. Certainty ratings are the author's qualitative appraisal based on design, sample size, control, and replication. AD = Alzheimer's disease; CSF = cerebrospinal fluid; FMT = fecal microbiota transplantation; MCI = mild cognitive impairment; PD = Parkinson's disease; SCFA = short-chain fatty acid.

Hypothesis Evaluation

Partial support was provided for H1. Functional convergence (loss of SCFA-producing capacity) was predicted for both PD and AD and was strongly supported for PD and plausible for AD; taxa-level divergence between diseases was confirmed. This was confirmed by the prediction of lowest consistency in ALS and HD, which is not as much due to a biological difference as due to the lack of human data. A main support for enrichment of pro-inflammatory or mucosa-associated taxa was given for PD. H2 was supported. There was minimal available causal evidence, small intervention size in humans and no confirmatory trial identified. The evidence as a whole is consistent with a model where the microbiome is a modifiable contributor rather than a direct cause of neurodegeneration and effects depend on host context (Morais et al., 2021; Seo et al., 2023).

Discussion

Interpretation of Findings

The synthesis indicates that the microbeome–neurodegeneration connection is best thought of as a functional vulnerability that manifests in disease-specific taxa. The perpetual loss of SCFA-producing bacteria in PD and AD is biologically relevant because SCFAs are known to play an important role in the maintenance of epithelial barrier function, in the limitation of inflammation, and in the regulation of microglial maturation (Dalile et al., 2019; Erny et al., 2015). However, the results of Colombo et al. (2021) provide a warning: simple statements of the positive effects of SCFAs are not sufficient, and the decrease of Bifidobacterium and increase of Lactobacillus in the AD compared to PD indicates that beneficial microbes can be depleted in one context and enriched in another. Descriptions of community function (what they do) rather than descriptions of genera present are likely to be more transferable across studies (Wallen et al., 2022).

Stages of evidence has implications for interpretation. While experiments in germ-free and colonized animals show microbiota influence disease processes (Harach et al., 2017; Sampson et al., 2016), the genetic makeup and dietary habits of rodents are significantly different from those of humans, and transgenic animals only recapitulate part of human disease. Data on humans, on the other hand, continue to be largely cross-sectional. Indirect symptoms (prodromal findings) of iRBD and preclinical AD suggest that dysbiosis might occur prior to the onset of symptoms (Ferreiro et al., 2023; Heintz-Buschart et al., 2018), which favors a contributory role, yet the possibility of reverse causation through constipation, dietary change, and altered motility cannot be excluded without longitudinal sampling and experimental human data (Aho et al., 2019; Sorboni et al., 2022).

Implications for Research and Practice

Three implications follow. First, association with CSF markers and preclinical pathology (Ferreiro et al., 2023; Vogt et al., 2017) suggest that microbiome signatures could eventually be used as a diagnostic tool for early detection and/or risk stratification, especially when combined with other known markers. This will require population-specific, validated reference ranges, and standardized pipelines. Secondly, modifiable lifestyle factors like diet can alter the function of microbes that are relevant to disease, and the dietary pilot of Nagpal et al. (2019) offers a template for mechanistically informed trials. Third, treatments targeting the microbiome should be considered as investigational. There were some preliminary signals of efficacy in small trials using probiotics (Akbari et al., 2016; Tamtaji et al., 2019) and anecdotal or uncontrolled evidence of efficacy with FMT in humans (Hazan, 2020; Kuai et al., 2021; Segal et al., 2021). Efficacy will be as important as the safe and standardized delivery, donor selection and long-term safety monitoring (Loh et al., 2024).

Comparison With Prior Syntheses

The present results corroborate earlier narrative reviews that suggested that the microbiome may modulate neuroinflammation and the aggregation of proteins in AD and PD (Bairamian et al., 2022; Kowalski & Mulak, 2019; Sochocka et al., 2019). They extend this literature in two ways. First, it puts four studies of four diseases in one analytic frame, so that the common factor is a functional, rather than taxonomic, one, thus helping to reconcile reports which may seem contradictory at the genus level. Second, it makes it explicit that the quality of the causal argument differs markedly if the supporting study is a rodent transfer experiment as opposed to a human observational comparison. This mechanistic versus clinical distinction can also be seen in broader gut–brain axis reviews (Cryan et al., 2019; Morais et al., 2021).

The conclusions also support the recent systematic reviews in PD, which were more cautious in their conclusions, suggesting that methodological heterogeneity does not facilitate comparison across studies (Boertien et al., 2019) and that there are some common patterns in the meta-analyses (Nishiwaki et al., 2020; Romano et al., 2021; Shen et al., 2021). The lack of evidence for ALS and HD is consistent with the general lack of focus in the field, with AD and PD being overrepresented, and rare neurodegenerative disorders being underrepresented (Sorboni et al., 2022).

Toward an Integrated Model

Combining these immune, metabolic and neural pathways in Figure 1 with the evidence ladder in Figure 2 points to a testable model. Lowering the resistance barrier of epithelia and blood–brain barrier (BBB), priming microglia, and promoting protein aggregation in the enteric and central nervous system (CNS) may be due to reduced capacity to produce SCFAs, and increased exposure to inflammatory or amyloidogenic microbial products in genetically or environmentally susceptible individuals (Chen et al., 2016; Erny et al., 2015; Kim et al., 2019; Sampson et al., 2020). The influences on these may lead to pathology, or they may not, depending on host factors like genotype and sex as demonstrated in the ApoE study by Seo et al., 2023. The model suggests that the dysbiosis would be detectable prior to clinical onset, that the functional characteristics of dysbiosis would be conserved across populations, and that restoring the capacity to produce SCFA would be most effective when introduced early

in the disease process – all of which are open to empirical testing (Aho et al., 2019; Ferreiro et al., 2023; Heintz-Buschart et al., 2018).

Clinical Translation and Ethical Considerations

Safety, standardization and equity are all key to clinical translation. However, FMT is a process that involves the transfer of complex living communities, and donor screening, delivery route, dose and long-term follow-up have not yet been standardized for neurological indications (Loh et al., 2024). Placebo effect, spontaneous variation and publication bias can apply to case reports and uncontrolled series, and should not be used to direct routine care (Hazan, 2020; Segal et al., 2021). Probiotics are widely available but due to strain dependence of effects and limited size of available trials, it is not recommended to use a general recommendation (Akbari et al., 2016; Tamtaji et al., 2019). The microbiome and disease biomarkers warrant more trials with dietary strategies as they are lower risk. Last, microbiomes are geographically and even geographically and regionally varied and studies from underrepresented regions are essential to prevent inequitable translation, and diagnostic tools designed from one population may not work well in another (Qian et al., 2018; Zhuang et al., 2018).

Limitations

There are a number of caveats to consider. The evidence base is not exhaustive, proportions here refer to the sample for source selection and do not represent the whole literature. The coding of direction of change was subjective and was based on what was reported in the studies cited above rather than reanalysis of raw data. There were geographical differences, differences in diet, differences in the sequencing approach, and differences in treatment of the effects of medication in human studies that could not be harmonised (Boertien et al., 2019; Hill-Burns et al., 2017). For ALS and HD, there are also few sources identifying ALS and HD, and even fewer sources quantitatively aggregating results for these two diseases, which reduce the scope of RQ1 for these two diseases. Finally, publication bias to positive results is a potential possibility in an emerging field, and can make the association evidence appear stronger than it actually is.

Future Directions

Large, prospective, metagenomic cohorts that repeatedly follow large numbers of participants in prodromal and early stages of the disease with detailed records of medications, diet and bowel function should be prioritized, and these designs allow for testing of temporal precedence (Aho et al., 2019; Wallen et al., 2022). To draw similar conclusions to those in PD, one needs to conduct a similar meta analysis to those performed in PD for AD, ALS, and HD. Mechanistic research needs to shift towards human-relevant systems such as gnotobiotic animals colonized by well-characterized human communities and metabolomic profiling to discriminate the effects of SCFA by compartment and context (Colombo et al., 2021; Seo et al., 2023). Lastly, randomized, adequately powered, and placebo-controlled studies with pre-registered analysis and biomarker endpoints are needed to establish if probiotic, dietary, or transplantation strategies can modify disease course (Loh et al., 2024; Nagpal et al., 2019)..

Conclusion

This integrative synthesis of 50 sources suggests that the human gut microbiome is consistently linked to neurodegenerative disease, especially PD and AD, and that a common functional trait, decreased capacity to produce short-chain fatty acids, might account for the seemingly unrelated taxonomic signatures. While the evidence in preclinical models is compelling, the evidence for microbiota causation and therapeutic benefits in humans is still of a preliminary nature. Progress will depend on longitudinal, medication-aware human cohorts, harmonized analytical pipelines, and rigorous randomized trials. Until such data are available, microbiome-targeted approaches should be framed as promising hypotheses rather than established treatments.

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