Journal of the Canadian Association of Gastroenterology, 2025, **8**, S36–S43
https://doi.org/10.1093/jcag/gwae031
Supplement Article

Current approaches to studying human resting-state function in inflammatory bowel disease

Theresa A. McIver[1,2,3], Charles N. Bernstein[1,2,3], Jennifer Kornelsen[1,2,4,*]

[1]Department of Radiology, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, MB, Canada
[2]University of Manitoba IBD Clinical and Research Centre, Winnipeg, MB, Canada
[3]Department of Internal Medicine, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, MB, Canada
[4]Neuroscience Research Program, Kleysen Institute for Advanced Medicine, Winnipeg Health Sciences Centre, Winnipeg, MB, Canada

[*]Corresponding author: Jennifer Kornelsen, Department of Radiology, University of Manitoba, SR226 Kleysen Institute for Advanced Medicine, 710 William Avenue, Winnipeg, MB, R2H 2A6, Canada (Jennifer.Kornelsen@umanitoba.ca).

Abstract

Crohn's disease and ulcerative colitis are 2 subtypes of Inflammatory Bowel Disease (IBD). The chronic, alternating periods of relapsing, and remitting inflammation of the gastrointestinal tract that underlie these diseases trigger a range of gut-related symptoms, in addition to being related to burdensome psychological and cognitive comorbidities. With advancing knowledge of the brain–gut axis and its dysregulation in diseases such as IBD, understanding IBD-related brain changes is an important focus for current research in this area. "Resting state" function refers to the spontaneous fluctuations in neural activity when a person is awake and resting—not focussing attention on a task or stimulus. The recent surge in human resting-state functional magnetic resonance imaging (rs-fMRI) studies suggest that resting function is altered in IBD, representing a potential neural biomarker to target in the development of novel interventions. There are, however, multiple factors that contribute to the approach of these studies, including factors related to participant sample characteristics (IBD subtype and incorporation of disease activity in group definition and comparison), application of different resting-state metrics to assess resting brain activity (via regional homogeneity or amplitude of low-frequency fluctuations) or functional connectivity (via independent component analysis, region-of-interest, seed-to-voxel, or graph theory analyses) and incorporation of additional, multimodal variables of interest. The present review provides a summary of current approaches to studying resting-state brain function in IBD, the most commonly identified brain regions/networks to exhibit aberrant function, and avenues for advancement that forthcoming research in this field can strive to address.

Key words: inflammatory bowel disease; Crohn's disease; ulcerative colitis; resting state functional magnetic resonance imaging; functional connectivity; regional homogeneity; amplitude of low frequency fluctuations.

Introduction

Inflammatory bowel disease

Crohn's disease (CD) and ulcerative colitis (UC) are 2 subtypes of chronic, immune-mediated inflammatory conditions that collectively represent Inflammatory Bowel Disease (IBD).[1] While chronic, alternating periods of remitting, and relapsing inflammation of the gastrointestinal tract are common to both CD and UC, the 2 subtypes differ in their site of inflammation and some symptomology.[2] Collectively, IBD is associated with numerous psychological comorbidities (predominantly depression and anxiety),[3–5] cognitive difficulties,[6] and fatigue.[7] IBD and its associated psychological comorbidities have a detrimental impact on quality of life.[8] Advancing knowledge of the pathophysiology underlying IBD is therefore an important focus for ongoing IBD research. The prevalence and impact of psychological and cognitive comorbidities in IBD further highlight the necessity to study brain changes in relation to the dysregulation of the brain–gut axis in IBD.

Human brain imaging in IBD

Research employing MRI of the human brain can assess morphological differences related to grey matter[9,10] and cortical complexity measures[11] and white matter integrity[12] as well as changes in brain function inferred from measures of blood oxygenation-level dependent (BOLD) signal fluctuations. Functional MRI (fMRI) can be applied in combination with a specific task/stimulus delivery or recorded over periods of wakeful rest (rs-fMRI). Whereas task-based fMRI supports inferences about what areas of the brain are involved in the execution of a given task or processing of delivered stimuli, rs-fMRI offers insight into changes to brain function unrestricted by an assigned task, attentional focus, or delivery of stimuli. Resting-state fMRI studies have identified differences for a broad range of clinical populations, including in different immune-mediated inflammatory diseases.[13,14] Research in some clinical populations has linked changes in resting-state function to the efficacy of treatments and interventions.[15,16] Thus, while there is much to gain from understanding the long-lasting implications for alterations in brain structure

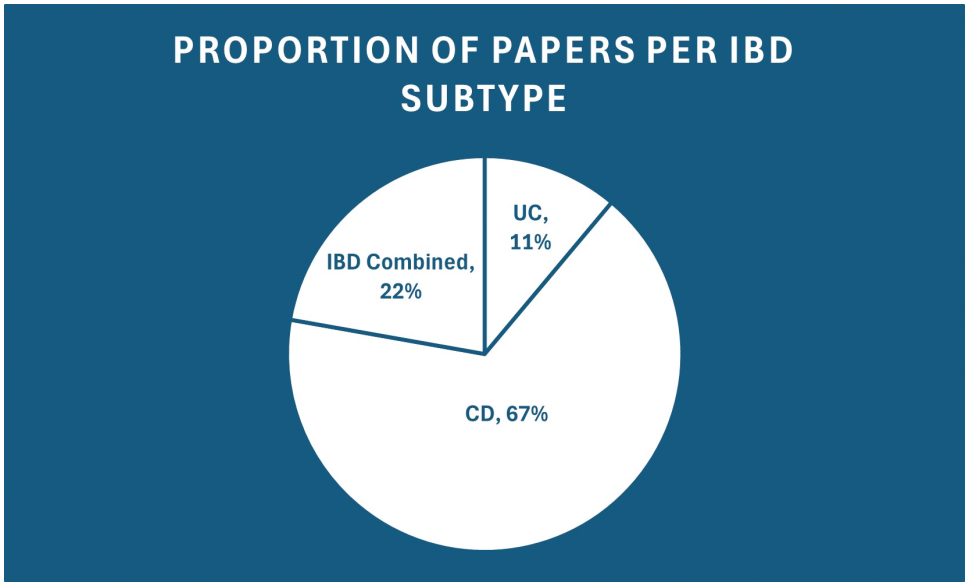

Figure 1. Chart presenting the percentage of studies considered within the present review that formed participant groups including people with Crohn's disease, ulcerative colitis, or both.

associated with IBD, identifying changes in brain function may provide a more accessible target for clinical intervention.

Resting-state approaches

Studying resting-state function can include consideration of temporal synchronicity of brain signal fluctuations across anatomically distinct brain regions (ie, resting-state functional connectivity (rsFC)) as well as variations in the low-frequency spontaneous neural activity within a given brain region (ie, resting-state activity).[17] Common functional connectivity approaches applied in the study of IBD include independent component analysis (ICA), region of interest (ROI)-to-ROI, ROI seed-to-voxel, and graph theory. Common approaches for assessing resting-state activity include regional homogeneity (ReHo) and amplitude of low-frequency fluctuations (ALFF). ICA is a data-driven approach where voxel-wise data are reduced into separate components that represent patterns of functional connectivity in a hierarchy of descending similarities from which the components isolating distinct neural networks can be selected. In contrast, ROI-to-ROI and seed (ROI)-to-voxel are 2 seed-based functional connectivity measures, where temporal patterns of signal fluctuation are compared between pairs of predefined ROIs or between a single ROI and voxels across the brain, respectively.[18] Graph theoretical approaches measure the topological properties of the brain to reveal network organization and efficiency.[19] Relative to measures of resting-state activity, ReHo is a metric for the synchronization of signal fluctuation among adjacent voxels used to make inferences about activity in a given region.[20] In contrast, ALFF measures the intensity of spontaneous BOLD signal fluctuations to provide information about the intensity of regional activity.[21]

For application in IBD, resting-state functional MRI can be used to compare different populations of interest, comparing groups of participants with IBD to healthy controls, or more specifically comparing groups of participants with CD or UC to healthy controls, and/or to one another. Similar group-based comparisons can be used to contrast participants with IBD in an active disease state to those in remission, those with a given comorbidity to those without, or the same group before and after a given intervention. Beyond group comparisons, regression models can be applied to study continuous variables and assess factors in relation to individual variability. Furthermore, a combination of these approaches can be applied to assess whether groups differ in the relationship that they exhibit between a resting-state metric (eg, functional connectivity) and another continuous variable (eg, depression scores). The capability to combine various resting-state metrics with different participant samples and the incorporation of additional variables highlights the versatility of studying resting-state function in IBD.

The approach to studying resting-state functional neural correlates of IBD can therefore include a variety of iterations, with central considerations including (1) IBD subtype specificity (CD, UC, or a combination of both), (2) restriction or reporting of IBD participant disease activity (active vs remitted), (3) Resting-state metric employed (assessing resting activity and/or functional connectivity), and (4) inclusion of additional variables of interest (eg, psychological comorbidities, disease duration, inflammatory markers, etc.). The intent of this review is to provide a summary of the extent to which these methodological considerations have been employed in the study of IBD-related rs-fMRI research and identify the most consistent findings from these different approaches, and areas for future research.

Research on rs-fMRI in IBD to date

IBD subtype specificity

Across the literature, studies exploring resting state changes in IBD have focussed prominently on CD (Figure 1). Roughly two-thirds of the studies considered in this review focus on participants with CD,[10,17,22–37] most often compared to healthy controls. This represents roughly 6× as many studies as those focussing on UC.[38–40] Studies with samples including

Table 1. Sample characteristics of participants across rs-fMRI studies.

Authors	Year	Participant groups and sample sizes	State of disease activity for IBD participants	
			Active	Remitted/Inactive
Crohn's disease				
Huang et al.	2024	CD active (62), CD remitted (59), HC (91)	Yes	Yes
Sun et al.	2024	CD with anxiety or depression (33), CD without anxiety or depression (31), HC (29)	No	Yes
Thapaliya et al.	2023	CD (25), HC (25)	Yes	No
Chen et al.	2023	CD with pain (24), CD without pain (24), HC (28)	No	Yes
Agostini et al.	2023	CD active (19), CD remitted (14), HC (18)	Yes	Yes
Li et al.	2022	CD (20), HC (22)	Yes	[a]NA
Qiu et al.	2022	CD (22), HC (22)	Yes	[a]Yes
Zhang et al.	2022	CD (45), HC (40)	No	Yes
Huang et al.	2022	CD active (58), CD inactive (57), HC (91)	Yes	Yes
Kong et al.	2022	CD (34), HC (20)	Yes	Yes
Li et al.	2021	CD (15), HC (26)	No	Yes
Kornelsen et al.	2020	CD (35), HC (21)	Yes	Yes
Fan et al.	2020	CD (42), HC (35)	No	Yes
Hou et al.	2019	CD (18), HC (18)	No	Yes
Bao at al.	2018	CD (60), HC (40)	No	Yes
Liu et al.	2018	CD (43), HC (37)	No	Yes
Thomann et al.	2017	CD (15), HC (14)	No	Yes
Bao et al.	2016	CD with pain (25), CD without pain (25), HC (32)	No	Yes
Ulcerative colitis				
Wang et al.	2022	UC, IBS, and HC, $n = 74$ each)	[a]Yes	Yes
Kornelsen et al.	2021	UC (76), HC (74)	[a]Yes	Yes
Fan et al.	2019	UC (41), HC (42)	Yes	No
IBD combined				
Wang et al.	2023	IBD (combined; subtype not specified: 37), HC (32)	Yes	No
Deng et al.	2023	IBD (combined; subtype not specified: 27), HC (29)	No	Yes
Goodyear et al.	2023	IBD (26 CD | 9 UC), HC (32)	Yes	Yes
Kornelsen et al.	2022	IBD (CD 35, UC 76), HC (74)	Yes	Yes
Prub et al.	2022	IBD patients with chronic abdominal pain (32; CD 26 | UC 6), HC (32)	[a]Yes	Yes
Thomann et al.	2021	IBD patients (31; CD 19 | UC 12), HC (13)	No	Yes

Studies comparing resting-state pre–post intervention are not listed above.
[a]Assumed inclusion in a sample based on the presentation of means and standard deviations of continuous variables for assessing disease activity.
Abbreviations: CD = Crohn's disease; HC = healthy controls; UC = ulcerative colitis.

both CD and UC in their IBD participants are the next most common, with 2× as many studies as those focussing on UC. Of the research which includes a combination of CD and UC participants, half of those studies performed at least a preliminary, direct, statistical comparison between CD and UC.[9,41,42] Those that do not directly contrast the 2 subtypes referred to limited sample size as an obstacle to proceeding with subgroup comparisons.[43–45] Notably, among the few studies that directly compare CD to UC, it does not appear common for the subtype groups to be of equal sample size (Table 1), highlighting a potential challenge for statistical comparison between the 2 subtypes across the literature. Sample size also presents an issue relative to incorporating disease activity status into statistical analysis.

IBD participant disease activity

Disease activity can be assessed in a variety of ways, including via subjective, patient-reported measures of symptoms or via objective, physical testing for markers of inflammation (eg, CD endoscopic index of severity, serum C-reactive protein (CRP), erythrocyte sedimentation rate, or faecal calprotectin). Among the most common patient-report measures for determining disease activity are the Harvey–Bradshaw Inventory[46] for CD and the Powell Tuck Inventory for UC.[47] Given that rs-fMRI has more commonly been explored in relation to CD than UC, the next most common metrics for assessing disease severity have been the Crohn's disease activity index (CDAI[48]) and the Inflammatory Bowel Disease Questionnaire as a measure of the impact of IBD on quality of life.[49] Data on disease activity are widely reported across the literature, however, it is not consistently, directly, incorporated into resting-state statistical analyses. In most cases, the original recruitment is limited to those in either stable remission *OR* active disease state (Table 1), with few studies including a mix of participants with varying disease activity. Across studies that focus on CD, less than half include separate groups to

directly compare those in remission to those in active disease state in the resting-state analysis. Others who recruited a mix of participants in varying disease states report data on disease activity but lack sufficient sample size to effectively integrate an additional grouping variable into the analysis approach. None of the studies that focus on UC directly incorporate data on disease activity into their resting-state analysis. Only 1 study of the 6 that includes both CD and UC included disease activity data in their resting-state analysis. Studies incorporating disease activity directly as a variable of interest in resting-state analysis have mostly arisen in the last 2 years.

Resting-state metric employed

Resting-state functional connectivity between different brain regions (as measured by ICA, ROI-to-ROI, ROI seed-to-voxel, and graph theory) is more commonly assessed than resting-state activity within a given region (as measured by ReHo and ALFF approaches) (Table 2). This prevalence rate can be observed across studies in CD, UC, and combined IBD groups. Employment of ReHo or ALFF in combination with a measure of inter-region functional connectivity is, in fact, more common than the independent application of either ReHo or ALFF.

Relative to resting-state metrics for activity within a given brain region, ALFF has been more commonly employed than ReHo. Of the metrics for functional connectivity between different brain regions/networks, studies employing ICA and ROI seed-to-voxel analysis outnumber those that apply ROI-to-ROI or graph theory. Graph theory is the least common approach for studying functional connectivity across different brain regions in studies of CD. Among the studies in UC and combined IBD, however, there is a more equal representation of functional connectivity approaches (Table 2).

Structural metrics are also sometimes employed in combination with functional connectivity metrics. For example, combinations of functional connectivity with VBM,[32] white matter microstructure,[28] and magnetic resonance spectroscopy[30] have been assessed. Multimodal approaches such as these are gaining in popularity, given their ability to integrate different kinds of data to provide a more comprehensive understanding of neural biomarkers in IBD.

Incorporation of additional variables of interest

The most common approach to assessing relationships between resting-state function and additional disease-specific, psychological, or cognitive measures has been to perform the central group contrasts (eg, CD or UC vs HC), extract the relevant parameter estimates from the resting-state data for the given (set of) ROI, and then separately assess the relationship between those variables using additional analyses (often, simply Pearson Correlation analysis), sometimes in separate statistical software. Of the additional variables considered, disease duration, depression, and anxiety emerge as the most prevalently examined across the literature. The hospital anxiety and depression scale (HADS[50]) is widely employed to assess anxiety and depression via separate subscales. These measures are most commonly assessed via correlation analyses. Abdominal pain is measured in some studies (via visual analogue scale), however, there are varied approaches taken to incorporate this variable. For example, Chen et al. and Bao et al. formed participant groups based on the presence or absence of abdominal pain in CD to directly contrast groups based on this symptom.[25,37] Thapaliya et al. directly incorporated abdominal pain scores as a continuous variable into resting-state analysis to assess which brain regions exhibited a significant relationship between functional connectivity and abdominal pain. Others report but do not directly integrate pain scores into resting-state analysis. Less frequently, serum C-reactive protein, erythrocyte sedimentation rate, and faecal calprotectin (Calpro) have been reported among some studies that included participants with CD.[22,28,33,34,41] With the exception of Goodyear et al., however, these variables have generally not been integrated directly into resting-state analysis.

In addition, there is a smaller subset of research on resting-state changes in IBD associated with different interventions. The impact of electro-acupuncture and moxibustion on brain resting-state activity[51] and functional connectivity[52] before and after treatment among those with CD have been explored. Additionally, Neeb et al. studied the impact of transcranial direct current stimulation on pain reduction and associated functional connectivity in a mixed sample of participants with CD or UC with varying disease activity.[53] Critically, while the vast majority of research on rs-fMRI in IBD has been cross-sectional, these intervention-focussed studies offer repeated measures of neuroimaging (and other relevant variables) over time.

Broad overview of findings

Drawing general conclusions about IBD-related differences in brain resting-state function is complicated by the varied methodological approaches in the area. The disparity in the sheer volume of research focussed on CD as opposed to UC or mixed subtypes simultaneously confers a more advanced and complex perspective on resting-state differences in CD. Repeated comparison of subgroups categorized by disease activity across studies in CD suggest differences for both active and inactive CD states compared with HC, in addition to differences between the 2 disease states. While the nature of differences between CD disease states (active vs remission) varies across studies based on resting-state metric employed, there are several brain regions that emerge more broadly across the CD-focussed literature. These include the cingulate cortex (anterior, middle, and posterior aspects), the precuneus, the hippocampus, the parahippocampal gyrus, the superior frontal gyrus, the supplementary motor area, the supramarginal gyrus, and the superior parietal lobes. The differences associated with these regions represent differences across various established resting-state networks—most prominently, the default mode network, fronto-parietal network, and salience network, although CD has been found to exhibit differences relative to both visual and language networks as well.

While the present review offers a brief summary of brain regions commonly associated with differences in resting state for CD (collapsing across assessments of localized spontaneous activity and functional connectivity as well as active/remission disease state), a more thorough review of resting-state results for UC as well as CD should be performed in the context of resting-state activity as well as functional

Table 2. The use of resting-state activity and functional connectivity metric organized by study.

Study by author and year	ReHo	ALFF	ICA	ROI-to-ROI	ROI seed-to-voxel	Graph theory	Combined assessment of activity and functional connectivity
Crohn's disease							
Huang et al. (2024)	No	Yes	No	No	Yes	No	Yes
Sun et al. (2024)	No	No	No	No	Yes	No	
Thapaliya et al. (2023)	No	No	Yes	No	No	No	
Chen et al. (2023)	No	No	No	No	Yes	No	
Agostini et al. (2023)	No	No	Yes	No	No	No	
Li et al. (2022)	No	No	Yes	No	No	No	
Qiu et al. (2022)	No	No	No	Yes	No	No	
Zhang et al. (2022)	No	No	No	No	Yes	No	
Huang et al. (2022)	Yes	No	No	No	No	No	
Kong et al. (2022)	No	Yes	No	No	No	No	
Li et al. (2021)	Yes	Yes	No	No	Yes	No	Yes
Kornelsen et al. (2020)	No	No	Yes	Yes	No	No	
Fan et al. (2020)	No	No	No	No	Yes	No	
Hou et al. (2019)	No	No	No	Yes	No	No	
Bao et al. (2018)	No	Yes	No	No	Yes	No	Yes
Liu et al. (2018)	No	No	Yes	No	No	Yes	
Thomann et al. (2017)	No	No	Yes	No	No	No	
Bao et al. (2016)	Yes	No	No	No	No	No	
Ulcerative colitis							
Wang et al. (2022)	No	No	No	No	No	Yes + dynamic functional analysis	
Kornelsen et al. (2021)	No	No	Yes	Yes	No	No	
Fan et al. (2019)	No	Yes	No	No	Yes	No	Yes
IBD combined							
Wang et al. (2023)	No	No	No	No	Yes	No	
Deng et al. (2023)	No	No	No	No	No	Yes	
Goodyear et al. (2023)	No	Yes	No	Yes	No	No	Yes
Kornelsen et al. (2022)	No	No	Yes	Yes	No	No	
Prub et al. (2022)	No	No	Yes	No	No	No	
Thomann et al. (2021)	Yes	Yes	Yes	No	No	No	No

Studies comparing resting-state pre–post intervention are not listed above.
ALFF = amplitude of low-frequency fluctuations; ICA = independent component analysis; ReHo = regional homogeneity; ROI = region of interest.

connectivity. Armed with stronger conclusions regarding the specificity of the resting-state differences in CD and UC, further comparisons can be made to determine whether the observed differences are unique to IBD or more generalizable to other immune-mediated inflammatory diseases like rheumatoid arthritis.

Of the few studies that directly contrast CD to UC, those that report a significant difference between the groups suggest greater resting activity and functional connectivity for UC, spanning regions in frontal, parietal, and occipital cortices.[9,42] While Fan et al. did limit UC participants to those in an active state,[40] research on resting state in UC has yet to otherwise establish a distinction between disease activity states.

Beyond these most essential differentiations in the research outcomes (and the scope of the present review), one can also consider outcomes related to the multitude of psychological and cognitive covariates that have been explored. Indeed, some studies have found that differences in resting-state function for participants with IBD are correlated (either negatively or positively) with self-report measures of pain[24,25,37] or psychological or cognitive assessment scores.[29,30,35,36]The reproducibility of these findings would be strengthened by continuing research in the area, as the nature of the relationship and brain regions identified in these findings are not consistent across all studies that include these measures as additional variables of interest.

Future directions

A widespread limitation and area for improvement is the limited sample size that hampers the incorporation of additional variables of interest directly into the rs-fMRI data analysis. While many studies include the collection and reporting of variables like disease activity/severity scores, these measures are included as a group contrast variable/predictor variable in the resting–state analysis of less than half of CD-focussed papers, and none of the UC-focussed papers. The sample sizes across the literature considered in this review have been sufficient for the main group comparisons performed (most commonly: CD vs HC, UC vs HC, IBD vs HC), but further assessment of categorical groupings defined by both IBD subtype and disease activity have less commonly been employed due to lower group sample sizes. Differences between active and inactive disease states have been found among the studies that have focussed on statistically comparing the resting-state correlates of disease activity in IBD, highlighting a need for further research to explore how disease state may interact with the relationship between resting-state difference and participants' experience of comorbidities including depression, anxiety, fatigue, and cognitive performance.

Greater sample size would also more strongly support the direct integration of additional continuous variables as predictors in resting-state functional analysis. While extracting the relevant resting-state analysis output and performing separate statistical analyses to test for associations with additional variables facilitates an assessment of the relationship between additional variables and output from ROIs identified by initial group contrasts (ex: CD vs HC), this approach omits examination of the main effect of those variables in relation to other brain regions among those with IBD, or potential interactions involving the grouping variable and resting-state metrics from across the brain.

Another stark finding is the lack of longitudinal research designs examining resting-state activity or functional connectivity in IBD. With the exception of the handful of studies that assessed the efficacy of interventions to restore resting-state function in IBD to that observed in HC, the research on resting-state alterations in IBD is exclusively cross-sectional. Pursuing longitudinal research designs would provide invaluable insight into changes in brain function and structure over time. Such data could be used to advance our understanding of causal mechanisms in the pathophysiology of IBD and its psychological and cognitive comorbidities and provide crucial insight into developmental and age-related progression of changes to brain resting-state function in IBD—an area that has yet to be extensively explored.

Finally, as initially acknowledged, there is potential for implications from rs-fMRI research to translate into clinical applications in IBD, including guiding the development of future interventions. For example, the identification of brain imaging biomarkers of depression in IBD would be advantageous for tailoring pharmacological or non-invasive brain stimulation (e.g., transcranial direct current stimulation) treatments for those experiencing depression in IBD. Incorporation of multimodal data collection and integrative analysis approaches can be employed to provide knowledge on the relationship between varied measures including structural and functional magnetic resonance imaging, psychological and cognitive measures, inflammatory markers, genetics, and more. The Canadian Biomarker Integration Network in Depression reported that the multimodal combination of clinical, neuroimaging, and molecular data decreased the misclassification of individuals' response to treatment to 37.4% compared to the 46.9% obtained by single modality measures.[54] The synthesis of multimodal neuroimaging data has already shown a clinically useful 82% efficacy in predicting remission of depression following electroconvulsive therapy.[55] Insight from rs-fMRI research could further be incorporated into interventions that use neurofeedback with the help of real-time fMRI[56] to target cortical or subcortical regions identified by rs-fMRI research. Regardless of the direction that future clinical research may take in building on the resting state changes in IBD, there is fundamental value in advancing our understanding of the functioning of the brain–gut axis and the mechanisms by which it is altered in IBD.

Conclusion

Across the literature examining differences in resting-state function in IBD, there is marked variability in the methodology applied in relation to sample participant characteristics, analysis approaches, and variables of interest. Far more studies have focussed on CD than on UC or mixed IBD subtype participant samples, and CD has rarely been directly statistically compared to UC (a clear gap in the literature to be addressed moving forward). To continue in the remarkable progress that research in this area has made in recent years, future research should seek to increase sample sizes to afford more comprehensive analyses and integration of multimodal approaches as well as employing more longitudinal research designs to address research questions related to causal mechanisms in the pathophysiology of IBD.

Acknowledgments

T.A.M. and J.K. conceived the review topic and drafted the manuscript. C.N.B. provided essential review and feedback.

Supplement sponsorship

This article appears as part of the supplement "27th Anniversary Key Topics in Gastroenterology in 2024." The symposium and this supplement were funded by grants from the following sponsors:

- Platinum: Abbvie Canada, Janssen Inc, Pfizer Canada, Takeda Canada, Fresenius-Kabi
- Silver: Boston Scientific, Ferring Pharmaceuticals, Organon, Eli Lilly and Company

Conflicts of interest

The authors report no conflicts of interest.

In addition to this COI statement, ICMJE disclosure forms have been collected for all co-authors and can be accessed as supplementary material here.

Data availability

There are no new data associated with this article.

References

1. Singh N, Bernstein CN. Environmental risk factors for inflammatory bowel disease. *United European Gastroenterol J*. 2022;10(10):1047–1053. https://doi.org/10.1002/ueg2.12319
2. Burisch J, Munkholm P. The epidemiology of inflammatory bowel disease. *Scand J Gastroenterol*. 2015;50(8):942–951. https://doi.org/10.3109/00365521.2015.1014407
3. Neuendorf R, Harding A, Stello N, Hanes D, Wahbeh H. Depression and anxiety in patients with inflammatory bowel disease: a systematic review. *J Psychosom Res*. 2016;87:70–80. https://doi.org/10.1016/j.jpsychores.2016.06.001
4. Barberio B, Zamani M, Black CJ, Savarino EV, Ford AC. Prevalence of symptoms of anxiety and depression in patients with inflammatory bowel disease: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol*. 2021;6(5):359–370. https://doi.org/10.1016/S2468-1253(21)00014-5
5. Yongwen Ng J, Chauhan U, Armstrong D, et al. A comparison of the prevalence of anxiety and depression between uncomplicated and complex IBD patient groups. *Gastroenterol Nurs*. 2018;41(5):427–435. https://doi.org/10.1097/SGA.0000000000000338
6. Hopkins CW, Powell N, Norton C, Dumbrill JL, Hayee H, Moulton CD. Cognitive impairment in adult inflammatory bowel disease: a systematic review and meta-analysis. *J Acad Consult Liaison Psychiatry*. 2021;62(4):387–403. https://doi.org/10.1016/j.psym.2020.10.002
7. D'Silva A, Fox DE, Nasser Y, et al. Prevalence and risk factors for fatigue in adults with inflammatory bowel disease: a systematic review with meta-analysis. *Clin Gastroenterol Hepatol*. 2022;20(5):995–1009.e7. https://doi.org/10.1016/j.cgh.2021.06.034
8. Kredentser MS, Graff LA, Bernstein CN. Psychological comorbidity and intervention in inflammatory bowel disease. *J Clin Gastroenterol*. 2021;55(1):30–35. https://doi.org/10.1097/MCG.0000000000001463
9. Kornelsen J, Witges K, Labus J, Mayer EA, Bernstein CN. Brain structure and function changes in inflammatory bowel disease. *Neuroimage Rep*. 2022;2(2):100097. https://doi.org/10.1016/j.ynirp.2022.100097
10. Zhang S, Chen F, Wu J, et al. Altered structural covariance and functional connectivity of the insula in patients with Crohn's disease. *Quant Imaging Med Surg*. 2022;12(2):1020–1036. https://doi.org/10.21037/qims-21-509
11. Kornelsen J, McIver T, Uddin MN, et al.; Comorbidity and Cognition in Multiple Sclerosis (CCOMS) Study Group. Altered voxel-based and surface-based morphometry in inflammatory bowel disease. *Brain Res Bull*. 2023;203:110771. https://doi.org/10.1016/j.brainresbull.2023.110771
12. Hou J, Dodd K, Nair VA, et al. Alterations in brain white matter microstructural properties in patients with Crohn's disease in remission. *Sci Rep*. 2020;10(2145):1–9. https://doi.org/10.1038/s41598-020-59098-w
13. De Rosa AP, Esposito F, Valsasina P, et al.; INNI Network. Resting-state functional MRI in multicenter studies on multiple sclerosis: a report on raw data quality and functional connectivity features from the Italian Neuroimaging Network Initiative. *J Neurol*. 2023;270(2):1047–1066. https://doi.org/10.1007/s00415-022-11479-z
14. Flodin P, Martinsen S, Altawil R, et al. Intrinsic brain connectivity in chronic pain: a resting-state fMRI study in patients with rheumatoid arthritis. *Front Hum Neurosci*. 2016;10(Mar 2016):107. https://doi.org/10.3389/fnhum.2016.00107
15. Gajofatto A, Cardobi N, Gobbin F, Calabrese M, Turatti M, Benedetti MD. Resting-state functional connectivity in multiple sclerosis patients receiving nabiximols for spasticity. *BMC Neurol*. 2023;23(1):128. https://doi.org/10.1186/s12883-023-03171-0
16. Hajebrahimi F, Velioglu HA, Bayraktaroglu Z, Helvaci Yilmaz N, Hanoglu L. Clinical evaluation and resting state fMRI analysis of virtual reality based training in Parkinson's disease through a randomized controlled trial. *Sci Rep*. 2022;12(1):8024. https://doi.org/10.1038/s41598-022-12061-3
17. Hou J, Mohanty R, Nair VA, et al. Alterations in resting-state functional connectivity in patients with Crohn's disease in remission. *Sci Rep*. 2019;9(7412):1–9. https://doi.org/10.1038/s41598-019-43878-0
18. Nieto-Castanon A. Functional connectivity measures. In: *Handbook of Functional Connectivity Magnetic Resonance Imaging methods in CONN*. Hilbert Press; 2020.
19. Wang J, Zuo X, He Y. Graph-based network analysis of resting-state functional MRI. *Front Syst Neurosci*. 2010;4(June):1–14. https://doi.org/10.3389/fnsys.2010.00016
20. Zang Y, Jiang T, Lu Y, He Y, Tian L. Regional homogeneity approach to fMRI data analysis. *Neuroimage*. 2004;22(1):394–400. https://doi.org/10.1016/j.neuroimage.2003.12.030
21. Chen F, Wang L, Ding Z. Alteration of whole-brain amplitude of low-frequency fluctuation and degree centrality in patients with mild to moderate depression: a resting-state functional magnetic resonance imaging study. *Front Psychiatry*. 2022;13:1–9. https://doi.org/10.3389/fpsyt.2022.1061359
22. Huang M, Ma G, Zou Y, et al. A potential brain functional biomarker distinguishing patients with Crohn's disease with different disease stages: a resting-state fMRI study. *Front Neurosci*. 2024;18:1–11. https://doi.org/10.3389/fnins.2024.1361320
23. Sun J, Sun W, Yue K, et al. Abnormal amygdala subregion functional connectivity in patients with Crohn's disease with or without anxiety and depression. *Behav Neurol*. 2024;2024:1–7. https://doi.org/10.1155/2024/1551807
24. Thapaliya G, Eldeghaidy S, Radford SJ, Francis ST, Moran GW. An examination of resting-state functional connectivity in patients with active Crohn's disease. *Front Neurosci*. 2023;17:1265815. https://doi.org/10.3389/fnins.2023.1265815
25. Chen F, Zhang S, Li P, et al. Disruption of periaqueductal gray-default mode network functional connectivity in patients with Crohn's Disease with abdominal pain. *Neuroscience*. 2023;517:96–104. https://doi.org/10.1016/j.neuroscience.2023.03.002

26. Agostini A, Benuzzi F, Ballotta D, Rizzello F, Gionchetti P, Filippini N. Differential brain structural and functional patterns in Crohn's disease patients are associated with different disease stages. *Inflamm Bowel Dis*. 2023;29(8):1297–1305. https://doi.org/10.1093/ibd/izad029
27. Li L, Ma J, Hua X, et al. 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;16:1–9. https://doi.org/10.3389/fnins.2022.855470
28. Qiu Y, Li Q, Wu D, et al. Altered mean apparent propagator-based microstructure and the corresponding functional connectivity of the parahippocampus and thalamus in Crohn's disease. *Front Neurosci*. 2022;16:1–10. https://doi.org/10.3389/fnins.2022.985190
29. Huang M, Li X, Fan W, et al. Alterations of regional homogeneity in Crohn's disease with psychological disorders: a resting-state fMRI Study. *Front Neurol*. 2022;13:1–10. https://doi.org/10.3389/fneur.2022.817556
30. Kong N, Gao C, Zhang F, et al. Neurophysiological effects of the anterior cingulate cortex on the exacerbation of Crohn's disease: a combined fMRI–MRS study. *Front Neurosci*. 2022;16:1–10. https://doi.org/10.3389/fnins.2022.840149
31. Li L, Ma J, Xu JG, et al. Brain functional changes in patients with Crohn's disease: a resting-state fMRI study. *Brain Behav*. 2021;11(8):1–10. https://doi.org/10.1002/brb3.2243
32. Kornelsen J, Wilson A, Labus JS, Witges K, Mayer EA, Bernstein CN. Brain resting-state network alterations associated with Crohn's disease. *Front Neurol*. 2020;11:1–9. https://doi.org/10.3389/fneur.2020.00048
33. Fan Y, Bao C, Wei Y, et al. Altered functional connectivity of the amygdala in Crohn's disease. *Brain Imaging Behav*. 2020;14(6):2097–2106. https://doi.org/10.1007/s11682-019-00159-8
34. Bao C, Liu P, Liu H, et al. Difference in regional neural fluctuations and functional connectivity in Crohn's disease: a resting-state functional MRI study. *Brain Imaging Behav*. 2018;12(6):1795–1803. https://doi.org/10.1007/s11682-018-9850-z
35. Liu P, Li R, Bao C, et al. Altered topological patterns of brain functional networks in Crohn's disease. *Brain Imaging Behav*. 2018;12(5):1466–1478. https://doi.org/10.1007/s11682-017-9814-8
36. Thomann A, Griebe M, Thomann P, Reindl W, Wolf C. Altered intrinsic brain function in Crohn's disease. *J Crohns Colitis*. 2017;11(suppl_1):S126–S127. https://doi.org/10.1093/ecco-jcc/jjx002.225
37. Bao CH, Liu P, Liu HR, et al. Differences in regional homogeneity between patients with Crohn's disease with and without abdominal pain revealed by resting-state functional magnetic resonance imaging. *Pain*. 2016;157(5):1037–1044. https://doi.org/10.1097/j.pain.0000000000000479
38. Wang H, Labus JS, Griffin F, et al. Functional brain rewiring and altered cortical stability in ulcerative colitis. *Mol Psychiat*. 2022;27(3):1792–1804. https://doi.org/10.1038/s41380-021-01421-6
39. Kornelsen J, Witges K, Labus J, Mayer EA, Bernstein CN. Brain structure and function changes in ulcerative colitis. *Neuroimage Rep*. 2021;1(4):100064. https://doi.org/10.1016/j.ynirp.2021.100064
40. Fan W, Zhang S, Hu J, et al. Aberrant brain function in active-stage ulcerative colitis patients: a resting-state functional MRI study. *Front Hum Neurosci*. 2019;13:1–10. https://doi.org/10.3389/fnhum.2019.00107
41. Goodyear BG, Heidari F, Ingram RJM, et al. Multimodal brain MRI of deep gray matter changes associated with inflammatory bowel disease. *Inflamm Bowel Dis*. 2023;29(3):405–416. https://doi.org/10.1093/ibd/izac089
42. Thomann AK, Schmitgen MM, Kmuche D, et al. Exploring joint patterns of brain structure and function in inflammatory bowel diseases using multimodal data fusion. *Neurogastroenterol Motil*. 2021;33(6):1–10. https://doi.org/10.1111/nmo.14078
43. Wang J, Liu G, Xu K, Ai K, Huang W, Zhang J. The role of neurotransmitters in mediating the relationship between brain alterations and depressive symptoms in patients with inflammatory bowel disease. *Hum Brain Mapp*. 2023;44(16):5357–5371. https://doi.org/10.1002/hbm.26439
44. Deng J, Sun J, Lu S, et al. Exploring neural activity in inflammatory bowel diseases using functional connectivity and DKI–fMRI fusion. *Behav Brain Res*. 2023;443(April):114325. https://doi.org/10.1016/j.bbr.2023.114325
45. Prüß MS, Bayer A, Bayer KE, et al. Functional brain changes due to chronic abdominal pain in inflammatory bowel disease: a case–control magnetic resonance imaging study. *Clin Transl Gastroenterol*. 2022;13(2):e00453. https://doi.org/10.14309/ctg.0000000000000453
46. Evertsz' FB, Hoeks CCMQ, Nieuwkerk PT, et al. Development of the patient Harvey Bradshaw index and a comparison with a clinician-based Harvey Bradshaw index assessment of Crohn's disease activity. *J Clin Gastroenterol*. 2013;47(10):850–856. https://doi.org/10.1097/mcg.0b013e31828b2196
47. Powell-Tuck J, Bown RL, Lennard-Jones JE. A comparison of oral prednisolone given as single or multiple daily doses for active proctocolitis. *Scand J Gastroenterol*. 1978;13(7):833–837. https://doi.org/10.3109/00365527809182199
48. Best WR, Becktel JM, Singleton JW. Rederived values of the eight coefficients of the Crohn's Disease Activity Index (CDAI). *Gastroenterology*. 1979;77(4 Pt 2):843–846. https://doi.org/10.1016/0016-5085(79)90384-6
49. Irvine EJ, Feagan B, Rochon J, et al. Quality of life: a valid and reliable measure of therapeutic efficacy in the treatment of inflammatory bowel disease. Canadian Crohn's Relapse Prevention Trial Study Group. *Gastroenterology*. 1994;106(2):287–296. https://doi.org/10.1016/0016-5085(94)90585-1
50. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand*. 1983;67(6):361–370. https://doi.org/10.1111/j.1600-0447.1983.tb09716.x
51. Bao C, Liu P, Liu H, et al. Different brain responses to electro-acupuncture and moxibustion treatment in patients with Crohn's disease. *Sci Rep*. 2016;6(36636):1–12. https://doi.org/10.1038/srep36636
52. Bao C, Wang D, Liu P, et al. Effect of electro-acupuncture and moxibustion on brain connectivity in patients with Crohn's disease: a resting-state fMRI study. *Front Hum Neurosci*. 2017;11(559):1–10. https://doi.org/10.3389/fnhum.2017.00559
53. Neeb L, Bayer A, Bayer KE, et al. Transcranial direct current stimulation in inflammatory bowel disease patients modifies resting-state functional connectivity: a RCT. *Brain Stimul*. 2019;12(4):978–980. https://doi.org/10.1016/j.brs.2019.03.001
54. Sajjadian M, Uher R, Ho K, et al. Prediction of depression treatment outcome from multimodal data: a CAN-BIND-1 report. *Psychol Med*. 2023;53(12):5374–5384. https://doi.org/10.1017/S0033291722002124
55. Bruin WB, Oltedal L, Bartsch H, et al. Development and validation of a multimodal neuroimaging biomarker for electroconvulsive therapy outcome in depression: a multicenter machine learning analysis. *Psychol Med*. 2023;54(3):495–506. https://doi.org/10.1017/s0033291723002040
56. Tsuchiyagaito A, Smith JL, El-Sabbagh N, et al. Real-time fMRI neurofeedback amygdala training may influence kynurenine pathway metabolism in major depressive disorder. *Neuroimage Clin*. 2021;29:1–10. https://doi.org/10.1016/j.nicl.2021.102559