Review

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Review

Neuromodulation and the Gut-Brain Axis: Therapeutic Mechanisms and Implications for Gastrointestinal and Neurological Disorders

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Abstract: The gut-brain axis (GBA) represents a complex, bidirectional communication network that intricately connects the gastrointestinal tract with the central nervous system (CNS). Understanding and intervening in this axis opens a pathway for therapeutic advancements. In light of this, the current review assesses the effectiveness of neuromodulation techniques in treating neurological and gastrointestinal disorders by modulating the GBA, involving key elements such as gut microbiota, neurotrophic factors, and proinflammatory cytokines. Through a comprehensive literature review encompassing PubMed, Google Scholar, Web of Science, and the Cochrane Library, and analyzing 182 relevant articles, this research highlights how neuromodulation can positively impact the management of functional gastrointestinal disorders (FGIDs), chronic pain, inflammation, and a range of GI disorders like Crohn's disease and ulcerative colitis. Despite existing challenges, the ability of neuromodulation to adjust disrupted neural pathways, alleviate pain, and mitigate inflammation is significant in improving the quality of life for patients, thereby offering exciting prospects for future advancements in patient care.

Keywords: gut-brain-axsis; Neuromodulation; Deep Brain stimulation; vagus nerve stimulation; Irritable Bowel Syndrome; inflammatory bowel disease

1. Introduction

The Gut-Brain Axis (GBA) is a bidirectional communication system that connects the enteric nervous system (ENS) of the gastrointestinal tract to the central nervous system (CNS) of the brain [1]. It includes a wide range of physiological processes such as digestion, metabolism, immune function, and even cognitive functions such as mood and behavior [2]. Understanding the intricate workings of the GBA is critical for investigating the mechanisms of various neurological and

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gastrointestinal disorders. Neuromodulation refers to a medical approach that precisely targets and modulates nerve activity within the nervous system to enhance neurological functioning and patient quality of life. This field is rapidly advancing, propelled by breakthroughs in neuroscience and medical engineering technology [3]. Different types of neuromodulation techniques are distinguished by their unique targets and methods of affecting the neurological system [3]. In this review, we explored the current literature on the GBA, neuromodulation and the possible uses for neuromodulation for the management of GBA disorders covering indications, possible mechanisms of actions, outcomes, and adverse effects in an effort to spot the light on what we believe is a potentially promising field that could impact and improve the quality of life for millions of patients worldwide suffering from disease with not so many options for management and with many reports describing newer understanding of the role the GBA plays in them.

2. Methodology

Our search strategy involved conducting systematic searches through PubMed, Google Scholar, Web of Science, and Cochrane Library databases using different combinations of the following search and Mesh terms (GBA, Neuromodulation, Deep Brain Stimulation (DBS), vagus nerve stimulation (VNS), sacral nerve modulation, Spinal Cord Stimulation (SCS), Transcranial Magnetic Stimulation (TMS), epidural motor cortex stimulation (EMCS), Occipital nerve stimulation (ONS), transcranial direct current stimulation(tDCS), transcutaneous direct current stimulation, remote electrical neuromodulation (REN), Gastrointestinal Diseases, Irritable Bowel Syndrome (IBS), Gastroparesis, Inflammatory Bowel Diseases, Neurodegenerative disease, Parkinson's disease (PD), neuropsychiatric disorders, benefits, outcomes, mechanism of action, pathophysiology, functional GI disorders, microbiota), in some instances and when search results seemed too wide , the search was limited to articles published in 2018 or after (i.e. last five years) to have a synthesis of more recent understanding in our review. Results were then screened by titles and abstracts for relevance, and 182 articles were reviewed.

3. Results and Discussion

3.1. The Gut-Brain-Axis:

3.1.1. Key Components of the Gut-Brain Axis:

a. Enteric Nervous System (ENS):

ENS constitutes an extensive network of intrinsic neurons distributed throughout the gastrointestinal tract [4]. It functions independently of the CNS and is responsible for regulating essential gastrointestinal processes [4]. These functions include peristalsis, nutrient absorption, and gut motility. The ENS acts as an autonomous control system for gastrointestinal functions [4].

b. Vagus Nerve:

The Vagus Nerve (cranial nerve X) serves as the primary neural pathway connecting the gut and the brain [5]. It consists of sensory and motor fibers that facilitate bidirectional communication [5]. Sensory fibers transmit information from the gut to the brain, relaying signals related to satiety, nutrient availability, and gastrointestinal discomfort[6]. Motor fibers convey instructions from the brain to modulate gut functions such as gastric secretion and motility [6]. This dual communication allows for continuous feedback and regulation between the gut and the brain.

c. Gut Microbiota:

The gut microbiota comprises a diverse community of microorganisms, including bacteria, viruses, fungi, and archaea, residing within the gastrointestinal tract [7]. This microbial population exceeds the number of human cells in the body [7].

The beneficial roles of gut microbiota are the facilitation of metabolism through metabolic pathways and enzymatic activity, the synthesis of vitamins and metabolites, and the inhibition of pathogens [8]. Dysbiosis and subsequent illness may occur due to an imbalance between the microbial flora in the gut, characterized by disruption of both beneficial and harmful bacteria as well

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as decreased bacterial diversity [9]. Dysbiosis can lead to a depletion of TJ proteins, and an increase in intestinal wall permeability due to the overproduction of pro-inflammatory cytokines such as tumor necrosis factor and interleukin 6 [10]. It is noteworthy that dysbiosis may also influence the onset and progression of several diseases, such as diabetes, inflammatory bowel disease, autism, and PD as evidenced in a variety of studies in both human and animal models [11,12]. The gut microbiota actively participates in GBA communication by producing bioactive compounds and metabolites[13]. These include neurotransmitters, short-chain fatty acids, and other signaling molecules that influence neural activity, immune responses, and physiological processes within the host organism[13]. The gut microbiota's role is integral to shaping both gastrointestinal and neurological functions.

In humans, evidence of an interaction between gastrointestinal bacteria and brain cells was first shown more than 20 years ago in the observation that patients with hepatic encephalopathy often showed a dramatic improvement when they took oral antibiotics [14].

In the meantime, emerging data support the role of microbiota in influencing anxiety and depressive-like behaviors [15] and, more recently, dysbiosis in autism. In fact, according to the severity of the disease, certain changes in the microbiota are observed in patients with autism [16]. Data have been provided that both brain-gut and gut-brain dysfunctions occur, the former being dominant, particularly in IBS [17].

The damage to the GBA can determine changes in intestinal motility and secretion, cause visceral hypersensitization, and lead to cell modification of the enteroendocrine and immune systems.

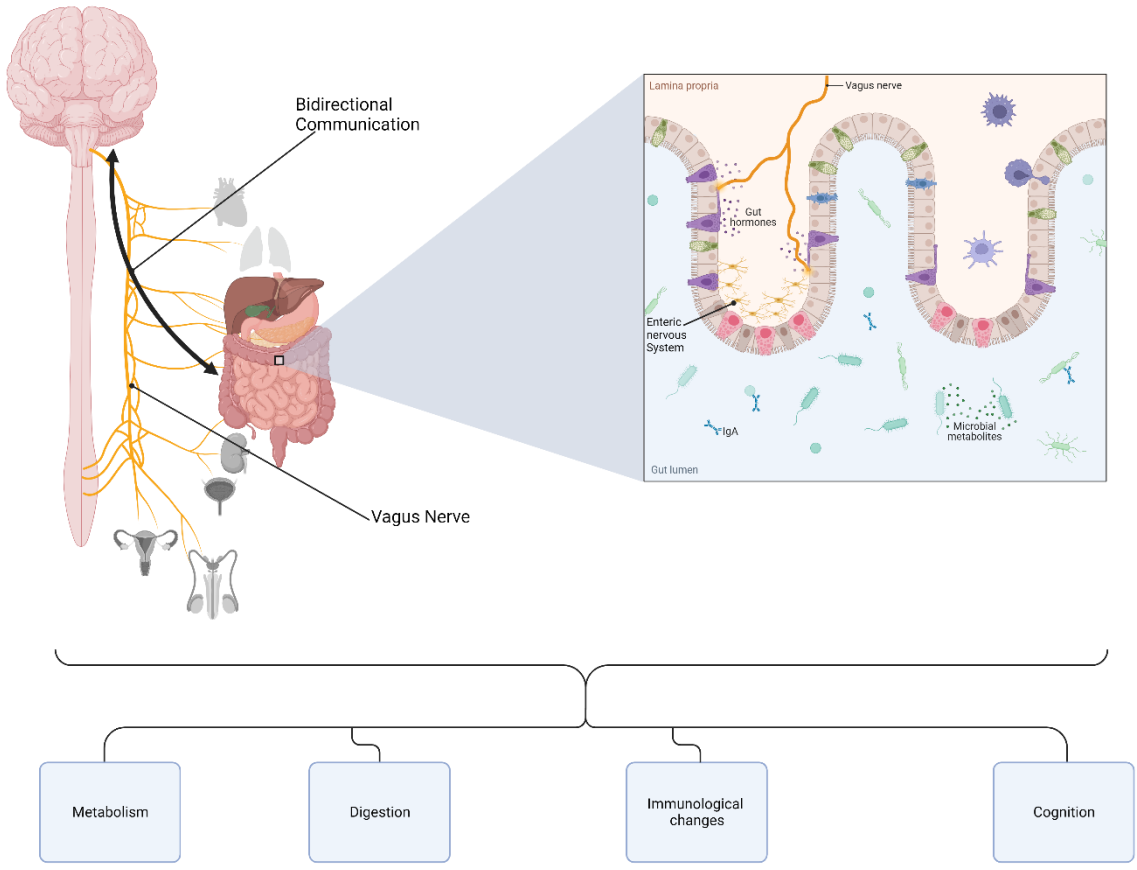

Figure 1. Gut-Brain-Axis key components and functions.

3.1.2. Physiology of the Gut-Brain Axis:

a. Neurotransmitters:

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GBA relies on a complex array of neurotransmitters to facilitate its communication pathways [18]. These neurotransmitters act as molecular messengers that transmit signals between the gut and the brain, thereby influencing various physiological processes. Key neurotransmitters involved in GBA communication include serotonin and gamma-aminobutyric acid (GABA) [19]. Serotonin, primarily produced in the gut, is a critical player in regulating mood, cognition, and gastrointestinal functions [19]. GABA, an inhibitory neurotransmitter, can modulate stress responses and influence gut motility [19]. The precise balance of these neurotransmitters is essential for maintaining homeostasis within the GBA.

b. Hormones:

Hormones are integral components of the GBA, exerting profound effects on both gut and brain functions [20]. Cortisol, often referred to as the stress hormone, plays a central role in the GBA by regulating stress responses. Elevated cortisol levels can impact gut permeability and mucosal function [21]. Ghrelin, known as the hunger hormone, and leptin, which are responsible for appetite regulation and energy balance, are also featured prominently in GBA physiology. These hormones convey information about nutritional status to the brain, influencing food intake and energy expenditure [22]. The intricate interplay between these hormones within the GBA contributes significantly to overall homeostasis.

3.1.3. Neural Communication between the Gut and the Brain:

The neural communication pathways within the GBA constitute a remarkable system of information exchange that impacts various aspects of physiology and cognition. Understanding these intricate pathways is essential to grasp how gut-related signals influence brain function and vice versa.

a. Sensory Information Transmission:

Sensory information originating from the gut travels along dedicated neural routes, with the vagus nerve playing a central role. This cranial nerve serves as the primary conduit for transmitting visceral sensations and signals from the gut to the brain. As sensory input from the gastrointestinal tract ascends through the vagus nerve, it eventually reaches the brain stem [23]. Here, crucial processing occurs, enabling the relay of information to higher brain regions. The brainstem acts as a gateway for GBA signals, with connections to various brain areas that regulate autonomic functions, emotional responses, and homeostatic balance.

b. Brain Regions Influenced by GBA Signals:

Within the brain, the sensory information from the gut can impact several key regions, including:

Hypothalamus: The hypothalamus serves as a central hub for regulating autonomic functions, hormonal responses, and appetite. GBA signals can influence hypothalamic circuits, modulating processes like satiety, thermoregulation, and stress responses [24].

Limbic System: The limbic system, particularly the amygdala and the hippocampus, plays a pivotal role in emotional and memory-related processes [25]. GBA signals can influence emotional states and memory consolidation, contributing to the intricate link between gut health and mood disorders.

Pre-Frontal Cortex: The pre-frontal cortex, responsible for executive functions and decision-making, is susceptible to GBA influence. Altered GBA signaling has been associated with cognitive impairments and behavioral changes [26].

3.1.4. Pathophysiological Involvement of Brain-Gut-Axis in Different Disorders

3.1.4.1. Irritable Bowel Syndrome (IBS)

The disorders of gut-brain interaction (DGBIs) are considered one of the most common gastrointestinal (GI) disorders. IBS is one of these disorders and is one of the most searched. IBS manifests as changes in bowel functions escorted by abdominal discomfort with a lack of detectable biochemical and structural anomalies [27]. However, the etiology of IBS has not been fully described, but various factors are well-known to be associated with it. Uncovering the pathogenesis of IBS is

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imperative for the development of pharmacotherapeutic agents. The visceral hypersensitivity, gut-brain interactions, and microbiota dysbiosis are all factors that entail the pathogenesis of IBS [28].

Unfortunately, there is no definitive treatment for IBS. It's usually controlled by the removal of factors that exacerbate it, such as certain medicines, stress, and dietary habits. Nonetheless, modulation of the GBA is under investigation as an attractive target for the development of novel treatments [29].

Population studies have shown that IBS is very common [30,31]. For example, the Rome IV and III, IBS diagnostic questionnaires as well as 80 items of data were used in a recently conducted global study with 24 countries to assess indicators relating to DGBIs. The findings show that 40 % of the global population is affected by DGBIs which affect individual quality of life and healthcare use [32]. In addition, the population of IBS is usually dominated by females in Western countries [33].

IBS has usually been explained as a disorder of visceral hypersensitivity and GI motor disturbances, which can cause or lead to abdominal pain or discomfort and diarrhea or constipation [30]. However, there is a lack of understanding of the pathophysiology of IBS. Pathogenetic factors can have contributed to this disorder, such as genetic susceptibility, GBA dysfunction, and innate immunity issues. In the meantime, it`s difficult to determine which of these factors can elicit or exacerbate IBS, in particular, because the symptoms are marked by significant interindividual differences [34]. Therefore, for IBS, treatment often targets the patient’s primary or most troublesome symptom, as opposed to being based on the underlying pathophysiology as with other organic GI diseases [35].

Studies showed that disturbance of the structural and functional GBA can cause alteration in CNS reflexes and perceptual responses, which can potentially instigate GI disorders, such as IBS [36].

3.1.4.2. Parkinson’s Disease

Parkinson’s disease is considered a chronic and progressive disorder, characterized by the degeneration of midbrain dopaminergic neurons, leading to widespread alpha-synuclein (α-syn) accumulation [37].

It has been established that the gut microbiota plays a role in affecting neurotrophic factors, controlling inflammation, and producing pro-inflammatory cytokines, T cells, or B cells thus playing an essential role in myelination processes and microglial activation [38]. That's why it can affect behavior and cognition, which in turn increases the risk of developing diseases related to the nervous system and mental health [39].

Movement symptoms that support the diagnosis of PD are usually preceded by other motor symptoms, in particular gastrointestinal symptoms, suggesting that the microbiome-intestine-brain axis plays an important role in the mechanisms leading to PD [40]. Studies have shown that synucleinopathy may start in the enteric tissue and make its way to the brain with innervating autonomic fibers [41]. Changes in the activity of bacterial metabolites and disruption of microbial balance dysbiosis in the gut are believed to have a significant influence on communication between the gut and the brain during the development of Parkinson's disease. Recent evidence suggests a significant role for gut-associated processes in the development of Parkinson's disease [42].

Alterations of the colon's components have also been established to be related to Parkinson's disease and other neurodegenerative diseases, according to a meta-analysis carried out by Gerhardt and colleagues that included 642 PD patients and 531 healthy controls [43].

A microbiota with a stable composition consisting of high levels of Bifidobacteria and Bacteroides and low levels of Firmicutes and Proteobacteria is typically associated with low levels of lipopolysaccharide and is considered to be indicative of a healthy gut epithelium, despite large individual differences in the composition of the microbiota. However, there are often differences in the microbiota of patients with PD, which are similar to those observed in patients with inflammatory bowel disease [44].

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3.1.4.3. Neuropsychiatric Disorders

Changes in the composition of human gut microbiota seem to be associated with neuropsychiatric and mood disorders [45] and neurotransmitter imbalances [46]. Additionally, increasing evidence has linked the gut microbiota with symptoms of autism spectrum disorder (ASD) that are regularly affected by gastrointestinal problems and gut microbiota dysbiosis [47]. In addition, many patients who experience gastrointestinal discomfort are more likely to present mental disorder comorbidities [45].

Studies show that there is an association between diet, nutrition, anxiety, and depression, suggesting that dietary changes may be an alternate treatment or a preventative measure for anxiety and depression. The correlation between an unhealthy diet and the propensity to develop mental illnesses has received more attention in recent years [48]. Dietary preferences, perceptions of sweetness and fatty foods as well as taste thresholds can also be influenced by stress and depression [49]. A 10-year longitudinal research study conducted in France demonstrated a correlation between poor nutrition and depression incidence with healthy diet patterns being associated with lower depressive symptoms [50]. To determine the direction of correlation, conflicting results have been seen in randomized control trials and prospective studies. A high-quality diet, independent of its form, with greater fish and vegetable consumption, was related to a decreased incidence of depression, with a dose-type association with compliance with the healthy diet, according to a meta-analysis of prospective studies. By contrast, the meta-analysis showed that a lack of nutrition was not associated with increased depression risk, and significant differences were observed from one study to another [51].

Studies have been also performed to identify the relationship between gut microbiota and depression. The correlation between this mental disorder and the flora in the gut has been confirmed by Naseribafrouci et al. as they showed that individuals with major depressive disorder have higher levels of the genera Oscillibacter and Alistipes [52].

3.2. Neuromodulation:

Neuromodulation is a medical technique that involves the focused delivery of signals to regulate the nerves in the nervous system. It's a technology that involves the modification of nervous activity to improve the patient's neurological function and, thus, their quality of life. Neuromodulation has entered an accelerated phase of development, making use of the ongoing advances being made in neuroscience and medical engineering technology [53]. Various neuromodulation modalities can be categorized according to their specific targets and methods of influencing the neurological system [3]. The aforementioned categories include Deep Brain Stimulation (DBS), Vagus Nerve Stimulation (VNS), Spinal Cord Stimulation (SCS), and Transcranial Magnetic Stimulation (TMS) [54]. DBS encompasses a surgical procedure wherein a device is implanted to administer targeted electrical impulses to distinct regions of the brain. DBS is primarily designed to address neurological conditions that primarily affect the brain, such as Parkinson's disease and various movement problems [55]. VNS is a therapeutic approach that specifically focuses on the vagus nerves located inside the neck region. The VNS device is commonly employed in the management of treatment-resistant depression and epilepsy. It functions by delivering periodic and gentle electrical energy pulses to the brain through the vagus nerve [56]. SCS involves the utilization of a device that administers a low-level electric current to the spinal cord. The utilization of this treatment modality is commonly observed in cases of chronic pain syndromes, particularly those involving neuropathic pain [57]. TMS is an emerging modality of brain stimulation that entails the application of an electromagnetic coil in direct contact with the scalp. TMS is often employed within the field of psychiatry, with a particular focus on its application in the treatment of depression [58].

Additional types of neuromodulation encompass Sacral nerve stimulation, a technique that transmits impulses to the sacral nerve to enhance bladder control [59]. Responsive nerve stimulation is a therapeutic approach that entails the continuous monitoring of neurological activity to administer personalized and immediate therapy [60]. Epidural motor cortex stimulation is mostly employed for pain management, whilst Occipital nerve stimulation (ONS) is utilized to treat certain forms of

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headaches or migraines by targeting the occipital nerves [61,62]. Transcranial direct current stimulation (tDCS) and Transcutaneous electrical nerve stimulation (TENS) are non-invasive methodologies developed to elicit brain and nerve stimulation, commonly employed in the domains of pain treatment and rehabilitation therapy [63,64]. Remote electrical neuromodulation (REN) is a nascent therapeutic modality that involves the remote administration of electrical pulses, typically employed to alleviate migraines or manage pain [65].

3.3. Effects of Neuromodulation on Gut-Brain-Axis

3.3.1. Physiological Changes in the Gut-Brain Axis after Neuromodulation Including Changes in GI Physiology

Figure 2 and Figure 3 summarize key effects and changes in GBA physiology after neuromodulation.

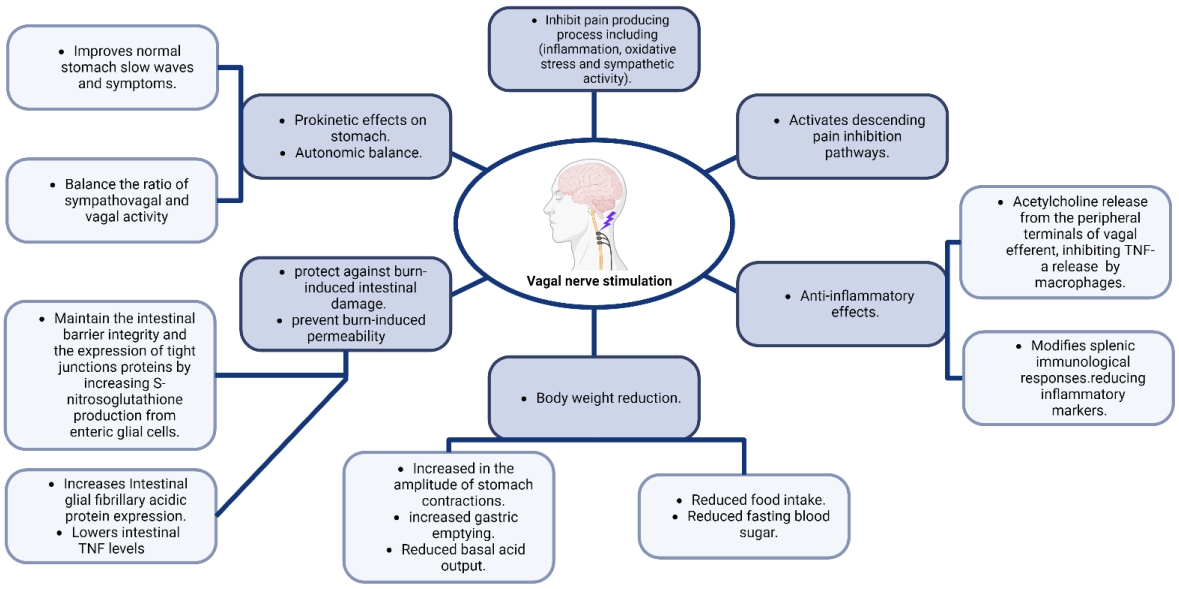

Figure 2. Summary of VNS Effects on Gut-Brain-Physiology.

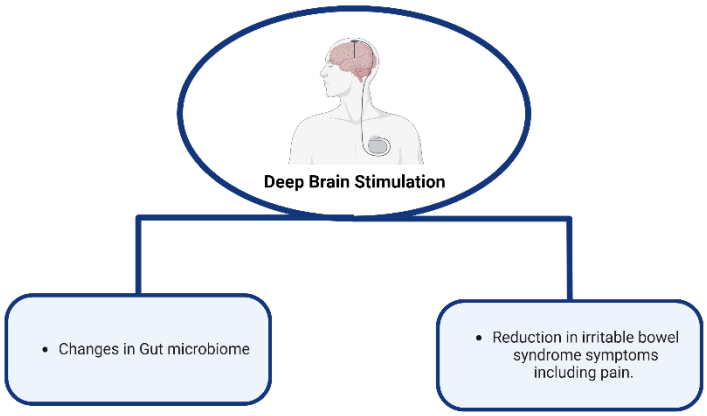

Figure 3. Effects of DBS on Gut-Brain Axis.

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3.3.1.1. Neuromodulation Effect on Pain

In a case report, results from the assessment of a 55-year-old lady who received bilateral DBS in the anterior limb of the internal capsule and who had obsessive-compulsive disorder and IBS are provided. Following the brain stimulation therapy, there was a reported significant reduction in IBS symptoms. This relief was dependent on certain stimulation settings, showed consistency over time, and wasn't directly related to reductions in the symptoms of obsessive-compulsive disorder. These findings imply that DBS has a positive effect on IBS [66].

The vagus nerve (VN) is increasingly being shown to affect nociceptive processing in the spinal cord and brain. It has been demonstrated that nociceptive mechanical and chemical stimulus causes vagal afferents to respond, which in turn causes the brainstem to reflect nociceptive signals [67,68]. Patients who receive VNS for epilepsy and depression usually report feeling less pain. Evidence suggests a connection between pain and VN activity since the VN is known to decrease pain-causing processes such as inflammation, oxidative stress, and sympathetic activity. Additionally, it stimulates parts of the brain that can block the "pain matrix" in the brain, which in turn modifies the way opioids function as an analgesic [69]. Nutrient content may influence the perception of painful visceral sensations in several gastrointestinal illnesses, including IBS, by enhancing the creation of aversive visceral memories via vagal afferent pathways [70].

VNS activates vagal afferents that go to the Nucleus Tractus Solitarius (NTS), which suppresses experimentally produced pain. Descending pain inhibition pathways are then activated as a result of neurons in the NTS projecting to the Central Amygdala Nucleus (CAN), the Nucleus Raphe Magnus, and the Locus Coeruleus. Visceral pain is decreased by low-intensity VNS that particularly targets vagal afferent Ad fibers, indicating that a portion of the vagal afferents that innervate the viscera may have abilities to control visceral pain [71].

3.3.1.2. Effects of Neuromodulation on GI Motility and Permeability

It has been shown that it is possible to achieve prokinetic effects by increasing vagal tone by VNS, deep breathing, moderate-pressure massage treatment, or other exercises that have a substantial impact on heart rate and heart rate variability [72].

Four randomized sessions, comprising a control session, the conditioned stimulus (CS), CS paired with transcutaneous auricular vagus nerve stimulation (taVNS), and CS mixed with sham-electrical stimulation (sham-ES), were carried out in research involving healthy individuals. Each session began with a period of fasting and ended with a test meal. While taVNS or sham-ES were given between 0 and 30 minutes after the meal, CS was delivered between 10 and 30 minutes after the meal. Assessing stomach slow waves and autonomic functioning involved recording the electrogastrogram and the electrocardiogram. The proportion of normal stomach slow waves and the symptom score were both considerably lowered by CS, and both were greatly improved by taVNS but not by sham-ES, according to the results. Additionally, CS raised the sympathovagal ratio and lowered vagal activity, while taVNS balanced these effects brought on by CS. These results imply that after exposure to a conditioned stimulus, taVNS has a prokinetic effect on stomach function and autonomic balance [73].

By stimulating enteric glial cells (EGCs), Costantini et al. [74] showed that VNS protects against burn-induced intestinal damage. Without altering systemic inflammation, this protection is achieved by controlling the reaction to damage inside the gut tissue itself, and the generation of cytokines in the spleen was shown to be not necessary for the maintenance of gut membrane integrity by VNS. Furthermore, S-nitrosoglutathione administration has been shown to produce outcomes that are comparable to those seen in animals that have received VNS, indicating that VNS may maintain the integrity of the intestinal barrier and the expression of proteins related to TJs by increasing the ability of activated EGCs to produce S-nitrosoglutathione [75].

Injuries that result in severe burns cause EGCS to become more activated, which increases the production of the mRNA for intestinal glial fibrillary acidic protein. When VNS is used alone, it increases intestinal glial fibrillary acidic protein expression and thus reduces burn-induced intestinal permeability, and lessens gut histological damage. In one experiment, animals who had vagotomies

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before receiving VNS showed intestinal permeability levels similar to those of animals that had just had burns, demonstrating the protective effect of efferent vagal nerve transmission. The intestinal TJ proteins myosin light chain kinase and phosphorylated myosin light chain, all of which are essential for maintaining TJ integrity, as well as the elevation in intestinal TNF caused by burn, were likewise avoided and reduced by VNS. These results provide insight into the mechanism through which VNS prevents the loss of the intestinal barrier and subsequent intestinal inflammation [74].

Researchers found that VNS significantly lowers levels of intestinal TNF while successfully preventing trauma-induced intestinal permeability and intestinal damage in a mouse model modeling traumatic brain injury. Boosted levels of enteric glial fibrillary acidic protein also showed that VNS boosted the activity of EGCs in the same settings which shows that the CNS can directly affect intestinal barrier failure [76].

Through the activation of myosin light chain kinase and subsequent phosphorylation of myosin II light chain, which results in the contraction of the actin-myosin ring, inflammation can compromise the epithelial barrier and change the expression of TJ proteins. There is a lot of gut inflammation after burn injuries, which raises myosin light chain kinase and amplifies myosin II light chain phosphorylation, leading to the separation of TJ proteins. A protective effect of VNS is seen on the gut epithelial barrier with a "therapeutic window" for VNS intervention since it can be used before or within 90 minutes after burn damage. When used during this window, VNS can either stop barrier breakdown or promote its recovery. In these circumstances, the gut's morphology, permeability, and protein expression are consistent. Similar to the sham-operated control group, VNS-treated mice in one study showed decreased inflammation and localized TNF production in the gut [75].

3.3.1.3. Effects of Neuromodulation on GI Inflammation and Immunity

Vagal efferents have been shown to have an anti-inflammatory activity by Tracey's team. In their study, they found that in a rat model of endotoxic shock, VNS causes the release of acetylcholine from the peripheral terminals of vagal efferents, which in turn inhibits the production of TNF-a by macrophages [77].

According to a study [78], low-frequency (5 Hz) VNS has been shown to treat colitis in rats. Additionally, VNS may have an anti-inflammatory impact on Crohn's disease patients who have autonomic instability [79]. In one study, it was shown that in the majority (5 out of 7) of patients with mild to moderate active Crohn's disease, VNS resulted in clinical, biochemical, and endoscopic remission after 6 months. Additionally, VNS returned autonomic balance to levels comparable to those in healthy people [80].

Endotoxin and intestinal inflammation have been proven to cause systemic inflammatory responses that can be reduced by VNS. Additionally, through interacting with the splenic sympathetic nerve, the Vagus nerve indirectly modifies immunological responses in the spleen. Daily VNS for three hours spread over five days significantly decreased inflammatory markers and improved colitis symptoms in another rat research that involved colonic inflammation [6].

3.3.1.4. Effects of Neuromodulation on Gut Microbiota

According to a systematic review, Alterations in the relative abundances of the various bacterial species in the gut have been associated with the use of neuromodulation. The results also showed that neuromodulation therapies cause modest changes in the gut microbiome. However, it did not result in changes in the variety of species or the differences across microbial communities [81].

Dynamic changes in microbial composition are seen in studies examining the links between the gut microbiota and device-assisted treatments (DATs) for PD. Specific changes in gut bacterial composition result from the acute use of DATs such as DBS and Levodopa-Carbidopa Intestinal Gel (LCIG). Clostridium_XlVa and Parabacteroides are overrepresented in DBS samples, possibly as a result of antibiotic usage. On the other hand, Pseudoflavonifractor is overrepresented in LCIG treatment whereas Escherichia/Shigella and Gemmiger are underrepresented. With DBS, there is a rise in Euryarchaeota and Spirochaetes, whereas with LCIG, there is an overrepresentation of Prevotellaceae and Bacillus. Long-term usage of these treatments results in unique, diverse

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alterations. Notably, the microbiota's reaction to DAT exposure varies depending on how long it continues. Although the exact causes of these alterations are not entirely known, they may be brought on by changing physiological responses and reciprocal interactions between gut microbiota and DATs [82].

In one research, electroacupuncture at certain acupoints, including DU20 and KI1, decreased pain and delirium-like symptoms in mice with a model of surgical pain and delirium brought on by a foot incision. Mice that experienced surgical pain and delirium-like behavior showed altered gut microbiota, spinal cord, somatosensory cortex, and hippocampus microglia activation, and increased dendritic spine removal in the cortex. In addition to reducing pain and delirium-like symptoms, electroacupuncture therapy also balanced the gut microbiota, reduced microglia activation, and stopped dendritic spine removal. This shows that through regulating gut-brain connections and microglial activity, electroacupuncture may have therapeutic promise for treating surgical pain and associated delirium-like symptoms [83].

3.3.1.5. Effects of Neuromodulation on Weight Gain and Food Intake

In a study involving fifteen Large White pigs, they were divided into three groups (A, B, and C) and underwent implantation of a vagus nerve stimulator. Group A had stimulation deactivated, while groups B and C had it activated. Group C's purpose was solely to assess the impact of stimulation on heart rate, invasive arterial and venous pressures, and the bispectral index. Food intake showed no significant differences between A and B, but both groups exhibited a consistent increase in body weight. In group C, during VNS, arterial pressures significantly decreased, while heart rate and the bispectral index markedly increased. Ultimately, all animals were sacrificed to assess the effects of implantation and stimulation on the vagus nerve, and in both groups, the lesions were primarily localized in connective tissue rather than nervous tissue. All animals in groups A and B exhibited a thick fibrous capsule at the implantation site. Group B showed increased levels of fibrosis, inflammation, vascularization, and nervous fiber degeneration compared to group A. However, necrosis was more pronounced in group A. Analyzing all aspects of the lesions, inflammation seemed to be the most severe in group A, while group B exhibited more extensive fibrosis. Both groups demonstrated comparable levels of fiber degeneration [84].

According to a review article, multiple studies seem to agree that during vagal stimulation, body weight is significantly reduced [85].

One study looked at how conscious rats' long-term stomach motility, secretion, and weight management were affected by a neuromodulation surgery employing a microchip (MC). Within two weeks after MC implantation, the use of MC-induced neuromodulation caused rats' daily food intake to drop by 6% and their body weight increase to slow by 20%. Glucose levels in the fasting control group similarly dropped by 5.5%. When compared to the control group, the frequency of stomach contractions in the MC-treated rats remained consistent, but the amplitude of the contractions dramatically increased. In MC-treated rats, maximum acid output (MAO) did not change, while the basal acid output (BAO) dropped by 29.25% without affecting the H+ concentration, and gastric emptying increased by 10% [86].

3.3.1.6. Special Consideration: Microbiota-Induced Vagus Nerve Stimulation in Cerebral Ischemia

A potentially effective treatment for cerebral ischemia involves controlling microglia to reduce neuroinflammation. In one study, the signals of the GBA were examined about berberine-modulated microglia polarization after cerebral ischemia. The transient receptor potential vanilloid 1 (TRPV1) receptor, hydrogen sulfide (H2S) metabolism, and stimulation of the vagus nerve were all included in the study. A test using metabolomics was performed to investigate the brain microenvironment. The results showed that berberine restored behavioral impairments in temporary middle cerebral artery blockage rats by modulating microglia polarization and reducing neuroinflammation via the microbiome. When given berberine, vagus nerve activity was increased, which could be inhibited by various antibiotic combinations, capsazepine, or sodium molybdate, respectively. VNS, accomplished by both assimilatory and dissimilatory sulfate reduction with enhanced synthetic

 doi:10.20944/preprints202404.0188.v1

enzymes, was linked to the synthesis of H2S generated by berberine. When berberine was supplied, the TRPV1 receptor's sulfation in turn caused the vagus nerve to become activated and encouraged the production of c-fos and ChAT in the nucleus tractus solitarius. Additionally, sphingolipid metabolism was disturbed by the major metabolic change brought on by berberine in the cerebral cortex, hippocampus, and cerebral spinal fluid, which is a crucial feature that is altered by antibiotic therapy [87].

3.3.2. Effects of Neuromodulation on the Gut-Brain-Axis Disorders

Functional gastrointestinal disorders (FGIDs) are frequent and have a significant impact on a person's quality of life. Although there are many approaches for distinct FGID symptoms, neuromodulation, a relatively recent treatment, has shown a favorable therapeutic impact on FGIDs.

3.3.2.1. Irritable Bowel Syndrome (IBS)

The most prevalent functional gastrointestinal disorder, affecting up to 7-21% of the general population, is IBS [88]. Visceral hypersensitivity (or changed pain perception), poor brain-gut connection, altered microbiota, and altered gastrointestinal motility are the core pathophysiology of IBS [88]. Visceral hypersensitivity is thought to be the most common cause of stomach pain or discomfort; visceral hypersensitivity is thought to be caused by increased intestinal permeability and gut mucosal immune activation.

3.3.2.1.1. Tryptophan

Serotonin (5-hydroxytryptamine; 5-HT) 5-HT is a common gut-related transmitter, with enteroendocrine (EC) cells of the gut epithelium producing 90%-95% of the total 5-HT pool in the human body. Tryptophan hydroxylase (TPH) regulates 5-HT synthesis [89]. By influencing EC cells, the gut microbiota also plays an important role in controlling 5-HT synthesis and release. In a post-infectious IBS model of rats, quercetin can lower the density of EC cells and the expression of TPH. As a consequence, quercetin lowers 5-HT levels and alleviates visceral pain sensations in IBS mice [90].

3.3.2.1.2. Transcutaneous Auricular VNS (tVNS)

42 individuals with constipation-dominant IBS were given taVNS [91]. The patients were randomly assigned to either undergo taVNS using silicon electrodes implanted at bilateral symba conchas or sham electrical stimulation (through the elbow). taVNS increased the weekly number of full spontaneous bowel movements, reduced abdominal discomfort, and improved overall IBS symptoms and quality of life. The improvement in rectal sensation and rectal distention-induced relaxation of the internal anal sphincter were noteworthy findings of this investigation, implying a vagal afferent and sacral efferent route. These effects were mediated through the vagal-sacral circuit in the following way: The NTS was stimulated, which then projected to other areas of the brain, resulting in increased sacral efferent activity, which acted on the rectum and anal sphincter [92]. Auricular vagal nerve stimulation (aVNS) with identical stimulation parameters was also found to speed up the transit of the distal colon (not innervated by the vagus nerve) with a contemporaneous increase in activated neurons in the NTS in a mouse model of opioid-induced constipation [93]. These findings imply that aVNS may influence colorectum motility and feeling via both the vago-vagal and vago-sacral pathways.

3.3.2.1.3. Tripolar Spinal Cord Stimulation

Coffin et al. have shown that hyperexcitability of spinal nociceptive pathways causes visceral hypersensitivity in IBS patients [94]. The precise mechanism of action of SCS is unknown, however, based on animal research, one probable mechanism may be the suppression of pain pathways in the dorsal columns of the spinal cord [95]. Palecek has highlighted the significance of the dorsal column route in the control of visceral pain by selectively suppressing the response to visceronoxious

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stimulus [96]. The precise method through which SCS modulates intestinal motility and causes pain alleviation is unknown. Auli et al. studied the impact of direct electric stimulation on enteric motor neurons in human intestinal strips in vitro [97]. They discovered that activation of inhibitory neurons causes the release of nitric oxide and purine, whereas stimulation of excitatory neurons causes the release of acetylcholine and tachykinins. Purine agonists and medicines that boost acetylcholine production and release, on the other hand, have been demonstrated in tests to have significant analgesic effects [98].

3.3.2.2. Inflammatory Bowel Disease (IBD)

Inflammatory bowel illness, which includes Crohn's Disease (CD), Ulcerative Colitis (UC), and Microscopic Colitis (MC), is alarmingly frequent, affecting roughly 1% of the global population and growing in prevalence [99]. IBD has a substantial influence on psychological well-being and social functioning as well. Both CD and UC involve significant inflammation and disruption of the gut immune system [100]. The vagus nerve, pelvic nerves, sympathetic innervation of the stomach, and intrinsic neurons of the ENS all have an impact on inflammation.

Vagal nerve stimulation can reduce inflammation in the gut in at least three ways: by stimulating afferent neurons that signal to the brain to activate efferent pathways, which may include sympathetic outputs from the CNS [101]; by activating vagal efferent pathways; and by stimulating vagal afferents to release transmitters from their peripheral ends. Evidence for the impact of vagal efferents on enteric neurons includes the fact that intestinal inflammation activates a vagally mediated circuit that leads to the activation of vagal motor neurons related to the inflamed gut [102]. VNS decreased mechanically induced inflammation of the small intestine in normal mice, mice with denervated spleens, and T-cell deficient animals [103]. In Nicotinic Acetylcholine Receptor (7nAChR) knockout mice, VNS proved ineffective. Enteric neurons innervated 7nAChR-expressing macrophages, and 7nAChR activation lowered their excitability. According to the findings, resident macrophages are a target via which VNS mediates its anti-inflammatory activity.

3.3.2.3. Gastroesophageal Reflux Disease (GERD)

Gastroesophageal Reflux Disease (GERD) is a chronic condition in which the reflux of stomach contents into the esophagus produces discomfort or difficulties. It is divided into three types: non-erosive reflux disease (NERD), erosive esophagitis, and Barrett's esophagus [104]. Major GERD pathophysiologies include (a) impaired esophageal clearance due to impaired esophageal motility (e.g., weak esophageal peristalsis); (b) anti-reflux barrier dysfunction at the esophagogastric junction (EGJ) due to hypotensive lower esophageal sphincter (LES), transient LES relaxations (tLESRs), and/or dyssynergia between LES and the crural diaphragm (e.g. the presence of hiatal hernia); and c) downstream gastric factors: delayed gastric emptying and gastric acid pocket [105,106].

3.3.2.3.1. Transcutaneous Electrical Acustimulation (TEA)

Acute TEA at bilateral ST36 and bilateral PC6 acupoints has been shown to increase stomach accommodation and pace-making activity, as well as diminish postprandial dyspepsia symptoms in GERD patients [107]. In patients with GERD, a 4-week TEA at bilateral ST36 and bilateral PC6 alleviated reflux symptoms, increased distal esophageal motility, decreased the incidence of inefficient esophageal contractions during wet swallows, and enhanced stomach accommodation and pace-making activity [108]. The researchers concluded that the improvement in GERD symptoms was due to TEA's integrative effects on various gastric processes, which were mediated through the vagal mechanism. In another research, TEA at ST36 and PC6 was combined with deep breathing training in GERD patients [109]. A 4-week therapy with this combination technique reduced acid reflux and GERD symptoms while simultaneously increasing LES pressure and vagal activity and decreasing serum nitric oxide.

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3.3.2.3.2. Transcutaneous Abdominal Electrical Stimulation

Although the mechanism is unknown, it appears that transcutaneous abdominal electrical stimulation is intended to cause abdominal muscular contractions, hence increasing LES pressure. The LES pressure measured by esophageal manometry is known to be the combined pressure of the LES and crural diaphragm. This type of stimulation might raise the pressure in the crural diaphragm. However, there is no data to back up the idea. Transcutaneous abdominal electrical stimulation decreased acid exposure duration and the DeMeester score by more than 50% in GERD patients who were unresponsive to regular proton pump inhibitor treatment in a pilot open-label study [110].

3.3.2.4. Autism Spectrum Disorder

Autism spectrum disorder (ASD) is a neurodevelopmental illness with a wide range of symptoms, including social deficits and confined, repetitive activities [111]. ASD therapy is notoriously difficult, and it may benefit from identifying underlying systems that overlap with those disrupted in other developmental disorders, which have more clear treatment choices. DBS in the prefrontal cortex, hypothalamic nucleus, and central thalamus have been proven in preclinical investigations to relieve VPA (Valproate acid)-induced autism-like symptoms [112]. VNS is an FDA-approved therapy for reducing the severity of persistent epilepsy and depression, and it has emerged as a viable adjuvant therapy for people with autism [113]. ASDs are usually associated with dysregulated parasympathetic nervous system and decreased vagal tone, which is linked to autistic behavioral and linguistic impairments [114]. The use of VNS in children with epilepsy and ASD has yielded promising outcomes [115]. Several studies have shown that gamma-band response (30-80 Hz) is highly dependent on cellular balance of excitation and inhibition (E/I) signal transduction [116], mediating several basic neural functions such as sensorimotor integration, perceptual integration, working memory, network synchronization, and higher-order cognition [117], all of which are disrupted in multiple ASD systems [118].

3.3.2.4.1. Vagus Nerve Stimulation

Seizure reduction was comparable amongst persons with and without autism in the biggest research of VNS treatment in individuals with ASD to date [115]. After 12 months of VNS therapy, 56% of people without autism had a 50% reduction in seizures, whereas 62% of those with autism had a 50% reduction in seizures. Individuals with and without autism had comparable gains in attentiveness, verbal communication, memory, and academic/professional success. Patients with autism, on the other hand, exhibited a considerably higher improvement in mood after 12 months of VNS therapy than persons without autism. Stimulation of the vagus nerve causes strong, phasic neuronal activity in the locus coeruleus, the principal source of norepinephrine in the CNS [119]. VNS increases norepinephrine levels in the hippocampus and cortex, which is consistent with VNS-dependent noradrenergic system activation [120]. Furthermore, VNS considerably raises levels of brain-derived neurotrophic factor (BDNF), a neurotrophin strongly associated with neural plasticity that is dysregulated in autistic people [121].

3.3.2.4.2. Transcranial Magnetic Stimulation (TMS)

Consistent with the role of altered cortical development in ASD, regions of the frontal and prefrontal cortex related to language production and social skills have a spike in synaptogenesis and plasticity between years 1 and 3 [122], when autistic symptoms related to these processes usually become apparent. TMS generates transitory, localized electrical fields in the cerebral cortex by electromagnetic induction, producing depolarization and firing of local neurons [123]. Repetitive TMS (rTMS) produces patterns of numerous TMS pulses over a selected brain region at frequencies ranging from 0.5 to 20 Hz [124]. At low frequencies, rTMS causes long-term suppression of cortical excitability on the target cortical tissue, but at higher frequencies, rTMS causes long-term stimulation of cortical excitability. rTMS could have clinical utility as an intervention in ASD. Some studies indicate that: low-frequency stimulation of the dorsolateral prefrontal cortex (DLPFC) can reduce

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repetitive behaviors, improve neurophysiological markers of perception, and reduce irritability; low-frequency supplementary motor area (SMA) stimulation can improve movement-related cortical potentials; and low-frequency stimulation of the premotor cortex can improve sensorimotor integration [125–127].

3.3.2.4.3. Transcranial Electric Stimulation (tES)

Transcranial electric stimulation modalities include tDCS, transcranial random noise stimulation (tRNS), and transcranial alternating current stimulation (tACS). tDCS employs a continuous mild electrical current to cause bidirectional, polarity-dependent changes in cortical areas, allowing for the measurement of effects at the cognitive, physiological, and motor levels [128,129]. The use of tDCS can be utilized to either raise or reduce cortical excitability and/or certain brain oscillations. Gamma activity can also be modulated by tDCS. tRNS is a low-intensity, randomly alternating biphasic current that is delivered directly to the scalp at frequencies ranging from 0.1 to 640 Hz [130]. While both tDCS and tRNS are successful in modifying cortical excitability and plasticity processes, only tACS has been explicitly linked to frequency-specific regulation of oscillatory dynamics, with evidence of its influence on gamma activity in both animals and humans. tACS uses sinusoidal or biphasic currents at a predetermined frequency to interact with the brain's endogenous oscillatory activity to entrain huge populations of neurons [131]. tACS works by synchronizing spiking activity to various driving frequencies, thereby entraining neuronal firing to the electrically applied field and exerting strong neuromodulatory effects. These gamma tACS-induced improvements were shown to be strongly associated with changes in blood oxygenation level-dependent (BOLD) activity in the stimulated M1 area [132]. Higher-order behavioral processes have also been targeted using tACS gamma-entrainment approaches. Hoy and colleagues discovered a selective improvement in working memory performance after gamma-tACS [133]. Since there is an overall reduction of gamma activity in ASD, applying gamma-tACS to these regions might be able to entrain and restore, at least partially, neurotypical gamma activity in the ASD population.

3.3.2.5. Parkinson's Disease

Parkinson's disease is a chronic, progressive illness characterized by the degeneration of a large number of dopaminergic neurons in the basal ganglia circuitry. The lack of dopamine contributes to clinical motor symptoms such as bradykinesia, tremor, stiffness, postural instability, and gait impairment [134]. Recent epidemiological and clinical studies suggest that “mild cognitive impairment” (MCI) may be a complex typical of the early stages of PD [135].

3.3.2.5.1. Deep Brain Stimulation

DBS is efficient in modulating abnormal basal ganglia motor circuit activity by acting on particular nuclei such as the subthalamic nucleus, the globus pallidus interna, and the thalamus. This method entails implanting pacing devices that provide constant high-frequency stimulation of the targeted region. The STN, a critical motor relay component whose failure has been related to Parkinson's disease symptoms, has been the most widely utilized target for DBS during the last decade [136]. Numerous studies have also demonstrated that STN DBS gives lasting symptom relief even 5 or 10 years following surgery, but with worsening of cognition and gait because of the underlying degenerative disorder's unrelenting progression [137]. In the case of DBS in the subthalamic nucleus for Parkinson's disease, there is an enhanced firing rate in the globus pallidus despite the suppression of excitatory STN neurons that project to the globus pallidus [138]. Furthermore, globus pallidus neurons have spike activity that is entrained to the stimulus pulses. DBS is hypothesized to segregate dendritic/somatic activity from axonal output activity, suppressing the former while driving the latter at or near the frequency of stimulation [139].

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3.3.2.5.2. Transcranial Magnetic Stimulation

Shirota et al. explored the efficacy and stimulation frequency effect of rTMS over the SMA in PD. Results showed a decrease (improvement) of 6.84 points in the Unified Parkinson's Disease Rating Scale (UPDRS) part III in the 1 Hz group at the last follow-up (12 weeks post-intervention) [140]. Although the molecular mechanisms underlying these changes are not yet conclusive, several theories have been postulated. The initial alterations in neuronal ionic conductivity caused by electrolysis events caused by propagating electromagnetic currents appear to be associated with short-term consequences [141]. The release of neurotransmitters is another potential mechanism for short-term effects. High-frequency rTMS administered to the left dorsolateral prefrontal cortex has been linked to tonic dopamine release in the ipsilateral caudate and orbitofrontal cortex [142]. Meanwhile, the long-term effects of TMS are thought to be mediated via neuroplastic processes. The word "neuroplasticity" refers to the CNS's ability to respond to a wide range of external and internal stimuli via a functional, dynamic remodeling of its structures and connections [134]. This is especially significant in patients with PD, because changes in cortical excitability and neuroplasticity are heavily influenced by dopamine bioavailability, and the implementation of dopaminergic therapy can influence the subsequent neurophysiologic and behavioral effects of stimulation [143].

3.3.2.6. Alzheimer's Disease

Alzheimer's Disease (AD) affects roughly 3% of the population between the ages of 65 and 74 and more than 50% of the population over the age of 85 [144]. Symptoms usually begin with issues with episodic memory, and as the disease develops, additional cognitive domains, such as language and executive function, are impaired [145]. Pathologically, AD is distinguished by the presence of extracellular amyloid- (A) plaques and intra-neuronal tau neurofibrillary tangles (NFT).

3.3.2.6.1. Deep Brain Stimulation

In animals and/or humans, possible targets include the fornix, entorhinal cortex (EC), nucleus basalis of Meynert (NBM), anterior thalamic nuclei, mammillothalamic tract, hippocampus, and ventral capsule [146–148]. EC stimulation reduced impairments in a variety of spatial and recognition memory tests in both young and old animals in the TgCRND8 and 3Tg mouse models of AD [149]. Biological findings included increased neurogenesis as well as decreased plaque burden and A peptide concentration, albeit these effects on amyloid pathology may be age-dependent [150]. In preliminary trials, activation of hippocampus outflow channels resulted in significant reversals of hypometabolism and stability of cognitive deterioration in certain individuals. To date, the majority of publications have been prospective, demonstrating that DBS in memory pathways can have physiological, network-wide metabolic changes and alter various elements of memory function.

3.3.2.6.2. Transcranial Magnetic Stimulation

rTMS for AD resulted in statistically significantly improved short-term cognitive function of participants (standard mean difference [SMD] for Mini-Mental State Examination (MMSE) and Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) = 0.42; 95% CI, 0.18 to 0.67, P = 0.0006 [151]; mean pre-post MMSE change 1.08; 95% CI, 0.35 to 1.80) [152], with high-frequency rTMS rated as the best short-term intervention for general cognitive function when compared to other electrical stimulation interventions. Furthermore, statistically significant effects on cognitive function were seen when multiple sites (SMD = 0.47; 95% CI, 0.14 to 0.79; P = 0.005) were stimulated compared to single-site stimulation (SMD = 0.24; 95% CI, –0.45 to 0.92; P = 0.50), with cognitive scores improving as patients received longer-term treatment (more than 10 sessions) and higher frequency (20 Hz versus 10 Hz or 1 Hz) [151].

3.3.2.7. Depression

Major depression is a frequent and difficult disorder that can have a significant impact on quality of life, everyday functioning, and, ultimately, life expectancy [153].

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3.3.2.7.1. Transcranial Direct Current Stimulation

Transcranial direct current stimulation has also been studied as a therapy for serious depression, but its efficacy is still debated due to inconsistencies in published data. Some tDCS studies have found that anodic stimulation of the left DLPFC can significantly reduce depression scores for up to 30 days after treatment [154], whereas a meta-analysis found no effect of cognition independent of mood improvement [155], implying that identifying a specific effect of tDCS on cognition within a clinical trial design is difficult given general cognitive improvements in patients during a trial. Optimizing DLPFC stimulation in a subject-specific manner, as well as researching additional tDCS of other cortical areas implicated in mood and emotion, such as the parietal cortex [156], may increase the efficacy of tDCS for depression therapy.

3.3.2.8. Schizophrenia

Schizophrenia is frequently characterized by changes in cortical functional connectivity. Auditory verbal hallucinations are described in 50-70% of schizophrenia patients and are frequently resistant to pharmaceutical therapy [157].

3.3.2.8.1. Transcranial Direct Current Stimulation

Transcranial direct current stimulation-anodal stimulation is thought to improve excitatory synaptic transmission by increasing glutamate neurotransmission [129,158] and inhibiting gamma-aminobutyric acid transmission in the cortex [159]. On the other hand, it may control dopamine nervous system activity, increase serotonin neurotransmission [160], and reduce acetylcholine neurotransmission [161]. These ideas concerning tDCS's mechanism of action may explain why it helps with emotion detection in people with schizophrenia. Anodic (excitatory) stimulation of the left DLPFC in conjunction with cathodic (inhibitory) stimulation of the left temporal-parietal junction was found to significantly reduce the occurrence of auditory verbal hallucinations in schizophrenia patients in a recent tDCS study [157]. Importantly, the decrease in auditory verbal hallucinations lasted for three months after the tDCS therapy ended. Hypoactivity of the prefrontal cortex has also been linked to a variety of learning and memory impairments in schizophrenia, adding to its promise as a target for tDCS management. Anodic tDCS to the left DLPFC improved probabilistic association learning in a subset of schizophrenia patients [162].

3.4. Implications

As neuromodulation plays a pivotal role in addressing gastrointestinal (GI) diseases by employing therapeutic strategies that modulate crucial neural pathways governing gut function, this intervention proved instrumental in managing a spectrum of conditions including IBS, gastroparesis, and inflammatory bowel disease (IBD), showcasing its versatile applicability. Techniques like VNS and sacral nerve modulation stand at the forefront, offering effective modulation to regulate gut motility, mitigate symptoms, and significantly enhance the overall quality of life for individuals grappling with GI disorders. From a broader perspective, neuromodulation techniques encompass a diverse array of procedures precisely engineered to modify neural activity within targeted areas of the nervous system. Specifically within the realm of GI diseases, these techniques exert their influence on neural pathways intricately linked with the ENS and other vital components of the GBA. The overarching objective remains consistent: to finely regulate essential facets such as gut motility, visceral pain perception, and inflammation. By achieving this, patients experience noteworthy relief from distressing symptoms, marking a considerable enhancement in their quality of life while navigating the challenges posed by GI conditions. Focusing on the ENS, neuromodulation techniques such as VNS and sacral nerve modulation are carefully tailored to exert influence. Through this modulation of neural activity within the enteric system, these interventions effectively regulate gut motility. For example, in conditions characterized by disrupted motility like gastroparesis or intestinal pseudo-obstruction, neuromodulation steps in to restore coordinated contractions, facilitating the effective propulsion of digestive contents through the GI tract. Addressing chronic

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abdominal pain, a prevalent and debilitating symptom across numerous GI diseases like IBS and IBD is a hallmark achievement of neuromodulation techniques [163,164]. These interventions excel in managing visceral pain perception by strategically influencing pain pathways within the intricate nervous system [165]. The targeted stimulation diminishes pain signals and elevates the pain threshold, providing substantial relief to patients burdened by persistent discomfort and abdominal pain. Furthermore, the profound impact of inflammatory processes in the pathology of several GI disorders, including Crohn's disease and ulcerative colitis, cannot be overstated [166,167]. The most widely used animal models of colitis involve the application of inflammatory agents such as dextran sodium sulfate (DSS) or 2,4,6-trinitrobenzene sulfonate (TNBS) through the luminal membrane. Electrical vagal stimulation has been shown in two studies to inhibit inflammation in such models, but neither of these studies investigated which vagal neurons are involved in this effect [78,168]. Seven patients with ileocolonic Crohn's disease were implanted with a cervical vagus nerve electrode and continuously stimulated for 6 months in a small pilot trial [79]. The device was well tolerated, with only a few reports of throat pain and voice changes during the ON phases. Two patients with a more severe form of Crohn's disease dropped out due to symptoms worsening; however, the remaining five patients achieved clinical and endoscopic remission, including one who remained in remission for 42 months after surgery and no longer required azathioprine.

Ileus, also known as gut stasis, is a potentially fatal condition that occurs frequently following abdominal surgery or insult [169]. Previously, drugs targeting inflammatory processes (for example, nonsteroidal anti-inflammatory drugs), inhibitory neural pathways (antiadrenergic), or motility-stimulating mechanisms (for example, metoclopramide) were used to prevent and treat this condition [170]. VNS is effective in preventing and treating ileus in a rat model caused by manipulation of the small intestine [171,172]. The efficacy of stimulating vagal pathways to treat ileus was also confirmed in a rat model in which the vagus nerve was activated via pharmacological stimulation (injection of a thyrotropin-releasing hormone agonist into the CNS) [173]. Vagal stimulation prevented the slowing of gut transit, most likely by inhibiting inflammation. Another study, in which ileus was also induced in rats by intestinal manipulation, suggested that indirect electrical stimulation of vagal pathways could prevent ileus without suppressing inflammation [174].

Gastroparesis is a chronic disorder characterized by delayed gastric emptying in the absence of obstruction, as well as postprandial distress, nausea, and vomiting [175]. Pharmaceutical treatments are ineffective [176,177]. Electrical stimulation of the gastric corpus with parameters that stimulate vagal afferent fibers has been found to reduce nausea as well as postprandial satiety [178,179]. One review and one meta-analysis of Gastric Electrical Stimulation (GES) for the treatment of gastroparesis published in the last few years found benefit only in some trials [176,180]. The meta-analysis found that while 16 open-label, follow-up trials showed total symptom score reductions (nausea or nausea and vomiting, postprandial discomfort), 5 studies comparing symptoms with stimulation turned on or off randomly (the patients serving as their controls) found no difference between the on and off conditions[181].

Neuromodulation interventions showcase significant potential in modulating inflammation within the gut [182]. By exerting influence over immune responses and inflammatory pathways, these techniques contribute to a notable reduction in inflammation and its associated detrimental effects on GI tissues. This comprehensive approach offers a promising avenue for effectively managing these challenging conditions.

4. Conclusion and Future Trends

The exploration of neuromodulation techniques in the context of the GBA offers promising avenues for addressing a spectrum of neurological and gastrointestinal disorders. The bidirectional communication between the gastrointestinal tract and the CNS, orchestrated by the GBA, underscores the intricate interplay between physiological processes and cognitive functions. Neuromodulation emerges as a versatile and effective therapeutic approach, showing promise in the management of drug-resistant epilepsy, treatment-resistant depression, and FGIDs. The significance of VNS in influencing gastrointestinal motility, permeability, and protection against inflammatory

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damage signifies its role as a natural treatment for conditions like Crohn's disease and ulcerative colitis. While challenges and potential complications exist, the potential of neuromodulation to modulate abnormal circuit activity, alleviate chronic abdominal pain, and manage inflammatory processes in various GI disorders highlights its impactful role in improving the quality of life for individuals grappling with these challenging conditions. Looking ahead, the future of neuromodulation in tackling gastrointestinal disorders holds exciting prospects. Ongoing research suggests that the application of neuromagnetic therapies, device-assisted treatments (DATs), and electroacupuncture therapy could further refine our understanding of gut-brain connections and potentially open new avenues for therapeutic interventions. As the field continues to advance, it is anticipated that fine-tuned neuromodulation techniques, such as transcutaneous auricular VNS (tVNS) and tripolar SCS, will play an increasingly pivotal role in reducing inflammation, improving symptoms, and enhancing the quality of life for individuals with FGIDs like IBS. Additionally, the ongoing exploration of DBS and TMS for modulating abnormal circuit activity and addressing chronic pain and inflammatory processes in gastrointestinal disorders suggests a continued evolution in the application of neuromodulation techniques for improved patient outcomes.

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