European Psychiatry 41 (2017) 68–74

Contents lists available at ScienceDirect

European Psychiatry

journal homepage: http://www.europsy-journal.com

Original article

A single session of repetitive transcranial magnetic stimulation of the prefrontal cortex reduces cue-induced craving in patients with gambling disorder☆

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ARTICLE INFO

Article history:
Received 27 July 2016
Received in revised form 30 October 2016
Accepted 2 November 2016
Available online 3 February 2017

Keywords:
Craving
Dorsolateral prefrontal cortex
Gambling behavior
Gambling disorder
Repetitive transcranial magnetic stimulation

ABSTRACT

Background: Gambling disorder (GD) is common and disabling addictive disorder. In patients with substance use disorders, the application of repetitive transcranial magnetic stimulation (rTMS) over the dorsolateral prefrontal cortex (DLPFC) offers promise to alleviate craving. We hypothesized that applying real compared to sham rTMS over the left DLPFC would reduce gambling craving in patients with GD.

Methods: In a randomized sham-controlled crossover design, 22 treatment-seeking patients with GD received real or sham treatment with high frequency rTMS over the left DLPFC followed a week later by the other type of treatment. Before and after each rTMS session, participants rated their gambling craving (from 0 to 100) before and after viewing a gambling video used as a cue. We used the Yale-Brown Obsessive Compulsive Scale adapted for Pathological Gambling to assess gambling behavior before and 7 days after each rTMS session.

Results: As compared to sham (mean +0.74; standard deviation ± 3.03), real rTMS significantly decreased cue-induced craving (−2.12 ± 3.39; $F_{(1,19)} = 4.87$; $P = 0.04$; partial $\eta^2 = 0.05$; 95% CI: 0.00–0.21). No significant effect of rTMS was observed on gambling behavior.

Conclusions: Patients with GD reported decreased cue-induced craving following a single session of high frequency rTMS applied over the left DLPFC. Further large randomized controlled studies are needed to determine the usefulness of rTMS in GD.

1. Introduction

Previously considered as pathological gambling among Impulse Control Disorders in DSM-IV, gambling disorder (GD) is now classified as a DSM 5 substance-related and addictive disorder, and is characterized by persistent and recurrent gambling behavior that can lead to devastating consequences for those with the disorder and their families. Gambling becomes the primary focus in the lives of these individuals, predominating all other emotional or social investments. The reported prevalence of GD in adults ranges from 0.5 to 7.6% [1].

Though several approaches have been developed to help those with GD quit gambling [2,3], national regulatory agencies have approved no uniform treatment guidelines, and novel approaches are needed. The short-term efficacy of cognitive-behavioral therapy, motivational interviewing, and motivational enhancement therapy has been reported [3], and mixed results have been obtained using serotonergic antidepressants, opioid antagonists, and mood stabilizers [4].

Craving, a key feature of substance-related and addictive disorders, is defined as a pressing, urgent, and irrepressible desire

☆ Clinical Trials Registration: registry name: clinicaltrials.gov; URL: https://www.clinicaltrials.gov; registration number: NCT02552524.

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http://dx.doi.org/10.1016/j.eurpsy.2016.11.001
0924-9338/

to give in to an addictive behavior that usually results in loss of control [5,6]. Reports of imaging studies of animal models and humans have described the involvement of a distributed brain network, including the dopaminergic system and cortical and subcortical loops and suggested disruption of the inhibitory control of the dorsolateral prefrontal cortex (DLPFC) in the addiction cycle and craving [7,8]. Greater craving in patients with GD [9–11] and other substance use disorders (such as alcohol [12] and cocaine [13]) has been associated with higher risk for relapse and dropout from cognitive-behavioral therapy. Thus, decreasing craving has been considered a beneficial target to decrease addictive behavior [14].

Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive brain stimulation technique that can modulate activity and connectivity of the brain in humans [15]. TMS consists in applying brief current pulses through a coil placed on the scalp of a subject. This generates a magnetic field allowing the induction of a weak electrical current in the brain. High frequency (HF) stimulation ($>$ 5 Hz) is considered to have excitatory effects on the targeted cortical excitability whereas low frequency (LF) stimulation ($\leq$ 1 Hz) is considered to have inhibitory effects [16]. These effects can outlast the stimulation period. A recent meta-analysis [17] and reviews [18,19] showed that such stimulation over the right, left, and bilateral DLPFC can decrease craving and substance intake in patients abusing alcohol, nicotine, cocaine and food. The efficacy of rTMS in patients with behavioral addiction was mainly investigated in patients with eating disorders (food craving, anorexia nervosa and bulimia nervosa). The efficacy of rTMS to modulate food craving was comparable to the effects of rTMS to modulate substance craving in patients with substance use disorders (SUD) [17]. To our knowledge, only one open-label study has investigated the clinical effect of LF rTMS over the left DLPFC in patients with GD [20]. The authors did not report any beneficial effect of TMS on gambling behavior. Nevertheless, in most of the studies in patients with SUD and eating disorders, the left DLPFC was stimulated using HF, excitatory, protocols [18]. Cue-induced craving paradigms were considered as the most ecological approaches to assess craving and were used in a large majority of these studies [18,19].

As rTMS can decrease craving in patients with SUD and eating disorders, we undertook this pilot randomized sham-controlled crossover study to investigate the effect of a single application of HF-rTMS over the left DLPFC on craving and gambling behavior in a group of 22 adults seeking treatment for GD. We hypothesized that treatment with real compared to sham rTMS would reduce cue-induced craving and gambling behavior in patients with GD.

2. Methods and materials

2.1. Study design

In a sham-controlled, crossover study, 22 patients with gambling disorder received one session of real and one session of sham rTMS separated by a one-week wash-out period, to avoid carryover effects and evaluate effect on gambling behavior (Fig. 1). After screening and an initial visit in which patients underwent cerebral magnetic resonance imaging (MRI) to establish the location of the DLPFC, they were randomized into two groups of 11 patients each to receive the real or sham treatment first followed by the other treatment a week later, using a method of allocation with variable-sized blocks and allocation according to a 1:1 ratio. Participants and investigators, except the experimenter applying the rTMS, were blinded to the treatment condition. At the end of each session, the experimenter asked patients whether they believed they received the real or sham treatment to assess the integrity of the blinding of patients and evaluated the safety of the rTMS by collecting the possible side effects.

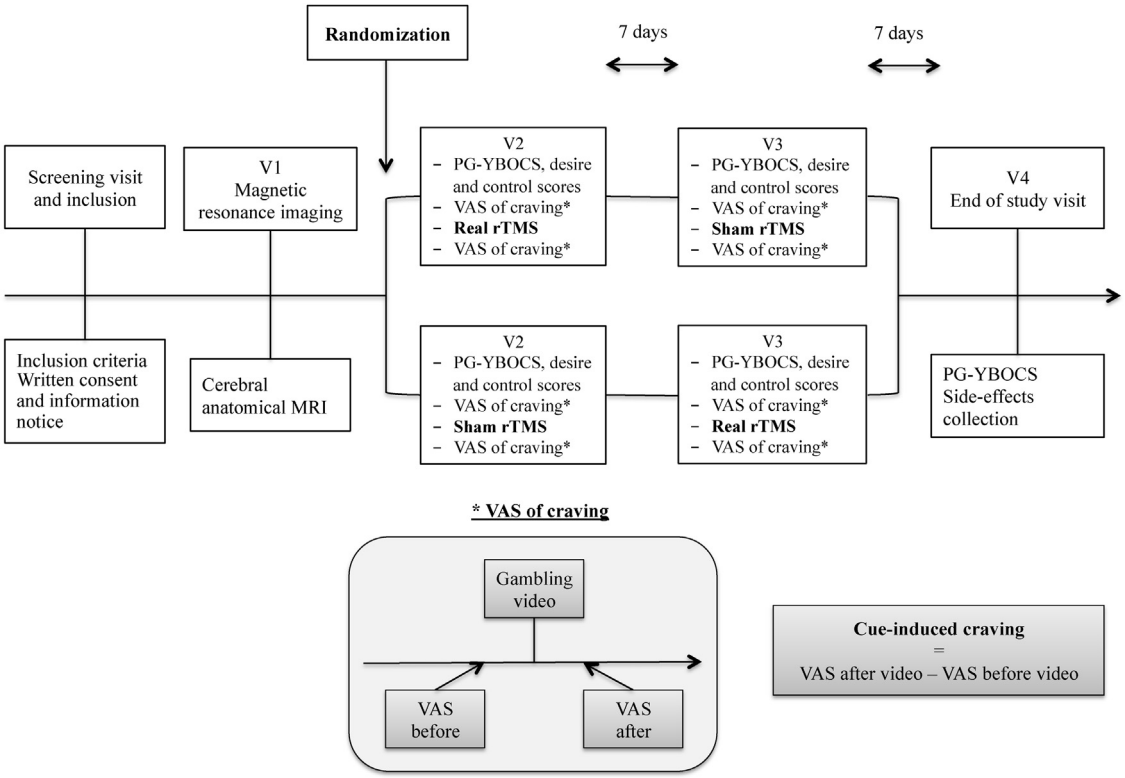

Fig. 1. Study design. MRI, magnetic resonance imaging; PG-YBOCS, Yale-Brown Obsessive Compulsive Scale adapted for pathological gambling; rTMS, repetitive transcranial magnetic stimulation; V1, V2, V3, and V4, Visits 1, 2, 3, and 4; VAS before, VAS after, completion of the visual analogue scale before and after watching gambling video.

The study was approved by a local ethics committee (CPP Sud-Est I) and registered in the clinicaltrial.gov database (NCT02552524). All participants received a detailed description of the study, after which they provided written informed consent. They were informed that rTMS could be an experimental treatment for GD but that no durable clinical benefice could be expected from one single session. Stimulation sessions were carried out at the University Hospital of Saint-Étienne, between December 2013 and June 2015. Participants received 50 euros if they completed the study.

2.2. Participants

A physician expert on GD, co-investigator of the study, proposed the study to treatment-seeking patients with GD according to the DSM IV-TR criteria. Twenty-two adult patients were enrolled. All patients remained diagnosed for gambling disorder using DSM 5 criteria. We assessed the severity of gambling using the South Oaks Gambling Screen (SOGS) [21]. The sample size was determined based on previous studies investigating the effect of a single session of rTMS on craving in patients with SUD. In the recent metaanalysis by Janssen and colleagues, the mean number of patients/study over 9 studies was 22.2 [17].

Exclusion criteria were: contraindications to rTMS (history of epilepsy, any implanted metal devices in contact with coil, pregnancy; relative exclusion criteria: individuals taking medications that lower the seizure threshold or with history of brain injury); current DSM IV-TR Axis I condition: substance dependence or abuse (excepted nicotine), current psychiatric disorder, as revealed by the Mini-International Neuropsychiatric Interview [22]; unstable psychiatric medication (i.e., change in dose and/or type of treatment during the last month). Table 1 delineates socio-demographic and clinical characteristics of the participants.

2.3. Outcome measures

2.3.1. Primary outcome: effect of rTMS on self-reported measurement of cue-induced craving

After and before each rTMS session, real and sham, participants were asked to grade their desire to gamble on a one-item 100-mm visual analogue scale (VAS) before watching a 2-minute 30-second video cue and immediately afterward (Fig. 1). The same video, specific to the subject's favorite gambling type (casino, horserace betting, scratch cards, or sport betting), was used for real and sham rTMS session for each patient. We subtracted the VAS score before watching the video from the score afterward to define the cue-induced craving score. The effect of rTMS on cue-induced craving score was the subtraction of these score obtained after and before each rTMS session.

Table 1
Demographic and clinical characteristics of 22 patients with gambling disorder who received real and sham treatments with repetitive transcranial stimulation applied over the left dorsolateral prefrontal cortex. Results are given as mean (standard deviation).

Characteristic	Value
Age (years)	51.0 (13.7)
Gender (male/female)	14/8
Educational level (years after first grade)	10.9 (1.4)
Current use of psychiatric medication (with/without)	9[a]/13
Psychiatric history (yes/no)	9/13
Score on South Oaks Gambling Screen	12.8 (2.8)
Duration of gambling disorder (months)	162.5 (122.8)
Preferred type of gambling	
Slot machine	9
Scratch cards	7
Horserace betting	5
Sport betting	1

6 patients received antidepressant (Selective Serotonin Reuptake Inhibitors), 2 atypical antipsychotic, 6 benzodiazepine at bedtime and one hydroxyzine at bedtime.
[a] No change in treatment for at least 1 month, no anti-craving drugs.

2.3.2. Clinical outcomes

To assess gambling behavior, we used the Yale-Brown Obsessive Compulsive Scale adapted for pathological gambling (PG-YBOCS), a 10-item hetero-questionnaire that evaluates the severity of GD over a recent time interval (usually within the past week) [23]. Participants were also asked to grade from 0 to 10 both their desire to gamble and control over that desire over the past week. An investigator blinded to the rTMS condition evaluated their responses regarding gambling behavior a total of 3 times – before each real or sham treatment with rTMS (visits 2 and 3) and 7 days after completion of the second stimulation session (visit 4; Fig. 1). The difference between the scores 7 days after and before the treatment was considered to represent the effect of the rTMS on gambling behavior.

2.4. rTMS parameters

Patients underwent rTMS delivered using a MagPro X100 stimulation system (Mag2Health, France) with a 70-mm figure-8 coil. Stimulations were applied at a frequency of 10 Hz with intensity set at 110% of the resting motor threshold (RMT) and consisted of 94 trains of 3.2-second duration at 10-second intervals, for a total of 3008 pulses per session and total treatment duration of 20 minutes 30 seconds. Stimulation parameters were chosen to optimize the total number of pulsations [24], in line with safety regulations. The RMT was defined as the minimum strength of magnetic field required to elicit 5 motor-evoked potentials of at least 50 microV amplitude in 10 trials of the right thenar muscle as evoked by delivery of single TMS pulses to the contralateral motor cortex [25]. The individual RMT was determined at the beginning of the first rTMS session.

2.4.1. Site of stimulation

The coil was placed over the left DLPFC using a neuronavigation system (Visor2, eemagine Medical Imaging Solutions GmbH, Berlin, Germany) guided by a robot (SmartMove™, Advanced Neuro Technology [ANT], Enschede, The Netherlands). The coil was held tangential to the scalp with the handle pointing back and away from the midline at 45°. We determined the location of the DLPFC as the middle part of the middle frontal gyrus of the patient according to the anatomical T_1-weighted MRI obtained prior to the first stimulation session [26].

2.4.2. Sham rTMS

Sham stimulations were delivered using a commercial sham coil (same external appearance but with mu-metal plates) at the identical location and with the same stimulation parameters as the real stimulations. To improve the blinding of the participants to the stimulation condition, in both real and sham conditions, a local electrical stimulation was delivered over the ipsilateral supraorbital area with 2 disposable electromyography electrodes using a transcutaneous electrical nerve stimulation (TENS) stimulator (Cefar Primo Pro, CefarCompex, Sweden) [27].

2.5. Statistical analyses

In case of non normal distribution revealed by the Shapiro-Wilk test, we used a normalization approach (the signed square root of the absolute value). We tested our primary outcome by analyzing the effects of real and sham rTMS sessions on cue-induced craving using repeated measures analyses of variance (rm-ANOVA) with treatment (real and sham) and order of treatment deliverance

Table 2
Cue-induced craving before and after each rTMS session.

	Baseline			After rTMS			Effect of rTMS
	Before video	After video	Cue-induced craving	Before video	After video	Cue-induced craving	
Real rTMS	40.4 (6.2)	55.9 (6.0)	+15.5 (5.7)	34.3 (6.3)	37.8 (5.4)	+3.4 (3.1)	−12.1 (4.2)
Sham rTMS	48.2 (6.6)	49.3 (6.9)	+1.1 (0.9)	31.5 (5.7)	35.2 (6.3)	+3.8 (0.8)	+2.6 (2.4)

Results are given as mean and standard error of the mean [SEM].

(real-sham versus sham-real; to measure a carry-over effect) as conditions nested within subject effect and time (interaction order*treatment). The cue-induced craving score before rTMS (baseline) was added as covariate in the model to control for its influence on rTMS induced changes.

As secondary measures, we investigated the influence of clinical and socio-demographic characteristics of subjects (gender, age, duration of illness, psychiatric history, current use of psychiatric drug) by entering each measures as covariate in the rm-ANOVA model.

Finally, to investigate the effect of rTMS on gambling behaviors (PG-YBOCS, desire and control to gamble), we used the same rm-ANOVA model with corresponding baseline scores as covariate.

Analyses were completed with SAS V9.2 (SAS Institute, Cary, NC, USA). In case of missing clinical data, we assigned the group average for the missing values (mean substitutions). Significance was set at $P < 0.05$.

3. Results

3.1. Effect of rTMS on cue-induced craving

The Shapiro-Wilk test revealed a non-normal distribution of our primary outcome measure (see descriptive measures on Table 2). Data were thus standardized using the signed square root of their absolute value. The Shapiro-Wilk test on these normalized data showed a normal distribution ($P = 0.55$).

As compared to sham (mean +0.74; standard deviation ± 3.03), real rTMS significantly decreased cue-induced craving (−2.12 ± 3.39; $F_{(1,19)} = 4.87$; $P = 0.04$; partial $\eta^2 = 0.05$; 95% CI: 0.00–0.21; Fig. 2). No effect of the order of deliverance of treatment (real-sham versus sham-real) was observed ($F_{(1,19)} = 0.65$; $P = 0.43$).

Secondary analyses revealed that none of the clinical characteristics of the population such as gender ($F_{(1,39)} = 0.12$; $P = 0.72$), age ($F_{(1,39)} = 0.41$; $P = 0.53$), illness duration ($F_{(1,39)} = 0.11$; $P = 0.74$), psychiatric history ($F_{(1,39)} = 0.63$; $P = 0.43$) and current use of psychiatric drug ($F_{(1,39)} = 0.23$; $P = 0.63$) were significantly associated with the outcome measure.

3.2. Effects of rTMS on gambling behavior

The rm-ANOVA revealed no significant interaction between treatment with rTMS and PG-YBOCS scores ($F_{(1,19)} = 0.17$; $P = 0.68$), scoring of desire to gamble ($F_{(1,19)} = 0.46$; $P = 0.51$) and scoring of control to gamble ($F_{(1,19)} = 1.31$; $P = 0.27$). Details of scores are given in Table 3.

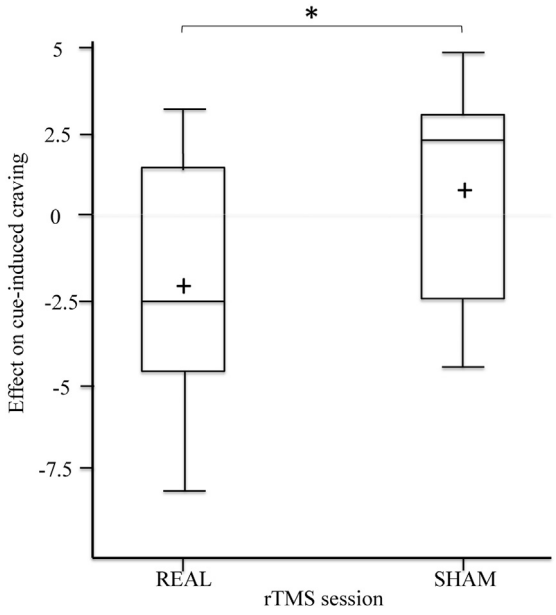

Fig. 2. Effect of real and sham treatments with repetitive transcranial magnetic stimulation (rTMS) on craving induced by watching a gambling video in 22 treatment-seeking adults with gambling disorder. Normalized data are presented. Crosses represent sample means; centerlines show the medians; box limits indicate the 25th and 75th percentiles; whiskers extend 1.5 times the interquartile range from the 25th and 75th percentiles. Decrease in cue-induced craving was significantly higher after real than sham rTMS (mean: −2.12 ± standard deviation: 3.39 versus +0.74 ± 3.03; $F_{(1,19)} = 4.87$; $P = 0.04$; partial $\eta^2 = 0.05$; 95% CI: 0.00–0.21).

3.3. Safety and blinding issues

Participants demonstrated no serious adverse events throughout the study, but some described mild discomfort at the start of stimulation. With regard to blinding, 5 of the 22 patients (22,7%) could correctly recognize real and sham stimulation sessions. For each distribution the Fisher's exact test was calculated (Table 4). No statistical differences were reported ($P = 0.72$).

4. Discussion

We aim to investigate the effect of a single session of HF rTMS over the DLPFC on cue-induced craving and gambling behavior in patients with GD. Following treatment with real compared to sham rTMS, participants reported a moderate decrease in cue-induced

Table 3
Gambling behavior before and 7 days after each rTMS session.

	Real rTMS			Sham rTMS		
	Baseline evaluation	7 days' evaluation	Effect of rTMS	Baseline evaluation	7 days' evaluation	Effect of rTMS
PG-YBOCS	22.7 ± 1	18 ± 1.6	−4.7 ± 1.6 (−21%)	20.5 ± 1.4	18.3 ± 1.6	−2.2 ± 1.6 (−11%)
NSc desire	7.0 ± 0.3	5.7 ± 0.4	−1.3 ± 0.4 (−18%)	5.9 ± 0.4	6.2 ± 0.5	+0.3 ± 0.7 (+5%)
NSc control	3.4 ± 0.4	5.3 ± 0.5	+1.8 ± 0.6 (+55%)	3.5 ± 0.5	4.6 ± 0.6	+1.0 ± 0.6 (+31%)

Results are given as mean and standard error of the mean [SEM]. Gambling behavior is evaluated using PG-YBOCS (Yale-Brown Obsessive Compulsive Scale adapted for pathological gambling) and numerical scale (NSc) to score desire and control to gamble from 0 to 10.

Table 4
Blinding assessment: distribution of guessing among participants in each experiment.

	Correct group	
	Real	Sham
Guessed group		
Real	15	15
Sham	4	6

In the table, each cell represents the absolute number of patients according to the cross-tabulation guessing *versus* correct group. For each distribution the Fisher's exact test was calculated. No statistical differences were reported ($P = 0.72$).

craving. We observed no significant difference in gambling behavior measured by the PG-YBOCS and by participants' numeric scoring of their desire and control to gamble between treatment with real and sham rTMS.

These results are in line with findings of studies that have shown a beneficial effect of noninvasive brain stimulation applied over the left DLPFC on craving and cue-induced craving in patients with SUD [17–19]. In their meta-analysis, Jansen and colleagues [17] reported the efficacy of real compared to sham application of noninvasive brain stimulation techniques over the DLPFC in reducing substance and food craving, with a significant medium effect size (Hedge's g = 0.476). Regarding behavioral addiction, our results also corroborate results from previous studies investigating the effect of rTMS on food craving in patients with eating disorders [28–30]. As an example, Van den Eynde and associates [28] reported that the application of HF-rTMS over the left DLPFC lowered cue-induced food cravings in 38 patients with bulimic eating disorder. Our results, however, contrast with those of previous studies that showed no modulation of food cravings following rTMS in healthy volunteers with high craving for specific foods [31] and with findings of studies in patients with bulimia nervosa [32]. To the best of our knowledge, only one clinical study has investigated the effect of deep TMS in patients with GD [20]. In this open-labeled study, 5 participants received 15 sessions of deep TMS applied over the left DLPFC with an H-coil (one session/day) at one-Hz frequency and 110% of the RMT. However, the authors of that study failed to report whether deep rTMS had any beneficial effect on gambling behavior or on comorbid depression and anxiety in their sample. Discrepancies between methods as well as parameters (LF over the left DLPFC) and material used for stimulation may explain differences between these results and ours. More recently, in a Latin square design study with 3 arms, Zach and colleagues (2016) investigated the effects of HF rTMS of the medial prefrontal cortex (PFC), continuous theta burst stimulation (cTBS) of the right DLPFC and sham rTMS on gambling reinforcement and related responses in 9 healthy men with GD [33]. A slot machine was used as reinforcing stimulus. They found that real rTMS reduced desire to gamble induced by the slot machine, that can be considered as an indirect measure of cue-induced craving. These latter results are line with ours although the authors stimulated different regions with different parameters (activation of the medial PFC and inhibition of the right DLPFC) and didn't aim at directly evaluating effect of rTMS on craving.

We failed to show a difference in results between single treatments with real or sham rTMS on gambling behavior as evaluated by PG-YBOCS and participants' grading of their desire and control to gamble. In their study, Zach et al. (2016), indirectly evaluated gambling behavior measuring bet size and speed of play at a slot machine, with also no effect of rTMS or cTBS [33]. Many fewer studies investigate the effect of rTMS on substance use or eating behavior than the number that evaluate craving. Studies of tobacco use have measured outcomes by the number of cigarettes smoked or validated scales for nicotine dependence [34,35], or those studying eating disorders have evaluated the number of binges and purges [28,32]. A significant decrease in cigarette consumption after 2 [34] or 10 sessions [35] of real but not sham rTMS has been reported in patients with tobacco use disorder, but results in patients with eating disorder have been mixed. One sham-controlled crossover study showed a beneficial effect of a single session of real rTMS on the number of binges [28], but Walpoth et al. (2008) showed no significant effects of real rTMS on purges and binges following 15 treatment sessions [32]. More treatment sessions may be necessary to modify addictive behavior. The duration of the effect of one rTMS session is limited. Effect on craving disappeared after 4 hours in Camprodon and colleagues study (2007) [36]. In an open-label study, Politi et al. (2008) observed a significant decrease in craving for cocaine only after the seventh stimulation session in patients with SUD [37]. In the current pilot study, we investigated the effect of a single session of rTMS on GD, but investigation of protocols with repeated stimulation sessions would be interesting to investigate long-term effects.

Methodologically, as in most studies in the field of addiction [18,19], we used HF stimulation (10 Hz) delivered at a supra-threshold intensity (110% of the RMT) as simulation parameters, with a total of 3008 pulses. Because craving outcome in patients with behavioral addiction has been associated with the quality of sham stimulation [31], we used an improved sham condition that combined local superficial TENS stimulation and rTMS using a sham coil as it was previously done in the field of depression [27]. We found less than 25% of the participants guessing correctly rTMS allocation. In addiction field, only Barth and colleagues (2011) also tested the validity of the sham system and found 40% of correct discrimination [31].

We chose to stimulate the DLPFC. All studies but one in the field of addiction research have used an empirical method to localize this area of the brain [38]; we are the first to employ a neuronavigation system and robot-guided coil method based on the subject's MRI. Neuronavigation is assumed to be superior to the "5-cm rule" and the "10/20" method for targeting the DLPFC [39–41] and seems to have increased the therapeutic effects of rTMS in several diseases, including depression [26,42,43]. Regarding lateralization, we chose to stimulate the left DLPFC. Studies in the field of addiction research have compared stimulation of the left and right DLFPC and showed no statistically significant difference [17,44]. However, a recent metaanalysis [45], focusing on the effect of rTMS for craving in patients with SUD, revealed that real stimulation was superior to sham only in studies targeting the right DLPFC. Moreover some researchers have stimulated other regions than the DLPFC within the craving-related network [46]. In patients with tobacco use disorder, Rose and colleagues (2011) reported effects of HF-rTMS applied over the superior frontal gyrus on cue-induced craving [47], as Dinur-Klein and colleagues (2014) stimulating the anterior insula and lateral PFC using a unique H-coil design [48]. Recently a single-blinded, sham-controlled study showed promising results inhibiting the medial PFC in cocaine use disorder using continuous theta burst stimulation [46]. Furthermore, Downar's group (2012) reported full remission from depression and binge-eating/purging episodes for more than 2 months in a patient with severe refractory bulimia nervosa after 20 sessions of neuronavigated HF-rTMS applied over the right then left dorsomedial PFC [49].

To go further, some authors [46,50] suggest that there will likely not be a single 'optimal' protocol for all individuals and to select targets based on neural substrates of phenotypes. Pathological gamblers constituted a heterogeneous population [51], some problem gamblers described urges emerging through gambling cues, in positive affect situations whereas others described urges rather in negative affect-stressful situations [52]. Thus various

adapted strategies could be proposed: amplify executive control circuitry (excitatory stimulation of the DLPFC, dACC, and insula), attenuate limbic circuitry involved in craving (e.g., medial prefrontal/frontal pole inhibitory stimulation) and/or damp negative valence systems (PFC and insula excitatory stimulation) [53].

This study has some limitations. First the relatively small sample size may have led to lack of statistical power. One can hypothesize that the heterogeneity observed in pathological gamblers may have influenced rTMS response. Further studies should differentiate several subgroups of gamblers to investigate the effect of rTMS. Second we chose to use a single-item VAS to assess craving, allowing a fast and easily repeatable measurement of craving. However, this method does not fully capture the different aspects of craving, and this measurement is subjective. Craving induction paradigm could also be improved by exposure to control neutral cues [54].

To conclude, our study showed that a single treatment session with HF-rTMS over the left DLPFC can decrease cue-induced craving in patients with GD, which might lead to reduced gambling behavior. Large randomized controlled studies with repeated sessions of rTMS are needed to confirm these promising results and to establish the real role of rTMS as a treatment for patients with GD.

Role of the funding source

A local bidding process of Saint-Étienne University Hospital financed the study. The funding source had no role in study design or collection, analysis, and interpretation of data.

Disclosure of interest

The authors declare that they have no competing interest.

Acknowledgements

The authors would like to thank Rosalyn Uhrig, M.A., for her assistance in English-language editing, Pr. Béatrice Trombert-Paviot, for her help in statistical analysis, and acknowledge Drs. Anne Barcet, Agathe Marquet, and Marie Faure for their help in carrying out this study.

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