BMJ Open  Effects of repeated transcranial magnetic stimulation in the dorsolateral prefrontal cortex versus motor cortex in patients with neuropathic pain after spinal cord injury: a study protocol

Maomao Huang,1,2 Xi Luo,3 Chi Zhang,3 Yu-Jie Xie,3 Li Wang,3 Tenggang Wan,3 Ruyan Chen,3 Fangyuan Xu,3 Jian-Xiong Wang1,2

ABSTRACT

Introduction  Neuropathic pain is one of the common complications of spinal cord injuries (SCI), which will slow down the recovery process and result in lower quality of life. Previous studies have shown that repeated transcranial magnetic stimulation (rTMS) of the motor cortex (M1) can reduce the average pain and the most severe pain of neuropathic pain after SCI. The dorsolateral prefrontal cortex (DLPFC) area is a common target of rTMS. Recently, a few studies found that rTMS of DLPFC may relieve the neuropathic pain of SCI. Compared with the M1 area, the efficacy of rTMS treatment in the DLPFC area in improving neuropathic pain and pain-related symptoms in patients with SCI is still unclear. Therefore, our study aims to evaluate the non-inferiority of RTMS in the DLPFC vs M1 in patients with neuropathic pain after SCI, in order to provide more options for rTMS in treating neuropathic pain after SCI.

Methods and analysis  We will recruit 50 subjects with neuropathic pain after SCI. They will be randomly assigned to the DLPFC- rTMS and M1- rTMS groups and be treated with rTMS for 4 weeks. Except for the different stimulation sites, the rTMS treatment programmes of the two groups are the same: 10 Hz, 1250 pulses, 115% intensity threshold, once a day, five times a week for 4 weeks. VAS, simplified McGill Pain Questionnaire, Spinal Cord Injury Pain Date Set, Pittsburgh Sleep Quality Index and Hamilton Anxiety Scale will be evaluated at baseline, second week of treatment, fourth week of treatment and 4 weeks after the end of treatment. And VAS change will be calculated.

Ethics and dissemination  The Ethics Committee of the Affiliated Hospital of Southwest Medical University has approved this trial, which is numbered KY20200041. Written informed consent will be provided to all participants after verification of the eligibility criteria. The results of the study will be published in peer-reviewed publications.

Trial registration number ChiCTR2000032362.

INTRODUCTION

Spinal cord injury (SCI) is a severe disabling disease. The annual incidence of SCI all over the world ranges from 8 to 246 per million people per year.1 One of the common complications after SCI is neuropathic pain (NPP), and about 40% of patients would suffer from persistent NPP.2 NPP is often characterised by paroxysmal, puncturing, burning, pulsating, tingling and other spontaneous or induced unpleasant abnormal sensations, which may slow down the rehabilitation process, reduce the quality of life and cause considerable social economic burden.3 4 Repeated transcranial magnetic stimulation (rTMS) is a non-invasive treatment that can cause immediate and lasting changes in cortical excitability. Clinical studies and guidelines suggested that rTMS in the motor cortex (M1) region can be used to treat NPP.5 Previous studies have shown that rTMS of M1 can reduce the average pain and the most severe pain of NPP after SCI.6 7
The dorsolateral prefrontal cortex (DLPFC) area is also a common target of rTMS for treating mood disorder and cognitive impairment, such as depression. Recent researches suggested that NPP can produce long-lasting prefrontal cortex dysfunction, manifested as pain-related cognitive dysfunction, attention shift disorder and mood disorder. The proportions of NPP with depression and anxiety are as high as 65.6% and 73.7%, respectively. Simultaneously, DLPFC area also may affect pain through several brain function networks, such as the regulation of cognitive control networks, reward/fear pathway reaction etc. It has shown that the left DLPFC area is likely to be a potential target for rTMS in treating various chronic pain diseases. A clinical trial suggests that rTMS in the DLPFC area can effectively relieve NPP in patients with SCI, but the total sample size was only 12. A study with larger sample size is needed to verify the conclusion that rTMS in the DLPFC area is effective in treating NPP. Besides, the control group in that study were sham-treated. M1 is a classic target of rTMS in the treatment of NPP. As far as we know, there is currently no randomised clinical study comparing the effects of rTMS in the DLPFC and that in M1 in the treat NPP after SCI. Considering that rTMS in DLPFC may affect multiple functions of pain, mood and cognition at the same time, we designed this non-inferiority study. Therefore, our study aims to evaluate the non-inferiority of rTMS in the DLPFC area comparing with that in M1 in patients with NPP after SCI and provide more options for rTMS to treat NPP after SCI.

METHODS
Design
The current study is a single-blind randomised controlled trial, in which patients with NPP after SCI will be randomly divided into the rTMS-DLPFC group and rTMS-M1 group (figure 1). We do not consider the sham group in the study design. Mainly because the purpose of our study is to compare the efficacy of rTMS on the DLPFC with the classical motor cortex (M1) in NPP after SCI. Besides, a previous study has shown that compared with the sham group, rTMS of the DLPFC may be effective in relieving NPP in SCI patients. Therefore, the control group in our study will be designed as rTMS of the M1 region, a positive control design, instead of a sham stimulation group. All the patients will be from the Rehabilitation Medicine Department, The Affiliated Hospital of Southwest Medical University. Importantly, physicians carrying out the assessments will not be informed of the group information.

Research objects and groups
Sample size calculation
PASS statistical software will be used to calculate the sample size. The sample size is calculated based on the Visual Analogue Scale (VAS), which is the main outcome indicator. According to previous studies, the variance of VAS after rTMS treatment in M1 area and DLPFC area is set to be 1.8. The average value of VAS after rTMS treatment in M1 area is set to be 6.0. We assume that a margin of non-inferiority of 10% is acceptable in clinical, so the margin of non-inferiority is to be 0.6. And the true difference is estimated to be ~1.0. The one-sided type I error and statistical power are set to be 2.5% and 80% respectively. Each group require 21 participants at a 1:1 allocation ratio, and totally 50 participants will be needed considering a dropout rate of 15%.

Diagnostic criteria
The diagnostic criteria for SCI are as follows: (1) there is an exact cause of SCI, such as trauma or myelitis; (2) clinical manifestations conform to the definitions of quadriplegia and paraplegia in the ‘International Standard for Neurological Classification of SCI (Revised in 2011)’; (3) there are sensory and motor impairments below the injury level on the basis of the American Spinal Injury Association (ASIA) standard developed by the ASIA and (4) definitely existing SCI confirmed by CT or MR.

The diagnostic criteria for NPP are set according to the diagnostic grading standard recommended by the International Pain Research Association in 2008. The participants should meet following conditions: the pain is in a clear neuroanatomical range; the medical history suggests that there are related lesions or diseases in the peripheral or central sensory system; at least one auxiliary examination confirms the existence of related lesions or diseases.

The inclusion criteria are as follows: (1) Patients diagnosed with NPP after SCI; (2) The average VAS score of the patient self-assessment is 2.0–8.0 points in the past week; (3) Age between 18 and 60 years old; (4) At least...
the coil is held tangentially to the scalp. It achieves high-angle and distance of the stimulation coil are locked and mechanical arm through position, speed and torque. The patients must remove the metal from the head and according to the level of motion of each patient, the precision positioning of the transmission system. The multidimensional face recognition is performed by a full-colour high-definition depth camera written in the core code algorithm. And the human head target is mapped to a certain position in the camera coordinate system to accurately reconstruct the 3D head model and brain model space. The camera coordinate system enters the manipulator coordinate system through the camera calibration. As a controller, the servo driver controls the mechanical arm through position, speed and torque. The angle and distance of the stimulation coil are locked and the coil is held tangentially to the scalp. It achieves high-precision positioning of the transmission system. The rTMS therapy will be performed by therapists who have received professional training and have been engaged in rTMS therapy for more than 3 years. The treatment room is a separate room with a quiet and safe environment. According to the level of motion of each patient, the patient would comfortably lie flat on the treatment bed. The patients must remove the metal from the head and face, such as glasses, hairpins. The figure eight coil will be placed to the DLPFC area or the M1 area according to their group. The patients are relaxed as much as possible before treatment, and the resting motor threshold (RMT) will be measured. One side of the primary motor cortex will be stimulated by a single rTMS pulse, and the motor evoked potentials will be recorded by the surface electrode at the site of stimulating the first dorsal interosseous muscle of the contralateral hand. RMT is defined as the minimum stimulation intensity that elicits a 50 uV motor evoked potential in 5 out of 10 single pulse stimulation of M1 at rest. 21 1250 pulses at an intensity of 115% RMT will be applied at 10 Hz (each train with 30 s interval). The rTMS therapy will be performed once a day, 5 days per week, and last for 4 weeks. During the study period, the participants will receive regular general care, health education and rehabilitation treatment according to their own condition, such as standing training, electrical stimulation, joint passive activity and other rehabilitation treatments. If the patient is taking anti-NPP medication regularly before participating in the trial, they do not need to stop the medication. During the trial period, if the VAS score of pain reaches 6.0 or affects sleep or rehabilitation, anti-NPP drugs can be added to the participants. During the trial, each participant’s application of drugs will be recorded in detail, including anti-NPP drugs and other drugs. If the participants have epilepsy or other conditions during the treatment, they will receive formal treatment in the inpatient department. Once the participants have epilepsy or any other conditions that prevent the patients from continuing the trial during rTMS intervention, they will drop out of the trial. The data prior to dropping out of trials will be recorded and analysed statistically.

Outcomes
Other professional evaluators will assess all patients blindly at different time points on the basis of various assessments (table 1).

In addition, we will use a questionnaire to record the baseline age, gender, symptoms, duration, ASIA grade, type of paralysis, the site of SCI, previous treatment and medication of participants (week 0). The VAS is used to evaluate the overall pain. The total length of VAS is recorded with 100 mm. The 0 point is at 0 mm, which is no pain; and the 100 points are at 100 mm, which represents the most severe pain.22 During the 4 weeks with treatment and 4 weeks after the treatment, all patients would measure the overall pain intensity by themselves using the VAS. The primary outcome is the average VAS score in the past week at each evaluation time point. We are most interested in assessment at the end of the treatment. Besides, we will calculate the VAS change at the second and fourth week of treatment, and 4 weeks after the end of treatment as it can provide additional information for pain control.

The secondary outcomes include multi-dimensional evaluation of pain, Pain interference, Sleep situation as well as Anxiety. The multidimensional evaluation of pain would be assessed using the simplified McGill Pain

Huang M, et al. BMJ Open 2022;12:e053476. doi:10.1136/bmjopen-2021-053476
Questionnaire. This scale is used for the subjective assessment of pain, including Pain Rating Index (PRI), VAS and present pain intensity (PPI). PRI consists of 11 sensory and 4 affective descriptors for pain, all of which denote none, mild, moderate and severe with a score of 0–3, respectively. PPI is rated on a scale of 0 to 5 points, with 0 as painless and 5 as extreme pain. The International Spinal Cord Injury Pain Date Set will be used to assess the degree of pain interference in daily life. Its contents include: (1) how many different types of pain there were in the past week; (2) the location of pain; (3) the type of pain; (4) the intensity of pain in the past week, assessed by the VAS; (5) the duration of each pain; (6) the effects of pain on activities, participation in recreational and social activities, satisfaction and pleasure in family-related activities, interference with daily activities, mood and nocturnal sleep and (7) Is the pain being treated?

The Pittsburgh Sleep Quality Index (PSQI) will be applied to evaluate the sleep quality of the participants in the past 1 month, which consists of 19 self-evaluation items and 5 other evaluation items, including subjective sleep quality, sleep time, sleep efficiency, falling asleep time, sleep drugs, sleep disorders and daytime dysfunction. Each item is scored by grade 0–3, with a total score of 0–21. The higher the score, the worse the quality of sleep. The total score of PSQI ≤7 points is regarded as normal sleep, and >7 points as sleep problems.

The Hamilton Anxiety Scale will be used for evaluation the anxiety situation. The scale consists of 14 subitems, each of which measures the specific manifestations of anxiety (anxious mood, tension, fears, insomnia, cognitive, cardiovascular-symptoms, respiratory symptoms, etc). Each subitem is divided into five grades: 0, 1, 2, 3, 4. 0 means no symptoms and 4 represents severe symptoms, seriously affecting life. The total score of the scale is 56, <7 (no anxiety), 7–14 (possible anxiety), 15–20 (anxiety), 21–28 (obvious anxiety), >28 (severe anxiety).

**Evaluation time**

A total of four evaluations will be conducted, which will be evaluated before treatment, at the second and fourth week of treatment, and 4 weeks after the end of treatment.

**Data collection and management**

All recruited patients will be coded with numbers. Patient data will be collected using a case report form, including basic information, site of SCI, baseline assessment data and follow-up outcomes. The blinded physiotherapists will finish follow-up assessments when patients come back for a check. All data will be stored uniformly by the researcher, and others will not be allowed to obtain them.

**Quality assurance and safety oversight**

Ethics Committee of the Affiliated Hospital of Southwest Medical University will supervise the whole process of the research.

**Statistical analysis**

We will use SPSS V.23 statistical software to analyse the data and the statistical significance level will be set at p<0.05. χ² test or Fisher’s exact test will be applied to analyse the categorical data, such as gender or symptom. Data not conforming to normal distribution will be analysed using non-parametric statistical tests. Additionally, repeated measure analysis of variance and post hoc test will be used to analyse statistically significant differences in intergroup and intragroup data.

We plan to conduct the intention-to-treat analysis and per-protocol analysis at the same time in this study. Consistent results will help determine the research conclusions. If they are inconsistent, we will do further analysis and discussion. Besides, we will try our best to reduce the lack of data. If the data are missing, we will use pattern mixture models to fill the missing outcome data.

**Ethics and dissemination**

The conduct of this trial will conform to the principles of the Declaration of Helsinki and ethical guidelines. This research is approved by the Ethics Committee of the Affiliated Hospital of Southwest Medical University (ethics number: KY2020041). All participants will sign the written informed consent to participate in the study. The results of the study will be published in peer-reviewed publications.
Patient and public involvement

The Ethics Committee of the affiliated Hospital of Southwest Medical University reviewed the whole study protocol and put forward their opinions. In the trial phase, the feedback of the participants on the whole intervention will be collected to improve the study protocol. We will eventually inform the participants and the public on the follow-up reports.

DISCUSSION

So far, this study is the first clinical trial to compare the clinical effects between rTMS in the DLPFC area and M1 area on NPP after SCI. And our study aims to evaluate the non-inferiority of rTMS in the DLPFC area comparing with that in M1.

The most frequently selected target of rTMS for NPP after SCI is the M1 area. The mechanism of chronic NPP is very complex, involving multiple brain regions, and the M1 area may not be the only effective choice. Studies have begun to observe the effect of rTMS in other areas on pain relief, such as parietal lobe or DLPFC. The DLPFC zone is a special area of function and structure, including the dorsal part of Brodmann Zone 8, 9, and 46; it is a key node of some brain networks and closely related to cognitive, emotion and sensory processing. Emotional and cognitive processes are involved in pain regulation. A number of brain functional imaging studies had shown that the DLPFC area participates in pain regulation mechanisms; the DLPFC area atrophy in various chronic pain conditions. DLPFC area is also involved in NPP after SCI. Compared with healthy controls, the metabolism of the left DLPFC area of patients with chronic NPP after SCI was slowed and grey matter volume was reduced, which suggested that DLPFC may also play an essential role in SCI NPP. The MRI signal of the DLPFC may also play an essential role in SCI NPP. The MRI signal of the DLPFC area in patients with NPP after SCI was significantly different from the normal population and those without pain after SCI; moreover, the imaging changes in DLPFC area are significantly correlated with pain intensity.

Based on the above research, DLPFC area may be a potential important cortical target of rTMS in treating NPP after SCI. The rTMS in the left DLPFC area can alleviate capsaicin-induced spontaneous pain. Leung et al found that a short-course rTMS at the left DLPFC can alleviate mild traumatic brain injury-related headache and associated neuropsychological dysfunctions. A preliminary study with a small patient sample suggested that rTMS of the DLPFC may be effective in relieving NPP in SCI patients. On those basic, we hope to clarify the efficacy of rTMS in the DLPFC in the treating NPP and pain-related symptoms, and designed this trial programme.

The DLPFC is one of the cerebral cortices that are critically involved in pain modulation. There have been several hypotheses about the mechanism that rTMS acts on the DLPFC area to improve NPP. High-frequency rTMS (HF-rTMS) in the DLPFC area may activate the pain control circuit and activity of the anterior buckle through the release of endogenous opioids, thereby alleviating pain. The rTMS of the left DLPFC could also improve pain by enhancing brain activity of the frontal-buckle circuit involved in emotional control. These studies suggest that DLPFC is not the only area activated, but it may be a critical network node related to nociceptive sensory processing and pain regulation, and also a potential intervention target for rTMS treatment. rTMS in the left prefrontal cortex can modulate the deeper limbic structures that may be participated with the affective dimension of pain, including the cingulate gyrus, hippocampus, orbitofrontal cortex and insula. Moreover, activation of the left prefrontal cortex by HF-rTMS may inhibit descending pain networks related to the periaqueductal grey and nucleus cuneiformis. rTMS has different functions depending on the frequency used. Our study plans to use 10Hz rTMS, based on previous research. Healthy adults with a 10Hz rTMS stimulation in the left prefrontal cortex demonstrated a striking increase in thermal pain thresholds. As for patients with chronic NPP, 10Hz rTMS in the DLPFC area had an average pain reduction of 19% and could increase mechanical and thermal pain thresholds significantly.

In terms of outcome evaluation, we mainly focused on pain and pain-related symptoms, including mood and sleep. There has been a lot of research to explore the relationship between them. Patients with NPP after SCI are often accompanied with different degrees of anxiety and depression. Moreover, pain and depression have a negative impact on each other through several mechanisms, and one of them may be the cognitive control. Multiple studies have shown that high-frequency DLPFC rTMS can treat depression by increasing the cognitive control of negative emotions. The DLPFC is not only a primary node within a cognitive control network but also a key networks node implicated in pain modulation. Different from the motor cortex stimulation, which may directly inhibit the pain signal transmission in the spinal cord, DLPFC activation can reduce pain through cognitive control. The role of DLPFC in execution and attention is also considered to be related to the cognitive regulation of the pain process. In addition to mood disorders, about 40% of patients with NPP after SCI experience sleep disorders, which means it is difficult to fall asleep or stay asleep. Because the pain often has a two-way relationship with insomnia, with changes in one reciprocally affecting another. The study has shown that rTMS has the advantages of optimising sleep structure, improving sleep quality and maintaining therapeutic efficacy compared with drug therapy and other behavioural intervention. The rTMS on the DLPFC significantly increased the total sleep time of patients with insomnia. There is evidence that the intervention targeted at insomnia may relieve pain. Therefore, rTMS in the DLPFC area may simultaneously affect pain, sleep and mood, and establish a virtuous circle among them to replace the vicious circle. This may be the most significant advantage of the rTMS in the DLPFC area.

So, we believe that rTMS in the DLPFC may be not poorer to M1 in treating NPP with SCI. Our research is clinical research and does not involve specific neurobiological mechanisms research. The treatment of NPP...
by rTMS in the DLPFC area may be related to synaptic plasticity, some cytokines and signal pathways. For example, rTMS accommodated the brain plasticity by motivating the synthesis and release of brain-derived neurotrophic factor (BDNF) and γ-aminobutyric acid (GABA). Both BDNF and GABA were related to pain, depression and sleep regulation. If our research shows positive results, it may be necessary to strengthen neurobiological mechanisms research in the future.

There are some limitations to this trial. This is a preliminary exploratory study, so the follow-up time in this trial is only 4 weeks after the end of treatment. We will follow-up for a longer time in a future study. This will be a single-blind study. Patients will not be blinded, so expectations about treatment may affect the accuracy of the assessment. And VAS has high reliability and validity and is widely used, but it belongs to subjective pain assessment index. In addition, based on our study purpose and previous research, we do not consider the design of the sham stimulation group, so the placebo effect and the expectation of the treatment may not be completely distinguishable from the real treatment effect. And we will consider this issue in the analysis and discussion of the results after the trial is completed.

**Trial status**

This publication is based on version 1 of the rTMS protocol dated on 1 January 2021. The official start of the trial status is ongoing.

**Author affiliations**

1Department of Rehabilitation, The Affiliated Hospital of Southwest Medical University, Luzhou, Sichuan, China

2Laboratory of Neurological Disease and Brain Function, The Affiliated Hospital of Southwest Medical University, Luzhou, Sichuan, China

3Rehabilitation Medicine Department, The Affiliated Hospital of Southwest Medical University, Luzhou, Sichuan, China

**Acknowledgements**

We would like to thank all members of the rTMS Study Group for their support. They thank all the study participants for their involvement and patient advisers in this trial.

**Contributors**

MH and J-XW have designed this trial protocol and drafted the manuscript. J-XW and FX have gained the project funding and provided consultation during the research. CZ and Y-JX are physicians who recruit patients. XL and TW are physical therapist who using the rTMS for patients with neuropathic pain after SCI. LW and RC are responsible for the assessment at baseline and following-up. UW is a research assistant on the project who is responsible for the data collection and analysis. All authors have read and approved the final manuscript. All authors reviewed and revised the manuscript before submission and approved its content.

**Funding**

This work will be supported by the Research Project of Science and Technology Department of Sichuan Province (Project number: 2020YFS0515), the Research Fund of Southwest Medical University (Project number: 2019ZQN110 and 2020ZRNB018), the Sichuan Medical Association Project Fund (Project number: Q19035, 2019HR12), the Nuclear Medicine and Molecular Imaging Key Laboratory of Sichuan Province (Project number: HYX19023 and HYX19005), Special Project of Social work and Health Management of Luzhou Federation of Social Sciences in 2021 (SGJKZ20128).

**Competing interests**

None declared.

**Patient and public involvement**

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Consent obtained directly from patient(s).

**Provenance and peer review**

Not commissioned; externally peer reviewed.

**Open access**

This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

**ORCID iD**

Jian-Xiong Wang http://orcid.org/0000-0002-6861-7483

**REFERENCES**

1 Furlan JC, Sakakibara BM, Miller WC, et al. Global incidence and prevalence of traumatic spinal cord injury. *Can J Neurol Sci* 2013;40:456–64.

2 Mehta S, Orenzuk K, McIntyre A, et al. Neuropathic pain post spinal cord injury Part 1: systematic review of physical and behavioral treatment. *Top Spinal Cord Inj Rehabil* 2013;19:61–77.

3 Finnerup NB, Jensen TS. Spinal cord injury pain–mechanisms and treatment. *Eur J Neurol* 2004;11:73–82.

4 Mann R, Schaefer C, Sadowsky A, et al. Burden of spinal cord injury-related neuropathic pain in the United States: retrospec* tive chart review and cross-sectional section. *Spinal Cord* 2013;51:564–70.

5 Lefaucheur J-P, Aleman A, Baeken C, et al. Evidence-Based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): an update (2013–2018). *Clin Neurophysiol* 2020;131:474–528.

6 Jetté F, Côté I, Meziane HB, et al. Effect of single-session repetitive transcranial magnetic stimulation applied over the hand versus leg motor area on pain after spinal cord injury. *Neuromodulation* 2011;14:366–43.

7 Tazoe T, Perez MA. Effects of repetitive transcranial magnetic stimulation on recovery of function after spinal cord injury. *Arch Phys Med Rehabil* 2015;96:S145–55.

8 Randver R. Repetitive transcranial magnetic stimulation of the dorsolateral prefrontal cortex to alleviate depression and cognitive impairment associated with Parkinson’s disease: a review and clinical implications. *J Neurol Sci* 2018;393:88–99.

9 Randver R, Davali K, Toomsoo T. High-frequency repetitive transcranial magnetic stimulation applied over the hand versus leg motor area on pain after spinal cord injury. *Neuromodulation* 2016;19:368–75.

10 Shiers P, Pradhan G, Mwirigi J, et al. Neuropathic pain creates an enduring prefrontal cortex dysfunction corrected by the type II diabetic drug metformin but not by gabapentin. *J Neurosci* 2018;38:7337–50.

11 Cherif F, Zouari HG, Cherif W, et al. Depression prevalence in neuropathic pain and its impact on the quality of life. *Pain Res Manag* 2020;2020:1–8.

12 Seminowicz DA, Moayedi M. The dorsolateral prefrontal cortex in acute and chronic pain. *J Pain* 2017;18:1027–35.

13 Brighina F, Piazza A, Vitello G, et al. rTMS of the prefrontal cortex in the treatment of chronic migraine: a pilot study. *J Neurol Sci* 2004;227:67–71.

14 Freigang S, Lehner C, Fresnoza SM, et al. Comparing the impact of Multi-Session left dorsolateral prefrontal and primary motor cortex Neuronavigated repetitive transcranial magnetic stimulation (rTMS) on chronic pain patients. *Brain Sci* 2021;11, doi:10.3390/brainsci11080961. [Epub ahead of print: 22 07 2021].

15 Che X, Cash RFH, Luo X, et al. High-frequency rTMS over the dorsolateral prefrontal cortex on chronic and provoked pain: a systematic review and meta-analysis. *Brain Stimul* 2021;14:1135–46.

16 Nardone R, Höller Y, Langthaler PB, et al. tTMS of the prefrontal cortex has analgesic effects on neuropathic pain in subjects with spinal cord injury, *Spinal Cord* 2017;55:20–5.

17 Zhao C-G, Sun W, Ju F, et al. Analgesic effects of directed repetitive transcranial magnetic stimulation in acute neuropathic pain after spinal cord injury. *Pain Med* 2020;21:1216–23.

18 Pommier B, Créach C, Beauchev V, et al. Robot-guided neuronavigated rTMS as an alternative therapy for central (neuropathic) pain: clinical experience and long-term follow-up. *Eur J Pain* 2016;20:907–16.

19 Sampson SM, Kung S, McAlpine DE, et al. The use of low-frequency repetitive transcranial magnetic stimulation in refractory neuropathic pain. *J Ect* 2011;27:33–7.
20 Treede RD, Jensen TS, Campbell JN, et al. Neuropathic pain: redefinition and a grading system for clinical and research purposes. Neurology 2008;70:1630–5.

21 Rossini PM, Burke D, Chen R, et al. Non-Invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: basic principles and procedures for routine clinical and research application. An updated report from an I.F.C.N. Committee. Clin Neurophysiol 2015;126:1071–107.

22 Cai C, Gong Y, Dong D, et al. Combined therapies of modified Taiji miraculous Movements and a modified Tens unit for lumbar intervertebral disc herniation. Evid Based Complement Altern Med 2018;2018:1–6.

23 Melzack R. The McGill pain questionnaire: major properties and scoring methods. Pain 1975;1:277–99.

24 Widerström-Noga E, Biering-Sørensen F, Bryce T, et al. The International spinal cord injury pain basic data set. Spinal Cord 2008;46:818–23.

25 Buyssse DJ, Reynolds CF, Monk TH, et al. The Pittsburgh sleep quality index: a new instrument for psychiatric practice and research. Psychiatry Res 1989;28:193–213.

26 HAMILTON M. The assessment of anxiety states by rating. Br J Med Psychol 1959;32:50–5.

27 Yilmaz B, Kesikburun S, Yaşar E, et al. The effect of repetitive transcranial magnetic stimulation on refractory neuropathic pain in spinal cord injury. J Spinal Cord Med 2014;37:397–400.

28 Yoon EJ, Kim YK, Shin HI, et al. Cortical and white matter alterations in patients with neuropathic pain after spinal cord injury. Brain Res 2013;1540:64–73.

29 Gustin SM, Wrigley PJ, Siddall PJ, et al. Brain anatomy changes associated with persistent neuropathic pain following spinal cord injury. Cereb Cortex 2010;20:1409–19.

30 Hsu JH, Daskalakis ZJ, Slumberger DM. An update on repetitive transcranial magnetic stimulation for the treatment of co-morbid pain and depression. Pain Headache Rep 2018;2:22:51.

31 Brighina F, De Tommaso M, Giglia F, et al. Modulation of pain perception by transcranial magnetic stimulation of left prefrontal cortex. J Headache Pain 2011;12:185–91.

32 Leug A, Metzger-Smith V, He Y, et al. Left dorsolateral prefrontal cortex rTMS in alleviating MTBI related headaches and depressive symptoms. Neuromodulation 2018;21:390–401.

33 Hadjipavlou G, Dunckley P, Behrens TE, et al. Determining anatomical connectivities between cortical and brainstem pain processing regions in humans: a diffusion tensor imaging study in healthy controls. Pain 2006;123:169–78.

34 Schweinhardt P, Kalk N, Wartolowska K, et al. Investigation into the neural correlates of emotional augmentation of clinical pain. Neuroimage 2008;40:759–66.

35 George MS, Wassermann EM. Rapid-Rate transcranial magnetic stimulation and ECT. Convuls Ther 1994;10:251–4.

36 Borckardt JJ, Smith AR, Reeves ST, et al. Fifteen minutes of left prefrontal repetitive transcranial magnetic stimulation acutely increases thermal pain thresholds in healthy adults. Pain Res Manag 2007;12:287–90.

37 Borckardt JJ, Smith AR, Reeves ST, et al. A pilot study investigating the effects of fast left prefrontal rTMS on chronic neuropathic pain. Pain Med 2009;10:840–9.

38 Ulrich PM, Lincoln RK, Tackett MJ, et al. Pain, depression, and health care utilization over time after spinal cord injury. Rehabil Psychol 2013;58:158–65.

39 Antczak JM, Poleszczuk A, Wichniak A, et al. The influence of the repetitive transcranial magnetic stimulation on sleep quality in depression. Psychiatr Pol 2017;51:545–57.

40 Moisset X, de Andrade DC, Bouhassira D. From pulses to pain relief: an update on the mechanisms of rTMS-induced analgesic effects. Eur J Pain 2016;20:689–700.

41 Miller EK, Cohen JD. An integrative theory of prefrontal cortex function. Annu Rev Neurosci 2001;24:167–202.

42 Funahashi S. Neuronal mechanisms of executive control by the prefrontal cortex. Neurosci Res 2001;39:147–65.

43 Widerström-Noga EG, Felipe-Cuervo E, Yezierski RP. Chronic pain after spinal injury: interference with sleep and daily activities. Arch Phys Med Rehabil 2001;82:1571–7.

44 Cardenas DD, Emir B, Parsons B. Examining the time to therapeutic effect of pregabalin in spinal cord injury patients with neuropathic pain. Clin Ther 2015;37:1081–90.

45 Aleman A. Use of repetitive transcranial magnetic stimulation for treatment in psychiatry. Clin Psychopharmacol Neurosci 2011;33:53–9.

46 Feng J, Zhang Q, Zhang C, et al. The effect of sequential bilateral low-frequency rTMS over dorsolateral prefrontal cortex on serum level of BDNF and GABA in patients with primary insomnia. Brain Behav 2019;9:e01206.

47 Roehrs TA, Workshop Participants. Does effective management of sleep disorders improve pain symptoms? Drugs 2009;69 Suppl 2:S5–11.

48 Barr MS, Farzan F, Davis KD, et al. Measuring GABAergic inhibitory activity with TMS-EEG and its potential clinical application for chronic pain. J Neuroimmune Pharmacol 2013;8:535–46.

49 Nijs J, Meeus M, Versijpt J, et al. Brain-Derived neurotrophic factor as a driving force behind neuropilinopathy in neuropathic and central sensitization pain: a new therapeutic target? Expert Opin Ther Targets 2015;19:565–76.

50 McAllister AK. Neurotrophins and neuronal differentiation in the central nervous system. Cell Mol Life Sci 2001;58:1054–60.

51 Hayley S, Pouter MO, Merali Z, et al. The pathogenesis of clinical depression: stressor- and cytokine-induced alterations of neuroplasticity. Neuroscience 2005;135:659–78.

52 Chen JT, Guo D, CampANELLI D, et al. Presynaptic GABAergic inhibition regulated by BDNF contributes to neuropathic pain induction. Nat Commun 2014;5:5331.