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Targeting the gut–microbiota–brain axis in irritable bowel disease to improve cognitive function – recent knowledge and emerging therapeutic opportunities

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Abstract: The brain–gut axis forms a bidirectional communication system between the gastrointestinal (GI) tract and cognitive brain areas. Disturbances to this system in disease states such as inflammatory bowel disease have consequences for neuronal activity and subsequent cognitive function. The gut–microbiota–brain axis refers to the communication between gut-resident bacteria and the brain. This circuits exists to detect gut microorganisms and relay information to specific areas of the central nervous system (CNS) that in turn, regulate gut physiology. Changes in both the stability and diversity of the gut microbiota have been implicated in several neuronal disorders, including depression, autism spectrum disorder Parkinson's disease, Alzheimer's disease and multiple sclerosis. Correcting this imbalance with medicinal herbs, the metabolic products of dysregulated bacteria and probiotics have shown hope for the treatment of these neuronal disorders. In this review, we focus on recent advances in our understanding of the intricate connections between the gut–microbiota and the brain. We discuss the contribution of gut microbiota to neuronal disorders and the tangible links between diseases of the GI tract with cognitive function and behaviour. In this regard, we focus on irritable bowel syndrome (IBS) given its strong links to brain function and anxiety disorders. This adds to the growing body of evidence supporting targeted therapeutic strategies to modulate the gut microbiota for the treatment of brain/mental-health-related disease.

Keywords: brain gut-axis; cognition; gastrointestinal tract; inflammatory bowel disease; microbiota; neurodegeneration.

1 Introduction

The gut–brain axis monitors and integrates gastrointestinal (GI) function with cognitive and emotional brain areas (Dodds et al. 2022; Dogra et al. 2022). The human gut consists of approximately 500 million neurons connected to the brain through the nervous system. The vagus nerve is one of the largest nerves connecting the gut to the brain and relays information in both directions. This brain gut-axis encompasses the central nervous system (CNS), the autonomic nervous system, the enteric nervous system, and the hypothalamic pituitary adrenal system. The autonomic nervous system drives afferent signals from the gut to the CNS via enteric, spinal and vagal pathways (Fokam et al. 2022). The hypothalamic pituitary adrenal system forms an arm of the limbic system that provides primary biological responses to stress-based stimuli (Musleh-Vega et al. 2022; Ryuk et al. 2022; Varanoske et al. 2022). The hypothalamic pituitary adrenal system and nerves within the GI-tract allow the neuronal control of intestinal function, which reciprocally affords the gut to influence mood, cognition and mental behaviour (Fairbrass et al. 2022; Forssten et al. 2022; Hinzpeter et al. 2022; Jantsch et al. 2022; Varanoske et al. 2022). These connections were first identified through understanding the control of hunger and satiety, with gut-activity controlling the ventromedial nuclei, lateral hypothalamic area, and the arcuate nucleus of the hypothalamus to convey the sensation of fullness. More recent studies now highlight the role of the gut in cognitive, behavioural and psychological control beyond simple feeding and hunger (Fokam et al. 2022). In this regard, GI conditions such as irritable bowel syndrome (IBS) and

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gastroesophageal reflux disease have been strongly linked to brain function and anxiety disorders (Wu et al. 2022a). In animal studies, stress can inhibit signals sent through the vagus nerve leading to GI problems. Similarly, studies in humans have found that patients with IBS or Crohn's disease have reduced vagal tone, indicating a reduced function of the vagus nerve. This highlights the importance of the vagus nerve in the gut-brain axis and its role in stress, fuelling studies targeting the brain–gut axis for the development of therapeutics for mental health disorders (Bi et al. 2022; He et al. 2022a; Rupp and Stengel 2022). These will be discussed herein.

2 Gut microbiota

The human microbiota is fundamental to GI physiology, pathology and signalling from the gut to the brain (Figure 1). The gut microbiota constitute several species of microorganisms, including bacteria, yeast and viruses. The number of microorganisms inhabiting the GI tract exceeds 10^{14}, with bacterial cells predominate (Higgins et al. 2022). Four major phyla are present in the gut and include *Firmicutes, Bacteriodetes*, *Actinobacteria*, and *Proteobacteria* (Belizario and Napolitano 2015). Deviations in the composition of the gut microbiota are linked to a plethora of disease states including (but not limited to) diabetes, obesity, hepatic steatosis, IBS and cancer. Thus, suggesting that various pathways involved in energy metabolism, immunity, lipid synthesis and glucose metabolism are affected by dysbiosis in the gut. A wealth of studies have focused on understanding the development of the microbiome in humans in the context of health outcomes, with the ultimate aim of improving knowledge of microbiome–host molecular interactions (Barrio et al. 2022; Durack and Lynch 2019). The main aim of these studies is to develop effective approaches to restore perturbed human microbial ecosystems to improve health and prevent disease.

The composition of the human gut microbiota has been annotated using DNA based methods, including next-generation sequencing (NGS) of 16S ribosomal RNA genes and shotgun sequencing. These also permit the inference of microbiota functions and the production of metabolic products. Metabolites of the microbiota can be measured in stool and serum samples using metabolomics (Song et al. 2022). MetaHit and the Human Microbiome Project have provided the most up-to-date understanding of the human-associated microbiome, identifying more than 2000 species including *Proteobacteria, Firmicutes, Actinobacteria and Bacteroidetes phyla* (Li et al. 2022a; Zhu et al. 2022). In humans, many of the identified species are anaerobic with ~20% of bacterial phyla GI resident. The microbiota also encompasses viruses, archae, protozoa and fungi (Szostak et al. 2022). Remarkably, since diet, lifestyle and genetics shape the composition of the gut microbiota, individuals from the same ethnic origin often share comparable intestinal microbiota traits (Deschasaux et al. 2018). However, these studies are limited since faecal represent only a proxy for intestinal microbiota composition, with invasive biopsies required to fully understand microbiota traits, which are unsuitable for healthy control subjects. New sampling technologies are however emerging, including the Brisbane Aseptic Biopsy Device and the intelligent capsule (reviewed in Tang et al. 2020).

It is now accepted that humans share a core microbiome, with common members of microbial species (Ahn and Hayes 2021). Different individuals however show substantially varying densities amongst conserved taxa that is a potential source of inter-individual susceptibility to disease. Within the GI system, a loss of bacterial diversity leads to a range of pathologies, including IBS, arthritis, diabetes, eczema, coeliac, obesity and Crohn's disease (Giridharan et al. 2022; Gubert et al. 2022; Guo et al. 2022; Hamamah et al. 2022; Higgins et al. 2022; Honarpisheh et al. 2022; Hu et al. 2022a,b). This is because a species-rich GI ecosystem offers inherent redundancy, with diversity compensating for absent or lacking species. This increases robustness against environmental influences including diet and lifestyle (Szostak et al. 2022). Gut microbiota are key to the general functionality of the GI system as they permit the fermentation of dietary fibres and mucus (non-digestible substrates). Microbes in the gut also produce short chain fatty acids (SCFAs), including butyrate, propionate, and acetate, the levels of which are dysregulated in disease states. Butyrate is a major energy source for human colonocytes with anti-cancer properties and the ability to promote gluconeogenesis (Coccurello et al. 2022; Shirvani-Rad et al. 2022). Propionate is the major microbial fermentation metabolite in the human gut with health effects that extend beyond the gut epithelium, with roles in satiety and gluconeogenesis (Bindels et al. 2012; Hosseini et al. 2011; Lin et al. 2012). Acetate plays a role in appetite control through its direct impact on the hypothalamus, and can inhibit lipolysis, increase the hepatic uptake of cholesterol and reduce hyperglycaemia (Nogal et al. 2021). Acetate also promotes the growth of other beneficial bacteria.

Gut microbial enzymes also enhance the metabolism of bile acid, generating unconjugated and secondary bile acids that act as key signalling molecules in the brain (Figure 1). Recent studies by Marrocco and colleagues highlighted how environmental stimuli shift the production of

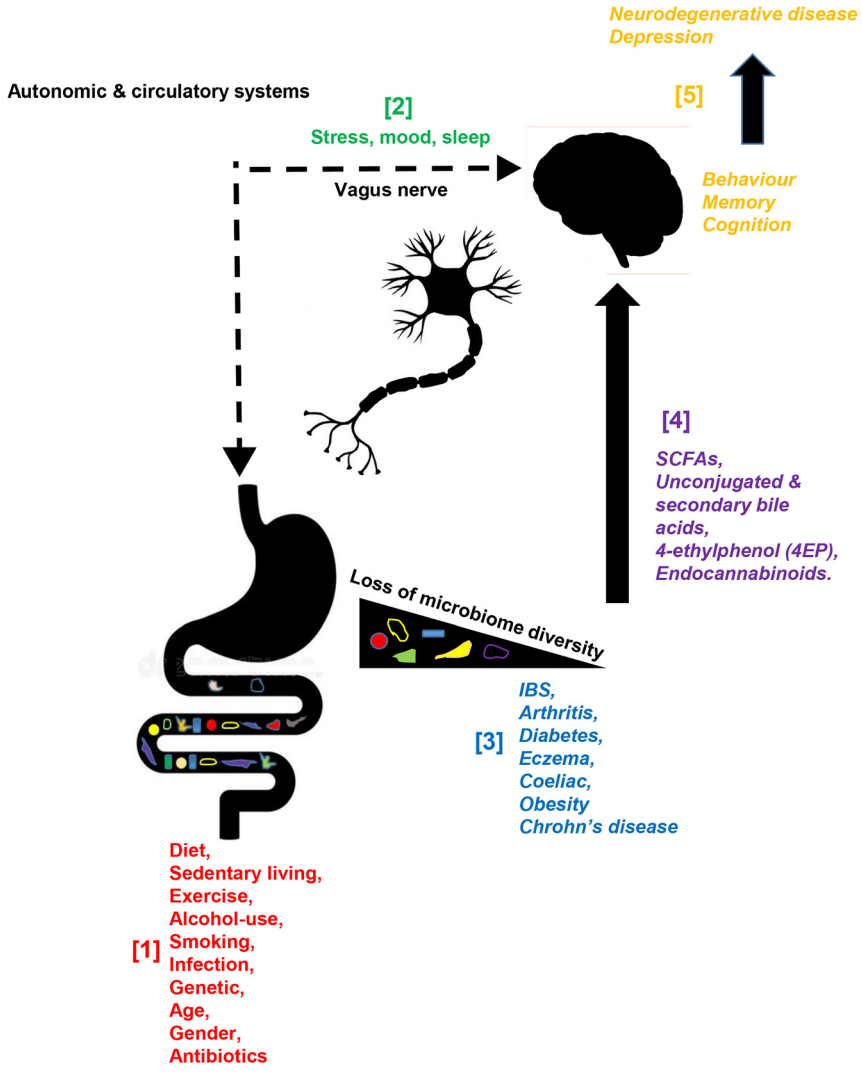

Figure 1: Importance of the gut microbiota in the regulation of cognitive function and brain activity. Microbes in the GI system control the communication between the metabolic system and the CNS through the microbiota–gut–brain axis. These connections are mediated through the autonomic and circulatory systems. [1] Factors contributing to a loss of microbiome diversity. [2] Stress, mood and sleep reciprocally regulate gut function and the microbiome. [3] Microbiome dysbiosis leads to a range of GI-associated disease states. [4] An altered microbiome alters the production of GI metabolites that influence brain function. [5] Collectively, these influence brain function and memory leading to neurological disorders.

SCFAs and bile salts leading to changes in hippocampal neurogenesis, neurotrophin production, short-term plasticity and cognitive behaviour (Marrocco et al. 2022). It has similarly emerged that the products of the gut microbiota control stress responses, anxiety and memory function (Chakrabarti et al. 2022), most notably the conversion of tyrosine to 4-ethylphenol (4EP) that is associated with changes in region-specific brain activity and functional connectivity (Needham et al. 2022). A loss of endocannabinoid signalling as a result of reduced peripheral levels of fatty acid precursors of endocannabinoid ligands in the gut has also been shown to promote depression (Chevalier et al. 2020). This is of particular impact since depression remains one of the most common yet poorly understood diseases courtesy of its elusive pathogenesis. Herein, we focus on IBS as a GI disorder linked to dysbiosis and discuss its emerging links to behaviour, anxiety and depression.

3 IBS: background and association with the microbiome

IBS is a common pathological condition and the prototypic GI disorder (El-Salhy et al. 2019). IBS is diagnosed according to symptom-based classification and Rome IV criteria

(Bai et al. 2017) into four subcategories: [1] diarrhoea-predominant IBS (IBS-D); [2] constipation-predominant IBS (IBS-C); [3] mixed diarrhoea and constipation IBS (IBS-M); and [4] unspecific IBS (IBS-U) (Drossman 2016). IBS-D accounts for approximately 1/3 IBS cases (Hungin et al. 2003; Lovell and Ford 2012). IBS is multifactorial with GI dysmotility, inflammation, visceral hypersensitivity and altered intestinal microbiota all contributing to disease pathology (Ohman and Simren 2013; Putignani et al. 2016). Diet, stress and genetic predisposition and have also been implicated (Konig and Brummer 2020; Maccaferri et al. 2012; Matto et al. 2005; Ohman and Simren 2013). Stress acts upon the emotional limbic system and leads to the release of cortisol and adrenocorticotropic hormone, known drivers of IBS (Patacchioli et al. 2001; Zou et al. 2008). Reciprocally, IBS influences the CNS, with dysmotility, visceral sensitivity, and anxiety reported in IBS patients, all of which are controlled by psychosocial processes (Musleh-Vega et al. 2022; Naliboff et al. 2020; Patacchioli et al. 2001; Ryuk et al. 2022; Varanoske et al. 2022). Treatment strategies for IBS focus on disease management, often including antispasmodics for visceral hypersensitivity and abdominal pain, anti-diarrhoea tablets, and nutritional intervention (Wu et al. 2022b). Given the emerging links between IBS and the brain, psychotherapy has shown promise as a bespoke intervention (Blanchard et al. 2008). The efficacy of these modalities are however case dependent (Ford et al. 2017) and more effective and widely applicable treatments are urgently required.

More than ~70% of IBS patients harbour a compromised microbiota. The most common findings are increased *Streptococcus* spp. a reduction in *Lactobacillus* spp. and an abundance of *Bacteroidetes* (El-Salhy et al. 2019; Konig and Brummer 2020; Maccaferri et al. 2012). This translates as a loss of beneficial bacteria and an increase in pathogenic species. Changes in the microbiome are at their most predominant following infection, where *Staphylococcus aureus, Campylobacter Clostridium perfringens, Shigella*, and *Bacillus cereus* become abundant. The depletion of butyrate-producing bacterial strains is also common during early IBS development (Ohman and Simren 2013; Putignani et al. 2016; Shanahan and Quigley 2014).

Studies in this area are vast, but knowledge is limited by inconsistencies in the literature. This heterogeneity is likely due to the range of methodologies employed, genetic differences in study subjects and differences in control subjects/animals. The most common beneficial bacteria in the GI are bifidobacteria which improve intestinal function, enabling nutrient absorption and resistance to invasion by foreign bacteria (Buckley et al. 2021). *Lactobacillus* are also essential beneficial bacteria that protect the GI mucosa, with reduced levels commonly reported in IBS patients (Konig and Brummer 2020; Maccaferri et al. 2012; Matto et al. 2005; Ohman and Simren 2013; Putignani et al. 2016). Jeffery and colleagues used shotgun 16S rRNA gene microbiome profiling and metabolomics to identify specific microbiome signatures within IBS patients, revealing *Lachnospiraceae* and enrichment in amino acid biosynthesis as key events during IBS progression (Jeffery et al. 2020). *Lachnospiraceae* are important butyrate producers residing in the GI microbiota, highlighting the importance of this SCFA to health gut function. Shotgun metagenomics across a large IBS cohort, also identified the enrichment of evolutionarily distinct Firmicutes species in disease models, including pathogenic *C. difficile, C. sordellii* and *C. perfringens, Faecalicatena gnavus* and *C. clostridioforme* and *Fusicatenibacter saccharivorans*. Fecal microbiota analysis from patients with IBS also show excessive histamine levels due to high levels of *Klebsiella aerogenes*, a gram negative bacteria that expresses a variant of histidine decarboxylase (De Palma et al. 2022). This holds particular interest for the effects of IBS on cognition since histidine can modulate the properties of neurons and synapses and is implicated in the emergence of neurodevelopmental disorders. Blocking histamine receptors also inhibits visceral hypersensitivity within IBS mice (Ray 2022). Lower levels of neuroendocrine hormones that regulate tryptophan-serotonin-melatonin synthesis and glutamine/GABA have also been reported in IBS cohorts, both of which are key to cognitive behaviour (Tanaka et al. 2022). This knowledge fuelled investigation of the efficacy of faecal microbiota transplantation (FMT) for IBS patients in randomised, double-blind, placebo-controlled studies. The outcomes of these trials were contradictory with one reporting an improvement in IBS symptoms, the other reporting no beneficial effects. The current consensus is that FMT represents an effective treatment for patients with IBS only when well-defined donor with a favourable and specific microbial signature is available (El-Salhy et al. 2020). Of note, subdiaphragmatic vagotomy (a surgical technique removing all vagal fibers) was shown to prevent the development of depression-like phenotypes in FMT-treated mice, highlighting how the brain–gut–microbiota axis and its association with the vagus nerve play a key role in the development of depression (Pu et al. 2021; Wang et al. 2021; Yang et al. 2023). Collectively, these studies highlight the tangible links between the gut microbiota, IBS and the development of neuronal function/behaviour disorders.

4 GI microbiome and cognitive function

A growing body of evidence highlights how the GI microbiome directly influences cognition and behaviour (Brunt et al. 2021; Buttiker et al. 2021; Canipe et al. 2021; Carlson et al. 2018; Chakrabarti et al. 2022; Cheatham et al. 2022; Davari et al. 2013; Ettinger 2022; Feng et al. 2017; Gao et al. 2019; Sun et al. 2020). Reciprocally, neuronal stimulation modulates the microbiome (Figure 1), exemplified by the effects of repetitive transcranial stimulation on the levels of *Firmicutes* in rodents (Ziomber-Lisiak et al. 2022). Similar studies in humans are however lacking and limited to individual case reports. One example includes changes in the ratio of *Bacteroidetes* and *Firmicutes* reported in a female patient receiving a weak (~2 mA) current to the right dorsolateral prefrontal cortex and contralateral supraorbital region for 20 min a day, twice per-week (Artifon et al. 2020).

Gut microbes influence behaviour through neural, endocrine, and immune pathways (Bhatt et al. 2023; Choi et al. 2022; Dogra et al. 2022; Dong et al. 2022). Dysbiosis is linked to Schizophrenia, bipolar disorders, Autism, depression and anxiety (Aaldijk and Vermeiren 2022; Chang et al. 2022). Serotonin is produced by *Lactococcus, Lactobacillus, Streptococcus, Morganella, Klebsiella, Hafnia, Bacteroides, Bifidobacterium, Propionibacterium, Eubacterium, Roseburia* and *Prevotella* in the GI tract (Aaldijk and Vermeiren 2022; Banskota and Khan 2022; Bhatt et al. 2023), which acts to regulate appetite, sleeping patterns, mood and cognition. Of note, low levels of serotonin are a key feature of IBS patients. Environmental contaminants such as particle matter 2.5 (PM2.5) that influence the microbiota also cause neurotoxicity (Balaguer-Trias et al. 2022), with tangible links between these two phenomena of interest to environmental related stress disorders. The GI microbiota also maintain dopamine levels in the brain via *Prevotella, Bacteroides, Lactobacillus, Bifidobacterium, Clostridium, Enterococcus* and *Ruminococcus*. Patients with chronic insomnia show altered levels of these GI *lactobacilli.* Coprobacter in the GI system, which also correlates with poor cognitive performance (Escobar et al. 2022; Hu et al. 2022c; Xavier et al. 2023). Butyrate from the GI inhibits histone deacetylase (HDAC). This is of interest since HDAC inhibitors have shown promise for the treatment of brain trauma and dementia (Zhang et al. 2022).

At the species level, *Coprococcus catus* and *Bacteroides barnesiae* have been reported to be lower in patients with depression (Li et al. 2022b). Enterobacter and *Burkholderia* also positively correlate with depressive symptoms but negatively correlate with memory, somatosensory integration, and emotional processing/cognition/regulation (Tsai et al. 2022). Radjabzadeh and colleagues recently identified 13 microbial taxa that were dysregulated in patients with depression, including *Eggerthella, Subdoligranulum, Coprococcus, Sellimonas, Lachnoclostridium, Hungatella, Ruminococcaceae (UCG002, UCG003 and UCG005), Lachnospiraceae UCG001, Eubacterium ventriosum* and *Ruminococcus gauvreauii*. These bacteria regulate glutamate, butyrate, serotonin and gamma amino butyric acid (GABA) synthesis, all of which are key neurotransmitters for depression (Radjabzadeh et al. 2022). Changes in bile acid profiles as a result of alterations in gut microbiome composition are also associated with higher levels of anxiety in patients with major depressive disorder (MahmoudianDehkordi et al. 2022). Together, these studies highlight the promising potential of the development of gut microbiome-directed therapies for the treatment of depression.

Alterations to the gut microbiome can also been linked to autism spectrum disorder (ASD), a developmental disorder characterized by impaired social interaction. Children with ASD show shifts in fungal communities, increased acetic acid concentrations and alterations in several bacterial taxa (Jones et al. 2022). Du and colleagues characterised alterations of gut microbiota, SCFA levels and brain function in a cross-sectional study of 30 diabetic cognitive impaired (DCI) patients. These showed a higher abundance of *Gemmiger, Bacteroides, Roseburia, Prevotella*, and *Bifidobacterium* and lower levels *Escherichia* and *Akkermansia*, leading to reduced concentrations of acetic acid, propionic acid, isobutyric acid and butyric acid (Du et al. 2022). Increased levels of amino acid transporters in the intestines of mouse ASD models that lead to high levels of serum glutamine and increased excitation/inhibition ratios in the brain have also been reported (Yu et al. 2022a).

Alterations in intestinal microbiomes and lipid metabolism have also been linked to prolonged disorders of consciousness in patients who survived severe traumatic brain injury. These typically involve a vegetative state and minimally conscious state, with *Faecailbacterium, Enterococcus and Methanobrevibacter* implicated (Yu et al. 2022b). Blastocystis (a single cell parasite in the gut) is associated with cognitive traits and decreased executive function (Mayneris-Perxachs et al. 2022a). Alterations in the gut microbiome that lead to IBD are also strongly linked to psychological health (Fairbrass et al. 2022).

5 Emerging opportunities for therapeutic intervention

CNS function can be improved through targeted interventions against the composition of gut microbiota. Examples of this for the seven major probiotics used in humans are shown in Figure 2. Restoring the metabolites of beneficial microbes has shown similar promise (Barrio et al. 2022). GABA, 5-HT dopamine, acetylcholine and neuropeptide Y levels can all be increased by probiotic treatment (Wu et al. 2022a,b). Lactic acid bacterial strains have beneficial effects on short-term spatial and non-spatial learning and memory. These effects are mediated through increased GABA production that improves both stress and mood responses (Chen et al. 2022; Nobile et al. 2022; Tanaka et al. 2022). Danggui-Shaoyao-San (a traditional medicine) alleviates the symptoms of cognitive impairment in mice through its effects on the composition of intestinal flora (Liu et al. 2022a). The microbiota–gut–brain axis also controls chronic cerebral hypoperfusion through SCFA production. Accordingly, SCFA supplementation is neuroprotective (He et al. 2021; Huang et al. 2021; Peng et al. 2022; Xiao et al. 2022). *Lactobacillus plantarum* MA2 (MA2), a probiotic isolated from traditional Chinese Tibetan kefir grains, improves cognitive deficits and anxiety in ASD rats, and attenuates Aβ accumulation in the brain (Wang et al. 2022). Supplementation with *Bacteroides uniformis* has also been reported to improve the ASD-like behaviour by decreasing intestinal amino acid transport and subsequent serum glutamine levels (Yu et al. 2022a,b).

Altered microbial functions that control glutamate/GABA and proline metabolism strongly impact depression (Mayneris-Perxachs et al. 2022b). In mice, human microbiota transplantation and dietary proline could rescue mood and behaviour. *L. plantarum*-derived probiotics also prevent pathogen-induced neurological dysfunction through modulation of the GI-brain axis. *Lactobacillus rhamnosus GR-1* also attenuates learning and memory deficits (Gu et al. 2022). N-3 PUFA treatment improves neuropsychiatric behaviour in rat models of geriatric depression (Tung et al. 2022). The protective effects of Porphyra tenera against PM 2.5-induced cognitive dysfunction have also been reported (Park et al. 2022). *Dendrobium officinale* polysaccharide can attenuate cognitive impairment in mice evoked through the disruption of circadian rhythm (Sun et al. 2022). Altering the gut microbiota with the FXR agonist GW4064 also ameliorates behavioural deficits in animal models of autism (Liu et al. 2022b). Huang and colleagues showed that Nordic berries positively influence cognitive outcomes through their effects on the gut microbiota (He et al. 2022b). Gastrodin derived from gastrodia elata improves cognitive activity and neuroprotection in AD mice through the prevention of neuroinflammation mediated by the gut microbiota (Fasina et al. 2022). The gut metabolite indole-3 propionate, produced by *Clostridium sporogenes* has also been shown to promote axonal regeneration following sciatic injury (Serger et al. 2022). These studies provide only a snapshot of the wealth of

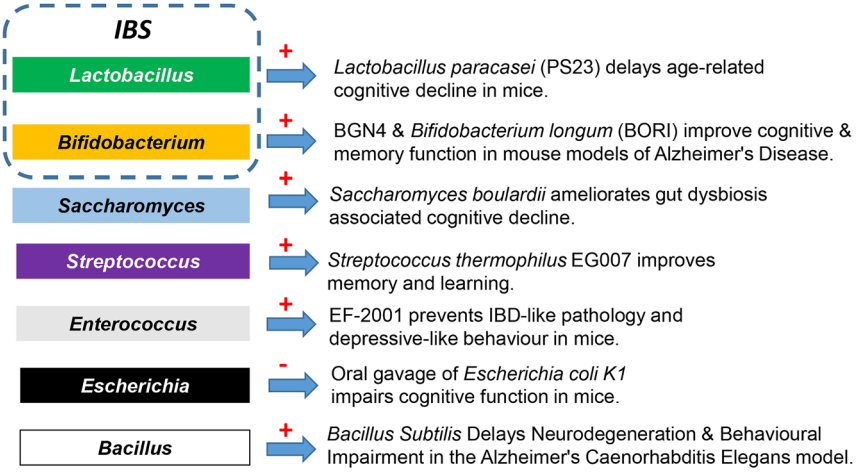

Figure 2: Benefits of probiotic therapy for cognitive function. Examples of experimental animal studies of cognition for the major probiotics used in humans are shown. (+) Indicates beneficial effects on cognitive function; (–) indicates negative effects. Most probiotics used in IBS treatment fall under *Lactobacillus* & *Bifidobacterium*. These assist the digestive system, strengthen the intestinal barrier and ameliorate cognitive impairment and depressive disorders.

literature that now indicates the importance of the gut microbiota in the regulation of cognitive function and brain activity.

6 Conclusions

It is now accepted that microbes in the GI system regulate brain function. Less-well understood is how specifically the gut microbiome and neurons mutually interact and the microbiota species signatures that are key to this communication. Further understanding of the mechanisms through which gut microbiota regulate the production, transportation and function of neurotransmitters can improve understanding of how microbiome dysbiosis affects mood and behaviour. This will ultimately inform the utility of targeted probiotic interventions and metabolite supplementation for CNS related cognitive diseases. The impact of progress in this area is highlighted by depression, one of the most common mental disorders experienced worldwide with a prevalence of 11–15% that continues to rise. The microbiome may hold the key to our understanding and treatment of these common yet poorly understood neuronal diseases.

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