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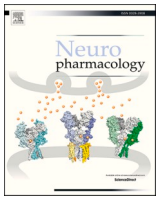

Are neuromodulation interventions associated with changes in the gut microbiota? A systematic review

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ABSTRACT

The microbiota-gut-brain axis (MGBA) refers to the bidirectional communication between the brain and the gut microbiota and recent studies have linked the MGBA to health and disease. Research has so far investigated this axis mainly from microbiota to brain but less is known about the other direction. One approach to examine the MGBA from brain to microbiota is through understanding if and how neuromodulation might impact microbiota. Neuromodulation encompasses a wide range of stimulation techniques and is used to treat neurological, psychiatric and metabolic disorders, like Parkinson's Disease, depression and obesity. Here, we performed a systematic review to investigate whether neuromodulation is associated with subsequent changes in the gut microbiota. Searches in PsycINFO and MEDLINE were performed up to March 2022. Included studies needed to be clinical or preclinical studies comparing the effects of deep brain stimulation, electroconvulsive therapy, repetitive transcranial magnetic stimulation, transcranial direct current stimulation or vagal nerve stimulation on the gut microbiota before and after treatment or between active and control groups. Seven studies were identified. Neuromodulation was associated with changes in relative bacterial abundances, but not with (changes in) α-diversity or β-diversity. Summarizing, currently reported findings suggest that neuromodulation interventions are associated with moderate changes in the gut microbiome. However, findings remain inconclusive due to the limited number and varying quality of included studies, as well as the large heterogeneity between studies. More research is required to more conclusively establish whether, and if so, via which mechanism(s) of action neuromodulation interventions might influence the gut microbiota.

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1. Introduction

The brain and the gut engage in extensive bidirectional communication, via various immune, endocrine, metabolic and neural pathways, in which microbiota residing in the gastrointestinal tract play an important role (Carabotti et al., 2015). Together, this is referred to as the microbiota-gut-brain axis (Cryan et al., 2019) (MGBA), and has been implicated in health and disease (Sekirov et al., 2010). The human gut provides a nutrient-rich environment for the resident microbiota which can influence the host through the production of metabolites such as short-chain fatty acids (SCFAs), cytokines, hormones and (precursors of) neurotransmitters (Carabotti et al., 2015; Dethlefsen et al., 2007). Moreover, microbiota contribute to the gut's role in protection against pathogens by modulating the intestinal barrier and the mucosal immune system (Carabotti et al., 2015). Gut microbiota can also modulate the enteric nervous system and vagal afferent fibers (Bonaz et al., 2018). The vagal nerve originates from the brain stem and branches to several organs in the neck, thorax and abdomen, thereby constituting a direct neural pathway between the brain and the gut (Howland, 2014). Alternatively, vagal efferent fibers innervate the upper gastrointestinal

Abbreviations: DBS, deep brain stimulation; dTMS, deep transcranial magnetic stimulation; ECT, electroconvulsive therapy; HPA-axis, hypothalamic-pituitary-adrenal-axis; KEGG, Kyoto Encyclopedia of Genes and Genomes; MGBA, microbiota-gut-brain axis; PD, Parkinson's Disease; rTMS, repetitive transcranial magnetic stimulation; SCFA, short-chain fatty acid; tDCS, transcranial direct current stimulation; VNS, vagal nerve stimulation.

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tract and modulate the gastrointestinal environment, e.g. through reduction of gastrointestinal inflammation and permeability by strengthening tight junctions of intestinal epithelial cells, thereby influencing the gut microbial community (Bonaz et al., 2018). In addition to vagal activity, parasympathetic modulation is achieved through lumbosacral projections, resulting in increased gut motility, secretion and absorption (Browning and Travagli, 2014). Conversely, activity in the sympathetic nervous system decreases the aforementioned gastrointestinal functions (Browning and Travagli, 2014). Apart from communication via neural pathways, the brain also influences the intestinal environment by modulating the stress response via the sympathoadrenal medullary system and the hypothalamic-pituitary-adrenal (HPA)-axis (Herman et al., 2016).

Considering the extent of physiological signaling routes between the brain and the gut microbiota, it is not surprising that many mental and metabolic disorders have been linked to dysfunction along the MGBA (Sekirov et al., 2010). Concurrently, the gut microbiota composition has been found to differ between healthy individuals and those suffering from psychiatric disorders (Nikolova et al., 2021), inflammatory bowel diseases (Pittayanon et al., 2020), neurodegenerative disorders (Shen et al., 2021; Hung et al., 2022) and obesity (Pinart et al., 2022). To date, the majority of studies have investigated the MGBA from the direction of gut microbiota to brain, e.g. through means of psychobiotics (Dinan et al., 2013) or fecal microbiota transplantation (Settanni et al., 2021). However, the direction from brain to gut microbiota is less-studied, with some notable examples of research investigating the effects of stroke (Singh et al., 2016), stress (Karl et al., 2018; Galley et al., 2017) and cognitive behavioral therapy (Jacobs et al., 2021) on the gut microbiome.

An interesting opportunity to improve our understanding of the MGBA regarding the direction from brain to gut microbiota, is by examining the effects of neuromodulation, a term encompassing different stimulation techniques that alter the electrical activity of neurons (Lewis et al., 2016). Commonly used approaches of neuromodulation include deep brain stimulation (DBS), electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS) and vagal nerve stimulation (VNS). These neuromodulation approaches represent a variety of techniques that are used for different disease indications and are heterogeneous in their targets and procedures. Where the former four techniques target the central nervous system, the latter targets part of the peripheral nervous system, i.e. the vagus nerve. Both DBS and invasive VNS involve chronic stimulation of neurons with electrical pulses that are delivered by a surgically implanted generator (Howland, 2014; Montgomery and Gale, 2008). Non-invasive applications of VNS have now also been developed and involve transcutaneous stimulation of vagal fibers (Redgrave et al., 2018). Stimulation of the left cervical branch is used for example, in treating epilepsy and depression, whereas stimulation of the right cervical branch is explored for the treatment of heart failure (Howland, 2014). DBS is an established treatment for Parkinson's Disease (PD) (Benabid et al., 2009) and also shows promise in treatment of major depressive disorder (Kisely et al., 2018) and obsessive-compulsive disorder (De Koning et al., 2011). ECT is usually provided in several 1-h sessions during which brain seizures are induced through passage of electrical stimuli via electrodes that are placed on the scalp (Subramanian et al., 2022). ECT is the most effective treatment for individuals with severe major depressive disorder that otherwise do not respond to psychotherapy or pharmacological interventions (Lisanby, 2007) and ECT is also used for the treatment of catatonia, mania and schizophrenia (Weiner and Reti, 2017). Similar to ECT, rTMS and tDCS are both non-invasive forms of neuromodulation for which multiple sessions are required. rTMS is usually performed with a two-dimensionally-shaped magnetic coil which stimulates superficial cortical neurons by producing rapid alternating pulses of magnetic stimulation (Klomjai et al., 2015). More recent rTMS procedures make use of a three-dimensionally-shaped coil ("helmet" design) which is able to stimulate deeper brain regions and is referred to as deep TMS (dTMS) (Ginou et al., 2014). tDCS makes use of scalp electrodes to deliver low-amplitude currents to the brain (Paulus, 2011). The therapeutic application of rTMS and tDCS has been investigated in a variety of diseases, including major depressive disorder (Cao et al., 2018; Razza et al., 2020), anxiety (Vergallito et al., 2021), obesity (Hall et al., 2018), chronic pain (O'Connell et al., 2014) and stroke rehabilitation (Kubis, 2016). Despite neuromodulation's efficacy in treating aforementioned disorders, its exact underlying mechanism of action remains elusive. Proposed mechanisms have been related to factors involved within the MGBA. For instance, treatment of depression with neuromodulation has been associated with an alteration or restoration of functional and structural brain connectivity (Conroy and Holtzheimer, 2021), neurotransmission (Medeiros et al., 2012), neuroendocrine and immune pathways (Perrin and Pariante, 2020) and activity within the autonomic nervous system (Howland, 2014). Notably, non-invasive VNS approaches have also shown promise in treating patients who suffer from gastrointestinal symptoms (Gottfried-Blackmore et al., 2020; Shi et al., 2021).

All in all, it is worth investigating whether neuromodulation treatment is associated with changes in the gut microbiota since the brain and the gut microbiota communicate via the MGBA and dysfunction along this axis has been related to a number of diseases for neuromodulation is a well-established treatment or shows therapeutic promise. No published review has addressed this question until now and, since this is a novel area of research, it is expected to find a limited number of studies. Therefore, a systematic review was conducted with a broad scope to evaluate the effects of treatment with DBS, ECT, rTMS, tDCS or VNS on the gut microbiota in humans or animals. The aim of this systematic review is to summarize the literature available to see where this field of research is currently at and to provide future directions.

2. Materials and methods

2.1. Identification and selection of studies

This systematic review was conducted following the reporting guidance of the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) 2020 statement (Page et al., 2021). The research protocol was pre-registered to the International Prospective Register of Systematic Reviews (PROSPERO; CRD42020190001). A comprehensive literature search was conducted using the databases MEDLINE and PsycINFO. Search terms were developed in collaboration with a health sciences librarian (JGD) and consisted of two components: 1) neuromodulation interventions, and 2) assessment of gut microbiota (see Table S1). No database filters were applied. Database searches were conducted up to March 2022. Additional snowballing searches were performed using Google, the International Clinical Trials Registry Platform (ICTRP), and clinicaltrials.gov, to identify relevant conference abstracts and clinical trials. Researchers of registered trials were contacted whether relevant (preliminary) data was available to share. Reference lists of the identified full-text articles were searched manually to identify additional relevant studies. Identified records were imported in Rayyan (Ouzzani et al., 2016). Using Rayyan, records were independently screened on title and abstract by at least two assessors (AL and VK or SCV). Thereafter, articles were independently screened based on their full text. Disagreement was resolved through discussion to achieve consensus. Studies were included if they: 1) concerned a study in humans or animals, 2) involved one or more of the following neuromodulation interventions: DBS, ECT, rTMS, tDCS and VNS, 3) compared the gut microbiota pre- and post-intervention, or with a control group, 4) were a case study, a (controlled) clinical trial or a case-control study, and 5) were available in English or Dutch.

2.2. Data extraction and risk of bias assessment

Data was extracted by one reviewer (VK) in Microsoft Excel using an extraction form based on the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al., 2022). The main outcome was any microbiota data, including measures of fecal microbiome composition or diversity, or prediction of the microbiota's functional capacity. Additional registered outcomes included measures that could influence the gut microbiota data, such as age, sex, ethnicity, antibiotic or probiotic use, medication use, dietary habits and fecal sample collection and analysis, clinical status, treatment protocol and animal housing. Possibility of bias in human studies was assessed by two independent assessors (VK and MB) using version 2 of the Cochrane "Risk-of bias tool for randomized trials (RoB 2)" for studies that were randomized controlled trials (Sterne et al., 2019), the "Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I)" for non-randomized studies (Sterne et al., 2016) and the "Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Case Reports" for case reports (Moola et al., 2017). For animal studies, possibility of bias was assessed using the "Systematic Review Centre for Laboratory animal Experimentation (SYRCLE's) Risk of Bias tool" (Hooijmans et al., 2014) by two independent assessors (VK and AK). For all risk of bias assessments, disagreement was resolved through discussion to achieve consensus. Missing data relevant to data extraction and risk of bias assessment were requested from the studies' corresponding authors. A qualitative synthesis of data was performed without additional analyses.

3. Results

3.1. Selection and inclusion of studies

A total of 1514 articles were identified based on the search criteria. After removal of duplicate studies, 1463 studies were screened for eligibility based on titles and abstracts (see Fig. 1). Additional snowball searches identified 12 clinical trials which mention the use of a neuromodulation intervention and assessment of fecal microbiota in their

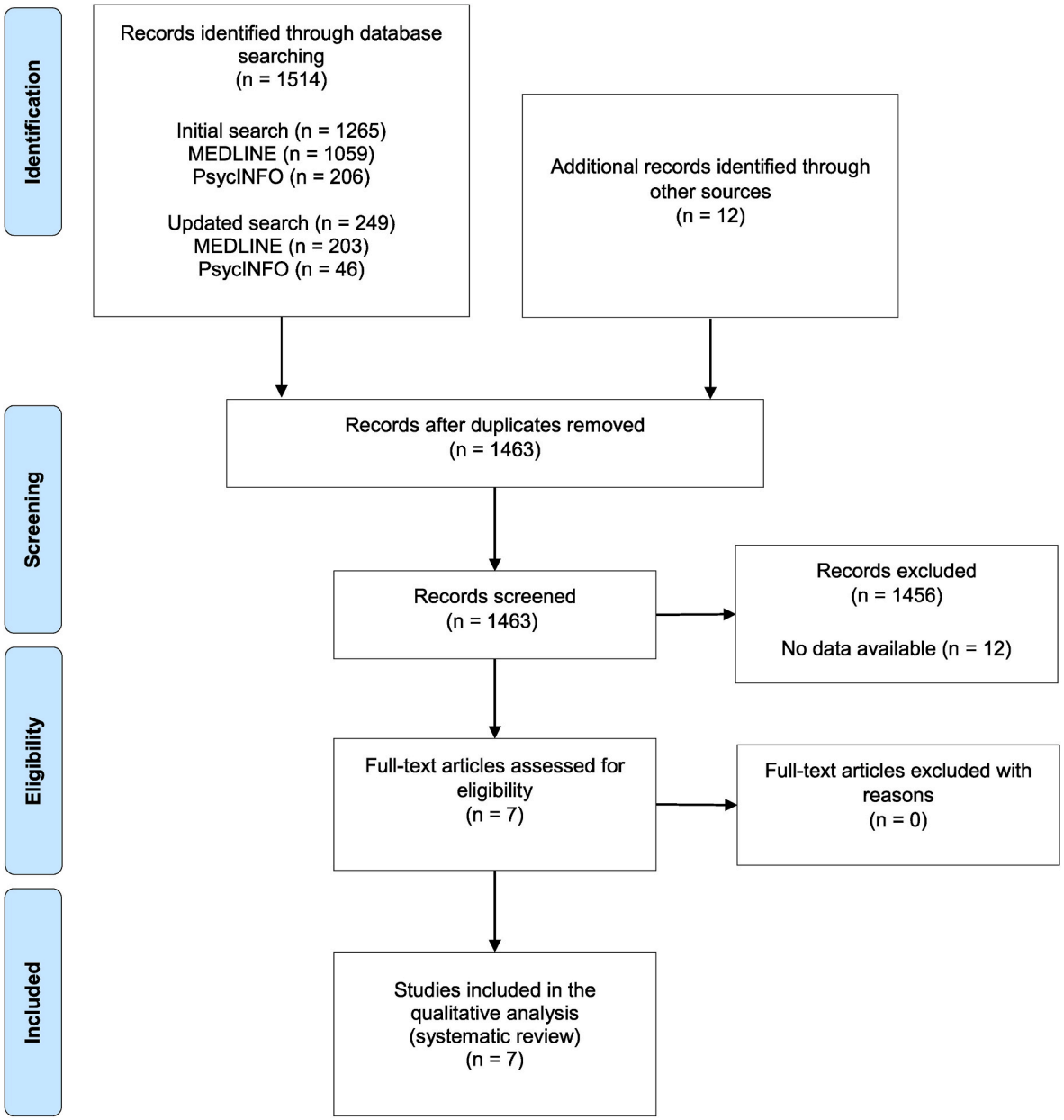

Fig. 1. PRISMA flow diagram showing the screening and inclusion of studies in the systematic review.

protocols (see Table S2). Of these trials, no preliminary data was available to share. Seven articles were identified that met the inclusion criteria and were subsequently included in the systematic review.

The included studies were performed among both humans and animals, assessing different types of neuromodulation interventions (i.e., ECT (Kanayama et al., 2019), tDCS (Artifon et al., 2020), dTMS (Ferrulli et al., 2021), rTMS (Seewoo et al., 2022), DBS (Lubomski et al., 2022), VNS (Phillips Campbell et al., 2016; Haney et al., 2018) in a variety of diseases (i.e., schizophrenia (Kanayama et al., 2019), overweight and sugary food cravings (Artifon et al., 2020), obesity (Ferrulli et al., 2021), PD (Lubomski et al., 2022) and disease models (i.e., amyotrophic lateral sclerosis (Haney et al., 2018), heart failure (Phillips Campbell et al., 2016), depression (Seewoo et al., 2022) (see Table 1). Neuromodulation protocols generally consisted of multiple sessions of stimulation, ranging from 14 to 30 sessions over a period of 2–10 weeks, or chronic stimulation provided for 4 to 6 several weeks, except for Haney et al. (2018) which administered VNS in a single session of 1 h (Haney et al., 2018). All studies obtained fecal samples and performed 16 S rRNA gene sequencing for the identification, classification and quantitation of bacteria within the samples. Details concerning fecal sample collection, handling and analyses are provided in Table S3. Most studies obtained at least two fecal samples, one prior to the neuromodulation treatment and one after treatment, with the exception of one study in which only one sample was obtained, i.e. after 43 days of VNS treatment (Phillips Campbell et al., 2016). Information regarding use of medication, antibiotics and prebiotics, dietary habits and animal housing conditions are summarized in Table 2. Many of the included studies reported administration of anesthetics (Kanayama et al., 2019; Phillips Campbell et al., 2016; Haney et al., 2018), anesthesia reversals (Haney et al., 2018) and/or pain control agents (Phillips Campbell et al., 2016; Haney et al., 2018) during neuromodulation sessions or surgery. Two studies reported use of medication prior and during the study period (Kanayama et al., 2019; Lubomski et al., 2022). Two studies reported that no antibiotics and/or probiotics were used prior to fecal sample collection and/or during the study (Ferrulli et al., 2021; Lubomski et al., 2022). Five studies reported about dietary habits and food intake (Kanayama et al., 2019; Ferrulli et al., 2021; Seewoo et al., 2022; Lubomski et al., 2022; Phillips Campbell et al., 2016).

3.2. Risk of bias

The complete risk of bias assessment is shown in Tables S4–S7. The randomized controlled trial (Ferrulli et al., 2021) was judged to have some concerns of bias, and the clinical trial (Lubomski et al., 2022) was judged with an overall moderate risk of bias. The case study by Kanayama et al. (2019) was judged with low risk of bias on five of the eight checklist items, with high risk of bias on two and unclear risk of bias on the remaining items. The case study by Artifon et al. (2020) was judged with a high risk of bias on six items and a low risk of bias on two items. Regarding the three animal studies, two (Seewoo et al., 2022; Haney et al., 2018) were judged with a low risk of bias in eight out of ten domains and with an unclear risk of bias on the remaining domains. The other (Phillips Campbell et al., 2016) was judged with a low risk of bias in all ten domains.

3.3. Disease outcome after neuromodulation

Three studies (Artifon et al., 2020; Lubomski et al., 2022; Haney et al., 2018) did not report whether the neuromodulation intervention had an effect on disease outcome, although Haney et al. (2018) do mention that the VNS stimulation parameters were also used previously in their experiments to promote swallowing and upper airway function in SOD1-G93A mice (Lever et al., 2010) (see Table 3). Disease outcome of the rats in the study by Seewoo et al. (2022) was later reported in Hennessy et al. (2022) where it was found that rTMS did not rescue depressive-like behaviors induced with chronic restraint stress, as measured on the forced swim test. The other three studies found that the neuromodulation interventions significantly reduced severity of disease-related symptoms (Kanayama et al., 2019; Ferrulli et al., 2021; Phillips Campbell et al., 2016).

3.4. Fecal microbiome profile of disease state

Four studies reported differences in fecal microbiome profiles between patients and healthy controls at baseline (Lubomski et al., 2022), before and after establishment of the disease model (Seewoo et al., 2022; Haney et al., 2018), and between the disease model animals versus the control animals (Phillips Campbell et al., 2016) (see Table S8). None of these studies found significant changes or differences regarding α-diversity or β-diversity, except for Lubomski et al. (2022) where fecal microbiota profiles between PD patients and healthy controls could be separated at baseline. Lastly, three of these studies reported significant differences in relative bacterial abundances (Seewoo et al., 2022; Lubomski et al., 2022; Phillips Campbell et al., 2016).

3.5. α-diversity, β-diversity and relative bacterial abundances

None of the five studies that reported on α-diversity measures found significant differences in α-diversity measures before or after neuromodulation treatment (Ferrulli et al., 2021; Seewoo et al., 2022; Lubomski et al., 2022; Haney et al., 2018) or between groups receiving active treatment versus sham treatment (Phillips Campbell et al., 2016) (see Table 3). Of the four studies that assessed β-diversity, three reported that fecal microbiome compositions before and after treatment (Seewoo et al., 2022; Haney et al., 2018) or between treatment groups (Phillips Campbell et al., 2016) could not be separated. The other (Lubomski et al., 2022) found that β-diversity was increased in samples post-intervention compared to samples obtained pre-intervention. All of the six studies that assessed relative bacterial abundances found changes or differences on several taxonomic levels that were associated with the neuromodulation intervention (see Table 3).

3.6. Functional metabolic pathways and additional findings

Two studies (Seewoo et al., 2022; Phillips Campbell et al., 2016) performed functional analyses on metagenomic data to infer functional properties of the fecal microbiome (Langille et al., 2013) using the Kyoto Encyclopedia of Genes and Genomes (KEGG). Both studies found certain KEGG pathways to be associated with neuromodulation. Three studies reported additional findings regarding correlations of relative bacterial abundances or KEGG pathways with other outcome measures (e.g., disease outcome, behavioral measures) (Ferrulli et al., 2021; Seewoo et al., 2022; Phillips Campbell et al., 2016). Haney et al. (2018) reported that the microbiota profiles of the seven mice which received atipamezole after surgery to reverse anesthesia could not be separated from those who did not receive this. In contrast, mice from different breeder pairs could be distinguished based on fecal microbiome composition, yet separated analyses for offspring from each breeder pair did not result in different outcomes concerning the effects of VNS treatment on the fecal microbiome.

4. Discussion

This systematic review investigated whether neuromodulation treatment is associated with changes in the gut microbiota. Seven studies were identified and assessed different types of neuromodulation interventions (ECT (Kanayama et al., 2019), tDCS (Artifon et al., 2020), dTMS (Ferrulli et al., 2021), rTMS (Seewoo et al., 2022), DBS (Lubomski et al., 2022) and VNS (Phillips Campbell et al., 2016; Haney et al., 2018) in a variety of diseases (schizophrenia (Kanayama et al., 2019), overweight and sugary food cravings (Artifon et al., 2020), obesity (Ferrulli et al., 2021) and PD (Lubomski et al., 2022) and animal disease models

Table 1
Selected characteristics of the included studies.

Study, country	Study type/ animal	Diagnosis/disease model and model induction	Neuromodulation intervention	(Mean) age, years (SD)	N[a] (male/female), experimental conditions (no./ condition)	Fecal sampling time-points, comparisons
Kanayama et al. (2019), Japan	Case study	Schizophrenia (DSM-5)	ECT14 sessions, 3/week	59	1 (0/1)	1. 1 day before first ECT session 2. 2 days after final ECT session Before and after ECT
Artifon et al. (2020), Brazil	Case study	Overweight and sugary food cravings (WHO specification)	tDCS 20 sessions, 2/week, 20 min/session, 2 mA, anode on the right dorsolateral PFC and cathode on the contralateral supraorbital region	38	1 (0/1)	1. Before first tDCS session 2. After first tDCS session 3. After final tDCS session Before and after first and final tDCS session
Ferrulli et al. (2021), Italy	Randomized clinical trial	Obesity	dTMS 15 sessions, 3/week, targeted bilaterally to the PFC and insula	44.9 (2.2)	22 (5/17) •High frequency dTMS (18 Hz) (n = 9) •Low frequency dTMS (1 Hz) (n = 6) •Sham stimulation (n = 7)	1. Before first dTMS session 2. After final dTMS session Before and after dTMS, between experimental conditions
Lubomski et al. (2022), Australia	Clinical trial	Parkinson's Disease (UK Parkinson's Disease Society Brain Bank Diagnostic Criteria)	DBS Bilateral subthalamic nucleus, continuous intervention for 4 weeks	PD: 66.4 (9.9) HC: 57.3 (12.7)	31 (16/15)[b] •DBS (n = 10) •LCIG (n = 11) •HC (n = 10)	PD: 1. Week −2 2. Week 0, DBS or LCIG surgery and initiation 3. Week 2 4. Week 4 HC: 1. Week 0 Before and two/four weeks after DBS or LCIG initiation Between PD patients and healthy control at baseline
Haney et al. (2018), USA	Animal study (mouse)	ALS ALS-prone mice strain: B6SJL-Tg(SOD1*G93A)^{dl}1Gur (SOD1^{dl})	Right cervical VNS Single session, 1 h, 20 Hz	5 months	60 (30/30)[c] •SOD1dl + VNS (n = 10) •SOD1dl + sham VNS (n = 10) •SOD1dl + no VNS surgery (n = 10) •WT + VNS (n = 10) b •WT + sham VNS (n = 10) •WT + no VNS surgery (n = 10)	1. 1 day before VNS surgery 2. 7 days after VNS surgery Before and after VNS treatment, between treatment groups
Phillips Campbell et al. (2016), USA	Animal study (guinea pig)	Heart failure PO operation: aortic banding to induce heart failure	Right or left cervical VNS Continuous, 20 Hz, for 43 days (starting 7 days after PO, VNS implantation 2 weeks before PO)	9 weeks	40 (40/0)[d] •Sham PO + sham VNS (n = 9) •PO + sham VNS (n = 12) •PO + left-VNS (n = 9) •PO + right-VNS (n = 10)	1. 43 days after VNS initiation (50 days after PO) Between treatment groups (after treatment)
Seewoo et al. (2022), Australia	Animal study (rat)	Depression CRS: rats placed in a transparent tube for 2.5 h/day for 13 days to restrain movement	rTMS 30 sessions, 10 min per session, 3 sessions/day, 5 days/week (starting 2 weeks after CRS), 10 Hz, left hemisphere	5–6 weeks	31 (31/0) •CRS (n = 7) •CRS + rTMS (n = 12) •CRS + sham rTMS (n = 12)	1. Week 0 (baseline): before CRS 2. Week 2: after two weeks of CRS, before first rTMS session 3. Week 4: after last rTMS session 4. Week 6: follow-up Before and after CRS, before and after rTMS treatment, between treatment groups

Abbreviations: ALS = amyotrophic lateral sclerosis, CRS = chronic restraint stress, DBS = deep brain stimulation, dTMS = deep transcranial magnetic stimulation, ECT = electroconvulsive therapy, HC = healthy control, HF = high frequency, LCIG = levodopa–carbidopa intestinal gel, LF = low frequency, NR = not reported, PD = Parkinson's Disease, PFC = prefrontal cortex, PO = pressure overload, rTMS = repetitive transcranial magnetic stimulation, SD = standard deviation, tDCS = transcranial direct current stimulation, VNS = vagal nerve stimulation, WT = wild type.

[a] Number of included subjects or animals at baseline.

[b] One fecal sample from an LCIG patient at week 2 was excluded from analyses due to insufficient quality reads. Two DBS-receiving and four LCIG-receiving PD patients were not able to provide a faecal sample at week −2 (as reported in the Supplementary materials).
[c] Two mice stopped breathing during recovery of VNS surgery and were replaced with other mice.
[d] Fecal samples were collected from 27/40 animals (6/9 sham PO + sham VNS, 6/12 PO + sham VNS, 8/10 PO + right-VNS, 7/9 PO + left-VNS).

(amyotrophic lateral sclerosis (Haney et al., 2018), heart failure (Phillips Campbell et al., 2016) and depression (Seewoo et al., 2022). First, all five studies that assessed α-diversity did not find neuromodulation-associated alterations in this biodiversity measure. Second, three of the four studies that assessed β-diversity could not separate fecal microbiome samples pre- or post-neuromodulation or between neuromodulation treatment groups, except for Lubomski et al. (2022), which reported that samples post-DBS treatment were increasingly dissimilar over time compared to pretreatment samples. Third, all six studies that examined relative bacterial abundances found neuromodulation-associated changes on several taxonomic levels. Lastly, two studies also found neuromodulation-associated alterations in inferred function of the fecal microbiome. Taken together, these studies suggest that neuromodulation treatments are associated with moderate changes in the gut microbiome as reflected in relative bacterial abundances.

4.1. Are neuromodulation-associated changes in gut microbiota beneficial to the host?

It remains elusive whether the neuromodulation-associated bacterial alterations in themselves would also contribute to improved or worsened health outcomes and this question should be addressed with highest caution due to paucity of data and heterogeneity of included studies. This could be assessed by performing a fecal microbiota transplant with feces of the neuromodulation-treated subjects to germ-free animals in order to examine effects of these specific microbiota profiles (Singh et al., 2016; Galley et al., 2017). However, the reviewed studies did not perform such experiments. Alternatively, potential beneficial or detrimental effects on the gut microbiota might also be inferred from characteristics of bacterial species that increased or decreased in their relative abundance after neuromodulation treatment. For example, Phillips Campbell et al. (2016) found that the total relative abundance of *Bacteroidetes*, *Streptococcus*, *Clostridium* and *Desulfovibrio* was decreased after 43 days of treatment with left-VNS compared to sham VNS. These four genera are known to metabolize phosphatidylcholine into trimethylamine (Romano et al., 2015) which is then metabolized into trimethylamine-*N*-oxide by enzymes in the liver (Tang et al., 2015). Notably, increased levels of this latter compound has been associated with increased risk of disease-related adversities in patients with chronic heart failure (Trøseid et al., 2015) and it has also been shown to accelerate plaque formation in mice (Wang et al., 2011). Therefore, a decrease in the aforementioned genera might have had beneficial effects on the host within this specific study.

Interestingly, some studies (Artifon et al., 2020; Ferrulli et al., 2021; Seewoo et al., 2022) found a neuromodulation-associated increase of several genera and species (e.g., *Roseburia intestinalis*, *Faecalibacterium prausnitzii*) that are known to produce butyrate (Louis and Flint, 2009), a well-known SCFA metabolized from dietary fibers. Butyrate is thought to benefit host physiology through multiple effects, for instance on intestinal barrier function and immune regulation (Canani et al., 2011). Thus, an increase in butyrate-producing species could be considered as beneficial. However, the studies did not *directly* assess the entire microbiota function through metabolomic profiling which prevents making such conclusions based on genomic profiling only (Heintz-Buschart and Wilmes, 2018). All in all, based on the current evidence, it cannot be concluded whether the neuromodulation-associated alterations of the gut microbiota were beneficial. This would be interesting to investigate in order to further understand potential mechanisms of action of the different neuromodulation interventions.

4.2. Which mechanisms could underly neuromodulation-induced changes in the gut microbiota?

Overall, studies found neuromodulation-associated changes in relative bacterial abundances and not in the diversity of the bacterial community. This might imply that neuromodulation is not associated with effects on the microbial ecosystem as a whole, but rather on specific taxa. How exactly these changes in relative bacterial abundances relate to the neuromodulation intervention and through which mechanisms treatment with neuromodulation could exert such effects remain elusive, although it can be hypothesized that direct effects could be exerted via neural, immune and endocrine pathways of the MGBA. Unequivocally, this question should be specified to each type of neuromodulation intervention and to each therapeutic application. Although the neuromodulation interventions all share the characteristics of altering neuronal activity, their specific features, and likely also methods of action, vary widely (e.g., duration of stimulation, targeted brain region or peripheral nerve, use of medication). Hence, the mechanism(s) of action through which a neuromodulation technique might influence the gut microbiota likely also depends on the technique applied. For example, potential effects of VNS could be exerted mainly via neural pathways through modulating gastrointestinal motility and inflammation (Bonaz et al., 2016), which could then influence the gut microbiota (Bonaz et al., 2018), whereas ECT might influence gut microbiota by modulating HPA-axis activity and immune activation (Perrin and Pariante, 2020; Bolwig, 2011). Only one study in the current review (Ferrulli et al., 2021) addressed potential mechanisms through which neuromodulation could have influenced the gut microbiota. The authors found a decrease in serum norepinephrine levels after the final high frequency dTMS session which also correlated with several genera (i.e., *Eubacterium*, *Parasutterella*, *Bacteroides*). It was hypothesized that norepinephrine reduced due to a dTMS-induced activation of the dopaminergic reward system and/or mediate the HPA-axis, resulting in decreased serum and gut luminal norepinephrine levels. Consequently, this could influence the gut microbiota by changing the intestinal environment, since norepinephrine has been reported to have modulatory effects on intestinal blood flow and colonic motor function, interaction with the intestinal immune system and stimulatory effects on expansion of bacterial pathogens (Mittal et al., 2017).

Even within a single neuromodulation approach the stimulation parameters can differ and lead to different outcomes. This was also illustrated in the reviewed studies. For instance, Haney et al. (2018) administered 1 h of VNS whereas Phillips Campbell et al. (2016) administered VNS chronically for 43 days. Different stimulation parameters were also investigated within studies. Ferrulli et al. (2021) applied both high frequency and low frequency dTMS to the obese patients, Phillips Campbell et al. (2016) investigated VNS on both the left and right cervical branch. Notably, the latter two studies found differing effects on gut microbiota and disease-outcome depending on the stimulation parameters (Ferrulli et al., 2021; Phillips Campbell et al., 2016). This could suggest that the mechanism(s) of action through which neuromodulation interventions influence the gut microbiota, can depend on the stimulation paradigm used. Moreover, these findings raise the question whether the neuromodulation-associated alterations in the gut microbiota could be related to neuromodulation's therapeutic effectiveness. Many of the reviewed studies addressed this question by associating change in disease-specific outcomes to changes of relative bacterial abundances and found several significant correlations (Ferrulli et al., 2021; Seewoo et al., 2022; Phillips Campbell et al., 2016). In addition, it would be interesting to see whether pre-treatment microbiome profiles are predictive of clinical response.

Table 2
Use of medication, antibiotics and prebiotics, dietary habits and animal housing conditions of the included studies.

Study	Medication use	Antibiotic/probiotic use	Dietary habits (and instructions)/food intake or weight	Housing
Human studies				
Kanayama et al. (2019)	During ECT session: thiopental or ketamine as anesthesia 2 years before ECT and during study period: risperidone (9 mg/day) for schizophrenia symptoms Many years before and after ECT: magnesium oxide (1.2 g/day) and sennoside (36 mg/day)	NR	Comparable eating habits before and after ECT based on medical records	NA
Artifon et al. (2020)	NR	NR	NR	NA
Ferrulli et al. (2021)	None[a]	No use of antibiotics, prebiotics, probiotics or laxatives prior 14 days prior to screening visit or during study	Hypocaloric diet during entire study period[b]. Reduction of food intake confirmed by dietitian via interview at every follow-up visit Use of probiotics and yoghurt prohibited during the study period	NA
Lubomski et al. (2022)	During study period: oral medications with variable dosages determined by patient motor responses	During DBS surgery: prophylactic antibiotic to minimize risk of hardware infection and Cephazolin three days after surgery (3 × 1 g/day, intravenous) No antibiotics or probiotics at least one month before each fecal sample collection	Instructed to continue regular diets	NA
Animal studies				
Haney et al. (2018)	Anesthesia: ketamine (90 mg/kg)-xylazine (11.25 mg/kg) cocktail subcutaneous Pain control: buprenorphine (1 mg/kg) and flunixin meglumine (2.2 mg/kg) subcutaneous Anesthesia reversal: atipamezole (0.22 mg/kg) subcutaneous[c]	NR	NR	Mice receiving VNS or sham VNS were housed together randomly, mice receiving no VNS surgery were housed together
Phillips Campbell et al. (2016)	VNS implantation and PO-induction: Pre-treatment: atropine (0.1 mg/kg) and buprenorphine (0.05 mg/kg) subcutaneous, ketamine (80 mg/kg) intraperitoneal Anesthesia: 3% isoflurane via induction chamber, maintenance with 1–3% isoflurane	NR	Ad libitum access to food, no differences in body weight between sham VNS group and left-VNS/right-VNS group	Guinea pigs were singly housed
Seewoo et al. (2022)	Prior to MRI acquisition: 4% isoflurane via induction chamber, maintenance with 2% isoflurane. Medetomidine (0.15 mg/kg/h) subcutaneously. Post-MRI: atipamezole (0.1 mg/ml)[d]	NR	Ad libitum access to food. Diet was kept consistent and weights were recorded weekly, but not recorded	Rats from the same experimental groups were co-housed in pairs

Abbreviations: DBS = deep brain stimulation, ECT = electroconvulsive therapy, MRI = magnetic resonance imaging, NA = not applicable, NR = not reported, PO = pressure overload, VNS = vagal nerve stimulation.
[a] Subjects treated with anti-obesity medications or medications related to decreased seizure threshold were not included in the study.
[b] The hypocaloric diet included calorie intakes of circa 45%–50% carbohydrates, 30% fat, 20–25% protein and 20–25 g fibers a day.
[c] Given to 7 mice (4 SOD1^{dl}, 3 WT; 2 VNS, 5 sham) that developed slowing of breath and mild respiratory distress after surgery.
[d] Described in Seewoo et al. (2020). MRI was performed prior to all fecal sampling points (from correspondence with the author).

Table 3
Main outcomes of the included studies.

Study	Disease outcome	α-diversity	β-diversity	Relative bacterial abundances	Additional findings
Human studies					
Kanayama et al. (2019)	↓ BPRS and BFCRS score	NR	NR	**After final ECT session** Genus level: ↑ *Lactobacillus* ↑ *Bacteroides* ↓ *Clostridium*	NR
Artifon et al. (2020)	NR	NR	NR	**After first tDCS session** Phylum level: ↓ Bacteroidetes/Firmicutes ratio **After final tDCS session** Phylum level: ↓ Bacteroidetes/Firmicutes ratio Species level: ↑ *Roseburia intestinalis*, *Faecalibacterium prausnitzii*, *Bacteroides vulgatus*, *Bacteroides uniformis*	NR
Ferrulli et al. (2021)	**After final dTMS session** *HF vs LF and sham dTMS* ↓ weight *HF vs baseline* ↓ resting energy expenditure percentage ↓ respiratory quotient	**Within treatment groups** No difference in Shannon's, Simpson's and Chao1's indices before and after final dTMS session	NR	**After final dTMS session** Phylum level: *LF vs baseline* ↓ Bacteroidetes, Firmicutes Genus level: *HF vs baseline, sham and LF dTMS* ↑ *Alistipes* *HF vs baseline and LF* ↑ *Odoribacter* *HF vs baseline and sham dTMS* ↑ *Faecalibacterium* ↓ *Lactobacillus* *Sham dTMS vs baseline and LF* ↑ *Bilophila*, *Gemmiger*	**After first dTMS session** *HF vs baseline* ↑ Norepinephrine **After final dTMS session** *HF and LF vs baseline* ↓ Norepinephrine *HF group* Correlations between: •ΔBMI variation and ↑ *Phascolarctobacterium* genus •↓ norepinephrine and genera Δ *Eubacterium*, Δ *Parasutterella* Δ *Bacteroides*
Lubomski et al. (2022)	NR	**Within and between treatment groups** No differences in Shannon and Simpson's indices at week −2, week 0, week 2 and week 4	Increasing β-diversity in samples after DBS treatment (i.e., week 0 vs week 4, week 2 vs week 4) compared to samples before DBS initiation (i.e., week −2 vs week 0)	**After 2 weeks of DBS** Genus level: ↑ *Clostridium_XIVa*, *Bilophila*, *Parabacteroides*, *Pseudoflavonifractor* ↓ *Dorea* **After 4 weeks of DBS** Genus level: ↑ *Parabacteroides* **After 4 weeks of DBS & LCIG** Genus level: ↑ *Pseudoflavonifractor*	Correlation between: •*Verrucomicrobiaceae* family and ↑ constipation severity •*Lachnospiraceae* family and Bristol Stool Scale and HbA1c
Animal studies					
Haney et al. (2018)	NR	**Between treatment groups** No significant differences in Chao1 and Simpson's indices 1 day before or 7 days after VNS	No separation between treatment groups 7 days after VNS Separation between mice from different breeder pairs between groups at 1 day before and 7 days after VNS	NR	Administration of atipamezole after surgery to reverse anesthesia in 7 mice did not significantly influence the gut microbiome composition (beta-diversity assessment)
Phillips Campbell et al. (2016)	**43 days after VNS initiation** *PO + left-VNS/ right-VNS* Maintenance of PO-induced ↑ LVEDV, LVESV	**Between treatment groups** No differences in number of observed OTUs, Phylogenetic diversity whole tree and Chao1 index 43 days after VNS initiation	No separation between treatment groups	**43 days after VNS initiation** *PO + left-VNS/PO + right-VNS* Phylum level: Mitigated PO-induced ↑ Actinobacteria/Proteobacteria ratio Family level: Mitigated PO-induced ↑ *Lachnospiraceae* Genus level: Mitigated changes PO-induced ↑ *Bacteroides*, *Lactobacillus*, *Dehalobacterium* and ↓ *Ruminococcus*, *Mogibacteriaceae*, *SHA-98*, *Victivallaceae*, *Desulfovibrio* *PO + left-VNS versus PO + sham-VNS* Genus level: ↓ total abundance of *Bacteroidetes*, *Streptococcus*, *Clostridium*, *Desulfovibrio*	**Functional metabolic pathway analysis** *PO + left-VNS* Mitigated PO-induced ↓ bacterial genera expressing genes associated with ATP-binding cassette transport Mitigated PO-induced ↑ bacterial genera expressing genes associated with amino sugar and nitrogen metabolism **Correlations between** •↑ *Sarcina*, *Blautia*, *Dorea*, *Epulopiscium* genera and ↓ LVEF •↑ *Blautia, Epolupiscium* genera and ↑ LVESV •↑ *Sarcina*, *Dorea*, *Erysipelotrichaceae* genera and ↑ LVEDV
Seewoo et al. (2022)	No rescue of CRS-induced depression-like behavior[a]	**Within rTMS treated group** No change in number of observed OTUs, abundance-coverage estimator,	No separation between samples from different time-points within the rTMS treated group, the sham group and the control group	**4 weeks after rats were subjected to 2 weeks of CRS, no active/sham rTMS**[b] Class level: ↓ Negativicutes	**Functional metabolic pathway analysis** *After 2 weeks without active or sham rTMS (control)* ↑ ko03450, ko00941, ko05131

(*continued on next page*)

Table 3 (*continued*)

Study	Disease outcome	α-diversity	β-diversity	Relative bacterial abundances	Additional findings
		Shannon entropy and inverse Simpson index diversity during course of rTMS		Order level: ↓ Acidaminococcales Family level: ↓ *Acidaminococcaceae* Genus level: ↓ *Phascolarctobacterium*, *Roseburia*, *Fusicatenibacter* ↑ *Intestinimonas* **After 2 weeks of active rTMS** Genus level: ↑ *Roseburia* (trend-level significance, p = 0.081)[c]	*After 2 weeks of sham rTMS* ↑ ko04210, ko00930 ↓ ko00312 *After 2 weeks of active rTMS* ↓ apoptosis pathway (ko04210) **Volatility analysis**[d] No differences in volatility between treatment groups **Correlations between bacterial abundances and KEGG pathways with several MRI and behavioral measures** Several significant correlations in the sham-rTMS group

Abbreviations: ATP = adenosine triphosphate, BFCRS = Bush-Francis Catatonia Rating Scale, BPRS = Brief Psychiatric Rating Scale, CRS = chronic restraint stress, DBS = deep brain stimulation, dTMS = deep transcranial magnetic stimulation, ECT = electroconvulsive therapy, HF = high frequency, LCIG = levodopa–carbidopa intestinal gel, LF = low frequency, LVEDV = left ventricular end-diastolic volume, LVEF = left ventricular ejection fraction, LVESV = left ventricular end-systolic volume, NR = not reported, OTU = operational taxonomic unit, PO = pressure overload, rTMS = repetitive transcranial magnetic stimulation, tDCS = transcranial direct current stimulation, VNS = vagal nerve stimulation.

[a] Reported in Hennessy et al. (2022).

[b] These findings suggest that CRS induced gut microbiota changes that continued to establish over time.

[c] No significant effects were found in the active and sham rTMS group, potentially indicating that both sham and active rTMS prevented long-term CRS-induced changes.

[d] Volatility is "the degree of compositional change over time" (Bastiaanssen et al., 2021).

Lastly, it could be the case that neuromodulation-associated changes of the gut microbiota are due to other aspects of the intervention, such as use of medication during the treatment. For instance, the reported increase of the genus *Lactobacillus* after the final ECT session in Kanayama et al. (2021) might (also) be ascribed to ketamine, which was used as an anesthetic during ECT sessions and has been shown to increase the abundance of *Lactobacillus* in rats in low doses (2.5 mg/kg). Thus, it is unclear whether this increase was due to induction of seizures and/or to ketamine's effects on the gut microbiota (Wilkowska et al., 2021). Similarly, Lubomski et al. (2022) found initial alterations in several bacteria (i.e., *Clostridium_XlVa*, *Bilophila*, *Pseudoflavonifractor*, *Dorea*) that did not sustain after four weeks of DBS treatment. The authors hypothesized that these changes could be caused by pre-implantation fasting and postoperative use of antibiotics (i.e., cephazolin). Moreover, gut microbiota changes could also be exerted indirectly through effects that (an effective) neuromodulation treatment has. For instance, if an intervention would successfully treat a certain disease (e.g., depression, PD, obesity, heart failure) or reduce disease-related symptoms, this could be accompanied by a change in eating behaviors and/or physical activity, which could then influence the gut microbiota (Conlon and Bird, 2015; Dorelli et al., 2021).

4.3. Limitations

In this review, findings from a heterogeneous collection of studies were summarized with the purpose to describe the current state of research on potential effects of neuromodulation on the gut microbiome, and to serve as a starting point for future studies. Our efforts did not reach *definitive* conclusions regarding the question whether neuromodulation alters gut microbiota. In order to establish whether this is indeed the case, more robust evidence is needed. A systematic review and/or meta-analysis of well-designed animal studies or randomized controlled trials are required that look at a specific neuromodulation intervention in a specific disease. Unfortunately, such evidence was not available at the moment, which illustrates that the MGBA is a novel area of research in which top-down mechanisms are understudied.

Several aspects of the included studies led to reduced quality of evidence concerning neuromodulation-associated effects on the gut microbiota. To start, two out of seven studies were case reports and therefore not equipped to provide causal interference and have a high risk of publication bias (Nissen and Wynn, 2014). Especially regarding microbiota outcome, findings from these case reports must be interpreted with much caution as there is substantial day-to-day variation of the microbiome in healthy individuals (Vandeputte et al., 2021). Therefore, it is unclear whether the reported changes in relative bacterial abundances are associated with the neuromodulation intervention or reflect regular temporal fluctuations of the microbiome.

Another limitation is the lack of dietary information. Since diet is known to have an effect on microbiome composition (Conlon and Bird, 2015) and two human studies adopted neuromodulation to treat obesity (Artifon et al., 2020; Ferrulli et al., 2021), it is conceivable that neuromodulation-associated effects on the microbiome have been influenced by changes in dietary patterns. In Lubomski et al. (2022), participants were instructed to continue their regular diet, yet it was not mentioned whether this was actually monitored. The case study by Artifon et al. (2020) did not provide any information regarding diet. Studies that did monitor dietary habits and food take might not have used adequate methods to be able to pick up relevant changes in dietary patterns, such as caloric intake and nutrient content. For instance, dietary information was based on medical records in Kanayama et al. (2019) and on an interview with a dietitian in Ferrulli et al. (2021) where all participants were following a hypocaloric diet during the study period. In order to quantify and adjust for the effects of diet on the gut microbiome composition, more thorough measures such as a food frequency questionnaire should be employed (Bowyer et al., 2018).

Moreover, microbiome outcomes in the animal studies could have been influenced by co-housing strategies, as it has been shown that gut microbiota profiles of cage mates become more similar (Hildebrand et al., 2013) due to microbial transfer as rodents are coprophagic (Ebino, 1993). Mice in Haney et al. (2018) that received VNS or sham VNS, were housed together randomly, mice receiving no VNS surgery were housed together, and rats in Seewoo et al. (2022) were co-housed in pairs within the same experimental group. It is unclear whether co-housing has concealed or amplified treatment-related effects in these studies. Regardless of the direction of bias, differences in housing strategies hinders comparison between studies. Other aspects of microbiome studies that reduced comparability in this review are methods of fecal sampling, of 16 S rRNA gene extraction and sequencing, and choice of database to classify bacterial taxonomies since these methods are known to influence the estimations of relative bacterial abundances of the fecal microbiome (Abellan-Schneyder et al., 2021; Jones et al., 2021; Marizzoni et al., 2020). Finally, the comparability of the included human

studies is further hindered by the fact that the study populations represented different populations regarding their primary disorder (i.e., schizophrenia (Kanayama et al., 2019), overweight and sugary food cravings (Artifon et al., 2020), obesity (Ferrulli et al., 2021) and PD (Lubomski et al., 2022) and comorbidities.

5. Future directions

It has recently been advocated that more rigorous studies are needed to discern causality from association regarding how the gut microbiota can influence the central nervous system and behavior, specifically in humans (Cryan and Mazmanian, 2022). The same holds true for the direction from brain to gut microbiota and studies investigating neuromodulation interventions present interesting opportunities to learn more about this direction. In order to address whether neuromodulation can influence the gut microbiota through the MGBA, future studies should obtain outcome measures that are related to this axis and to potential mechanisms of action of the specific neuromodulation intervention studied. For instance, studies could include measures of gastrointestinal function, immune and endocrine signaling, or activity within the autonomic nervous system. Additionally, studies should be designed to be better equipped to disentangle the effects of neuromodulation itself from other aspects or consequences of the therapy (e.g., use of medication or antibiotics, changes in dietary patterns and lifestyle) by including the relevant control groups and controlling for factors than can influence the gut microbiota. In addition, studies should not only assess which microbes are present, but also which functions they perform (Heintz-Buschart and Wilmes, 2018) through metabolic profiling to further the mechanistic understanding of the gut microbiota's involvement. Finally, it should be noted that there are other opportunities to study the MGBA from a brain to microbiota perspective, such as using psychological interventions (e.g., cognitive behavioral therapy (Jacobs et al., 2021) or optogenetic approaches by which activity of specific neurons or neuronal circuits can be modulated with light (Lalumiere, 2011).

Author contributions

AL and MEB formulated the research question and co-designed the study. VK co-conducted study selection and extraction, supported by MEB and AL. VK co-conducted risk of bias assessment, supported by MEB and AK. VK wrote the manuscript with input from all authors, who all critically reviewed the article prior to submission.

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Declaration of competing interest

The authors declare no conflicts of interests.

Data availability

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Appendix A. Supplementary data

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