

# Functional Brain Changes Due to Chronic Abdominal Pain in Inflammatory Bowel Disease: A Case-Control Magnetic Resonance Imaging Study

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**INTRODUCTION:** Various chronic pain conditions go along with functional and structural brain changes. This study aimed to investigate functional and structural brain changes by magnetic resonance imaging (MRI) in inflammatory bowel disease (IBD) patients with chronic abdominal pain.

**METHODS:** Sixty-four subjects were included in the final analysis (32 IBD patients with chronic abdominal pain; 32 age-matched and sex-matched controls). All patients suffered from chronic abdominal pain, defined as a score of  $\geq 3/10$  on the visual analog scale for at least 3 months in the past 6 months. Besides structural MRI, resting state functional MRI was used to compare functional connectivity of 10 networks between groups.

**RESULTS:** Patients with IBD showed no structural brain alterations but a significantly increased resting state functional connectivity of the secondary somatosensory cortex within the salience network.

**DISCUSSION:** Because the secondary somatosensory cortex saves sensory stimuli and compares novel information with latter experiences, these functions may be maladaptive in IBD patients with abdominal pain.

**SUPPLEMENTARY MATERIAL** accompanies this paper at <http://links.lww.com/CTG/A745>, <http://links.lww.com/CTG/A746>

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## INTRODUCTION

Chronic abdominal pain represents one of the main disease burdens in patients with inflammatory bowel disease (IBD). While present in up to 38% of all patients with IBD (1), it is associated with decreased quality of life and increased disease-specific suffering and psychiatric comorbidities (1).

Modern neuroimaging techniques, such as resting state functional magnetic resonance imaging (rs-fMRI), voxel-based morphometry (VBM), and diffusion tensor imaging (DTI), revealed that various chronic pain conditions are associated with functional and structural changes of brain regions involved in pain processing, memorizing, and sensation (2). However, only a few studies so far evaluated brain changes specifically in patients with IBD. Results of these studies are heterogeneous and partially conflicting: In structural MRI, areas of increased and/or decreased gray matter volumes (GMVs) were found (3–6). Two studies investigated rs-fMRI in patients with IBD (7,8). Assessing

alterations in the functional connectivity in so-called resting state networks (SNs), which are intrinsic networks that reflect fundamental functional characteristics of the brain, revealed an abnormal connectivity in the default mode network, which is active during rest and daydreaming, in Crohn disease (CD) (8).

Although previous neuroimaging studies identified structural and functional brain alterations in CD and/or ulcerative colitis (UC) with/without pain, no study included specifically a group of IBD patients with chronic abdominal pain. Thus, this study applied structural MRI and rs-fMRI to analyze brain changes in IBD patients with chronic abdominal pain compared with age-matched and sex-matched controls.

## METHODS

The study conformed to the Declaration of Helsinki and was approved by the local ethics committee (Charité—Universitätsmedizin Berlin, Germany; ClinicalTrials.gov identifier: NCT02433470).

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Participants read and signed written informed consent. Subjects completed (i) eligibility screening (inclusion criteria: 18–80 years; IBD diagnosis; chronic abdominal pain defined as  $\geq 3$  months in the past 6 months; and pain intensity of  $\geq 3/10$  on the visual analog scale), (ii) baseline assessments (pain measurements, disease relevant questionnaires, and blood/stool samples), and (iii) an MRI scan (3 Tesla MRI with a 32-channel head coil [Tim Trio; Siemens, Erlangen, Germany]). In addition, we screened individually age-matched (maximal  $\pm 2$  years difference) and sex-matched healthy controls without any history of IBD and/or chronic abdominal pain. The following three MRI-sequences were acquired: (i) GMV using VBM (high-resolution 3D T1-weighted MRI using a magnetization-prepared rapid gradient echo sequence); (ii) white matter using DTI (single-shot echo-planar imaging sequence); and (iii) rs-fMRI acquired spontaneous fluctuations in the blood oxygen level dependent signal and an isotropic T2-weighted fluid-attenuated inversion recovery sequence.

Whole-brain DTI analysis using tract-based spatial statistics and whole-brain voxel-based morphometry were performed as described previously (9,10) using the FMRIB Software Library (version 5.0) and the VBM8 Toolbox incorporated in SPM8 (<http://www.fil.ion.ucl.ac.uk/spm/>) running on MATLAB R2011b. Analysis of resting state functional connectivity of 10 well-identified resting SNs was performed with independent component analysis and dual regression using FMRIB Software Library. Detailed description of MRI processing and statistical analysis are provided in the Supplementary Materials (see Supplementary Digital Content 1, <http://links.lww.com/CTG/A746>).

## RESULTS

Seventy subjects were included: 36 patients with IBD (mean age:  $33.19 \pm 9.65$  years; men: 8, women: 28) and 34 controls (mean age:  $33.38 \pm 8.90$  years; men: 8, women: 26). However, only 64 subjects were taken into further analyses because of disruptive

factors (Figure 1). Baseline characteristics are summarized in Table 1 and further detailed in Supplementary Table 1 (see Supplementary Digital Content 2, <http://links.lww.com/CTG/A745>). No significant baseline differences were present between groups.

No statistically significant differences were detected between patients with IBD and healthy controls in structural MRI (VBM and DTI). In addition, correlation analysis with pain measurements, scores in questionnaires (Harvey-Bradshaw Index, Inflammatory Bowel Disease Questionnaire for Quality of Life, irritable bowel syndrome-severity scoring system, and Pain Catastrophizing Scale), and duration of disease did not reveal significant associations.

However, when analyzing 10 identified common rs-fMRI networks, IBD patients with chronic abdominal pain showed a significantly increased resting state functional connectivity of the left secondary somatosensory cortex with the salience resting SN (Montreal Neurological Institute coordinates peak-voxel  $-56; 28; 20$ ,  $P = 0.036$ ) (Figure 2).

## DISCUSSION

Using VBM and DTI, we did not detect any significant structural alteration of gray and white matter of patients with IBD-associated chronic abdominal pain compared with healthy controls. Using rs-fMRI, we identified an increased functional connectivity of the left secondary somatosensory cortex with the salience resting SN in patients with IBD-associated chronic abdominal pain.

The key regions of the SN include the anterior insular cortex and the dorsal anterior cingulate cortex, which are both connected with the somatosensory cortex and all are activated by noxious or painful stimuli. The SN plays an important role in behavioral salient events and is involved in the regulation of cognitive control (11). Alterations of the SN were found in other chronic pain conditions, such as failed back surgery syndrome, persistent somatoform disorder, and cluster headache. It has been widely described that central chronification

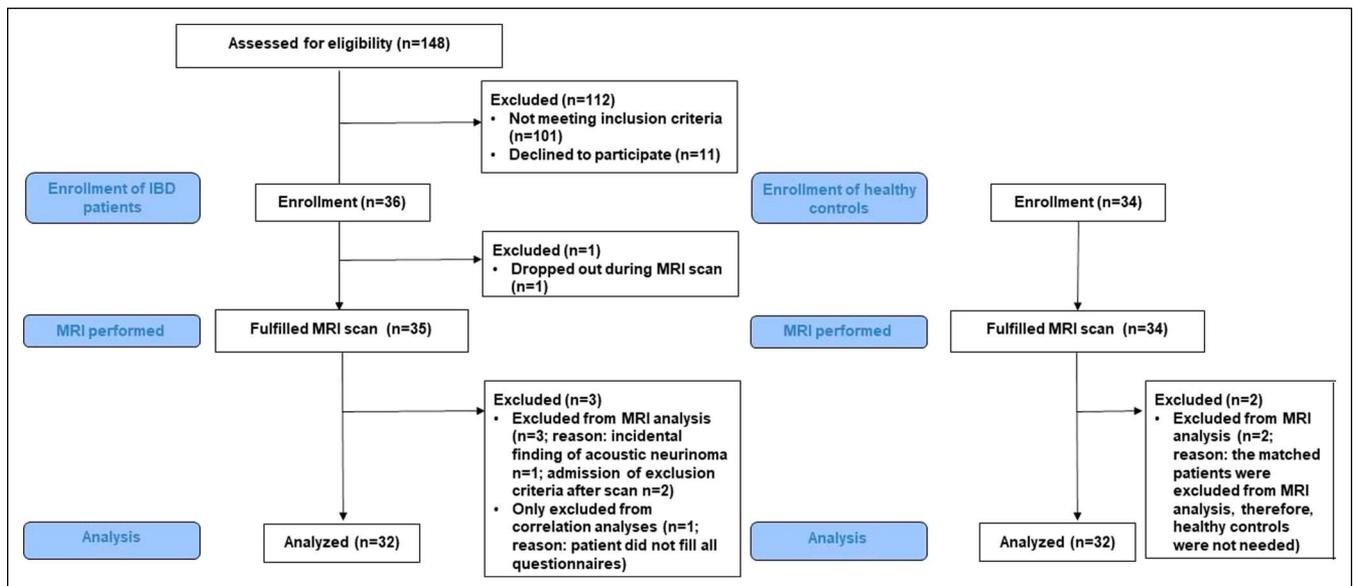


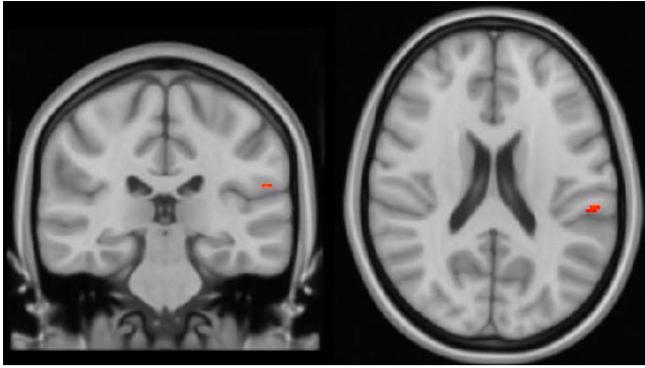
Figure 1. Flow chart of study enrollment/analyses. MRI, magnetic resonance imaging.

**Table 1. Disease characteristics**

	Patients	Controls	P
Number (n)	32	32	
Sex (n)			
Male	7	7	1.0
Female	25	25	1.0
Age, yr	33.19 ± 9.65	33.38 ± 8.90	0.94
Handedness (n)			
Right	30	30	
Left	2	2	
BMI	24.11 ± 4.45	23.51 ± 4.24	0.59
Disease (n)			
Ulcerative colitis	6	—	
Crohn disease	26	—	
Duration of disease, yr	8.64 ± 7.63	—	
Disease activity score (SCCAI or HBI)	3.74 ± 3.56	—	
Medication (n)			
Conventional immunosuppressants <sup>a</sup>	18	—	
Anti-TNF antibody	19	—	
Pain medication—regular intake	14	—	
Site of maximal pain (n)			
Right	22	—	
Left	3	—	
Diffuse	7	—	
Baseline values—questionnaires			
Pain Catastrophizing Scale [highest possible score: 52]	21.84 ± 10.53	—	
Becks Depression Inventory [highest possible score: 63]	12.45 ± 6.81	—	
IBD-Q [highest possible score: 224]	142.52 ± 30.12	—	
IBS-SSS [highest possible score: 500]	247.94 ± 82.76	—	
Average pain in the last 6 mo, VAS (0–10)	5.08 ± 1.42	—	
Baseline values—pain			
PPT, right abdomen, kg	1.76 ± 0.63	—	
PPT, left abdomen, kg	1.89 ± 0.78	—	
PPT, right hand, kg	4.36 ± 1.2	—	
PPT, hand left, kg	4.19 ± 1.13	—	
VFM, right abdomen, kg	190.08 ± 125.47	—	
VFM, left abdomen, kg	191.54 ± 131	—	
VFM, right hand, kg	200.52 ± 118.90	—	
VFM, hand left, kg	185.97 ± 125.82	—	
Baseline values—inflammatory markers			
ESR, mm/hr [normal: <20 mm/hr]	18.19 ± 15.44	—	
CRP, mg/L [normal: <5 mg/L]	7.54 ± 13.09	—	
Calprotectin, mg/kg [normal: <50 mg/kg]	430.52 ± 381.07	—	

Data presented in mean ± SD. Disease activity was measured with either the Simple Clinical Colitis Activity Index (SCCAI) or Harvey-Bradshaw Index (HBI). CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IBS-SSS, irritable bowel syndrome severity scoring system; IBD-Q, inflammatory bowel disease questionnaire for quality of life; PPT, pain pressure threshold; TNF, tumor necrosis factor; VAS, visual analog scale; VFM, Von-Frey monofilaments.

<sup>a</sup>Includes corticosteroids, azathioprine, methotrexate, mesalazine, and 6-mercaptopurine.



**Figure 2.** Significant increased functional connectivity within the salience network. Dual regression independent component analysis found that salience network resting state functional connectivity is altered by chronic abdominal pain in patients with IBD. Compared with controls, the IBD group showed a significantly increased functional connectivity of the left secondary somatosensory cortex with the salience network (Montreal Neurological Institute coordinates peak-voxel  $-56; 28; 20$ ,  $P = 0.036$ ; FWE corrected for multiple comparisons). FWE, family-wise error; IBD, inflammatory bowel disease.

mechanisms are based on functional activity changes and hyperexcitability in pain-related neuronal networks (12). A recent study revealed an increased connectivity between the functionally localized back representation in the somatosensory cortex and the SN in patients with chronic lower back pain (13). In line, we found evidence that functional connectivity differs in IBD patients with abdominal pain. Thus, alterations in the connectivity of the SN to other pain-processing brain areas may play a role in the development and maintenance of chronic pain in IBD. Indeed, the secondary somatosensory cortex is involved in saving experiences of previous stimuli and the comparison of novel information with latter sensory experiences. Thus, these brain functions may be altered in patients with IBD suffering from abdominal pain.

Contrary to a study in CD, which identified an increased connectivity in the default mode network, we lack those findings (8). Previous structural MRI studies in IBD found contrary results: (i) decreased GMV in CD, but not in UC (4); (ii) increased white matter hyperintensities and decreased GMV in CD and UC (6); and (iii) a third study indicating parts with higher GMV in CD (5). Our study did not identify significant differences in structural MRI. This is in line with another study reporting an absence of changes in GMV of patients with UC in remission (4). However, results of these studies are difficult to compare because inclusion criteria differed (recruitment of either or both CD and/or UC patients with or without abdominal pain). In the future, more studies on structural MRI in a homogenous IBD cohort with large sample sizes are needed to finally answer the question whether there are changes in GMV.

This study has some limitations. First, because of ethical reasons, patients continued anti-inflammatory and analgesic medication, which may have influenced the results. However, medication had to remain stable for 4 weeks. Second, we focused on IBD patients with chronic abdominal pain but did not apply exclusion criteria for inflammatory state of disease. Third, the area of significance comprised only 5 voxels. This

is on the borderline of being interpreted as meaningful. In addition, because of the explorative character of the study, we did not adjust the  $P$  value for testing multiple networks. Nevertheless, significant findings located in areas associated with pain processing contribute to the understanding that functional connectivity may be altered in patients with IBD.

In summary, our study presents novel findings of an abnormal resting state functional connectivity of the secondary somatosensory cortex with the SN in IBD patients with chronic abdominal pain. These findings support the hypothesis that chronic abdominal pain affects the central nervous system and modulates functional brain connectivity.

## CONFLICTS OF INTEREST

**Guarantor of the article:** Magdalena S. Prüß, MD.

**Specific author contributions:** M.S.P.: study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, statistical analysis, obtained funding, and study supervision. A.B.: study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, and statistical analysis. K.-E.B.: study concept and design, acquisition of data, analysis and interpretation of data, and drafting of the manuscript. J.B.F. and M.S.: analysis and interpretation of data, critical revision of the manuscript for important intellectual content, and technical and material support. R.A.: analysis and interpretation of data and critical revision of the manuscript for important intellectual content. R.M.: critical revision of the manuscript for important intellectual content and technical and material support. B.S.: study concept and design, analysis and interpretation of data, critical revision of the manuscript for important intellectual content, and study supervision. L.N.: study concept and design, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, statistical analysis, and study supervision.

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## Study Highlights

### WHAT IS KNOWN

- ✓ Various chronic pain conditions lead to functional and structural brain changes.
- ✓ To date, only a few studies evaluated brain changes specifically in patients with inflammatory bowel disease (IBD).
- ✓ Results of these studies are heterogeneous and partially conflicting.

### WHAT IS NEW HERE

- ✓ Our study presents novel findings of an abnormal resting state functional connectivity of the salience resting state network with the left secondary somatosensory cortex in IBD patients with chronic abdominal pain.
- ✓ Because the secondary somatosensory cortex saves sensory stimuli and compares novel information with latter experiences, these functions may be maladaptive in IBD patients with abdominal pain.
- ✓ These findings support the hypothesis that chronic abdominal pain in IBD also affects the central nervous system and modulates functional brain connectivity.

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