

## REVIEW

# The microbiota–gut–brain axis in Huntington’s disease: pathogenic mechanisms and therapeutic targets

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## Keywords

diet; gut dysbiosis; gut-brain axis; Huntington’s disease; microbiome; microbiota; mycobiome; neurodegeneration

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Huntington’s disease (HD) is a currently incurable neurodegenerative disorder and is typically characterized by progressive movement disorder (including chorea), cognitive deficits (culminating in dementia), psychiatric abnormalities (the most common of which is depression), and peripheral symptoms (including gastrointestinal dysfunction). There are currently no approved disease-modifying therapies available for HD, with death usually occurring approximately 10–25 years after onset, but some therapies hold promising potential. HD subjects are often burdened by chronic diarrhea, constipation, esophageal and gastric inflammation, and a susceptibility to diabetes. Our understanding of the microbiota–gut–brain axis in HD is in its infancy and growing evidence from preclinical and clinical studies suggests a role of gut microbial population imbalance (gut dysbiosis) in HD pathophysiology. The gut and the brain can communicate through the enteric nervous system, immune system, vagus nerve, and microbiota-derived-metabolites including short-chain fatty acids, bile acids, and branched-chain amino acids. This review summarizes supporting evidence demonstrating the alterations in bacterial and fungal composition that may be associated with HD. We focus on mechanisms through which gut dysbiosis may compromise brain and gut health, thus triggering neuroinflammatory responses, and further highlight outcomes of attempts to modulate the gut microbiota as promising therapeutic strategies for HD. Ultimately, we

## Abbreviations

3-NP, 3-nitro propionic acid; AAA, aromatic amino acid; ABX, antibiotics; AD, Alzheimer’s disease; ALS, amyotrophic lateral sclerosis; ASD, autism spectrum disorder; BA, bile acid; BBB, blood–brain barrier; BCAA, branched-chain amino acid; BCFA, branched-chain fatty acid; BMI, body mass index; CA, cholic acid; CA, corpora amylacea; CAG, cytosine-adenine-guanine; CAIP, cholinergic anti-inflammatory pathway; CART, cocaine- and amphetamine-regulated transcript; CCK, cholecystokinin; CDCA, chenodeoxycholic acid; CNS, central nervous system; CRP, C-reactive protein; CSF, cerebrospinal fluid; CXCL8, C-X-C motif chemokine ligand 8; EE, environmental enrichment; EEC, enteroendocrine cells; ENS, enteric nervous system; ER, endoplasmic reticulum; ET, essential tremor; EX, exercise; F/B, Firmicutes-to-Bacteroides; FMT, fecal microbiota transplantation; FXR, farnesoid X receptor; GABA,  $\gamma$ -aminobutyric acid; GF, germ-free; GIT, gastrointestinal tract; GLP-1, glucagon-like peptide 1; HD, Huntington’s disease; HDGEC, Huntington’s disease gene expansion carrier; HTT, huntingtin; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; IEC, intestinal epithelial cell; IF, intermittent fasting; IFN- $\gamma$ , interferon-gamma; IL, interleukin; IL-7R, interleukin-7 receptor; iNOS, inducible nitric oxide synthetase; KD, ketogenic diet; KO, KEGG orthology; LPS, lipopolysaccharide; MDD, major depressive disorder; MeDi, Mediterranean diet; mHTT, mutant huntingtin; MMP, matrix metalloproteinase; MMSE, Mini-Mental State Examination; mRNA, messenger RNA; MS, multiple sclerosis; MTM, mithramycin; ND, neurodegenerative disorder; NOD1, nucleotide-binding oligomerization domain-containing protein 1; PA, polyamine; PD, Parkinson’s disease; PERMANOVA, permutational multivariate analysis of variance; PGP, protein gene product; PRR, pattern recognition receptors; QA, quinolinic acid; ROS, reactive oxygen species; SCFA, short-chain fatty acid; SH, standard housing; SPF, specific pathogen-free; STAT-1, signal transducer and activator of transcription-1; TFC, total functional capacity; TGF- $\beta$ 1, transforming growth factor-beta1; TJ, tight junctions; TLR, toll-like receptor; TNF- $\alpha$ , tumor necrosis factor-alpha; TRKD, time-restricted ketogenic diet; TUDCA, tauroursodeoxycholic acid; UDCA, ursodeoxycholic acid; VaCHT, vesicular acetylcholine transporter; VIP, vasoactive intestinal polypeptide; VNS, vagal nerve stimulation; WT, wild-type; YAC, yeast artificial chromosome; ZO, zonula occludens.

discuss the dearth of data and the need for more longitudinal and translational studies in this nascent field. We suggest future directions to improve our understanding of the association between gut microbes and the pathogenesis of HD, and other 'brain and body disorders'.

## Introduction

Huntington's disease (HD) is a devastating neurodegenerative disorder (ND) in which subjects are heavily plagued with cognitive, psychiatric, motor, gastrointestinal, and metabolic impairments [1]. Genetically, HD is caused by an autosomal inherited cytosine-adenine-guanine (CAG) trinucleotide repeat length expansion in the human *huntingtin* (*HTT*) gene located on the short arm of chromosome 4, at position 16.3 and encodes for a protein of 3144 amino acids, with a molecular weight of 350 kDa [2,3]. The genetic defect results in the production of a mutant huntingtin (mHTT) protein consisting of long polyglutamine repeats. A positive correlation between repeat length and disease severity exists. A repeat range length of CAG between 10 and 35 is present in healthy populations whilst 36–39 repeats evoke low penetrance; subjects with >39 repeats will likely develop HD [4,5]. The global prevalence of HD is approximately 5 per 100 000 [5], although founder effects can lead to much higher prevalence in particular regions and countries. Juvenile-onset and adult-onset HD subjects receive first diagnoses below and above 20 years of age respectively [6], with approximately 95% of cases exhibiting adult onset [7].

The polyglutamine-expanded mutant protein (mHTT) engages in abnormal interaction with other molecules, as well as dysfunctional protein aggregation, leading to a range of molecular and cellular consequences, including endoplasmic reticulum (ER) stress, mitochondrial dysfunction, selective cell dysfunction and neuronal cell death [8–10]. Thus, HD bears similarities with other proteinopathies such as Alzheimer's disease (including Amyloid- $\beta$  and Tau proteotoxicity) and Parkinson's disease (including  $\alpha$ -synuclein proteotoxicity) [11]. HTT is ubiquitously expressed in the body, including the gastrointestinal tract (GIT) which begins from the esophagus and ends in the anus [12]. HD subjects are burdened with GI disruptions including diarrhea, gastroesophagitis, poor nutrient absorption, dysphagia (difficulty swallowing), weight loss, anal incontinence, and constipation [13–15].

Additionally, HD patients have significantly lower body mass index (BMI) compared to healthy controls,

despite normal or increased (hyperphagic) food intake [16–18]. Other non-motor symptoms include apathy, poor memory, hallucinations (psychosis), depression, and attentional deficits [19]. These non-motor symptoms show overlap with Parkinson's disease (PD); however, these symptoms are more prevalent in HD and correlate with disease progression in HD [6,20]. Importantly, increased incidence of diabetes, cardiovascular events, circadian disruptions, and sexual dysfunction are also comorbidities often seen in HD subjects [21–23].

The GIT is colonized by trillions of microbes (microbiota), including bacterial, archaeal, viral, and fungal species. The beneficial role of these gut residents in host health has been extensively demonstrated, as they promote various biological processes, including epithelial integrity and immune homeostasis, digestion of ingested food and protection against pathogenic invasion [24].

After the gut, the oral cavity is the second largest colonized portion of the human body [25]. It is vastly populated by over 770 diverse microorganisms and plays a vital role in systemic health [26]. Importantly, the oral microbiota is in close contact with the external environment, serving as a primary gateway and can influence the overall health of an individual [27]. Oral cavity-specific microbes and their metabolites may escape to distant organ sites such as the small intestine, heart, lung, brain, and placenta and elicit inflammatory consequences [28]. However, the mechanisms through which this occurs require more delineation.

When microbiota composition shifts to a pathological state (dysbiosis), it may contribute to dysfunction and disease. The role of oral and gut microbiota dysbiosis in neurodegenerative and neuropsychiatric disorders has been explored in numerous studies using human and experimental models and has been extensively reviewed elsewhere [29,30]. However, the potential role of oral dysbiosis in HD progression remains unexplored. Of particular relevance to the present article, several independent studies in humans and preclinical models have linked the gut microbiota to HD pathogenesis [31].

Gut dysbiosis is an alteration of the intestinal microbial profile and has been linked to the development

and progression of numerous disease conditions [32]. Contributing factors to dysbiosis include leaky gut, unhealthy diet, other lifestyle factors, age, as well as medications (and other pharmacological agents consumed recreationally) [33,34]. Importantly, gut dysbiosis has been shown to influence disease onset and progression in HD [1].

The gut and the central nervous system share a bidirectional connection [35–37]. Gene–environment–gut microbiota interactions in HD have been demonstrated, making the gut–brain axis in HD a new research focus, and inspiring novel microbiota-targeted therapeutic approaches [34,38]. This review provides a detailed overview of gut microbiota alterations in HD, as unraveled in clinical and preclinical studies (Table 1), the neuroimmunomodulatory role and influence of these microbes, and their secretory products in HD pathogenesis. We also discuss the microbiota–gut–brain axis in HD relative to other NDs and summarize therapeutic strategies to remodel the gut microbiota to delay disease onset and alleviate HD pathology safely and efficaciously.

## Gut health and disease in HD

### GI disturbances in HD

Tight junctions (TJ) are formed by neighboring intestinal epithelial cells (IECs) and are essential for upholding the intestinal barrier and regulating the movement of substances such as water, ions, nutrients, and solutes across the intestinal epithelium [39]. These junctions are formed by an assembly of multiple proteins such as occludin, claudins, zonula occludens (ZOs), tricellulin, cingulin, and junctional adhesion molecules [40]. These proteins are pivotal to the maintenance of intestinal barrier integrity [39]. Alterations in the distribution of TJ proteins have been reported in PD patients and linked to increased intestinal permeability, with the latter correlating with the accumulation of  $\alpha$ -synuclein in the enteric nervous system (ENS) [41,42]. Decreased expression of occludin, but not zonula occludens-1 (ZO-1), has been observed in colonic samples from PD patients [43]. Similarly, the gut barrier is compromised in HD, with HD presymptomatic gene carriers and patients showing signs of GI impairment and bowel abnormalities comparable to inflammatory bowel disease (IBD). Fatal weight loss, a devastating manifestation seen in HD, has been linked with the GI dysfunction described above [13].

Decreased body weight, impaired gut motility, nutrient malabsorption, decreased mucosal thickness, shortened villi length and diarrhea have been reported in HD

mouse models [13,44]. The R6/1 and R6/2 HD mice are models of adult-onset and juvenile-onset HD respectively [45,46] and have been described in detail in Box 1. Increased intestinal epithelial permeability is interchangeably described as 'leaky gut'. Studies have shown that in the early stage (12–14 weeks) in the R6/1 HD model, there is no difference in intestinal permeability and gut macroscopy (with the latter characterized as colon length, cecal weight, and length), between HD and wild-type (WT) littermates [1,38]. However, differences are visibly detected at the late disease stage (20 weeks) in both male and female HD mice. Decreased colon length in these mice was also reported [1,38]. In the same vein, R6/2 HD mice showed increased intestinal permeability and decreased colon length at 16 weeks of age [44] (Fig. 1).

### Gut barrier integrity

Gut barrier integrity is vital in maintaining intestinal and host health. In healthy individuals, the gut acts as a barrier, preventing the movement of bacteria from the intestinal lumen into the systemic circulation [44]. The mucus secreted by the gut layers and the tight junctions between epithelial cells, consisting of TJ proteins such as zonula occludens (e.g., ZO-1), claudins, and other junction adhesion molecules, obstructs pathogen entrance and maintains tissue homeostasis [47,48].

The gut microbiota and their secretory products can modulate the integrity of the blood–brain barrier (BBB); thus, BBB dysfunction has been suggested as an early biomarker of neurodegeneration [49]. Increased BBB leakage is evident in Alzheimer's disease (AD) and PD patients as well as in mouse models of these diseases [49,50]. Similarly, the BBB is disrupted in HD and evidence of decreased expression of BBB TJ proteins in R6/2 HD mice has been presented [51,52]. However, this was not corroborated by Stan *et al.* [44], as they did not observe significant differences in the expression of occludin and ZO-1 levels in the cortex and colon at 12 and 16 weeks of age between R6/2 HD mice and WT littermates. At 18 weeks of age, a very late stage in this juvenile-onset mouse model of HD, Stan *et al.* [44] did observe a decreased expression of occludin in the colon mucosa of R6/2 HD mice, as well as disruptive epithelial remodeling. This disparity of findings, despite using the same HD model (R6/2 transgenic mice), could be attributed to CAG repeat size (which can vary within the same transgene across different mouse colonies), and other genetic, environmental and experimental variables. Importantly, the R6/2 HD mice in Stan

**Table 1.** Summary of study characteristics and significant microbiota alterations in Huntington's disease. HC, healthy control; HD, Huntington's disease; HDGECs, Huntington's disease gene expansion carriers; PD, phylogenetic diversity; RCT, randomized clinical trial; WT, wild-type.

Sample type, age, and sex/strain	Study site	Intervention	Microbiota alterations	Sex-specific microbiota alterations	Microbial association with health measures	Method	Refs
<b>Clinical studies</b>							
42 HDGECs [22 males, 20 females], 36 HC [15 males, 21 females] 24–75 years Feces	Melbourne, Australia	NA	HDGEC compared to HC: Decrease in $\alpha$ -diversity (observed species and Fisher's index) Significant differences in $\beta$ -diversity (unweighted UniFrac distances) Lower: Genus: <i>Eubacterium</i>	Males only Phyla: Euryarchaeota, Firmicutes, Verrucomicrobia Families: Acidaminococcaceae, Bifidobacteriaceae, Coriobacteriaceae, Erysipelotrichaceae, Methanobacteriaceae, Peptococcaceae, Peptostreptococcaceae and Rikenellaceae	Cognition, motor function, and disease progression Species: <i>Eubacterium hallii</i>	16S rRNA sequencing	[118]
33 HD [15 males 18 females], 33 HC [15 males 18 females] 42.6–48 years Feces	Beijing, China	NA	HD compared to control: increased $\alpha$ -diversity (Chao 1, observed species, and Faith's PD) Significant differences in $\beta$ -diversity (unweighted UniFrac distances) Higher Phylum: Actinobacteria, class: Deltaproteobacteria Order: Desulfobirionales Families: Oxalobacteraceae, Lactobacillaceae, Desulfovibrionaceae Genera: <i>Intestinimonas</i> , <i>Bilophila</i> , <i>Lactobacillus</i> , <i>Oscillibacter</i> , <i>Gemmiger</i> , and <i>Dialister</i> HC compared to HD: Higher Genus: <i>Clostridium XVIII</i> Higher bacterial genera: <i>Pseudomonas</i> , <i>Acinetobacter</i> , and <i>Burkholderia</i> Fungal genera: <i>Candida</i> , <i>Davidiella</i> , <i>Malassezia</i> , <i>Rhodotorula</i> , and <i>Ramularia</i>	NA	Total functional capacity Genus: <i>Intestinimonas</i> Cognition Genus: <i>Lactobacillus</i>	16S rRNA sequencing	[12]
Postmortem 7 HD [5 males, 2 females] No HC Brains				NA	NA	16S rRNA and ITS1 sequencing	[121]

**Table 1.** (Continued).

Sample type, age, and sex/strain	Study site	Intervention	Microbiota alterations	Sex-specific microbiota alterations	Microbial association with health measures	Method	Refs
RCT 41 HDGECs [20 males, 21 females], 36 HC [15 males, 21 females] 24–75 years Feces	Melbourne, Australia	Probiotics <i>Lactobacillus rhamnosus</i> , <i>Saccharomyces cerevisiae</i> ( <i>boulardii</i> ), and <i>Bifidobacterium animalis</i> <i>ssp lactis</i>	NA	HC females only Significantly different only after treatment Family: Eggerthellaceae	Cognition, motor function, and disease progression: Species: <i>E. hallii</i>	16S rRNA sequencing	[119]
<b>Preclinical studies</b> R6/1 HD [6–8 males per group], WT [6–8 males per group] Feces	NA	High fiber diet	R6/1 HD mice compared to WT: No difference in $\alpha$ -diversity (richness, Shannon) Significant differences in $\beta$ -diversity (Aitchison distance) Higher Phyla: Desulfobacterota Families: Bacteroidaceae, Butyricococcaceae, Oscillospiraceae, Ruminococcaceae Lower Phyla: Actinobacteriota, Campylobacterota, Fusobacteriota and Proteobacteria Families: Campylobacteraceae, Carnobacteriaceae, Corynebacteraceae, Gemellaceae, Micrococccaceae, Neisseriaceae, Selenomonaceae, Weeksellaceae Order: Lactobacillales	NA	NA	16S rRNA sequencing	[240]
R6/1 HD [7 males, 11 females], WT [10 males, 7 females] Feces	NA	NA	R6/1 HD mice compared to WT: Higher Phylum: Bacteroidetes Order: Bacteroidales WT compared to R6/1 HD mice Higher Phylum: Firmicutes Order: Clostridiales	Higher in males only Phyla: Actinobacteria and Proteobacteria Lower in males Family: Deferribacteres	NA	16S rRNA sequencing	[130]

**Table 1.** (Continued).

Sample type, age, and sex/strain	Study site	Intervention	Microbiota alterations	Sex-specific microbiota alterations	Microbial association with health measures	Method	Refs
R6/1 HD [9 per sex], WT NA [9 per sex] Feces	NA	NA	R6/1 HD mice compared to WT: Significantly different Species: <i>Clostridium mt 5</i> , <i>Treponema phagedenis</i> , <i>Clostridium leptum</i> <i>CAG:27</i> , <i>Desulfatirhabdium butyrivorans</i> , <i>Plasmodium chabaudi</i> , <i>Defuluribacillus alkalisensatis</i> , <i>Plasmodium yoelii</i> and <i>Chlamydia abortus</i>	NA	NA	Shotgun metagenomics	[31]
R6/2 HD [4–6 males], WT [4–6 males] Feces	NA	NA	R6/2 HD mice compared to WT: Higher Phylum: Bacteriodes Significantly different Family: Enterobacteriaceae Genera: <i>Bacteroides</i> , <i>Parabacteroides</i> , <i>Lactobacillus</i> and <i>Coprobacillus</i> WT compared to R6/1 HD mice Higher Phylum: Firmicutes R6/1 HD mice compared to WT Increased $\alpha$ -diversity (Shannon) Significant differences in $\beta$ -diversity (Aitchison distance) Higher <i>Penicillium solitum</i> and <i>Meyerozyma guilliermondii</i> Lower <i>Glarea lozoyensis</i> , <i>Malassezia restricta</i> , <i>Penicillium digitatum</i> , <i>Yarrowia lipolytica</i> , and <i>Aspergillus fischeri</i> , <i>Aspergillus uvarum</i> , and <i>Aspergillus alliaceus</i>	NA	Blood glucose Genera: <i>Lactobacillus</i> and <i>Desulfovibrio</i> Body weight Family: Enterobacteriaceae Genus: <i>Parabacteroides</i> Increased intestinal permeability Phylum: Proteobacteria Genus: <i>Parabacteroides</i>	16S rRNA sequencing	[44]
R6/1 HD [9 males], WT [9 males] Feces	NA	NA	WT compared to R6/1 HD mice Higher Phylum: Firmicutes R6/1 HD mice compared to WT Increased $\alpha$ -diversity (Shannon) Significant differences in $\beta$ -diversity (Aitchison distance) Higher <i>Penicillium solitum</i> and <i>Meyerozyma guilliermondii</i> Lower <i>Glarea lozoyensis</i> , <i>Malassezia restricta</i> , <i>Penicillium digitatum</i> , <i>Yarrowia lipolytica</i> , and <i>Aspergillus fischeri</i> , <i>Aspergillus uvarum</i> , and <i>Aspergillus alliaceus</i>	NA	NA	Shotgun metagenomics	[144]
R6/1 HD [7–8 per sex], WT [7–8 per sex] Feces	NA	Environment enrichment (EE) and exercise EE	NA	Males Significantly different in EE R6/1 HD compared to EE WT Order: Lachnospirales, Bacteroidales, Oscillospirales and Lactobacillales Significantly different in standard housing (SH) R6/1 HD compared to SH WT	NA	16S rRNA sequencing	[38]

**Table 1.** (Continued).

Sample type, age, and sex/strain	Study site	Intervention	Microbiota alterations	Sex-specific microbiota alterations	Microbial association with health measures	Method	Refs	
				Order: Coriobacteriales, Bacteroidales, Monoglobales Significantly different in EX R6/1 HD compared to EX WT Order: Gastranaerophilales, Oscillospirales, Desulfotribionales and Bacteroidales Females Significantly different in EE R6/1 HD compared to EE WT Order: Deferribacterales and Peptostreptococcales-Tissierellales Bacteroidales and Lachnospirales				

**Box 1.** Animal models of HD

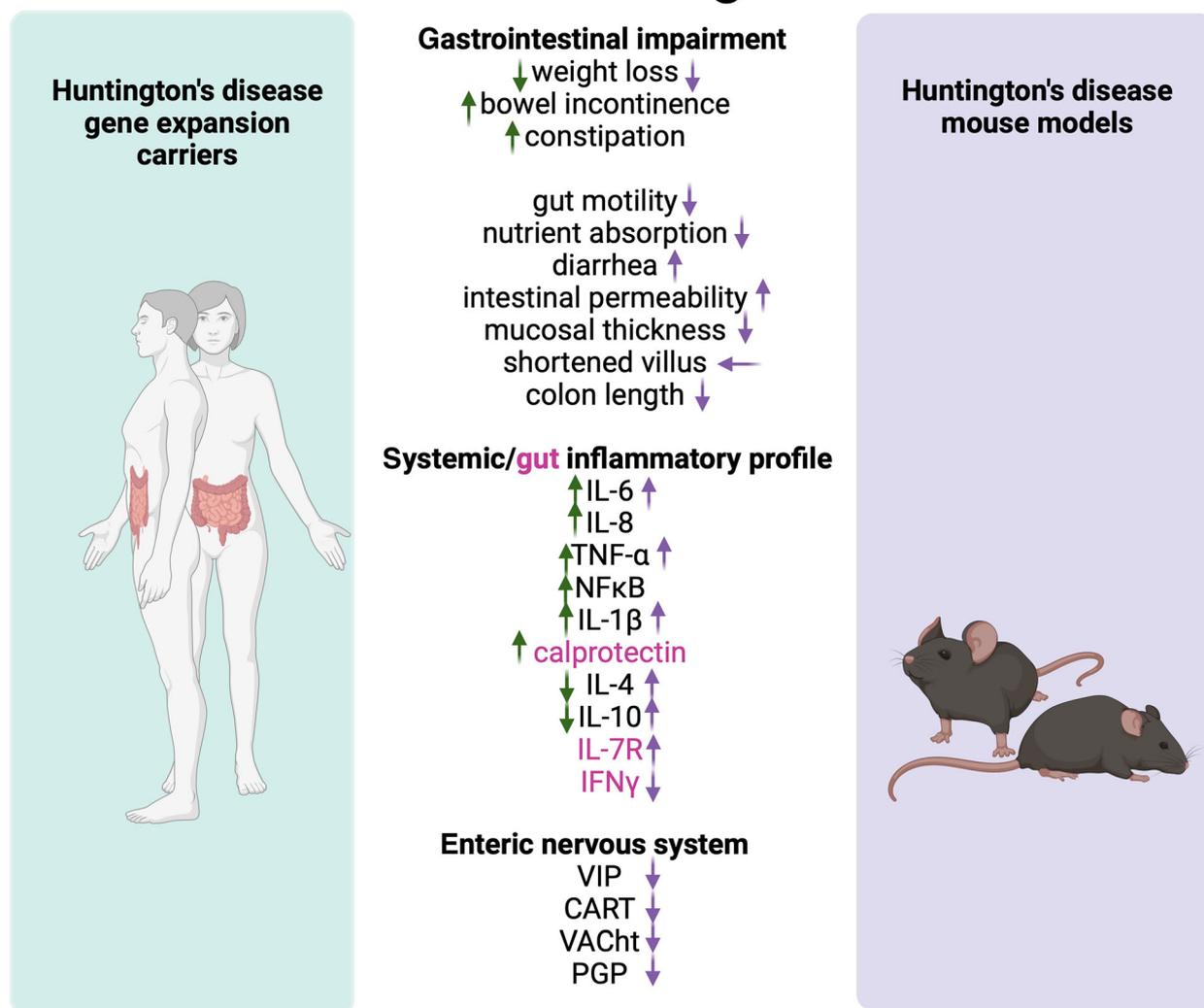
The R6/1 and R6/2 lines were developed in 1996 and were the first transgenic mouse models of HD, with each solely expressing exon 1 of the human *huntingtin* (*HTT*) gene with 115 and 120–150 CAG repeats respectively thus producing 31% and 75% of endogenous HTT protein [45,46]. The transgene (derived from a HD patient) expression in these mice is driven by the human *HTT* promoter and although both lines exhibit HD-like deficits and pathophysiology, the R6/2 mouse develops disease phenotype most rapidly and a marked accumulation of HTT aggregates in the brain [45,311]. The bacterial artificial chromosome (BAC) transgenic mouse model of HD (BACHD) expresses full-length human mutant huntingtin with 97 glutamine repeats and exhibits progressive motor deficits, neuronal synaptic and psychiatric anomalies as well as late-onset selective cortical and striatal atrophies [312,313]. Yeast artificial chromosome (YAC) 128 is a transgenic mouse model of HD expressing a human mHTT gene containing 128 CAG repeats while the YAC18 control mouse line possesses 18 CAG repeats in the human HTT transgene [62,68]. The OVT73 sheep model of HD has the full-length human *HTT* cDNA transgene and a total of 73 CAG repeats and represents an early prodromal disease stage [314]. These and other models of HD have been extensively reviewed elsewhere [315].

*et al.*'s study had a CAG repeat size ranging between 242 and 257 instead of 120–150 as described in Box 1. A previous study had reported that further increases in CAG repeat size (into the extreme range, beyond 150 repeats) can paradoxically prolong survival, and delay the onset of disease and neurodegeneration in the R6/2 HD mice [53].

**The enteric nervous system in HD**

The enteric nervous system (ENS) is in the wall of the GIT and is composed of neuronal and glial cells, and associated neural circuitry, that is crucial for the regulation of diverse GI functions [54]. Enteric neuropeptides consist of small chains of amino acids and are an important class of signaling biomolecules produced by neurons and other cell types in the brain and the gut and regulate immune activities in the gut as well as bidirectional communication between the brain and the gut [55]. Notably, enteric neuropeptides can exert excitatory or inhibitory influences on gut motility [56]. The role of gut innervation and communication

# Gut status in Huntington's disease



**Fig. 1.** Schematic illustration of the current known gut status and immune dysregulation in Huntington's disease subjects and animal models. Abnormalities in the gastrointestinal tract of Huntington's disease subjects and mice as well as the decreased expression of enteric neuropeptides. Immune dysregulation is also depicted, with differential levels of pro-inflammatory and anti-inflammatory cytokines in Huntington's disease subjects and mouse models. ↑: increase, ↓: decrease, ←: promotes. Green arrows represent clinical findings from human studies and purple arrows represent preclinical findings from animal studies. Created with [BioRender.com](https://www.biorender.com).

between the ENS and central nervous system (CNS) in NDs has been extensively reviewed [57] and possible ways through which the gut microbiota and their derived components and metabolites influence the CNS and ENS in neurological disorders have been summarized [58]. However, it is pertinent to highlight that mHTT is expressed ubiquitously in the body, not just the CNS, and mHTT protein notably aggregates in the GIT (stomach, duodenum and rectum and the ENS), as seen in mouse models of HD [13].

In addition to mHTT-immunoreactive inclusions (aggregates), decreased expression of the enteric

neuropeptides such as vasoactive intestinal polypeptide (VIP), cocaine- and amphetamine-regulated transcript (CART), protein gene product (PGP) and vesicular acetylcholine transporter (VaChT) have been reported in R6/2 HD mice [13]. Notably, these findings were supported in a case study of a 56-year-old woman with mild HD (40 CAG repeats in the HTT, which is usually associated with later onset) who not only showed decreased expression of these neuropeptides but also morphological abnormalities in the villi [59]. Taken together, the altered expression of enteric neuropeptides and the presence of mHTT aggregates in the

GIT, as well as associated morphological abnormalities, highlight the significant role of the ENS and the need for a better understanding of the interactions between gut microbes and the ENS in HD.

### Inflammatory responses in HD

The mammalian gut is the largest immune organ and consists not only of the gut microbes but of gut epithelia, goblet cells, and Paneth cells as well as macrophages, dendritic cells, and T-cells that are responsible for maintaining barrier integrity and immune cell homeostasis [60,61]. Alterations in immune profiles in HD subjects are known and there is evidence of innate immune activation in premanifest and manifest HD gene carriers, thus immune dysfunction has been implicated in the pathogenesis of HD [62–67]. The HTT gene mutation is expressed by immune cells from HD patients and this may contribute directly, or indirectly, to changes in inflammatory cytokines [65]. Additionally, microglia, monocytes, and macrophages from HD patients are hyper-reactive when stimulated by lipopolysaccharide (LPS). This hyperactivity was also reproduced in the YAC128 mouse model of HD (but not the control YAC18 mice), which suggests a crucial role of immune cell derangement in HD pathogenesis [62,68].

Increased levels of the proinflammatory cytokines TNF- $\alpha$ , IL-6, and IL-8 were observed in the plasma of HD patients, while the anti-inflammatory cytokines IL-4 and IL-10 increased significantly with disease progression [62]. IL-8 positively correlated with worsening disease symptoms and negatively with Total Functional Capacity (TFC), a measure of functional independence. Interestingly, increased plasma levels of IL-6 were observed in premanifest individuals about 16 years before the onset of motor symptoms [62].

However, in another study, decreased plasma levels of IL-4 were seen in HD, but no significant differences in IFN- $\gamma$ , IL-1 $\beta$ , IL-2, IL-6, IL-8, IL-10, IL-12p70, IL-13, or TNF- $\alpha$  were reported [12]. Importantly, the genus *Intestinimonas* was positively correlated with IL-4 while *Bilophila* was negatively associated with IL-6 [12]. Additional evidence of chronic immune activation in HD patients and animal models as well as clinical trial findings of immune-based therapies for HD have been extensively reviewed elsewhere and are beyond the scope of this review [69]. NF $\kappa$ B, which is involved in immune cell regulation, is upregulated by mHTT [70] and consequently upregulates IL-6 and IL-8 [71,72]. Furthermore, its inflammatory cascade can be suppressed by gut bacteria such as *Faecalibacterium prausnitzii* and select strains of *Clostridium* [73].

Recently, a systematic review and meta-analysis of 10 human studies assessing peripheral markers of inflammation in HD revealed elevated plasma levels of IL-6 and IL-10 in HD subjects compared to healthy controls [74]. Although C-reactive protein (CRP) was also elevated in the HD group, it was non-significant [74]. Notably, there were no differences in the plasma/serum levels of these biomarkers among premanifest and manifest subjects [74].

Comparably, evidence of intestinal inflammation has been presented and linked with the occurrence and progression of PD. Immunologic profiling of colonic biopsies obtained from PD patients ( $n = 14$ ) and matched healthy controls ( $n = 14$ ) showed increased mRNA expression of TNF- $\alpha$ , IFN- $\lambda$ , IL-1 $\beta$ , and IL-6 as well as the glial markers, glial fibrillary acidic protein (GFAP) and Sox-10, particularly in the ascending colon of PD patients [75]. Additionally, the levels of these differentially expressed mRNAs were negatively correlated with disease duration. Stool immune profiling showed elevated levels of IL-1 $\alpha$ , IL-1 $\beta$ , CXCL8 and CRP in PD patients ( $n = 156$ ) relative to healthy controls ( $n = 110$ ) but was not correlated with subject age or disease duration [76].

Calprotectin is a robust biomarker of GI inflammation and a non-invasive approach to diagnosing and assessing Crohn's disease and ulcerative colitis [77]. Increased levels of fecal and serum calprotectin are known in PD [78–80]. Elevated plasma levels of calprotectin were uncovered in moderate HD patients compared to healthy controls [81]. More evidence linking intestinal inflammation to NDs has been summarized elsewhere [57,82].

Like HD patients, heightened inflammatory responses have been shown in experimental models of HD and are extensively summarized here [83]. Notably, elevated levels of serum IL-6, IL-10, IL-1 $\beta$  and IL12p70 and plasma IL-6, TGF- $\beta$ 1 and matrix metalloproteinase (MMP)-9 were reported in the R6/2 HD mice [62,84]. Male R6/1 HD mice showed higher levels of IL-7R in the proximal colon while females showed a decrease in IFN- $\gamma$  [1]. Taken together, these studies suggest a link between systemic inflammation and gut microbes in HD and open an opportunity to investigate the therapeutic potential of live biotherapeutics for targeted immunomodulation.

### The vagus nerve in the microbiota-gut-brain axis

The autonomic nervous system is a component of the peripheral nervous system that regulates involuntary physiological processes and activities such as

breathing, heart rate, blood pressure digestion and sexual arousal [85]. It consists of three distinct divisions which are the parasympathetic, sympathetic and enteric nervous systems [85]. The vagus nerve is the 10th cranial nerve and a crucial component of the parasympathetic nervous system [86]. It is a mixed nerve fiber composed of approximately 80% afferent and 20% efferent fibers [87].

The vagus nerve as the link between the CNS and the ENS, and the way in which the gut microbiota hijacks it to communicate with the brain, have been extensively described elsewhere [35,88,89]. Briefly, gut microbes can produce metabolites and neuroactive molecules such as  $\gamma$ -aminobutyric acid (GABA), serotonin, dopamine, and acetylcholine, that send signals between the afferent neurons in the ENS and the brain via the vagus nerve [90]. Cholecystokinin (CCK) regulates GIT function by inhibiting gastric emptying and food intake through the activation of CCK-1 receptors on the vagal afferent fibers innervating the GIT [90]. Short-chain fatty acids such as butyrate can directly affect vagal afferent terminals while long-chain fatty acids such as oleate can activate vagal afferent fibers by a CCK-dependent mechanism [91].

The vagus nerve has immunomodulatory properties. Importantly, a cholinergic anti-inflammatory pathway (CAIP) is mediated through the release of acetylcholine by the efferent vagus nerve fibers [91]. Once activated, CAIP can dampen peripheral inflammation by suppressing the synthesis and release of TNF- $\alpha$ , decrease intestinal permeability by reinforcing tight junctions, and possibly alter microbiota composition [91]. This has been extensively discussed elsewhere [91,92]. Enteroendocrine cells (EECs) constitute 1% of the IECs and release their content in the presence of nutrients such as carbohydrates, proteins, and triglycerides, modulating gut functions such as motility, secretion, and food intake [93]. EECs interact with the vagal afferents either directly through the release of serotonin or gut hormones such as CCK, glucagon-like peptide 1 (GLP-1), and peptide YY [93]. Toll-like receptors (TLRs) recognize bacterial products such as LPS and are expressed by EECs. TLR4s are expressed on the vagal afferent fibers [94], and these fibers can sense bacterial products and activate the brain [91].

There is evidence of low modulation of autonomic cardiovagal activity in HD patients as characterized by a reduction in heart rate variability at rest and during deep respiration, suggesting autonomic dysfunction [95] and this seems to occur approximately 20 years before the onset of motor deficits [96]. Stress inhibits the vagal nerve [91]. Vagal tone, which describes the level of vagal activity is correlated with stress response

regulating capacity [88]. A low vagal tone is evidenced in patients with IBD and irritable bowel syndrome (IBS), thus permitting peripheral inflammation [97,98]. Treatments that target the vagal nerve increase vagal tone and decrease cytokine production [88].

Major depressive disorder (MDD) is often associated with NDs such as HD, PD and AD and subjects may not effectively respond to currently approved antidepressants [99]. Importantly, 15–69% of HD patients suffer from comorbid MDD [99], thus suicide is a leading cause of death in HD patients compared to the general population [100]. Monoamine neurotransmitters such as serotonin (5-hydroxytryptamine), norepinephrine and dopamine regulate emotions and can influence MDD [101]. Stimulating the vagal afferent fibers in the gut influences the monoaminergic brain system, which plays a crucial role in major psychiatric conditions such as mood and anxiety disorders [88]. Gut bacteria may have a beneficial effect on mood and anxiety, partly by influencing vagal activity [88,102,103]. However, vagotomy studies have also shown that the gut microbiota and their secretory products may promote depressive behavior in rodents in a vagal nerve-dependent way [104–106].

Vagal nerve stimulation (VNS) entails implanting a small device to send electrical impulses to the vagus nerve [107]. Consistent evidence suggests that VNS has promising potential as an add-on treatment for IBD [108], PD [109], treatment-resistant depression [110] and AD [111] but has not been investigated in HD yet. Moreover, our knowledge of the microbiota-vagus-brain interactions in HD is limited and the dearth of literature in this essential area justifies the need for properly designed studies in preclinical models of HD and potentially in patients.

## Gut microbiome in HD

The most dominant bacterial phyla among the intestinal microbiota are Bacteroides and Firmicutes. Their abundance may be inversely altered in disease states. Thus, the ratio of these phyla has been indicated as a biomarker of gut health and stability and correlates with various diseases, including obesity and inflammatory bowel syndrome [112,113]. A change in this ratio has also been linked to aging and, consequently, neurodegeneration [114,115]. Microbial profiling of 1550 healthy participants from the Ukrainian population showed that, in both sexes, the Firmicutes-to-Bacteroides (F/B) ratio increases with age [116]. Similarly, in healthy sexually mature male Sprague–Dawley rats, the relative abundance of Firmicutes increased with age, but Bacteroides declined. This ratio is also

positively associated with BMI [116] and body weight [112]. However, variable F/B ratios have also been reported in healthy individuals and healthy preclinical models in other studies, raising questions about its reliability as an indicator of normal intestinal homeostasis [115,117]. Moreover, there is evidence that microbial richness increases with age, while the reverse is the case with bacterial diversity [115]. Thus, there is a compelling need to understand the gut microbiota signatures in HD subjects and experimental models of HD relative to their healthy counterparts.

### The gut microbiota of patients with HD

The gut microbiome of HD patients has not been extensively studied compared to other NDs such as AD, PD, amyotrophic lateral sclerosis (ALS) and multiple sclerosis (MS). Altered microbial profiles in HD gene expansion carriers (HDGECs – a combination of premanifest and manifest subjects;  $n = 42$ ) compared to healthy controls ( $n = 36$ ) have been shown [118,119]. While there was no difference in microbial profiles between premanifest and manifest, decreased  $\alpha$ -diversity and differences in  $\beta$ -diversity was reported in the HDGEC group, compared to controls and these findings were reproduced in a subsequent study from the same group [118,119]. Furthermore, a lower abundance of the common gut microbe *Eubacterium hallii* was negatively correlated with severe motor symptoms in manifest HD patients as well as with proximity to disease onset in premanifest individuals. Contrarily, *E. hallii* was positively associated with cognitive function [118].

Intriguingly, microbial profiling of fecal samples from a different population (participants from China; as opposed to participants studied by Wasser *et al.*, who were from Australia) revealed a significant increase in species richness ( $\alpha$ -diversity) and differences in microbial structure ( $\beta$ -diversity) in HD patients ( $n = 33$ ) compared to controls ( $n = 33$ ), as well as altered relative abundance of different taxa [12]. Specifically, an increased abundance of the phylum Actinobacteria, the class Deltaproteobacteria, the order Desulfovibrionales, the families Oxalobacteraceae, Lactobacillaceae, Desulfovibrionaceae, and the genera *Intestinimonas*, *Bilophila*, *Lactobacillus*, *Oscillibacter*, *Gemmiger*, and *Dialister*, were seen in HD patients compared to controls, whereas the genus *Clostridium XVIII* was significantly elevated in healthy controls compared to HD patients. Importantly, the butyrogenic bacteria *Intestinimonas* was positively correlated with TFC, while *Lactobacillus* was negatively associated with cognitive outcomes as assessed by the Mini-Mental State Examination (MMSE) score [12]. The

disparity in findings between these clinical studies may be attributed to factors such as ethnicity, geography, host genetics, age, and sample size [12].

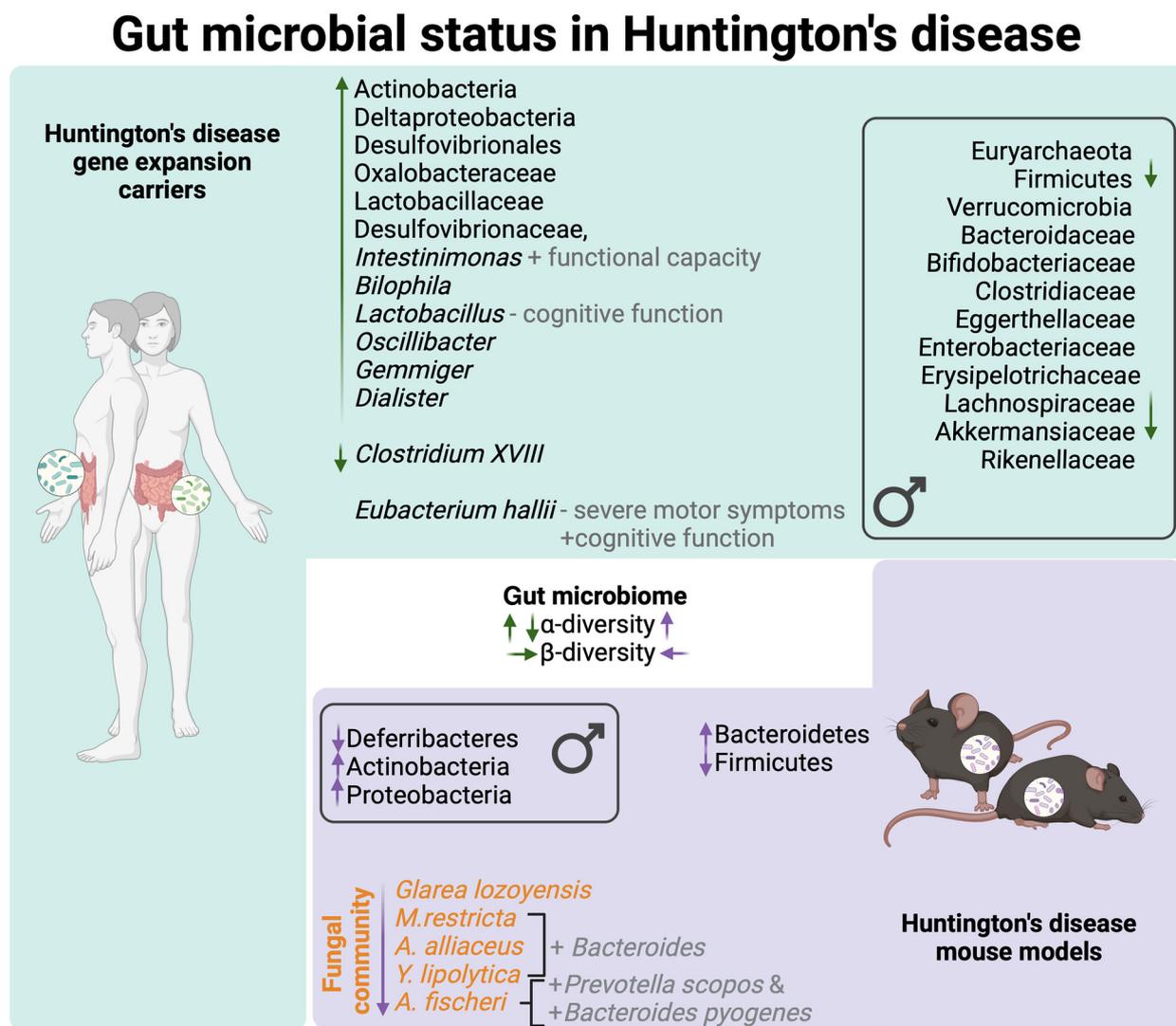
Sex-specific differences in HD microbiota have been reported in HD patients [118]. Wasser *et al.* observed significant differences in the abundance of the phyla Euryarchaeota, Firmicutes, Verrucomicrobia, and the families Bacteroidaceae, Bifidobacteriaceae, Clostridiaceae, Eggerthellaceae, Enterobacteriaceae, Erysipelotrichaceae, Lachnospiraceae, Rikenellaceae among others in male HD subjects compared to controls, but not in females [118] (Fig. 2). This is in line with evidence from other studies showing sex-specific differences in gut microbiota composition in NDs as extensively reviewed elsewhere [120].

Like fungal infections (discussed later), evidence for bacterial DNA in cerebrospinal fluid (CSF) and neural tissues in, HD, PD, and AD and ALS has been demonstrated [121–128]. In HD brains, a high abundance of bacterial genera including *Pseudomonas*, *Acinetobacter*, and *Burkholderia* was reported [121]. However, a main caveat of this study was that post-mortem samples from HD patients ( $n = 7$ ), but no control subjects were assessed, although they referenced a previous study that included controls [121]. Additionally, the sequencing runs lacked appropriate controls, and the possibility of post-mortem contamination calls for a cautious interpretation [121].

Furthermore, amyloid deposits have been reported in the brains of ALS, AD, PD, and HD patients [129]. Amyloid peptides, known for their antimicrobial/antifungal activity, can be triggered by microbial infections, giving rise to an innate immune response. Corpora amylacea (CA) are amyloid bodies reportedly found in the striatum of HD patients and have also been observed in other NDs [124]. Although fungal proteins in CA were identified in CNS samples of AD, PD, and ALS patients and reacted to fungal antibodies, CA from AD patients seemed to be more abundant [122,124,125,128].

### The gut microbiota in murine models of HD

There is consistent evidence of altered microbial composition in the R6/1 HD model, especially at 12 weeks of age [1,31,38,130]. 16S rRNA sequencing analysis revealed an elevated abundance of Bacteroidetes and a proportional decrease in Firmicutes, while the reverse was seen in WT [130]. Specifically, microbiome signatures in WT mice primarily consisted of Clostridiales from the Firmicutes phyla while HD microbiome signatures mostly consisted of Bacteroidales from the Bacteroidetes phyla [130]. Further analysis revealed increased



**Fig. 2.** Schematic illustration of the current known gut microbial status in Huntington's disease subjects and animal models. Variations in gut microbial composition in Huntington's disease subjects and mice are known. The known connections between altered gut bacteria and their associations with neurological function in the context of Huntington's disease are shown. Additionally, bacterial-fungal interactions and sex-specific patterns within the gut microbiota are highlighted. ↑: increase, ↓: decrease, ←: promotes, +: positive correlation, -: negative correlation. Green arrows represent findings from human studies and purple arrows represent findings from animal studies. Created with [BioRender.com](https://www.biorender.com).

microbial diversity in HD males and reported no similar observation in females. Deferribacteres were significantly lower in HD males, while Actinobacteria and Proteobacteria were significantly higher in HD males compared to male WT littermate controls; no such differences in the trio were observed in females [130]. These preclinical discoveries in HD mice are consistent with sex differences in gut microbiota subsequently described in HD clinical studies [118,119].

Interestingly, shot-gun sequencing metagenomics revealed 30 genotype-specific microbiome signatures at 12 weeks of age in R6/1 HD mice relative to WT littermate controls [31]. These signatures include

*Clostridium mt 5*, *Treponema phagedenis*, *Clostridium leptum CAG:27*, *Desulfatirhabdium butyrativorans*, *Plasmodium chabaudi*, *Defulfuribacillus alkaliarsenatis*, *Plasmodium yoelii* and *Chlamydia abortus* [31]. Notably, examination of microbial genes and KEGG orthology (KO) pathway signatures at week 12 showed a key difference in decreased levels in galactose metabolism and benzoate degradation and increased levels in sulfur metabolism, lysine degradation, glutathione metabolism and butanoate metabolism in HD microbiome relative to WT [31].

The microbiome is shaped by stability and volatility with the latter being described as an alteration in

microbiota composition over time. Gut microbiome stability is crucial for host health and volatility has been associated with disease states such as IBD and stress [131,132]. Kong *et al.* [31] uncovered heightened volatility in HD mice compared to the stability seen in WT littermates and highlighted fatty acid metabolism, fatty acid biosynthesis, tryptophan metabolism, and propanoate metabolism as some of the pathways mainly influenced by volatility in the HD microbiome.

Similarly, evidence of gut dysbiosis has been presented in R6/2 HD mice at 16 weeks of age with increased relative abundance of Bacteroidetes and decreased Firmicutes in these mice relative to WT and is consistent with what was seen previously in R6/1 HD mice [44]. Although there were no differences in  $\alpha$ -diversity, microbiota composition was significantly different between both genotypes. Bacteria significantly and distinctly associated with the R6/2 HD mice were *Bacteroides*, *Parabacteroides*, *Lactobacillus*, *Coprobacillus*, and the Enterobacteriaceae. Like HD subjects, the R6/2 HD mice are prone to have elevated blood glucose and this study uncovered a positive correlation between blood glucose and *Lactobacillus* and a negative correlation with *Desulfovibrio*. Additionally, body weight was negatively associated with Enterobacteriaceae and *Parabacteroides* while increased intestinal permeability was positively linked to the abundance of gram-positive bacteria, notably the Proteobacteria and *Parabacteroides* phylum and genus respectively [44].

### The gut mycobiota in HD

Over 400 fungal species in humans have been identified [133] with fungal communities accounting for 0.1% of fecal microbial DNA. The distal colon is the most colonized portion of the intestine with respect to fungal communities [134]. Human and murine mycobiomes are mainly dominated by the phyla Ascomycota and Basidiomycota. Although the influence of the gut mycobiome in neurological disorders has been reviewed [135], it is pertinent to highlight that high levels of fungal antigens as well as fungal polysaccharides were detected in AD patients through a multi-omics approach [123]. *Malassezia* spp., *Phoma*, and *Saccharomyces cerevisiae* were identified in the CNS of AD patients [136]. Alonso *et al.* further showed the presence of fungal species in various brain regions of AD patients but none in healthy controls, suggesting fungal infections [123–125]. Similar observations were seen in ALS and PD subjects. The genera *Candida*, *Malassezia*, *Fusarium*, *Botrytis*, *Trichoderma* and *Cryptococcus* were more prominent in the neural tissues of ALS patients relative to the control neural tissues [122]. Intriguingly,

fungal structures were detected in brain sections of HD patients and following genomic sequencing uncovered fungal genera (*Candida*, *Davidiella*, *Malassezia*, *Rhodotorula*, and *Ramularia*) which were similarly observed in other NDs except *Ramularia*, which appeared to be an HD-specific genus [121].

The evidence provided suggests that opportunistic fungal species such as *Candida albicans* can translocate from the gut to the brain and trigger an inflammatory response, as shown in monocolonized germ-free (GF) mice [137]. Although aging has been described as a contributing factor to gut dysbiosis and may increase the possibility of such migration, there was no evidence of fungal dysbiosis in aged specific pathogen-free (SPF) mice (24 months) [137]. Moreover, the relative abundance of fungal species in older and younger SPF mice showed no significant difference [137] and depletion of gut bacteria communities (using broad-spectrum antibiotics) rapidly expanded caecal colonization by *Ca. albicans* in the mice [137].

Commensal fungi play an indispensable role in host health and immunity. Fungi such as *Yarrowia lipolytica* have been demonstrated as probiotics [138]. Importantly, gut fungi can produce neurotransmitters and other metabolites that exert a neuroimmunomodulatory role [134,139,140]. However, the mycobiome has been implicated in diverse diseases such as gastric cancer, colorectal cancer, and inflammatory bowel disease, and recently Alam *et al.* showed that the fungal microbiome upregulated IL-33 secretion in pancreatic cells and consequently drove type 2 immunity [141] and *Ca. albicans* induced the expression of IL-35 in M2 macrophages [142]. Importantly, disruptions in the bacterial-fungal relationship have been linked to neurological disorders such as autism spectrum disorder (ASD), AD, and PD [143].

While the fecal bacterial phyla and families in HD have been characterized by a few studies, the fungal gut residents have received unequal attention. Significant alterations of the intestinal fungal community in the R6/1 HD mouse model compared to controls, specifically at 12 weeks of age, which is before the onset of motor deficits, have been shown [144]. Not only was there a significant difference in  $\beta$ -diversity in HD mice as well as increased  $\alpha$ -diversity compared to WT, but the authors also uncovered a signature of 15 fungal species driving the major compositional differences between WT and HD. Further analysis revealed bacteriome-mycobiome interactions in this HD model and a strong positive association of HD-depleted fungal species *Glarea lozoyensis*, *Malassezia restricta*, *Aspergillus alliaceus*, and *Y. lipolytica* with the genera *Bacteroides*, and a positive association of *Aspergillus*

*fischeri* solely with *Prevotella scopos* and *Bacteroides pyogenes*. Intriguingly, *Lactobacillus reuteri* was negatively associated with *G. lozoyensis*, *M. restricta*, *A. alliaceus*, and *Y. lipolytica* [144] (Fig. 2).

A decrease in fungal richness was observed in the 3xTg AD mouse model compared to WT, though not significantly. Importantly, a significant increase in the fungal Dipodascaceae family was reported [145] and in WT mice an abundance of Basidiomycota and Ascomycota was observed, compared to the AD mice.

Chitin, a polysaccharide component of fungal cell walls, is a precursor for chitinase, the latter highly recognized as a biomarker for HD with elevated levels reported in CSF [146]. This enzyme is produced by astrocytes and macrophages [147,148]. Chitin has also been reported in AD samples from the CNS. Additionally, fungal proteins, enolase, and  $\beta$ -tubulin were uncovered in the CA from AD patients [125].

Overall, the gut mycobiome signature in HD subjects requires more characterization which would improve our understanding of trans-kingdom network interactions and how they influence immune activity and the onset and progress of HD. Furthermore, we need to understand how fungal-altering approaches can influence bacterial communities, as this may have therapeutic implications.

## Gut microbiota-derived metabolites in HD

Gut microbiota-derived metabolites are effectors of crosstalk between the gut and the brain and have been suggested as credible biomarkers [149]. These biomolecules modulate neuronal function and influence diverse pathways in age-related NDs [120]. Here we discuss a few of them and their influence on HD pathophysiology.

### Bile acids

Bile acids (BAs) are terminal derivatives of cholesterol metabolism and can influence immune homeostasis in hosts. Primary bile acids such as cholic acid (CA) and chenodeoxycholic acid (CDCA) undergo modification by intestinal microbiota, transforming them into secondary BAs which are transported to the liver through the enterohepatic circulation, or systemically [150,151].

Bile acids regulate intestinal epithelial integrity as well as innate immune responses. Secondary BAs promote autophagy, especially the activation of the host's TGR5 receptor [152,153]. Conversely, primary BAs inhibit autophagy by binding to the host's Farnesoid X receptor (FXR) on myeloid cells, thus suppressing

autophagy, and proinflammatory responses, and promoting gut intestinal epithelial barrier function [153,154].

There is a reciprocal interaction between BAs and the intestinal microbiota. BAs can directly exert antimicrobial actions or indirectly modulate gut resident communities through FXR-induced antimicrobial peptides [153,155,156]. Conversely, gut microbes influence BA metabolism. Notably, a low abundance of BAs in the intestinal lumen upregulates LPS-producing gram-negative bacteria such as *Bacteroides*, while the reverse supports the abundance of gram-positive microbes such as Firmicutes [155,157].

Antibiotic treatment inhibits the expression of CYP7A1, an enzyme involved in cholesterol breakdown and bile acid synthesis [158,159]. Differential expression of this gene has also been reported in GF mice [160]. These lines of evidence buttress the critical role of the gut microbiome in maintaining bile acids and their metabolic pathways.

Furthermore, BAs have been identified in the brains of rats [161]. Keene *et al.* [162] showed that systemically administered bile acids can reach the brain and exert a neuroprotective role. Conversely, the Baloni *et al.* [163] study showed that BAs synthesis pathway genes are expressed in the brains of AD patients and reported an association between BAs and cognitive deficits.

Tauroursodeoxycholic acid (TUDCA) is an endogenous hydrophilic bile acid synthesized by the conjugation of the secondary bile acid ursodeoxycholic acid (UDCA) with taurine. TUDCA is well tolerated and produced at low levels in humans. UDCA is an FDA-approved medication for treating cholestasis and Ursodiol, a commercial form of UDCA, has been tested in clinical trials for the treatment of HD [164,165].

Huntington's disease is associated with neuronal mitochondrial perturbations [166]. There is strong evidence that TUDCA can stabilize mitochondrial membrane potential, decrease reactive oxygen species (ROS) production, and attenuate apoptotic pathways in HD [162]. TUDCA significantly decreased 3-nitro propionic acid (3-NP)-mediated striatal neuronal apoptosis in studies using *in vivo* models of neuronal excitotoxicity [162,167]. TUDCA-treated R6/2 HD mice showed minimized striatal degeneration and improved sensorimotor and cognitive phenotypes, as characterized by the rotarod and open field tests, respectively [168].

Overall, the neuroprotective role of these BAs and their precursor UDCA has been demonstrated in humans and experimental models of diseases, including HD, AD, PD, MS, and ALS, and has been extensively

reviewed with ongoing clinical trials detailed here [164,165,169–172].

### Purine metabolites

Host nucleotide metabolism is greatly influenced by the gut microbiota [173,174]. For example, in fruit flies, *Lactobacillus plantarum* decreased dietary purine metabolites, *Lactobacillus brevis* and *Lactobacillus murinus* specifically decreased dietary adenosine, whereas *Acetobacter persici* increased allantoin, an end-product of purine metabolism, in aged flies [173]. Allantoin has been shown to improve neurogenesis in the hippocampus as well as enhance cognition and memory in normal naïve mice [175].

Bacteroides may promote urate conversion to allantoin and thus influence serum uric acid levels in humans [176]. Xanthine oxidase is a secretory product of the gut microbiota and is important for the oxidative metabolism of purines [177]. Impaired purine metabolism and signaling have been implicated in the pathogenesis of HD. Post-mortem brain tissues of HD subjects showed markedly increased urea and this was equally seen in a transgenic prodromal sheep model of HD, OVT73 [178]. Additionally, elevated plasma and CSF levels of inosine, hypoxanthine, xanthine, uric acid, and uridine have been reported in both HD mouse models and HD patients [179,180] whilst decreased plasma levels of adenosine triphosphate (ATP) and pipercolic acid were negatively associated with Bacteroides in R6/1 HD mice [31].

Early-onset HD patients show a cognitive decline which may eventually result in dementia [181]. Purinergic receptors have been associated with cognitive disturbances in NDs [182]. Notably, increased expression of P2X7R mRNA and protein have been unraveled in the cortical and striatal neurons of transgenic mouse models of HD and the administration of P2X7R antagonists has been shown to improve motor deficits and prevent body weight loss in R6/1 HD mice [183,184]. Similarly, administration of the adenosine receptor A2AR antagonist istradefylline rescued working memory defects and long-term depression anomalies in the cortico-striatal synapse [185]. There is a strong positive association of formate, mannose, and xanthine with superior cognition [186]. Lower levels of xanthine, hypoxanthine, and adenosine have been observed in the frontal cortex of AD patients [187]. Moreover, transcriptional signatures of R6/2 HD mice showed an upregulation of *Pnp* and *Xdm*, both involved in purine metabolism [188]. Thus, modulating purinergic systems has been highlighted as a suitable therapeutic strategy for HD [179,189].

### Branched-chain amino acids and branched-chain fatty acids

Although the diet is a chief source of branched-chain amino acids (BCAAs), gut microbiota are actively involved in the *de novo* synthesis and uptake of amino acids [190]. BCAAs are important for the synthesis of neurotransmitters involved in memory and learning, such as acetylcholine, glutamate, and GABA [191]. Plasma levels of these neurotransmitters have been negatively linked with dementia [192,193]. Decreased BCAAs such as isoleucine, leucine, and valine have been identified as potential biomarkers in HD models, including presymptomatic HD sheep (OVT73) [194] and evidence of an association between BCAA levels with CAG repeat length and disease progression has been shown [195,196]. In contrast, the Castilhos *et al.* study [197] does not support this, and Andersen reported enhanced cerebral BCAA metabolism, especially isoleucine in the R6/2 HD model [198].

Nonetheless, alterations in BCAA levels have been implicated in metabolic disorders and NDs including AD, PD and ALS and have been extensively discussed [199,200]. Decreased plasma and fecal levels of aromatic amino acids (AAAs) and BCAAs in PD patients have been reported as well as a decreased expression of *ilvB*, *ilvC*, *ilvD*, and *ilvN*, genes involved in BCAA biosynthesis pathways [201]. Interestingly, the altered AAA and BCAA levels were significantly correlated with microbial taxa Desulfococcaceae, Acidaminococcaceae, and Erysipelotrichaceae, while Streptococcaceae, *Streptococcus*, and *Lactobacillus* shared a negative association [201].

Branched-chain fatty acids (BCFAs) are primary saturated fatty acids and are derivatives of protein fermentation by microbes in the distal colon [202]. They include isovalerate, isobutyrate and 2-methylbutyrate, and are common in ruminant products such as milk, meat, and lanolin [203,204]. BCFAs play a crucial role in the human gut in infancy [205]. BCFAs are the main component of membrane lipids in bacteria, particularly the *Bacillus*, *Lactobacillus*, and *Bifidobacterium* genera [206]. Unlike short-chain fatty acids, there is a paucity of literature on the influence of BCFAs on host health [202]. However, there is evidence of their anti-inflammatory activities demonstrated using *in vivo* and *in vitro* models. For instance, the BCFA diet alleviated necrotizing enterocolitis in neonatal rats, increased production of the anti-inflammatory cytokine IL-10 (up to threefold) and increased the relative abundance of *Bacillus subtilis* and *Pseudomonas aeruginosa* [205]. Additionally, BCFAs dampened LPS-induced IL-8 mRNA expression and NFκB

signaling in Caco-2 human intestinal epithelial cell lines [207]. Assessment of fecal levels of isobutyrate, 2-methylbutyrate or isovalerate in R6/1 HD mice at 12 weeks revealed no significant differences [38]. Thus, the influence of BCFAs on HD pathology as well as other NDs warrants further exploration.

### Short-chain fatty acids

Short-chain fatty acids (SCFAs) such as acetate, propionate, and butyrate are derived from the fermentation of dietary fiber and resistant starch by anaerobic intestinal bacteria [202]. SCFAs play a vital role in host immune health and metabolism, and their influence on, and alterations in, NDs have been extensively reviewed [208]. Shotgun-sequencing metagenomics of fecal samples from 12 weeks of age did not show a significant difference in the abundance of butyrate-producing bacteria *Roseburia intestinalis*, *Clostridium symbiosum*, and *Eubacterium rectale* relative to WT, neither did targeted metabolomic profiling of plasma from R6/1 HD mice at 12 weeks of age reveal significant alterations in SCFAs compared to WT littermate controls [31]. However, male R6/1 HD mice subjected to physical activity showed reduced fecal concentrations of butyrate and valerate [38]. A subsequent study provided evidence of elevated plasma acetate levels in R6/1 HD males at early and late stages of disease (14 and 20 weeks) relative to WT littermates and also reported a difference in propionate levels in female R6/1 HD mice at 20 weeks [1].

Low fecal and high plasma concentrations of SCFAs have been shown in PD patients and associated with gut microbiota composition and disease severity (specifically motor and cognitive function as assessed by the Movement Disorder Society–Unified Parkinson's Disease Rating Scale and MMSE respectively) [209]. Elevated levels of SCFAs have been linked to exacerbated AD pathology. Specifically, SPF APPPS1 mice showed elevated levels of acetate, propionate, and butyrate compared to GF APPPS1 mice, and supplementation with the three SCFAs significantly increased amyloid plaques in both GF and SPF mice [210]. Altered serum levels of SCFAs, notably valeric and caproic acid, have been linked to pathogenesis and cognitive impairment in schizophrenia [211].

Furthermore, decreased fecal levels of propionic, butyric, and isobutyric acid have been reported in patients with essential tremor (ET) compared to healthy subjects but lower levels of isovaleric and isobutyric acid compared to PD patients and this was associated with a decreased abundance of

*Faecalibacterium* and *Catenibacterium* in ET subjects [212]. Interestingly, a negative association between propionic acid and constipation and autonomic dysfunction was uncovered while isobutyric and isovaleric acids were negatively linked to tremor severity [212].

### Polyamines

Polyamines (PAs) such as putrescine, spermine, and spermidine are polycationic aliphatic amines derived from L-ornithine from the decarboxylation of amino acids and play vital roles in biochemical and physiological processes [213,214]. Polyamines can be endogenously produced, exogenously supplemented through diet, or synthesized by intestinal bacteria. Microbial polyamines regulate mucosal homeostasis, intestinal epithelial cell proliferation and barrier integrity [215,216]. Evidence of the neuroprotective role of PAs has been provided in various NDs [217]. In the quinolinic acid (QA)-induced excitotoxic rat model, spermidine ameliorated memory impairment in a dose-dependent manner as assessed by the object recognition test, as well as decreased QA-induced astrogliosis [218]. Similarly, pretreatment with spermidine decreased motor impairments, oxidative stress, and neuroinflammation in the 3-NP model of striatal damage, in a dose-dependent manner [219] and alleviated PD pathology in *Drosophila* and *Caenorhabditis elegans* by preventing the loss of locomotor activity (in flies) dopaminergic neurons and by inducing autophagy [220]. Conversely, alterations in PA metabolism have been implicated in the pathology of HD. Evidence of decreased spermine was found in the putamen of human HD brains and suggested to be indicative of atrophy [213]. Using *in vitro* models of HD, treatment with spermine, and spermidine but not putrescine, was found to increase mHTT aggregates [221]. Overall, elevated levels of PAs have been linked to cognitive deficits and synaptic loss in NDs including HD, AD, and PD, therefore the dual role (beneficial/deleterious) of these metabolites calls for a better understanding [214,217,222–224].

## Interventions targeting the gut microbiome in HD

### Psychobiotics

Probiotics are live microorganisms (e.g., bacteria, fungi) with activities beneficial to host health including suppressing the growth of pathogenic bacteria and protecting the intestinal epithelial barrier. Probiotics can have fermentative action and digest dietary fiber

to release SCFAs, neurotransmitters and other biological molecules [225]. Some SCFA-producing bacteria include *Lactobacillus*, *Bifidobacterium*, *Akkermansia*, *F. prausnitzii*, *C. leptum*, and *E. rectale*. Prebiotics on the other hand are non-digestible high dietary fiber substances that serve as substrates for intestinal microbes which eventually convert them to SCFAs [226]. There are a plethora of studies providing consistent evidence of the efficacy of probiotics and prebiotics in modulating the gut microbiome and consequently, disease outcomes in clinical trials and preclinical models of NDs including AD, PD, and MS, and have been summarized elsewhere [227,228]. Notably, the use of oral probiotics significantly improved constipation in PD patients as well as non-motor symptoms of anxiety and depression [229,230]. Moreover, foods rich in polyamines have been associated with improved cognition [231,232], hence the increasing interest in probiotics that can elevate the abundance of polyamine-producing gut commensals.

Wasser *et al.* [119] recently reported findings of the first randomized controlled clinical trial of a probiotic intervention in HDGECs ( $n = 41$ ) and healthy controls ( $n = 36$ ). The probiotic capsule was enriched with *Lactobacillus rhamnosus*, *S. cerevisiae (boulardii)*, and *Bifidobacterium animalis ssp lactis* and had no adverse effects on participants. The probiotic capsule, administered for only 6 weeks, had no significant effect on gut function and dysbiosis, neither did it improve cognition and memory. However, they did observe a lower abundance of the Eggerthellaceae family in female healthy controls post-treatment. The authors suggested the absence of a significant beneficial effect of the capsule may be attributed to the short duration of the trial among other factors. Overall, more studies are needed to identify efficacious probiotics-based therapies for HD with minimal adverse risks.

Furthermore, there is evidence that the consumption of dietary polyphenols such as resveratrol, and curcumin can attenuate neurodegenerative pathologies, and these compounds are also classified as prebiotics [233]. They are metabolized by gut bacteria and elicit antioxidant and anti-inflammatory actions [234]. Luteolin, a flavone richly found in fruits, vegetables, and herbs has promising benefits. Luteolin-fed HD fruit flies showed ameliorated motor defects, reduced protein HTT aggregates, and increased survival [235]. In a dose-dependent manner, luteolin improved spatial learning deficits (as assessed by the Morris water maze) and decreased cortical A $\beta$  plaques in 3 $\times$ Tg-AD mice [236]. It also inhibited ER stress response and consequently neuroinflammation.

Luteolin supplementation has been shown to modulate the gut microbiota. One study reported increased *Erysipelatoclostridium* and *Pseudomonas* as well as decreased *Faecalibaculum* [237] and another, increased abundance of *Lactobacillus*, *Bacteroides*, *Roseburia* and *Butyricoccus* [238]. Interestingly, the carotenoid, crocin had a more efficacious effect compared to Luteolin in the HD flies described above [235]. Overall, the therapeutic potential of other phytoconstituents for HD, as well as the associated clinical trials, have been extensively covered [239].

## Dietary interventions

Diet-based approaches have been considered a therapeutic strategy for HD. Here we present some of the recent evidence in support of dietary interventions.

Gubert *et al.* [240] recently discovered the promising potential of a high-fiber (HF) diet in improving disease phenotype in the male R6/1 HD mice. HF diet improved cognition and the depressive-like phenotype, as characterized by the novel object recognition and Porsolt swim tests respectively [240]. Notably, HF significantly improved GI health measures as evidenced by increased fecal water content, softened stool consistency, and decreased gut transit time in WT mice comparably to HD mice, suggesting ease of constipation. Additionally, HF increased colon length and caecum weight in both genotypes but only increased caecum length in WT [240].

Importantly, dietary fiber did not modulate body weight, water intake, brain weight or motor function as characterized by rotarod performance, DigiGait and limb-clasping tests [240]. There was no significant difference in  $\alpha$ -diversity (richness and Shannon indices) but there was a significant difference in  $\beta$ -diversity (Aitchison distance). Permutational multivariate analysis of variance (PERMANOVA) testing revealed significant interactions between genotype and diet on microbiome composition at weeks 14 and 20 [240].

Interestingly, microbiota composition between HF-fed WT and HD mice significantly differed at 14 weeks of age. R6/1 HD mice on a HF diet mice showed an increased relative abundance of the Phyla Desulfobacterota and the families Bacteroidaceae, Butyricocccaceae, Oscillospiraceae, Ruminococcaceae and a decreased relative abundance of the phyla Actinobacteriota, Campylobacterota, Fusobacteriota and Proteobacteria, the families Campylobacteraceae, Carnobacteriaceae, Corynebacteraceae, Gemellaceae, Micrococcaceae, Neisseriaceae, Selenomonaceae, Weeksellaceae and the order Lactobacillales [240]. Furthermore, Phylogenetic Investigation of Communities

by Reconstruction of Unobserved States (PICRUST) analysis revealed a decreased expression of pathways associated with nitrate reduction and protein N-glycosylation in HF-fed R6/1 HD mice bacterial communities [240]. The possible pathogenic roles of dysregulations of these pathways in HD and other NDs have been extensively discussed elsewhere [241–244].

A ketogenic diet (KD) involves consuming whole foods that have high fat content and low carbohydrates. KD-induced microbiota alterations are well documented in neurological disorders including epilepsy [245], AD, and PD, but not so much in HD, and have been summarized elsewhere [246,247]. A case study of a 41-year-old subject with progressive HD (47 CAG repeats) on a Time-Restricted Ketogenic Diet (TRKD) for 48 weeks, during which the subject consumed two meals daily without snacks, provides evidence of improved motor function, quality of life and behavior problems, especially apathy. However, there was no improvement in cognition and no significant changes in weight [248]. Of course, such case studies represent low-level evidence, and need to be followed up with well-powered randomized controlled trials. In R6/2 HD mice, KD delayed the onset of weight loss from 9 to 11 weeks and had no adverse effect on memory, motor coordination and locomotion [249]. Interestingly, KD-fed WT males but not females showed improved motor and locomotor function compared to non-KD WT mice. In the BACHD model of HD, 3 months of dietary ketosis altered the microbiome with a significantly increased abundance of *Akkermansia muciphila* compared to mice on a normal diet and improved circadian and motor function [250]. It is pertinent to highlight studies with contradictory findings. For instance, Olson *et al.* [251] showed that KD exacerbated cognitive impairments in conventional SPF in a gut-microbiota-dependent manner, Lauritzen *et al.* reported that KD aggravated neurodegeneration in transgenic mice with hippocampal neuronal mitochondria dysfunction and Zhao *et al.* demonstrated visual-spatial memory impairment and diminished brain growth as long-term effects of KD in a rat model of epilepsy [252,253].

Mediterranean diet (MeDi), a centuries-old dietary pattern, is chiefly composed of plant sources, fish, and extra virgin olive oil, with little to no inclusion of red meat, poultry, dairy products. Low adherence to the MeDi diet was associated with higher BMI and increased intake of high-caloric meals was highlighted as a risk factor for shortening time to clinical onset of HD (phenoconversion) in premanifest gene carriers, while consuming meals with dairy products was linked

with a two-fold risk of phenoconversion [254]. In a Spanish cohort of HD and premanifest HD gene carriers, moderate adherence to MeDi was associated with positive outcomes including better quality of life, lower motor impairment and decreased risk for abdominal obesity [255]. The outcomes of other studies that investigated the effect of the MeDi diet in HD have been reviewed elsewhere [256]. Furthermore, it is still unclear whether the gut microbiota modulated this neuroprotective effect of MeDi in HD, as no microbiome measures were reported. However, other studies in adult populations have reported that MeDi increased bifidobacterial counts, total SCFA [257] as well as the relative abundance of butyrate producers, *F. prausnitzii*, *Eubacterium*, *Roseburia* [258], and decreased abundance of the pathogenic colonizer *Escherichia coli* associated with inflammatory activities [259].

The neuroprotective role of intermittent fasting (IF) or time-restricted feeding in NDs including HD in humans and experimental models has been addressed previously [260] but with no focus on alterations in microbial profiles. IF induced autophagy and promoted mHTT clearance in YAC128 HD mice [261]. Heterogenous evidence from human and animal studies suggests that IF can alter microbial diversity and composition and the relative abundance of species such as *Akkermansia*, *Faecalibacterium*, *Lactobacillus*, and *Roseburia* and can dampen the production of proinflammatory cytokines IL-6, IL-1 $\beta$ , TNF- $\alpha$  [262] and even CRP [263].

### Environmental interventions and physical activity

Environmental enrichment (EE) encompasses the introduction of novel stimuli to engage sensory, cognitive, motor, and social activities, and its neuroprotective role has been extensively reviewed in previous literature. Various studies have shown the therapeutic benefits of EE and physical exercise (EX) in delaying the onset and progression of disease in R6/1 mice [264,265]. Intriguingly, the microbiota profiles in R6/1 HD mice exposed to different housing conditions for a duration of 6 weeks, namely EE and EX, compared to standard housing (SH), exhibit distinct patterns [38]. The most notable distinguishing signatures were the bacterial orders Bacteroidales, Lachnospirales, and Oscillospirales. Briefly, in male WT mice, SH showed Coriobacteriales and Monoglobales, EE affected Oscillospirales and Lactobacillales, and EX affected Desulfocivibrionales and Bacteroidales, respectively. Whereas male HD mice in SH conditions showed Coriobacteriales and Bacteroidales, EE affected Lachnospirales and Bacteroidales, and EX affected

Gastranaerophilales and Oscillospirales. For female WT mice across all three housing conditions, a consistent presence of Bacteroidales and Lachnospirales was reported. In contrast, female HD mice exhibited microbiota compositions depending on the housing conditions. SH housing showed Bacteroidales and Lachnospirales, EE affected Deferribacterales and Peptostreptococcales-Tissierellales, and EX affected Lachnospirales and Bacteroidales. Overall, the effects of lifestyle, diet, physical activity and other environmental factors on HD pathology in humans and preclinical models have been extensively reviewed elsewhere [266] and the influence of these factors on gut microbiota in NDs have been discussed [34]. However, our understanding of interactions between physical activity and HD-specific microbiota in humans is limited, and warrants further studies.

### Antibiotics

Broad-spectrum antibiotics (ABX) can have long-term effects on microbial diversity, structure, and function as well as colonization periods [267,268]. Moreover, higher oral ABX exposure has been positively associated with increased AD [269], PD [267] and ALS risk in individuals [270]. Yet, there is evidence of the neuroprotective and anti-inflammatory activities of select antibiotics in clinical and experimental models. In transgenic fruit flies expressing the human mHTT, administration of rifaximin (broad-spectrum antibiotic, poorly absorbed in the GIT) or 1% penicillin–streptomycin (absorbable) not only depleted the commensal bacteria but improved disease phenotype characterized by lower aggregates of amyloidogenic N-terminal fragments of HTT compared to controls as well as delayed onset of motor deficits [271]. Interestingly, flies colonized by *Escherichia coli* showed an elevated abundance of HTT aggregates, motor defects as well and shorter lifespans [235]. In a different study, HD flies treated with rapamycin, lithium, or a combination of both were protected against neurodegeneration compared to vehicle-treated, with the combinatorial treatment offering even more neuroprotection [272].

Minocycline, a second-generation derivative of tetracycline, is clinically safe and crosses the blood–brain barrier. Its protective role in neurologic diseases has been demonstrated [273]. Phase one and two trials of Minocycline in HD patients (NCT00029874) are documented but the findings are unreported. Intraperitoneal administration of minocycline delayed disease progression and mortality in R6/2 HD mice [274]. It also downregulated caspase-1 and -3 mRNA expression as well as inducible nitric oxide synthetase (iNOS)

activation, these trio have been associated with exacerbated HD phenotype [274]. However, minocycline did not prevent weight loss or decrease fasting blood glucose levels. Similar findings in R6/2 HD mice have been demonstrated [275,276]. Surprisingly, the combination of minocycline and dietary supplementation of coenzymeQ<sub>10</sub> significantly improved body weight from 13 to 16 weeks of age [276].

The antibiotic mithramycin (MTM), now called plicamycin, is an FDA-approved anti-tumoral, anti-hypercalcemia drug, naturally derived from *Streptomyces agrillaceus*. In addition to its vital role in regulating cell proliferation and differentiation, it suppresses the expression of protooncogenes including c-myc [277]. Intraperitoneally-MTM-treated R6/2 HD mice showed improved survival, motor performance (rotarod) and significant resistance to brain neuropathology [278].

R6/1 HD mice administered a non-absorbable ABX cocktail of ertapenem sodium, vancomycin hydrochloride and neomycin sulphate did not show improved motor outcomes but ABX altered gait and locomotion (increased propel-brake ratios) in male HD mice, increased percentage of freezing over time in females as well as decreased extinction in female HD mice [1]. Furthermore, increased body weight and decreased food intake in HD males and female mice, but increased water intake in male mice only. Additionally, ABX increased fecal water content in male HD mice but did not modulate gut permeability at 20 weeks in both sexes. Also, ABX increased fecal output in HD males and increased fecal output in WT and HD females [1]. This ability of absorbable or non-absorbable ABX to modulate disease pathology and symptoms and remodel gut resident communities is not exclusive to HD and has been demonstrated in other NDs [279–281].

The gut microbiota influence hematopoiesis (production of blood cells) by regulating type 1 interferons and consequently Signal Transducer and Activator of Transcription 1 (STAT1) signaling [282]. Thus, ABX can limit murine hematopoiesis and significantly suppress multipotent progenitors [283]. Moreover, the depletion of intestinal microbiota disrupts basal STAT1 signaling and T cell homeostasis [283]. Interestingly, these hematopoietic defects induced by ABX can be rescued by administering the microbiota-derived product Nucleotide-binding Oligomerization Domain-containing protein 1 (NOD1) ligand [282].

The spleen, the largest secondary lymphoid organ, and a reservoir for immune cells such as macrophages and monocytes, plays a crucial role in hematopoiesis and regulating peripheral innate immune response

[284]. These functions are heavily influenced by the gut microbiota and their secretory products as described above. In fact, the gut microbiota are significantly altered in splenectomized patients and mice [285,286]. The most common cause of death in HD patients is pneumonia [287]. The bacterial load in the spleen has been correlated with the occurrence of bacteremia during pneumonia in humans, baboons and mice [288]. There is consistent evidence of increased splenic macrophages and lymphocytes in murine models of NDs such as AD, PD, and ALS, giving rise to a systemic proinflammatory response [289]. The genes *TNF- $\alpha$* , and *IL-6* were upregulated in the spleens of rats with depression-like phenotype [290].

Our understanding of the influence of ABX on the gut-brain spleen axis in HD is limited, but studies in healthy mice have reported interesting observations. For instance, 14 days administration of a broad-spectrum ABX cocktail consisting of ampicillin, neomycin, and metronidazole to healthy male mice decreased spleen weight and disrupted the population of splenic immune cells [291]. It also significantly decreased the expression of the microglial marker *Iba1* in the cerebral cortex [291]. Untargeted metabolomics analysis of the plasma, spleen and cerebral cortex of these mice revealed altered metabolite signatures [291].

Peripheral Ly6C<sup>high</sup> monocytes are versatile innate immune cells implicated in the pathogenesis of neurologic, inflammatory and cardiovascular disorders including MS, spinal cord injury, ALS, AD, PD, depression, colitis, heart ischemia and atherosclerosis [292–301]. Pattern recognition receptors (PRR) ligands are constitutively expressed by the gut microbiota and regulate the splenic Ly6C<sup>high</sup> monocytes' homeostasis and function during steady state [292]. Interestingly, 2–6 days administration of a broad-spectrum ABX cocktail consisting of vancomycin, neomycin, and metronidazole to female mice significantly reduced the expression of PRR ligands in the serum and this decrease was associated with reduced numbers of splenic Ly6C<sup>high</sup> monocytes and their disrupted activities [292]. However, this treatment did not impair hematopoiesis in the bone marrow [282]. Notably, intraperitoneal injection of PRR ligands significantly restored the population and function of splenic Ly6C<sup>high</sup> monocytes in the ABX-treated mice [292].

Overall, the microbiota–gut–brain axis in HD is a developing field of research and the sustainability and long-term efficacy of ABX manipulation (and other manipulations) of gut microbiota in HDGECs needs to be better understood. After all, we “contain multitudes” for a reason, and any manipulation of

microbiota has the potential to produce both positive and negative consequences.

### Fecal microbiota transplantation

As discussed earlier, gut dysbiosis is a causative factor in the onset and progression of neuropathological conditions. Fecal microbiota transplantation (FMT), a therapeutic strategy, involves the artificial transfer of gut microbiota from healthy subjects to disease subjects to alleviate gut dysbiosis in the recipient. Remodeling the gut microbial communities to treat diseases has been used for centuries. Hence, FMT is not a novel approach and is currently a standardized, less invasive treatment for *Clostridium difficile* infection compared to colectomy, with a Fischer study reporting an 87% cure rate [302] and a Spartz study providing more evidence [303].

Guzzardi *et al.* recently showed that cognitive phenotype is ‘transferrable’ through FMT. GF mice recipients of fecal matter from children with high cognitive performance showed superior cognitive phenotype as assessed by the Y-maze test, while recipients of children with low cognitive scores performed poorly [186]. Similarly, FMT from young donor mice (3–4 months) not only remodeled the hippocampal metabolome and transcriptome but reversed aging-associated markers in peripheral and hippocampal immune cells of aged recipient mice (19–20 months) and alleviated aging-induced behavioral anomalies [33].

Interestingly, the U.S. Food and Drug Administration recently approved two drugs chiefly derived from fecal samples of healthy subjects for the treatment of *C. difficile*-induced colitis [304,305]. The current application of FMT in various neurological and psychiatric diseases, including AD, PD, ALS, and MS, has been extensively reviewed [306–308]. However, there is a dearth of literature on the exploration of FMT as a therapeutic tool in HD patients and experimental models.

Attempts to modulate HD disease outcome in R6/1 HD mice via FMT following antibiotics (ABX) depletion of the host gut microbiota have been made [1]. Notably, FMT from WT mice into HD mice modulated the cognitive phenotype in a sex-specific manner, with females showing better improvement as characterized by Y-maze and fear-conditioning tests. FMT decreased fecal output and water content in both males and females, as well as gut transit time. Furthermore, age-dependent, genotype, and sex-specific changes in gut macroscopic structure with FMT treatment were demonstrated. Additionally, FMT increased fecal bacterial load at week 12 in both genotypes

compared to vehicle-treated groups. This study also demonstrated FMT's efficiency in restoring microbial richness and composition, reported poor engraftment in HD males, and suggested that this resistance to colonization could be attributed to aggravated gut pathology [1].

## Concluding remarks and future directions

Modulating the gut microbiome in HD is a promising treatment strategy. There is a paucity of literature, which underscores the need for additional studies to delineate the complexities of the microbiota–gut–brain axis in HD. Microbial profiling is crucial to elucidate gut ecological changes arising from HD interventions such as diet and physical activity. Moreover, microbiome–drug interactions in HD require more characterization and special consideration should be given to inter-individual gut microbiota variations as this knowledge could inform personalized medicine. Future experiments to assess microbial strain-specific effects in HD are warranted. Additionally, there is a compelling need for a more thorough assessment of the gut mycobiome, virome, and phageome, and their metabolites, in HDGECs compared to healthy individuals, and to ultimately improve our understanding of the complex web of trans-kingdom interactions, and their impact on HD onset and progression.

Furthermore, the link between oral dysbiosis and HD warrants delineation. As HD progresses, individuals have limited ability to maintain proper oral hygiene, thus they are more vulnerable to dental caries and periodontal diseases which can aggravate systemic inflammation and other HD symptoms. Therefore, interventions aimed at ameliorating possible oral dysbiosis in HDGECs may mediate dramatic improvement in quality of life. Importantly, characterization of the oral microbiome in these subjects could unravel microbial communities as a novel biomarker for HD.

Targeting the vagus nerve through VNS (which has anti-inflammatory potentials) could also be of interest to restore microbiota-gut-brain-axis homeostasis in disease conditions characterized by dysbiosis, intestinal inflammation and psychiatric manifestations, such as HD. Such candidate interventions need to be systematically tested in valid preclinical models.

Finally, enviromimetics [309] and their subclass, exercise mimetics [310] could be a complementary therapy for HD treatment and represent a non-pharmacological approach to improve the quality of life of HD subjects, but further research is required to fine-tune and personalize such interventions.

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## Conflict of interest

The authors declare no conflict of interest.

## Author contributions

MNE conceptualized and wrote the first draft of the manuscript; CG and AJH provided critical feedback, edited and revised subsequent drafts. CG made the figures and graphical abstract.

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