Study protocol

Study life: 2024.09.07

fMRI study of the neural mechanism of rTMS stimulation of the left dorsolateral prefrontal lobe in the treatment of nicotine dependence

I. Research background

Addiction, the most serious substance use disorder, is a chronic brain disease shaped by strong biosocial factors and has devastating consequences for both individuals and society. In China and even the world, nicotine addiction, or dependence, has long been an extremely serious social and medical problem, endangering public health and one of the important causes of death around the world. About 15.2% of the global population smokes daily, which represents more than 933 million people who smoke. [2] According to the "China Smoking Harm to Health Report 2020" released in 2021, the number of smokers in China exceeds 300 million, the smoking rate remains at a high level, and the number of deaths due to smoking exceeds 1 million every year.

At present, the main treatment methods at home and abroad, such as nicotine replacement therapy, varenicline and bupropion drug therapy and psychological cognitive behavior therapy, have a low smoking cessation rate and a high relapse rate. In recent years, a growing number of studies have found that Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive, non-invasive treatment for reducing cravings in addicts. The basic principle is that according to the electromagnetic exchange effect, the magnetic field generated by the strong current in the coil penetrates the skull into the cerebral cortex, causing local small current in the corresponding cortex, changing the local electrical activity of the cerebral cortex, so as to play a therapeutic role.

At present, there are a few studies using rTMS to stimulate the right or/and left dorsolateral prefrontal lobe for the treatment of nicotine dependent patients, and the short-term improvement is obvious, but the sample size is small, there is no uniform conclusion and the related neural mechanism is not clear. Our preliminary results show that rTMS has a significant improvement and efficacy in heroin addiction.

Ⅱ.Research method

In this project, fMRI technology combined with psychobehavioral science was used to study the scientific problem of "the efficacy of left dorsolateral prefrontal rTMS in the treatment of nicotine dependent patients and the relationship between the efficacy and the internal function and interaction characteristics of the large brain networks of ECN, DMN and SN" from an all-round perspective. After enrollment, the nicotine addicts first received relevant psychobehavioral data and fMRI data collection, and then received continuous rTMS treatment for 2 weeks. After treatment, the above data were collected again, and then received 1-month follow-up follow-up. Psychobehavioral data were collected once a week for nicotine addicts. Finally, the collected neuroimage data were analyzed to compare the difference in efficacy between the true and false treatment groups, and to clarify the relationship between the efficacy of nicotine dependent patients after rTMS treatment and the internal functions of the large brain networks of ECN, DMN and SN as well as the interaction characteristics of the networks, so as to provide a scientific basis for the development of effective individualized treatment programs.

Ⅲ.Test means

1) Subject recruitment

In order to ensure the ethical feasibility, this study intends to include 50 nicotine addicts receiving rTMS treatment (25 in the true rTMS treatment group and 25 in the false rTMS treatment group) and 25 healthy controls. The demographic matching contents of nicotine addiction group and healthy control group included age, sex, education level, left and right handedness.

The inclusion criteria of nicotine addiction group:

① met the criteria of nicotine addiction in the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5);

② Right-handed;

③ Did not receive drug treatment; Age range: 20-65 years old.

Exclusion criteria for all subjects:

② history of epilepsy;

② Previous history of craniocerebral trauma, surgery, and serious mental or nervous system diseases;

③ No contraindications for MRI examination (no dentures, residual metal in the body due to surgery or trauma, claustrophobia);

④ poor compliance;

⑤ Polydrug abusers.

2) rTMS treatment plan

(1) Target selection: The therapeutic target of rTMS is located in the left dorsolateral prefrontal lobe. For accurate positioning, we used a dedicated TMS navigator to determine the specific location of the left dorsolateral prefrontal lobe (MNI coordinates: X=-50, Y=30, Z=36) on the skull surface through registration with the subjects' head MRI images, and marked it on the subjects' individually fitted TMS cap. (Terraneo A, Leggio L, Saladini M, Ermani M, Bonci A, Gallimberti L. Transcranial magnetic stimulation of dorsolateral prefrontal cortex reduces cocaine use: A pilot study. Eur Neuropsychopharmacol, 2016, 26(1): 37-44.)

(2) rTMS parameters: TMS stimulation frequency is 10Hz, stimulation intensity is 100% of the motion threshold, 5s on, 10s off, for 10 minutes, a total of 2000 pulses.

(3) rTMS treatment time: The total treatment time for each person is two weeks, five times a week, a total of 10 times.

3) Data collection

(1) Psychological behavioral data collection

It includes anxiety Rating Scale (HAMA), self-rating Depression Scale (BDI), smoking survey (FTND), basic craving assessment, craving degree assessment (cue), desired quitting degree assessment and NUI assessment. The psychobehavioral scale was assessed each time before fMRI data collection. Nicotine basal craving assessment and craving degree assessment (cue) were assessed before and after fMRI collection and before and after each rTMS treatment to assess craving changes.

(2) Imaging data collection

Imaging data were collected using Siemens integrated PET/MRI equipment, 16-channel phased array head coils and fMRI stimulator equipment.

a) BOLD-fMRI imaging: GRE-EPI sequence was adopted, and scanning parameters were as follows: TR=2000 ms, TE=30 ms, layer thickness = 4mm, layer interval =0 mm, FOV=25.6cm×25.6cm, matrix =64×64, flip angle=90 degrees, NEX=1.

b) 3D structural imaging of brain gray matter: MPRAGE sequence was adopted, and scanning parameters were as follows: TR=1900 ms, TE= 2.43ms, TI=900ms, FOV=25.6cm×25.6cm, matrix =256×256, layer thickness = 1mm, layer interval =0 mm, flip angle=20◦, NEX=1.

4) Follow-up after treatment

All nicotine addicts were followed up every Friday after rTMS treatment, and nicotine addiction Smoking survey (FTND), basal craving assessment, craving degree assessment (cue) and NUI assessment were performed. Anxiety Rating Scale (HAMA) and Depression Self-Rating Scale (BDI) were added at the last follow-up. The short-term follow-up period was one month to understand the treatment effect and current related status of the subjects.

5) Imaging data processing

(1) Main data processing software:

Matlab2013b, SPM12 (http://www.fil.ion.ucl.ac.uk/spm)

DPABI (http://rfmri.org/dpabi)

FSL (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/)

Freesurfer (http://freesurfer.net/)

Gift (http://mialab.mrn.org/software/)

DTI - studio (https://www.mristudio.org/wiki/Tutorial)

PANDA (http://www.nitrc.org/projects/panda/)

GRETNA (http://www.nitrc.org/projects/gretna/)

MRIcro (http://www.mccauslandcenter.sc.edu/mricro/)

The Caret (http://brainvis.wustl.edu/wiki/index.php/Caret:Download)

BrainNet viewer (http://www.nitrc.org/projects/bnv/)

MIMneuro (https://www.mimsoftware.com/nuclear_medicine/mim_neuro)

Syngo. Via VB10 (https://health.siemens.com/ikm/syngo/syngo-via-apps/)

And self-programming and so on.

(2) fMRI data follow-up processing:

Local consistency (Reho), low-frequency amplitude (ALFF) and power spectrum were used to detect the activation range and intensity of ECN, DMN and SN-related brain regions. The functional connections between ECN, DMN and SN related brain regions were analyzed by seed point correlation analysis and independent component analysis. The effect linkage analysis of ECN, DMN and SN was carried out using the physiological and psychol

ogical interaction model. Through the above analysis, the intrinsic functional changes of E CN, DMN and SN large brain networks in the basal state of nicotine addicts after rTMS treatment and the changes of network interactions, and the relationship between them and relapse were discussed.

Ⅳ.Key technologies

1) cognitive experiment design: the cognitive fmri study of heroin addiction has been o ver 10 years, and the experience of cognitive experimental design has been accumulated.

2) image data collection: this project USES Siemens second generation of integrated pet/ mri equipment, which has all the conditions and techniques for the completion of the fmri -3d high recognition volume imaging and diffusion tensor imaging, and the scanning is us ed to ensure the high signal-to-noise ratio and reliability of the data.

3) data processing technology: this group has fully master the data processing method o f functional image, including the processing method of the static state of the task, the pro cessing method of the task state, and the processing method of the thickness of the brain gray matter, the thickness of the cortex and the integrity of the white fiber beam, and the use of the spm-relative dpabi-deabiding giftand fsl-and the afnig freesurferl dti-studio and other data analysis software.