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Exploring the Gut-Brain Axis: Gut Microbiome Influence on Immune-Mediated Movement Disorders

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ABSTRACT

In recent years, there has been substantial growth in research concerning the gut microbiome, largely due to its recognized role in influencing human physiology and immune function. The microbiome represents a complex ecosystem that interacts with infections, potentially shaping host responses along the gut-brain axis and impacting health outcomes. Imbalances in gut microbiota have been linked to various neurodegenerative diseases, including multiple sclerosis, Guillain-Barré syndrome, and autoimmune encephalitis. This bibliometric study aimed to deepen our understanding of the relationship between gut microbiota and immune-mediated movement disorders, addressing gaps in research knowledge and investigating underlying mechanisms. Through an analysis of research themes, countries, institutions, and publication trends, we utilized the Scopus database and VOSviewer software to conduct a comprehensive examination. Our findings, spanning the years 2015 to 2023, revealed that the United States and Germany were leading contributors to global research in this area. Furthermore, Parkinson's disease emerged as a prominent topic within the context of movement disorders associated with gut microbiota dysbiosis. Overall, this bibliometric analysis highlights the evolving landscape of gut microbiome research, emphasizing the need for continued exploration to inform preventive strategies and enhance infection management worldwide.

Keywords: gut microbiome, immune-mediated movement disorder, movement disorder.

INTRODUCTION

Over decades, research in gut microbiota affecting movement disorders experienced significant expansion due to its implication in shaping human physiology and even immunity. Microbiomes have a tremendous and dynamic ecosystem that engage interaction with infection, modulating host responses to pathogens in the gut-brain axis potentially influencing the outcomes[1][2]. This study was crucial to discerning domains characterized by research lacunae, which necessitated comprehensive investigation into its underlying mechanism. The rise of unhealthy lifestyles in society, coupled with the prevalence of instant food, has led to a decline in the quality of the gut microbiome, which in turn affects human life. This study aims to assess the impact of modern lifestyles on the gut microbiome and identify potential links between gut microbiome composition and the development of movement disorders. By analyzing existing literature, this study hopes to provide a comprehensive understanding of the relationship between the gut microbiome and immune-mediated movement disorders, which can inform future research in this field.

Recent research has revealed a previously neglected role for the gut in neurotransmitter production. Notably, the gut harbors significant quantities of various neurotransmitters, often at levels equal to or exceeding those found in the brain[3]. Furthermore, the gut contributes a greater proportion of total body neurotransmitters compared to the brain. While current data primarily investigates microbial modulation of neurotransmitters within the gut and periphery, it is intriguing to speculate on the potential for remote effects on the brain[4]. This highlights the need for further research to elucidate the mechanisms by which gut bacteria might influence central nervous system function. Simultaneously, imbalanced gut microbiomes manifest into multiple sclerosis, Guillain-Barré syndrome, autoimmune encephalitis and other neurodegenerative

[1] Tim Vanuytsel, Premysl Bercik, and Guy Boeckxstaens, 'Understanding Neuroimmune Interactions in Disorders of Gut–Brain Interaction: From Functional to Immune-Mediated Disorders', *Gut* 72, no. 4 (April 2023): 787–98, https://doi.org/10.1136/gutjnl-2020-320633.

[2] Andrew B. Shreiner, John Y. Kao, and Vincent B. Young, 'The Gut Microbiome in Health and in Disease', *Current Opinion in Gastroenterology* 31, no. 1 (January 2015): 69–75, https://doi.org/10.1097/MOG.0000000000000139.

[3] Timothy R. Sampson and Sarkis K. Mazmanian, 'Control of Brain Development, Function, and Behavior by the Microbiome', *Cell Host & Microbe* 17, no. 5 (May 2015): 565–76, https://doi.org/10.1016/j.chom.2015.04.011.

[4] Yijing Chen, Jinying Xu, and Yu Chen, 'Regulation of Neurotransmitters by the Gut Microbiota and Effects on Cognition in Neurological Disorders', *Nutrients* 13, no. 6 (19 June 2021): 2099, https://doi.org/10.3390/nu13062099.

diseases[5]. The aim of this bibliometric study was to advance further cognizance on the influence of gut microbiomes in relation to immune-mediated movement disorders.

RESEARCH METHODS

We delved into several scopes of discussion, including trends related to research themes, countries, institutions, and years. This study incorporated an array of methods using Scopus database for data collection and VOSviewer software version 1.6.19 for data visualization and analysis. There are 370 documents found from Scopus database, the range of research published in 2015-2023. Keywords used in this research are "gut microbiome", "immune-mediated movement disorder", and "prevalence". Researchers extracted data from the Scopus database, including publication titles, authors, affiliations, keywords, publication years, and citation information. Two visualizations are used in the main panel: The network visualization, and the overlay visualization. In **the network visualization**, items are represented by their label and by default also by a circle, those sizes determined by the weight of the term. The distance between two dotes in the visualization approximately indicates the relatedness of the journals in terms of co-citation links, and their interrelations are depicted, while link thickness denotes the magnitude of co-occurrence between terms. **The overlay visualization** is identical to the network visualization except that items are colored differently. The color determined from the publish year, where by default colors range from blue (lowest score-oldest) to green to yellow (highest score-newest)[6].

Despite the recognized importance of the gut microbiome in influencing susceptibility to infection and immune response to pathogens, research in this area remains limited. This study investigates the disparity between the global concern regarding the gut microbiome and infection, and the actual number of research studies conducted in this field. Specifically, this analysis identified major contributors and current research status and evaluated future development prospects and research trends in this field.

[5] Yan Wang and Lloyd H. Kasper, 'The Role of Microbiome in Central Nervous System Disorders', *Brain, Behavior, and Immunity* 38 (May 2014): 1–12, https://doi.org/10.1016/j.bbi.2013.12.015.

[6] Nees Jan van Eck and Ludo Waltman, 'VOSviewer Manual', 2023.

RESULT AND DISCUSSION

Trend in Publication Output

The bibliometric analysis of publication around 2015 to 2023 included 370 articles. Figure 1 revealed a gradual increase in the number of publications related to gut microbiome and immune-mediated movement disorder. Data analysis of publication trends reveals a growing amount of research on the gut microbiome and its impact on immune-mediated movement disorders. This increase coincides with the rising incidence of immune-mediated movement disorders, underscoring the global attention and need for continuous research updates on disease progression and potential trajectories to mitigate the global burden. The peak of the data is reached in 2023, even though there is a decrease amount of paper insignificantly in 2016 and 2019.

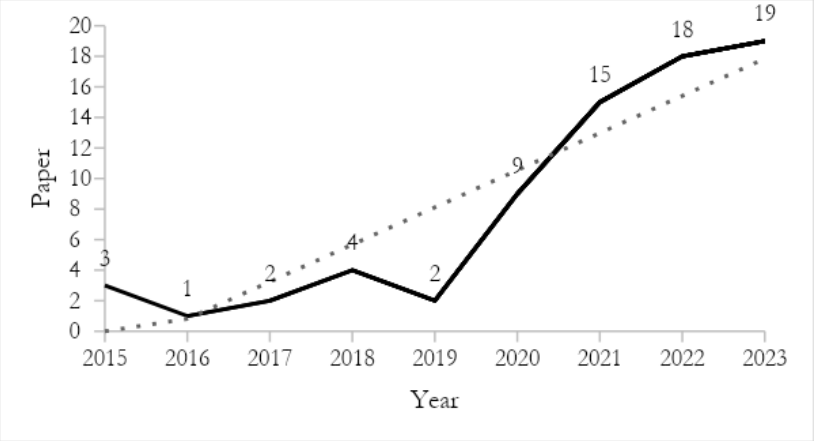

Figure 1: Research trend on assessing the influence of gut microbiome publication trends and impacts in relation to infection and the manifestation of immune-mediated movement disorders in the Scopus database (2015-2023)

Co-Occurrence Analysis Findings

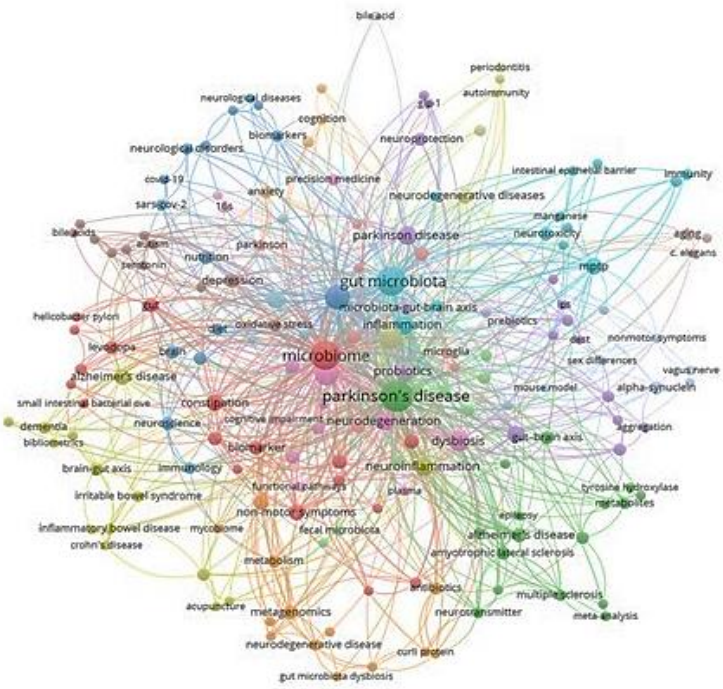

Figure 2: Network visualization result of co-occurrence analysis of gut microbiome publication trends impact in relation to infection and the manifestation of immune-mediated movement disorder.

Figure 2 provided insights into the network of terms and main research themes as key concepts in the field of influence of gut microbiome to infection and manifestation of immune-mediated movement disorder. From the analysis revealed numbers of prominent terms co-occurred in the literature. Those are "gut microbiota", "microbiome", and "Parkinson's disease". One to another these terms interlinked and relevance within the research domain, it proposes terms shown highly linear and have connection during its mechanism. Which believe gut microbiota play main role in immune-mediated movement disorder, one of those is Parkinson's disease[7]. In addition to being one of the factors driving the development of Parkinson's disease, the gut microbiome serves as a biomarker

[7] Jeffrey M. Boertien et al., 'Increasing Comparability and Utility of Gut Microbiome Studies in Parkinson's Disease: A Systematic Review', *Journal of Parkinson's Disease* 9, no. s2 (30 October 2019): S297–312, https://doi.org/10.3233/JPD-191711.

to validate new PD diagnoses[7,8,9]. Other than that, the gut microbiota and their secretory products can modulate the integrity of the blood–brain barrier (BBB). Consequently, BBB dysfunction has been proposed as an early biomarker of neurodegeneration[10].

Besides that, there are sub themes emerging from the analysis, such as "inflammation" and "microbiome-gut brain axis". There is substantial evidence indicating that the gut-brain axis plays a crucial role in neurological diseases. The gut and the brain can communicate through a number of different pathways, including the enteric nervous system, the immune system, the vagus nerve, and microbiota-derived metabolites, such as short-chain fatty acids, bile acids, and branched-chain amino acids[11]. An altered gut microbiota may have significant implications on immune responses in both the gut and distal effector immune sites, such as the central nervous system[12]. The vagus nerve serves as a conduit between the central nervous system (CNS) and the enteric nervous system (ENS), and the manner in which the gut microbiome utilizes it to communicate with the brain has been extensively described elsewhere[131415]. In brief, gut microbes can produce metabolites and neuroactive molecules such as gamma-aminobutyric acid (GABA), serotonin, dopamine, and acetylcholine, which send signals

[8] Arun T Nair et al., 'Gut Microbiota Dysfunction as Reliable Non-Invasive Early Diagnostic Biomarkers in the Pathophysiology of Parkinson's Disease: A Critical Review', *Journal of Neurogastroenterology and Motility* 24, no. 1 (30 January 2018): 30–42, https://doi.org/10.5056/jnm17105.

[9] Angelica Varesi et al., 'The Interplay between Gut Microbiota and Parkinson's Disease: Implications on Diagnosis and Treatment', *International Journal of Molecular Sciences* 23, no. 20 (14 October 2022): 12289, https://doi.org/10.3390/ijms232012289.

[10] João André Sousa et al., "Reconsidering the Role of Blood-Brain Barrier in Alzheimer's Disease: From Delivery to Target," *Frontiers in Aging Neuroscience* 15 (February 16, 2023), https://doi.org/10.3389/fnagi.2023.1102809.

[11] Millicent N. Ekwudo, Carolina Gubert, and Anthony J. Hannan, "The Microbiota–Gut–Brain Axis in Huntington's Disease: Pathogenic Mechanisms and Therapeutic Targets," *The FEBS Journal*, March 2024, https://doi.org/10.1111/febs.17102.

[12] Benedetta Parodi and Nicole Kerlero de Rosbo, 'The Gut-Brain Axis in Multiple Sclerosis. Is Its Dysfunction a Pathological Trigger or a Consequence of the Disease?', *Frontiers in Immunology* 12 (21 September 2021), https://doi.org/10.3389/fimmu.2021.718220.

[13] Sigrid Breit et al., "Vagus Nerve as Modulator of the Brain–Gut Axis in Psychiatric and Inflammatory Disorders," *Frontiers in Psychiatry* 9 (March 13, 2018), https://doi.org/10.3389/fpsyt.2018.00044.

[14] Ekwudo, Millicent N., Carolina Gubert, and Anthony J. Hannan. "The Microbiota–Gut–Brain Axis in Huntington's Disease: Pathogenic Mechanisms and Therapeutic Targets." *The FEBS Journal*, March 2024. https://doi.org/10.1111/febs.17102.

[15] Fülling, Christine, Timothy G. Dinan, and John F. Cryan. "Gut Microbe to Brain Signaling: What Happens in Vagus…." *Neuron* 101, no. 6 (March 2019): 998–1002. https://doi.org/10.1016/j.neuron.2019.02.008.

between the afferent neurons in the ENS and the brain via the vagus nerve[16]. A study on experimental autoimmune encephalomyelitis mice revealed that the gut microbiota has a significant impact on the balance between pro- and anti-inflammatory immune responses[17]. Other than that, A classical signaling pathway exists between the central nervous system, gut, and microbiome that regulates satiety. Changes in dietary patterns, controlled by the central nervous system, can affect the availability of nutrients to gut microbiota and, as a result, impact their composition[18]. Unhealthy food intake and lack of hygiene can affect the regulation of the gut-brain axis through inflammatory activity. Therefore, "inflammation" is an important contributor in the co-occurrence visualization.

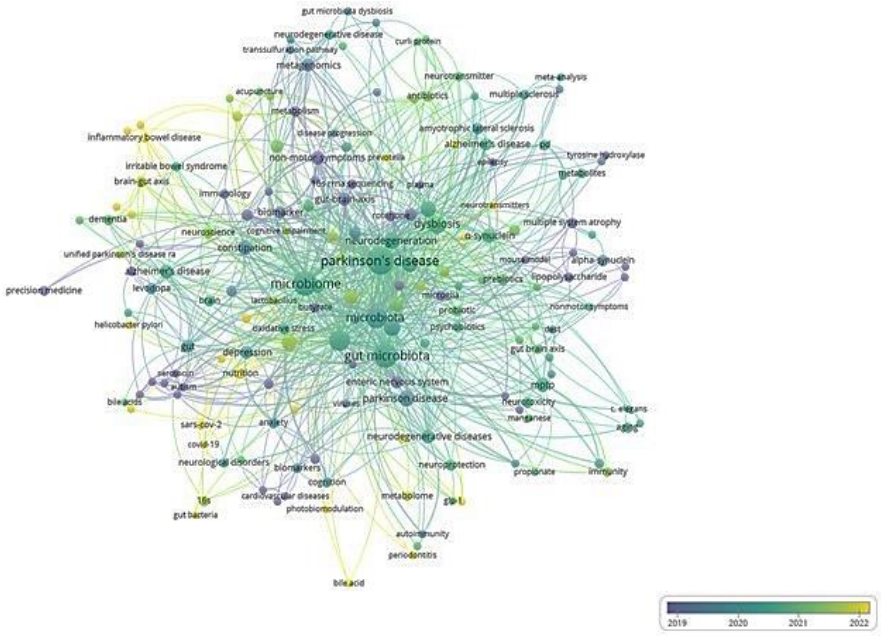

Figure 3: Overlay visualization result of co-occurrence analysis of gut microbiome publication trends impact in relation to infection and the manifestation of immune-mediated movement disorder.

The theory that the gut microbiota-brain axis is a focus of global research is underscored by the strong co-occurrence of these terms. While Parkinson's

[16] Galland, Leo. "The Gut Microbiome and the Brain." *Journal of Medicinal Food* 17, no. 12 (December 2014): 1261–72. https://doi.org/10.1089/jmf.2014.7000.

[17] Qian Gao et al., 'Bibliometric Analysis of Global Research Trends on Regulatory T Cells in Neurological Diseases', *Frontiers in Neurology* 14 (12 October 2023), https://doi.org/10.3389/fneur.2023.1284501.

[18] Wang and Kasper, 'The Role of Microbiome in Central Nervous System Disorders'.

disease has dominated research gaps over the past decade, recent trends indicated by yellow nodes suggest a shift toward topics such as inflammatory bowel disease, the brain-gut axis, and COVID-19, which may be influenced by disease developments between 2019 and 2020. In particular, the prominence of "IBS" (irritable bowel syndrome) in Figure 3 suggests a potential link between gut microbiome imbalances and immune-mediated movement disorders. A study states that the most dominant bacterial phyla in the gut microbiota are Bacteroides and Firmicutes. Their abundance can be inversely altered in disease states, so the ratio of these phyla has been proposed as a biomarker of gut health and stability and correlates with several diseases, including obesity and inflammatory bowel syndrome[19][20].

Contributing Country

The bibliometric analysis also examines prominent countries that are actively contributing to the advancement of literature in the field, as evidenced by the overall link strength to other documents. This suggests that their ongoing research efforts are contributing significantly to the advancement of the field. Table 1 shows the top ten countries among all nations that are contributing in this field of research and the corresponding number of publications.

Table 1: Top ten countries publishing papers on assessing the influence of gut microbiome publication trends and impact in relation to infection and the manifestation of immune-mediated movement disorders in the Scopus database (2015-2023)

No	Country	Documents	Citations	Total Link Strength
1	United States	126	9124	68
2	China	106	3224	25
3	China	34	2510	42
4	United Kingdom	24	916	14
5	United Kingdom	20	606	25
6	Canada	17	476	13
7	Netherlands	15	1981	20

[19] Stojanov, Spase, Aleš Berlec, and Borut Štrukelj. "The Influence of Probiotics on the Firmicutes/Bacteroidetes Ratio in the Treatment of Obesity and Inflammatory Bowel Disease." *Microorganisms* 8, no. 11 (November 1, 2020): 1715. https://doi.org/10.3390/microorganisms8111715.

[20] Magne, Fabien, Martin Gotteland, Lea Gauthier, Alejandra Zazueta, Susana Pesoa, Paola Navarrete, and Ramadass Balamurugan. "The Firmicutes/Bacteroidetes Ratio: A Relevant Marker of Gut Dysbiosis in Obese Patients?" *Nutrients* 12, no. 5 (May 19, 2020): 1474. https://doi.org/10.3390/nu12051474.

8	Japan	15	533	5
9	Australia	14	229	7
10	Taiwan	13	500	4

The results of the analysis highlight countries that are actively expanding knowledge and research in this field. It is expected that the participation of these developed countries will contribute significantly to the advancement of understanding in this area, with their strong research support and resources.

The data show that the United States leads with the highest number of research publications, followed by China, reflecting that Asian countries can also lead global research advances. In the United States, the prevalence of immune-mediated movement disorders is linear. Autoimmune encephalitis alone is estimated to affect 20,000 people per year[21]. Besides, the analysis also presents how many times each document cited, co-cited references reflect the historical development and roots of the field, while references with citation bursts reveal the emerging hotspots within it. Through the combination of keyword and citation analyses, we have identified the current research hotspots and trends.

Notably, these findings indicate a growing global focus on the gut microbiome and infections as they manifest in immune-mediated movement disorders. It is hoped that this will lead not only to further research, but also to the development of various management and mitigation strategies for this complex issue.

CONCLUSION

Through VOSviewer this bibliometric analysis underscores the waning attention and research focus on gut microbiome publication trends and impact in relation to infection and the manifestation of immune-mediated movement disorders. It underscores the value of consistent research to gain insights, formulate preventive measures, and enhance infection management on a global scale. In its development, this writing still needs to be expanded in terms of sources as it currently relies solely on English-language literature and explanations in the form of descriptions and elaborations of data generated by the generator. In the future, it is hoped that there will be more real research that can provide data related to this topic in the field.

[21] Alberto Cucca, Hamzeh A. Migdadi, and Alessandro Di Rocco, 'Infection-Mediated Autoimmune Movement Disorders', *Parkinsonism & Related Disorders* 46 (January 2018): S83–86, https://doi.org/10.1016/j.parkreldis.2017.07.019.

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