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Research article

Add-on high frequency deep transcranial magnetic stimulation (dTMS) to bilateral prefrontal cortex reduces cocaine craving in patients with cocaine use disorder

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HIGHLIGHTS

- Deep transcranial magnetic stimulation (dTMS) is a noninvasive technique.
- dTMS has shown anticraving properties in patients with alcohol use disorder.
- We tested whether the anticraving effect of dTMS extended to cocaine use disorder.
- We found significantly reduced cocaine craving as long as dTMS sessions lasted.
- The effect of dTMS on cocaine craving should be tested with maintenance sessions.

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ABSTRACT

Introduction: Cocaine dependence is a substantial public health problem. The aim of this study is to evaluate the effect of high frequency deep transcranial magnetic stimulation (dTMS) on craving in patients with cocaine use disorder (CUD).
Methods: Seven men (mean age, 48.71 years; standard deviation [SD], 9.45; range 32–60 years) with CUD and no concurrent axis 1 or 2 disorder save nicotine abuse, underwent three sessions of alternate day 20 Hz dTMS in 20 trains delivered to the dorsolateral prefrontal cortex (DLPFC) preferentially to the left hemisphere, for 12 sessions spread over one month, added to unchanged prior drug treatment. We used a visual analogue scale (VAS) to measure cocaine craving the week before, each week during, and one month after dTMS treatment.
Results: DLPFC stimulation significantly reduced craving over time: within-subjects main effect of time of treatment (ANOVA, $F[3,18] = 46.154$; $p < 0.001$; $\eta^2 = 0.88$). The reduction of craving from baseline was significant at two weeks ($p < 0.001$), and four weeks ($p < 0.001$) of treatment, and at the week eight, four weeks after treatment interruption ($p = 0.003$), although the increase of craving was significant from week four and eight ($p = 0.014$).
Conclusion: dTMS over left DLPFC reduced craving in CUD patients in a small sample that is to be considered preliminary. However, maintenance sessions would be needed to maintain the achieved results. Our findings highlight the potential of noninvasive neuromodulation as a therapeutic tool for cocaine addiction.

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1. Introduction

Cocaine use disorder (CUD) is a medical, psychological and social public health problem associated with risk-taking behavior and unhealthy lifestyle, which in turn increase crime, violence, and neonatal drug exposure [1]. Global annual general population prevalence rates for CUD were 0.3–0.4% in the 15–65 age range [2], but regional differences may exist, with highest rates in the American continent, intermediate in Europe, and lowest in Asia and Australasia [3]. It is estimated that one out of six people who try cocaine at least once will go on to develop cocaine dependence [4]. To face the complex CUD problem, adequate therapeutic measures are basic, but unfortunately, drug treatment showed limited success for opioid [5] and cocaine dependence [6]. Potentially useful nonpharmacological tools in treating drug dependence/drug use disorders include somatic treatments [7–10] and psychotherapy [11], but their value is still not well-defined. However, recent neuroimaging studies have provided insights into the neural networks affected by and involved in drug (ab)use [12,13]. The modulation of these dysfunctional neural circuits through invasive and noninvasive brain stimulation may provide a valuable therapeutic approach.

Relapsing CUD is frequently associated with subjective reports of craving, which usually precede drug seeking and taking. A growing number of studies implicate a distributed, bi-hemispheric neural network in the pathophysiology of craving, involving the nucleus accumbens, the amygdala, the anterior cingulate, the orbitofrontal and the dorsolateral prefrontal cortices (DLPFC) [14]. The DLPFC is involved in reward, motivation and decision making circuits providing the substrate for integration of cognitive and motivationally relevant information and the inhibitory control over seductive options harboring the promise of immediate reward [12,15]. Clinical evidence implicates prefrontal cortex (PFC) hypofunction in the loss of inhibitory control over drug seeking [16–18]. Transcranial magnetic stimulation (TMS) is a noninvasive brain stimulation technique that may target the circuits involved in drug dependence with fewer side-effects/contraindications than medications [19]. Previous studies reported a reduction of nicotine [20] and alcohol craving after cycles of deep transcranial magnetic stimulation (dTMS) over bilateral DLPFC [21–23]. In addition, a single session of repetitive TMS (rTMS) over the right DLPFC significantly reduced cocaine craving, a reduction that persisted four hours after the end of the session [7].

dTMS is a further development of rTMS that does not use the classical figure-of-eight coil, but rather a newly designed coil, called Hesed (H)-coil. The latter enables the stimulator to reach deeper cortical layers, localized at a 6-cm distance from the skull surface, i.e., about 4-4.5 cm deeper than the classical rTMS. As a consequence, the electrical field generated by dTMS was found in a human brain model to be considerably wider than that of rTMS [24], and this was confirmed in a subsequent human study [25]. Given the putative biological substrate of substance use disorders, which involves interactions and connections between the PFC and striate/accumbens [26], it is sensible to hypothesize that dTMS is more likely to benefit CUD than classical rTMS [27].

We aimed to evaluate the effect of high-frequency bilateral DLPFC dTMS with left preference on CUD and on cocaine craving. We predicted that adding on dTMS on ongoing drug treatment would reduce CUD severity and craving for cocaine.

2. Materials and methods

The study was conducted at the Psychiatry Unit of the Sant'Andrea University Hospital, Sapienza University, Rome, Italy.

2.1. Participants

We studied seven right-handed male outpatients (aged 32–60 years) meeting DSM-IV-TR criteria for CUD. Exclusion criteria included other concurrent substance use disorder except nicotine dependence, any psychiatric disorders, specific contraindications to dTMS (history of seizures and carrying a pacemaker); [24] and having received dTMS in the past 12 months. Comorbid psychiatric conditions were ruled out using the SCID interview. All patients were on medications for at least one month, to which they were unresponsive; treatment remained unchanged for the entire duration of the study. Four patients were on oxcarbazepine (average oral dose, 900 mg/day), one on oral aripiprazole (5 mg/day), two patients on oral triazolam (average dose = 0.125 mg/day). Patients were asked to rate their craving on a 10 cm visual analogue scale (VAS) ranging from 0 ("not at all") to 10 ("more than ever"). VASs are used to rate various symptoms, like pain, malaise, and discomfort and have been used to rate drug or alcohol craving [28]. Patients reported their VAS ratings immediately before the first dTMS session, and immediately after the subsequent dTMS sessions.

2.2. dTMS procedure

For dTMS sessions we used Brainsway's H1 coil deep TMS System (Brainsway, Har Hotzvim, Jerusalem, Israel). The H1 coil is designed to elicit neuronal activation in medial and lateral prefrontal regions, including the orbitofrontal cortex, with a preference for the left hemisphere [29]. H1 coils were positioned over patient's scalp. The optimal spot on the scalp for stimulation of the right *abductor pollicis brevis muscle* was located for each patient, and the motor threshold established by delivering single stimulations to the motor cortex. The motor threshold, defined as the lowest stimulation intensity producing five motor evoked potentials (MEPs) of at least 50 μV in 5 of 10 stimulations, was measured by gradually increasing stimulation intensity. Stimulation site was located 5.5 cm anterior to the point at which maximum stimulation of the *abductor pollicis brevis* muscle was reached. dTMS treatment was delivered by expert, trained, certified physicians (CR, SDP, DP, and VRF) in trains of 15 Hz at 100% of the measured motor threshold. Each patient received 20 15-Hz trains per session at 100% of the measured motor threshold, with 2-s duration each and 20 s intertrain intervals, for a total of 720 stimuli per session. Each session lasted a bit less than a quarter of an hour. The complete cycle of the dTMS treatment consisted of three weekly sessions on alternate days for 4 consecutive weeks, for a total of 12 sessions (total number of trains delivered was 240 and total number of pulses 8640). Our current protocol differed from the one we used for alcohol use disorder [21–23], because the patients involved in those studies were comorbid with major depressive or dysthymic disorders and needed the adoption of the classical depression dTMS protocol.

Written informed consent was obtained from all participants. The study endorsed the Principles of Human Rights, as adopted by the World Medical Association at the 18th WMA General Assembly, Helsinki, Finland, June 1964 and subsequently amended by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013. It received approval from the local ethical committee prior to its initiation.

2.3. Statistical analysis

Baseline characteristics of the sample are reported in Table 1. VAS scores were calculated at baseline (T1, before the first session), and at the end of the sessions after two (T2), four (T3), and eight weeks (T4). We performed a One-Sample Kolmogorov-Smirnov Test (*K-S*) that showed a normal distribution of values at each time point. Changes were then analyzed by mixed-model analysis of variance (ANOVA) with time (T1, T2, T3, T4) as

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