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.

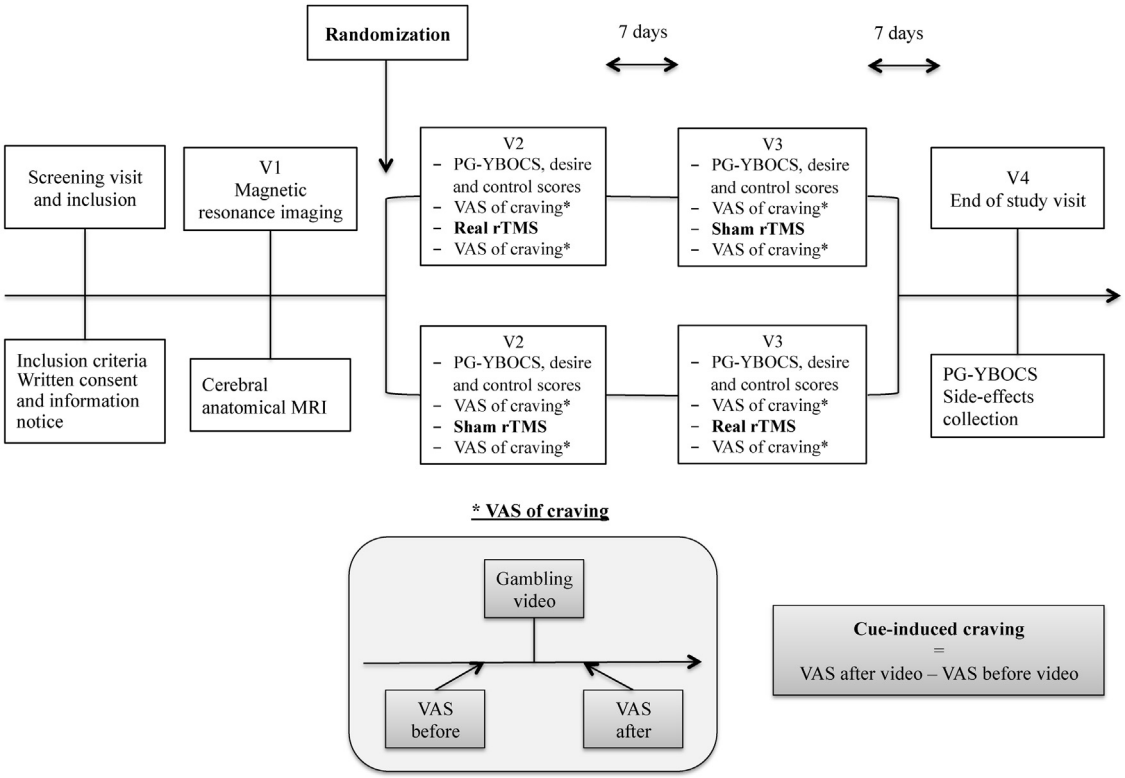

Fig. 1. Study design. MRI, magnetic resonance imaging; PG-YBOCS, Yale-Brown Obsessive Compulsive Scale adapted for pathological gambling; rTMS, repetitive transcranial magnetic stimulation; V1, V2, V3, and V4, Visits 1, 2, 3, and 4; VAS before, VAS after, completion of the visual analogue scale before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