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HOW TRANSCRANIAL MAGNETIC STIMULATION REDUCES COCAINE CRAVING

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Sommario

Introduction

Cocaine addiction is a disorder that affects millions of people around the world. In spite of respectable progresses in understanding the neural foundations of addiction disorders in general, to this day therapeutic options remain limited. Recent studies have called attention to the potential of transcranial magnetic stimulation (TMS) as a modern, safe and relatively cost effective treatment for some addiction disorders, particularly cocaine dependence.

Chapter 1 Addiction

1.1 Addiction

Addiction is usually defined as a condition that is manifested by compulsive substance use despite harmful consequences. More specifically, a behavior that is thought to produce pleasure and reduce negative effects is repeatedly put in place and it's characterized by both recurrent failure to control the behavior and continuation of the behavior despite adverse consequences. Compulsivity and impulsivity are highly involved in the addiction cycle, which can be organized in three different stages: binge/intoxication, withdrawal/anticipation and preoccupation/anticipation, commonly known as the craving stage:

- Binge/Intoxication: the stage at which an individual consumes an intoxicating substance and experiences its rewarding or pleasurable effects;
- Withdrawal/Negative Affect: the stage at which an individual experiences a negative emotional state in the absences of the substance;
- Preoccupation/ Anticipation: the stage at which one of seeks substances again after a period of abstinence. (Nestler, Luscher, 2019)

1.2 Drug addiction

Drug addiction is a disorder described on the basis of behavioral abnormalities such as loss of control over drug intake and compulsive drug taking regardless of damaging repercussions. These behavioral abnormalities develop gradually over time after repeated exposures to a substance of abuse and can endure for months or years after discontinuation of substance use.

It is important to understand how addictive drugs act on the brain at first and how, with repeated exposure, produce long lasting changes that drive the compulsive behavior that defines addiction. (Nestler, 2004)

Reiterated exposure to a drug of abuse alters the activity of individual neurons and the strength of their synaptic contacts in the brain's reward system, a group of structures that are activated by rewarding or reinforcing stimuli, such as food, sex, monetary gain or drugs. It regulates responses to emotional stimuli, motivation to organize and consume rewards, executive control over that consumption and models future behavior through learning and memory related functions. (Nestler, Luscher, 2019)

Addictive drugs act on the brain by increasing dopaminergic signaling from the ventral tegmental area (VTA), one of the main dopamine producing area in the brain, through the mesolimbic dopamine pathway to the nucleus accumbens (NAc), an area located in the ventral striatum that is strongly linked to motivation and reward. [1]

This enhancement in dopamine release is implied in coding rewards not for reward specifically, but for saliency, which includes aversive, novel and unexpected stimuli. It is also thought that dopamine encodes for the motivation to procure the reward rather than the reward itself. These views about the role of DA in reinforcement imply that drugs are

[1] https://www.youtube.com/watch?v=f7E0mTJQ2KM

reinforcing not just because they are pleasurable but because by increasing DA they are being processed as salient stimuli that will innatively motivate further purchasing of more drug (regardless of whether the drug is consciously perceived as pleasurable or not) and will facilitate conditioned learning. Cocaine in particular, on which this review will focus on, is considered one of the most reinforcing substances of abuse. It acts by blocking DA transport molecules (DAT) responsible for dopamine disposal, causing it to remain for a longer period of time in the midbrain areas of NAc and VTA. (Nestler, Luscher, 2019)

1.3 CRAVING

The first factor to be targeted in the treatment of cocaine addiction is craving.

Craving is one of the most remarkable symptoms of addiction, as enunciated by the addiction cycle initially mentioned. It is taken into consideration these days to the extent that is catalogued as one of the diagnostic criteria in the category “Addiction and Related Disorders”. Craving is explained as a pressing, urgent and irrepressible desire to surrender to the addictive behavior and usually results in loss of control. Besides the mere desire to take a drug, it also comprises the expectation of positive effects and the relief of negative effects as a consequence of this action, and despite long periods of abstinence, craving can manifest again and rise the likelihood of relapse.

According to some studies, craving is rooted by activation of the reward and motivation circuits. The principal neural structures implicated are: the nucleus accumbens, dorsal striatum, orbitofrontal cortex, anterior cingulate cortex, dorsolateral prefrontal cortex (DLPFC), amygdala, hippocampus and insula. Even though the left DLPFC looks to play a role in increasing self-control over cravings, the right DLPFC may be involved in the inhibitory control of affective impulses. However, since there is no empirical evidence for hemispheric differences in DLPFC in addiction, it is hard to define conclusions. (Grall-Bronnec, Sauvaget, 2014)

Addiction disorders share a large variety of features, including the therapeutic approaches, which are usually based on psychotherapy and specifically on pharmacotherapy. Regrettably, to these days, no efficient pharmacotherapeutic method has been found. Due to this, in the recent years, new treatment modalities, such as transcranial magnetic stimulation, have been investigated. (Grall- Bronnec, Sauvaget, 2014)

Chapter 2 TMS

2.1 TMS

Transcranial magnetic stimulation (TMS) is a non-invasive brain stimulation technique utilized for the first time by Barker in 1985 and is a therapeutic implement that allows to modulate cerebral plasticity outside the skull. Its functioning is based on the electromagnetic induction principle of Faraday which states that energy can be transformed into magnetic fields, and those fields can be transformed into electric energy.

Hence, electric field pulses are delivered into the brain. Magnetic fields, generated with a coil positioned over the scalp, move past through the electrically insulated skull, enabling magnetic stimuli to produce strong and moderately spatially focal intracranial currents in the underlying brain tissue.

TMS application method may vary according to the researcher or the clinician purpose. There are three relevant modalities: simple transcranial magnetic stimulation (sTMS), which delivers a single magnetic pulse over the brain cortex, coupled pulse transcranial magnetic stimulation (cTMS), which delivers two magnetic pulses separated by a variable time interval, and repetitive transcranial magnetic stimulation (rTMS) which exerts its effects through a regular magnetic pulse train. (Zorzo, et al, 2019)

Depending on the anatomical loci and parameters, TMS may induce short or long term, facilitative or suppressive, neuronal and behavioral effects. The terms facilitation and suppression explain whether the TMS sequence increases or reduces motor evoked ptentials (MEPs) during stimulation of the primary motor cortex; the effects outside the motor cortex are not completely understood. (Diana, et al, 2017)

Before selecting a stimulation parameter, the professional has to measure the patient’s motor activation threshold to make sure that TMS treatments are performed below that threshold. Resting motor activation threshold (RMT) is the minimum necessary intensity required in order to generate an evoked potential (EP) in a target resting muscle.

Expressing stimulation intensity as RMT is crucial given the existence of interindividual variety of resting cortical excitability.

The aim of TMS is to produce relatively small changes in the membrane potential that modulate intrinsic neuronal excitability without directly producing action potentials and these changes should generate lasting and constant alterations in the neurons.

The apparatus involves a complex electric system (Figure 1) that would be able of making thousands of amperes flow in milliseconds towards a stimulation coil which, sequentially, will generate a magnetic field (Figure 2). Specifically, a central unit is required to designate the amount of current and to synchronize its delivering, capacitors that accumulate electric charge, wiring, and a stimulation coil that could vary. (Zorzo, et al, 2019)

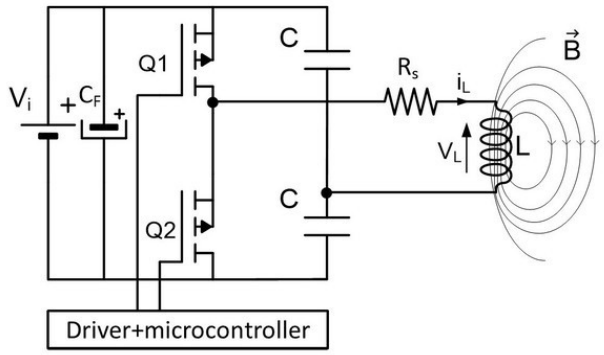

Figura 1 *Schematic diagram of the electric system that feeds the coil in a magnetic stimulator. L is the emission point. (Zorzo, et al, 2019)*

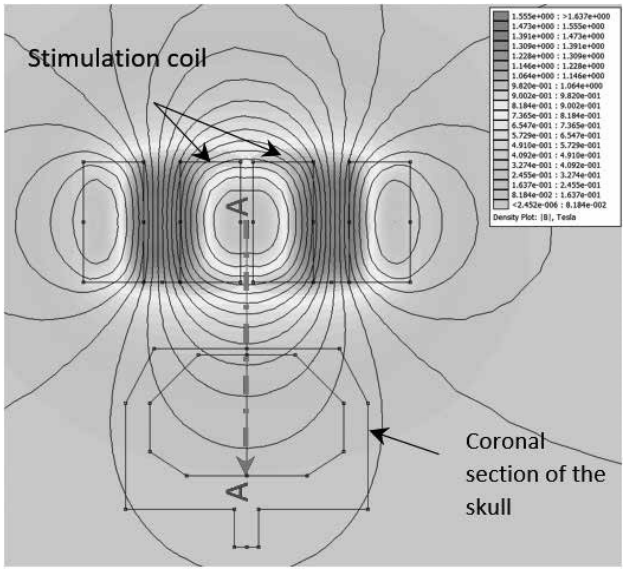

Figura 2 1 Theoretical distribution of induced magnetic fields by a stimulation coil. Line A-A indicates the penetration power that allows it to penetrate skull and encephalon. (Zorzo, et al, 2019)

The geometry of the coil will determine the intensity, stimulus penetration, and stimulated area focality. Hence, circular coils would stimulate broad brain cortex regions, while eight-shaped coils may be more focused. These differences are due to the coils' configuration – in the eight shaped one, it is two joined circular coils- which allows each coil to transport the current in opposite directions, producing an electric field sum where they join. Thus, stimulation focality depends on the coil diameter, and it is more focal when the diameter is low. The extension of cortical activation depends on a variety of factors, like coil shape, pulse-generated wave and, naturally, the coils' position over the skull and stimulation intensity as well. (Zorzo, et al, 2019)

Ultimately, the parameters used will determine the results obtained in TMS treatment of psychiatric disorders. Therefore, it is essential to suit the frequency, intensity, pulse number, time interval between trials, and session number. Stimulation frequency oscillates between 1 and 60 Hz, but the most frequently used range from 1 to 10 Hz, according to the professional's goal. Pulse intensity is very variable, usually in a range between 1 and 2 Teslas (T). Regarding TMS pulse number, these could vary from 15 to 2400. Time interval

between trials is also variable, the most frequently used intervals range between 10 and 30 s. Finally, the number of required sessions depends on the medical condition, its severity in clinical practice and on the experimental goals in cognitive neuroscience. (Zorzo, et al, 2019)

2.1 rTMS

Repetitive TMS modifies the excitability of stimulated cortex and interconnected brain regions, and these effects endure even after the period of stimulation.

Repetitive TMS (rTMS) is used to induce long lasting modifications, facilitation or inhibition. In this technique, trains of several pulses are delivered through several stimulation patterns. It repeatedly stimulates the scalp on the same point at a frequency which ranges from 1 to 20 Hz or more. The parameters are its intensity, frequency, length of trains of pulses, and time interval between trains. The results of rTMS are longer than TMS single pulse. These long-term alterations in the functioning of the cortex produce effects that lead to inhibition or facilitation, depending on the frequency of stimulation,

The effect of rTMS on dopaminergic neurotransmission and cortical excitability shows that this technique can be used in the study and treatment of multiple neuropsychiatric disorders related to abnormal dopamine activity and modified cortical excitability, such as depression, obsessive-compulsive disorder, schizophrenia, and drug addiction . (Bellamoli, et al, 2014)

High frequency stimulation (>5 Hz) is thought to have excitatory effects on the cortical activities, whereas low frequency stimulation (<1 Hz) is thought to have inhibitory effects. (Bolloni, et al, 2018). Given their deep brain localization, dopaminergic neurons are indirectly stimulated during rTMS, through their superficial projections, particularly the DLPFC, which is implicated in cognitive control and the physiopathology of impulse control disorders, such as addiction disorders. rTMS on the DLPFC may thus indirectly modulate

dopaminergic pathways, and therefore have an impact on symptoms of addiction, by reducing craving as we will see in the next paragraph. (Diana, et al, 2017)

2.3 rTMS and Cocaine

Camprodon and colleagues conducted a preliminary study to investigate rTMS as a potential treatment for the craving experienced by cocaine addicted individuals. They examined whether a single session of rTMS over DLPFC could reduce cocaine craving among six male participants suffering from cocaine addiction. Secondary assessment criteria were changes in anxiety, happiness, sadness, and unspecified discomfort. The participants concluded a medically assisted withdrawal program whose length was not defined and did not depend on other substances. Participants were delivered two sessions of high frequency (10Hz) rTMS at 90% of motor threshold MT, one to the right and one to the left DLPFC, with a week break between the two sessions. Each session consisted of 20 trains lasting 10s, followed by 1 minute pauses. Participants were asked to complete a set of 15 visual analogue scales (VAS) ranging from “not at all” to “more than ever.” Each VAS assessed one of the primary or secondary assessment criteria on three occasions: 10 minutes before the intervention, immediately after and 4 hours after rTMS session.

The authors discovered that a single session of high frequency rTMS to the right DLPFC, but not to the left DLPFC, decreased level of craving for cocaine. This is a transient effect that resolves within 4 h after stimulation, in fact, there are not significant differences regarding craving between pre TMS time and 4 hours after.

Anxiety significantly decreased after right- sided stimulation. Happiness was increased after right-sided and sadness after left-sided stimulation. Discomfort was increased equally by left- and right-sided stimulation.

This research demonstrated for the first time that high frequency rTMS delivered over the right DLPFC is effective in reducing craving associated with chronic use of cocaine. (Camprodon et al, 2007)

Also Politi et al. (2008) studied the effects of rTMS over the DLPFC on cocaine cravings among 36 cocaine-dependent participants studied after detoxification therapy, which lasted an unknown amount of time. Ten daily sessions of high frequency (15 Hz) rTMS over the left DLPFC at 100% of MT were administered, each one consisting of 20 trains of 2 seconds separated by a 30 seconds break. The participants underwent daily clinical assessment of symptoms associated with cocaine craving. These authors discovered that the daily sessions of high frequency rTMS of the left DLPFC reduced cocaine craving. Cocaine cravings reduced slowly but consistently throughout the sessions (Politi, et al, 2008).

As in the previous study, a control group was not present and the researchers evaluated the TMS effects through the VAS, and found out that craving was reduced. Despite the different paradigm applied, these two studies suggest that rTMS reduces cocaine craving. Moreover, they demonstrated the central role of DLPFC in modulating craving.

Terraneo et al (2016) examined the effects of rTMS on cocaine intake by delivering it over the left DLPFC, and depressive symptoms as secondary outcomes. Before the experiment, all participants tested positive for cocaine intake via urine drug test. They used a figure-of-eight coil (as per Camprodon, et al., 2007 and Politi, et al., 2008) to administer the treatment, which consisted of eight sessions of rTMS at 15 Hz frequency and 100% MT, 60 pulses per train, and 40 stimulation trains, with 15 seconds of inter- stimulus interval. The study was divided in two stages and, unlike the previous experiments, the researchers included a control group. A total of 32 cocaine addicts were randomly assigned to the experimental group (rTMS over left DLPFC) or the control group over a period of 29 days. The rTMS treatment was applied everyday for the first 5 days, and once

a week for the following 3 weeks. At the end of stage 1, the participants could choose whether to continue in the same group or switch to the other. During stage 2, participants belonging to control group in stage 1 received the same protocol of stimulation applied in the rTMS experimental group. At the end of stage 1, 16 patients (100%) concluded the treatment in the rTMS group, while 13 patients (81%) completed the pharmacological treatment in the control group. The authors analyzed the urine drug tests in the two groups at the end of stage 1, and found a higher number of cocaine-free urine samples in the rTMS group. Regarding the craving VAS, the scores were lower in the experimental group as well. The ten subjects that switched to the rTMS group in stage 2 showed significant improvement with favorable outcomes comparable to those of the rTMS group. No differences were found in secondary outcomes. An important aspect of the Terraneo et al study is the direct comparison between rTMS-treated patients and pharmacological treatment patients, since rTMS appeared to be more effective.

Rapinesi et al administered 12 sessions of rTMS through the H-coil to seven cocaine addicts, three times a week alternately over the course of 4 weeks. It was not specified whether they were still dependent on cocaine or not. Bilateral rTMS was delivered at high frequency (15 Hz) and 100% MT in 20 trains with 2 seconds break between the stimuli for a total of 8,640 pulses (720 pulses/session). They measured cocaine craving with VAS as an outcome assessed the week before, each week during the treatment and 1 month after rTMS. At the end of the study, the researchers found a significant craving reduction from baseline to 2 weeks and 4 weeks and from baseline to 1 month later. From week 4 to week 8 though, craving was significantly increased. This study gave the first evidence of medium-term effect (baseline to 1 month after treatment) of bilateral rTMS on the DLPFC as a whole in cocaine craving. However, factors such as the small sample and absence of a control group did not allow the authors to make any definitive conclusion.

Table 1

Studies that have implemented TMS in the treatment of cocaine users

	n	TMS device parameters	Target Area	Control group	Assessment	Results
Terraneo	32	rTMS (8coil), 8 sessions, 40 trains, 15 Hz 100% MT, 2400 pulses	DLPFC, left	Pharm	Urine craving	More cocaine-free urine samples in rTMS group
Rapinesi	7	rTMS (H coil), 12 sessions, 20 trains, 20 Hz, 100% MT 720 pulses	DLPFC, bilateral	No	Craving (vas)	Reduction in craving
Politi	36	rTMS, (8coil) 10 sessions 20 trains 15 Hz, 100% MT, 600 pulses	DLPFC, left	No	Craving (vas)	Reduction in craving
Camprodon	6	rTMS, 2 sessions, 20 trains 10 Hz, 90% MT, 2000 pulses	DLPFC, right and left	No	Craving (VAS)	Reduction in craving with right rTMS

CONCLUSIONS

The results of rTMS sessions on cocaine craving give confirmation and support for future TMS studies on addiction treatment. The studies analyzed in this review have some methodological limitations: they were mainly exploratory and used fairly small sample sizes. Future research should recognize the optimal parameters (appropriate target, intensity, frequency and length) of rTMS stimulation to provide the safest and most efficient treatment of drug addiction disorders. In terms of stimulation paradigms, studies differed in both coil employed and parameters adopted. The majority of rTMS studies in cocaine use disorder (CUD) utilized the figure-of-8 coil to target the DLPFC (left side), a central node in the frontostriatal network whose activity is inhibited in addiction disorders. Cortical dysfunction may account for the impaired executive control that is required to resist drug-related stimuli and cease drug-seeking behavior. For this reason, papers reviewed here aimed at prefrontal brain regions, in order to enhance cortical activity, improve behavioral control, and through this inhibit drug intake. From a neurobiological perspective, the clinical beneficial effects of TMS over DLPFC are supported by the evidence, which demonstrated the increase of dopaminergic activity in the NA, which is depressed in addiction.

Further studies are needed, and should employ standard methodological procedures to find the exact location of targeted areas to improve efficacy of stimulation, consider subjective (craving) measurements in relation to neurophysiologic substrates to have a more complete and deep understanding of the neuropathology, and consider timeline follow-up to assess the lasting nature of neural changes induced by rTMS carefully.

For this reason, studies with multiple rTMS sessions in larger, sham controlled and randomized groups are needed.

The absence of a control group in the majority of these studies does not allow to investigate deeply a possible placebo effect, so it is difficult to derive the real effect of rTMS treatment. (Bellamoli, et al, 2014)

It is to take into account that none of the studies carried on to this day demonstrated complete abstinence from drug use and the period of rTMS to maintain the achievements produces is required to be examined with longer follow up studies.

Therefore, it could be useful to undertake studies that measure psychological variables, to reach a more complete assessment of the treatment effects. However, results appear to be encouraging and foster future investigations, since there is no FDA approved pharmacotherapy to date, and behavioral approaches to cocaine use disorder have had limited success. (Diana, et al, 2017).

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