

The Use of Repetitive Transcranial Magnetic Stimulation on the Microbiota-Gut-Brain Axis, Depression, Irritable Bowel Syndrome and Autism

Marco Vinícios de Oliveira Santana¹, Carlos Henrique Marchiori^{1*}, Klebert de Paula Malheiros¹

¹Teacher and Researcher of the Department of Biology and Medicine do Instituto Marco Santana, Goiânia, Goiás, Brazil

<p>Abstract: Transcranial Magnetic Stimulation (TMS) is a non-invasive neuromodulation technique, with minimal adverse effects and few contraindications. The procedure has been used in the therapeutic arsenal of patients with depression, showing therapeutic benefits proven in research around the world. TMS is a technique already widely used in the treatment of mood disorders depression bipolar disorder and autism. This bibliographic summary aims to verify the combined repetitive TMS and gut microbiota modulation through the gut-brain axis. The research approach will involve the identification, selection and critical analysis of relevant studies. The aim is to obtain a comprehensive understanding of the current evidence base and to identify gaps in the existing literature that can be explored in future research. The sampling process will begin with the identification of relevant keywords and search terms related to the use of Transcranial Magnetic Stimulation. Some examples may include “autism”, “depression”, “disorders”, “gut”, “nervous system” among others. These keywords will be used to conduct a comprehensive search in academic databases such as PubMed, ScienceDirect, CAPES journals and other relevant databases. The data collection will be carried out by accessing the full texts of the studies selected for review. Relevant information such as study objectives, methodology used, population studied, interventions performed, outcome measures and authors’ conclusions will be extracted. The data will be analyzed using a thematic approach, which consists of identifying and categorizing the main emerging themes in the reviewed literature. In other words, this approach involves identifying recurring patterns or topics within the texts studied. After identifying these themes, they will be organized and discussed in relation to existing research and relevant theories. The objective is to provide a detailed and critical review of the literature on TMS, contextualizing the findings within the current panorama of knowledge in the area. Fifty-six articles were selected, including national and international texts, published between 1980 and 2024.</p>	<p style="text-align: center;">Research Paper</p>
	<p>*Corresponding Author: <i>Carlos Henrique Marchiori</i> Teacher and Researcher of the Department of Biology and Medicine do Instituto Marco Santana, Goiânia, Goiás, Brazil</p>
	<p>How to cite this paper: Marco Vinícios de Oliveira Santana <i>et al</i> (2024). Teachers and Researchers of the Department of Biology and Medicine do Instituto Marco Santana, Goiânia, Goiás, Brazil. <i>Middle East Res J. Med. Sci.</i> 4(6): 159-173.</p>
	<p>Article History: Submit: 12.10.2024 Accepted: 11.11.2024 Published: 13.11.2024 </p>
<p>Keywords: Benefits, Disorder, Neuromodulation, Non-Invasive, Syndrome.</p>	
<p>Copyright © 2024 The Author(s): This is an open-access article distributed under the terms of the Creative Commons Attribution 4.0 International License (CC BY-NC 4.0) which permits unrestricted use, distribution, and reproduction in any medium for non-commercial use provided the original author and source are credited.</p>	

1.0. INTRODUCTION

The brain-gut axis plays an important role in generating and maintaining symptoms of these diseases, such as abdominal pain, weight loss, diarrhea, anemia, and fatigue. It represents a complex system with multiple interconnections between the brain-endocrine pathways, the autonomic nervous system, and the gastrointestinal tract. This system influences the development of inflammatory bowel disease Crohn's disease ulcerative colitis, gastroesophageal reflux disease, and irritable bowel syndrome. It predisposes to and maintains psychological disorders such as anxiety and depression in up to 35% of patients. It also represents the connection pathway between the central nervous system and the intestine in the development of gastrointestinal cancer

(Figure 1) (Carrington *et al.*, 2014; Shen, 2015; Köhler *et al.*, 2016; Dinan and Cryan, 2017; Saldanha *et al.*, 2023; Lohet *et al.*, 2024; Oliveira, *et al.*, 2024).

Diet can affect the survival and metabolism of bacteria in the intestinal microbiota, causing changes in the pattern of bacterial colonization, that is, in the modulation of the microbiota. In this way, diet can lead to the prevalence of microbiota generated by inflammatory processes in the body. Covered by an immense network of nerve cells, it is responsible for producing several neurotransmitters and, unlike other organs, which only receive information from the brain, the neuronal network of the intestine also sends information and is capable of interfering with our mental

activity (Carrington *et al.*, 2014; Shen, 2015; Köhler *et al.*, 2016; Dinan and Cryan, 2017; Saldanha *et al.*, 2023; Oliveira *et al.*, 2024).

Our gut and brain are closely interconnected. The gut produces neurotransmitters, allowing us to experience reality through sensations like hunger, cold, pleasure, and even love. There are two main ways to increase the good bacteria in your gut: diet or supplementation. Eating certain foods helps to increase the good bacteria and thus improve your intestinal flora. Some examples of foods for good bacteria in your gut are kefir, yogurt, sauerkraut, and kombucha (Carrington *et al.*, 2014; Shen, 2015; Köhler *et al.*, 2016; Dinan and Cryan, 2017; Saldanha *et al.*, 2023; Oliveira *et al.*, 2024).

The gut has been nicknamed the second brain for a reason. About 100 million nerve cells are lining the organ and other parts of the gastrointestinal system, which runs from the esophagus to the rectum, a region that scientists call the Enteric Nervous System (ENS). The close connection between the brain and the gut significantly influences mental health. Studies show that the gut microbiota plays a crucial role in producing neurotransmitters, such as serotonin and dopamine, which play a fundamental role in mood and emotional well-being. Many of the neurons in the vagus nerve carry information from the gut to the brain, and not the other way around (Figure 2) (Burgell and Scott, 2012; Carrington *et al.*, 2014; Bharucha *et al.*, 2015; Whitehead *et al.*, 2015; Xiang *et al.*, 2019; Satish *et al.*, 2021; Lohet *et al.*, 2024; Oliveira *et al.*, 2024).

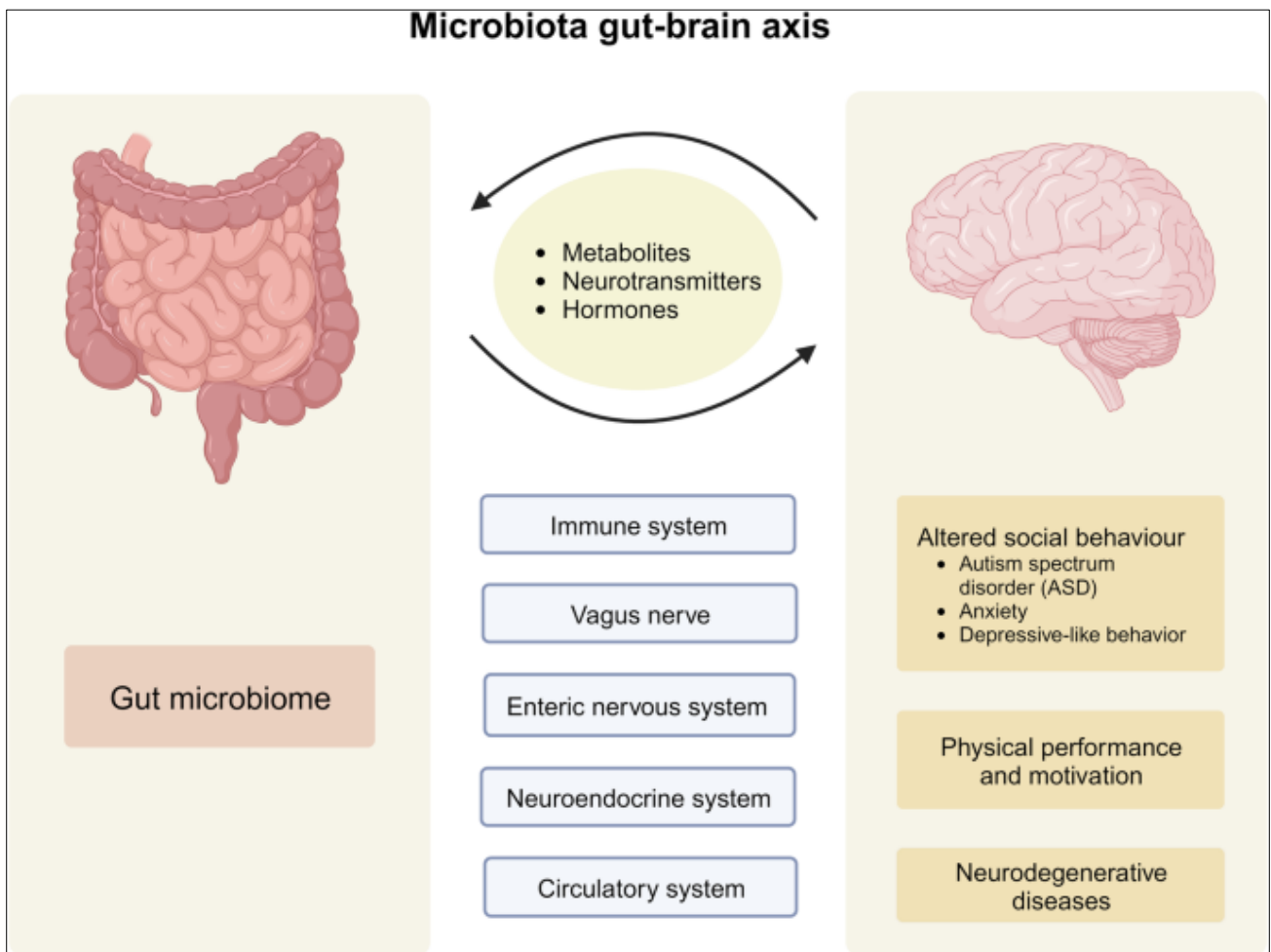


Figure 1: The microbiota–gut–brain axis. The immune system, vagus nerve, enteric nervous system, neuroendocrine system, and circulatory system mediate the bidirectional communication between the gut microbiome and the brain. Alterations in gut microbiota have been linked to the development of autism spectrum disorders, anxiety, depressive-like behavior, impaired physical performance, and motivation, as well as neurodegenerative diseases

Sources: BioRender <https://www.biorender.com/> and Doi.10.1038/s41392-024-01743

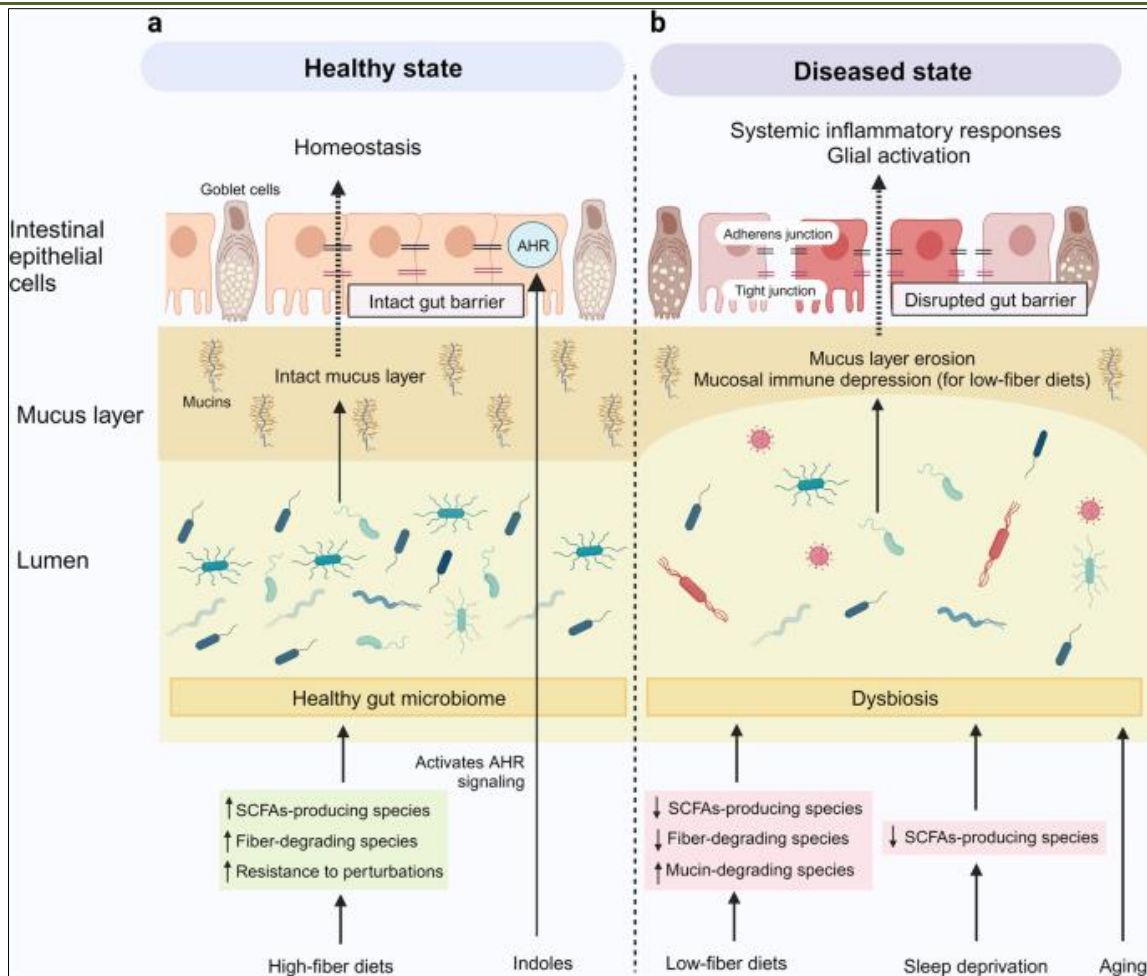


Figure 2: a-Improving microbiota-gut-brain axis via the intestinal barrier. High-fiber diets contribute to a healthy gut microbiome and enhance intestinal barrier integrity by increasing SCFAs-producing species, and fiber-degrading species and promoting resistance to perturbations. Indole and its derivatives improve intestinal barrier integrity by activating epithelial aryl hydrocarbon receptors (AHR). a-Low-fiber diets, aging, and sleep deprivation contribute to dysbiosis and disrupt intestinal barrier integrity by reducing SCFAs-producing species and fiber-degrading species while increasing mucin-degrading species. Low-fiber diets induce mucosal and systemic immune depression by impairing the metabolic fitness of CD4+ T cells
Sources: BioRender <https://www.biorender.com/> and Doi.10.1038/s41392-024-01743

Recent studies have demonstrated the relationship between the composition and diversity of the intestinal microbiota and changes in mood and behavior. Therefore, one of how this mechanism influences mental health may occur through the production of neurotransmitters such as serotonin, melatonin, and GABA. Small intestinal bacterial overgrowth is a disorder in which the inadequate movement of intestinal contents allows certain normal bacteria in the intestine to grow excessively, causing diarrhea and Impaired Nutrient Absorption (IMA). In addition to probiotics, another food source that can help increase good bacteria in the intestine is fiber. This is because while probiotics are a way to replenish beneficial microorganisms, fiber serves as food for these bacteria, helping them grow and proliferate (Bharucha *et al.*, 2015; Shen, 2015; Thaha *et*

al., 2015; Köhler *et al.*, 2016; Dinan and Cryan, 2017; Xiang *et al.*, 2019).

2. TRANSCRANIAL MAGNETIC STIMULATION (TMS)

The TMS technique is already widely used in the treatment of mood disorders, depression, and bipolar disorder. A doctor prescribes TMS sessions which can be administered by a doctor or by health professionals such as nurses, psychologists, and physiotherapists who are properly trained and always under medical supervision. This stimulation can modulate the excitability of brain regions, promoting therapeutic effects in diseases such as depression, chronic pain, schizophrenia, and autism spectrum disorder, for example. A deep brain stimulation system has three parts: a stimulator that delivers gentle electrical pulses to electrodes placed in the motor region

of your brain and an extension that connects the two. The procedure has risks, like any surgery, but it is not new

(Figure 3) (Montenegro and Cantilino, 2016; Li *et al.*, 2022; Feng *et al.*, 2024; Zimmer, 2024).



Figure 3: Transcranial Magnetic Stimulation (TMS) is a neuromodulation technique whereby the polarization of neurons is induced by an electromagnetically generated electric field across the scalp; ion movement within the brain occurs without electrical current flowing across the skull. This is differentiated from similar techniques, such as Transcranial Direct Current Stimulation (tDCS), which uses electrodes placed on the scalp

Source: <https://myrehabteam.com.au/blog/what-is-transcranial-magnetic-stimulation/>

Hands Without Borders (MSF) uses a technique called neural stimulation, which performs treatments through the conscious touch of the hands-on specific points, strengthening the three basic pillars of the human body, the nervous, immune, and blood systems, benefiting the. TMS can act by modulating cortical excitability in the brain for a year. Therefore, this

technique can be used in the treatment of brain pathologies that involve changes in cortical excitability, such as epilepsy, stroke, dystonia, Parkinson's disease, depression, and schizophrenia. Psychostimulants, such as Methylphenidate (Ritalin), are the first choice for treatment (Figure 4) (Montenegro and Cantilino, 2016; Mehta *et al.*, 2024; Zimmer, 2024).

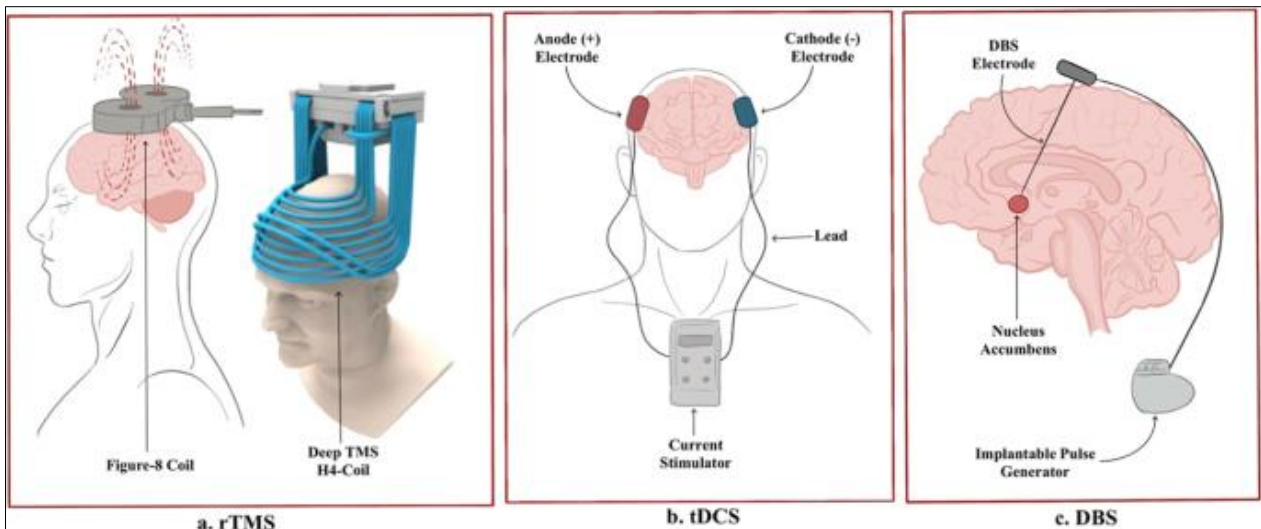


Figure 4: Diagrams to illustrate the three neuromodulation techniques investigated: (a) rTMS (Deep TMS image acquired from Brainsway, Inc.), (b) tDCS, (c) DB

Source: [Doi.org/10.1038/s41386-023-01776-0](https://doi.org/10.1038/s41386-023-01776-0)

The Cognitive Behavioral Therapy (ADHD) involves four steps: 1. Psychoeducation, 2. Assessment of comorbidities, 3. Psychotherapy itself, and 4. Interventions in the environment. During

psychoeducation, the patient receives information about ADHD. Maintaining a healthy lifestyle is very important to control ADHD symptoms. Physical exercise, for example, develops brain functions that control

impulsivity and hyperactivity, in addition to releasing endorphins that calm the brain (Montenegro and Cantilino, 2016; Ribeiro, 2016; Zimmer, 2024).

2.1. Benefits of Transcranial Magnetic Stimulation

- It has an individualized approach for various conditions.
- It promotes well-being and quality of life.
- It is a non-invasive technique and does not interfere with the body's systems.
- It offers results for long-lasting periods (Vuong and Hsiao, 2017; Martins *et al.*, 2022; Zimmer, 2024).

What is the procedure? The TMS sessions are painless and can last from 20 minutes to 50 minutes.

Patients usually need to undergo daily sessions at the beginning of the treatment, followed by maintenance sessions once a week or once a month (Rosa, 2013; Laucheur *et al.*, 2014; Ribeiro, 2016).

2.2. The TMS in Irritable Bowel Syndrome

Irritable Bowel Syndrome (IBS) is a common functional gastrointestinal disorder characterized by abdominal pain and, in most cases IBS. Irritable Bowel Syndrome can substantially reduce the quality of life, especially in those with comorbid mood symptoms, while treatments remain inadequate (Figure 5) (Whitehead *et al.*, 1980; Niddam *et al.*, 2011; Adam *et al.*, 2020).

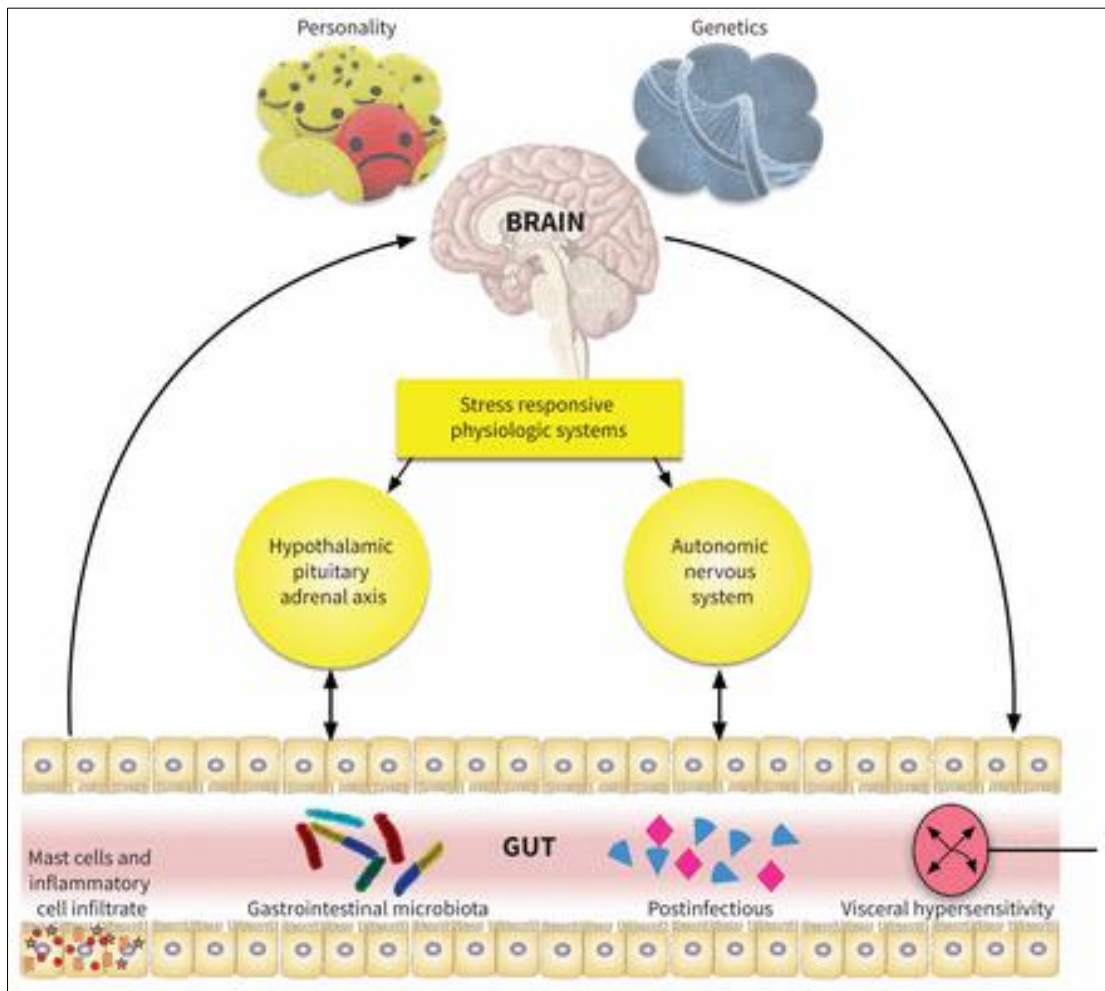


Figure 5: A schematic summary of the factors that have been implicated in the pathophysiology of Irritable Bowel Syndrome (IBS) within the context of the brain-gut axis. This figure also demonstrates the concept of visceral hypersensitivity in IBS, in which the pain threshold to rectosigmoid mechanical distension is lower in patients with IBS than in healthy controls, suggesting that the viscera are more sensitive

Source: Doi.org/10.1053/j.gastro.2022.04.017

Neuroimaging studies in IBS patients have demonstrated metabolic alterations in brain regions involved in pain and emotions, such as the hippocampus,

medial prefrontal cortex (mPFC), and insular cortex with psychotropic medications (gram frac 150 mg/day, buspirone 30 mg/day, and oxazepam 15 mg/day) along

with nutritional support enteral nutritional suspension, 500 ml/day. As a noninvasive form of brain stimulation, Repetitive Transcranial Magnetic Stimulation (rTMS) has been shown to reduce both pain and depression. A recent evidence-based synthesis demonstrated

significant analgesia after stimulation of the Dorsolateral Prefrontal Cortex (DLPFC) (Figure 6) (Ribeiro *et al.*, 2011; Bakker *et al.*, 2015; Gros *et al.*, 2021; Lembo *et al.*, 2022; Moleski, 2022; TJDFT, 2024).

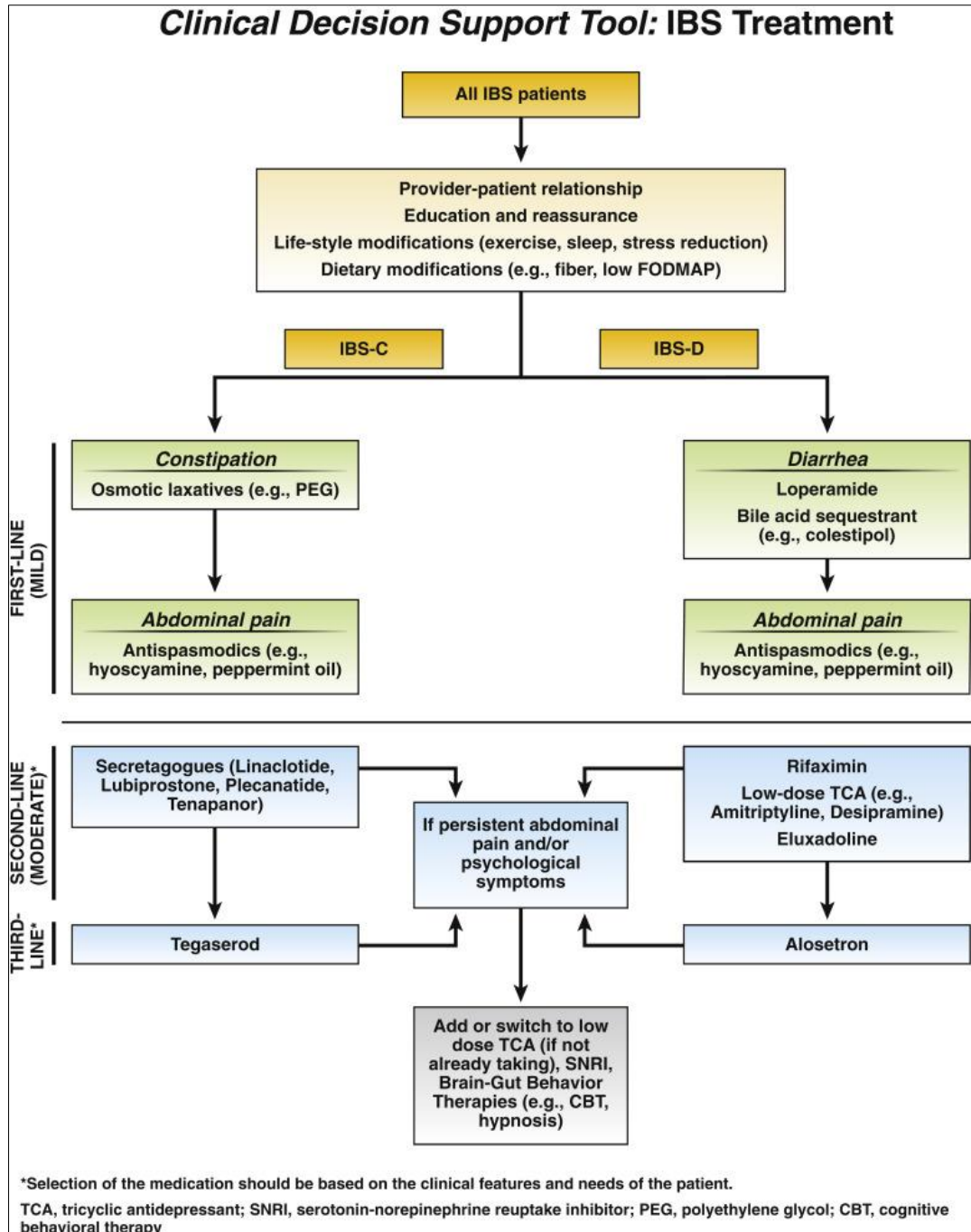


Figure 6: Pharmacological management of Irritable Bowel Syndrome-Diarrhea (IBS-D)

Source: Doi.org/10.1053/j.gastro.2022.04.017

In Neurogastroenterology, one example is sacral nerve stimulation for fecal incontinence, which has been widely used for patients for over two decades. However, the treatment of other conditions, such as

inflammatory diseases, obesity, nausea and gastroparesis, also has scientific support, mainly due to the anti-inflammatory effects of vagus nerve stimulation, the action of peripheral nerves and the modulation of the

Central Nervous System (CNS) (Niddam *et al.*, 2011; Ribeiro *et al.*, 2011; Bakker *et al.*, 2015; Moleski, 2022; TJDF, 2024).

2.3. Therapeutic Protocols of TMS in Depression

Themes that are beginning to form the contours of the next generation of therapeutic rTMS protocols, some of which already have a sufficient level of evidence for clinical practice:

2.3.1. New Therapeutic Targets:

The dorsomedial frontal cortex, easily reached with a double cone coil, may be a better target than the dorsolateral cortex, at least in some patients, as demonstrated by Downar in 2015.

2.3.2. Reduction of Session Time and TMS with Multiple Targets per Session:

A large study has already demonstrated the equivalence of efficacy between a 6-minute theta-burst session and a 30-minute-effects of High-Frequency Repetitive Transcranial Magnetic (HF-TMS) session, also opening up the possibility of increasing the efficacy

found in 2 "biotypes" of depression with the application of rTMS to 2 targets in the same session.

2.3.3. Reduction in Treatment Time:

Instead of 4 to 6 weeks to obtain maximum response, protocols with a greater number of pulses and multiple sessions per day accelerated TMS have been able to increase the time required for training to respond to 2 weeks or even just 2 days.

2.3.4. Response Enhancement Techniques:

An increase in the efficacy of inhibitory TMS in depression has already been demonstrated using the Priming technique. The method also has the potential for use in motor rehabilitation, tinnitus, and other situations that seek to enhance the deficiency.

2.3.5. Functional Neuroimaging Methods

Aim to decipher at least part of the heterogeneity of depression and predict, with up to 94% certainty, which patients will respond to TMS (Figure 7) (George *et al.*, 2010; Carpenter *et al.*, 2012; Bakker *et al.*, 2015; McGirr *et al.*, 2015; Pigott, 2015; Dedoncker *et al.*, 2016; Duprat *et al.*, 2021).

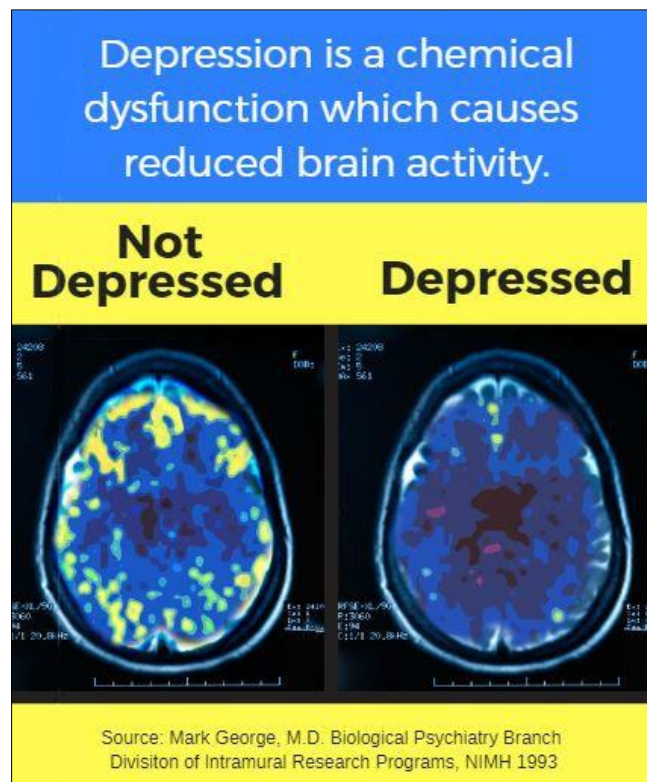


Figure 7: Transcranial Magnetic Stimulation therapy for depression

Source: Keystone Behavioral Health and <https://keystonehealth.org/keystonebehavioralhealth/tms-therapy-depression/>

2.4. TMS in Autism Spectrum Disorder (ASD)

Scientists are studying the feasibility of treating children with autism with neuromodulation, a treatment that involves applying an electromagnetic field to modify and modulate the nervous system after a new study

showed that brain stimulation can correct social deficiencies. The alteration of the intestinal microbiota of autistic children is also related to their eating habits and nutritional diet since children with the disorder have a very high food selectivity, which leads to a nutritional

deficiency and consequently to a metabolic disorder. Gas is the accumulation of air in the stomach or intestine and can cause symptoms such as abdominal pain, a swollen belly, excessive flatulence with or without a bad smell, or constant burping (Chen *et al.*, 2020; Machado and Haertel, 2014; Kang *et al.*, 2017; Xiang *et al.*, 2019; Xu *et al.*, 2019; Saldanha *et al.*, 2023; Oliveira *et al.*, 2024).

What is also known is that those with ASD have an imbalance in the bacteria in their intestines. Some

studies show that the intestinal microbiota of an autistic person is different, there is a change in the balance of the microbiota characterized by the loss of beneficial bacterial mass. The images show the activation of a brain with autism and without autism subjected to the same type of stimulus (Figure 8) (Ameis and Catani, 2014; Vuong and Hsiao, 2017; Kong *et al.*, 2019; Tidy and Knott, 2021; Martins *et al.*, 2022).

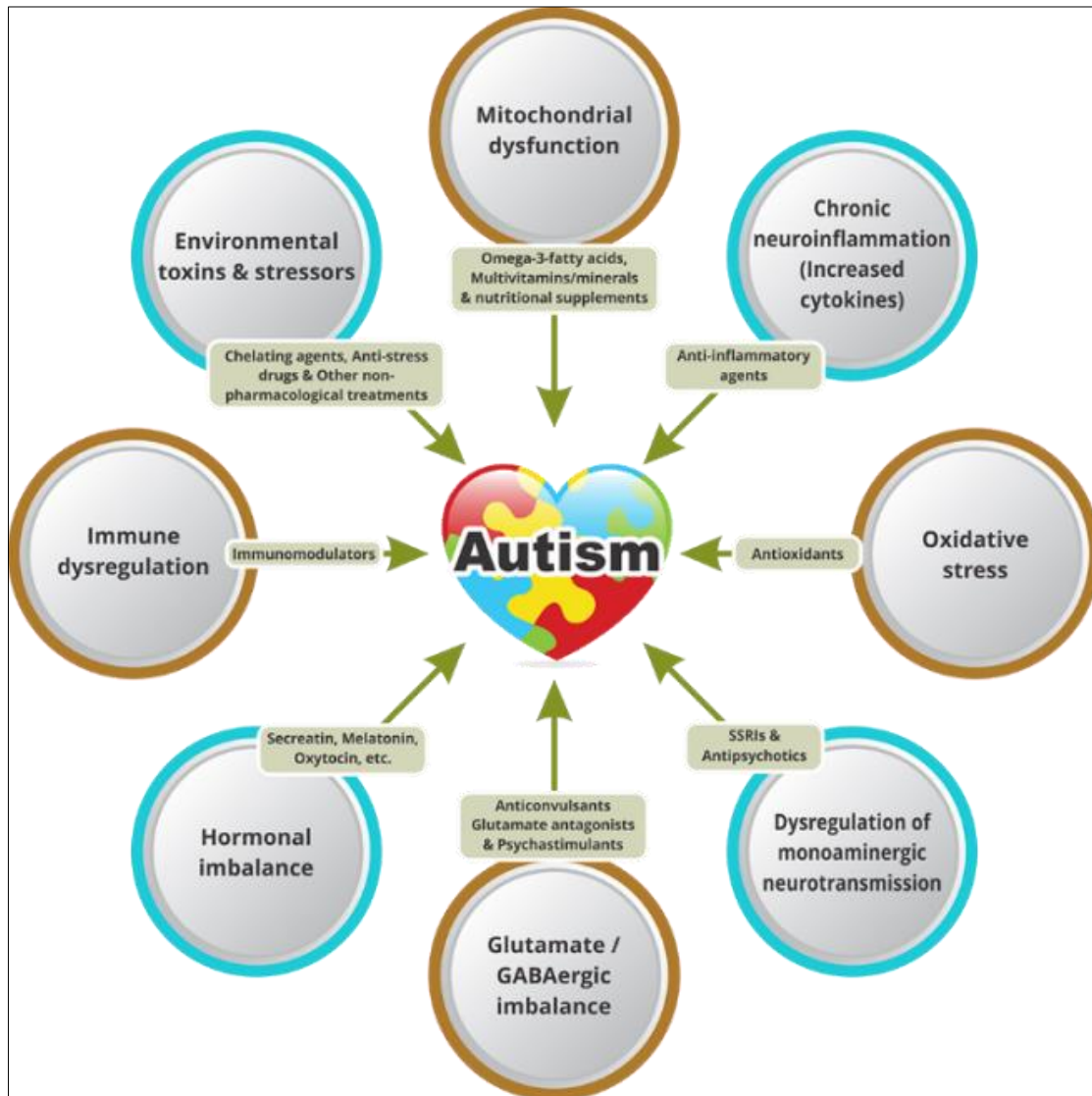


Figure 8: Autism Spectrum Disorder (ASD) is generalized as autism, but what else is on the spectrum? ASD is considered a spectrum disorder because there is an array of symptoms that can be demonstrated in several different ways with varying severity

Source: <https://www.neurogen.in/autism>

The use of probiotics, prebiotics, or fecal microbiota transplantation can also influence the composition of the microbiota, and the function of the intestinal barrier and alter the immune responses of the mucosa, suggesting a beneficial effect of probiotics in ASD, with numerous known microbial mechanisms

related to the disease, such as disruption of the intestinal barrier induced by dysbiosis, various types of changes in the intestinal microbiota, production of toxins and immunological and metabolic dysfunctions (Belmonte *et al.*, 2014; Rao *et al.*, 2014; Kang *et al.*, 2017; Vuong and Hsiao, 2017; Martins *et al.*, 2022; Oliveira *et al.*, 2024).

Several types of dysbiosis, alterations in the intestinal microbiota, alter the production of serum metabolites and appear to induce an autism-like behavioral phenotype. In addition, many studies have shown the presence of dysbiosis in individuals with ASD. In this scenario, considering that each individual may present a different type of dysbiosis, and each type of dysbiosis requires different forms of treatment, knowing the composition of the bacteria in the intestinal microbiota through genetic sequencing is ideal for carrying out guided and personalized intestinal modulation (Rao, 2004; Belmonte *et al.*, 2014; Rao *et al.*, 2014; Rao *et al.*, 2016; Kang *et al.*, 2017; Vuong and Hsiao, 2017; Oliveira *et al.*, 2024).

Notice how multiple brain regions are activated in the image on the left and how only one region is intensely activated in the autistic brain on the right. Imagine that in the autistic brain, there are “narrow, barrier-strewn roads” connecting distant areas of the brain and wide, open avenues connecting nearby areas. Researchers call this local hyperconnectivity and distant hypoconnectivity. What defines whether a road is narrow or wide, whether it is open or blocked, is the junction between neurons, called a synapse, which is the point at

which neurons meet. The synapse is electrically “programmable.” This is how our memory works. You could say that our memories are “reinforced” synapses (Machado and Haertel, 2014; Rao *et al.*, 2014; Oliveira *et al.*, 2024).

Everything you capture through your senses reaches your consciousness in the form of electrical impulses and is stored because the synapses that were traversed during perception have been strengthened. This process of strengthening or weakening synapses based on electrical impulses involves a sequence of events that have been extensively studied and are represented in the synapse shown here (Machado and Haertel, 2014; Oberman *et al.*, 2016). The process of cellular consolidation of memory. What determines whether a memory will be transient or lasting is primarily the pattern and repetition of the electrical pulses that trigger this process. The synchrony between multiple neurons in a pathway is also very important. Memory researchers often say: “Neurons that fire together, wire together” [Cambridge researcher Matthew Belmonte, published in the Journal of Neuroscience in 2004] (Figure 9) (Machado and Haertel, 2014; Oberman *et al.*, 2016; Oliveira *et al.*, 2024).

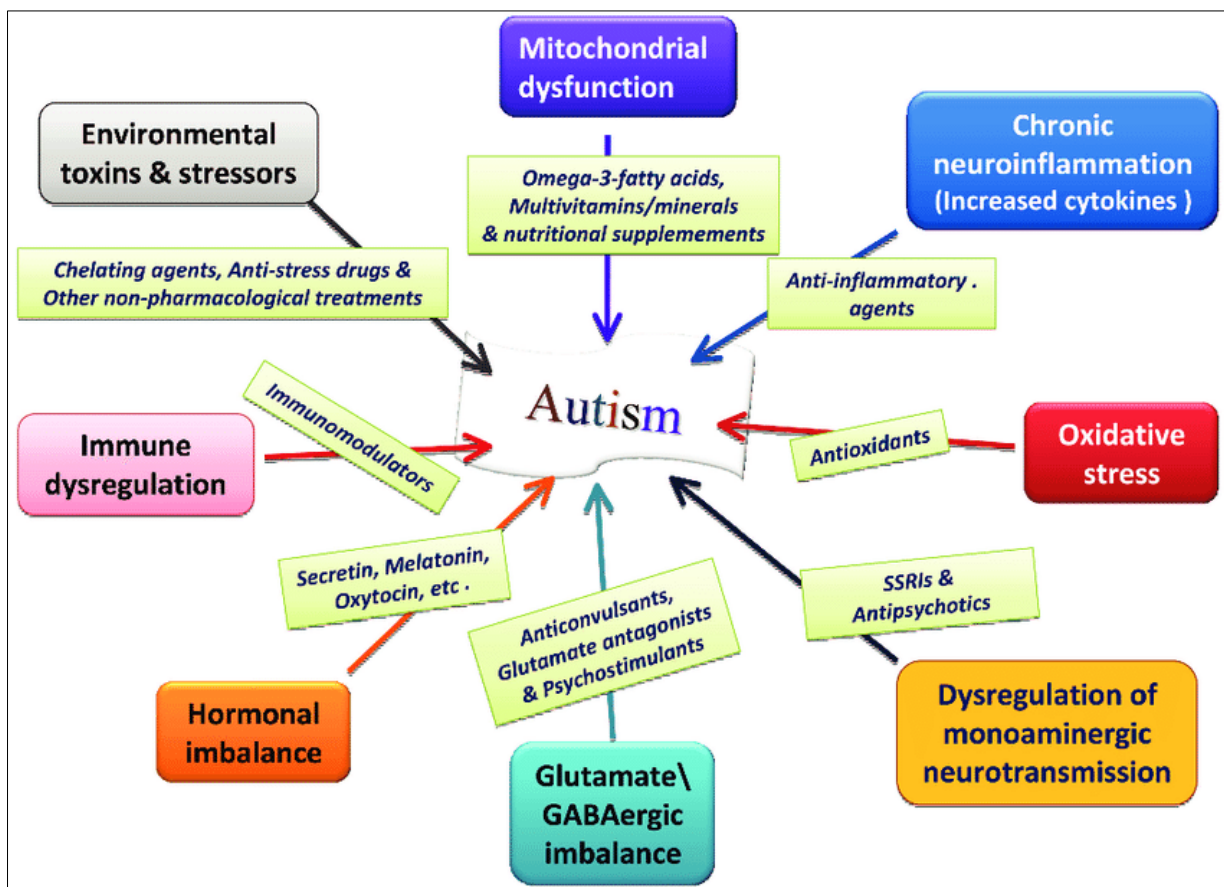


Figure 9: Drug therapy and different targets in autism

Source: https://www.researchgate.net/figure/Drug-therapy-and-different-targetsinnautism_fig1_235619896

Autism spectrum disorder encompasses a range of neurodevelopmental conditions defined by specific impairments in social communication and interaction, along with restricted behaviors, interests, and repetitive activities. No targeted pharmacological or physical interventions are currently available for autism spectrum disorder. However, emerging evidence has indicated a potential association between the development of autism spectrum disorder and dysregulation of the gut-brain axis

(Machado and Haertel, 2014; Oberman *et al.*, 2016; Oliveira *et al.*, 2024).

The rTMS has demonstrated positive results in several psychiatric disorders; however, its efficacy in the treatment of autism spectrum disorder and the accompanying gastrointestinal effects, particularly the effects on the gut-brain axis, remains unclear (Figure 10) (Andre-Obadia *et al.*, 2014; Machado and Haertel, 2014; Muhle *et al.*, 2018).

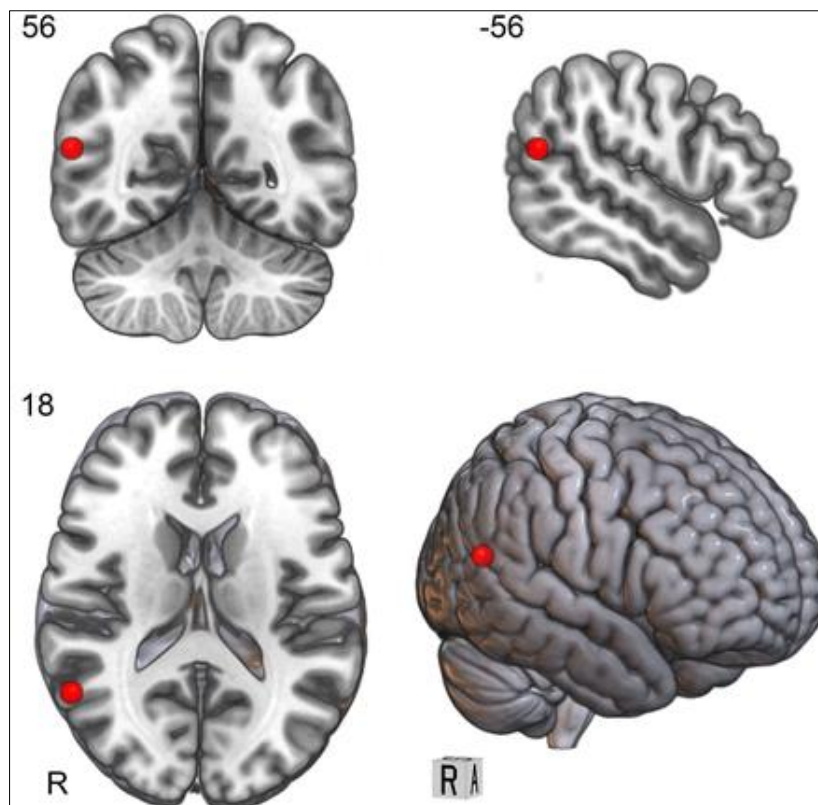


Figure 10: Site of rTMS coil localization (MNI coordinates $x=56, y=-56, z=18$). MNI, Montreal Neurological Institute; rTMS, repetitive transcranial magnetic stimulation
Source: Doi: 10.1136/bmjopen-2020-046830

The Food and Drug Administration (USA) has approved two separate TMS devices, including high- and low-frequency rTMS systems, for the treatment of ASD. High-frequency (10–20 Hz) and low-frequency (1–5 Hz) rTMS devices have been examined for potential therapeutic effects against ASD (Brasil-Neto *et al.*, 2003; Deng *et al.*, 2013). 20 Hz rTMS increased regional cerebral blood flow bilaterally in the frontal cortex, and surprisingly, 1 Hz rTMS decreased regional cerebral blood flow only in the contralateral prefrontal cortex. This raises the possibility of therapeutic applications that selectively activate or inhibit specific brain areas in different neuropsychiatric syndromes using this noninvasive procedure. Either low- or high-frequency rTMS can (Brasil-Neto *et al.*, 2003; Deng *et al.*, 2013).

2.4. OBJECTIVE

This bibliographic summary aims to verify the combined Repetitive Transcranial Magnetic Stimulation and gut microbiota modulation through the gut-brain axis.

3. METHODS

The research approach will involve the identification, selection and critical analysis of relevant studies. The aim is to obtain a comprehensive understanding of the current evidence base and to identify gaps in the existing literature that can be explored in future research. The sampling process will begin with the identification of relevant keywords and search terms related to the use of Transcranial Magnetic

Stimulation. Some examples may include “autism”, “depression”, “disorders”, “gut”, “nervous system” among others. These keywords will be used to conduct a comprehensive search in academic databases such as PubMed, ScienceDirect, CAPES journals and other relevant databases. The data collection will be carried out by accessing the full texts of the studies selected for review. Relevant information such as study objectives, methodology used, population studied, interventions performed, outcome measures and authors’ conclusions will be extracted. The data will be analyzed using a thematic approach, which consists of identifying and categorizing the main emerging themes in the reviewed literature. In other words, this approach involves identifying recurring patterns or topics within the texts studied. After identifying these themes, they will be organized and discussed in relation to existing research and relevant theories. The objective is to provide a detailed and critical review of the literature on TMS, contextualizing the findings within the current panorama of knowledge in the area. Fifty-six articles were selected, including national and international texts, published between 1980 and 2024.

4. SELECTED STUDIES AND CONSIDERATIONS

The gastrointestinal tract has a complex network of neural circuits that control essential functions of the alimentary system, such as digestion, nutrient

absorption, and waste elimination. In this tract, modulation occurs through the interaction of the central nervous system, the autonomic nervous system, and the enteric system, in health and disease. Where our emotional states and reactions to the external world influence and are influenced by the electrical states of the intestinal tissue and the microbiome. When imbalance sets in, neuroplasticity, a rearrangement of electrical triggers with metabolic repercussions, begins to integrate a new memorized circuit that will act at this frequency, until a new rearrangement is achieved (Belmonte *et al.*, 2014; Rao *et al.*, 2014; Kang *et al.*, 2017; Vuong and Hsiao, 2017; Menees *et al.*, 2018; Martins *et al.*, 2022).

The patient underwent daily TMS induction sessions for epileptic seizures called seizure disorder or epilepsy region for two weeks. The neuromodulation sessions were preceded by local abdominal treatment using tear therapy, a 448KHz radiofrequency. After two weeks, the treatment frequency was three times a week, with an increase in the therapeutic resources of respiratory endurance exercises. During this period, the patient was instructed to use an auricular vagal electrostimulation at home in the late afternoon, when symptoms were exacerbated, or during times of increased symptoms (Figure 11) (Brasil-Neto *et al.*, 2003; Rosa, 2013; Laucheur *et al.*, 2014; Machado and Haertel, 2014).

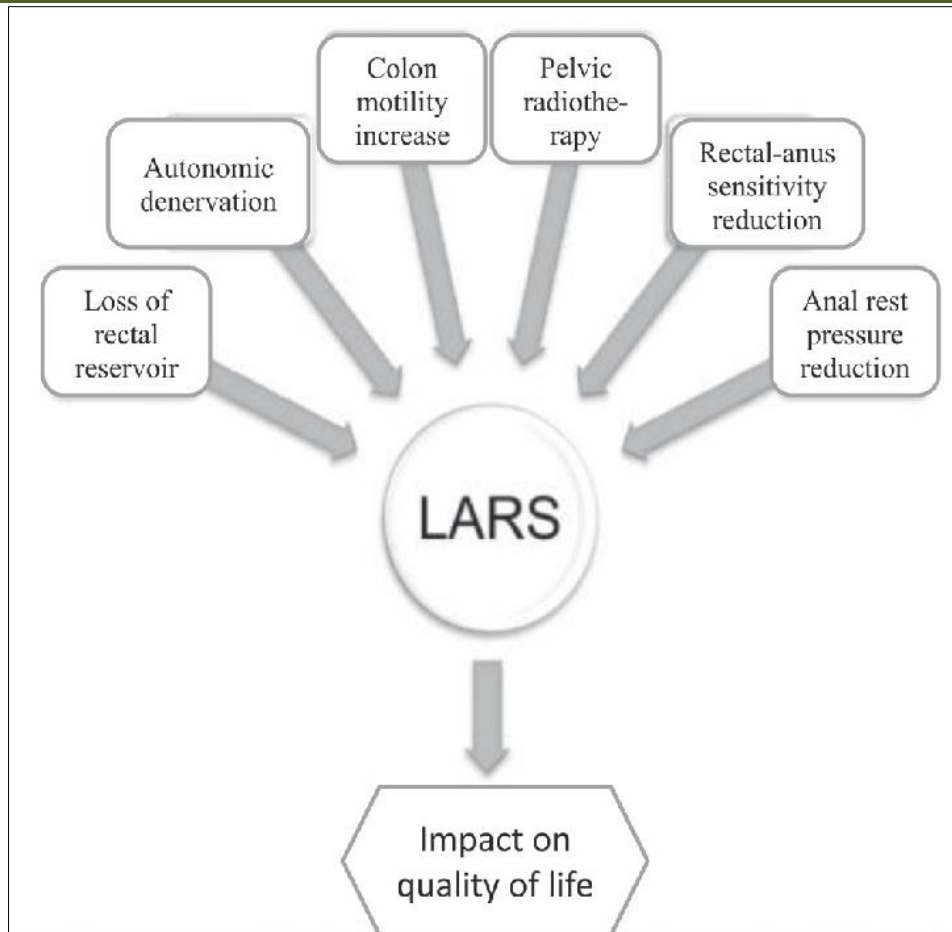


Figure 11: Physiopathology of Rectal Resection Syndrome (LARS)

Source: https://www.researchgate.net/figure/Physiopathology-of-LARS_fig1_320218544

Neuromodulator resources, such as intraoperative vagal stimulation, have proven effective in regulating intestinal transit when frequencies in the 5 Hz or 20 Hz band are used for just 2 minutes, before and after colorectal resection, using implantable electrodes. The reduction of pro-inflammatory cytokines is the likely therapeutic mechanism of the technique. However, it is associated with ultra-low Rectal Resection Syndrome (LARS), a severe, extremely limiting bowel

dysfunction that affects 60-90% of patients, with symptoms of fecal incontinence of gas and/or feces, fecal urgency (inability to avoid a bowel movement for 15 minutes), clustering of new fecal evacuation within 15 minutes of the last bowel movement, and frequent bowel movements increased bowel movement frequency (Figure 12) (Brasil-Neto *et al.*, 2003; Oberman *et al.*, 2016; Muhle *et al.*, 2018).

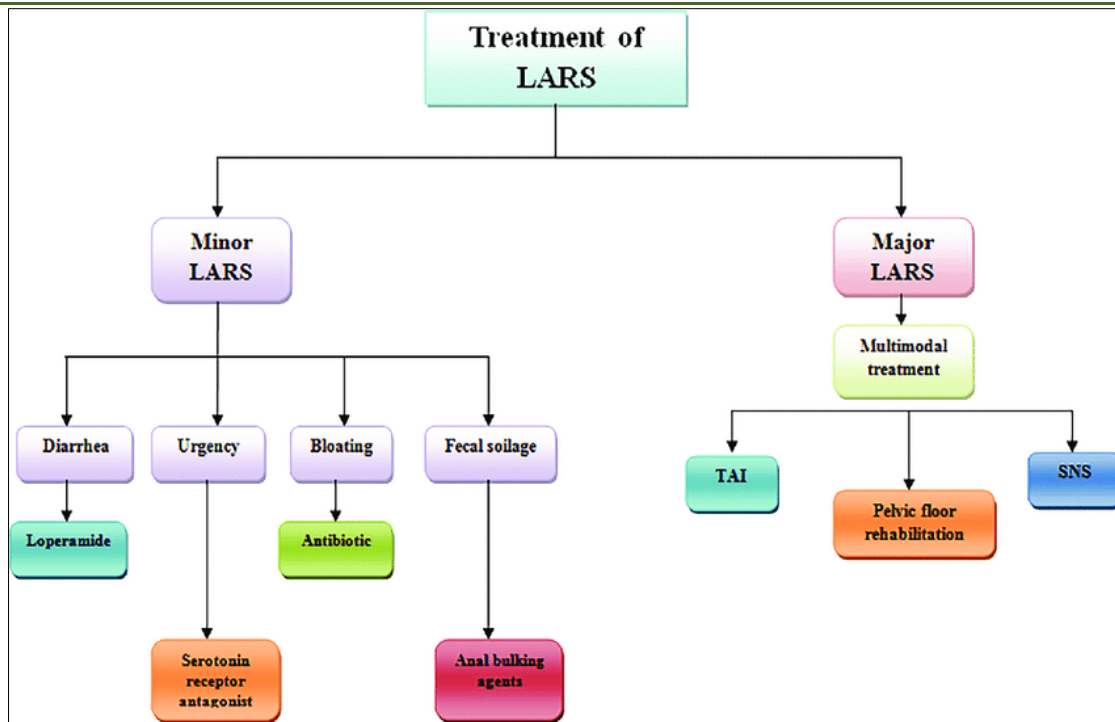


Figure 12: Treatment algorithm of low anterior resection syndrome. SNS: Sacral nerve stimulation; TAI: Transanal Irrigation

Source: https://www.researchgate.net/figure/Treatment-algorithm-of-low-anterior-resection-syndrome-SNS-Sacral-nerve-stimulation_fig2_342580757

The TMS can be applied to a wide variety of situations, helping to improve various aspects, from mental disorders to motor symptoms such as gait or balance disorders. This is because different protocols are available for different diagnoses, that is, the stimulation of the magnetic field is directed to a specific area of the nervous system involved in the disease that the patient has (Oberman *et al.*, 2016).

Its particularities, therefore, contribute to the fact that patients with different conditions can benefit. In autism, gastrointestinal comorbidities are associated with sleep problems; mood abnormalities; argumentativeness; oppositional, demanding, or disruptive behavior; anxiety; sensory reactivity; cruelty; obsessive-compulsive behavior; self-mutilation, aggression; lack of expressive language; and social impairment (Oberman *et al.*, 2016; Oliveira *et al.*, 2024).

More research is needed to clarify the best treatment approaches, long-term results, and safety profiles of these therapies. Furthermore, to develop successful and targeted therapies for individuals with autism spectrum disorder, a deeper understanding of the underlying processes and intricate relationships between rTMS (c), gut microbiota, and the brain is essential (Feng *et al.*, 2024).

Studies such as these serve as a foundation for deepening knowledge about the correlations of combined repetitive transcranial magnetic stimulation as a therapeutic intervention for autism and provide important information for the development of clinical trials. The TMS, together with neuroimaging methods, has brought new perspectives and possibilities to the field of autism spectrum disorder. Therefore, these new tools are enabling the discovery of discoveries in the area of combined rTMS and microbiota modulation (Feng *et al.*, 2024; Oliveira *et al.*, 2024).

The interaction between rTMS and gut microbiota in children with autism spectrum disorder (ASD), with a focus on the gut-brain axis. We investigated the integration of rTMS and gut microbiota modulation as a targeted approach for the treatment of ASD based on recent literature. This paper verified the potential synergistic effects of rTMS and gut microbiota interventions, describing the underlying mechanisms, and proposing a potential therapeutic strategy for specific subsets of individuals with ASD (Andre-Obadia *et al.*, 2014; Feng *et al.*, 2024).

5.0. CONCLUSION

The TMS technique is already widely used in the treatment of mood disorders, depression, and bipolar disorder. TMS sessions are prescribed by a doctor and can be administered by a doctor or by health

professionals such as nurses, psychologists, and physiotherapists who are properly trained and always under medical supervision. This stimulation can modulate the excitability of brain regions, promoting therapeutic effects in diseases such as depression, chronic pain, schizophrenia, and autism spectrum disorder, for example

REFERENCES

- Adam, D., Farmer, Wood, E., & Ruffle, J. K. (2020). An approach to the care of patients with irritable bowel syndrome. *CMAJ*, *192*, E27582.
- Ameis, S. H., & Catani, M. (2015). Altered white matter connectivity as a neural substrate for social impairment in autism spectrum disorder. *Cortex*, *62*, 158-181.
- Andre-Obadia, N. (2014). Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). *Clinical Neurophysiology*, *125*(11), 2150e206.
- Bakker, N., Shahab, S., Giacobbe, P., Blumberger, D. M., Daskalakis, Z. J., Kennedy, S. H., & Downar, J. (2015). rTMS of the dorsomedial prefrontal cortex for major depression: safety, tolerability, effectiveness, and outcome predictors for 10 Hz versus intermittent theta-burst stimulation. *Brain Stimulation*, *8*(2), 208-215.
- Belmonte, M. K., Allen, G., Beckel-Mitchener, A., Boulanger, L. M., Carper, R. A., & Webb, S. J. (2014). Autism and abnormal development of brain connectivity. *Journal of Neuroendocrinology*, *24*(42), 9228-9231.
- Bharucha, A. E. (2015). Epidemiology, pathophysiology, and classification of fecal incontinence: state of the science summary for the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Workshop. *American Journal of Gastroenterology*, *110*, 127-136.
- Brasil-Neto, J. P., Boechat-Barros, R., & Mota-Silveira, D. A. (2003). The use of slow-frequency transcranial magnetic stimulation in the treatment of depression at Brasília University Hospital: preliminary findings. *Arquivos Neuro-Psiquiatria*, *61*, 83-86.
- Burgell, R. E., & Scott, S. M. (2012). Rectal hyposensitivity. *Journal of Neurogastroenterology and Motility*, *18*, 373-384.
- Carpenter, L. L., Janicak, P. G., Aaronson, S. T., Boyadjis, T., Brock, D. G., Cook, I. A., Dunner, D. L., Lanocha, K., Solvason, H. B., & Demitrack, M. A. (2012). Transcranial magnetic stimulation (TMS) for major depression: a multisite, naturalistic, observational study of acute treatment outcomes in clinical practice. *Depression and Anxiety*, *29*(7), 587-596.
- Carrington, E. V. (2014). A systematic review of sacral nerve stimulation mechanisms in treating fecal incontinence and constipation. *Neurogastroenterology & Motility*, *26*, 1222-1237.
- Chen, K. (2020). Therapeutic effects of the in vitro cultured human gut microbiota as transplants on altering gut microbiota and improving symptoms associated with autism. *Spectrum Disorders Microbiology and Ecology*, *80*(2), 475-486.
- Dedoncker, J., Vervaeet, M., Van Autreve, S., Lemmens, G. M., & Baeken, C. (2016). Accelerated intermittent theta burst stimulation treatment in medication-resistant major depression: A fast road to remission? *Journal of Affective Disorders*, *200*, 6-14.
- Deng, Z. D., Lisanby, S. H., & Peterchev, A. V. (2013). Electric field depth-focality tradeoff in transcranial magnetic stimulation: simulation comparison of 50 coil designs. *Brain Stimulation*, *6*, 1-13.
- Dinan, T. G., & Cryan, J. F. (2017). Brain-gut-microbiota axis - mood, metabolism, and behaviour. *Nature Reviews Gastroenterology & Hepatology*, *14*(2), 69-70.
- Duprat, R. (2021). Repetitive transcranial magnetic stimulation (rTMS) in autism spectrum disorder: protocol for a multicentre randomized controlled clinical trial. *BMJ Open*, *11*, e046830.
- Feng, P., Zhang, Y., Zhao, Y., Zhao, P., & Li, E. (2024). Combined repetitive transcranial magnetic stimulation and gut microbiota modulation through the gut-brain axis for prevention and treatment of autism spectrum disorder. *Frontiers Immunology*, *15*, 134-404.
- George, M. S. (2010). Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. *Archives General Psychiatry*, *67*(5), 507-516.
- Gros, M., Gros, B., Mesonero, J. E., & Latorre, E. (2021). Neurotransmitter dysfunction in irritable bowel syndrome: emerging approaches for management. *Journal Clinical Medicine*, *10*(15), 3429.
- Kang, D. (2017). Microbiota transfer therapy alters gut ecosystem and improves gastrointestinal and autism symptoms: an open-label study. *Microbiome*, *5*(1), 10.
- Köhler, C. A., Maes, M., Slyepchenko, A., Berk, M., Solmi, M., Lanctot, K. L., & Carvalho, A. F. (2016). The gut-brain axis, including the microbiome, leaky gut, and bacterial translocation: Mechanisms and pathophysiological role in Alzheimer's disease. *Current Pharmaceutical Design*, *22*(40), 1-15.
- Kong, X. M. (2019). New and preliminary evidence on altered oral and gut microbiota in individuals with autism spectrum disorder (ASD): Implications for aid diagnosis and subtyping based on microbial biomarkers. *Nutrients*, *11*(9), 21-28.

- Laucheur, J. P. (2014). Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). *Clinical Neurophysiology*, 125(21), 50-206.
- Lembo, A. (2022). Clinical practice guideline on the pharmacological management of irritable bowel syndrome with diarrhea. *Gastroenterology*, 163(1), 137-151.
- Leung, F. W., & Rao, S. S. (2009). Fecal incontinence in the elderly. *Gastroenterology Clinics North America*, 38, 503–511.
- Li, J., Xu, K., & Le, Q. (2022). Case evidence of repetitive transcranial magnetic stimulation in the management of refractory irritable bowel syndrome with comorbid depression. *Brain Stimulation*, 15, 434e436.
- Loh, J. S. (2024). Microbiota–gut–brain axis and its therapeutic applications in neurodegenerative diseases. *Signal Transduction Targeted Therapy*, 9, 37.
- Machado, A., & Haertel, L. M. (2014). Neuroanatomia funcional. São Paulo: Ateneu.
- Martins, H., Molina, B., & Santiago, A. C. (2022). Intestinal microbiota and its relationship with autism: an integrative review. *Concilium*, 22(6), 699–710.
- McGirr, A., Van den Eynde, F., Tovar-Perdomo, S., Fleck, M. P., & Berlim, M. T. (2015). Effectiveness and acceptability of accelerated repetitive transcranial magnetic stimulation (rTMS) for treatment-resistant major depressive disorder: an open label trial. *Journal Affective Disorders*, 173, 216-220.
- Mehta, D. D. (2024). A systematic review and meta-analysis of neuromodulation therapies for substance use disorders. *Neuropsychopharmacology*, 49, 649–680.
- Menees, S. B., Almario, C. V., Spiegel, B. M. R., & Chey, W. D. (2018). Prevalence of and factors associated with fecal incontinence: results from a population-based survey. *Gastroenterology*, 154, 1672–1681.
- Moleski, S. M. (2022). Irritable bowel syndrome (IBS). MSD Manual. Retrieved Oct, 08, 2024, from <https://www.msmanuals.com/pt/profissional/dist%C3%BArbios-gastrointestinais/s%C3%ADndrome-do-intestino-irrit%C3%A1vel-sii/s%C3%ADndrome-do-intestino-irrit%C3%A1vel-sii?ruleredirectid=762>
- Montenegro, M. C., & Cantilino, A. (2016). Transcranial magnetic stimulation: what should the psychiatrist know? *Debates in Psychiatry*, 6(3), 23-36.
- Muhle, R. A., Reed, H. E., Stratigos, K. A., & Veenstra-VanderWeele, J. (2018). The emerging clinical neuroscience of autism spectrum disorder: a review. *JAMA Psychiatry*, 75, 514 –523.
- Niddam, D. M., Lu, C. L., Cheng-Wen, K., & Hsieh, J. C. (2011). Reduced hippocampal glutamate-glutamine levels in irritable bowel syndrome: preliminary findings using magnetic resonance spectroscopy. *Journal Clinical Medicine*, 106(8), 1503e11.
- Oberman, L. M., Enticott, P. G., Casanova, M. F., Rotenberg, A., Pascual-Leone, A., & McCracken, J. T. (2016). TMS in ASD Consensus Group. Transcranial magnetic stimulation in autism spectrum disorder: Challenges, promise, and roadmap for future research. *Autism Research*, 9(2), 184-203.
- Oliveira, A. L., Rocha, K. M., Bastos, M. C., Faria, M. F., & Macêdo, G. B. (2024). Microbiological influences of the gut-brain axis in autism spectrum disorder. *Foco Journal*, 17(6), e5317.
- Pigott, H. E. (2015). The STARD trial: It is time to reexamine the clinical beliefs that guide the treatment of major depression. *Canadian Journal Psychiatry*, 60(1), 9-13.
- Rao, S. S. (2004). Pathophysiology of adult fecal incontinence. *Gastroenterology*, 126, S14–S22.
- Rao, S. S. (2014). Translumbar and transsacral magnetic neurostimulation for the assessment of neuropathy in fecal incontinence. *Diseases Colon Rectum*, 57, 645–652.
- Rao, S. S. (2016). Anorectal disorders. *Gastroenterology*, 150, 1430–1442.
- Ribeiro, L. M. (2011). Influence of individual response to stress and psychiatric comorbidities on irritable bowel syndrome. *Journal of Clinical Psychiatry*, 38(2), 77-83.
- Ribeiro, S. P. (2016). CBT and executive functions in children with TDAH. *Brazilian Journal of Cognitive Therapies*, 12(2), 126-134.
- Rosa, M. A. O. (2013). Transcranial magnetic stimulation in psychiatry: basic guide. São Paulo: Sarvier.
- Saldanha, N. B. (2023). Healthy gut, healthy mind: the science behind the gut-microbiota-brain axis. *Brazilian Journal Health Review*, 65, 25605–25616.
- Satish, S. C. (2021). Effects of translumbosacral neuromodulation therapy on gut and brain interactions and anorectal neuropathy in fecal incontinence: A randomized study. *Technology Neural Interface*, 24(7), 1269-1277.
- Shen, H. H. (2015). Microbes on the mind. *Proceedings National Academy Sciences*, 112(30), 9143–9145.
- Thaha, M. A. (2015). Sacral nerve stimulation for fecal incontinence and constipation in adults. *Cochrane Database Systematic Reviews*, CD004464.
- Tidy, C., & Knott, L. (2021). Childhood disintegrative disorder. Patient info. Retrieved Oct, 12, 2024, from

<https://patient.info/doctor/childhood-disintegrative-disorder-hellers-syndrome>.

- Tribunal de Justiça do Distrito Federal e dos Territórios – TJDF. (2024). Irritable bowel syndrome. Retrieved Oct, 08, 2024, from <https://www.tjdft.jus.br/informacoes/programas-projetos-e-acoos/pro-vida/dicas-de-saude/pilulas-de-saude/sindrome-do-intestino-irritavel>
- Vuong, H. E., & Hsiao, E. Y. (2017). Emerging roles for the gut microbiome in autism spectrum disorder. *Biological Psychiatry*, *81*, 411–423.
- Whitehead, W. E. (2015). Treatment of fecal incontinence: state of the science summary for the National Institute of Diabetes and Digestive and Kidney Diseases workshop. *American Journal Gastroenterology*, *110*(1), 138-146.
- Whitehead, W. E., Engel, B. T., & Schuster, M. M. (1980). Irritable bowel syndrome: physiological and psychological differences between diarrhea-predominant and constipation-predominant patients. *Digestive Diseases Sciences*, *25*, 404–413.
- Xiang, X., Patcharatrakul, T., Sharma, A., Parr, R., Hamdy, S., & Rao, S. S. C. (2019). Cortico-anorectal, spino-anorectal, and cortico-spinal nerve conduction and locus of neuronal injury in patients with fecal incontinence. *Clinical Gastroenterology Hepatology*, *17*, 1130–1137.e2.11.
- Xu, M., Xu, X., Li, J., & Li, F., (2019). Association between gut microbiota and autism spectrum disorder: A systematic review and meta-analysis. *Frontiers Psychiatry*, *10*, 473.
- Zimmer, R. (2024). Transcranial Magnetic Stimulation. Retrieved Oct, 08, 2024, from <https://www.ricardozimmer.com.br/materia/estimulacao-magnetica-transcraniana/>