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Multiple Sessions of High-Frequency Repetitive Transcranial Magnetic Stimulation as a Potential Treatment for Gambling Addiction: A 3-Month, Feasibility Study

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Keywords
Gambling disorder · Neuromodulation · Dorsolateral prefrontal cortex · Gambling symptom assessment scale · Noninvasive brain stimulation · Treatment

Abstract
Gambling disorder (GD) is a behavioral addiction, in which dysfunctions in prefrontal activity have been proposed as relevant pathophysiological correlates. The aim of the present study was to preliminarily investigate the feasibility of a noninvasive neuromodulation intervention targeting the prefrontal cortex to treat GD in an open-label setting. We included 8 treatment-seeking patients with GD (7 males; 1 female; mean age: 40.6 ± 11.2). The study consisted of 3 phases: (1) outpatient screening phase, (2) 2-week intensive repetitive transcranial magnetic stimulation (rTMS) treatment phase (twice daily, 5 days/week for 2 weeks); and (3) 3-month maintenance follow-up phase (twice daily, once a week). Each high-frequency (15 Hz) rTMS session was delivered targeting the left dorsolateral prefrontal cortex. GD severity and treatment response were assessed at the baseline and during the follow-up. No relevant side effect was reported. We found a 71.2% Gambling Symptom Assessment Scale mean score reduction after 2 weeks of rTMS treatment; the days spent gambling decreased from 19.63 ± 7.96 to 0.13 ±

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0.35 days. Clinical improvements were maintained throughout the study period. The lack of a control group limits the interpretation of these results. In conclusion, these results consolidate the rationale that rTMS interventions deserve further investigation as a potential treatment for GD. These protocols should be tested in larger randomized controlled studies, to determine the real benefits of neuromodulation in the clinical course of patients with GD. ***Registration Number:*** ClinicalTrials.gov Identifier NCT03336879.

Introduction

Gambling disorder (GD) is a behavioral addiction, characterized by repetitive gambling behavior despite serious adverse consequences. GD patients engage in compulsive gambling behaviors despite incurring in economic and relational losses, as well as a decline in social functioning [1]. Effective treatment strategies for GD remain a challenge.

Converging evidence supports a central role for decreased cognitive control [2] and reward dysregulation in GD pathophysiology [1]. Impaired activity in the prefrontal pathways may contribute to the progressive loss of control over gambling urges and behaviors [2, 3], playing a critical role in the gambling-related addictive cycle.

Repetitive transcranial magnetic stimulation (rTMS) has emerged as a promising treatment for addiction, particularly to target drug craving [4], as well as cognitive [3] and other addiction-related symptoms [5]. It is a noninvasive neuromodulation technique that exerts its action through a magnetic field producing a localized electrical field in the brain [4]. Different prefrontal areas have been targeted in addictive disorders [4], mainly supposed underpinning response inhibition alterations (i.e., right inferior frontal cortex [2]). Among these studies, Gay et al. [6] reported decreased cue-induced gambling craving following a single session of HF-rTMS applied over the left dorsolateral prefrontal cortex (dlPFC) in GD patients.

The aim of the present study was to investigate the feasibility of a 3-month HF-rTMS protocol in a sample of treatment-seeking GD patients. Consistently with some previous rTMS studies on GD [6, 7] and cocaine addiction [5], the target area was the left dlPFC. In order to obtain proof of concept, the primary aim was to test the effects of left dlPFC HF-rTMS on gambling-related symptoms, including gambling behavior relapses, during a 3-month follow-up.

Methods

Ten treatment-seeking patients, between the ages 18 and 65, who met DSM-5 diagnostic criteria for GD, were screened for the study. The study was carried out at the University Hospital of Chieti and at the outpatient unit "La Promessa" in Rome.

All included participants were medically healthy, drug-free, or with a stable (6 months) pharmacological regimen and had no current DSM-5 diagnosis of alcohol or substance use disorders, with the exception of nicotine. In all cases with a stable pharmacological treatment, the neuromodulation protocol was added to the current treatment without adjustment in the dosage.

Exclusion criteria were severe psychiatric comorbidity (i.e., schizophrenia), current alcohol or substance use disorder, any neurological disorder, any cognitive dysfunction affecting the possibility to provide an informed consent, and any disorder interfering with the safety of rTMS procedures (i.e., metal implants, history of seizure).

All participants signed a written informed consent form. The study was approved by the local Ethics Committee (University of Chieti-Pescara, Italy), and it was conducted in accordance with the Declaration of Helsinki.

The study consisted of 3 phases: (1) an outpatient screening phase, during which patients were screened to assess their eligibility, (2) a 2-week, intensive, rTMS treatment phase, during which subjects received 20 stimulation sessions (2 daily, 5 days/week for 2 weeks); and (3) a 12-week, weekly follow-up phase, during which subjects received 2 consecutive rTMS sessions (2 daily, once a week for 12 weeks, for a total of 24 sessions).

During the study period, participants underwent a weekly as-usual intervention of psychosocial support.

Transcranial Magnetic Stimulation

rTMS was delivered using a MagPro R30 with the Cool-B80 figure-of-eight coil (MagVenture, Falun, Denmark). Each intervention phase (phase 2) began with the determination of resting motor threshold. Consistently with our previous work [7], the stimulation protocol included rTMS sessions lasting 13 min (15 Hz frequency, pulse intensity 100% of the resting motor threshold, 60 pulses per train, inter-train interval of 15 s, 40 trains/session, 2,400 pulses/session) and targeted the left DLPFC, located with BeamF3 method (a system to find the F3 position using 3 skull measurements). The coil location was marked on the cap, in order to ensure accuracy and consistency across sessions. At the end of any session, the "Side Effect" questionnaire and the PANAS scale were administered to evaluate potential side effects.

Clinical and Psychometric Measures

Clinical and psychometric data had been acquired at baseline (T0), after 2 weeks of the intensive treatment phase (T1) and once a month during the follow-up phase (T2, T3, T4). GD severity and treatment response were assessed by using following psychometric tests: the Gambling Symptom Assessment Scale (G-SAS) and the Pathological Gambling Adaptation of the Yale-Brown Obsessive-Compulsive Scale to asses gambling symptoms severity through a self-reported and a clinician-administered questionnaire, respectively; the Gambling behaviors Timeline Follow Back to report the days of gambling relapse (in the previous month for all visits except for T1, in which patients reported days of gambling in the last 2

weeks); and the Beck Depression Inventory and the Zung Self-Rating Anxiety Scale for the severity of depressive and anxiety symptoms.

Statistical Analysis

Statistical analysis was performed using SPSS for Windows, version 20.0 (SPSS Inc., Chicago, IL, USA). All analyses were conducted using nonparametric testing. Wilcoxon test for paired variables was used to monitor changes in scores on psychometric scales and days of gambling relapse during the follow-up period. Correlations between scores on psychometric scales and G-SAS variations were measured by means of Spearman's rank correlation coefficient. We applied the Bonferroni's correction for multiple testing to the primary related tests (i.e., gambling measures). Accordingly, the critical value to reach a level of significance was adjusted to $p < 0.0167$ (i.e., = 0.05/3).

Results

Eight patients (7 males; 87.5%) were included in the rTMS treatment protocol. Two patients were excluded for the detection of co-occurring alcohol and cocaine use disorders, respectively. Mean age was 40.6 ± 11.2 (range 28–63) years. Other relevant sociodemographic variables and comorbidity data are presented in Table 1. Four patients were under stable psychopharmacological treatment: one was treated with antidepressants (venlafaxine 75 mg/day), one with antidepressants and mood stabilizers (bupropion 150 mg/day; lithium carbonate 450 mg/day), and the other 2 only with mood stabilizers (one with lithium carbonate 900 mg/day; one with olanzapine 10 mg/day).

Compared to baseline, we observed a reduction of G-SAS mean scores at T1 visit (–71.2%; Table 2). During the follow-up period, we found the following G-SAS reductions compared to the baseline were observed: –73.1% at T2; –82.4% at T3; –75.6% at T4. With the exception of T1, G-SAS reductions were significantly different compared to the baseline also after correction for multiple comparisons.

We also found a significant reduction in the days of gambling measured by the Timeline Follow Back. At baseline, patients reported 19.63 ± 7.96 days of gambling. During the 2-week neuromodulation intensive phase, patients reported 0.13 ± 0.35 days of gambling, with a significant reduction compared to baseline. During the maintenance stimulation protocol, patients reported 0.25 ± 0.71 days of gambling at T2, 0.88 ± 1.64 days of gambling at T3 and 1.38 ± 2.50 at T4. The number of days spent gambling remained significantly lower than the baseline during all the follow-up period, also after the correction procedure. No significant changes were found in clinician-administered Pathological Gambling Adaptation of the Yale-Brown Obsessive-Compulsive Scale, Beck Depression Inventory, and Self-Rating Anxiety Scale scores during the study period (Table 2).

Table 1. Demographic and clinical characteristics of treatment-seeking GD patients at baseline

	n (%)/mean ± SD
Number	8 (100)
Age, years	40.6±11.2
Gender, males	7 (87.5)
Education, years	13.5±3.07
Employment	
Unemployed	2 (25)
Employed	5 (62.5)
Retired	1 (12.5)
Marital status	
Single	2 (25)
Married	4 (50)
Divorced	2 (25)
History of substance use comorbidity	1 (12.5)
Mood disorder comorbidity	4 (50)
Current pharmacological treatment	4 (50)

GD, gambling disorder.

Discussion

In the paper, we present preliminary evidence for potential clinical effect of multiple sessions of HF rTMS in a small sample of treatment-seeking GD patients. Due to the exploratory nature of the study and the lack of any control group, these results should be interpreted cautiously, with no possible conclusion on the efficacy of the intervention. Nevertheless, these preliminary data permit some speculations on the potential role of neuromodulation in the treatment of GD, contributing to prompt and address future research in the field.

This is the first clinical study showing a sustained effect of a HF-rTMS intervention in the treatment of gambling-related symptoms, resulting in a reduction of relapses in gambling episodes. To date, only 4 short-term studies have explored the effects of TMS in GD [6, 8–10]. Rosenberg et al. [8] were the first to explore the neuromodulation treatment option for GD in an open-label study. Five patients underwent 15 sessions of LF (1 Hz) deep TMS to the left dlPFC with an H-coil. Despite an initial improvement, the authors failed to demonstrate treatment efficacy. In a recent study, Zack et al. [10] ex-

Table 2. Changes in gambling-related symptoms, relapses, and psychometric scales after rTMS treatment

	Baseline, mean (SD)	T1			T2			T3			T4		
		mean (SD)	ΔT1–T0	significant, *p* value	mean (SD)	ΔT2–T0	significant, *p* value	mean (SD)	ΔT3–T0	significant, *p* value	mean (SD)	ΔT4–T0	significant, *p* value
G-SAS	20.5 (12.6)	5.9 (7.3)	−14.6 (7.8)	0.018	5.5 (10.6)	−15.0 (8.3)	**0.012**	3.6 (7.6)	−16.9 (9.6)	**0.012**	5.0 (8.3)	−15.5 (8.7)	**0.012**
Days of gambling	19.6 (8.0)	0.1 (0.4)	−19.5 (8.0)	**0.012**	0.3 (0.7)	−19.4 (7.7)	**0.012**	0.9 (1.6)	−18.8 (7.7)	**0.012**	1.4 (2.5)	−18.3 (8.2)	**0.012**
PG-YBOCS	16.8 (11.0)	3.8 (4.6)	−13.0 (9.4)	0.027	4.3 (10.1)	−10.9 (8.1)	0.027	1.7 (4.5)	−13.4 (8.1)	0.027	3.7 (7.1)	−12.0 (8.3)	0.043
BDI	10.1 (5.6)	4.9 (5.9)	−5.3 (6.5)	0.058	3.8 (7.9)	−6.4 (7.6)	0.049	3.6 (6.8)	−6.5 (7.1)	0.051	2.1 (3.8)	−7.6 (6.0)	0.018
SAS	31.9 (7.7)	27.3 (4.3)	−4.6 (7.1)	0.141	28.7 (8.6)	−2.0 (5.7)	0.236	25.7 (6.0)	−5.8 (9.5)	0.206	25.3 (3.7)	−8.0 (5.4)	0.066

Follow-up visits were performed after 2 weeks of intensive rTMS treatment (T1), and after 4 (T2), 8 (T3) and 12 (T4) weeks of rTMS maintenance treatment.
Applying the Bonferroni's correction, the critical value to reach a level of significance was adjusted to $p < 0.0167$ (i.e., = 0.05/3). Significant *p* values have been reported in bold.
G-SAS, Gambling Symptom Assessment Scale; PG-YBOCS, Pathological Gambling Adaptation of the Yale-Brown Obsessive-Compulsive Scale; BDI, beck depression inventory; SAS, Zung Self-Rating Anxiety Scale.

plored the respective effects of 2 different one-session stimulation protocols in 9 GD patients, focusing on decision making, cognitive control, gambling reinforcement, and physiological arousal measures. Sauvaget et al. [9] reported improvement in cue-induced craving after a single right dlPFC low-frequency stimulation, both in an active and a sham group. This study raises the problem of a significant placebo effect, also consolidating the notion that the inhibition of dlPFC is not more effective than sham stimulation in the treatment of GD [9]. Last, a study involving GD patients reported decreased cue-induced cravings following a single session of HF rTMS applied over the left dlPFC [6], as compared with sham stimulation. Though a single session was not able to determine effects on gambling behaviors, the authors argued HF-rTMS could represent a promising option to treat GD. Though in an exploratory fashion, the results of the present study sustain this hypothesis and stimulate the need for future placebo-controlled investigations in larger GD samples, to establish the real role of neuromodulation in the clinical course of patients with GD.

In conclusion, our study suggests that multiple sessions of HF-rTMS over the left dlPFC can be tested as a potential treatment in patients with GD. Considering limitations concerning the small sample size and the lack of control group, this study provides a proof-of-concept for larger prospective trials. Stimulating the left dlPFC is a feasible intervention to further be tested as a potential treatment to reduce severity of gambling symptoms in patients with GD.

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Statement of Ethics

All participants signed a written informed consent form. The study was approved by the local Ethics Committee (University of Chieti-Pescara, Italy), and it was conducted in accordance with the Declaration of Helsinki.

Disclosure Statement

The authors have no conflicts of interest to declare.

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There is no funding source to declare.

Author Contributions

M.P., G.M., and M.D.G. were primarily responsible for study design. M.P., G.M., C.M., and L.D.R. contributed to protocol design, data interpretation, and article writing. P.A.S., L.G., and A.B. were involved in protocol design and data interpretation. M.P., F.F., and members of the Brainswitch Study Group screened, evaluated, assessed, and stimulated GD patients. All authors revised and approved the final version of the manuscript.

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