Am J Transl Res 2024;16(10):6029-6040
www.ajtr.org /ISSN:1943-8141/AJTR0158586

Original Article

Evidence linking gut-brain axis and Crohn's disease, focusing on neurotrophic dysfunctions and radiological imaging analysis - a systematic review

Julian Furtado Silva, William Moraes de Souza, Juliana Delgado Campos Mello, Hugo Dugolin Ceccato, Priscilla de Sene Portel Oliveira, Maria de Lourdes Setsuko Ayrizono, Raquel Franco Leal

Inflammatory Bowel Disease Research Laboratory, Gastrocenter, Colorectal Surgery Unit, School of Medical Sciences, University of Campinas (UNICAMP), Campinas, São Paulo, Brazil

Received June 20, 2024; Accepted September 22, 2024; Epub October 15, 2024; Published October 30, 2024

Abstract: Objective: To conduct a systematic review (SR) to find evidence for a connection between Crohn's disease (CD) and the gut-brain axis (GBA). Methods: This study conducted a systematic review (SR) employing a search strategy and strict inclusion criteria. It was conducted by searching for studies published between 2017 and 2024 in the following databases: PUBMED, PUBMED PMC, BVS-BIREME, SCOPUS, WEB OF SCIENCE, EMBASE, and COCHRANE. Results: Fifty original research articles were included. Among these, 20 studies addressed neuroimaging methods to evaluate CD patients' functional or structural brain changes. Neurodegenerative diseases were the second most addressed topic in the studies, with 18 articles related to different diseases such as Parkinson's disease, Alzheimer's disease, dementia, Amyotrophic Lateral Sclerosis, Multiple Sclerosis, and Multiple System Atrophy. Eight articles addressed sleep disorders related to CD; two explored Electroencephalography changes; one investigated Brain-Derived Neurotrophic Factor serum levels and one correlated vagotomy with CD. Conclusion: Interest in the link between CD and GBA is increasing, but studies remain varied and inconclusive, spanning from epidemiology to brain imaging and neglecting to investigate a mechanistic relationship. This SR underscores the need for further research to better understand the potential role of GBA in the prognosis and etiology of CD, highlighting its complexity.

Keywords: Brain-gut axis, gut-brain axis, Crohn's disease

Introduction

Inflammatory Bowel Disease (IBD) is a term that comprises a group of chronic, idiopathic inflammatory diseases affecting the gastrointestinal tract (GIT), primarily represented by Crohn's Disease (CD), Ulcerative Colitis (UC), and Indeterminate Colitis (IC). In CD, we observe transmural inflammation, which can affect the entire gastrointestinal tract, from the mouth to the anus. This multifaceted condition is believed to arise from genetic predisposition, environmental factors, and changes in the intestinal microbiota. This combination leads to dysregulation of innate and adaptive immune responses, resulting in mucosal damage and impairment of epithelial barrier function [1].

Recent findings indicate that the Gut-Brain Axis (GBA) could substantially influence the pathophysiology and presentation of CD. The GBA represents a sophisticated bidirectional communication network that enables interaction between intestinal stimuli-like immune responses and metabolites from the gut microbiota. It also regulates intestinal motor and secretory functions in conjunction with the central nervous system (CNS) [2, 3].

The GBA's functioning is not yet fully understood, particularly regarding its interaction with the intestinal microbiota and immune responses. Nonetheless, the interest in the relationship between the GBA and CD is reflected in the wide variety of topics addressed in the literature. These studies encompass a range of neurological alterations or diseases, such as Parkinson's disease (PD), Alzheimer's disease (AD), sleep disorders, and the evaluation of neuroanatomical changes in CD patients [4-7].

https://doi.org/10.62347/OWYY4960

The GBA, or Microbiota-Gut-Brain Axis, includes the CNS - comprising the brain and spinal cord, the autonomic nervous system (ANS), the enteric nervous system (ENS), and the hypothalamic-pituitary-adrenal (HPA) axis [2]. It plays a crucial role in regulating various intestinal functions, such as motility, hormone secretion, and control of intestinal permeability, as well as in regulating brain functions, such as behavior, sleep regulation, and stress response [8]. The ENS regulates intestinal functions such as muscle contraction to propel food, fluid secretion, and nutrient absorption. It also sends signals to the brain about the state of the gut, including the presence of food, bacteria, or inflammatory signals. The vagus nerve is a significant communication pathway between the gut and the brain. It transmits sensory signals from the gut to the brain and motor signals from the brain to the gut. These signals can influence intestinal motility, hormone and neurotransmitter secretion, and even pain perception [2, 8, 9].

The intestinal microbiota communicates with the CNS through their products, such as short-chain fatty acids, secondary bile acids, and tryptophan metabolites [10, 11]. While some of these metabolites interact directly with enteroendocrine cells, enterochromaffin cells, and the immune system present in the intestinal mucosa and mucus to transmit ascending signals, others can cross the intestinal barrier and enter the systemic circulation, possibly reaching the blood-brain barrier (BBB) [11, 12]. Another possibility is that microbial signals communicate through neural pathways involving vagal and spinal afferents [13]. However, whether these metabolites directly reach specific brain regions in concentrations sufficient to affect particular brain circuits remains unclear.

The HPA axis plays an important role in human cognitive function. It is one of the main neuroendocrine systems that respond to stress by producing glucocorticoids such as cortisol. Adequate cortisol concentrations are essential for neurodevelopment and cognitive processes such as learning and memory. Evidence suggests that the stress response can impact the GBA throughj the HPA axis [14].

There is a growing interest in the literature in intestinal events' influence on the CNS's functioning. The GBA, in particular, plays a vital role in the link between gastrointestinal and neurological diseases. Evidence suggests the influence of CD on neurological alterations or diseases, just as various neurological events are associated with alterations in the gastrointestinal ecosystem [15]. The ENS, a key player in intestinal immunity and inflammatory response, can have significant bidirectional consequences for the intestine and the CNS. Its dysfunction can lead to visceral hypersensitivity and chronic pain, which are common symptoms in CD [16, 17]. Furthermore, neuroimmune interactions within the intestine during disease activity can mediate heightened intestinal permeability, resulting in elevated systemic levels of inflammatory factors. The dysbiosis, increased intestinal permeability, and translocation of bacteria and their metabolites in CD are being studied and recognized as important factors contributing to structural and functional alterations in the CNS [15]. This underscores the urgency and importance of our research, as chronic intestinal inflammation is associated with peripheral changes that disrupt CNS homeostasis, making it a focus of research on neurological disorders such as sleep disorders and neurodegenerative diseases. The focus of this SR was to gather evidence of the interaction between the GBA and CD.

Materials and methods

Study design

This is a systematic literature review. It was conducted by gathering all literature data that meet the eligibility criteria and by answering the question about the "Evidence of interaction between Crohn's Disease and the Gut-Brain Axis".

Strategies for method development

The study was constructed based on the recommendations in the "Preferred Reporting Items for SRs and Meta-Analyses (PRISMA)" of 2015 [18]. The PICO methodology was used to frame the research question to be answered, which stands for: P: Population; I: Interventions; C: Comparators; O: Outcome (**Table 1**).

Inclusion criteria

The following criteria were adopted for the inclusion of studies in this Systematic Review:

Table 1. Development of the systematic review's guiding question using the PICO methodology

Population	Patients with Crohn's disease
Interventions	Studies illustrating cohorts of patients with Crohn's disease exhibiting signs or neurological disorders
Comparators	Studies involving patients without Crohn's disease presenting signs or neurological disorders
Outcomes	Association or lack of association between Crohn's disease and signs or neurological disorders

1. Studies published in the literature from January 2017 to March 2024. 2. Studies on humans: (1) Population with IBD; (2) Adults (over 18 years old). 3. Studies analyzing signs, disorders, and neurological diseases in the presence of a CD diagnosis. 4. Observational studies (case-control, cohort, and cross-sectional). 5. Intervention studies (randomized clinical trials).

Systematic review strategy

This study was conducted as a SR, examining all relevant empirical evidence that met specific inclusion criteria. The primary aim was to investigate a specific question: "Evidence of interaction between Crohn's Disease and the Gut-Brain Axis". The process included the following key steps: formulating the research question, selecting appropriate databases for comprehensive exploration, defining the search timeframe, developing detailed search terms, systematically conducting searches across the selected databases, applying predefined inclusion and exclusion criteria, extracting pertinent data, selecting relevant studies, evaluating the quality and relevance of each study, and applying exclusion criteria as necessary.

On November 22, 2022, a search was conducted in the PROSPERO database to identify existing SRs on the topic of interest. PROSPERO is an international public database of SR protocols maintained by the Centre of Reviews and Dissemination at the University of York and funded by the National Institute for Health Research (NIHR). No records of SRs with the same focus as the current study were found. Consequently, the present study was registered in the PROSPERO system.

Selection of studies for comprehensive analysis

The free software Rayyan (Qatar Computing Research Institute - QCRI) was used for archiving, organizing, and selecting articles [19]. The selection of published articles was conducted in two stages. In the first stage, reviewers JFS and WMS independently assessed the titles and abstracts of the articles for inclusion or exclusion, with a third reviewer (JDCM) resolving conflicts. In the second stage, the same two reviewers independently assessed the full text of selected articles, with the third reviewer resolving conflicts as before.

Results

The search was conducted across seven databases for articles published between 2017 and 2024, with the final search conducted on March 8, 2024. A total of 4,513 studies were identified, and after excluding duplicates, 3,487 articles remained for analysis. The first phase of article analysis began with reading abstracts, selecting 253 studies for the second stage, which involved full-text reading. Following eligibility criteria, 50 articles were included in the SR (**Figure 1**).

Of the 50 reviewed articles, 26 investigated various neurological disorders such as sleep disorders or neurodegenerative diseases like PD, AD, Dementia, Amyotrophic Lateral Sclerosis (ALS), Multiple Sclerosis (MS), and Multiple System Atrophy (MSA). Twenty-three articles examined the gut-brain interaction in CD through different methods, including neuroimaging analysis (20 articles), electroencephalogram (EEG) studies (2 articles), and one study on the serum level of Brain-derived neurotrophic factor (BDNF) in CD patients. Additionally, one study on vagotomy in CD patients was included. The studies exhibited considerable heterogeneity, even when addressing the same topic, resulting in occasionally conflicting findings. **Tables 2**-**4** show the studies and topics covered. Detailed results of the included studies can be found in Supplementary Tables 1, 2, 3. **Figure 2** illustrates the methods used in the literature for functional or structural brain analysis in CD patients and neurological diseases.

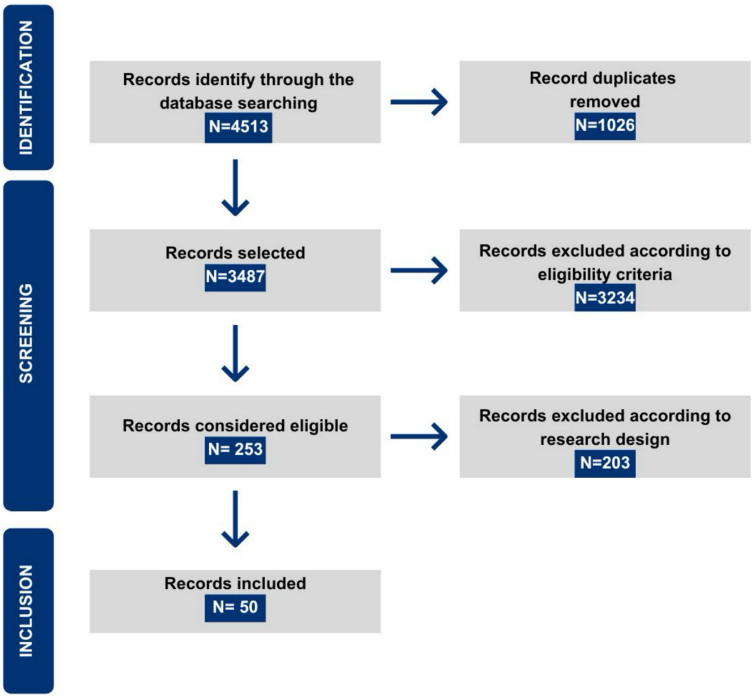

Figure 1. Diagram illustrating the inclusion of articles in the systematic review.

Discussion

Studies that deal with neurological disorders

Neurodegenerative diseases: While the association between PD and CD was particularly emphasized, the methods and outcomes varied considerably across studies. Among the 50 selected articles, 18 investigated the association between CD and neurodegenerative diseases. Of these, ten focused on PD, two on multiple types of dementia, one on AD, one on ALS, two on MS, and one on MSA.

Parkinson's disease and Crohn's disease: PD is recognized as the most prevalent neurodegenerative motor disorder globally. Emerging evidence suggests a potential link between PD and chronic low-level intestinal inflammation, which may trigger the aggregation of abnormal alpha-synuclein, an essential protein for PD pathogenesis. This protein could spread to the brain through the vagus nerve or breach the blood-brain barrier, whose permeability can be influenced by chronic intestinal inflammation [68, 69]. This association has sparked interest in further exploring the potential link between these two diseases.

Five articles in the SR on PD explored data from electronic medical record analysis. Camacho-Soto et al. [32] showed that PD was inversely associated with CD. On the other hand, Park et al. [37] demonstrated that CD patients have a 2.2 times higher chance of developing PD, with corticosteroid treatment being a protective factor in these cases. Likewise, Weimers [44] observed that patients with CD had a 30% higher overall risk of PD when compared to healthy patients. However, Loosen et al. [36] and Wang et al. [38] did not find a significant correlation between the diseases.

It is important to note that in the study by Camacho-Soto and Loosen, there was control for access and frequency of medical visits, which may explain why there was a contrasting result compared to other studies. This is because greater access to healthcare services can lead to surveillance bias, as there is a higher chance of diagnosis if the patient visits healthcare services more frequently. When Weimers [39] adjusted the analysis for the number of medical visits, the increased risk of PD in patients with CD disappeared, which confirms Loosen's findings.

Freuer et al. [33] and Witoelar et al. [40] evaluated the association between PD and CD using GWAS to assess overlapping genes related to both diseases. While the former, focusing on causality analysis, did not show a significant causal association between PD and CD, the latter found genetic overlap, albeit associated with shared susceptibility gene loci.

Other studies on PD have explored the field of genetics, such as Hui et al. [34] and Kang et al. [35]. The former study found an association between the LRRK2 gene and genetic effects similar in PD and CD through exome sequencing. In the latter, shared genetic variants were identified in both diseases, which may indicate a possible common genetic basis between

Table 2. Studies about neurological disorders (neurodegenerative diseases and sleep disorders)

Neurological disorder	Author/Year
Multiple System Atrophy	Shadrin et al. 2021 [20]
Dementias	Sand et al. 2022 [21], Zingel et al. 2021 [22]
Sleep disorders	Bar-Gil Shitrit et al. 2018 [23], Chen et al. 2021 [24], Chrobak et al. 2018 [25], Georgiana-Emmanuela et al. 2020 [26], Hastaliklari et al. 2019 [27], Iskandar et al. 2020 [28], Kyle Hoffman et al. 2022 [29], Sofia et al. 2020 [30]
Alzheimer's Disease	Aggarwal et al. 2020 [31]
Parkinson's Disease	Camacho-Soto et al. 2018 [32], Freuer et al. 2022 [33], Hui et al. 2018 [34], Kang et al. 2022 [35], Loosen et al. 2023 [36], Park et al. 2019 [37], Wang et al. 2024 [38], Weimers et al. 2019 [39], Witoelar et al. 2017 [40], Zheng et al. 2022 [41]
Neurodegenerative Diseases	Li et al. 2022 [42]
Amyotrophic Lateral Sclerosis	Li et al. 2021 [43]
Multiple Sclerosis	Sonnenberg et al. 2023 [44]

Table 3. Studies employing neuroimaging, electroencephalography, or serum BDNF analysis in Crohn's disease

Examination techniques	Author/Year
MRI and variations	Agostini et al. 2023 [46], Bao et al. 2018 [47], Chen et al. 2023 [48], Fan et al. 2020 [49], Hou et al. 2019 [51], Hou et al. 2020 [52], Kong et al. 2022 [54], Kornelsen et al. 2020 [55], Li et al. 2021 [56], Liu et al. 2018 [57], Nair et al. 2019 [58], Qiu et al. 2022 [59], Thapaliya et al. 2023 [61], Thapaliya et al. 2023 [62], Thomann et al. 2017 [6], Thomann et al. 2021 [63], Thommann et al. 2017 [64], Yeske et al. 2024 [65], Zhang et al. 2021 [66]
EEG	Hall et al. 2023 [50], Kelleci et al. 2019 [53]
Serum evaluation of BDNF	Sochai et al. 2021 [60]

Table 4. Study about vagotomy and Crohn's disease

Neurological disorder	Author/Year
Vagotomy	Liu et al. [67]

them. On the other hand, Zheng et al. [41] worked with analysis of peripheral blood transcriptomic databases, finding 178 genes differentially expressed in common between the two diseases (113 genes increased and 65 genes decreased).

Despite epidemiological studies presenting conflicting results and limitations, genetic studies provide data that raise the possibility of interaction between PD and CD. In this sense, future studies could focus on more careful analyses to avoid the biases found in the aforementioned studies.

Alzheimer's disease, other dementias, and Crohn's disease: Sand et al. [21] and Zingel et al. [22] investigated the potential association between CD and the risk of developing various types of dementia using medical record data analysis. However, their findings were contradictory. Sand et al. [26] reported an elevated risk of all-cause dementia among CD patients, with a particularly heightened risk for frontotemporal dementia. In contrast, Zingel et al. [27] found that CD was not significantly associated with an increased risk of dementia.

Additionally, Aggarwal et al. [31] explored the link between AD and CD in a retrospective study utilizing medical record databases while excluding other causes of dementia. Their findings indicated that individuals with CD who were over 65 years old and of Caucasian ethnicity had significantly higher odds of developing AD ($P < 0.0001$).

Amyotrophic lateral sclerosis, multiple system atrophy, and multiple sclerosis: There is evidence suggesting that ALS is related to immune system dysregulation, and it has been associated with a range of autoimmune or immune-

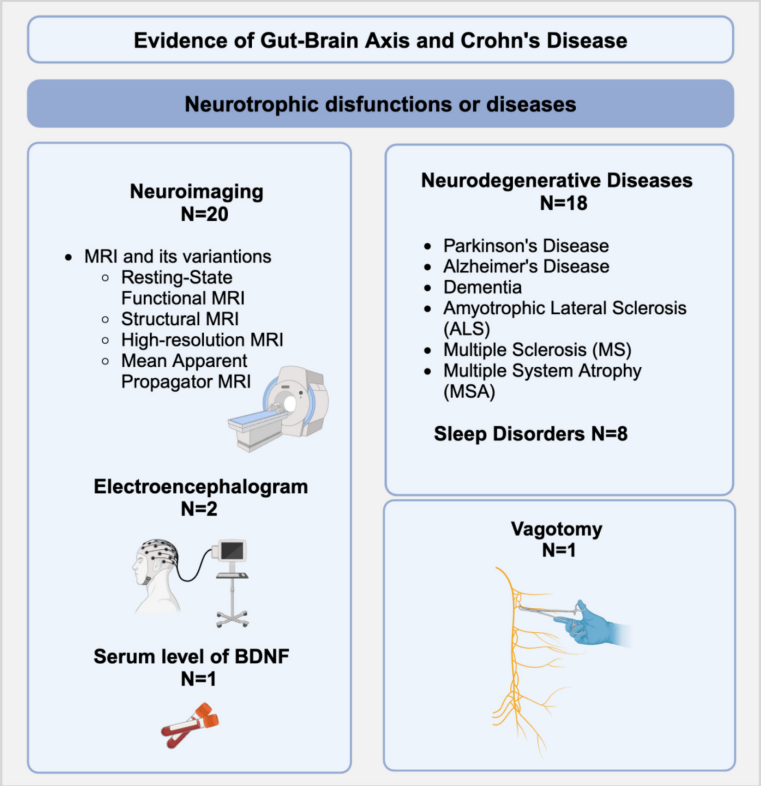

Figure 2. Summary of methods used in the literature for functional or structural brain analysis in patients with CD and neurological diseases, along with the number (N) of related papers: MRI = Magnetic Resonance Imaging; BDNF = Brain-Derived Neurotrophic Factor. Created using Biorender software.

related disorders that could potentially be precursors to its development [70]. Li et al. [43] explored the genetic correlation between ALS and around ten immune-mediated diseases, including CD. The authors investigated ALS and CD through GWAS to assess genetic associations. However, they found minimal and non-significant genetic association between CD and ALS.

Another neurodegenerative disease explored was MSA, which is also associated with abnormal aggregation of alpha-synuclein found in glial cells in this condition [71]. Through genomic association study data, Shadrin et al. [20] proposed a shared genetic etiology between MSA and CD in the C7 gene, indicating that genetic variability within C7 could modulate the risks of MSA and CD.

Yang et al. [45] and Sonnenberg et al. [44] studied MS, which is characterized by an inflammatory disease of the CNS that evolves with decreased cognitive capacity, bladder control, and mobility limitations [72]. The possibility of an association between MS and CD was raised due to their common epidemiological and immunological patterns [73]. The first study identified three shared single nucleotide polymorphisms between MS and CD; however, none were significant. The second found an association between MS and simultaneous diagnosis of CD.

One of the articles [42] of this SR addressed more than one neurodegenerative disease (PD, AD, and ALS) in the same analysis, using Mendelian Randomization Analysis. This statistical approach uses known genetic variants to investigate causal relationships, in this case, between CD and other neurodegenerative diseases. This method did not suggest any causal effect of CD on PD, ALS, or AD.

Studies on sleep disorders

Eight studies included in the review explored sleep disorders in CD patients. Four [25-30] studied data from subjective analyses using the Pittsburgh Sleep Quality Index (PSQI). Three studies reported higher sleep disturbance symptoms and poorer quality in CD patients compared to healthy adults, correlating worse outcomes with active disease. However, Hastaliklaria et al. found no significant differences in PSQI scores in CD patients and showed a higher eveningpreference in these patients. Bar-Gil Shitrit et al. [23] used Ambulatory Polysomnography in studies examining objective sleep quality parameters. They found that CD patients had less REM sleep and lighter sleep than control subjects. Iskandar et al. [28] objectively analyzed sleep using an actigraph and correlated it with the Harvey Bradshaw clinical scale. The result was surprising, showing that CD patients did not exhibit a significant alteration in sleep quality compared to control groups. Chen et al. [24] conducted a genetic study exploring databases to investigate the

relationship between CD patients and sleep characteristics, finding no causal effect between the studied aspects and the disease. Meanwhile, Hoffman et al. [29] evaluated the association between Obstructive Sleep Apnea (OSA) and CD by investigating medical history information from over 4 million Americans. They found an increased risk of CD patients developing OSA.

Studies that rely solely on questionnaires to analyze sleep are limited, since they are subjective regarding the perception of the disease. Additionally, Iskandar's study [28] exposes this limitation by showing that the perception of sleep by CD patients did not confirm the data collected by actigraphy. When analyzing the use of Polysomnography for this purpose, it is important to note that it does not simulate the patient's usual sleep situation, as they are in an ambulatory environment for the exam, unlike actigraphy, where data is collected during the patient's usual sleep routine. Therefore, it is not possible to analyze how sleeping in a non-habitual environment would impact the sleep of CD patients compared to healthy individuals. Thus, future studies could compare objective parameters to clarify any biases.

Studies that employed radiological, blood, and other exams

Neuroimaging exams: Twenty studies were included that used Magnetic Resonance Imaging (MRI) techniques to study the brains of CD patients in different ways. The most used was Resting-state functional MRI (rs-fMRI). Structural MRI (sMRI), high-resolution MRI (hrMRI), and mean apparent propagator MRI (MAP-MRI) were also used. Many findings are purely descriptive and do not correlate with specific clinical findings or neuronal functions. The results most frequently indicate neuronal changes related to abnormal brain activity and connectivity in CD patients, suggesting abnormal functionality related to visceral sensation regulation, pain processing, and neuroimmunity. Additionally, CD patients showed activation patterns similar to those found in older healthy adults, suggesting early brain aging in CD patients compared to controls without the disease. Similar to studies on neurodegenerative diseases, studies that addressed MRI methods were also heterogeneous and showed varied results related to changes in different brain areas. However, it is essential to note that the results were unanimous in showing that there are functional or structural alterations in the brains of CD patients compared to healthy adults.

Electroencephalogram and serum BDNF levels: Kelleci et al. [53] and Hall et al. [50] studied brain alterations in CD patients using EEG analysis, demonstrating that EEG abnormalities were significantly more common in CD patients and that the diagnosis of this disease is a determining factor in the risk of developing altered brain network signatures [50].

On the other hand, Sochal [60] explored the relationship between serum BDNF levels and CD. BDNF is a protein involved in several important brain functions, such as maintaining and forming synapses and neuronal connections. The study showed that CD patients had higher serum BDNF levels than healthy adults, which positively correlated with the severity of pain.

Study about vagotomy

Vagotomy is a surgical procedure that partially interrupts or removes the vagus nerve and is typically used to treat peptic ulcers. Some authors suggest that this procedure might affect the intestinal inflammatory response, potentially impacting the development and progression of CD. In a study by Liu et al. [67], which analyzed medical records, a positive association was found between vagotomy and CD patients. This suggests that vagotomy could contribute to immune dysregulation and an increased risk of CD.

Limitations and challenges of the systematic review

One of the limiting factors was the prevalence of studies that addressed IBD in general, grouping CD and UC in the same analysis without specifying data pertaining solely to CD. This lack of specificity precluded the inclusion of such studies in this SR. Additionally, the absence of control groups (without CD) in some studies was another exclusion criterion, as it rendered these studies incompatible with the PICO (Patient, Intervention, Comparison, Outcome) framework requirements, thereby failing to address the primary question of this review. Moreover, most studies identified were obser-

vational, which inherently limits their ability to provide conclusions beyond correlative findings.

Another limitation was the lack of studies exploring the mechanistic pathway and molecular interaction between the GBA and CD. One reason for this could be our focus on human studies, a choice made to ensure the relevance of our findings to clinical practice. Regarding neuroimaging research on CD, the studies were quite descriptive and did not explain the findings in-depth.

These challenges underscore the complexity of conducting an SR on this topic and highlight the need for more targeted and methodologically rigorous studies to draw more definitive conclusions regarding the neurological aspects of CD and its interaction with the GBA.

Conclusion

There is a growing interest in elucidating the relationship between CD and the GBA. The extant literature encompasses diverse studies with heterogeneous methodologies, ranging from epidemiological investigations to research on functional and structural brain alterations. Despite this diversity, there is no consensus regarding the precise relationship between CD and GBA, underscoring the necessity for further research. This SR has highlighted the significant potential of this field to enhance our understanding of the prognosis and even the etiology of CD. Consequently, advancing research in this area promises to yield valuable insight that may inform more effective interventions and deepen our comprehension of the intricate mechanisms linking CD with neurological and psychiatric manifestations.

Acknowledgements

We would like to thank the librarian, Ana Paula de Morais, for her assistance in finding the articles in the database. We also thank Prof. Tristan Guillermo Torriani for reviewing the English version of the manuscript. This work was supported by the National Council for Scientific and Technological Development (CNPq) [Grant scholarship number #302557/2021-0 for R.F. L.]. J.F.S. (author) and H.D.C. (coauthor) received a Master of Science scholarship from the Brazilian Coordination for the Improvement of Higher Education Personnel (CAPES - Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil), Finance Code 001. W.M.S. (coauthor) received an undergraduate scholarship from CNPq [2023].

Disclosure of conflict of interest

None.

Abbreviations

AD, Alzheimer's disease; AIS, Insomnia Scale; ALS, Amyotrophic Lateral Sclerosis; ANS, Autonomic nervous system; BBB, Blood-brain barrier; BDNF, Brain-derived neurotrophic factor; CD, Crohn's Disease; CNS, Central Nervous System; EEG, Electroencephalogram; ENS, Enteric nervous system; FC, Functional Connectivity; GBA, Gut-Brain Axis; GIT, gastrointestinal tract; HBI, Harvey-Bradshaw Index; HPA, hypothalamic-pituitary-adrenal axis; hr-MRI, High-resolution MRI; IC, Indeterminate Colitis; MAP-MRI, Mean Apparent Propagator Magnetic Resonance Imaging; MRI, Magnetic Resonance Imaging; MS, Multiple Sclerosis; MSA, Multiple System Atrophy; NIHR, National Institute for Health Research; OSA, Obstructive Sleep Apnea; PD, Parkinson's Disease; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PSQI, Pittsburg Sleep Quality Index; rs-fMRI, Resting-State Functional Magnetic Resonance Imaging; sMRI, Structural MRI; SR, Systematic Review; UC, Ulcerative Colitis.

Address correspondence to: Dr. Raquel Franco Leal, Inflammatory Bowel Disease Research Laboratory, Gastrocenter, Carlos Chagas Street, 420, Cidade Universitária Zeferino Vaz, Campinas, São Paulo 13083-878, Brazil. Tel: +55-19-991375374; E-mail: rafranco.unicamp@gmail.com; rafranco@unicamp.br

References

[1] Dolinger M, Torres J and Vermeire S. Crohn's disease. Lancet 2024; 403: 1177-1191.

[2] Carabotti M, Scirocco A, Maselli MA and Severi C. The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems. Ann Gastroenterol 2015; 28: 203-209.

[3] Mowat C, Cole A, Windsor A, Ahmad T, Arnott I, Driscoll R, Mitton S, Orchard T, Rutter M, Younge L, Lees C, Ho GT, Satsangi J and Bloom

S; IBD Section of the British Society of Gastroenterology. Guidelines for the management of inflammatory bowel disease in adults. Gut 2011; 60: 571-607.
[4] Zhang B, Wang HE, Bai YM, Tsai SJ, Su TP, Chen TJ, Wang YP and Chen MH. Inflammatory bowel disease is associated with higher dementia risk: a nationwide longitudinal study. Gut 2021; 70: 85-91.
[5] Zhu F, Li C, Gong J, Zhu W, Gu L and Li N. The risk of Parkinson's disease in inflammatory bowel disease: a systematic review and meta-analysis. Dig Liver Dis 2019; 51: 38-42.
[6] Thomann AK, Griebe M, Thomann PA, Hirjak D, Ebert MP, Szabo K, Reindl W and Wolf RC. Intrinsic neural network dysfunction in quiescent Crohn's disease. Sci Rep 2017; 7: 11579.
[7] Liu X, Yu R, Zhu L, Hou X and Zou K. Bidirectional regulation of circadian disturbance and inflammation in inflammatory bowel disease. Inflamm Bowel Dis 2017; 23: 1741-1751.
[8] Osadchiy V, Martin CR and Mayer EA. The gut-brain axis and the microbiome: mechanisms and clinical implications. Clin Gastroenterol Hepatol 2019; 17: 322-332.
[9] Mayer EA, Nance K and Chen S. The gut-brain axis. Annu Rev Med 2022; 73: 439-453.
[10] Tolhurst G, Heffron H, Lam YS, Parker HE, Habib AM, Diakogiannaki E, Cameron J, Grosse J, Reimann F and Gribble FM. Short-chain fatty acids stimulate glucagon-like peptide-1 secretion via the G-protein-coupled receptor FFAR2. Diabetes 2012; 61: 364-371.
[11] Yano JM, Yu K, Donaldson GP, Shastri GG, Ann P, Ma L, Nagler CR, Ismagilov RF, Mazmanian SK and Hsiao EY. Indigenous bacteria from the gut microbiota regulate host serotonin biosynthesis. Cell 2015; 161: 264-276.
[12] Samuel BS, Shaito A, Motoike T, Rey FE, Backhed F, Manchester JK, Hammer RE, Williams SC, Crowley J, Yanagisawa M and Gordon JI. Effects of the gut microbiota on host adiposity are modulated by the short-chain fatty-acid binding G protein-coupled receptor, Gpr41. Proc Natl Acad Sci U S A 2008; 105: 16767-16772.
[13] Goehler LE, Gaykema RP, Opitz N, Reddaway R, Badr N and Lyte M. Activation in vagal afferents and central autonomic pathways: early responses to intestinal infection with Campylobacter jejuni. Brain Behav Immun 2005; 19: 334-344.
[14] Rusch JA, Layden BT and Dugas LR. Signalling cognition: the gut microbiota and hypothalamic-pituitary-adrenal axis. Front Endocrinol (Lausanne) 2023; 14: 1130689.
[15] Günther C, Rothhammer V, Karow M, Neurath M and Winner B. The gut-brain axis in inflammatory bowel disease-current and future perspectives. Int J Mol Sci 2021; 22: 8870.
[16] Drokhlyansky E, Smillie CS, Van Wittenberghe N, Ericsson M, Griffin GK, Eraslan G, Dionne D, Cuoco MS, Goder-Reiser MN, Sharova T, Kuksenko O, Aguirre AJ, Boland GM, Graham D, Rozenblatt-Rosen O, Xavier RJ and Regev A. The human and mouse enteric nervous system at single-cell resolution. Cell 2020; 182: 1606-1622, e23.
[17] Hess A, Roesch J, Saake M, Sergeeva M, Hirschmann S, Neumann H, Dörfler A, Neurath MF and Atreya R. Functional brain imaging reveals rapid blockade of abdominal pain response upon anti-TNF therapy in Crohn's disease. Gastroenterology 2015; 149: 864-866.
[18] Galvão T, Pansani T and Harrad D. Principais itens para relatar Revisões sistemáticas e Meta-análises: a recomendação PRISMA. Epidemiologia e Serviços de Saúde 2015; 24: 335-342.
[19] Ouzzani M, Hammady H, Fedorowicz Z and Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Syst Rev 2016; 5: 210.
[20] Shadrin AA, Mucha S, Ellinghaus D, Makarious MB, Blauwendraat C, Sreelatha AAK, Heras-Garvin A, Ding J, Hammer M, Foubert-Samier A, Meissner WG, Rascol O, Pavy-Le Traon A, Frei O, O'Connell KS, Bahrami S, Schreiber S, Lieb W, Müller-Nurasyid M, Schminke U, Homuth G, Schmidt CO, Nöthen MM, Hoffmann P, Gieger C, Wenning G; European Multiple System Atrophy Study Group, Gibbs JR, Franke A, Hardy J, Stefanova N, Gasser T, Singleton A, Houlden H, Scholz SW, Andreassen OA and Sharma M. Shared genetics of multiple system atrophy and inflammatory bowel disease. Mov Disord 2021; 36: 449-459.
[21] Rønnow Sand J, Troelsen FS, Horváth-Puhó E, Henderson VW, Sørensen HT and Erichsen R. Risk of dementia in patients with inflammatory bowel disease: a Danish population-based study. Aliment Pharmacol Ther 2022; 56: 831-843.
[22] Zingel R, Bohlken J and Kostev K. Association between inflammatory bowel disease and dementia: a retrospective cohort study. J Alzheimers Dis 2021; 80: 1471-1478.
[23] Bar-Gil Shitrit A, Chen-Shuali C, Adar T, Koslowsky B, Shteingart S, Paz K, Grisaru-Granovsky S, Goldin E, Epstein Shochet G and Shitrit D. Sleep disturbances can be prospectively observed in patients with an inactive inflammatory bowel disease. Dig Dis Sci 2018; 63: 2992-2997.
[24] Chen M, Peng WY, Tang TC and Zheng H. Differential sleep traits have no causal effect on inflammatory bowel diseases: a mendelian randomization study. Front Pharmacol 2021; 12: 763649.
[25] Chrobak AA, Nowakowski J, Zwolińska-Wcisło M, Cibor D, Przybylska-Feluś M, Ochyra K,

Rzeźnik M, Dudek A, Arciszewska A, Siwek M and Dudek D. Associations between chronotype, sleep disturbances and seasonality with fatigue and inflammatory bowel disease symptoms. Chronobiol Int 2018; 35: 1142-1152.

[26] Gîlc-Blanariu GE, Ştefnescu G, Trifan AV, Moscalu M, Dimofte MG, Ştefnescu C, Drug VL, Afrsnie VA and Ciocoiu M. Sleep impairment and psychological distress among patients with inflammatory bowel disease-beyond the obvious. J Clin Med 2020; 9: 2304.

[27] Sahbaz C and Biberci EK. Chronotype and sleep quality in patients with inflammatory bowel disease. Med Bull Haseki 2020; 58: 72-77.

[28] Iskandar HN, Linan EE, Patel A, Moore R, Lasanajak Y, Gyawali CP, Sayuk GS and Ciorba MA. Self-reported sleep disturbance in Crohn's disease is not confirmed by objective sleep measures. Sci Rep 2020; 10: 1980.

[29] Hoffman K, Mansoor E, Panhwar MS, Regueiro M, Cooper G and Qazi T. Prevalence of obstructive sleep apnea is increased in patients with inflammatory bowel disease: a large, multinetwork study. Crohns Colitis 360 2022; 4: otac026.

[30] Sofia MA, Lipowska AM, Zmeter N, Perez E, Kavitt R and Rubin DT. Poor sleep quality in Crohn's disease is associated with disease activity and risk for hospitalization or surgery. Inflamm Bowel Dis 2020; 26: 1251-1259.

[31] Aggarwal M, Alkhayyat M, Abou Saleh M, Sarmini MT, Singh A, Garg R, Garg P, Mansoor E, Padival R and Cohen BL. Alzheimer disease occurs more frequently in patients with inflammatory bowel disease: insight from a nationwide study. J Clin Gastroenterol 2023; 57: 501-507.

[32] Camacho-Soto A, Gross A, Searles Nielsen S, Dey N and Racette BA. Inflammatory bowel disease and risk of Parkinson's disease in Medicare beneficiaries. Parkinsonism Relat Disord 2018; 50: 23-28.

[33] Freuer D and Meisinger C. Association between inflammatory bowel disease and Parkinson's disease: a Mendelian randomization study. NPJ Parkinsons Dis 2022; 8: 55.

[34] Hui KY, Fernandez-Hernandez H, Hu J, Schaffner A, Pankratz N, Hsu NY, Chuang LS, Carmi S, Villaverde N, Li X, Rivas M, Levine AP, Bao X, Labrias PR, Haritunians T, Ruane D, Gettler K, Chen E, Li D, Schiff ER, Pontikos N, Barzilai N, Brant SR, Bressman S, Cheifetz AS, Clark LN, Daly MJ, Desnick RJ, Duerr RH, Katz S, Lencz T, Myers RH, Ostrer H, Ozelius L, Payami H, Peter Y, Rioux JD, Segal AW, Scott WK, Silverberg MS, Vance JM, Ubarretxena-Belandia I, Foroud T, Atzmon G, Pe'er I, Ioannou Y, McGovern DPB, Yue Z, Schadt EE, Cho JH and Peter I. Functional variants in the LRRK2 gene confer shared effects on risk for Crohn's disease and Parkinson's disease. Sci Transl Med 2018; 10: eaai7795.

[35] Kang X, Ploner A, Wang Y, Ludvigsson JF, Williams DM, Pedersen NL and Wirdefeldt K. Genetic overlap between Parkinson's disease and inflammatory bowel disease. Brain Commun 2023; 5: fcad002.

[36] Loosen SH, Yaqubi K, May P, Konrad M, Gollop C, Luedde T, Kostev K and Roderburg C. Association between inflammatory bowel disease and subsequent development of restless legs syndrome and Parkinson's disease: a retrospective cohort study of 35,988 primary care patients in Germany. Life (Basel) 2023; 13: 897.

[37] Park S, Kim J, Chun J, Han K, Soh H, Kang EA, Lee HJ, Im JP and Kim JS. Patients with inflammatory bowel disease are at an increased risk of Parkinson's disease: a South Korean nationwide population-based study. J Clin Med 2019; 8: 1191.

[38] Wang HL, Wang ZY, Tian J, Ma DR and Shi CH. Association between inflammatory bowel disease and Parkinson's disease: a prospective cohort study of 468,556 UK biobank participants. Front Aging Neurosci 2024; 15: 1294879.

[39] Weimers P, Halfvarson J, Sachs MC, Saunders-Pullman R, Ludvigsson JF, Peter I, Burisch J and Olén O. Inflammatory bowel disease and Parkinson's disease: a nationwide swedish cohort study. Inflamm Bowel Dis 2019; 25: 111-123.

[40] Witoelar A, Jansen IE, Wang Y, Desikan RS, Gibbs JR, Blauwendraat C, Thompson WK, Hernandez DG, Djurovic S, Schork AJ, Bettella F, Ellinghaus D, Franke A, Lie BA, McEvoy LK, Karlsen TH, Lesage S, Morris HR, Brice A, Wood NW, Heutink P, Hardy J, Singleton AB, Dale AM, Gasser T, Andreassen OA and Sharma M; International Parkinson's Disease Genomics Consortium (IPDGC), North American Brain Expression Consortium (NABEC), and United Kingdom Brain Expression Consortium (UKBEC) Investigators. Genome-wide pleiotropy between parkinson disease and autoimmune diseases. JAMA Neurol 2017; 74: 780-792.

[41] Zheng H, Qian X, Tian W and Cao L. Exploration of the common gene characteristics and molecular mechanism of Parkinson's disease and Crohn's disease from transcriptome data. Brain Sci 2022; 12: 774.

[42] Li H and Wen Z. Effects of ulcerative colitis and Crohn's disease on neurodegenerative diseases: a Mendelian randomization study. Front Genet 2022; 13: 846005.

[43] Li CY, Yang TM, Ou RW, Wei QQ and Shang HF. Genome-wide genetic links between amyotrophic lateral sclerosis and autoimmune diseases. BMC Med 2021; 19: 27.
[44] Sonnenberg A, Duong HT, McCarty DJ and El-Serag HB. Concurrence of inflammatory bowel disease with multiple sclerosis or Hodgkin lymphoma. Eur J Gastroenterol Hepatol 2023; 35: 1349-1353.
[45] Yang Y, Musco H, Simpson-Yap S, Zhu Z, Wang Y, Lin X, Zhang J, Taylor B, Gratten J and Zhou Y. Investigating the shared genetic architecture between multiple sclerosis and inflammatory bowel diseases. Nat Commun 2021; 12: 5641.
[46] Agostini A, Benuzzi F, Ballotta D, Rizzello F, Gionchetti P and Filippini N. Differential brain structural and functional patterns in Crohn's disease patients are associated with different disease stages. Inflamm Bowel Dis 2023; 29: 1297-1305.
[47] Bao C, Liu P, Liu H, Jin X, Shi Y, Wu L, Zeng X, Zhang J, Wang D, Calhoun VD, Tian J and Wu H. Difference in regional neural fluctuations and functional connectivity in Crohn's disease: a resting-state functional MRI study. Brain Imaging Behav 2018; 12: 1795-1803.
[48] Chen F, Zhang S, Li P, Xu K, Liu C, Geng B, Piao R and Liu P. Disruption of periaqueductal gray-default mode network functional connectivity in patients with Crohn's disease with abdominal pain. Neuroscience 2023; 517: 96-104.
[49] Fan Y, Bao C, Wei Y, Wu J, Zhao Y, Zeng X, Qin W, Wu H and Liu P. Altered functional connectivity of the amygdala in Crohn's disease. Brain Imaging Behav 2020; 14: 2097-2106.
[50] Hall CV, Radford-Smith G, Savage E, Robinson C, Cocchi L and Moran RJ. Brain signatures of chronic gut inflammation. Front Psychiatry 2023; 14: 1250268.
[51] Hou J, Mohanty R, Nair VA, Dodd K, Beniwal-Patel P, Saha S and Prabhakaran V. Alterations in resting-state functional connectivity in patients with Crohn's disease in remission. Sci Rep 2019; 9: 7412.
[52] Hou J, Dodd K, Nair VA, Rajan S, Beniwal-Patel P, Saha S and Prabhakaran V. Alterations in brain white matter microstructural properties in patients with Crohn's disease in remission. Sci Rep 2020; 10: 2145.
[53] Kelleci UA, Calhan T, Sahin A, Aydin-Ozemir Z, Kahraman R, Ozdil K, Sokmen HM and Yalcin AD. Electroencephalography findings in Crohn's disease. Clin EEG Neurosci 2019; 50: 129-133.
[54] Kong N, Gao C, Zhang F, Zhang M, Yue J, Lv K, Zhang Q, Fan Y, Lv B, Zang Y and Xu M. Neurophysiological effects of the anterior cingulate cortex on the exacerbation of Crohn's disease: a combined fMRI-MRS study. Front Neurosci 2022; 16: 840149.
[55] Kornelsen J, Wilson A, Labus JS, Witges K, Mayer EA and Bernstein CN. Brain resting-state network alterations associated with Crohn's disease. Front Neurol 2020; 11: 48.
[56] Li L, Ma J, Xu JG, Zheng YL, Xie Q, Rong L and Liang ZH. Brain functional changes in patients with Crohn's disease: a resting-state fMRI study. Brain Behav 2021; 11: e2243.
[57] Li L, Ma J, Hua X, Zhou Y, Qiu Y, Zhu Z, Zheng Y, Xie Q, Liang Z and Xu J. Altered intra- and inter-network functional connectivity in patients with Crohn's disease: an independent component analysis-based resting-state functional magnetic resonance imaging study. Front Neurosci 2022; 16: 855470.
[58] Nair VA, Dodd K, Rajan S, Santhanubosu A, Beniwal-Patel P, Saha S and Prabhakaran V. A verbal fluency task-based brain activation fMRI study in patients with Crohn's disease in remission. J Neuroimaging 2019; 29: 630-639.
[59] Qiu Y, Li Q, Wu D, Zhang Y, Cheng J, Cao Z and Zhou Y. Altered mean apparent propagator-based microstructure and the corresponding functional connectivity of the parahippocampus and thalamus in Crohn's disease. Front Neurosci 2022; 16: 985190.
[60] Sochal M, Małecka-Panas E, Gabryelska A, Fichna J, Talar-Wojnarowska R, Szmyd B and Białasiewicz P. Brain-derived neurotrophic factor is elevated in the blood serum of Crohn's disease patients, but is not influenced by anti-TNF-α treatment-A pilot study. Neurogastroenterol Motil 2021; 33: e13978.
[61] Thapaliya G, Eldeghaidy S, Asghar M, McGing J, Radford S, Francis S and Moran GW. The relationship between Central Nervous System morphometry changes and key symptoms in Crohn's disease. Brain Imaging Behav 2023; 17: 149-160.
[62] Thapaliya G, Eldeghaidy S, Radford SJ, Francis ST and Moran GW. An examination of resting-state functional connectivity in patients with active Crohn's disease. Front Neurosci 2023; 17: 1265815.
[63] Thomann AK, Schmitgen MM, Kmuche D, Ebert MP, Thomann PA, Szabo K, Gass A, Griebe M, Reindl W and Wolf RC. Exploring joint patterns of brain structure and function in inflammatory bowel diseases using multimodal data fusion. Neurogastroenterol Motil 2021; 33: e14078.
[64] Thomann AK, Reindl W, Wüstenberg T, Kmuche D, Ebert MP, Szabo K, Wolf RC, Hirjak D, Niesler B, Griebe M and Thomann PA. Aberrant brain structural large-scale connectome in Crohn's disease. Neurogastroenterol Motil 2019; 31: e13593.

[65] Yeske B, Hou J, Chu DY, Adluru N, Nair VA, Beniwal-Patel P, Saha S and Prabhakaran V. Structural brain morphometry differences and similarities between young patients with Crohn's disease in remission and healthy young and old controls. Front Neurosci 2024; 18: 1210939.
[66] Zhang S, Chen F, Wu J, Liu C, Yang G, Piao R, Geng B, Xu K and Liu P. Altered structural covariance and functional connectivity of the insula in patients with Crohn's disease. Quant Imaging Med Surg 2022; 12: 1020-1036.
[67] Liu B, Wanders A, Wirdefeldt K, Sjölander A, Sachs MC, Eberhardson M, Ye W, Ekbom A, Olén O and Ludvigsson JF. Vagotomy and subsequent risk of inflammatory bowel disease: a nationwide register-based matched cohort study. Aliment Pharmacol Ther 2020; 51: 1022-1030.
[68] Spielman LJ, Gibson DL and Klegeris A. Unhealthy gut, unhealthy brain: the role of the intestinal microbiota in neurodegenerative diseases. Neurochem Int 2018; 120: 149-163.
[69] Lionnet A, Leclair-Visonneau L, Neunlist M, Murayama S, Takao M, Adler CH, Derkinderen P and Beach TG. Does Parkinson's disease start in the gut? Acta Neuropathol 2018; 135: 1-12.
[70] Beers DR and Appel SH. Immune dysregulation in amyotrophic lateral sclerosis: mechanisms and emerging therapies. Lancet Neurol 2019; 18: 211-220.
[71] Papp MI, Kahn JE and Lantos PL. Glial cytoplasmic inclusions in the CNS of patients with multiple system atrophy (striatonigral degeneration, olivopontocerebellar atrophy and Shy-Drager syndrome). J Neurol Sci 1989; 94: 79-100.
[72] Thompson AJ, Baranzini SE, Geurts J, Hemmer B and Ciccarelli O. Multiple sclerosis. Lancet 2018; 391: 1622-1636.
[73] Kosmidou M, Katsanos AH, Katsanos KH, Kyritsis AP, Tsivgoulis G, Christodoulou D and Giannopoulos S. Multiple sclerosis and inflammatory bowel diseases: a systematic review and meta-analysis. J Neurol 2017; 264: 254-259.

Supplementary Table 1. Outcomes of studies on neurological disorders (neurodegenerative diseases and sleep disorders)

Author/Year	Neurological disorder	Assessment method	Outcome
Shadrin et al. 2021 [20]	Multiple System Atrophy	Genome-Wide Association Study Data	Multiple System Atrophy and CD share a genetic etiology, highlighting a locus on chromosome 5 at 5p13.1 containing the C7 gene. This locus exhibited high deleterious and moderate regulatory scores, suggesting that genetic variability within C7 could modulate the risks of MSA and CD.
Sand et al. 2022 [21]	Dementias	Analysis of electronic medical record database	Patients with CD had an increased risk for all-cause dementia (HR = 1.15 [95% CI: 1.05-1.27]), with a higher risk observed for frontotemporal dementia (HR = 2.70 [95% CI: 1.44-5.05]).
Zingel et al. 2021 [22]	Dementias	Analysis of electronic medical record database	CD is not significantly associated with an increased risk of dementia (HR: 1.17 [95% CI: 0.93-1.47]).
Bar-Gil Shitrit et al. 2018 [23]	Sleep disorders	Ambulatory Polysomnography	CD patients had less REM sleep (P = 0.03) and less light sleep (P = 0.05) than control patients.
Chen et al. 2021 [24]	Sleep disorders	Genome-Wide Association Study Data	Results indicated that none of the investigated sleep characteristics had a significant causal impact on CD.
Chrobak et al. 2018 [25]	Sleep disorders	Pittsburg Sleep Quality Index (PSQI) and Inflammatory bowel disease questionnaire (IBDQ)	CD patients had significantly lower total PSQI scores than controls, indicating a greater tendency for eveningness. Correlational analysis reveals that in the CD group, PSQI scores are significantly negatively associated with total IBDQ score, systemic symptoms, intestinal symptoms, and emotional and social functions.
Georgiana-Emmanuela et al. 2020 [26]	Sleep disorders	Clinical (CDAI), biochemical parameters for disease activity analysis and use of the PSQI questionnaire	Sleep quality was impaired in CD patients compared to controls (P = 0.00905).
Hastaliklari et al. 2019 [27]	Sleep disorders	PSQI and Morningness-Eveningness Questionnaire	Investigations into differences in chronotype and sleep quality between individuals with Crohn's disease (CD) and controls showed that eveningness (preference for the afternoon or evening) was more common in CD patients (P < 0.0001). Additionally, there was no significant difference in CD patients' PSQI scores.
Iskandar et al. 2020 [28]	Sleep disorders	PSQI, Epworth Sleepiness Scale (ESS), Actigraphy, and Harvey Bradshaw Index (HBI)	Sleep disorders were more subjectively self-reported in CD patients compared to controls (PSQI: 57% vs. 35%, P = 0.02) and in patients with disease activity compared to patients in remission (PSQI: 75.8% vs. 33.3%, P < 0.01; ESS: 45.5% vs. 19%, P = 0.03). However, there was no significant change in objective sleep quality analysis between groups.

Kyle Hoffman et al. 2022 [29]	Sleep disorders	Analysis of electronic medical record database	Increased risk of developing Obstructive Sleep Apnea in CD patients compared to control patients (P < 0.0001).
Sofia et al. 2020 [30]	Sleep disorders	PSQI and HBI	CD patients and controls shared similar PSQI (P = 0.31), and 77% of the CD population had PSQI > 5. The Cox proportional hazards model for hospitalization or surgery showed that PSQI > 8 predicted surgery or hospitalization (hazard ratio 5.37; 95% CI 1.39-27.54).
Aggarwal et al. 2020 [31]	Alzheimer's Disease	Analysis of electronic medical record database	CD was associated with higher AD risk (P < 0.0001).
Camacho-Soto et al. 2018 [32]	Parkinson's Disease	Analysis of electronic medical record database	PD was inversely associated with CD (OR = 0.83 [95% CI: 0.74-0.93]).
Freuer et al. 2022 [33]	Parkinson's Disease	Genome-Wide Association Study Data	No causal association between PD and CD (P = 0.48).
Hui et al. 2018 [34]	Parkinson's Disease	Exome sequencing	Association in the LRRK2 gene with similar genetic effects in PD and CD. The CD risk allele LRRK2 N2081D is located in the same kinase domain as G2019S, a mutation that is the leading genetic cause of familial and sporadic Parkinson's disease.
Kang et al. 2022 [35]	Parkinson's Disease	Genome-Wide Association Study Data	Weak but statistically significant genetic correlations were detected between PD and CD (P = 0.01). Genetic variants and shared genomic loci were identified in both diseases, indicating a possible common genetic basis.
Loosen et al. 2023 [36]	Parkinson's Disease	Analysis of electronic medical record database	There was no significant association between CD and PD in the total study cohort (patients evaluated were over 40 years old).
Park et al. 2019 [37]	Parkinson's Disease	Analysis of electronic medical record database	CD patients had a 2.2 times higher chance of developing PD than healthy patients (P = 0.023). The average age of PD diagnosis in CD was lower than in controls (53.7 vs. 64.9 years; P = 0.014).
Wang et al. 2024 [38]	Parkinson's Disease	Analysis of electronic medical record database	Results suggest that CD presence does not influence PD's occurrence.
Weimers et al. 2019 [39]	Parkinson's Disease	Analysis of electronic medical record database	The overall risk of PD was 30% higher in CD patients compared to reference individuals.
Witoelar et al. 2017 [40]	Parkinson's Disease	Genome-Wide Association Study Data	Significant genetic overlap of PD and CD with shared susceptibility loci.
Zheng et al. 2022 [41]	Parkinson's Disease	Peripheral blood transcriptomic database	One hundred seventy-eight commonly differentially expressed genes (113 increased and 65 decreased) between PD and CD were found. Functional analysis showed they were related to immune response and lipid binding. Twelve core genes: BUB1B, BUB3, DLGAP5, AURKC, CBL, PCNA, RAF1, LYN, RPL39L, MRPL13, RSL24D1, and MRPS11.

Li et al. 2022 [42]	Neurodegenerative Diseases	Mendelian Randomization analysis of single nucleotide polymorphisms to explore causal association between CD and neurodegenerative diseases	No causal effect of CD on PD (P = 0.54), AD (P = 0.26), or ALS (P = 0.41) was suggested.
Li et al. 2021 [43]	Amyotrophic Lateral Sclerosis	Genome-Wide Association Study Data	There was a minimal genetic association between ALS and CD; the strongest signal, rs2076756 (NOD2), in the Manhattan conjunction plot was identified between ALS and CD. There was no significant difference in the incidence rate of ALS between patients with previous CD compared to controls.
Sonnenberg et al. 2023 [44]	Multiple Sclerosis	Analysis of electronic medical record database	Results showed a significant association between multiple sclerosis and the simultaneous diagnosis of CD.
Yang et al. 2021 [45]	Multiple Sclerosis	Genome-Wide Association Study Data	Three shared single nucleotide polymorphisms between MS and CD were identified; none genome-wide significant in the single-trait GWAS.

Supplementary Table 2. Results from studies employing neuroimaging, electroencephalography (EEG), or serum BDNF analysis in Crohn's disease

Author/Year	Assessment method	Outcome
Agostini et al. 2023 [46]	Structural Magnetic Resonance Imaging (MRI) and Resting-State Functional Magnetic Resonance Imaging (rs-fMRI)	Patients with active CD (CD-A) showed reduced gray matter within the posterior cingulate cortex compared to patients with CD in remission (CD-R). Analysis of resting-state fMRI data revealed the following patterns: (1) increased connectivity within the left fronto-parietal network (in the superior parietal lobe) in CD-R patients compared to CD-A patients; (2) decreased connectivity in the motor network (in parietal and motor areas) in the CD-A group compared to healthy controls (HC); (3) reduced connectivity in the motor network; and (4) in the language network (in parietal areas and the posterior cingulate cortex) in CD-R patients compared to HC.
Bao et al. 2018 [47]	rs-fMRI	Compared to controls, CD showed higher bilateral Amplitude of Low-Frequency Fluctuations (ALFF) in the hippocampus and parahippocampal regions, right insula, and prefrontal cortex; decreased Functional Connectivity (FC) in the left inferior cortex, middle cingulate cortex, hippocampus, and fusiform area; significant ALFF differences in the anterior cingulate cortex, precuneus, insula, precentral gyrus, medial prefrontal cortex, and secondary somatosensory cortex.
Chen et al. 2023 [48]	rs-fMRI	The results showed differences between groups related to the functional connectivity of subregions of the Periaqueductal Gray (PAG). A decrease in functional connectivity was observed successively in the order of control patients, patients with CD without abdominal pain, and patients with CD with abdominal pain. This suggests that the intensity of abdominal pain is associated with reduced functional connectivity between these regions.
Fan et al. 2020 [49]	rs-fMRI	Compared to control patients, CD showed altered Functional Connectivity (FC) in the amygdala, insula, parahippocampal gyrus, anterior cingulate cortex, and middle cingulate cortex. Patients with abdominal pain showed decreased FC in the insula.
Hall et al. 2023 [50]	Electroencephalogram (EEG)	They showed that CD patients presented altered states implicating the default mode network in parietal and visual regions, reflecting a shift in attentional modes' predominance. The results demonstrated that the diagnosis of CD is a determinant factor in the risk of developing altered brain network signatures.

Hou et al. 2019 [51]	MRI	In the Executive Control Network, resting-state FC was increased between the right middle frontal gyrus and the right inferior parietal lobule in CD compared to HC. In the Default Mode Network (DMN), resting-state FC showed increased CD patients between the right precuneus and the right posterior cingulate cortex compared to HC. Thus, the patient group exhibited elevated resting-state FC in both networks compared to the control group.
Hou et al. 2020 [52]	MRI	Fractional Anisotropy (FA) was significantly reduced in regions of the bilateral cingulate gyrus. Mean Diffusivity (MD) was significantly increased in areas of the left cingulate, left inferior frontal-occipital fasciculus, and bilateral superior longitudinal fasciculus. Axial Diffusivity (AD) was increased in regions of the bilateral cingulate and bilateral superior longitudinal fasciculus. Radial diffusivity values were significantly increased in areas of the right corticospinal tract, right inferior longitudinal fasciculus, and left superior longitudinal fasciculus (temporal part).
Kelleci et al. 2019 [53]	EEG	EEG alterations were significantly more common in CD patients than controls ($P = 0.001$). Slow wave abnormalities were the most common EEG abnormality detected in 13 (31%) patients. Epileptiform abnormalities were detected in 3 (7%) patients in the CD group. 94% (15/16) of EEG abnormalities were bilateral, and 6% (1/16) were on the right side.
Kong et al. 2022 [54]	HBI, Visual Analog Scale (VAS) and rs-fMRI	Patients with active CD showed higher spontaneous activity in the left anterior and medial cingulate cortex and higher levels of Glutamate in the anterior cingulate cortex ($P < 0.05$).
Kornelsen et al. 2020 [55]	MRI	In patients with CD, region of interest analyses showed increased FC between the frontoparietal network and salience network, decreased FC within the default mode network, increased FC between the right lateral prefrontal cortex of the frontoparietal network and the bilateral supramarginal gyrus of the salience network, decreased FC between the medial prefrontal cortex and the left lateral parietal node in the default mode network. Independent component analysis revealed cerebellar, visual, and salience network component alterations.
Li et al. 2021 [56]	rs-fMRI	The CD group showed higher Amplitude of Low-Frequency Fluctuations (ALFF) in the left anterior cingulate cortex, left superior frontal gyrus, and left supplementary motor cortex, and lower ALFF in the left hippocampus compared to controls ($P < 0.05$). They also exhibited higher Regional Homogeneity (ReHo) values in the left anterior cingulate cortex, bilateral superior frontal gyrus, left supplementary motor cortex, and left putamen compared to controls. In the FC analysis based on ALFF and ReHo, there was higher activity in the left precentral gyrus, left middle temporal gyrus, inferior frontal orbital cortex, middle frontal gyrus, and right rolandic operculum than controls.
Liu et al. 2018 [57]	rs-fMRI	Regarding Functional Connectivity (FC) in resting-state networks, the primary visual network showed decreased functional connectivity in the left calcarine cortex. In contrast, the language network showed increased functional connectivity in the left middle temporal gyrus (cluster-level $P < 0.01$). Significantly increased connectivity was found between the language network and the dorsal Default Mode Network (DMN) ($P < 0.05$). In the CD group, the connectivity strength related to the Left Calcarine Cortex within the primary network was significantly negatively correlated with disease duration ($P = 0.046$).
Nair et al. 2019 [58]	MRI and Verbal Fluency Score	There was no difference in Verbal Fluency Score between control patients and those with CD. In brain activation analyzed by MRI, regions activated in healthy controls in the left hemisphere included the inferior frontal gyrus, supplementary motor area, and fusiform gyrus. Right hemisphere activation involved the putamen and cerebellum. In patients with CD, activated regions in the left hemisphere included the insula, precuneus, angular gyrus, and supplementary motor area (SMA), and in the right hemisphere, the insula, SMA, cerebellum, and inferior frontal gyrus. Patients with CD in this study demonstrated activation patterns similar to those of older healthy individuals, as previously reported in the literature.

Qiu et al. 2022 [59]	Mean Apparent Propagator Magnetic Resonance Imaging (MAP-MRI) and rs-fMRI	The brain regions with different Mean Apparent Propagator (MAP) parameters are bilateral parahippocampal gyrus, bilateral thalamus, bilateral insula, left hippocampus, left putamen, left amygdala, left temporal pole: superior temporal gyrus, left rolandic operculum, left fusiform gyrus, right middle frontal gyrus, right superior medial frontal gyrus, and right anterior cingulate gyrus and right paracingulate gyrus. Regarding the FC analysis, they were lower in CD patients than in healthy controls. They were left thalamus-left parahippocampal gyrus (t = -3.117, P = 0.034), left thalamus-right parahippocampal gyrus (t = -3.407, P = 0.021), right thalamus-right parahippocampal gyrus (t = -2.959, P = 0.029), and right thalamus-left parahippocampal gyrus (t = -4.485, P = 0.006).
Sochai et al. 2021 [60]	Serum evaluation of BDNF, insomnia assessment: Athens Insomnia Scale (AIS) and VAS and Laitinen Pain Scale	Patients with CD had a higher serum BDNF level than healthy controls (P = 0.010). No correlation was found between clinical severity and BDNF. There were positive correlations between BDNF level and AIS scores (r = 0.253, P = 0.020), pain severity measured using VAS (r = 0.251, P = 0.021), and Laitinen Pain Scale (r = 0.218, P = 0.047). No differences were observed in BDNF levels before and after 14 weeks of anti-TNF-α therapy.
Thapaliya et al. 2023 [61]	rs-fMRI	They showed a significant reduction in the overall volume of cerebrospinal fluid in participants with CD compared to controls and a decrease in gray matter volume, white matter volume, and cortical thickness in the left precentral gyrus.
Thapaliya et al. 2023 [62]	rs-fMRI	Functional connectivity alterations at rest were documented in patients with CD in the frontoparietal network, visual networks, cerebellar networks, and attention networks, suggesting a specific neural phenotype of CD. Higher abdominal pain scores were associated with lower connectivity in the precuneus (visual network) and parietal operculum and connectivity in the cerebellum. Longer disease duration was associated with higher connectivity in the middle temporal gyrus and temporal plane (visual network).
Thomann et al. 2017 [6]	rs-fMRI	Abnormal connectivity was observed in CD patients only in the subsystems of the DMN (P < 0.05). Increased connectivity was found in the anterior cingulate, left superior medial frontal gyrus, and the middle cingulate cortex.
Thomann et al. 2021 [63]	MRI and rs-fMRI	Joint analysis of independent components detected structural alterations in the middle frontal and temporal regions and functional alterations in the superior frontal gyrus, middle and inferior frontal gyrus, inferior temporal gyrus, rectus, and subcallosal gyrus of CD patients compared to control patients.
Thommann et al. 2017 [64]	High-Resolution Magnetic Resonance Imaging	Transitivity, a measure of global segregation of the neural network, was significantly reduced in patients with CD (P = 0.003). Regionally, patients showed a reduction in nodal betweenness centrality in the right insula and cuneus and the left superior frontal cortex and a reduction in nodal degree in the left hemispheric cingulate, left lateral orbitofrontal cortex, and right medial orbitofrontal cortex.
Yeske et al. 2024 [65]	MRI	Patients with CD showed more significant brain similarity with older control patients than their healthy age-matched peers.
Zhang et al. 2021 [66]	rs-fMRI	Compared to controls, patients with CD showed gray matter volume in the left dorsal anterior insula and bilateral posterior insula. The Functional Connectivity (FC) of the parahippocampus/hippocampus with the left dorsal anterior insula and bilateral posterior insula was negatively correlated with the Crohn's Disease Activity Index (CDAI).

Supplementary Table 3. Outcome of the study on vagotomy

Neurological disorder	Assessment method	Outcome
Vagotomy [67]	Analysis of electronic medical record database	It showed a positive association between vagotomy and CD (HR = 3.63, 95% CI = 1.94-6.80 for truncal vagotomy, HR = 2.06, 95% CI = 1.49-2.84 for selective vagotomy).