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Case evidence of repetitive transcranial magnetic stimulation in the management of refractory irritable bowel syndrome with comorbid depression

Dear Editor

Irritable bowel syndrome (IBS) is a common functional gastrointestinal disease characterised by abdominal pain and in most cases comorbid mood symptoms. IBS can substantially reduce quality of life, especially in those with comorbid mood symptoms, while the treatments remain poor. Neuroimaging studies with IBS patients have demonstrated metabolic changes in brain regions involved in pain and emotions, such as the hippocampus, the medial prefrontal cortex (mPFC), and the insular cortex [1,2].

As a non-invasive form of brain stimulation, repetitive transcranial magnetic stimulation (rTMS) is able to reduce both pain and depression [3]. A recent evidence-based synthesis has demonstrated a significant analgesia following the stimulation of the dorsolateral prefrontal cortex (DLPFC) [4]. In addition, DLPFC stimulation has been approved by the Food and Drug Administration (FDA) to treat depression. In terms of IBS, two studies targeted the motor cortex and demonstrated mixed effects on experimentally induced pain [5,6], leaving no evidence on the clinical impact of rTMS in IBS.

Here we reported a case of DLPFC-rTMS in IBS with comorbid depression. DLPFC was targeted due to the efficacy in both pain and depression. Magnetic resonance spectroscopy (MRS) was used to measure cerebral metabolite levels, along with the evaluation of pain and mood symptoms in two-month follow-up.

1. Case report

The patient was a 24-year-old woman who suffered from recurrent abdominal pain for four years following an acute infectious diarrhea episode (mid-September 2017). On August 2nd, 2018, she underwent a laparoscopic appendectomy due to abdominal pain and lymph node enlargement around the appendix. However, the surgery did not reduce abdominal pain and she even experienced four episodes of small bowel obstruction post-surgery. In April 2020, the patient was diagnosed with IBS and was given spasmolysis drugs and probiotics, but the treatment had limited effects. On May 4th, 2020, the patient underwent a laparoscopic exploratory surgery due to a recurrence of small bowel obstruction, but no obvious organic lesions were found. In this period, the patient demonstrated negative emotions and self-injurious behaviours. She received a few psychological interventions, but the emotional symptoms still existed and she was then diagnosed with moderate depression in August 2020. For the past year, she has been treated with psychotropic medications (gramphracine 150mg/day, buspirone 30mg/day, and oxazepam 15mg/day) along with nutritional support (enteral nutritional suspension, 500ml/day). Due to recurrent abdominal pain, the patient was transferred to our hospital on August 26, 2021.

The patient provided a written consent for rTMS treatment. rTMS was delivered once daily on ten consecutive days (Fig. 1A) using a Magstim Rapid2 system (Magstim Company Ltd., UK) connected to a figure-of-eight coil. Each rTMS session delivered 1500 pulses at 10 Hz with 5-sec trains and 25-sec intervals at 120% resting motor threshold (RMT). RMT was determined by the minimum intensity to evoke motor evoked potentials (MEPs) > 0.05 mV in 5/10 trials and was re-examined in each session. The left DLPFC was located by the Beam F3 method. It is noted that psychotropic medications and nutritional support remained as usual during rTMS treatment.

Clinical and neurological assessments were performed before and after rTMS treatment, as well as at 1-month and 2-month follow up. Clinical assessments included the short-form McGill pain questionnaire (SF-MPQ), Hamilton Depression Rating Scale (HAMD-17), Hamilton Anxiety Rating Scale (HAMA-14), IBS-related quality of life (IBS-QOL), and IBS-symptom severity score (IBS-SSS). MRS was used to evaluate metabolite ratio values (divided by total creatine, tCr) in the left DLPFC, bilateral hippocampus, bilateral insula, and anterior cingulate cortex (ACC) with a 1.5T MRI scanner.

Our data indicated that DLPFC stimulation resulted in remarkable improvements in pain reports (Fig. 1B). Specifically, there was a clear reduction in the total score (39.3%), sensory (36.8%) and emotional (44.4%) dimension of pain, as well as visual analogue scale (VAS) score (33.3%). More importantly, the analgesic effects lasted for two months following stimulation. Depressive symptom was also reduced from moderate (=18) to mild (=15) following stimulation, and further decreased (=13) at 2-month follow-up. In addition, there were significant improvements in quality of life, anxiety symptoms and gastrointestinal symptoms. All these benefits lasted for two months following stimulation. It is worth noting that the dose of Oxazepam was halved 10 days after rTMS treatment due to the improvement in mood, while other treatments remained unchanged.

MRS data revealed no obvious changes in the DLPFC. Instead, DLPFC stimulation resulted in significant metabolic changes in distributed regions, characterised by increased glutamate and glutamine (Glx)/tCr in the bilateral hippocampus, enhanced N-

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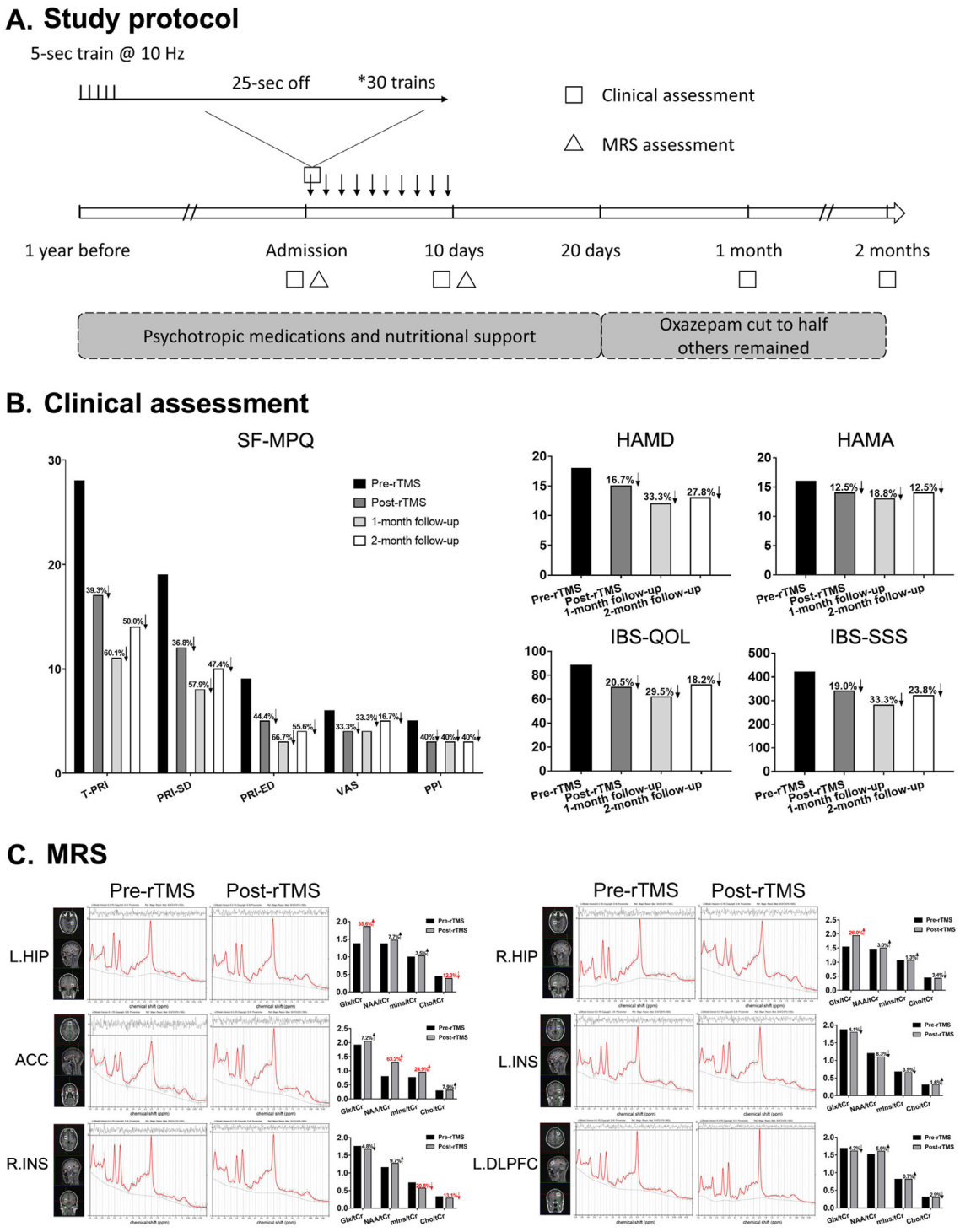

Fig. 1. Case protocol and results. (A) Experimental protocol. (B) Clinical assessment. There were long-term improvements in pain, mood, and quality of life following stimulation. (C) MRS assessment. MRS data revealed no obvious changes in the DLPFC, but with increased Glx/tCr in the bilateral hippocampus, enhanced NAA/tCr and mIns/tCr in the ACC, as well as with reduced mIns/tCr and Cho/tCr in the right insula. ^{1}H-MRS scans collected from the ACC, L.HIP, R.HIP, LDLPFC, L.INS, and R.INS in the same order in a 2 × 2 × 2 cm^3 voxel, using the point-resolved spectroscopy sequence (TE, 30 ms; TR, 1500 ms) on a 1.5 T Siemens Aera MRI scanner (Siemens Inc., Erlangen, Germany). Boxes indicate the placement of each single-voxel measurement on the MR image. The ratio Glx/tCr, NAA/tCr, mIns/tCr and Cho/tCr, relative to each voxel, were shown in the bar charts. Changes greater than 10% were marked in red.

acetylaspartate (NAA)/tCr and myo-inositol (mIns)/tCr in the ACC, as well as reduced mIns/tCr and choline (Cho)/tCr in the right insula (Fig. 1C).

Here we provided a case report of DLPFC-rTMS in the management of refractory IBS with comorbid mood disorders. She has demonstrated long-term improvements in pain, mood, and quality

of life following stimulation. In terms of potential mechanisms, MRS data revealed increased Glx/tCr in the bilateral hippocampus, which is a key component of the hypothalamic-pituitary-adrenal (HPA) axis regulating stress response and a series of body functioning such as digestion, immunisation and emotions. Moreover, there is evidence that IBS patients demonstrated dysregulated functioning of the HPA axis [2] and that DLPFC stimulation increased plasma ACTH and cortisol concentrations and decreased visceral sensitivity [7]. It is therefore possible that DLPFC stimulation can act on glutamate transmissions along the HPA axis, which may explain the relief of gastrointestinal and mood symptoms.

Our data also demonstrated prominent metabolic changes in the ACC and insular cortex, which are closely associated with the affective/emotional aspect of pain as well as interoception [8]. There is evidence that NAA and mIns in ACC were negatively associated with pain experience and mood [9]. A recent study also found cortical Cho levels to be positively associated with pain interference in chronic pain, suggesting a role of neuroinflammation in pain symptoms [10]. Our data provided direct evidence that DLPFC stimulation is able to modulate metabolic changes in the ACC and insular cortex, potentially severing as one of the mechanisms of DLPFC analgesia in IBS patient.

To conclude, we provide a case to support DLPFC-rTMS in the management of IBS with comorbid mood disorders. The patient demonstrated clear benefits in gastrointestinal symptoms, pain, and emotions. The marked improvement in pain was accompanied by a modest reduction in depression, which tends to suggest that this was not just an antidepressant effect. We also provide metabolic changes in the HPA axis as well as in the brain regions underlying pain and interoception. However, these findings need to be validated in large, randomised controlled trials.

Declaration of competing interest

None declared.

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