

**The Mexican dataset of an rTMS clinical trial on cocaine use disorder patients:
SUDMEX TMS**

Study recruitment

We recruited cocaine users according to inclusion and exclusion criteria (Table S1) via flyers to addiction and substance use disorder clinics and medical institutes in the Mexico City area, as well as through ads in social media. The study was conducted at the Clinical Research Division of the National Institute of Psychiatry in Mexico City, Mexico, and all procedures were approved by the Institutional Ethics Research Committee (CEI/C/070/2016). The trial was registered in ClinicalTrials.gov (NCT02986438). Before commencing any procedures, all participants were informed about the study and provided written informed consent, in line with the Declaration of Helsinki. Sample size was calculated using G*Power ¹, for a 2 x 2 ANOVA with $r = 0.3$ (calculated from craving changes in previous cocaine rTMS studies), to attain 80% power at $\alpha = 0.05$. All patients needed to be in psychosocial treatment for CUD, and most received medication. Types of treatments received during rTMS are in Table S2.

Study attrition

Of the 54 recruited patients, 30 were randomly allocated to active treatment and 24 to sham rTMS (Figure S1). Five patients assigned to active rTMS and four assigned to sham discontinued the study, leaving 25 patients in the Active group and 20 in the Sham group who completed the acute phase. Following the double-blind phase, 14 patients in the Sham group opted for compassionate use and received 2 weeks of acute phase rTMS therapy. In the maintenance phase: 1) 20 patients (15 initially allocated to Active and 5 to Sham) finished 3 months of twice-weekly rTMS sessions (T2); 2) 15 patients (initially 10 Active and 5 Sham) finished 6 months of rTMS sessions (T3); and 3) 7 patients (initially 3 Active and 4 Sham) finished 12 months of twice-weekly rTMS sessions (T4). None of the patients who discontinued the study at any point reported adverse effects from rTMS as their reason. Due to substantial attrition at T1 (2 weeks), when the study was at ~30% completion we changed the maintenance phase to last 3 months instead of 12 months for new participants after approval by the ethics committee. Data collected up to the 6-months visit were analyzed due to the small sample size at 12 months ($n = 7$).

Supplementary table 1. Study criteria.

Inclusion

- Minimum age of 18 years and maximum of 50 years old.
- Cocaine use for at least 1 year, with current average use of at least 3 times a week, with periods of continuous abstinence of less than one month during the last year.
- Reading level of at least 6th grade of primary school.
- Ability to give valid informed consent.
- Right-handed (to avoid laterality bias).
- Body mass index \leq 30.

Exclusion

- First-degree personal or family history of any clinically defined neurological disorder.
- Any electronic or metal implants or device (i.e., aneurysm clips, shunts, stimulators, cochlear implants, or electrodes, etc.).
- Splinters of metal or metal projectiles to the head or body.
- Current use of any investigational drug or of any medicine with anti- or pro-convulsive action such as tricyclic antidepressants or neuroleptics, unless prescribed for craving symptoms.
- History of schizophrenia, bipolar disorder, mania, or hypomania.
- History of any heart condition currently under medical care (i.e., myocardial infarction, angina pectoris, congestive heart failure, etc.)
- Women with reproductive potential not using an acceptable form of contraception, as well as pregnant or lactating women.
- Any history of seizures.
- Current dependence (by DSM-5 criteria) on substances other than cocaine and / or nicotine (cocaine use disorder).
- Claustrophobia.
- History of HIV infection or HIV antibody test positive (due to potential neuroinfection).

Elimination

- Expressed desire to stop participating.
- Those who for any reason stopped attending rTMS sessions, for 2 or more days for those in the acute phase, or 2 weeks for those in the maintenance phase.

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- Those who presented abnormal radiological findings warranting clinical attention outside the study to ensure the health of the participant.
 - The appearance of psychotic symptoms related to addictive disorder.
 - Presence of adverse effects related to the application of rTMS such as seizures and abnormal elevation of mood.

rTMS = repeated transcranial magnetic stimulation.

Supplementary table 2. Standard treatments received by each participant during rTMS therapy.

| ID | Group | Received another treatment | Psychosocial treatment* | Pharmacologic treatment | Number of medications | Medication 1 | Medication 2 | Medication 3 |
|----|-----------|----------------------------|-------------------------|-------------------------|-----------------------|---------------|--------------|---------------|
| 1 | Sham | yes | yes | yes | 2 | gabapentin | topiramate | NA |
| 2 | Sham | yes | no | yes | 2 | sertraline | clonazepam | NA |
| 5 | Sham | yes | no | yes | 1 | topiramate | NA | NA |
| 6 | Sham | no | no | no | 0 | NA | NA | NA |
| 8 | Sham | yes | yes | yes | 2 | fluoxetine | hydroxyzine | NA |
| 9 | Sham | yes | no | yes | 2 | citalopram | gabapentin | NA |
| 10 | Sham | yes | no | yes | 3 | fluoxetine | topiramate | hydroxyzine |
| 12 | Sham | yes | no | yes | 2 | atomoxetine | gabapentin | NA |
| 13 | Sham | yes | no | yes | 3 | escitalopram | topiramate | hydroxyzine |
| 18 | Sham | no | no | no | 0 | NA | NA | NA |
| 19 | Sham | yes | no | yes | 1 | oxcarbazepine | NA | NA |
| 22 | Sham | yes | no | yes | 2 | topiramate | paroxetine | NA |
| 27 | Sham | yes | yes | yes | 3 | sertraline | risperidone | valproic acid |
| 30 | Sham | yes | no | yes | 1 | topiramate | NA | NA |
| 33 | Sham | no | no | no | 0 | NA | NA | NA |
| 36 | Sham | yes | no | yes | 2 | topiramate | fluoxetine | NA |
| 40 | Sham | yes | no | yes | 2 | topiramate | citalopram | NA |
| 42 | Sham | yes | no | yes | 3 | topiramate | fluoxetine | atomoxetine |
| 45 | Sham | yes | no | yes | 3 | gabapentin | sertraline | hydroxyzine |
| 46 | Sham | yes | yes | yes | 3 | topiramate | venlafaxine | atomoxetine |
| 47 | Sham | no | no | no | 0 | NA | NA | NA |
| 50 | Sham | yes | no | yes | 3 | fluoxetine | topiramate | atomoxetine |
| 52 | Sham | yes | no | yes | 2 | fluoxetine | topiramate | NA |
| 3 | Treatment | yes | no | yes | 2 | topiramate | fluoxetine | NA |
| 4 | Treatment | yes | no | yes | 2 | bupropion | fluoxetine | NA |
| 7 | Treatment | no | no | no | 0 | NA | NA | NA |
| 11 | Treatment | no | no | no | 0 | NA | NA | NA |
| 14 | Treatment | yes | no | yes | 1 | pregabalin | NA | NA |
| 15 | Treatment | no | no | no | 0 | NA | NA | NA |
| 16 | Treatment | yes | no | yes | 2 | mirtazapine | topiramate | NA |

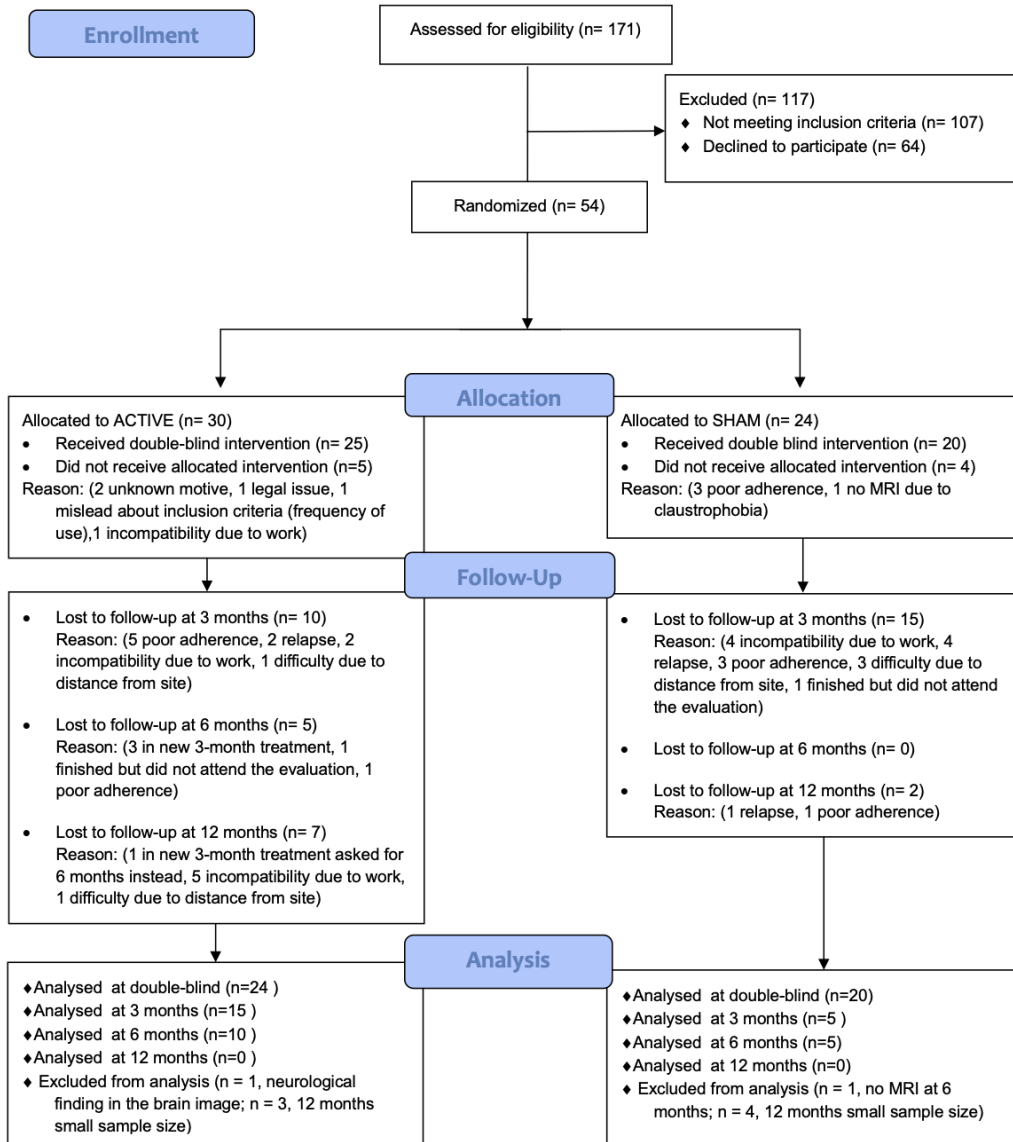
| | | | | | | | | |
|----|-----------|-----|-----|-----|---|---------------|-------------|-------------|
| 17 | Treatment | yes | no | yes | 2 | topiramate | quetiapine | NA |
| 20 | Treatment | yes | no | yes | 1 | topiramate | NA | NA |
| 21 | Treatment | yes | yes | yes | 2 | topiramate | sertraline | NA |
| 23 | Treatment | yes | no | yes | 3 | gabapentin | hydroxyzine | mirtazapine |
| 24 | Treatment | yes | no | yes | 2 | fluoxetine | topiramate | NA |
| 25 | Treatment | yes | yes | yes | 4 | gabapentin | citalopram | atomoxetine |
| 26 | Treatment | yes | yes | yes | 2 | oxcarbazepine | quetiapine | NA |
| 28 | Treatment | yes | no | yes | 2 | fluoxetine | topiramate | NA |
| 29 | Treatment | yes | no | yes | 1 | topiramate | NA | NA |
| 31 | Treatment | no | no | no | 0 | NA | NA | NA |
| 32 | Treatment | no | no | no | 0 | NA | NA | NA |
| 34 | Treatment | yes | no | yes | 2 | topiramate | NA | NA |
| 35 | Treatment | yes | no | yes | 3 | topiramate | fluoxetine | atomoxetine |
| 37 | Treatment | yes | no | yes | 1 | topiramate | NA | NA |
| 38 | Treatment | yes | no | yes | 3 | topiramate | mirtazapine | NA |
| 39 | Treatment | yes | no | yes | 2 | topiramate | trazodone | NA |
| 41 | Treatment | yes | no | yes | 3 | topiramate | citalopram | gabapentin |
| 43 | Treatment | yes | no | yes | 2 | fluoxetine | topiramate | NA |
| 48 | Treatment | yes | yes | yes | 3 | fluoxetine | topiramate | hydroxyzine |
| 49 | Treatment | yes | no | yes | 2 | fluoxetine | topiramate | NA |
| 51 | Treatment | yes | no | yes | 3 | topiramate | fluoxetine | NA |
| 53 | Treatment | yes | yes | yes | 2 | valproic acid | quetiapine | NA |
| 54 | Treatment | yes | yes | yes | 3 | fluoxetine | topiramate | atomoxetine |

The psychosocial treatment consisted of group therapy with a motivational approach focused on addiction, received at the addiction clinic of the National Institute of Psychiatry.

Supplementary figure 13. CONSORT flow diagram.



CONSORT 2010 Flow Diagram



Study timeline

At Visit 1, screened patients arrived for a clinical screening interview to confirm they met criteria. At Visit 2, enrolled patients underwent a full clinical assessment (Time 0 or T0). Initial MRI scanning occurred at Visit 3 (Baseline or MRI-T0). The clinical interview preceded MRI acquisition and always occurred within 3 days. Following MRI acquisition, we initiated the double-blind rTMS/sham *acute phase* (see below). Patients underwent regularly scheduled sessions (Active or Sham rTMS) for 10 days over 2 weeks. At the conclusion of 2 weeks (Visit 4; T1), they underwent clinical assessment and repeated MRI scanning, marking the end of the acute phase and the start of the open-label *maintenance phase*. The blind (active vs. sham) was decoded for each participant at the end of their acute phase. Patients assigned to Active rTMS entered the maintenance phase directly after T1. Patients assigned to Sham rTMS were given the choice to leave the study or continue with active open-label rTMS for compassionate use. Patients assigned to the Sham group who agreed to continue, received 2-weeks (10 days) acute treatment before continuing to the maintenance phase. The maintenance phase was initially designed to include 2 weekly rTMS sessions and clinical assessments and MRI scans at 3 months, 6 months and 12 months. However, the maintenance phase was subsequently changed to 3 months for new enrollments (see study attrition).

Clinical Assessments details

The following instruments were used in the overall clinical trial:

1. **MINI-PLUS:** Is a structured diagnostic interview, of short duration in which the main psychiatric disorders of Axis I of DSM-V and ICD-10 are explored for detection and / or diagnostic orientation, It is divided into modules, identified by letters, each corresponding to a diagnostic category. At the beginning of each module (except in the psychotic disorders module), the interview has one or more "filter" questions corresponding to the main diagnostic criteria for the disorder. At the end of each module, one or more diagnostic boxes are presented that allow the interviewer to indicate whether or not the diagnostic criteria for the disorder were met. This instrument will be used for the initial evaluation of the patient and verification of the inclusion and exclusion criteria ².
2. **SCID-II:** Evaluate personality disorders in a categorical way according to DSM-IV criteria. Each of the criteria is valued from the following score: 1: absent, 2: Present or true, it consists of 119 questions with a dichotomous answer that reduces the test

administration time, The test was applied only in the baseline measurement (T0), since it is a constant clinical feature ³.

3. **SCL90 R:** The SCL-90-R is a self-applied symptom questionnaire consisting of 90 items. Each item is answered on a 5-point Likert-type scale, from "0" (absence of the symptom) to "4" (total presence of the same). By correcting the test we obtain 9 symptomatic scales and 3 indexes of psychological distress. The symptomatic scales are as follows: Somatization, Obsession-compulsion, Interpersonal sensitivity, Depression, Anxiety, Hostility, Phobic anxiety, Paranoid ideation and Psychoticism. The discomfort indices are: a) the global severity index (GSI), b) the positive symptomatic discomfort index (PSDI) and c) the total of positive symptoms (PST). The test was applied in each clinical measurement (T0 to T4) to assess changes in symptoms in each phase ⁴.
4. **Addiction Severity Index (ASI):** The ASI is a semi-structured interview designed to address seven potential problem areas in substance-abusing patients: medical status, employment and support, drug use, alcohol use, legal status, family/social status, and psychiatric status. In 1 hour, a skilled interviewer can gather information on recent (past 30 days) and lifetime problems in all of the problem areas. The ASI provides an overview of problems related to substance, rather than focusing on any single area. The test was applied in each clinical measurement (T0 to T4) to assess changes in symptoms in each phase ⁵.
5. **BIS11:** The 11th version of the Barratt Impulsivity Scale is one of the most widely used instruments for assessing impulsivity. Its application is self-administered and it consists of 30 questions, grouped into three subscales: Cognitive impulsivity, Motor impulsiveness, Unplanned impulsiveness. Each of the questions has 4 possible answers (rarely or never, occasionally, often and always or almost always). The total score is the sum of all the items and the total of the subscales are the sum of the items corresponding to each of them ⁶.
6. **Hamilton Depression Rating Scale (HDRS):** The Hamilton Rating Scale for Depression was used to provide a measure of the severity of depression. The version we used is the one of 17 items, recommended by the United States National Institute of Mental Health. Its content focuses on the basic aspects and behavior of depression, with vegetative, cognitive and anxiety symptoms having the greatest weight in the total calculation of the scale. The cutoff points to define severity are: no depression (0-7); mild depression (8-16); moderate depression (17-23); and severe depression (≥ 24). This scale was applied in the basal measurement (T0) and all subsequent measurements. The test was applied in each clinical measurement (T0 to T4) to assess changes in symptoms in each phase ⁷.

7. **Hamilton Anxiety Rating Scale (HARS):** This scale assesses the severity of anxiety globally and is useful for monitoring response to treatment. It is made up of 14 items, with 13 references to anxious signs and symptoms and the last one that evaluates the patient's behavior during the interview. The interviewer scores from 0 to 4 points each item, assessing both its intensity and frequency. The total score is the sum of those of each of the articles. The range is from 0 to 56 points. The optimal HAM-A score ranges were: no/minimal anxiety ≤ 7 ; mild anxiety = 8-14; moderate = 15-23; severe ≥ 24 . The test was applied in each clinical measurement (T0 to T4) to assess changes in symptoms in each phase ⁸.
8. **Pittsburgh Sleep Quality Index (PSQI):** This instrument has been created to measure the quality of sleep in patients with psychiatric disorders. It is made up of 24 items, although only 19 are taken into account for its correction. In addition, it is divided into 7 dimensions: Subjective sleep quality, Sleep latency. Duration of sleep, Usual sleep efficiency, Sleep disturbances, Use of medication, Daytime dysfunction. It is answered with a Likert-type scale that goes from 0 to 4. For its correction, a sleep profile is obtained in each of the dimensions ranging from 0 to 3 and a total score that can range from 0 to 21. The test was applied in each clinical measurement (T0 to T4) to assess changes in symptoms in each phase ⁹.
9. **Treatment-As-Usual follow-up:** Consists of a record of the treatment that each subject had indicated at the beginning of the study, which was prescribed by the treating physician in the addiction clinic of the National Institute of Psychiatry, according to the protocols that they normally follow. The record indicated whether the subject received psychotherapy and/or pharmacological treatment, together with the type of psychotherapy and the name of the drug received, as well as changes to these treatments in each of the following measurements. This record was made in a format created for the present study which was applied both in the baseline assessment and in each of the subsequent assessments.
10. **Timeline Followback Method Assessment modified (mTLFB):** This is a record of the pattern of cocaine/crack use of each subject, made on a calendar-based format, where the consumption of the last two years up to the present was evaluated, indicating the number of days of use per month and the amount in grams consumed each full month (30 days). This format was applied in the baseline measurement (T0) where previous consumption was recorded and in each subsequent measurement to assess the longitudinal pattern of substance use every month before and during the trial ¹⁰.
11. **Cocaine Craving Questionnaire (CCQ):** This instrument evaluates the intensity of cocaine craving. The version used in this study has a format that evaluates craving at

the present time, and a format that evaluates the general state of craving during the last week. Each form consists of 45 items, each item is made up of a 7-point Likert scale in which the subject must indicate their degree of agreement or disagreement, with some items scored inversely. For its interpretation, the total of the items is added. The test was applied at each clinical measurement (T0 to T4) to assess changes in craving in each phase ¹¹.

12. **Cocaine Craving visual analogue scale (VAS):** This is an instrument for the subjective evaluation of the subject's craving at the present moment. The visual scale consists of a continuous 10 cm line (including 2 decimals), in which the left endpoint refers to "no craving" and the right endpoint "the most intense craving" and the subject must mark with a cross the intensity of their craving at that moment between one of the two extremes. This scale was applied in each clinical measurement (T0 to T4) to assess changes in craving in each phase ¹².
13. **Alcohol breath test:** An alcohol monitoring test was performed to identify the possible presence of substances in the subject before performing the MRI study. This was done in the initial evaluation (T0) and in each subsequent measurement (T1 to T4), with a breath alcohol analyzer, Lifeloc model FC10 (Wheat Ridge, CO, USA), which has a detection accuracy of $\pm .005$ BAC.
14. **Urine drug test:** Performed to identify the possible presence of substances of abuse in subjects prior to performing the MRI study. This test was performed with a Kabla (Monterrey, NL, Mexico) reagent strip device, model Instant view-Drug screen, using the lateral flow chromatographic immunoassay technique. The substances detected and their cut-off points are as follows: Amphetamines (1000 ng/mL), Benzodiazepines (300 ng/mL), Cocaine (300 ng/mL), Methamphetamine (1000 ng/mL), Morphine/Opiates (2000 ng/mL), Marijuana/Hashish (50 ng/mL). This test was applied in the baseline measurement and each of the subsequent ones. Results in Tables S6 & S7.
15. **Reincidence/Relapse follow-up:** A record of the cocaine abuse patterns of patients was carried out, to identify if they presented reincidence or relapses. This was applied in each of the subsequent measurements (T1 to T4). "Reincidence" was defined as the presence of at least one episode of consumption but without returning to previous consumption, and "relapse" was defined when consumption returned to the previous pattern.
16. **WHODAS:** Instrument that assesses the psychological and social functioning of people affected by a mental disorder. It provides information on four areas: Personal Care, Occupation, Family/Housing and Social Functioning. The clinician scores to what extent there is a degree of deterioration in the interviewed person through a

visual analog scale, which goes from 0 (absence of deterioration) to 5 (great deterioration). It is a descriptive scale that provides a total score and scores in each of the 4 dimensions. There are no cut points; the higher the score, the greater the disability. It was obtained in the baseline evaluation (T0) and in each of the subsequent ones (T1 to T4) ¹³.

17. **Edinburgh Handedness:** The Edinburgh Manual Laterality Inventory aims to assess manual dominance. This instrument evaluates the degree to which the subject uses the left or right hand for 4 predetermined actions and provides a numerical result, which is used to form three categories: predominant use of the left hand, similar use of both hands, and predominant use of the right hand. This instrument was applied in the baseline assessment (T0) only ¹⁴.

Clinical outcome measures

- Primary Outcome Measures:

1. Change in Cocaine Craving (CCQ) [Time Frame: Baseline, 2 weeks, 3 months]: Measured using a craving questionnaire for cocaine validated in Mexican population (Cocaine Craving Questionnaire or CCQ).
2. Change in Cocaine Craving (VAS) [Time Frame: Baseline, 2 weeks, 3 months]: Measured using a 100 mm visual analog scale (VAS).
3. Change in Cocaine Urine Test [Time Frame: Baseline, 2 weeks, 3 months]: Frequency of cocaine use measured using reagent strips from Instant View drug screening (> 300 ng/mL). Results are Positive or Negative.

- Secondary outcome measures:

1. Changes in Psychopathological Symptoms [Time Frame: Baseline, 2 weeks, 3 months]: Measured by the 90 Symptoms Questionnaire (SCL-90).
2. Changes in Depression [Time Frame: Baseline, 2 weeks, 3 months]: Measured by Hamilton Depression Rating Scale (HDRS) (21 items).
3. Changes in Anxiety [Time Frame: Baseline, 2 weeks, 3 months]: Measured by Hamilton Anxiety Rating Scale (HARS).
4. Changes in Drug Consumption and Related Problems [Time Frame: Baseline, 2 weeks, 3 months]: Measured by the Addiction Severity Index (ASI-lite).
5. Changes in Sleep Quality: PSQI [Time Frame: Baseline, 2 weeks, 3 months]: Measured by the Pittsburgh Sleep Quality Index (PSQI).
6. Changes in Impulsivity [Time Frame: Baseline, 2 weeks, 3 months]: Measured by the Barratt Impulsivity Scale-11 (BIS-11).

7. Lapse rate [Time Frame: Baseline, 2 weeks, 3 months]: Lapse is defined as at least one consumption event not in the same pattern as the baseline consumption. The report of self-consumption of cocaine and urine drug tests, with special attention to the presence of traces of cocaine.
 8. Relapse rate [Time Frame: Baseline, 2 weeks, 3 months]: Relapse is defined as consumption events in the same pattern as the baseline consumption. The report of self-consumption of cocaine and urine drug tests, with special attention to the presence of traces of cocaine.
- Tertiary outcome measure:
 1. Changes in resting state functional connectivity using magnetic resonance imaging

Transcranial magnetic stimulation

We performed a double-blind randomized controlled trial (RCT) with parallel groups (Sham/Real) with a final allocation ratio of 1:1.25 for 2 weeks of acute treatment named the *acute phase*, following with an open-label trial at timepoints 3, 6 and up to 12 months of chronic treatment maintenance, named the *maintenance phase*. The allocation was 1:1, however it would have been simple for TMS technicians to guess the group allocation for the last patients as they knew the final sample size and group membership of previous patients. Therefore, we decided to include a bigger sample for the randomization to avoid guessing of the group. For the acute phase, we used a MagPro R30+Option magnetic stimulator and an eight-shaped B65-A/P coil (Magventure, Denmark), and for the maintenance phase, we used a MagPro R30 stimulator and an eight-shaped MCF-B70 (Magventure, Denmark). The reason for using 2 different TMS models was practical, to be able to stimulate more patients. However, there are no differences in the induced field between models, only the cooling system and the sham possibility from the MagPro R30+Option. We used a 5-Hz excitatory frequency as is standard in our clinical setting due to the low presence of secondary effects and similar clinical improvement to 10-Hz in major depression, Alzheimer's disease, among others ¹⁵⁻¹⁹. Safety outcomes are reported in Table S3. The motor threshold was determined in each patient as described by Rossini et al. ²⁰, localizing M1 from vertex 5 cm along and 2 cm anteriorly the interaural line. The coil was placed at 45° with respect to the interhemispheric fissure (anterior-medial induced current) and single pulses were applied separated by 5 seconds. The intensity that caused at least 5 responses of the abductor *pollicis brevis* (APB) muscle from 10 pulses was considered the MT ²¹. MT was determined before the first session and on the 6th day of treatment. For the maintenance phase, MT was determined in each session (once per week). We localized left DLPFC using the 5 cm method in the first 16 participants and the Beam F3 method (Beam, Borckardt, Reeves, &

George, 2009) in the rest of the subjects to optimize DLPFC localization (only n = 11 were available at the time for this analysis). Sham electrodes were placed to simulate muscle contraction in the Sham group. The acute phase comprised 10 weekdays of 5,000 pulses per day (two sessions of 50 trains at 5 Hz, 50 pulses/train, 10 s inter-train interval and 15 min inter-session interval). The maintenance phase comprised 3 and 6 months of 5,000 pulses per day, 2 sessions per week. The motor threshold was maintained at 100% in all patients. Because a Brain Navigator was not available, we used a vitamin E capsule fiducial during MRI acquisition to identify the actual stimulation target where rTMS was delivered in n = 27. EMS oversaw all rTMS sessions and determined the capsule's location before the first MRI session using either the 5.5 cm anatomic criterion or the Beam F3 method (Table S4 & Fig. S2). We changed to the superior Beam F3 method after the first 16 participants to improve IDLPFC localization²². EMS marked IDLPFC on the scalp with a marker, then maintained the capsule's position using removable tape and a swimmer's cap. Subsequently, EMS checked the capsule location before scanning. That same marked location on the scalp based on the coordinates at which the fiducial (capsule) was placed was used for rTMS sessions.

Supplementary table 15. Safety outcomes for the acute phase.

| | SHAM | ACTIVE | p |
|-----------------------|--------------|---------------|----------|
| | (N=240) | (N=300) | |
| Headache | | | 0.026 |
| -0 | 216 (97.7%) | 244 (90.7%) | |
| -1 | 1 (0.5%) | 5 (1.9%) | |
| -2 | 0 (0.0%) | 10 (3.7%) | |
| -3 | 3 (1.4%) | 7 (2.6%) | |
| -4 | 1 (0.5%) | 2 (0.7%) | |
| -5 | 0 (0.0%) | 1 (0.4%) | |
| Neck pain | | | 0.058 |
| -0 | 188 (85.1%) | 242 (90.0%) | |
| -1 | 1 (0.5%) | 5 (1.9%) | |
| -2 | 18 (8.1%) | 17 (6.3%) | |
| -3 | 11 (5.0%) | 4 (1.5%) | |
| -4 | 3 (1.4%) | 1 (0.4%) | |
| -5 | 0 (0.0%) | 0 (0.0%) | |
| Scalp pain | | | 0.17 |
| -0 | 219 (99.1%) | 261 (97.0%) | |
| -1 | 2 (0.9%) | 2 (0.7%) | |
| -2 | 0 (0.0%) | 5 (1.9%) | |
| -3 | 0 (0.0%) | 1 (0.4%) | |
| -4 | 0 (0.0%) | 0 (0.0%) | |
| -5 | 0 (0.0%) | 0 (0.0%) | |
| Cognitive decline | | | 0.567 |
| -0 | 221 (100.0%) | 267 (99.3%) | |
| -1 | 0 (0.0%) | 0 (0.0%) | |
| -2 | 0 (0.0%) | 2 (0.7%) | |
| -3 | 0 (0.0%) | 0 (0.0%) | |
| -4 | 0 (0.0%) | 0 (0.0%) | |
| -5 | 0 (0.0%) | 0 (0.0%) | |
| Concentration decline | | | 0.346 |

| | | | |
|-----------------|--------------|--------------|-------|
| -0 | 221 (100.0%) | 265 (98.5%) | |
| -1 | 0 (0.0%) | 1 (0.4%) | |
| -2 | 0 (0.0%) | 1 (0.4%) | |
| -3 | 0 (0.0%) | 2 (0.7%) | |
| -4 | 0 (0.0%) | 0 (0.0%) | |
| -5 | 0 (0.0%) | 0 (0.0%) | |
| Hearing decline | | | 0.479 |
| -0 | 221 (100.0%) | 266 (98.9%) | |
| -1 | 0 (0.0%) | 1 (0.4%) | |
| -2 | 0 (0.0%) | 1 (0.4%) | |
| -3 | 0 (0.0%) | 0 (0.0%) | |
| -4 | 0 (0.0%) | 1 (0.4%) | |
| -5 | 0 (0.0%) | 0 (0.0%) | |
| Irritation | | | 0.053 |
| -0 | 218 (98.6%) | 259 (96.3%) | |
| -1 | 0 (0.0%) | 7 (2.6%) | |
| -2 | 3 (1.4%) | 3 (1.1%) | |
| -3 | 0 (0.0%) | 0 (0.0%) | |
| -4 | 0 (0.0%) | 0 (0.0%) | |
| -5 | 0 (0.0%) | 0 (0.0%) | |
| Seizures | | | |
| -0 | 221 (100.0%) | 269 (100.0%) | |
| Mood changes | | | 0.361 |
| -0 | 220 (99.5%) | 269 (100.0%) | |
| -1 | 0 (0.0%) | 0 (0.0%) | |
| -2 | 1 (0.5%) | 0 (0.0%) | |
| -3 | 0 (0.0%) | 0 (0.0%) | |
| -4 | 0 (0.0%) | 0 (0.0%) | |
| -5 | 0 (0.0%) | 0 (0.0%) | |

Scale from 0 = none to 5 = severe. 10 sessions per patient before attrition (Sham n = 24, Active n= 30).

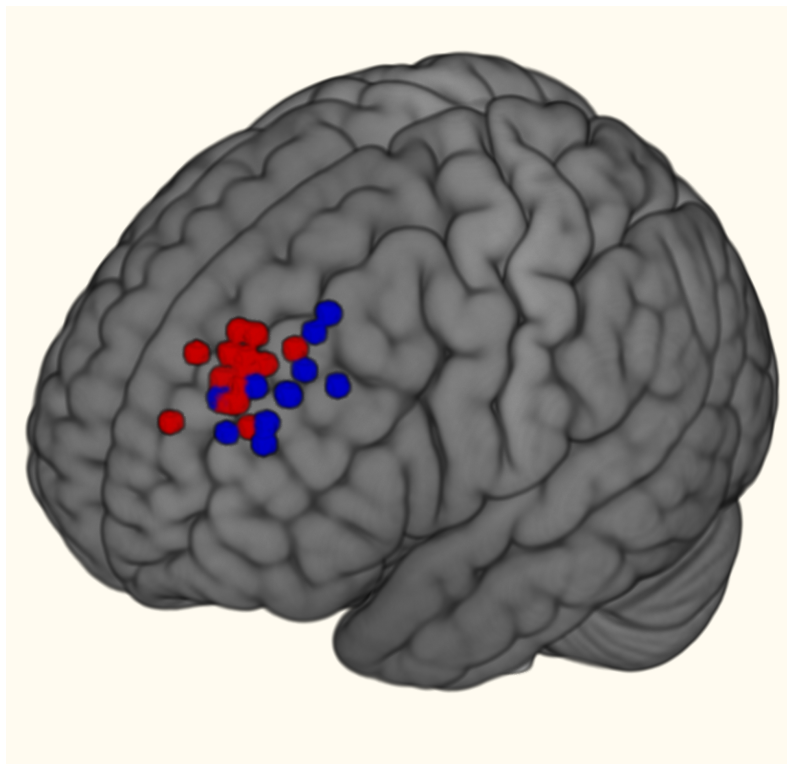
Supplementary table 16. Type of IDLPFC localization per patient.

| ID | Group | Method | MNIx | MNIy | MNIz |
|-----------|--------------|---------------|-------------|-------------|-------------|
| 2 | Sham | 5.5 cm | -20 | 62 | 26 |
| 4 | Active | 5.5 cm | -16 | 52 | 40 |
| 8 | Sham | 5.5 cm | -24 | 48 | 42 |
| 20 | Active | 5.5 cm | -28 | 46 | 42 |
| 21 | Active | 5.5 cm | -24 | 50 | 36 |
| 22 | Sham | 5.5 cm | -36 | 50 | 28 |
| 23 | Active | 5.5 cm | -30 | 42 | 40 |
| 24 | Active | 5.5 cm | -34 | 36 | 44 |
| 25 | Active | 5.5 cm | -26 | 42 | 46 |
| 26 | Active | 5.5 cm | -30 | 48 | 36 |
| 27 | Sham | 5.5 cm | -30 | 50 | 32 |
| 30 | Sham | 5.5 cm | -28 | 52 | 32 |
| 31 | Active | 5.5 cm | -26 | 48 | 36 |
| 32 | Active | 5.5 cm | -28 | 46 | 38 |
| 33 | Sham | 5.5 cm | -22 | 44 | 46 |
| 34 | Active | 5.5 cm | -24 | 50 | 34 |
| 36 | Sham | Beam F3 | -26 | 52 | 32 |
| 37 | Active | Beam F3 | -36 | 28 | 52 |
| 39 | Active | Beam F3 | -38 | 36 | 40 |
| 41 | Active | Beam F3 | -32 | 54 | 26 |
| 42 | Sham | Beam F3 | -36 | 32 | 48 |

| | | | | | |
|----|--------|---------|-----|----|----|
| 43 | Active | Beam F3 | -46 | 32 | 38 |
| 45 | Sham | Beam F3 | -40 | 48 | 30 |
| 46 | Sham | Beam F3 | -32 | 46 | 36 |
| 47 | Sham | Beam F3 | -40 | 42 | 36 |
| 48 | Active | Beam F3 | -40 | 42 | 36 |
| 49 | Active | Beam F3 | -42 | 50 | 26 |

The last 3 columns show the localization of the TMS in each patient in MNI coordinates.

Supplementary figure 14. TMS target locations between methods.



Red = 5.5 cm; blue = Beam F3.

Sham and double-blind protocol

Researcher JJGO created the randomization to allocate patients, which was entered into the MagVenture's Research Study System software and saved in a USB memory chip with the

protocol selection (Sham or Active rTMS) for each patient and delivered to RAL and EMS for the rTMS sessions. The USB was especially programmed to avoid showing any information to operators to maintain the blinding and only JJGO knew the group membership before the open label. The way the sham works in the stimulator is the following: the programmed USB is inserted and the software asks the TMS technician to place the coil with either side facing down to the scalp, without clues of which side of the coil is stimulating (upward or downward). The technician had no clinical knowledge of the patients to avoid bias. To enhance the sham and blinding, electrodes were placed on each patient on the left temporalis muscle to simulate muscle contraction in the Sham group. Out of 53 patients, the blinding was assessed in 30 of the patients and the results showed 63% of the patients guessed their group allocation correctly, while researchers guessed group allocations 52% correctly.

Fiducial to standard space

First, we registered the location of the stimulation region on the scalp, by manually locating the coordinates of the fiducial in the participants' space using fslview. To avoid any distortion in the algorithm, we co-registered a different high-definition structural image to the space of the fiducial image and made a deskulled version of it; this was done with ANTs. Using both the full-head and brain co-registered images, with MATLAB 2019a we located the point most proximal to the cortex in the projection with a 90° angle to the tangent of the head surface in a coronal slice. A single point-seed mask with these cortex coordinates was created for each participant and registered to the standard MNI152 template with ANTs. Finally, we registered the coordinates of all of these normalized stimulation locations with their coordinates in the standard MNI space and with this information calculated the average central stimulation region in the brain cortex.

TMS regions of interest

The IDLPFC ROIs were specified as per ²³. Briefly, cones with 12 mm radius were centered at each individual stimulation coordinate in MNI (Figure 2, main manuscript). The cones were built with decreasing intensity from the center to the periphery and were based on an approximation of the electric field induced by a standard figure-eight coil. A gray matter mask was used to mask the cones and each cone was normalized to an average value of 1. Normative connectivity was determined using this cone as a weighted mask and n = 1000 subjects from the Human Connectome Project.

Magnetic resonance imaging

Neuroimaging data were acquired using a Philips Ingenia 3T scanner (Philips, USA) with a 32-channel Philips head coil. For each MRI session we acquired the following sequences in order: 1) Resting state functional magnetic resonance imaging (rsfMRI), gradient echo planar imaging, TR/TE = 2000/30 ms, FOV = 240 mm, Matrix = 70 x 70, ReconMatrix = 80, slice thickness = 3.33 mm, FA = 75 degrees, voxel = 3 x 3 x 3.33 mm, axial, slices = 37, direction = AP, 2) Structural T1w 3D FFE Sagittal, TR/TE = 7/3.5 ms, FA = 8 degrees, FOV = 240 mm, matrix = 240 x 240, voxel = 1 x 1 x 1 mm, gap = 0. To correct for field inhomogeneities we acquired a rsfMRI sequence with 5 volumes in the opposite phase-encoding direction (PA). We also acquired a high angular diffusion-weighted imaging (HARDI) sequence not reported here.

Supplementary table 17. Normative Left DLPFC average stimulation cone seed map.

| Hemisphere | Brain region | Voxels | Peak r-value | Peak MNI coordinates | | |
|-----------------|---|--------|--------------|----------------------|-----|-----|
| | | | | x | y | z |
| Positive | | | | | | |
| Left | Dorsolateral prefrontal cortex | 3179 | 0.913 | -30 | 44 | 38 |
| Left | Anterior cingulate cortex | 3170 | 0.465 | -4 | 18 | 36 |
| Left | Anterior insula | 1317 | 0.442 | -34 | 14 | 8 |
| Left | Supramarginal gyrus | 1036 | 0.369 | -62 | -38 | 34 |
| Left | Superior frontal gyrus | 457 | 0.395 | -16 | 6 | 70 |
| Left | Cerebellum VI | 169 | 0.275 | -34 | -50 | -32 |
| Left | Middle frontal gyrus | 67 | 0.286 | -26 | 44 | -12 |
| Left | Precuneus | 32 | 0.217 | -10 | -74 | 42 |
| Left | Cerebellum VIIb | 20 | 0.215 | -40 | -42 | -48 |
| Left | Putamen | 17 | 0.216 | -20 | 14 | -2 |
| Right | Dorsolateral prefrontal cortex | 1858 | 0.547 | 32 | 48 | 32 |
| Right | Midcingulate cortex | 1202 | 0.353 | 12 | -32 | 42 |
| Right | Anterior insula | 1105 | 0.394 | 36 | 16 | 8 |
| Right | Supramarginal gyrus | 805 | 0.352 | 62 | -34 | 36 |
| Right | Cerebellum VI | 194 | 0.279 | 36 | -48 | -32 |
| Right | Cerebellum VIIIa | 80 | 0.235 | 38 | -44 | -52 |
| Negative | | | | | | |
| Left | Superior lateral occipital cortex/Angular gyrus | 378 | -0.238 | -50 | -66 | 30 |
| Left | Anterior middle temporal gyrus | 235 | -0.245 | -60 | -8 | -14 |
| Left | Hippocampus | 36 | -0.227 | -24 | -16 | -18 |
| Right | Ventromedial prefrontal cortex | 925 | -0.307 | 2 | 52 | -12 |
| Right | Posterior cingulate cortex/Precuneous | 902 | -0.273 | 2 | -56 | 26 |

| | | | | | | |
|-------|--|-----|--------|----|-----|-----|
| Right | Anterior middle temporal gyrus | 322 | -0.264 | 62 | -4 | -20 |
| Right | Superior lateral occipital cortex/Angular300 gyrus | | -0.254 | 52 | -60 | 32 |
| Right | Hippocampus | 58 | -0.238 | 26 | -14 | -18 |
| Right | Middle temporal gyrus | 45 | -0.22 | 66 | -34 | -8 |
| Right | Inferior frontal gyrus | 35 | -0.231 | 40 | 38 | -14 |

R = Pearson's *r*.

Supplementary table 18. Safety outcomes for the acute phase.

| Type of data | Clinical or cognitive test / MRI modalities | Data availability | Reference |
|--------------|---|-------------------|--|
| Clinical | Instant-view urine test | | Garza-Villarreal et al. 2021 |
| | MINI-Plus | | None |
| | ASI | | Garza-Villarreal et al. 2021 |
| | SCID-II | | Rasgado-Toledo, <i>et al</i> , 2023, Garza-Villarreal et al. 2021 |
| | SCL-R Revised | | None |
| | CCQ General & CCQ Now | | Rasgado-Toledo, <i>et al</i> , 2023, Zhao et al. 2023 & Garza-Villarreal et al. 2021 |
| | WHODAS | | None |
| | BIS-11 | | Rasgado-Toledo, <i>et al</i> , 2023, Zhao et al. 2023 & Garza-Villarreal et al. 2021 |
| | EHI short | | None |
| | HDRS | | Garza-Villarreal et al. 2021 |
| | HARS | | Garza-Villarreal et al. 2021 |

| | | |
|-----------|--|---|
| | PSQI | Garza-Villarreal et al. 2021 |
| | VAS | Rasgado-Toledo, <i>et al</i> , 2023, Zhao et al. 2023 |
| Cognitive | Berg's Card Sorting Test | Jiménez et al. 2019 |
| | Flanker task | Jiménez et al. 2019 |
| | Go/No-go task | Jiménez et al. 2019 |
| | Letter number sequencing | Jiménez et al. 2019 |
| | Digit span backward | Jiménez et al. 2019 |
| | Iowa gambling task | Jiménez et al. 2019 |
| | Tower of London | Jiménez et al. 2019 |
| | Reading mind in the eyes | Jiménez et al. 2019 |
| MRI | rs-fMRI (T2*) | Zhao et al. 2023, Garza-Villarreal et al. 2021 |
| | Structural scan (T1-weighted) | None |
| | High Angular Resolution Diffusion Imaging (DWI) | Rasgado-Toledo, <i>et al</i> , 2023, Zhang et al. 2021 |

Mini International Neuropsychiatric Interview - Plus; MINI- Plus, Addiction Severity Index; ASI, Structured Clinical Interview for DSM-IV Axis II Personality Disorders; SCID-II, Symptom Checklist-90-Revised; SCL-R, Cocaine Craving Questionnaire General CCQ-G and Now CCQ-N, World Health Organization Disability Assessment Schedule 2.0; WHODAS, Barratt Impulsiveness Scale v. 11; BIS-11, Edinburgh Handedness Inventory Short Form; EHI short, Hamilton Depression Rating Scale (HDRS), Hamilton Anxiety Rating Scale (HARS), Pittsburgh Sleep Quality Index (PSQI), and Cocaine Craving visual analogue scale (VAS).

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