



(REVIEW ARTICLE)



## The gut microbiome in Huntington disease: A review

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### Abstract

Huntington's disease (HD) is a neurological disease caused by a trinucleotide repeat increase in the huntingtin (htt) gene, which is widely expressed in the brain and peripheral tissues. While many studies have focused on the cognitive, psychological, and motor symptoms of HD, however, the scope of peripheral pathology and its possible impact on central symptoms has received less attention. We hypothesised that because disruption of the gastrointestinal microbiota (gut dysbiosis) has lately been identified in a number of neurological and psychiatric illnesses, it might also occur in HD. In the HD gut microbiota, bacteroidetes increased whereas firmicutes decreased proportionally. Despite a larger food consumption, the gut dysbiosis was associated with a reduction in body weight growth. The presence of greater faecal water content in hd was also linked to a shift in the gut microenvironment. In this review, we present an update on the association between microbiome and brain function as it relates to huntington's disease.

**Keywords:** Huntington's disease; Gut-Brain Axis; Neurodegenerative Disease; Gut-Microbiota

### 1. Introduction

#### 1.1. Gut brain axis

At birth, humans are invaded by trillions of microbes [1]. Early gut colonization is influenced, at least in the short term, by the route of birth (caesarean section or vaginal) [2]. Non pathogenic bacteria make up the vast majority of the bacteria [3,4], traditionally, these host-associated bacteria (human microbiota) and their genetic potential (human microbiome) have been studied by anatomical site, such as the skin, oral, respiratory, urogenital, and gastrointestinal (GI) tract [5,6]. The gut-brain axis, a bidirectional communication link between the gastrointestinal system and the central nervous system, is critical for maintaining homeostasis in neural (both enteric and central nervous system), hormonal, and immunological signaling [7].the gut can influence the brain via visceral communications, and the brain can control gastrointestinal functions [such as motility, secretion, and mucin synthesis] and immune activities (such as the modulation of cytokine production by mucosal immune system cells) through this complicated network [8].

Entero endocrine cells (EECS) are found throughout the gastrointestinal (GI) tract, which is the biggest endocrine organ in the human body, and are stimulated by both luminal nutrients and gut microbial compounds [9]. Most nutritional receptors, including as those for amino acids, peptones, SCFAS, long-chain fatty acids (LCFAS), and oleoylethanolamide (OEA), are found in these EECS. The management of numerous activities during digestion, the start of neurological and hormonal responses, or changes in mucosal ion transport, which affects hunger, insulin secretion, and motility, are all dependent on molecular sensing by these EECS [10]. Furthermore, because neurological and endocrine signalling between the gut and the brain is critical for the modulation of numerous GI functions, the gut sensing receptors that

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control hormone release play an important role. Several interacting factors, such as nutrition and microbiota composition, regulate the activation of distinct sensory receptors in the gut, resulting in up or down-regulation of hormone release, which can result in a variety of functional GI alterations. Remarkably, mounting evidence suggests that animals fed a high-fat diet experience numerous changes in gastrointestinal function, particularly in the secretion and signalling of gastrointestinal hormones, which may predispose to an increase in energy intake and, as a result, weight gain and obesity [11].

The gut is a sensory organ that is also a part of the enteric nervous system, which is a large division of the autonomic nervous system that contains between 200 and 600 million neurons [10]. The vagus nerve [the primary nerve of the autonomic nervous system's parasympathetic division] is essential for bidirectional signalling between the gastrointestinal and neurological systems. Bravo et al conducted a ground breaking study [12]. In mice, probiotic manipulation of the gut microbiota resulted in behavioral and neurochemical alterations, according to the findings. This was not observed in mice who had undergone vagotomy, indicating that the vagus nerve plays an important function in the gut brain axis. The human intestine also functions as an endocrine organ by producing microbial metabolites and neurometabolites such short chain fatty acids (SCFAS), vitamins, and neurotransmitters, all of which have been proven to influence gut-brain interaction [13]. Gaba and serotonin are neurotransmitters produced directly or indirectly by commensal bacteria that might alter host behavior [14, 15]. Species like *roseburia spp.* And *faecalibacterium* can create SCFAS like butyrate, propionate, and acetate after fermenting indigestible polysaccharides [16]. Butyrate and propionate, via regulating neuropeptide synthesis, can affect brain function, particularly appetite management and energy homeostasis [17].

## 2. Pathways of gut brain axis

### 2.1. Neurology pathway

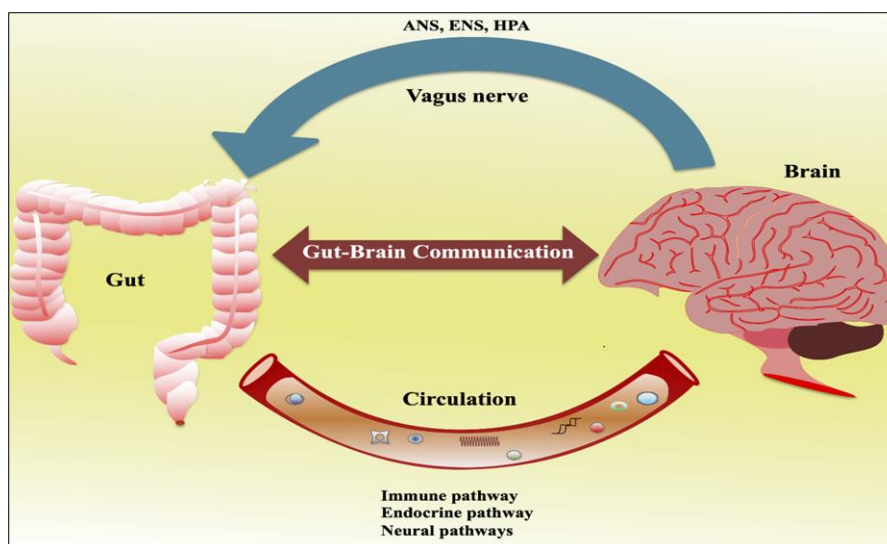
The neurologic pathway includes the vagus nerve, the enteric nervous system, and the activity of neurotransmitters in the gi tract. Neurologic regulation of afferent sensory nerves produces gaba, serotonin, melatonin, histamine, and acetylcholine directly; this pathway also produces physiologically active kinds of catecholamines in the gut lumen [18]. The autonomic nervous system can influence gut immune system activation by altering macrophage and mast cell responses to luminal bacteria, for example. Furthermore, the gut microbiota appears to have a role in normal gut intrinsic primary afferent neuron excitability [19, 20].

### 2.2. Endocrine pathway

The gut microbiota has an impact on nutritional availability and, as a result, the production of physiologically active peptides from enters endocrine cells, which can affect the gut-brain axis. The neuropeptide galanin, for example, is hypothesised to play a role in nociception, sleep/wake cycle control, eating, mood, blood pressure regulation, parental activity, and neurotrophic effects, among other essential neurobiological processes. Galanin stimulates the central branch of the hpa axis, which increases glucocorticoid secretion from the adrenal cortex [influencing the release of CRF and ACTH [21]. It may also cause cortisol secretion from the adrenal cortex and norepinephrine release from the adrenal medulla, implying that it plays a function in the 'HPA AXIS' stress response [22, 20].

### 2.3. Immune pathway

The gut microbiome impacts inflammatory metabolism in the GI tract during periods of dysbiosis, primarily through the immune system's secretion of cytokines like interleukin (IL-10 and IL-4) and other cellular communication mediators like interferon-gamma. Irritable bowel syndrome (IBS) is a type of irritable bowel syndrome (IBS), intestinal innate immune responses are triggered by irregular microbial populations, which increase gut epithelial permeability, activate gut pain sensory pathways, and dysregulate the enteric nervous system [18, 23, 24]. There are both brain-gut and gut-brain dysfunctions, with the former being more prevalent [25]. Disruptions in the gut-brain axis impact intestinal motility and secretion, contributing to visceral hypersensitivity and causing cellular alterations in the enteroendocrine and immune systems [18, 20, 26].



**Figure 1** Schematic diagram showing the communication between the gut and brain. This is a bidirectional Relationship that is strongly influenced by multiple pathways, including the autonomic nervous system (ANS), enteric nervous system (ENS), hypothalamic–pituitary–adrenal (HPA), immune pathways, Endocrine pathways, and neural pathways [27].

#### 2.4. Gut microbiota in neurodegeneration

The prevalence of neurodegenerative diseases is rising as the population ages. Neurodegeneration is a complex process that can be started by environmental stressors, such as oxidants, and results in the progressive degeneration of neurons. This causes an imbalance in the gut microbiota's metabolism, which alters the host's endocrine signalling [28]. Additionally, gut dysbiosis has been linked to the development of neurological disorders such as amyotrophic lateral sclerosis (ALS), Alzheimer's disease (AD), Huntington disease (HD), and Parkinson disease (PD) [29, 30].

#### 2.5. Huntington disease

The frequency of HD in European ancestry communities ranges between 3 and 7 instances per 100 000 [31] and appears to be rather consistent over generations. [32,33]. The disease is less common in Chinese and Black African groups, while the Japanese have a prevalence of less than 0.38 cases per 100,000 people. [31]. Huntington disease-like 2 or hdl-2, a rare HD phenocopy (see "the differential diagnosis of HD"), has an incidence among Black South Africans that is comparable to HD [34, 35]. Certain high-prevalence HD groups have also been observed, with a disease prevalence of more than 15 per 100,000 people. A founder effect, which can be seen in small geographically isolated places like Venezuela's Lake Maracaibo region, is one explanation for differential population prevalence [36]. A CAG repeat expansion in the huntingtin (Htt) gene on chromosome 4, which codes for polyglutamine in the huntingtin protein, causes Huntington disease (HD). The age of HD start is inversely proportional to the length of the expansion over a threshold of roughly 35 repeats, with variable age-dependent penetrance between 36 and 39 CAG repeats, but full penetrance at 40 or more repeats. Furthermore, it has been proposed that in the rare individuals with repeat lengths in the 27–35 range, there may be modest anomalies, possibly creating an endophenotype [37, 38]. HD is characterised by a triad of signs and symptoms, including motor, cognitive, and behavioural characteristics [39, 40]. Currently, onset is defined as the occurrence of "the unmistakable presence of an otherwise unexplained extrapyramidal movement disorder [for example, chorea, dystonia, bradykinesia, rigidity] in a person who possesses a CAG-expanded Htt allele [41, 42]. We add the presence of cognitive disorder as characteristic of HD, and an important contributor to disability. Emotional disorders and personality changes are common and may be a cause of distress, but are not universal, and seem not to progress steadily, as do the motor and cognitive changes.

### 3. Clinical features of HD

#### 3.1. Cognitive Disorder

Individuals with mild cognitive abnormalities are not uncommon prior to receiving a clinical diagnosis. These deficits are usually modest, and the individual may report them despite the absence of any obvious abnormalities on global clinical cognitive assessments. Specific, specialized neuropsychological tests like the negative emotion recognition task,

the stroop color word association test, and the spot the change task may be required to reliably measure hd cognitive loss even in early stages of the disease [43]. The increasing cognitive dysfunction in hd is referred to be "frontalsubcortical," and its usual pattern appears early in the disease. Bradyphrenia (slowness of thought), faulty recall, worsening of complex intellectual skills, and personality changes are all common cognitive symptoms. Individuals are frequently unaware of their limitations. Both procedural memory (the ability to learn and recall new motor abilities) and visuospatial memory are compromised in HD, which is sometimes referred to as a subcortical dementia. However, it appears that memory recall rather than memory storage is predominantly affected [44]. Aphasia, agnosia, and anosagnosia are common in "cortical" dementias like alzheimer disease, but they are uncommon in hd until late in the disease course. Executive function impairments occur, and they are similar to those reported in people with frontal lobe injuries. Pathology in the frontal lobes and frontalsubcortical circuitry is reflected in them. Early on in HD, attention and concentration are harmed, making it easier to become distracted [45].

### 3.2. Psychiatric disorder

The most variable feature of the HD clinical profile is the psychological aspects. The most prevalent psychiatric symptoms are depression, irritability, and impulsivity, but psychiatric presentations can be complex. Psychosis, mania, anxiety, and substance misuse can all emerge as a result of obsessive-compulsive and violent behaviours. Individuals with pre-manifest HD have a higher prevalence of mild psychological abnormalities than controls, both near and distant from illness onset [46]. These changes aren't severe enough to warrant a clinical diagnosis, but they do include higher scores on sadness, obsessive-compulsiveness, anxiety, and psychoticism scales. Surprisingly, the majority of the participants in this study were more than 10 years away from the expected beginning of disease [46].

### 3.3. Other clinical characteristics

Although weight loss is a common symptom in the later stages of HD, the origin of the cachexia remains unknown. It happens despite a larger caloric intake and increased appetite than controls [47]. In the early and middle phases of HD, hyperkinetic movement disorder is likely to play a role [48], however, metabolic profiling has revealed that these patients have a pro-catabolic phenotype [49]. The presence of high amounts of the orexigenic hormone ghrelin and low levels of the adipocyte hormone leptin in the plasma of HD patients adds to the case for a negative energy balance [50], a pattern that can be detected in catabolic conditions. The conflicting effects of these peripherally generated hormones on hypothalamic neurons regulate energy metabolism. Following the discovery of testicular degeneration in transgenic HD mice, researchers decided to investigate further [51], in HD patients, there was a decrease in germ cells and aberrant seminiferous tubule shape. These testicular abnormalities appear to be a toxic impact of mutant huntingtin, rather than a result of a malfunctioning hypothalamic pituitary gonadal system [52]. Because male fertility is unaffected in HD, this trait most likely arises later in life [53].

### 3.4. Correlation of Gut Brain Axis and Huntington Disease

Several neurological and mental disorders, including autism spectrum disorder, major depression, Parkinson's disease (PD), and Alzheimer's disease (AD), have been linked to gut dysbiosis [54, 55, 56, 57]. Numerous studies have revealed that gut dysbiosis is not merely as comorbidity in neurological illnesses, but that it may also play a role in modifying physiological, behavioural, and motor abnormalities [58, 59, 60]. There has been no research on the gut microbiota composition in HD patients. There are, however, multiple lines of evidence pointing to gut dysbiosis as a probable cause of HD. Specifically, circulating gut microbiota-derived chemicals were altered in HD patients and transgenic mice, suggesting that gut microbiota may be altered prior to illness onset [61, 62]. Furthermore, gastrointestinal dysfunction may impair weight loss, which is a common symptom of HD [63]. A significant shift in the bray-curtis index, but not in the unweighted unifrac index, suggests that the bacteria that differentiate the Wt and HD gut microbiomes are phylogenetically similar but differ in abundance. In contrast to research revealing gut microbiome modifications in other diseases, such as alzheimer's disease and chronic fatigue syndrome, we found an increase in alpha-diversity in male HD when compared to wt [64, 65]. In HD, we also saw a rise in *bacteroidetes* with a corresponding drop in *firmicutes*, similar to what we saw in alzheimer's disease, type 2 diabetes, and chronic fatigue syndrome [64, 65]. The spls-da analysis revealed that wt mice's gut microbiome profile is dominated by *clostridiales* from the *firmicutes* phyla, whereas HD mice's signature is dominated by *bacteroidales* from the *bacteroidetes* phyla. Cage effects were examined; however, they had no influence on the majority of the SPLS-Da signatures. *Bacteroidetes* is connected with weight loss while *firmicutes* is associated with weight gain, according to obesity research [66, 86].

Furthermore, changes in the b/f ratio have been linked to changes in short-chain fatty acid (SCFA) levels, which are a by-product of microorganisms fermenting dietary fibre and have downstream effects on the host's metabolism [67].

In Wt and hd mice, we discovered sex differences in the gut microbiota. The presence of significance on the unweighted unifrac index, but not on bray-curtis, indicates that the bacteria that differ between the two groups are phylogenetically distant but not in quantity. There have been multiple reports of sex differences in the gut microbiome outside of HD, which are likely mediated by sex hormones [68, 69]. Sexual dimorphism is a prevalent feature of a range of disorders, including metabolic, psychiatric, and other neurodegenerative diseases like parkinson's disease, alzheimer's disease, and huntington's disease [70- 75]

Increased water consumption was also found in HD mice, which is consistent with prior observations of xerostomia in HD patients and animals [76]. In mammals, the bulk of surplus water is expelled through urination, whereas a predetermined proportion is eliminated through faeces, ensuring that stool water content is always regulated. Because ingested water is rapidly absorbed by the body, primarily in the small intestine, an increase in faecal water content in conjunction with increased water consumption shows that water absorption in the small intestine is dysfunctional [77]. Because the Htt gene is broadly expressed in the peripheral, including the gut, there are a variety of ways that the HD gene mutation's expression could affect the gut microbiome in this mouse model. Colonic transit time is one of the factors determining microbial diversity, since it can affect the bioavailability and absorption of various by-products and water by microorganisms, potentially altering gut microbiota makeup [78, 79]. We found that hd mice had a greater faecal water content, indicating that there is a problem with either gut transit time or colon water absorption, which could induce a change in the gut environment and, as a result, the observed shift in microbiota composition. Furthermore, a few studies have shown that intestinal epithelial cells (IEC) in the GI tract can produce extracellular vesicles containing miRNA from the host, which can influence gut microbial gene expression [80,81]. Extracellular vesicle payload is determined by the cell of origin, and mutant Htt has been shown to alter the cellular miRNA profile [82, 83, 84, 85]. It's likely that the presence of Htt in the parent cell causes the IEC-derived vesicles to have different miRNA cargo, which changes the gut microbiome's expression [86]. Furthermore, in both in vivo and in vitro studies, plants with well-established antioxidant and neuroprotective effects have shown beneficial effects against the symptoms of HD [87].

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#### 4. Conclusion

In conclusion, various neurological discoveries into the gut–brain axis demonstrate that the gut microbiota have significant bidirectional contact with the CNS and affect the CNS's growth and activities, which promotes gut homeostasis. The bidirectional communication routes between gut bacteria and the CNS, dubbed the "microbiota-gut-brain axis" these days, are the focus of a growing corpus of study. The pathogenesis of neurological disorders such as depression, Alzheimer's disease, autism spectrum disorder, multiple sclerosis, and Parkinson's disease has been linked to dysregulation of this axis. There have been no investigations on the gut microbiota composition in HD to date. There are, however, multiple lines of evidence pointing to gut dysbiosis as a probable cause of HD. Specifically, circulating gut microbiota-derived chemicals were altered in HD patients and transgenic mice, suggesting that gut microbiota may be altered prior to illness onset. This mutant protein causes a cascade of molecular dysregulation and cellular damage when it is expressed. Motor, cognitive, and affective symptoms are common in HD patients, and they are frequently accompanied by skeletal muscle atrophy, gradual weight loss, impaired metabolic balance, and gastrointestinal (GI) dysfunction. *Firmicutes* is linked to weight growth, while *bacteroidetes* is linked to weight decrease. Weight loss, a common symptom of hd, could be influenced by gastrointestinal issues. HD mice had a greater faecal water content, implying that there is a problem with gut transit time or colon water absorption, which could contribute to a change in the gut environment. These findings are the first to show that disruption of the gut microbiota is linked to HD. The dysbiosis in the gut that was discovered here could be a modulator of the development and course of HD symptoms.

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#### Compliance with ethical standards

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##### *Disclosure of conflict of interest*

No conflict of interest.

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