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Research Article

15 Hz Repetitive Transcranial Magnetic Stimulation Over the Left Prefrontal Cortex Reduces Cocaine Craving

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Abstract

Background: recent studies support the association between addiction and the progressive alteration of cortical excitability. The dorsolateral prefrontal cortex is involved in regulating drug-seeking behaviour.

Objective: to evaluate the efficacy of 10 daily sessions of 15 Hz-rTMS (or sham TMS) over the left DLPC in the modulation of cocaine craving and consumption.

Methods: 61 patients with Cocaine Addiction were given rTMS, 10 daily sessions at 15 Hz over the left DLPFC parallel (active: n=35) or perpendicular (sham: n=7). Participants were asked to self rate their craving after each TMS session.

Results: Repeated measures ANOVA revealed that craving gradually diminished during sessions of TMS in both groups. However the change was only statistically significant in the real TMS group, with a large change in the seventh session (p= 0.03). No statistically significant difference between active and sham was found in 2-month abstention.

Conclusions: this study suggests that rTMS might be considered a potential therapeutic tool for the treatment of cocaine addiction, particularly in the period immediately following detoxification, in order to interfere with primary craving. A second cycle of rTMS could be useful to interfere with secondary craving.

Keywords: TMS; Addiction; Cocaine; Craving; Neuromodulation

Introduction

Recent studies support the association between addiction and the progressive alteration of cortical excitability, particularly focussing on the effect of chronic assumption of substance of abuse over the prefrontal cortex through the use of both cerebral stimulation and electroencephalographic techniques [1]

In particular, compulsive drug use could be promoted by deficits in prefrontal cortical function and consequential loss of inhibitory control [2-4].

Craving is a great burden for addicted people as they battle with the fear of losing control.

Craving is an uncontrollable impulse to assume abusive substances, often associated with intense anxiety, dysphoria, irritability, agitation, impulsive or explosive behaviours, as well as with somatic symptoms such as headache and asthenia. Craving can be separated into two components: an 'appetitive craving', that is searching for the abusive substance as a source of pleasure, and an 'aversive craving', that is anxiety of abstinence and abstinence itself. Thus, we can take into consideration a primary craving, physical or pharmacological, and a

secondary craving, psychic, which is long-lasting, if not chronic and persistent, related to the desire for the substance as a source of pleasure.

Craving can be triggered by environmental stimuli recalling abuse, or by certain psycho-emotional conditions, or by stressful events. Those affected by addiction are extremely vulnerable, even if abstinent for a long time. Thus, feelings of craving can be triggered by seeing someone taking cocaine or coming back to the place where cocaine was usually taken.

In consideration of all these biological and clinical factors, control of craving must play a key role in a therapeutic addiction project.

A recent study by Waite et al. proposed Neuro-Electro-Adaptive Therapy 12 (NEAT-12) as a putative anti-craving CES device [5].

Other interesting studies revealed that stimulation of the dorsolateral prefrontal cortex reduces cigarette cravings and food cravings [6-8].

An animal study revealed a marked reduction in prelimbic cortex excitability in compulsive drug-seeking rats, and that in vivo optogenetic prelimbic cortex stimulation decreased compulsive drug-seeking behaviours [9]. Thus, targeted stimulation of the prefrontal cortex could serve as a promising therapy for treating compulsive drug use.

rTMS is a safe, non-invasive tool for brain stimulation, able to modulate cortical excitability.

Abundant research has established that an electroencephalogram (EEG) recorded from a drug abuser has a predictable distribution of electrical power. The predictable electrical signals recorded by the EEG, distinctive for each brain region, are regulated by the homeostasis of a complex neuroanatomical brain system that utilizes all known neurotransmitters.

There is currently considerable evidence that all drug abuse, included cocaine, converges on a common circuitry, the reward system [10,11].

Abnormal behaviors involving dopaminergic gene polymorphisms often reflect an insufficiency of usual feelings of satisfaction, or Reward Deficiency Syndrome (RDS). RDS results from a dysfunction in the " brain reward cascade", a complex interaction among neurotransmitters (primarily dopaminergic and opioidergic). Individuals with a familiy history of alcoholism or other addictions may be born with a deficiency in the ability to produce or use these neurotransmitters. Exposure to prolonged periods of stress and alcohol or other substances also can lead to a corruption of the brain reward cascade function. An interesting study by Blum et al. evaluated the potential association of four variants of dopaminergic candidate genes in RDS.

Orbitofrontal cortex and anterior cingulated gyrus are activated during craving [12] and indirectly suppressed during rTMS of the dorsolateral prefrontal cortex.

Application of rTMS directly stimulates 2.5-3 cm of brain tissue below the intact scalp. An interesting PET study demonstrated that the effects of brain stimulation can extend beyond the directly stimulated cortex, through transsynaptic mechanisms, thus also modulating the excitability of subcortical neurons [13]. This line of evidence suggests that stimulation of the dorsolateral prefrontal cortex can induce neuroplasticity in the deep brain reward system.

The dorsolateral prefrontal cortex is involved in the mechanisms that regulated drug-seeking behaviour. The dorsolateral prefrontal cortex plays a key role in the inhibition of controlled response, through connections with the orbitofrontal cortex (OFC) and anterior cingulate cortex. Repetitive stimulation of the dorsolateral prefrontal cortex can promote inhibitory control over the compulsive searching out of abusive substances.

A recent animal study demonstrated that intracranial electrical stimulation (ICES) of the prefrontal cortex reduced drug-seeking behaviour [14].

In consideration of all these evidences we hypothesized that a daily session of rTMS over the left DLPC would reduce cocaine craving and cocaine consumption.

Experimental Procedures

All patients gave written informed consent following a complete description of the study. The study was approved by the Ethical Committee of San Raffaele Hospital, Milan, Italy, and was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice Guidelines. TMS treatment was carried out in the Psychiatric Ward of San Raffaele Hospital Ville Turro, Milan, Italy.

Participants

Inclusion criteria included meeting the DSM-IV criteria for Cocaine Abuse and Dependence, with participants aged between 18 and 65, right-handed, admitted to our ward or our outpatient clinic, who had maintained abstinent for at least three weeks prior.

The exclusion criteria included any clinical condition that would preclude the administration of TMS, according to Wasserman's guidelines [15].

The participants reported that Cocaine was the substance of abuse of their choice. However a history of other drug abuse was not considered as an exclusion criteria.

Participants underwent pharmacological detoxification, through intravenous administration of benzodiazepines, gradually reduced down to suspension.

At the end of detoxification, after at least three days of pharmacological therapy at stable dosages, participants started the TMS protocol. Some of the participants were taking SSRI or SNRI at stable dosages throughout the duration of the protocol.

Urine screening tests performed immediately before the beginning of the TMS protocol were negative for all substance of abuse.

The study included 13 female and 48 male participants. Participants were randomized by computer into two experimental groups (real TMS vs sham TMS).

rTMS procedure

rTMS was administered over the left DLPFC using a figure-8-shaped coil (Magstim Ltd, Whitland, Camarthenshire, UK). The resting motor threshold was determined through visual detection of the contraction of the abductor pollicis brevis muscle following stimulation of the left motor cortex.

Resting motor threshold was established as the lowest stimulus required to induce contraction of the right abductor pollicis brevis muscle at least 5 times out of 10.

The stimulation site was determined 5 cm before the site of stimulation of the abductor pollicis brevis muscle, on the same parasaggital plane.

Each participant underwent a total of 10 daily sessions of TMS over a two-week period. Each session consisted of twenty trains of two seconds at 15 Hz at an intensity of 100% of the individual's motor threshold, with 30-second inter-train intervals. Sham stimulation was identical to the real treatment, except for the orientation of the coil, which was perpendicular to the scalp.

Evaluation of craving

Cocaine craving was evaluated using a clinical evaluation scale of psychopathological symptoms connected with craving (irritability, irascibility, anxiety, dysphoria, aggressiveness, compulsive behaviours, explosive behaviours, cognitive dysfunctions, ideation dysfunctions, mood disorders, use of any other psychoactive drug, sleep disorders, any attempt at avoiding control, hallucinations and images related to cocaine assumption) [16,17]. Every symptom was classified within a range from 0 (absence of the symptom) to 3 (strong presence of the symptom). Participants were asked to self rate their craving immediately after each TMS session.

Statistical analysis

Outcome measures were analysed using the complex designs of two-way analyses of variance (ANOVA): intra-groups and repeated measures; treatment (real vs sham) as between-subject factor and time as a repeated factor. The dependent variable was the particular parameter measured: VAS score and Total Craving Score (resulting from the sum of the score of the individual symptom).

Results

The characteristics of participants

Participants who failed to complete 10 daily sessions of TMS were excluded from the analysis. The drop-out rates after 10 days of treatment were between 12.5% and 18.75% in the different groups (real vs sham).

61 participants, admitted to our ward for Cocaine Abuse and Dependence, completed the 10 daily sessions of TMS. 13 were females (21.31%) and 48 were males (78.69%). The mean age was 35.46 years (SD: ± 8.61).

With regard to their level of education, the mean school years were 11.36 (SD: ± 2.94). 78.69% of the participants were employed. The mean onset for substance abuse was 17.69 (SD: ± 5.52) years old. The mean onset for Cocaine abuse was 18.05 (SD: ± 5.87) years old. The earliest onset was 12. The oldest onset was 35. The ranking of the forms of administration of cocaine were sniffing (98.28% of the participants), smoking (27.12%) and injecting (13.79%). The mean dosage was 5.56 grams (SD: ± 4.77). The lowest dosage was 1 gram. The highest dosage was 22 grams (smoking dosage).

Most of the subjects also assumed other abusive substances in their lifetime (See Table 1).

Demographic characteristics of the participants	%
Substance of abuse	
Alcohol	75.41
Opiates	33.90
Cannabinoids	80.33
Amphetamins	20.69
Drugs	31.03
Ecstasy and MDMA	28.81
Hallucinogens	17.24
Tobacco	98.36

Family History	
First-degree Family History	67.71
Abuse first-degree Family History	31.67
Mood Disorder first-degree Family History	11.67
Anxiety first-degree Family History	31.67
First-degree Family History for other pathologies	8.33
Uncertain First-degree Family History	4.92
Neurologic first-degree Family History	11.67
Comorbidity	
Axis I	47.54
Mood Disorder	4.92
Unipolar Disorder	4.92
Bipolar Disorder	0.00
Panic Disorder	8.20
Generalised Anxiety Disorder	6.56
Post-Traumatic Stress Disorder	1.64
Social Phobia	3.28
Agoraphobia	3.28
Anxiety Disorder	18.03
Somatoform Disorder	1.64
Dismorfophobia	1.64
Obsessive-Compulsive Disorder	8.20
Induced Psychosis	21.31
Tics Disorder	4.92
Adjustment Disorder	8.20
Eating Disorder	8.20
Impulse Control Disorder	16.39
Sleep Disorder	67.24
Axis II	90.16
Cluster A	13.11
Paranoid Personality Disorder	11.48
Schizoid Personality Disorder	1.64
Schizotypal Personality Disorder	0.00
Cluster B	86.89
Antisocial Personality Disorder	34.43
Borderline Personality Disorder	42.62
Histrionic Personality Disorder	19.47
Narcissistic Personality Disorder	60.66
Cluster C	13.11
Avoidant Personality Disorder	3.28
Dependent Personality Disorder	8.20
Obsessive-Compulsive Personality Disorder	1.64
NOS Personality Disorder	1.67
Axis III	33.33
Pharmacological therapy assumption	11.86
Cognitive Deficits	40.68
ADHD in Infancy	10.00
Drugs during detoxification	
Benzodiazepines	82.76
Neuroleptics	35.09
SSRI	63.16
TCA	3.45
NSRI	7.02
Antiepileptics	29.82
Antihistaminics	72.41
Other drugs	17.24

In table 1 we summarized data related to the presence of any other psychiatric symptom, besides Cocaine Abuse and Dependence, and data related to psychiatric and neurologic family history.

Furthermore, a number of the subjects had experienced issues of a legal nature at least once in their life. In particular: crimes: 52.73%; fights: 22.41%; debts: 40.68%; prison: 6.90%; car accidents: 36.21%. 33.90% of the participants had lived in a therapeutic community before.

Table 1 summarises all the drugs used during detoxification.

35 participants (57.38%) underwent real transcranial magnetic stimulation, 26 participants (42.62%) underwent sham stimulation.

63.93% of the subjects were still abstinent 2 months after discharge (39 out of 61). 21 participants relapsed before 2 months after discharge. A 2-month follow up is unknown for one participant only.

Comparative Analysis: real TMS vs sham TMS

We made comparative analyses between the two different subgroups (real TMS vs sham TMS).

The two subgroups are homogenous for the variables considered in the study.

Cocaine Craving Evaluation

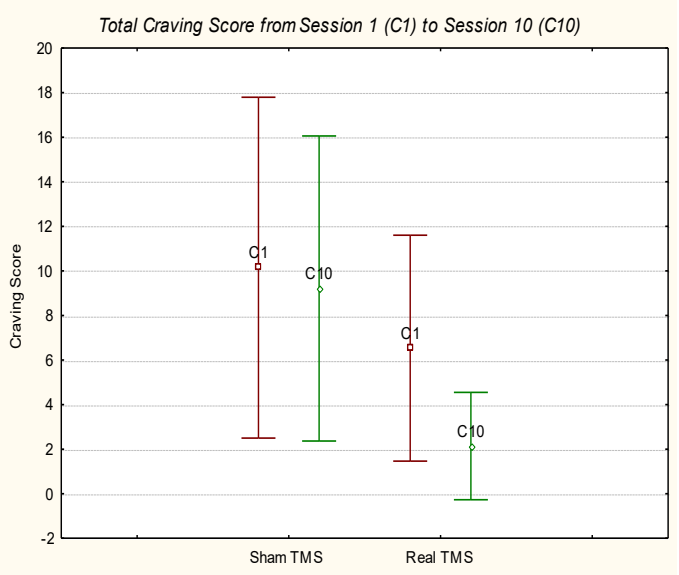
All participants tolerated transcranial magnetic stimulation well and didn't display any side effects or complications, except for transient headaches and slight pain in the scalp at the site of stimulation, which disappeared spontaneously at the end of the session.

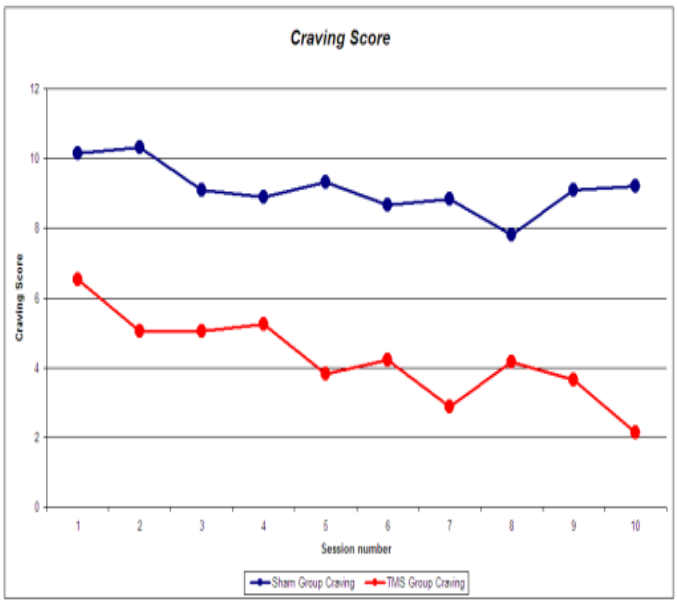
Table 2 describes the mean Craving Total Scores for each subgroup for each day of stimulation.

	Real TMS	**Sham TMS**
	Mean ± SD	Mean ± SD
Craving Total Scores		
Session 1	6.53 ± 5.34	10.15 ± 8.05
Session 2	5.03 ± 4.46	10.31 ± 8.60
Session 3	5.03 ± 5.48	9.10 ± 8.56
Session 4	5.24 ± 6.44	8.90 ± 8.72
Session 5	3.83 ± 3.65	9.31 ± 9.06
Session 6	4.23 ± 4.45	8.67 ± 7.18
Session 7	2.88 ± 3.18	8.85 ± 8.05
Session 8	4.15 ± 5.18	7.81 ± 7.15
Session 9	3.64 ± 4.48	9.08 ± 5.87
Session 10	2.13 ± 2.54	9.21 ± 7.21

Repeated measures analyses of variance (ANOVA) revealed that Cocaine craving gradually diminished during sessions of TMS, both in the real TMS group and in the sham TMS group. However change was only statistically significant in the real TMS group, with a large change in the seventh session (p value 0.03) (Table 3). The reduction of the craving total score observed in the sham group could be attributed to a placebo effect or to the physiological decrease of craving during hospitalization. However, T-test between Total Craving Score Session 1 and Total Craving Score Session 10 in both subgroups revealed a statistically significant difference only in the Real TMS subgroup (Table 3). Figure 1 shows Total Craving Score variation from Session 1 to Session 10 in both subgroups. Figure 2 shows the difference between the two subgroups.

	Craving Total Scores Variation	**p value**
Real TMS		
	Session 1→10	**0.000277**
	Session 1→2	0.09
	Session 2→3	1.00
	Session 3→4	0.85
	Session 4→5	0.16
	Session 5→6	0.73
	Session 6→7	**0.03**
	Session 7→8	0.14
	Session 8→9	0.42
	Session 9→10	**0.05**
Sham TMS		
	Session 1→10	0.4023
	Session 1→2	0.81
	Session 2→3	0.10
	Session 3→4	0.83
	Session 4→5	0.69
	Session 5→6	0.52
	Session 6→7	0.87
	Session 7→8	0.27
	Session 8→9	0.69
	Session 9→10	0.45





Follow up

We considered a 2-month abstention as a follow up variable.

63.93% of the subjects were still abstinent 2 months after discharge (39 out of 61). 21 participants relapsed within the 2 months after discharge. A 2-month follow up was unknown for one participant only.

74.29% of the subjects in the Real TMS group were still abstinent 2 months after discharge. 51.92% of the subjects in the Sham TMS group were still abstinent 2 months after discharge.

No statistically significant difference was found between the Real TMS and the Sham TMS groups (p value 0.07).

Discussion

This is the first evidence that sessions of rTMS on the left DLPFC could modulate cocaine craving.

In particular, our results suggest that a certain number of impulses are necessary to achieve a significant reduction (seven sessions, 4200 impulses).

Craving Total Score also diminished through the sessions in the Sham group, but the reduction never achieved statistical significance. This result suggests a possible placebo effect.

Our results are in line with other recent studies which proved that high-frequency stimulation of the dorsolateral prefrontal cortex can modulate nicotine craving [6] and food craving [7,8].

On the other side, two recent studies proved that stimulation of the right, and not of the left, dorsolateral prefrontal cortex reduces cocaine craving [18] and alcohol craving [19]. Our results don't contrast with these studies as they different stimulation parameters were used (110% resting motor threshold instead of 100%, 10 Hz instead of 15 Hz, 10s for each train instead of 2s). Furthermore, it was hypothesized that high-frequency rTMS over the right DLPFC could produce transsynaptic inhibition of the left DLPFC via transcallosal connections [20].

The rationale for the parameters used in our study comes from a prior open-label study published in 2008 [].

In our study the Real TMS group and the Sham group don't show statistically significant difference during a 2-month period of abstention, suggesting a transient positive effect of rTMS.

Our results suggest the importance of the application of rTMS in the period immediately following detoxification in order to interfere with primary craving with the suggestion of undergoing a second cycle of rTMS at a subsequent time in order to interfere with secondary craving/appetitive craving.

Our study also presents a number of limits. First of all, it is single-blind and not double-blind, which could result in bias during psychopathological evaluation. Secondly, the site of stimulation was determined with the '5-cm rule' and not with neuronavigation, which determines the exact site of stimulation for every single patient. Further studies using neuronavigation are required to validate our results.

In conclusion, Transcranial Magnetic Stimulation, applied with the parameters described in our study, might be considered a potential therapeutic tool for the treatment of Cocaine Abuse and Dependence.

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Declaration of interest

None.

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