Repetitive Transcranial Magnetic Stimulation in Gambling Disorder, part 1: open study.

Abbreviated title: Transcranial Magnetic Stimulation for Gambling Disorder

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A. Précis

Background: Gambling Disorder (GD) is a complex addictive disorder involving fronto-striatal connectivity and prefrontal top-down control modulation of reward-related brain areas. Repetitive transcranial magnetic stimulation (rTMS) seems to reduce cravings and improve cognitive function in substance dependent individuals. Moreover, rTMS has been shown to modulate dopaminergic and glutamatergic transmission, both involved in GD pathophysiology. However, the efficacy of rTMS in treating GD has not been evaluated and also, we lack a full characterization of rTMS effects on other important aspects, including effects on mood, cognition and changes in brain function.

Objectives: The primary goal of the current study is to investigate the effects of repetitive transcranial magnetic stimulation (rTMS) targeting the left DLPFC on gambling craving. The co-primary goal is to investigate rTMS effect on gambling behavior. Our secondary goals are to evaluate rTMS effects on: (1) mood; (2) cognitive functions.

Study population: Treatment seeking subjects affected by Gambling Disorder, 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) 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 stimulation (two consecutive sessions weekly), 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.

Outcomes measures: Our primary outcomes will be: (1) change in craving score as measured by the Visual Analogue Scale for Craving (VAS-craving) from pre- to post treatment [baseline and after rTMS treatment: 2 weeks, 3 months, 6 months]; (2) changes in gambling behavior as measured by TLFB self-reports, Pathological Gambling Adaptation of the Yale-Brown Obsessive-Compulsive Scale (PG-YBOCS), Gambling Symptom Assessment Scale

(G-SAS) [baseline and after rTMS treatment: 2 weeks, 3 months, 6 months]. Our secondary outcomes are: Changes in the scores on the the Montgomery-Asberg Depression Scale (MADRS) from pre- to post treatment [baseline and after rTMS treatment: 2 weeks, 3 months, 6 months]; (2) changes in the scores on the Hamilton Anxiety Rating Scale (HAM-A); (3) changes in the scores of the Iowa Gambling Task from pre- to post treatment [baseline and after rTMS treatment: 2 weeks, 3 months, 6 months]; (4) changes in the scores of the anhedonic symptoms assessed by Snaith Hamilton Pleasure Scale (SHAPS) and Temporal experience of Pleasure Scale (TEPS) from pre- to post treatment [baseline and after rTMS treatment: 2 weeks, 3 months, 6 months]; (5) changes in the scores of the anhedonic symptoms assessed by changes in Profile of Mood States (POMS) from pre- to post treatment [baseline and after rTMS treatment: 2 weeks, 3 months, 6 months].

B. Background

Gambling disorders

The neural background of Gambling Disorder has been recently shown by brain imaging technologies: current evidences corroborate a crucial role of prefrontal network in the complex construct of cognitive control (Moccia, Pettorruso et al., 2017). GD patients showed increased functional connectivity between regions of the PFC and mesolimbic reward system, as well as reduced connectivity in the area of the PFC, suggesting an imbalance between prefrontal areas and the mesolimbic reward system (Bechara, 2005; Heatherton and Wagner, 2010). This finding in GD is very similar to what has been reported in SUDs, suggesting a common pathophysiology for addictive disorders (Meng et al., 2014). Growing evidence suggest the potential importance of the fronto-striatal cortical pathway in the clinical control of GD severity, emphasizing a deficiency in the top-down inhibitory control of reward-related brain areas (Koehler et al., 2013). These developments in GD comprehension 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 (≥5Hz) 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. Moreover, high-frequency rTMS of the medial prefrontal cortex (PFC) and continuous theta burst stimulation (cTBS) of the right dorsolateral PFC has been shown to reduce impulsive choice in healthy volunteers and to reduce gambling reinforcement in non-comorbid men with PG (Zack et al, 2017).

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 GD.

C. Study Overview

This is an open-label study with a single arm: 15 Hz rTMS stimulation on the DLPFC. Participants will be 10 treatment-seeking patients, between the ages of 18-65, who meet diagnostic criteria for GD. 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 center 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 diagnosis of Gambling Disorder, based on the Diagnostic and Statistical Manual of Mental Disorder – Fifth Edition (DSM-5);
3. Drug-free.

Exclusion criteria

1. Current DSM-5 diagnosis of substance use disorders other than nicotine
2. Current DSM-V diagnosis of moderate to severe alcohol use disorders
3. Current DSM-5 diagnosis of schizophrenia, bipolar disorder, or other psychotic disorder;
4. Use in the past 4 weeks of any medication with known proconvulsant action; or current regular use of any psychotropic medications (benzodiazepines, antipsychotic medications, tricyclic antidepressants, anti-epileptics, mood stabilizers);

5. 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;
6. Any personal or family history (1st degree relatives) of seizures other than febrile childhood seizures;
7. 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;
8. 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 gambling-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 gambling behavior in general. At the end of each stimulation session, participants will rate their craving using a Visual Analogue 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 and gambling-cues exposure
6. HR/PB monitoring
7. VAS craving
8. Side effects questionnaire and PANAS
9. Interval ≥ 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.

During each stimulation session and immediately after, hearth 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 onthe 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 report 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).

Questionnaires and Rating Scales

- TMS Safety Screen: A questionnaire that aids in determining appropriateness of administering TBS. Completion time: < 5 minutes.
- Visual Analogue Scale for Craving (VAS-craving): VAS is a horizontal line, 100 mm in length, anchored by word descriptors at each end (0 = lower scores; 10 = higher scores). The patient marks on the line the point that they feel represents their perception of their current state. Completion time: < 5 minutes.
- Pathological Gambling Adaptation of the Yale-Brown Obsessive-Compulsive Scale (PG-YBOCS): A 10-item clinician-administered questionnaire that measures the severity of PG over the past one week. Completion time: < 5 minutes.
- Gambling Symptom Assessment Scale (G-SAS): A 12-item self-rated scale designed to assess gambling symptom severity and change during treatment. Completion time: < 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, subjetcs 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 (HAM-A): 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.
- 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.

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. Cognitive Assessment include:

- 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.

(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 GD.

During this phase, treatment response will be assessed by evaluating the long-term effect of treatment on relapse rate, gambling severity and craving, mood and cognition.

(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 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

***Primary**:* The primary goal of the current study is to investigate the effects of repetitive transcranial magnetic stimulation (rTMS) targeting the left DLPFC on gambling craving. The co-primary goal is to investigate rTMS effect on gambling behavior.
Secondary: Our secondary goals are to evaluate rTMS effects on: (1) mood; (2) cognitive functions.
Outcomes measures: Our primary outcomes will be: (1) change in gambling craving score as measured by the Visual Analogue Scale for Craving (VAS-craving) from pre- to post treatment [baseline and after rTMS treatment: 2 weeks, 3 months, 6 months]; (2) changes in gambling behavior as measured by TLFB self-reports, Pathological Gambling Adaptation of the Yale-Brown Obsessive-Compulsive Scale (PG-YBOCS), Gambling Symptom Assessment Scale (G-SAS) [baseline and after rTMS treatment: 2 weeks, 3 months, 6 months]. Our secondary outcomes are: (1) Changes in the scores on the the Montgomery-Asberg Depression Scale (MADRS) from pre- to post treatment [baseline and after rTMS treatment: 2 weeks, 3 months, 6 months]; (2) changes in the scores on the Hamilton Anxiety Rating Scale (HAM-A); (3) changes in the scores of the Iowa Gambling Task from pre- to post treatment [baseline and after rTMS treatment: 2 weeks, 3 months, 6 months]; (4) changes in the scores of the anhedonic symptoms assessed by Snaith Hamilton Pleasure Scale (SHAPS) and Temporal experience of Pleasure Scale (TEPS) from pre- to post treatment [baseline and after rTMS treatment: 2 weeks, 3 months, 6 months]; (5) changes in the scores of the anhedonic symptoms assessed by changes in Profile of Mood States (POMS) from pre- to post treatment [baseline and after rTMS treatment: 2 weeks, 3 months, 6 months].

1. Aims

Primary aim:

To determine the effects of rTMS on gambling craving and behavior in patients with GD.

- Changes in the Visual Analogue Scale for Craving (VAS-craving) from pre- to post treatment [baseline and after rTMS treatment: 2 weeks, 3 months, 6 months];
- Changes in the Pathological Gambling Adaptation of the Yale-Brown Obsessive-Compulsive Scale (PG-YBOCS) from pre- to post treatment [baseline and after rTMS treatment: 2 weeks, 3 months, 6 months].
- Changes in Gambling Disorder Severity as assessed by Timeline Follow Back (TLFB) from pre- to post treatment [baseline and after rTMS treatment: 2 weeks, 3 months, 6 months].
- Change in Gambling Behavior as assessed by Gambling Symptom Assessment Scale (G-SAS) from pre- to post treatment [baseline and after rTMS treatment: 2 weeks, 3 months, 6 months].

Secondary aims:

- Changes in the Iowa Gambling Task (IGT) Performance from pre- to post treatment [baseline and after rTMS treatment: 2 weeks, 3 months, 6 months];
- Changes in the scores of the Montgomery-Asberg Depression Scale (MADRS) from pre- to post treatment [baseline and after rTMS treatment: 2 weeks, 3 months, 6 months];
- Changes in the scores on the Hamilton Anxiety Rating Scale (HAM-A) from pre- to post treatment [baseline and after rTMS treatment: 2 weeks, 3 months, 6 months];
- Changes in the scores on the Snaith Hamilton Pleasure Scale (SHAPS) and on the Temporal experience of Pleasure Scale (TEPS) from pre- to post treatment [baseline and after rTMS treatment: 2 weeks, 3 months, 6 months];
- Changes in the scores of the Profile of Mood States (POMS), from pre- to post treatment [baseline and after rTMS treatment: 2 weeks, 3 months, 6 months];

Statistical Analysis

Behavioral measures on each of the cognitive tasks as well as questionnaire data from each of the experimental conditions will be compared within the experimental group 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).

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 10 patients for this open-label study. If data will suggest a potential role of rTMS in Gambling Disorder, we will proceed to a randomized placebo-controlled trial to verify our hypothesis.

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.

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