Neurophysiologie Clinique/Clinical Neurophysiology (2019) 49, 1—9

Disponible en ligne sur ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com/en

STUDY PROTOCOL

# Efficacy of high-frequency (15 Hz) repetitive transcranial magnetic stimulation (rTMS) of the left premotor cortex/dorsolateral prefrontal cortex in decreasing cocaine intake (the MagneTox study): A study protocol for a randomized placebo-controlled pilot trial

**Maenia Scarpino**[a,b], **Giovanni Lanzo**[a], **Maya Salimova**[c], **Francesco Lolli**[a,d], **Amedeo del Vecchio**[c], **Cesarina Cossu**[a], **Maria Bastianelli**[a], **Brunella Occupati**[e], **Cecilia Lanzi**[e], **Stefano Pallanti**[c], **Aldo Amantini**[a], **Guido Mannaioni**[c,1], **Antonello Grippo**[a,b,*,1]

[a] *SODc Neurofisiopatologia, Dipartimento Neuromuscolo-Scheletrico e degli Organi di Senso, AOU Careggi, Firenze, Italy*
[b] *IRCCS, Fondazione Don Carlo Gnocchi, Firenze, Italy*
[c] *Dipartimento di Neuroscienze, Psicologia, Area del Farmaco e Salute del Bambino (NEUROFARBA), Università degli Studi di Firenze, Firenze, Italy*
[d] *Dipartimento di Scienze Biomediche Sperimentali e Cliniche, Università degli Studi di Firenze, Firenze, Italy*
[e] *Unità di Tossicologia, Azienda Ospedaliero Universitaria Careggi, Firenze, Italy*

Received 17 May 2018; accepted 7 October 2018
Available online 26 October 2018

**KEYWORDS**
Addiction;
Cocaine use disorder;

**Summary**
*Background.* — Cocaine use disorder (CUD) is very common and has psychological and physical consequences. Patients with CUD present hypoactivity of the prefrontal cortical area. Thus, excitatory repetitive transcranial magnetic stimulation (rTMS) targeting the premotor

* Corresponding author at:. SODc Neurofisiopatologia, Dipartimento Neuromuscolo-Scheletrico e degli Organi di Senso, AOU Careggi, Largo brambilla 3, 50134 Firenze, Italy.
*E-mail address:* agrippo@unifi.it (A. Grippo).
[1] Contributed equally to the manuscript.

https://doi.org/10.1016/j.neucli.2018.10.002

Craving;
Decrease;
Repetitive transcranial magnetic stimulation

cortex/dorsolateral prefrontal cortex (PMC/DLPFC), given its ability to increase prefrontal area excitability and to modulate cortico-limbic activity, could result in a decrease in cocaine intake.
*Methods*. — We designed a protocol for a monocentric, randomized, double-blind, placebo-controlled, parallel-group pilot trial, with the principal aim of assessing the efficacy of rTMS on the reduction of cocaine intake. Patients with CUD will be recruited according to inclusion and exclusion criteria, and then randomized to undergo active or sham rTMS. Our rTMS protocol will consist of 15 days of 15 Hz rTMS targeting the left PMC/DLPFC. Toxicological and psychiatric assessments, urine drug tests, the Cocaine Craving Questionnaire (CCQ) and the Visual Analogic Scale (VAS) will be used to assess changes from baseline in cocaine intake and craving, mood and quality of life.
*Discussion*. — Only a few studies have evaluated the efficacy of rTMS for CUD treatment in humans, with limitations concerning small sample size, short treatment duration, different rTMS protocols and the absence of a placebo-controlled group. Our study will attempt to overcome these shortcomings and will provide data that can be used for future larger studies of non-invasive left PMC/DLPFC stimulation as a treatment for CUD.


## Background

Drug addiction represents a significant social problem. Addicts continue to compulsively seek and take drugs despite adverse social, physical, emotional and legal consequences. Among all the different drug addictions, cocaine use disorder (CUD) represents a major public health problem, being very common worldwide, especially in the Western world [15,16]. Cocaine is a psychoactive and addictive substance which, when taken chronically, causes dysregulation of neurotransmitter systems (especially dopamine pathways) [13,42,51,65], a state of hypoactivity in the dorsolateral prefrontal cortex (DLPFC) and brain volume reduction [32,39,45,63,64], as well as significant cardiovascular disease [56].

Given this significant morbidity related to cocaine use, numerous trials have been carried out in recent years to identify an adequate and effective medication for CUD treatment. However, to date, efforts in this field have not brought about meaningful results, such that the discovery of an effective pharmacological therapy has been elusive and long-term success rates are quite modest [46]. Currently, in clinical practice, addicts undergo a psychological and pharmacological therapy association strategy, which, however, does not provide the desired results concerning a decrease in cocaine intake and craving [57]. Therefore, the development of new treatment strategies for this disease continues to be a research priority, and, in order to be more effective, the mechanisms that underlie the development of addiction and craving should be addressed. For example, neuroimaging studies, carried out in addicted patients [28], have identified that the DLPFC shows changes, such as hypoactivity, that could be associated with inhibitory control, addiction and craving [34,35,54]. For this reason, alternative and innovative therapies, notably repetitive transcranial magnetic stimulation (rTMS) targeting the DLPFC, may play a prominent role, because of its ability to focally modulate neuronal excitability [17,54,60]. The increase in excitability in this cortical area could cause a greater release of dopamine at the level of the nucleus accumbens (NA) and ventral tegmental area (VTA), which are deeper structures connected with the DLPFC, responsible for reward circuitry. The increase in dopamine release could culminate in a reduction in cocaine intake and craving. rTMS is a non-invasive and safe brain stimulation technique [37] that uses magnetic pulses administrated through a coil set on cranial landmarks. Depending on the frequency used, rTMS can have an inhibitory [9] or excitatory effect [47]. Previous studies have shown prefrontal cortex hypoactivity [21,22,31] associated with decreased excitability in this cortical region in cocaine-addicted patients, so it may be worth using an excitatory rTMS protocol as an alternative treatment for CUD.

To date, the most consistent evidence in the literature regarding the mechanisms that underlie the development of addiction and craving based on DLPFC excitability modulation come from studies in rats [8,51], and only a few studies have applied these preliminary results to human subjects [24,25,38]. In addition, few studies have been carried out in human subjects using DLPFC excitability modulation induced by rTMS [2,5,49,61], by deep TMS [50] or alternatively using medial PFC excitability modulation induced by deep TMS [41] to evaluate their efficacy in CUD treatment. However, these studies have shown discrepancies in their findings, probably due to limitations in study design. These limitations concern the small sample size, ranging from a minimum of six patients [5] to a maximum of 36 [49], the short duration of treatment [5], the absence of a control group [49] and the frequency/pattern of stimulation [2]. In a study by Terraneo et al. [61], the main limitation was the absence of a placebo-controlled group. Therefore, in this pilot study, we will evaluate the efficacy of excitatory rTMS (15 days at 15 Hz) on the left premotor cortex (PMC)/DLPFC in reducing cocaine intake in addicted patients especially at one week after the end of last rTMS session but also at 8 weeks after treatment, comparing the results obtained in the active rTMS group versus placebo. In addition, our secondary aim will be to evaluate if this treatment is also

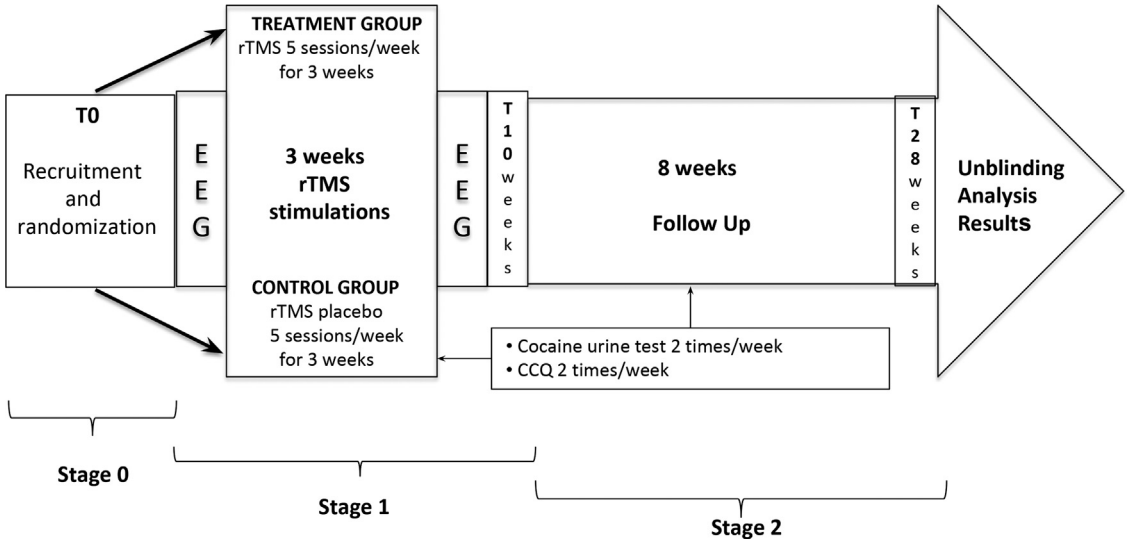


**Figure 1** Course-line MagneTox clinical trial.

effective in craving reduction and whether it has effects on patient mood and behavior.

## Aims

The principal aim of this pilot study will be to evaluate the efficacy of excitatory rTMS (15 days at 15 Hz) on the left PMC/DLPFC in reducing cocaine intake in addicted patients at one week after the end of the treatment, comparing the results obtained in the active rTMS group versus placebo.

The secondary aims of this study will be to evaluate if any decrease in cocaine intake is observed at 8 weeks following the last rTMS session, and whether decrease in craving is also observed.

The hypothesis is that the increase in excitability in the left PMC/DLPFC, due to the high-frequency rTMS procedure, should cause a greater release of dopamine at the NA and VTA levels, with the result of a decrease in cocaine intake and craving during the treatment, immediately after the treatment and up to 8 weeks following the last rTMS session.

Finally, we aim to assess if patients show changes in mood and behavior after rTMS treatment, such as a decrease in the state of anxiety or improvement of depressive symptoms.

## Methods

### Design

This is a randomized, monocentric, placebo-controlled, double-blind, parallel-group study [36]. The study will be carried out at the Toxicology Unit, Neurophysiology Unit and Psychiatry Unit of Careggi University Hospital, Florence, Italy. Cocaine-addicted patients will be randomly allocated to receive 15 sessions (3 weeks of five consecutive daily sessions and 2 days of rest) of either real rTMS (treatment group) or sham rTMS (control group). Participants will be recruited among those seeking treatment for CUD either referred to the Emergency Department, to the Outpatient Toxicology Clinic or sent by primary care physicians in the Florence metropolitan area with the goal of recruiting 60 cocaine-addicted patients over the course of 18 months. Outcomes will be measured at baseline, post-treatment and after 8 weeks of follow-up. The course-line of the MagneTox Clinical Trials is outlined in Fig. 1. A flow-chart outlining the study procedures is presented in Fig. 2.

### Ethical approval and trial registration

All the procedures conform to Good Clinical Practice, and the study protocol has been approved by the Local Ethics Committee of Azienda Ospedaliero-Universitaria Careggi (CEAVC SPE. 16.309; MagneTox trial, 17th July 2017).

All patients, after having been provided with a description of the study, will sign a written informed consent form before starting the treatment, in accordance with the Declaration of Helsinki.

### Screening

Study researchers will screen participants for eligibility. Once eligibility is confirmed, the patient will sign an informed consent. In line with the CONSORT guidelines [44,55], we will record the number and reasons for any participants who will be excluded or any who will decline consent or withdraw from the study.

### Inclusion criteria

The inclusion criteria are:

- male and female patients between 18 and 65 years of age;
- patients who meet the criteria for CUD reported in the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5) [1];
- positivity to cocaine use, determined by a urine drug test;

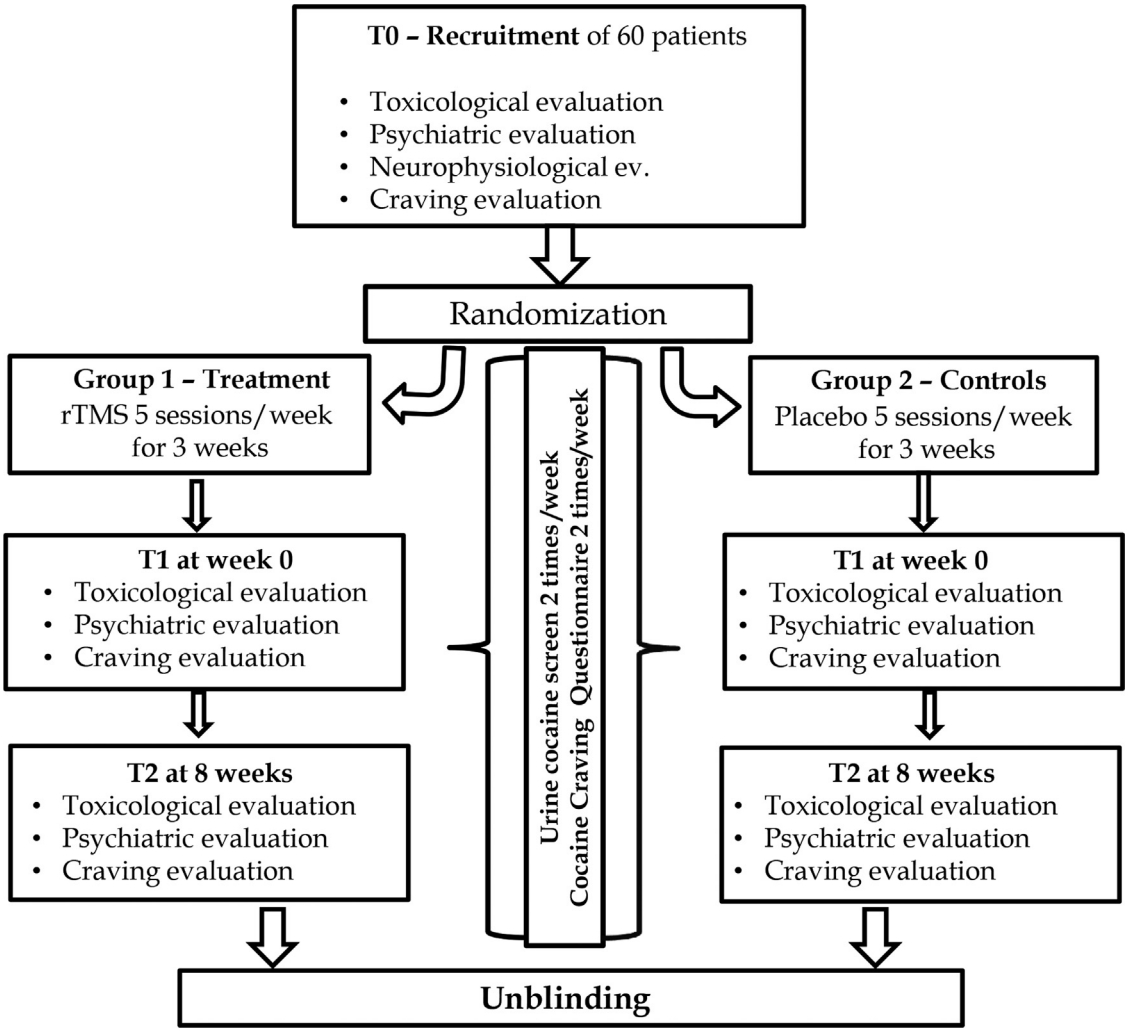


**Figure 2** Flow-chart outlining the study procedures.

- patients who are able to provide written informed consent after being notified about the treatment and the study protocol;
- patients under unmodified psychiatric pharmacological treatment for at least 4 weeks before the beginning of the rTMS treatment.

## Exclusion criteria

The exclusion criteria are:

- major depressive disorder, schizophrenia, bipolar disorder or other psychosis meeting the diagnostic criteria of the DSM-5;
- illiteracy or cognitive impairment (Mini-Mental State Examination < 26);
- women who are pregnant or lactating;
- other medical diseases that contraindicate rTMS treatment such as epilepsy;
- the presence of devices such as a pacemaker or cochlear prosthesis;
- previous rTMS treatments in order to avoid confounding factors;
- patients with concomitant alcohol and drug use;
- patients who cannot provide written informed consent.

## Study process

The study consists of three stages (Fig. 2):

- patient screening (stage 0);
- 15 days of randomized treatment (stage 1);
- 8 weeks of follow-up (stage 2).

### Stage 0

Participants will be recruited among those seeking treatment for CUD either referred to the Emergency Department, to the Outpatient Toxicology Clinic or sent by primary care physicians in the Florence metropolitan area. These patients will undergo toxicological and psychiatric assessment and will be screened using the inclusion and exclusion criteria. The clinical and biological baseline assessment will include:

- urine drug test in order to evaluate previous cocaine use and/or use of other substances (such as opioids, cannabis, amphetamines or ethanol);
- an evaluation of craving degree by using the Visual Analogic Scale (VAS) and the Cocaine Craving Questionnaire (CCQ) [26];
- a structured clinical interview for psychiatric evaluation [18].

Finally, during the toxicological assessment, the physician will evaluate the need to start or to continue with pharmacological treatment. In the case of a pre-existing treatment, it will not be changed during the entire period of the clinical trial. Instead, in the case of the need to start a new drug regimen, the rTMS treatment will be started only after pharmacodynamic equilibrium is achieved (at least after 4 weeks). However, the type and the dosage of the central nervous system (CNS) affecting drugs will always be reported for each patient. Moreover, the referred daily cocaine intake of patients will be checked and reported in an electronic patient chart as well as addictive comorbidities that are not included in the exclusion criteria.

After enrolling in the study, patients will be provided with a complete description of the study and will provide written informed consent (T0).

**Stage 1**
Generation of the randomization sequence will be conducted by a team member, using a block randomization algorithm. Thus, patients will be allocated to one of the two trial arms (real or sham rTMS). Before starting with the first rTMS session, an electroencephalogram (EEG) will be performed in order to exclude the presence of epileptic discharges. Participants will receive real or sham rTMS sessions over 15 consecutive weekdays. Each session will last between 30 and 40 minutes, including preparation time and 13 minutes of rTMS. Treatment will be delivered by a neurophysiology technologist trained in the administration of rTMS. A case record form for each trial patient will be kept to monitor session attendance or protocol violation. At each rTMS session, physicians will also evaluate possible adverse events (AEs), and reporting will conform to national legislation (D.L. 211/2003) [10]. In the event of mild side effects, such as a slight headache, patients will be not withdrawn but will be able to discontinue rTMS treatment if they wish. rTMS will be halted immediately if the participants experience a more serious AE, such as an epileptic seizure. After the last rTMS session is delivered, another EEG will be performed. The first stage will end with a clinical assessment similar to that performed at stage 0, one week after the end of the last rTMS session (T1). In addition, for the duration of stage 1, a biweekly urine drug test and craving evaluation using the CCQ will be performed.

**Stage 2**
This stage corresponds to 8 weeks of follow-up phase without treatment. During this period, patients will undergo a biweekly urine drug test and CCQ. At the end of this follow-up period, the patients will undergo the same clinical assessment carried out at stages 0 and 1 (T2).

## rTMS procedure

### Site localisation of the PMC/DLPFC

The target of cortical stimulation will be set based on cranial landmarks, according to the theoretical distance between the cortical region being targeted and a reference scalp point determined by TMS ('function-guided» procedure) [58]. The left cortical motor area will be used as a reference point. To determine the hand motor hotspot, the coil will be positioned over the supposed left motor cortex area, using motor evoked potentials (MEPs) recorded using the contralateral (right) first dorsal interosseous (FDI) muscle. Then, the coil will be moved until the location is identified at which a single-pulse TMS produces reproducible MEPs that are elicited at the lowest stimulation intensity [53]. Thus, the left PMC/DLPFC will be located 5 cm anterior and 2 cm lateral to the hand motor hotspot [48]. Once the position for TMS is determined, it will be marked on an elastic cap customized for each patient during all rTMS sessions. The coil will be fixed to an adjustable arm, and the landmarks on the cap will be repeatedly inspected during the rTMS session to ensure accurate positioning of the coil on different days. The procedures used to determine the position of the M1 area and the motor threshold will be repeated before each rTMS session. Through mapping of the FDI muscle response, the intensity of the rTMS will be acquired by obtaining the individual's resting motor threshold (rMT), which represents the membrane-related excitability of cortical axons. To ensure safety and efficacy, the rMT will be assessed daily for each participant during the 15 rTMS treatment sessions. Using the MEP method, the rMT will be established by determining the minimum stimulator output intensity required to obtain 5 out of 10 MEPs greater than 50 $\mu$V [66].

### Delivery of real rTMS

A MagPro X100 stimulator (Medtronic, Denmark) connected to a standard figure-of-eight coil with an outer half-radius of 75 mm (MCF-B65 Butterfly Coil) will be used. The coil centre will be placed at the left PMC/DLPFC with the coil handle pointing 45° relative to the midsagittal-line. Patients in this group will receive 15 sessions of high-frequency rTMS (15 Hz) with a pulse intensity of 100% of their individual rMT, consisting of 60 pulses per train with an inter-train pause of 15 s in 40 stimulation trains for a total of 2400 pulses in 13 min of stimulation. These parameters are based on a previous study [61] and respected safety guidelines [52].

### Delivery of sham rTMS

Sham stimulation will be given using the same stimulator and parameters as real rTMS; however, a placebo coil (MCF-P-B65 Placebo Coil) will be used. The placebo coil has a mechanical outline and sound level identical to the MCF-B65, but the magnetic field is reduced by almost 80%.

## Blinding

Participants and researchers conducting assessments will be blinded to the treatment allocation. Thus, the study will be conducted in a double-blinded fashion. To assess whether allocation concealment has been successful, participants will be asked to guess their treatment allocation at the end of the rTMS treatment and to indicate how certain they are of this guess. Participants will be debriefed upon completion of the 8 weeks' follow-up and unblinded to group allocation at the end of the clinical trial.

## Sample size calculation

This is a pilot study. The results of urinary drug tests during treatment and follow-up are considered the primary efficacy outcome, while craving degree evaluation, using the CCQ and VAS, is the secondary outcome. In this context [29], the sample size calculation will be based on an expected difference between the treatment groups of 20%, considering a significance level of 0.05% and a power of 80%, and with the hypothesis of a premature dropout or a non-initiation of the treatment for 20% of the patients. Thus, the estimated sample size will be $n = 60$ (30 participants per group).

## Feasibility

The catchment area will be the ''Provincia di Firenze'' with almost 1 million inhabitants (data from June 2015). Patients will be recruited in 13 centres for drug use disorders located in the Florence area (Tuscany) or in the Toxicology Unit of Careggi University Hospital in Florence. Our Neurophysiology Unit will perform up to four rTMS sessions each day, 5 days/week (from Monday to Friday). Considering the 3 weeks of scheduled treatment for every patient and 48 weeks/year, we could potentially enroll 64 patients/year. The decision as to whether to progress the study to a future large-scale randomized controlled trial (RCT) will be based on a number of criteria. These will include the number of patients we are able to recruit, the proportion of patients retained in the study, the proportion of patients completing the real rTMS/sham intervention, the acceptability of real rTMS/sham intervention and the effect size of treatment outcomes.

## Clinical outcomes

Analyses will use the intention-to-treat principle. To determine quality, completeness and variability of the outcome measures, we will employ descriptive statistical analyses and graphical methods. In univariate analysis for normally distributed variables, Student's *t*-test will be used, whereas for categorical variables the $Chi^2$ test will be performed. The size of the treatment effect on each outcome measure will be the difference in outcome data between those in the two treatment groups post-treatment and at follow-up. Group differences will be estimated using linear mixed effects regression models, controlling for the baseline level of the measured outcomes. To consider lacking data, we will employ a multiple imputation technique, according to Dempster et al. [11]. Kaplan—Meier curves will be used to plot the cumulated proportions of event-free patients (drug urine screen) in the two groups: significance between pairs of curves will be tested by log-rank. The aim of the analysis will be to establish a suitably precise effect size for the primary outcome for a future large-scale RCT at the post-treatment assessment.

## Discussion

In recent years, rTMS has been used for the treatment of some neurologic and psychiatric disorders, particularly those associated with abnormal dopamine activity and altered cortical excitability, such as depression [3,33], schizophrenia [23,59] or drug addiction [12,14,43]. Some authors recently proposed the use of rTMS for the treatment of cocaine-addicted patients [2,5,45,56]. In these subjects, rTMS targets the DLPFC because of evidence of hypoactivity in this cortical region related to addiction, craving and compulsive drug-seeking behaviors [28,34,54]. The development of new treatments, such as rTMS, for cocaine-dependent patients is a much-debated topic of great interest in recent years, representing a great therapeutic challenge. This is because, despite the significant morbidity related to cocaine use, no unequivocally effective pharmacological therapies have been identified to date [30]. Furthermore, the few recent studies that proposed rTMS for CUD treatment showed some limitations concerning the small size of the sample [5], the short treatment duration [5], the absence of a control group [49], the use of different rTMS protocols (including sub-optimal rTMS frequency [10 Hz] [2]), and the absence of a placebo control group [61]. The role of rTMS parameters in modulating the efficacy of stimulation is a topic of wide debate [27]. In particular, the frequency and pattern of stimulation seem to be key elements in the observed effects, as shown in some recent studies [7,61] in which the frequency/pattern was 20 Hz or 15 Hz compared to the study by Bolloni et al. [2] in which 10 Hz was used. However, at the same time, the positive effects obtained with active high-frequency rTMS on the DLPFC [61] had to be necessarily compared to those obtained in a placebo group. Another important point of debate is the side of stimulation. In particular, we decided to perform rTMS targeting the left PMC/DLPFC because of previous studies using functional magnetic resonance imaging showing that in patients with CUD, craving was associated with left DLPFC activation [19,40]. Moreover, rTMS targeting left DLPFC has been shown to reduce the urge to smoke and cigarette consumption [14] and to modulate food craving [62]. Several potential practical and operational issues may pose challenges to the completion of this study, particularly with regards to recruitment and attrition. Patients with CUD are often ambivalent about treatment, and this is reflected in poor adherence rates of certain treatments and high dropout. Thus, even though rTMS appears promising in CUD, it is unclear what the attendance and retention rates will be when the treatment is offered to CUD patients. Although participants show interest in undergoing rTMS, adherence and completion of the treatment may prove challenging, such as in cases in which the treatment is too uncomfortable, if the study is too cumbersome, or if the participant believes

that they are receiving the sham treatment. Concerning the latter point, although we will use a sham coil that elicits a more realistic TMS-like sensation, it is not clear whether participants will be able to distinguish between the real and sham treatment and what impact this will have on attrition rates. For this reason, we will exclude patients with previous experience with rTMS treatment. It is important to ascertain patient willingness to undergo random allocation to real or sham rTMS. Indeed, rTMS is a relatively demanding treatment, requiring daily attendance for an extended period. However, this type of RCT is considered the gold standard method of evaluating the clinical efficacy of rTMS treatment in other disorders, such as depression [20]. In addition, we are aware that another main limitation of our study protocol is represented by the lack of the use of neuro-navigation that may lead to inaccuracies in the localisation of the PMC/DLPFC target point. This could impact rTMS efficacy, and it must be taken into account in the case of negative results. Another possible limitation that could impact rTMS efficacy is represented by the pharmacological treatment to which patients with CUD are subjected, such as anticonvulsant and benzodiazepine drugs, but the withdrawal of pre-existing treatments is not allowed by our Local Ethics Committee. Finally, another limitation of our study protocol concerns the lack of neuroimaging data before and after rTMS treatment. This will not allow us to investigate the mechanism of action of rTMS in responder patients; however, the main aim of our study is not to investigate the pathophysiological mechanisms underlying the therapeutic effects.

## Conclusion

With this study, we will try to overcome the limits of previous ones, investigating the short- and long-term efficacy of modulating left PMC/DLPFC excitability through 15 Hz rTMS to treat CUD, by comparing the findings of active rTMS arm versus placebo. In fact, the strength of the study is that the protocol adheres to guidance on the optimal conduct of neuromodulation trials [4,6,44]. Moreover, this paper outlines the protocol for a pilot trial that can be used for future studies, for example, by providing effect sizes for a larger RCT that can provide evidence for non-invasive brain stimulation as a potential treatment for CUD.

## Trial status

The study has been registered on ClinicalTrials.gov with identifier number NCT03607591. Enrolment for this study began in October 2017. At the time of submission, we had enrolled 17 subjects.

## Disclosure of interest

The authors declare that they have no competing interest.

## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.neucli.2018.10.002.

## References

[1] American Psychiatric Association. Desk reference to the diagnostic criteria from DSM-5. Arlington: American Psychiatric Association; 2013.
[2] Bolloni C, Panella R, Pedetti M, Frascella AG, Gambelunghe C, Piccoli T, et al. Bilateral transcranial magnetic stimulation of the prefrontal cortex reduces cocaine intake: a pilot study. Front Psychiatry 2016;7:133.
[3] Blumberger DM, Vila-Rodriguez F, Thorpe KE, Feffer K, Noda Y, Giacobbe P, et al. Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation inpatients with depression (THREE-D): a randomised non-inferiority trial. Lancet 2018;391:1683—92.
[4] Brunoni AR, Fregni F. Clinical trial design in non-invasive brain stimulation psychiatric research. Int J Methods Psychiatr Res 2011;20:19—30.
[5] Camprodon JA, Martinez-Raga J, Alonso-Alonso M, Shih MC, Pascual-Leone A. One session of high-frequency repetitive transcranial magnetic stimulation (rTMS) to the right prefrontal cortex transiently reduce cocaine craving. Drug Alcohol Depend 2007;86:91—4.
[6] Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med 2013;158:200—7.
[7] Ceccanti M, Inghilleri M, Attilia ML, Raccah R, Fiore M, Zangen A. Deep TMS on alcoholics: effects on cortisolemia and dopamine pathway modulation. A pilot study. Can J Physiol Pharmacol 2015;93:283—90.
[8] Chen BT, Yau H, Hatch C, Kusumoto-Yoshida I, Cho SL, Hopf FW, et al. Rescuing cocaine-induced prefrontal cortex hypoactivity prevents compulsive cocaine seeking. Nature 2013;496:359—62.
[9] Chen R, Classen J, Gerloff C, Celnik P, Wassermann E, Hallett M, et al. Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. Neurology 1997;48:1398—403.
[10] Decreto Legislativo 211/2003 in merito all'applicazione della buona pratica clinica nell'esecuzione delle sperimentazioni cliniche di medicinali per uso clinico.
[11] Dempster AP, Laird NM, Rubin DB. Maximum Likelihood from Incomplete Data via the EM Algorithm. J R Stat Soc Ser B (Meth) 1977;39:1—38.
[12] deRidder D, Vanneste S, Kovacs S, Sunaert S, Dom G. Transient alcohol craving suppression by rTMS of dorsal anterior cingulate: an fMRI and LORETA EEG study. Neurosci Lett 2011;496:5—10.
[13] Diana M. The dopamine hypothesis of drug addiction and its potential therapeutic value. Front Psychiatry 2011;2:64.
[14] Eichhammer P, Johann M, Kharraz A. High-frequency repetitive transcranial magnetic stimulation decreases cigarette smoking. J Clin Psychiatry 2003;64:951—3.
[15] European Monitoring Centre for Drug Addiction. European Drug Report trends and developments, 2014.
[16] European Monitoring Centre for Drugs and Drug Addiction. European Drug report trends and developments; 2016.
[17] Feil J, Zangen A. Brain stimulation in the study and treatment of addiction. Neurosci Biobehav Rev 2010;34:559—74.

[18] First MB, Williams JBW, Karg RS, Spitzer RL. Structured clinical interview for DSM-5 disorders, clinical trials version (SCID-5-CT). Arlington, VA: American Psychiatric Association; 2015.
[19] Garavan H, Pankiewicz J, Bloom A, Cho JK, Sperry L, Ross TJ, et al. Cue-induced cocaine craving: neuroanatomical specificity for drug users and drug stimuli. Am J Psychiatry 2000;157:1789—98.
[20] Gaynes BN, Lloyd SW, Lux L, Gartlehner G, Hansen RA, Brode S, et al. Repetitive transcranial magnetic stimulation for treatment-resistant depression: a systematic review and meta-analysis. J Clin Psychiatry 2014;75:477—89.
[21] Goldstein RZ, Volkow ND. Drug addiction and its underlying neurobiological basis: neuroimaging evidence for the involvement of the frontal cortex. Am J Psychiatry 2002;159:1642—52.
[22] Goldstein RZ, Volkow ND. Dysfunction of the prefrontal cortex in addiction: neuroimaging findings and clinical implications. Nat Rev Neurosci 2011;12:652—69.
[23] Goyal N, Nizamie SH, Desarkar P. Efficacy of adjuvant high-frequency repetitive transcranial magnetic stimulation on negative and positive symptoms of schizophrenia: preliminary results of a double-blind sham-controlled study. J Neuropsychiatry Clin Neurosci 2007;19:464—7.
[24] Hanlon CA, Dowdle LT, Austelle CW, DeVries W, Mithoefer O, Badran BW, et al. What goes up can come down: novel brain stimulation paradigms may attenuate craving and craving-related neural circuitry in substance dependent individuals. Brain Res 2015;1628:199—209.
[25] Hanlon CA, Kearney-Ramos T, Dowdle LT, Hamilton S, DeVries W, Mithoefer O, et al. Developing repetitive transcranial magnetic stimulation (rTMS) as a treatment tool for cocaine use disorder: a series of six translational studies. Curr Behav Neurosci Rep 2017;4:341—52.
[26] Heinz AJ, Epstein DH, Schroeder JR, Singleton EG, Heishman SJ, Preston KL. Heroin and cocaine craving and use during treatment: measurement validation and potential relationships. J Subst Abuse Treat 2006;31:355—64.
[27] Huan YZ, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC. Theta burst stimulation of the human motor cortex. Neuron 2005;45:201—6.
[28] Jansen JM, Daams JG, Koeter MW, Veltman DJ, van den Brink W, Goudriaan AE. Effects of non-invasive neurostimulation on craving: a meta-analysis. Neurosci Biobehav Rev 2013;37:2472—80.
[29] Julious SA. Sample size of 12 per group rule of thumb for a pilot study. Pharm Stat 2005;4:287—91.
[30] Kampman KM. What's new in the treatment of cocaine addiction? Curr Psychiatry Rep 2010;12:441—7.
[31] Kaufman JN, Ross TJ, Stein EA, Garavan H. Cingulate hypoactivity in cocaine users during a GO-NOGO task as revealed by event-related functional magnetic resonance imaging. J Neurosci 2003;23:7839—43.
[32] Ke Y, Streeter CC, Nassar LE, Sarid-Segal O, Hennen J, Yurgelun-Todd DA. Frontal lobe GABAlevels in cocaine dependence: a two-dimensional, J-resolved magnetic resonance spectroscopy study. Psychiatry Res: Neuroimaging 2004;130:283—93.
[33] Kito S, Fujita K, Koga Y. Regional cerebral blood flow changes after low-frequency transcranial magnetic stimulation of the right dorsolateral prefrontal cortex in treatment-resistant depression. Neuropsychobiology 2008;58:29—36.
[34] Klauss J, Penido Pinheiro LC, Silva Merlo BL, de Almeida Correia Santos G, Fregni F, Nitsche MA. A randomized controlled trial of targeted prefrontal cortex modulation with tDCS in patients with alcohol dependence. Int J Neuropsychopharmacol 2014;17:1793—803.
[35] Koob GF, Volkow ND. Neurocircuitry of addiction. Neuropsychopharmacology 2010;35:217—38.
[36] Lancaster GA, Dodd S, Williamson PR. Design and analysis of pilot studies: recommendations for good practice. J Eval Clin Pract 2004;10:307—12.
[37] Lefaucheur J, André-Obadia N, Antal A, Ayache SS, Baeken C, Benninger DH, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). Clin Neurophysiol 2014;125:2150—206.
[38] Li X, Malcolm RJ, Huebner K, Hanlon CA, Taylor JJ, Brady KT, et al. Low-frequency repetitive transcranial magnetic stimulation of the left dorsolateral prefrontal cortex transiently increases cue-induced craving for methamphetamine: a preliminary study. Drug Alcohol Depend 2013;133:641—6.
[39] Licata SC, Renshaw PF. Neurochemistry of drug action. Ann N Y Acad Sci 2010;1187:148—71.
[40] Maas LC, Lukas SE, Kaufman MJ, Weiss RD, Daniels SL, Rogers VW, et al. Functional magnetic resonance imaging of human brain activation during cue-induced cocaine craving. Am J Psychiatry 1998;155:124—6.
[41] Martinez D, Urban N, Grassetti A, Chang D, Hu MC, Zangen A, et al. Transcranial magnetic stimulation of medial prefrontal and cingulate cortices reduces cocaine self-administration: a pilot study. Front Psychiatry 2018;9:80.
[42] Melis M, Spiga S, Diana M. The dopamine hypothesis of drug addiction: hypodopaminergic state. Int Rev Neurobiol 2005;63:101—54.
[43] Mishra BR, Nizamie SH, Das B, Praharaj SK. Efficacy of repetitive transcranial magnetic stimulation in alcohol dependence: a sham-controlled study. Addiction 2010;105:49—55.
[44] Moher D, Schulz KF, Altman DG, Group C. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. Lancet 2001;357:1191—4.
[45] Moreno-Lopez L, Catena A, Fernandez-Serrano MJ, Delgadorico E, Stamatakis EA, Perez-Garcia M, et al. Trait impulsivity and prefrontal gray matter reductions in cocaine-dependent individuals. Drug Alchol Depend 2012;125:208—14.
[46] O'Brien CP. Evidence-based treatments of addiction. Philos Trans R Soc Lond B Biol Sci 2008;363:3277—86.
[47] Pascual-Leone A, Valls-Sole J, Wassermann E, Hallett M. Responses to rapid-rate transcranial magnetic stimulation of the human motor cortex. Brain 1994;117:847—58.
[48] Pascual-Leone A, Rubio B, Pallardó F, Catalá MD. Rapid-rate transcranial magnetic stimulation of left dorsolateral prefrontal cortex in drug-resistant depression. Lancet 1996;348:233—7.
[49] Politi E, Fauci E, Santoro A, Smeraldi E. Daily sessions of transcranial magnetic stimulation to the left prefrontal cortex gradually reduce cocaine craving. Am J Addict 2008;17:345—6.
[50] Rapinesi C, Del Casale A, Di Pietro S, Ferri VR, Piacentino D, Sani G, et al. Add-on high-frequency deep transcranial magnetic stimulation (dTMS) to bilateral prefrontal cortex reduces cocaine craving in patients with cocaine use disorder. Neurosci Lett 2016;629:43—7.
[51] Rossetti ZL, Hmaidan Y, Gessa GL. Marked inhibition of mesolimbic dopamine release: a common feature of ethanol, morphine, cocaine and amphetamine abstinence in rats. Eur J Pharmacol 1992;221:227—34.
[52] Rossini PM, Burke D, Chen R, Cohen LG, Daskalakis Z, Di Iorio 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.
[53] Rossi S, Hallett M, Rossini PM, Pascual-Leone A, Safety of TMS Consensus Group. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic

stimulation in clinical practice and research. Clin Neurophysiol 2009;120:2008—39.
[54] Sauvaget A, Trojak B, Bulteau S, Jimenez-Murcia S, Fernandez-Aranda F, Wolz I. Transcranial direct current stimulation (tDCS) in behavioral and food addiction: a systematic review of efficacy, technical and methodological issues. Front Neurosci 2015;9:349.
[55] Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel-group randomized trials. Ann Intern Med 2010;152:726—32.
[56] Schwartz BG, Rezkalla S, Kloner RA. Cardiovascular effects of cocaine. Circulation 2010;122:2558—69.
[57] Shorter D, Domingo CB, Kosten TR. Emerging drugs for the treatment of cocaine use disorder: a review of neurobiological targets and pharmacotherapy. Expert Opin Emerg Drugs 2015;20:15—29.
[58] Sparing R, Buelte D, Meister IG, Paus T, Fink GR. Transcranial magnetic stimulation and the challenge of coil placement: a comparison of conventional and stereotaxic neuronavigational strategies. Hum Brain Mapp 2008;29:82—96.
[59] Stanford A, Sharif Z, Concoran C, Urban N, Malaspina D, Lisanby SH. rTMS strategies for the study and treatment of schizophrenia: a review. Int J Neuropsychopharmacol 2008;11:563—76.
[60] Sundaresan K, Ziemann U, Stanley J, Boutros N. Cortical inhibition and excitation in abstinent cocaine-dependent patients: a transcranial magnetic stimulation study. Neuroreport 2007;18:289—92.
[61] 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;26:37—44.
[62] Uher R, Yoganathan D, Mogg A. Effect of left prefrontal repetitive transcranial magnetic stimulation on food craving. Biol Psychiatry 2005;58:840—2.
[63] Volkow ND, Fowler JS, Wang GJ. The addicted human brain: insights from imaging studies. J Clin Invest 2003;111:1444—51.
[64] Volkow ND, Fowler JS, Wang G, Swanson JM. Dopamine in drug abuse and addiction: results from imaging studies and treatment implications. Mol Psychiatry 2004;9:557—69.
[65] Volkow ND, Wang GJ, Fowler JS, Logan J, Gatley SJ, Hitzemann R. Decreased striatal dopaminergic responsiveness in detoxified cocaine-dependent subjects. Nature 2007;386:830—3.
[66] Ziemann U, Hallett M. Basic neurophysiological studies with TMS. In: George MS, Belmaker RH, editors. Transcranial magnetic stimulation in neuropsychiatry. 1st ed. Washington, DC: American Psychiatric Press; 2000. p. 59—84.