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Editorial

The Gut-Liver-Brain Axis: From the Head to the Feet

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The gut-liver-brain axis, a multifaceted network of communication, intricately connects the enteric, hepatic, and central nervous systems [1,2]. One crucial aspect of this complex interaction is the impact of the brain on the functions of the intestines and liver, specifically in relation to the modulation of immune cell activities [3]. On the other hand, the gastrointestinal tract and liver have substantial impacts on cognitive function and overall mental health, primarily by influencing the composition of microbiota and regulating innate immune responses [2].

Most of the initial studies on the gut-liver-brain axis were focused on understating its potential role in functional gastrointestinal disorders (such as irritable bowel syndrome), given the neuroemotional stress that function as a trigger for such disorders [4–15]. However, more recent studies have investigated the potential role of the gut-liver-brain axis in other gastrointestinal disorders such as celiac disease or inflammatory bowel disease [16,17]. An imbalance or disruption in the gut-liver-brain axis has also been linked to several neurological conditions, including hepatic encephalopathy, delirium, autism, attention deficit hyperactivity disorder, depression, Alzheimer's and Parkinsons's disease [18–25]. However, the exact mechanisms behind this connection remain mostly elusive, but researchers propose links to the within-host evolution of gut microbiota, metabolic dysfunctions, and systemic inflammation caused by gut dysbiosis.

This Special Issue has cast its net wide, encompassing a spectrum of topics from foundational biological sciences to the avant-garde realms of machine learning and artificial intelligence applied to gut microbiota research [23]. In particular, venturing into the domain of neurodegenerative diseases, it was explored how colon inflammation may be linked to neuroinflammation and neurodegeneration, or how the gut microbiota has a role in safeguarding cognitive prowess, facilitated through the parasympathetic nervous system.

In light of these significant findings and considerations, we express our profound gratitude and are deeply honored to have spearheaded this Special Issue. Our heartfelt appreciation extends to all contributing authors for entrusting their groundbreaking research to the International Journal of Medical Sciences.

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List of Contributions

1. Campisciano, G.; Zanotta, N.; Quadrifoglio, M.; Careri, A.; Torresani, A.; Cason, C.; De Seta, F.; Ricci, G.; Comar, M.; Stampalija, T. The Bacterial DNA Profiling of Chorionic Villi and Amniotic Fluids Reveals Overlaps with Maternal Oral, Vaginal, and Gut Microbiomes. *Int. J. Mol. Sci.* **2023**, *24*, 2873. https://doi.org/10.3390/ijms24032873.
2. Carrascal, L.; Vázquez-Carretero, M.D.; García-Miranda, P.; Fontán-Lozano, Á.; Calonge, M.L.; Ilundáin, A.A.; Castro, C.; Nunez-Abades, P.; Peral, M.J. Acute Colon Inflammation Triggers Primary Motor Cortex Glial Activation, Neuroinflammation, Neuronal Hyperexcitability, and Motor Coordination Deficits. *Int. J. Mol. Sci.* **2022**, *23*, 5347. https://doi.org/10.3390/ijms23105347.
3. Park, S.; Wu, X. Modulation of the Gut Microbiota in Memory Impairment and Alzheimer's Disease via the Inhibition of the Parasympathetic Nervous System. *Int. J. Mol. Sci.* **2022**, *23*, 13574. https://doi.org/10.3390/ijms232113574.
4. Ferri, C.; Castellazzi, M.; Merli, N.; Laudisi, M.; Baldin, E.; Baldi, E.; Mancabelli, L.; Ventura, M.; Pugliatti, M. Gut Microbiota Changes during Dimethyl Fumarate Treatment in Patients with Multiple Sclerosis. *Int. J. Mol. Sci.* **2023**, *24*, 2720. https://doi.org/10.3390/ijms24032720.
5. Giuffrè, M.; Gazzin, S.; Zoratti, C.; Llido, J.P.; Lanza, G.; Tiribelli, C.; Moretti, R. Celiac Disease and Neurological Manifestations: From Gluten to Neuroinflammation. *Int. J. Mol. Sci.* **2022**, *23*, 15564. https://doi.org/10.3390/ijms232415564.
6. Giuffrè, M.; Moretti, R.; Tiribelli, C. Gut Microbes Meet Machine Learning: The Next Step towards Advancing Our Understanding of the Gut Microbiome in Health and Disease. *Int. J. Mol. Sci.* **2023**, *24*, 5229. https://doi.org/10.3390/ijms24065229.

References

1. Giuffrè, M.; Campigotto, M.; Campisciano, G.; Comar, M.; Crocè, L.S. A story of liver and gut microbes: How does the intestinal flora affect liver disease? A review of the literature. *Am. J. Physiol. Liver Physiol.* **2020**, *318*, G889–G906. [CrossRef]
2. Giuffrè, M.; Moretti, R.; Campisciano, G.; da Silveira, A.B.M.; Monda, V.M.; Comar, M.; Di Bella, S.; Antonello, R.M.; Luzzati, R.; Crocè, L.S. You Talking to Me? Says the Enteric Nervous System (ENS) to the Microbe. How Intestinal Microbes Interact with the ENS. *J. Clin. Med.* **2020**, *9*, 3705. [CrossRef] [PubMed]
3. Teratani, T.; Mikami, Y.; Nakamoto, N.; Suzuki, T.; Harada, Y.; Okabayashi, K.; Hagihara, Y.; Taniki, N.; Kohno, K.; Shibata, S.; et al. The liver-brain-gut neural arc maintains the T_{reg} cell niche in the gut. *Nature* **2020**, *585*, 591–596. [CrossRef] [PubMed]
4. Simrén, M.; Törnblom, H.; Palsson, O.S.; Van Oudenhove, L.; Whitehead, W.E.; Tack, J. Cumulative Effects of Psychologic Distress, Visceral Hypersensitivity, and Abnormal Transit on Patient-reported Outcomes in Irritable Bowel Syndrome. *Gastroenterology* **2019**, *157*, 391–402.e2. [CrossRef] [PubMed]
5. Moayyedi, P. Faecal microbiota transplantation for IBS: Still a long way to go. *Lancet Gastroenterol Hepatol.* **2019**, *4*, 656–657. [CrossRef]
6. Xu, D.; Chen, V.L.; Steiner, C.A.; Berinstein, J.A.; Eswaran, S.; Waljee, A.K.; Higgins, P.D.R.; Owyang, C. Efficacy of Fecal Microbiota Transplantation in Irritable Bowel Syndrome: A Systematic Review and Meta-Analysis. *Am. J. Gastroenterol.* **2019**, *114*, 1043–1050. [CrossRef]
7. Cremon, C.; Barbaro, M.R.; Ventura, M.; Barbara, G. Pre- and probiotic overview. *Curr. Opin. Pharmacol.* **2018**, *43*, 87–92. [CrossRef]
8. Francavilla, R.; Piccolo, M.; Francavilla, A.; Polimeno, L.; Semeraro, F.; Cristofori, F.; Castellaneta, S.; Barone, M.; Indrio, F.; Gobbetti, M.; et al. Clinical and Microbiological Effect of a Multispecies Probiotic Supplementation in Celiac Patients With Persistent IBS-type Symptoms: A Randomized, Double-Blind, Placebo-controlled, Multicenter Trial. *J. Clin. Gastroenterol.* **2019**, *53*, e117–e125. [CrossRef]
9. Ray, K. IBS: Mindful of probiotics for psychiatric comorbidities in IBS. *Nat. Rev. Gastroenterol. Hepatol.* **2017**, *14*, 386–387. [CrossRef]
10. Simrén, M.; Barbara, G.; Flint, H.J.; Spiegel, B.M.; Spiller, R.C.; Vanner, S.; Verdu, E.F.; Whorwell, P.J.; Zoetendal, E.G. Rome Foundation Committee. Intestinal microbiota in functional bowel disorders: A Rome foundation report. *Gut* **2013**, *62*, 159–176. [CrossRef]
11. Laird, K.T.; Tanner-Smith, E.E.; Russell, A.C.; Hollon, S.D.; Walker, L.S. Comparative efficacy of psychological therapies for improving mental health and daily functioning in irritable bowel syndrome: A systematic review and meta-analysis. *Clin. Psychol. Rev.* **2017**, *51*, 142–152. [CrossRef]
12. Dickson, I. Remotely delivered cognitive behavioural therapy superior to treatment as usual for IBS. *Nat. Rev. Gastroenterol. Hepatol.* **2019**, *16*, 326. [CrossRef] [PubMed]

13. Lackner, J.M.; Jaccard, J. Cognitive-behavioural therapy for IBS comes home: Mapping a route for efficacy and efficiency in the digital age. *Gut* **2019**, *68*, 1541–1542. [CrossRef] [PubMed]
14. Ma, X.P.; Hong, J.; An, C.P.; Zhang, D.; Huang, Y.; Wu, H.G.; Zhang, C.H.; Meeuwsen, S. Acupuncture-moxibustion in treating irritable bowel syndrome: How does it work? *World J. Gastroenterol.* **2014**, *20*, 6044–6054. [CrossRef] [PubMed]
15. Kennedy, P.J.; Cryan, J.F.; Dinan, T.G.; Clarke, G. Irritable bowel syndrome: A microbiome-gut-brain axis disorder? *World J. Gastroenterol.* **2014**, *20*, 14105–14125. [CrossRef]
16. Ding, J.H.; Jin, Z.; Yang, X.X.; Lou, J.; Shan, W.X.; Hu, Y.X.; Du, Q.; Liao, Q.S.; Xie, R.; Xu, J.Y. Role of gut microbiota via the gut-liver-brain axis in digestive diseases. *World J. Gastroenterol.* **2020**, *26*, 6141–6162. [CrossRef] [PubMed]
17. Giuffrè, M.; Gazzin, S.; Zoratti, C.; Llido, J.P.; Lanza, G.; Tiribelli, C.; Moretti, R. Celiac Disease and Neurological Manifestations: From Gluten to Neuroinflammation. *Int. J. Mol. Sci.* **2022**, *23*, 15564. [CrossRef]
18. Hildenbrand, F.F.; Murray, F.R.; von Känel, R.; Deibel, A.R.; Schreiner, P.; Ernst, J.; Zipser, C.M.; Böettger, S. Predisposing and precipitating risk factors for delirium in gastroenterology and hepatology: Subgroup analysis of 718 patients from a hospital-wide prospective cohort study. *Front. Med.* **2022**, *9*, 1004407. [CrossRef]
19. Wang, L.; Xie, Z.; Li, G.; Li, G.; Liang, J. Two-sample Mendelian randomization analysis investigates causal associations between gut microbiota and attention deficit hyperactivity disorder. *Front. Microbiol.* **2023**, *14*, 1144851. [CrossRef]
20. Nguyen, H.H.; Swain, M.G. Avenues within the gut-liver-brain axis linking chronic liver disease and symptoms. *Front. Neurosci.* **2023**, *17*, 1171253. [CrossRef]
21. Shi, K.; Li, L.; Wang, Z.; Chen, H.; Chen, Z.; Fang, S. Identifying microbe-disease association based on graph convolutional attention network: Case study of liver cirrhosis and epilepsy. *Front. Neurosci.* **2023**, *16*, 1124315. [CrossRef]
22. Kowalski, K.; Mulak, A. Brain-Gut-Microbiota Axis in Alzheimer's Disease. *J. Neurogastroenterol. Motil.* **2019**, *25*, 48–60. [CrossRef] [PubMed]
23. Suganya, K.; Koo, B.S. Gut-Brain Axis: Role of Gut Microbiota on Neurological Disorders and How Probiotics/Prebiotics Beneficially Modulate Microbial and Immune Pathways to Improve Brain Functions. *Int. J. Mol. Sci.* **2020**, *21*, 7551. [CrossRef] [PubMed]
24. Vakili, K.; Fathi, M.; Yaghoobpoor, S.; Sayehmiri, F.; Nazerian, Y.; Nazerian, A.; Mohamadkhani, A.; Khodabakhsh, P.; Réus, G.Z.; Hajibeygi, R.; et al. The contribution of gut-brain axis to development of neurological symptoms in COVID-19 recovered patients: A hypothesis and review of literature. *Front. Cell. Infect. Microbiol.* **2022**, *12*, 983089. [CrossRef] [PubMed]
25. Giuffrè, M.; Moretti, R.; Tiribelli, C. Gut Microbes Meet Machine Learning: The Next Step towards Advancing Our Understanding of the Gut Microbiome in Health and Disease. *Int. J. Mol. Sci.* **2023**, *24*, 5229. [CrossRef]

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