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Transcranial direct current stimulation in inflammatory bowel disease patients modifies resting-state functional connectivity: A RCT

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ABSTRACT

Background: Chronic pain is known to be associated with functional and structural changes in the brain. Inflammatory bowel disease (IBD) presents with chronic abdominal pain in almost 35% of all patients. This study investigates structural and functional changes in magnetic resonance imaging (MRI) after transcranial direct current stimulation (tDCS) applied to ameliorate pain in IBD.
Methods: This phase-III, placebo-controlled, randomized study included 36 patients with IBD and chronic pain. MRI scans were performed before and following tDCS, which was applied for 5 days.
Results/conclusion: For the first time, this study revealed an association of changes in resting-state functional MRI and pain reduction in IBD. There was a significant increase in functional connectivity after active tDCS within the visual medial and the right frontoparietal network being connected with the amygdala, the insula, and the primary somatosensory cortex indicating central pain mechanisms in IBD. Moreover, tDCS offers a novel therapeutic strategy for abdominal pain.

Introduction

Approximately 35% of all patients with inflammatory bowel disease (IBD) present with chronic abdominal pain [11,12]. Chronic pain is known to result in functional and structural changes in the brain [1–7]. Imaging studies identified a hyperexcitability in pain-associated brain areas [2–5,7] including the limbic system, somatosensory cortex, and insula, which are part of the so-called “pain-matrix” [8–10]. Only few studies investigated magnetic resonance imaging (MRI) changes in patients with IBD and abdominal pain. One study using resting-state functional MRI (fMRI) found that Crohn's disease (CD) patients exhibited lower values in regional homogeneity in the insula, cingulate cortex, and supplementary motor area [11]. Thomann et al. found an abnormal connectivity in the so-called default mode network in CD [12].

Transcranial direct current stimulation (tDCS), a non-invasive brain stimulation technique, showed to significantly reduce chronic abdominal pain in IBD [13]. While the above-mentioned cross-sectional studies demonstrated changes in MRI, no longitudinal study to date assessed if tDCS affects brain plasticity and function in patients with IBD. Therefore, we investigated functional/structural brain changes in IBD patients with chronic abdominal pain undergoing a central pain therapy with tDCS.

Methods

This trial was designed in a double-blinded, randomized, placebo-controlled, parallel designed way (ClinicalTrials.gov_Identifier: NCT02433470). The study conformed to the

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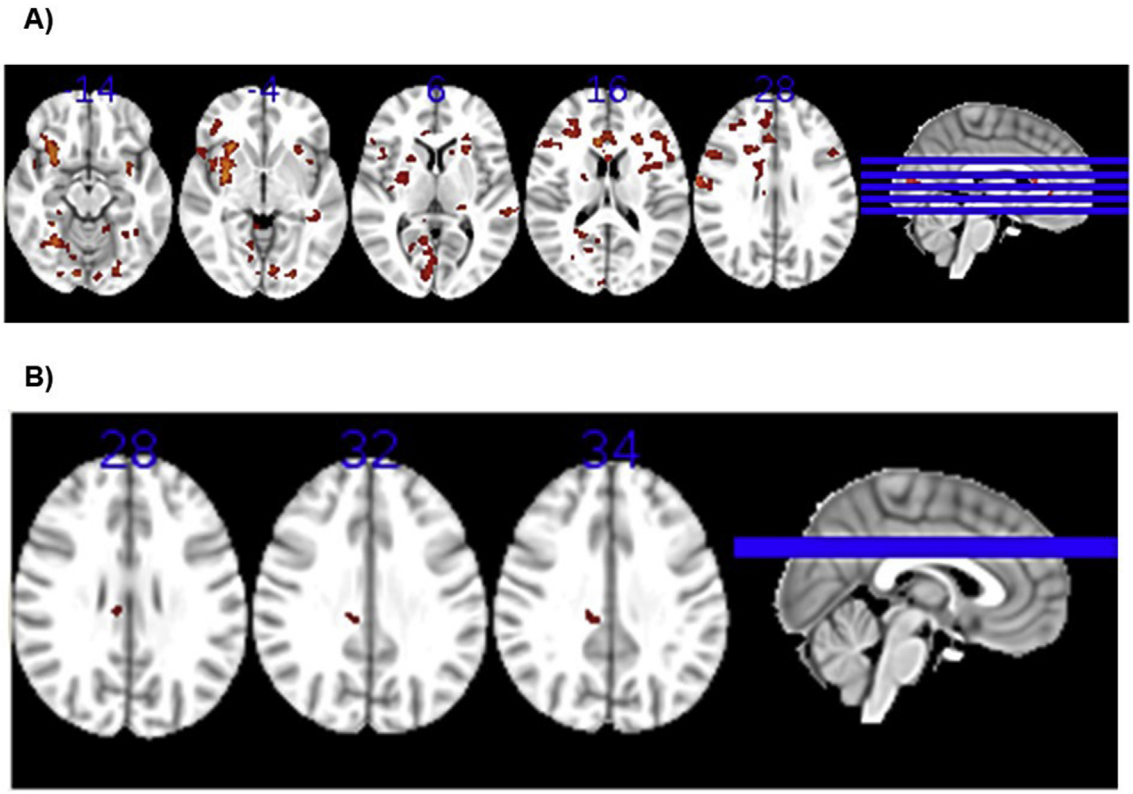

Fig. 1. Significantly increased functional connectivity. A). Significantly increased functional connectivity within the medial visual network. Comparison of the medial visual network between inflammatory bowel disease patients before and after a 5-day treatment with tCDS. After tCDS treatment, patients showed a significantly increased functional connectivity (in red) within the medial visual network bilaterally in the visual cortex (lingual gyrus, intracalcarine cortex, precuneus cortex, occipital pole and occipital fusiform gyrus). Increased functional connectivity was also detected in regions outside the visual network, predominantly in the insular cortex, postcentral gyrus, precentral gyrus on both sides as well in the right anterior division of the cingulate gyrus, but also bilaterally in parts of the temporal and frontal gyrus (paired *t*-test, $p < 0.05$, familywise error corrected). **B).** Significantly increased functional connectivity in the right fronto-parietal network. Comparison of the right fronto-parietal network between inflammatory bowel disease patients before and after a 5-day treatment with tCDS. After tCDS treatment, patients showed a significantly increased functional connectivity (in red) with the right fronto-parietal network in the posterior division of the right cingulate gyrus (paired *t*-test, $p < 0.05$, familywise error corrected). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Declaration of Helsinki and was approved by an ethic committee. Patients completed baseline assessments, 2 MRI scans (before and after therapy), 5-day tDCS (either anodal or placebo) and a follow-up evaluation (S_Figure_1). tDCS protocol, pain and other assessments has been described before [13].

Imaging

MRI examinations were performed with a 3-T MRI (Siemens, Tim Trio, Erlangen, Germany) scanner with a 32-channel head coil. We performed analyses of resting-state functional connectivity, white matter using diffusion tensor imaging (DTI) and gray matter using voxel-based morphometry (VBM). Exact MRI protocols were previously described [14,24,25]. Following sequences were acquired: (i) High-resolution 3D T1-weighted MRI scans using a magnetization-prepared rapid gradient echo sequence; (ii) DTI sequences using a single-shot echo-planar imaging sequence; (iii) BOLD resting-state scans using an echo-planar imaging sequence; (iv) 1 mm isotropic T2-weighted fluid-attenuated inversion recovery sequence; and (v) T1-and T2-weighted images.

Results

We included 36 patients (mean age: 35.36 ± 12.86 years) with IBD. S_Table_1 summarizes baseline/diseases characteristics.

No significant results in structural MRI (DTI, VBM) were found. However, compared with placebo, the active tDCS group revealed a significantly higher resting-state functional connectivity within the visual medial ($p = 0.027$) and the right frontoparietal network ($p = 0.048$) (S_Table_2). Notably, the cluster of stronger functional connectivity was found in the visual cortex but also in regions outside the visual medial networks including the amygdala, the cingulum, and the insula (Figure_1A). These brain areas reflect parts of the limbic system, which is known to be involved in the integration of pain perception and its corresponding emotions. Additionally, we found a higher functional connectivity of the visual network with the callosal body, the primary motor cortex, and the primary somatosensory cortex. The primary motor cortex was the location of the tDC stimulation, thus, significant results in that brain areas were expected. Within the right frontoparietal network significant higher functional connectivity was found to the cingulum and the callosal body (Figure_1B). The frontoparietal network is crucially involved in the selection of sensory contents by attention and in neurocognitive performance.

Discussion

The resting-state fMRI studies performed indicated a significantly higher functional connectivity in the visual medial and the right frontoparietal network. Thus, the present study shows for the first time an association of improvement of abdominal pain through tDCS with functional changes of the brain. Moreover, we confirmed the analgesic effect of tDCS [13] on abdominal pain in a novel IBD study cohort. Remarkably, this effect persisted one week(S_Figure_2).

The frontoparietal network is known to be involved in the selection of sensory contents by attention [15]. A study investigating visual cues, which can significantly modulate patient's pain ratings, found a significant association between the individual ability to modulate pain and pretest functional connectivity between the frontoparietal network and both the anterior cingulate cortex and the prefrontal cortex as pain modulatory regions [16]. The current literature of the visual network on pain is limited. A study investigating the effect of visually induced analgesia identified several posterior brain areas activated by the visual perception of the body. Functional connectivity between the visual body network (somatosensory area, insula, cingulate cortex) and the pain matrix was increased [17]. One explanation why the visual network was significantly altered in our study is that IBD patients have a tendency to a higher introversion than healthy individuals, which may play a role for a higher activation of this network [18]. However, further studies are needed to investigate the visual network in IBD.

Previous studies investigating fMRI changes in IBD present interesting findings: A study that tested the effects of uncertainty in CD indicated that CD patients had significantly stronger activations in the cingulate cortex, insula, amygdala, and thalamus compared to controls [19]. Another study in CD revealed impaired habituation to stressful stimuli and a significant altered activation in the amygdala, the hippocampus, the insula, and putamen [20,21]. In line, we found a significant higher functional connectivity in the amygdala, the visual cortex, the insula and the primary motor and somatosensory cortices in IBD patients after successful pain treatment. This suggests that these structures are closely related to chronic abdominal pain processing.

This study cannot distinguish between the effects of pain reduction or the tDC stimulation itself. Nevertheless, it is known that chronic pain is followed by functional reorganization and plastic changes in the brain [1,2,4,6,22]. The present findings support the notion of impaired functional connectivity in IBD patients with chronic abdominal pain. It has been described before that central chronification mechanisms are based on hyperexcitability in pain-related neuronal networks, which can be “normalized” with tDCS [1–7,22]. Anodal tDCS of the motor cortex enhances its excitability and secondarily changes thalamic activity leading to reduced pain perception [3,22,23].

In summary, our fMRI findings support the concept that chronic abdominal pain of IBD patients at least partially acts on a central level. The analgesic effects of tDCS may be mediated through subcortical structures. Future therapies should incorporate this knowledge about functional brain changes in IBD patients with chronic pain for an effective multimodal pain treatment.

Conflicts of interest

The authors have nothing to disclose and declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2019.03.001.

References

[1] Eisenberg E, Chistyakov AV, Yudashkin M, Kaplan B, Hafner H, Feinsod M. Evidence for cortical hyperexcitability of the affected limb representation area in CRPS: a psychophysical and transcranial magnetic stimulation study. Pain 2005 Jan;113:99–105.
[2] Latremoliere A, Woolf CJ. Central sensitization: a generator of pain hypersensitivity by central neural plasticity. J Pain 2009 Sep;10:895–926.
[3] Garcia-Larrea L, Peyron R, Mertens P, et al. Electrical stimulation of motor cortex for pain control: a combined PET-scan and electrophysiological study. Pain 1999 Nov;83:259–73.
[4] Wager TD, Atlas LY, Lindquist MA, Roy M, Woo CW, Kross E. An fMRI-based neurologic signature of physical pain. N Engl J Med 2013 Apr 11;368:1388–97.
[5] Neumann S, Doubell TP, Leslie T, Woolf CJ. Inflammatory pain hypersensitivity mediated by phenotypic switch in myelinated primary sensory neurons. Nature 1996 Nov 28;384:360–4.
[6] Mhalla A, de Andrade DC, Baudic S, Perrot S, Bouhassira D. Alteration of cortical excitability in patients with fibromyalgia. Pain 2010 Jun;149:495–500.
[7] Fregni F, Freedman S, Pascual-Leone A. Recent advances in the treatment of chronic pain with non-invasive brain stimulation techniques. Lancet Neurol 2007 Feb;6:188–91.
[8] Kuner R, Flor H. Structural plasticity and reorganisation in chronic pain. Nat Rev Neurosci 2016 Dec 15;18:20–30.
[9] Kumbhare DA, Elzibak AH, Noseworthy MD. Evaluation of chronic pain using magnetic resonance (MR) Neuroimaging approaches: what the clinician Needs to know. Clin J Pain 2016 Apr;33:281–90.
[10] Martucci KT, Ng P, Mackey S. Neuroimaging chronic pain: what have we learned and where are we going? Future Neurol 2014 Nov;9:615–26.
[11] 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 May;157:1037–44.
[12] Thomann AK, Griebe M, Thomann PA, et al. Intrinsic neural network dysfunction in quiescent Crohn's Disease. Sci Rep 2017 Sep 14;7:11579.
[13] Volz MS, Farmer A, Siegmund B. Reduction of chronic abdominal pain in patients with inflammatory bowel disease via transcranial direct current stimulation: a randomized controlled trial. Pain 2016;Feb;157:429–37.
[14] Neeb L, Bastian K, Villringer K, et al. No microstructural white matter alterations in chronic and episodic migraineurs: a case-control diffusion tensor magnetic resonance imaging study. Headache 2015 Feb;55:241–51.
[15] Ptak R. The frontoparietal attention network of the human brain: action, saliency, and a priority map of the environment. Neuroscientist : Rev J Bring Neurobiol, Neurol Psychiatr 2012 Oct;18:502–15.
[16] Kong J, Jensen K, Loiotile R, et al. Functional connectivity of the frontoparietal network predicts cognitive modulation of pain. Pain 2013 Mar;154:459–67.
[17] Longo MR, Iannetti GD, Mancini F, Driver J, Haggard P. Linking pain and the body: neural correlates of visually induced analgesia. J Neurosci 2012 Feb 22;32:2601–7.
[18] Robertson DA, Ray J, Diamond I, Edwards JG. Personality profile and affective state of patients with inflammatory bowel disease. Gut 1989 May;30:623–6.
[19] Rubio A, Pellissier S, Van Oudenhove L, et al. Brain responses to uncertainty about upcoming rectal discomfort in quiescent Crohn's disease - a fMRI study. Neuro Gastroenterol Motil : Off J Eur Gastrointest Motil Soc 2016 Sep;28:1419–32.
[20] Agostini A, Filippini N, Cevolani D, et al. Brain functional changes in patients with ulcerative colitis: a functional magnetic resonance imaging study on emotional processing. Inflamm Bowel Dis 2011 Aug;17:1769–77.
[21] Agostini A, Filippini N, Benuzzi F, et al. Functional magnetic resonance imaging study reveals differences in the habituation to psychological stress in patients with Crohn's disease versus healthy controls. J Behav Med 2012 Oct;36:477–87.
[22] Knotkova H, Nitsche MA, Cruciani RA. Putative physiological mechanisms underlying tDCS analgesic effects. Front Hum Neurosci 2013;7:628.
[23] Fregni F, Boggio PS, Lima MC, et al. A sham-controlled, phase II trial of transcranial direct current stimulation for the treatment of central pain in traumatic spinal cord injury. Pain 2006 May;122:197–209.
[24] Volz MS, Finke C, Harms L, Jurek B, Paul F, Flöel A, Prüss H. Altered paired associative stimulation-induced plasticity in NMDAR encephalitis. Ann Clin Transl Neurol 2016 Jan 16;(2):3.
[25] Neeb L, Bastian K, Villringer K, Israel H, Reuter U, Fiebach JB. Structural gray matter alterations in chronic migraine: implications for a progressive disease? Headache 2017 Mar;57(3):400–16.