

Protocol Title: Cracking addiction: does **BRAIN** Stimulation-induced neuroplasticity reverse prefrontal cortex hypoactivity in cocaine and neW stImulanTs addiCtion in **Humans (BRAIN SWITCH)?**

Abbreviated title: Transcranial Magnetic Stimulation for Cocaine Addiction

Protocol Number: 1496

Date of Approval: June 29, 2017

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A. Précis

Background: Cocaine use disorder (CUD) are a major public health concern, associated with high relapse rates, significant disability and substantial mortality. In Italy, it has been recently estimated that up to 4.8% of subjects between the ages of 15-64 have assumed cocaine at least once, whereas 1.3% subjects currently have a diagnosis of CUD. Unfortunately, current interventions are only modestly effective. Preclinical studies as well as human neuroimaging studies have provided strong evidence that the observable behaviors that characterize the addiction phenotype, such as compulsive drug consumption, impaired self-control, and behavioral inflexibility, reflect underlying dysregulation and malfunction in specific neural circuits. These developments have been accompanied by advances in neuromodulation interventions, both invasive as deep brain stimulation, and non-invasive such as repetitive transcranial magnetic stimulation and transcranial direct current stimulation. These interventions appear particularly promising as they may not only allow us to probe affected brain circuits in addictive disorders, but also seem to have unique therapeutic applications to directly target and remodel impaired circuits.

Objectives: The primary goal of the current study is to investigate the effects of repetitive transcranial magnetic stimulation (rTMS) targeting the left DLPFC on cocaine craving and consumption. Our secondary goals are to evaluate rTMS effects on: (1) cognitive functions; (2) mood; (3) resting state functional connectivity between the DLPFC and nodes of the executive control network, as well as between this network and other relevant networks; (4) percent BOLD signal changes in DLPFC during tasks known to activate this area.

Study population: Treatment seeking cocaine dependent subjects (N=80), aged 18-65 years

Design: After eligibility screening and informed consent, participants will undergo a baseline phase during which they will be randomized to receive high-frequency (15Hz) rTMS (active rTMS) or sham stimulation of the left DLPFC. Subsequently, the continued treatment phase will take place, during which rTMS sessions will be conducted twice per day, five times per week for 2 weeks, for a total of 20 sessions. During this phase, participants will also undergo self-help groups twice a week. After this phase, participants will start a 24-week outpatient phase. (2) During the first 12 weeks (rTMS follow-up) participants will undergo real or sham stimulation (two consecutive sessions per day, once a week), and behavioral assessments will be performed.

During the following 12 weeks (no rTMS follow-up), participants will not receive TMS but behavioral data will be collected to observe long-term effects of rTMS. Visits will take place every two weeks, during this phase. During the follow-up period, patients will continue to participate in self-help groups.

B. Background

Cocaine use disorders

Cocaine use disorder (CUD) are a major public health concern, associated with high relapse rates, significant disability and substantial mortality. In Italy, it has been recently estimated that up to 4.8% of subjects between the ages of 15-64 have assumed cocaine at least once, whereas 1.3% subjects currently have a diagnosis of CUD. Unfortunately, current interventions are only modestly effective. Preclinical studies as well as human neuroimaging studies have provided strong evidence that the observable behaviors that characterize the addiction phenotype, such as compulsive drug consumption, impaired self-control, and behavioral inflexibility, reflect underlying dysregulation and malfunction in specific neural circuits. These developments have been accompanied by advances in neuromodulation interventions, both invasive as deep brain stimulation, and non-invasive such as repetitive transcranial magnetic stimulation and transcranial direct current stimulation. These interventions appear particularly promising as they may not only allow us to probe affected brain circuits in addictive disorders, but also seem to have unique therapeutic applications to directly target and remodel impaired circuits.

Neuromodulation: Transcranial Magnetic Stimulation

rTMS, a non-invasive brain stimulation technique, has been used in experimental approaches to a variety of neuropsychiatric disorders (George et al., 2002). rTMS can alter cortical excitability, and hence induce changes in neuronal circuits (Fitzgerald et al. 2009, Cho & Strafella 2009). TMS generates electrical activity in localized brain regions following through the application of magnetic pulses produced by passing an electrical current through an electromagnetic coil. The direct effect on underlying brain tissue can be sufficiently focused to allow a mapping of the motor cortex (Wilson et al., 1993). MRI or Positron Emission Tomography (PET) studies of the cortical region stimulated by TMS have shown it to be reasonably delimited, and approximately the same size as that involved with voluntary movements of single fingers (Bohning et al., 2000a; Bohning et al., 2000b; Takano et al., 2004). The magnetic stimulation can be delivered as a single pulse or as a train of pulses. Initially used on the motor cortex, a single TMS pulse caused activation of a motor response. When applied as a train, supra-threshold rTMS at high frequencies ($\geq 5\text{Hz}$) caused a long-lasting facilitation of motor cortex excitability, whereas at low frequency (1 Hz) it caused a long-lasting inhibition (Siebner & Rothwell, 2003). In general, the longer the train of stimuli, the greater the duration of either facilitation or inhibition. With a constant frequency, the effects

last approximately 50-60% of the duration of the stimulus train. In a typical “figure eight” coil, the intensity of the magnetic field induced by current running through the coil is maximal under the cross point of the “eight,” near the cortical surface of the brain, therefore allowing for a focal stimulation of cortical areas. In addiction research, rTMS and other brain stimulation techniques have been mainly used as investigative tools to index altered cortical excitability induced by chronic exposure to drugs of abuse. Most of these studies were conducted to assess changes in excitability of the motor cortex (Boutros et al., 2001, 2005; Lang et al., 2008; Sundaresan et al., 2007; Ziemann et al., 1995). Recently, however, repeated brain stimulation using TMS has also been evaluated for its potential efficacy in reducing drug craving and associated addictive behaviors. In these studies, stimulation was typically applied to the DLPFC, and its ability to affect drug consumption and craving was measured (Amiaz et al., 2009; Camprodon et al., 2007; Eichhammer et al., 2003; Johann et al., 2003; Politi et al., 2008). In particular, three studies evaluated the effects of high-frequency rTMS in individuals with cocaine addiction. Camprodon and colleagues (2007) compared the effects of a single session of rTMS (10 Hz) targeting either right or left DLPFC on spontaneous craving in six subjects. Right but not left rTMS reduced craving although these findings were limited by the small sample and absence of a sham control. Findings from a subsequent study show that targeting the left DLPFC with high-frequency rTMS may also have an anti-craving effect (Politi et al., 2008). This was an open-label study in which 36 cocaine-dependent individuals received 10 daily sessions of active rTMS and reported decreased spontaneous cocaine craving. More recently, Terraneo and colleagues (Terraneo et al. 2015) also conducted another open-label pilot study with 32 cocaine addicted patients randomly assigned to receive 8 sessions of high-frequency rTMS of the left or standard pharmacological treatment. rTMS was associated with decreased craving and increased abstinence rates, as assessed by the number of cocaine-free urine drug tests, compared to the control group.

On the basis of these findings, the aim of this study is to test whether rTMS of the left DLPFC could be effective in treating CUD.

C. Study Overview

This is a between-subject double-blind, randomized, sham-controlled study with a 1:1 allocation into two parallel arms: 15 Hz, or sham rTMS stimulation. Participants will be 80 treatment-seeking patients, between the ages of 18-65, who meet diagnostic criteria for CUD (moderate to severe). Criteria for study enrollment are listed below. All participants will be

informed about study procedures and will provide written informed consent prior to the experiment, in line with the Helsinki Declaration developed by the World Medical Association.

Recruitment: We aimed to recruit patients from rural and urban areas, in order to take account of possible differences in substance consumption and addiction severity. Therefore, recruitment will take place in two different cities: Rome, a large metropolitan area, and Chieti, a small city in the centre of Italy, where the majority of patients will be enrolled from rural surroundings. Participants enrollment will be performed by a multidisciplinary team (physicians, psychologists), who have been trained and have extensive experience in performing the assessments included in the current study.

Inclusion criteria

1. Age 18 – 65;
2. Current DSM-V- diagnosis of cocaine use disorder (from moderate to severe);
3. Abstinence from cocaine for at least 48 hrs.

Exclusion criteria

1. Current DSM-V diagnosis of substance use disorders other than nicotine Current DSM-V diagnosis of moderate to severe alcohol use disorders
2. Current DSM-IV diagnosis of schizophrenia, bipolar disorder, or other psychotic disorder;
3. Use in the past 4 weeks of any medication with known pro-convulsant action; or current regular use of any psychotropic medications (benzodiazepines, antipsychotic medications, tricyclic antidepressants, anti-epileptics, mood stabilizers);
4. Any history of any clinically significant neurological disorder, including organic brain disease, epilepsy, stroke, brain lesions, multiple sclerosis, previous neurosurgery, or personal history of head trauma that resulted in loss of consciousness for > 5 minutes and retrograde amnesia for > 30 minutes;
5. Any personal or family history (1st degree relatives) of seizures other than febrile childhood seizures;

6. Any psychiatric, medical or social condition whether or not listed above, due to which, in the judgment of the PI and after any consults if indicated, participation in the study is not in the best interest of the patient;
7. For female patients: Pregnancy/breastfeeding.

Participants enrollment will be performed by a multidisciplinary team (physicians, psychologists), who have been trained and have extensive experience in performing such assessments. Participants will be presented with information about the study prior to data collection and they will be informed of their right to withdraw their information at any time, and that by taking part they are providing consent for the research team to use their anonymised data for research (including publications and other forms of dissemination). Furthermore, they will provide written informed consent prior to the experiment, in line with the Helsinki Declaration developed by the World Medical Association. The research team will not include people if they are unable to give informed consent. The Health and Human Sciences Ethics Committee at the University of Chieti approved the research before it commences.

D. Procedures

rTMS

Repetitive TMS will be delivered using a MagPro R30 with the Cool-B80 figure-of-eight coil (MagVenture, Falun, Denmark). Such coil allows for a focal stimulation of the DLPFC. Subjects will be seated in a recliner with their hands in a comfortable resting position, and the study investigator will insert earplugs, while the participant will wear a cap over the scalp. After skin preparation, surface electrodes will be taped over the region of the abductor pollicis brevis (APB) belly and associated tendon of the right hand. The coil will be placed over the hand-associated primary motor cortex of the right hemisphere with the handle directed posteriorly. While supra-threshold stimuli will be applied, the coil will be moved in steps of 1 cm to determine the optimal scalp position for producing motor evoked potentials (MEP) of maximal amplitude (lowest threshold) in the contralateral target hand muscle. This procedure will be performed in order to identify the resting motor threshold (RMT), which will be used to calculate the intensity of stimulation (100% of the RMT). Subsequently, the coil will be placed over the left dorsolateral prefrontal cortex using a TMS Navigator. The motor hotspot and the DLPFC location will be marked on the cap wore by the participant so to ensure accuracy and consistency across sessions. Two consecutive rTMS sessions lasting 13 minutes

each will be performed, with a minimum of 60 minutes interval between sessions. Each rTMS session will be delivered at the intensity of 100% of individual resting motor threshold, for a total of 40 trains (60 stimuli per train, inter-train interval of 15 seconds, for a total of 2400 stimuli). At the beginning of each session, participants will be exposed to cocaine-related cues for approx. 2 minutes. While viewing pictures (approx. 60 images), participants will be instructed to try to inhibit any craving elicited by the cues in an attempt to elicit activation in networks specifically related to controlling responses and cocaine use/substance abuse in general. At the end of each stimulation session, participants will rate their craving using a Visual Analog Scale (VAS).

Study days during which participants will receive stimulation will be planned as follow:

1. Arrival
2. Tox drug screen
3. Preparation (earplugs, cap)
4. RMT*
5. TMS (active or placebo) and cocaine-cues exposure
6. HR/PB monitoring
7. VAS cocaine craving
8. Side effects questionnaire and PANAS
9. Interval \geq 60 minuti
10. Steps 6,7 and 8 will be repeated

Participants will receive 20 sessions of rTMS during the continued rTMS treatment phase (2 sessions daily, 5 days/week), and subsequently will undergo 24 sessions during the follow-up (FU) phase (two consecutive sessions per day for 12 weeks), for a total of 44 sessions over the course of the study.

Sham stimulation will use the same coil placement as that used for active stimulation, and will match the number of pulses delivered during the 15Hz session. The selection of the operation mode (15 Hz, sham) will be pre-programmed by a staff member that will not be involved in data collection and analysis. Study personnel will not know which mode is being activated, thus preserving the double-blind.

During each stimulation session and immediately after, heart rate and blood pressure will be monitored. Also, at the end of the session, the ‘Side Effect’ questionnaire and the PANAS scale will be administered to evaluate potential side effects.

Side effects: The use of rTMS is considered safe when conducted within existing safety guidelines (Rossi et al. 2009). On the basis of these guidelines, it has been developed a screening tool, named the TMS safety screening, which will be administered to all study participants to determine their eligibility. Several side effects have been reported following TMS. The most important risk of rTMS is the possibility of inducing a seizure. The 1996 and 2008 International Consensus Safety Guidelines describe the maximum safe duration of an rTMS train based on intensity and frequency of the stimulation. Since the issuance of these guidelines, the incidence of TMS-induced seizures worldwide is very low, estimated as “rare” with low-frequency (< 1 Hz) rTMS and < 1% with high-frequency (> 1 Hz) rTMS. There have been no reports of any subject developing epilepsy or repeated spontaneous seizures after rTMS. All rTMS-induced seizures to date have been transient and self-limiting, without long-term sequelae.

Concurrent medication has been implicated as a risk factor in some of the seizures reported with rTMS. Some have suggested that certain medications, e.g. tricyclic antidepressants and neuroleptics, should be contraindicated in those receiving rTMS. To minimize risk, psychotropic medications will be exclusionary criteria in the current study, and use of illicit drugs will be monitored. Although data are lacking, a history of epilepsy, of seizures of other origin (other than febrile child fevers) could also be associated with an increase of TMS-induced seizures, and will therefore also be exclusionary criteria. To manage the small risk nevertheless present, a physician will be available while TMS sessions are in progress and will be called in the event of any medical issue.

Mild headache responding readily to non-opioid analgesics has been reported as on the most common side-effect of rTMS reported in depression treatment trials. It may result from direct stimulation of superficial facial muscles or nerves, as rTMS may cause an uncomfortable facial twitch. Headaches usually go away promptly with nonprescription medication, such as acetaminophen, which will be offered to subjects as needed.

Hearing Impairment: Rapid excitation of the stimulation coil produces clicks that have resulted in transient increase in the auditory threshold of human subjects. This should not occur if earplugs are used. If a subject reports or if an investigator observes that a subject’s earplug has loosened or fallen out, investigators will immediately stop applying.

rTMS-Induced Manic Effects: Mania has been induced in a small number of healthy and depressed subjects by high-frequency rTMS to the left dorsolateral prefrontal cortex.

In all the above cases, the psychiatric side-effects induced by rTMS were transient, resolving with the cessation of rTMS or rapidly responding to pharmacological treatment.

Although not limited to, the risk for psychiatric complications appears to be existing predominantly in subjects with pre-existing psychiatric morbidity. An important means of minimizing risk in the current proposed study is therefore to exclude this population. Furthermore, mood symptoms will be monitored using a validated rating scale, and will provide an additional indication of hypomanic or manic symptoms (YMRS, PANAS, CPRS).

Research MR

Since pregnancy is an exclusion criterion for MRI, women of child-bearing potential must have a negative urine pregnancy test before each MRI procedure. Pregnancy testing will be done within 24 hours of each MRI session.

MRI will be conducted on a Philips Achieva 3.0 T scanner (Philips Medical Systems, Best, The Netherlands) using a standard body coil transmission and an eight channel SENSE head coil reception. T2*-weighted, BOLD images will be acquired with single shot, gradient echo (GRE), echo-planar imaging (EPI). During the scan, the subject will hear a thumping or buzzing sound. Earplugs or MRI-compatible headphones will be provided to all individuals. Earplugs will be inserted by trained NIH staff. Under the present protocol, total time in the scanner will be no more than 60 minutes. We may also record blood pressure, skin conductance, skin temperature, and respiratory rate during the experiment with devices and systems that are compatible with the MRI environment.

During the scan, we will first collect structural data. Subsequently, we will collect resting state functional MRI (rs-fMRI). Participants will be asked to keep their eyes closed and not think of anything in particular. Resting state FC data will be acquired during 2 blocks of 6 minutes each. Finally, subjects will perform two tasks, in a randomized order. In the **cue reactivity task**, a set of 60 cocaine-related cues and 60 neutral images will be presented and subjects will be asked to attend them. The **continuous performance task** (CPT), a task suitable for sustained attention\executive control measure, will be realised by means of visual stimuli previous used by our group in a population of psychiatric patients.

The stimuli will be projected onto a screen via a projector. Subjects will be able to view the images via a mirror placed above their head in the scanner. Participants will remain in contact with the experimenters at all times via an intercom system built into the scanner.

Side effects: People are at risk for injury from the MRI magnet if they have pacemakers or other implanted electrical devices, brain stimulators, aneurysm clips (metal clips on the wall of a large artery), metallic prostheses (including metal pins and rods, heart valves, and cochlear implants), permanent eyeliner, implanted delivery pump, or shrapnel fragments. Welders and metal workers are also at risk for injury because of possible small metal fragments in the eye of which they may be unaware.

Risk Minimization: The patients are screened using the NMR center safety screening form prior to the study and will not receive an MRI scan if the screen is positive. Women who are pregnant may not undergo a research MRI. All women of childbearing potential will have a pregnancy test performed, which must be negative, before proceeding. Individuals with fear of confined spaces may become anxious during an MRI. There are no known long-term risks or consequences of MRI scans. The length of scan varies from 45 min to 120 min maximum

Questionnaires and Rating Scales

- Adult ADHD Self-Report Scale (ASRS): This questionnaire is an 18-item checklist designed by the World Health Organization (WHO) and Workgroup on Adult ADHD to determine whether a participant is suffering from symptoms related to attention-deficit/hyperactivity disorder. Completion time: ~ 5 minutes.
- TMS Safety Screen: A questionnaire that aids in determining appropriateness of administering TBS. Completion time: < 5 minutes.
- Toronto Alexithymia Scale (TAS-20): A 20-item self-report questionnaire to assess emotional awareness. Completion time: ~ 10 minute.
- Cocaine Craving Questionnaire (CCQ): This measure includes 45 items that measure current craving for cocaine. Completion time: ~ 10 minutes.
- Sensation Seeking Scale V (SSS-V, 127): A 40-item self-report questionnaire that assesses individual differences in sensation seeking. Completion time: < 10 minutes.
- Cocaine Selective Severity Assessment (CSSA): to measure cocaine withdrawal signs and symptoms. Completion time minutes: ~ 5 minutes.

As time permits during the screening visit and after consenting, baseline characterization measures will also be collected. Participants may be scheduled for an additional visit and the necessary additional time to complete these assessments prior to beginning the 10-day rTMS treatment session. Following this, subjects will have 8 follow-up visits (at the end of continued

rTMS treatment phase, at rTMS follow-up visit #2, #4, #8, #12, and once a month during no rTMS follow-up phase).

Characterization measures include:

- Hamilton Anxiety Scale (HARS): A 21-item self-report inventory, which assesses the severity of anxiety. Completion time: ~ 5 minutes.
- Montgomery-Asberg Depression Rating Scale (MADRS): A clinical assessment to identify symptoms of depression. This assessment is especially useful in identifying changes in depression symptoms over time. Completion time: < 10 minutes.
- Positive and Negative Affect Scale (PANAS): A self-report scale to assess state-level affect. Completion time: < 5 Minutes.
- Profile of Mood States (POMS): A questionnaire designed to measure present mood state by a list of adjectives on a 5-point Likert scale and measures six dimensions of affect, including tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, and confusion-bewilderment. The measure has been shown to produce reliable and valid profiles of mood state. Completion time: ~ 5 minutes.
- Snaith-Hamilton Pleasure Scale (SHAPS): A 14-item self-report scale designed to measure hedonic-tone/anhedonia. Completion time: ~ 5 minutes.
- Temporal Experience of pleasure Scale (TEPS): A 20-item self-report scale designed to evaluate individual trait dispositions in anticipatory and consummatory pleasure experiences. Completion time: ~ 15 minutes.
- Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF): A self-report scale designed to measure social ties between the participants and their friend, family, co-workers, etc. Completion time: ~ 15 minutes.
- Time-line follow back (TLFB). The TLFB will be used to assess substance use behavior. This assessment will be either self-administered or administered by one of the investigators. Participants will read the instructions and/or will be guided by the therapist or investigator in filling out the calendar. A lifetime TLFB will be administered at baseline and during each visit.
- Columbia-Suicide Severity Rating Scale (C-SSRS):to assess suicidality ideation. Completion time: < 5 min.
- Brief Psychiatric Rating Scale (BPRS- brief version): to assess psychiatric symptoms. Completion time: 15 min.
- Visual Analogical Scale for Food Craving (VAS food): to assess food craving. Completion time: ~ 5 min.

- Insomnia severity index (ISI): to evaluate sleep patterns and quality. Completion time: ~ 3 min.

Executive and Cognitive Function will be assessed at baseline, at the end of continued rTMS treatment phase, at the end of rTMS follow-up phase and at the end of the no rTMS follow-up phase. Executive Function and Cognitive Assessment include:

- Frontal Assessment Battery (FAB): to assess frontal dysexecutive phenotype. Completion time: ~ 10 min.
- Eriksen Flanker Task (Flanker): to assess the ability to suppress responses that are inappropriate in a particular context. Completion time: ~ 15 min.
- Iowa Gambling Task: to assess decision-making process. Completion time: ~ 15 min.

E. Study Design

The study itself will consist of three phases.

(1) an outpatient screening phase, during which patients will be screened to assess their eligibility to be enrolled in the study. This phase will include informed consent and randomization, and will conclude with baseline data collection.

Baseline data will be collected as reported in Table 1.

(2) a continued rTMS treatment phase, during which subjects will receive 20 stimulation sessions (2 daily, 5 days/week). In addition to this, participants will also attend self-help groups twice per week, as part of standard-of-treatment for CUDs.

During this phase, treatment response will be assessed by evaluating cocaine craving and consumption, psychiatric and medical symptoms and functioning. Data will be collected as reported in Table 1.

(3) a follow-up phase of 24 weeks, which will be structured as following. During the first 12 weeks (rTMS follow-up) subjects will be asked to return to the Outpatient Clinic for an outpatient visit. During these visits, participants will undergo real or sham stimulation (two consecutive sessions per day), and will also attend self-help groups once per week.

During the following 12 weeks (no rTMS follow-up), participants will not receive TMS but behavioral and other data will be collected to observe long-term effects of rTMS.

If subjects are unable or unwilling to attend these visits, they will be contacted by phone or email, and an attempt will be made to obtain measures in this manner.

F. Objectives

1. Goals

Primary Goal

The primary goal is to evaluate iTBS as an efficacious treatment in reducing cocaine craving and consumption.

Secondary Goal

The secondary goal is to characterize rTMS effects on neurobiological and behavioral processing in cue reactivity, cognitive functions, mood, reward processing, executive control, intrinsic network connectivity, at baseline, and following treatment intervention.

2. Aims

Primary aim:

To determine the effects of rTMS on cocaine craving and consumption in patients with CUD.

- Changes in CCQ score between the active rTMS and sham group;
- Percent of negative urine samples between the active rTMS and sham group

Secondary aims:

To evaluate the neurobiological and behavioral effects of rTMS the following outcomes will be evaluated:

- Changes in cognitive functions as assessed by the FAB and Fahnker task;
- Changes in decision-making processing as assessed by the Iowa gambling Task;
- Changes in mood and hedonic state as measured by the MADRS, HAM-A, SHAPS, PANAS, TEPS and POMS;
- DLPFC BOLD signal change in response to cocaine-related cues and during executive function execution,
- Changes in resting state functional connectivity between the DLPFC and other nodes of the executive control network (ECN), as well as nodes of the Salience Network (SN) and the Default Mode Network (DMN);

3. Statistical Analysis

Behavioral measures on each of the cognitive tasks as well as questionnaire data from each of the experimental conditions will be compared both within and between experimental groups using mixed, repeated-measures ANOVA, and linear mixed models. When assessing the statistical results from the behavioral and questionnaire data, a standard α -level of 0.05 will be used. Alpha-levels for multiple comparison follow-up tests will be corrected using an appropriate method (e.g., Bonferroni, Tukey, Scheffe).

The imaging data will be pre-processed and analyzed with MatLab. All functional images will be directly registered upon high resolution MPRAGE anatomical scans obtained during the same imaging session. Location and intensity of activations from individual and/or grouped data will be translated into 3D stereotaxic coordinates. Functional images of activation-induced BOLD signal changes will be determined using cross correlation or multiple regression analyses. Differences in structural and functional measures between active rTMS and sham participants will be assessed using between group comparisons (e.g., independent samples t -tests). Correlation and multiple regression approaches will be used to test for an association between clinical assessment measures and task-specific neural measures (e.g., correlation between cocaine craving scores and neural activation in the striatum).

Real vs Sham rTMS Power Analysis. Because no sham-controlled studies have been performed assessing the chronic effects of rTMS administration on behavioral or neurophysiological measures in patients with CUD, anticipating an effect size is difficult. However, open label studies have shown substantial behavioral changes in clinical populations and could have similar effects in reducing cocaine use. In order to capture a reliable effect while not committing a type II error, a medium-large effect size (Cohen's $d = 0.65$) will be used to calculate the necessary participants to compare real and sham iTBS treatments. Approximately 30 participants per group will be required to detect significant differences between these two independent groups at a nominal α level of 0.05 in a one-tailed t -test assuming a medium-large effect size. We anticipate approximately 80-85% retention rate at visit 24, based on previous studies conducted in similar patient populations by our group. Therefore, 80 participants will be recruited at baseline, 40 for real and 40 for sham iTBS, to acquire the necessary 30 participants in each group for analysis.

G. Data Management and Safety measures

Safety: Participants will be presented with information about the study prior to data collection and they will be informed of their right to withdraw their information at any time, and that by taking part they are providing consent for the research team to use their anonymised data for research (including publications and other forms of dissemination) (informed consent and information sheets are attached as annexes, Italian version). Furthermore, they will provide written informed consent prior to the experiment, in line with the Helsinki Declaration developed by the World Medical Association. The research team will not include people if they are unable to give informed consent. The Health and Human Sciences Ethics Committee at the University of Chieti approved the research before it commences.

Randomization: We aimed to recruit a total of 80 patients (40 per rTMS and 40 per sham-stimulation). The distribution will be generated randomly to allow for an equitable age and sex distribution.

Double-blind procedure: Sham stimulation will use the same coil placement as that used for active stimulation. The selection of the operation mode (15 Hz, sham) will be pre-programmed by member of the that will not be involved in data collection and analysis. Study personnel will not know which mode is being activated, thus preserving the double-blind.

Data collection and storage: Collected personal data will be identified via specific individual codes. Datasets will be anonymized by removing all direct identifiers, (e.g., name, address, telephone numbers), but also indirect identifiers and other information that could lead to "deductive disclosure" of participants' identities. The computer files will be password protected, and only accessed by agreed members of the team. Files will be shared to other involved institutions via secure server. Hard copies such as interview notes, questionnaires and psychometric scales will be kept securely locked in a cabinet that will only be accessed by agreed members of the research team. As a part of the informed consent, participants will be informed on what will happen to the data they will provide, and specifically: a) on how the data will be stored; b) on who will access the data; c) on how long the data will be kept for.

Table 1. Study timeline

	rTMS Week 1 (days)					rTMS Week 2 (days)					rTMS Follow-up (weeks)												no rTMS FU (months)			Tot.	
	0	1	2	3	4	5	6	7	8	9	10	1	2	3	4	5	6	7	8	9	10	11	12	1	2		3
Visit number	0	1	2	3	4	5	6	7	8	9	10	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	
Clinic visits	1	1				1					1			1					1				1	1	1	1	11
General anamnesys	1																										1
TMS safety questionnaire	1																										1
cocaine TLFB	1										1		1		1					1				1	1	1	9
BIS-11 e TAS-20	1																						1				2
Adult ADHD	1																						1				2
Brief-CCQ	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	23
CSSA, SSSFV	1																						1				2
Informed Consent	1																										1
rTMS 2 sess.		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	22
TMS side effects		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	22
ASRM, PANAS		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	22
VAS-food		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	22
Cigarettes consumption		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	22
Tox Drug Screen		1									1		1		1					1				1	1	1	9
BPRS, MADRS, HARS		1									1		1		1					1				1	1	1	9
C-SSRS, POMS		1									1		1		1					1				1	1	1	9
SHAPS, TEPS		1									1		1		1					1				1	1	1	9
ISI		1									1		1		1					1				1	1	1	9
Weight		1									1		1		1					1				1	1	1	9
FAB, Flanker, IGT		1									1													1			4
fMRI	1																						1				2

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