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Transcranial Magnetic Stimulation to treat Substance Use Disorders and Behavioral addictions: the state of the art

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Summary

Objectives. Substance Use Disorders (SUDs) are characterized by a high health and social impact, care burden, and frequent negative outcomes, especially due to the few pharmacological treatments available, the high relapse rate and poor pharmacological compliance. In this scenario, TMS is increasingly being studied as a tool to treat the neurbiological dysregulations underlying SUDs in an innovative way. The aim of this non-systematic review is to analyze the main and most significant applications of Transcranial Magnetic Stimulation in the field of addiction.
Materials and methods. A PubMed search was conducted using the keywords: "Transcranial Magnetic Stimulation; and Substance Use Disorder; Behavioural Addiction" in December 2020. Only original article written in English dealing with the treatment of cocaine, opioids, alcohol, cannabis and gambling disorder were included.
Results. Three hundred and thirty-four article were found. Based on the current evidence, rTMS can be classified as probably effective in the treatment of addiction, with promising effect size for high frequency rTMS stimulation protocol of the DLPFC mainly in cocaine/stimulant use disorders, and with some noteworthy pilot data in the area of gambling disorder. Double-blind, sham-controlled study design are mostly needed in order to confirm these potential benefits.
Conclusions. Future research should identify potential parameters (i.e., duration, number of stimulation treatments, stimulation frequency, intensity, brain region of target) of stimulation in rTMS studies for the most effective and safe treatment of drug addiction. The personalization of rTMS treatments, as well as the optimization of stimulation protocols, are the main issues that will involve future research in this area.

Key word: Transcranial Magnetic Stimulation, Substance Use Disorders, Behavioral addictions

Introduction

Substances use disorder (SUD) is defined, in the DMS-5, as "*a cluster of cognitive, behavioral, and physiological symptoms indicating that the individual continues using the substance despite significant substance-related problems*" [1]. In clinical practice it could be described as a chronic pathology with frequent relapses, compulsive seeking behavior, presence of a negative emotional state (e.g., dysphoria, anxiety, irritability, anhedonia) and loss of the ability to control the assumption [2]. This aspect in particular

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highlight a dopaminergic dysregulation in specific neural circuits [3]. A key role in the addiction cycle is played by the prefrontal cortex (PFC), involved in learning reinforcement and craving [4]. The function of PFC was deeply studied in preclinical works: a specific lesion of PFC carry to a loss of the inhibitory control, one of the main domain involved in substances seeking behaviors 5. Above the function of the PFC itself, all the dopaminergic system is primary involved in the anticipation and reward motivation [6]. Studies using positron emission tomography have shown that patients with SUD have a reduced number of striatal D2 receptors and a lower dopamine release than the general population [7]. This dopaminergic dysregulation is at the base of the "*incentive awareness theory*": a greater reactivity of the mesolimbic system is linked with drug addiction and craving 8. All these neuronal imbalance are reinforced by chronic use of the substance, which leads to dysfunctional synaptic and receptor adaptation [2].

One of the main concerns of clinicians about SUD is their treatment: very often there are only symptomatic drugs or substitutive therapy, with limited efficacy as demonstrated by high long-term relapse rates [9]. Nowadays, one of the most promising (and most investigated) therapy is Transcranial Magnetic Stimulation (TMS). The TMS protocols provide the administration of magnetic impulses generated by the passage of the electric current inside a copper coil. The intensity (measured by a percentage of the resting motor threshold; RMT) and frequency of the magnetic pulse, as well as the duration of the protocol, the target area and the shape of the coil used are the main parameters that characterize the different TMS treatments [10]. The protocols delivering several pulse trains (repetitive TMS; rTMS) in few minutes of stimulation are the most used worldwide [11]. TMS has already been approved for the treatment of resistant depression [12] using an high-frequency protocol (10 Hz) with 75 trains (40 pulses per train) stimulating at 120% of RMT the LDLPFC for about 19 minutes. Always in psychiatric field, deep TMS stimulation of anterior cingulate cortex was approved for obsessive-compulsive disorder with a 20 Hz protocol with 50 trains (2 sec duration) at 100% of RMT for a total of 2000 pulses administrated per session [13]. TMS stimulation was also approved by FDA for the treatment of headache with aura [14].

The rationale for rTMS in SUDs and other behavioral addictions has its roots in preclinical studies. A work conducted by Chen and coll. on 2013 [15], highlighted that the optogenetic stimulation of PFC in rats could reverse cocaine-induced prefrontal hypofunction, and blocked drug-seeking behaviors [16,17] in compulsive cocaine-seeking rats. The PFC of rats has its homologous in the dorsolateral prefrontal cortex (DLPFC) in humans [18]. Despite consensus on this matter is still missing, due to the relevant large anatomical diversity between the rodent and the human frontal/anterior cortices, this parallelism provides a first rationale of the non-invasive stimulation of this area with TMS procedures. Another reason for targeting the DLPFC is based also on the key role that this brain region plays in decision making processes [19]. Addiction is associated with increased impulsivity and impaired risky decision-making [20]. These decision-making processes in addiction can be modulated by rTMS on the DLPFC enhancing inhibitory control, which may lead to a reduction in the use of substances. Therefore, the stimulation of the DLPFC by high frequency pulses should increase its activity and its inhibitory control function. In particular, with drug-addicted subjects, this treatment should increase DLPFC function implementing the possibility to control craving and to cope it.

A further aspect to consider is that targeting prefrontal areas via TMS also affects dopaminergic neurotransmission. Strafella and coll. [21] found that high frequency rTMS on the prefrontal cortex in humans induces subcortical release of dopamine in caudate nucleus, whereas Cho and Strafella [22] showed that rTMS over the left DLPFC modulates the release of dopamine in anterior cingulated cortex and orbitofrontal cortex in the same hemisphere.

Finally, rTMS could also exert their effects modulating the expression of neurotrophic factors, such as BDNF, an active regulator of synaptic plasticity, within cortical and subcortical areas (Cirillo, Di Pino et al., 2017). More recently, non-synaptic events have been suggested as mediators of rTMS long-term effects, including plasticity-related gene expression and neurogenesis [23,24].

Given these evidences in the scientific literature, the aim of this work is to analyze the main and most significant applications of TMS in the field of addiction.

Materials and methods

A PubMed search was conducted using the keywords: "*Transcranial Magnetic Stimulation;Substance Use Disorder; Behavioural Addiction"*. No temporal criteria were applied. The research, conducted on December 2020, yielded 384 useful results. The most significative articles, written in English, concerning the treatment with TMS of the main substances of abuse (cocaine, opioids, alcohol, cannabis) were therefore selected. All non-original articles (such as reviews) were excluded from this non-systematic selection.

Results

Cocaine Use Disorder

Chronic cocaine use is among the most difficult substance-use disorders to treat. Nearly 1 in every 7 people seeking treatment for drug abuse is dependent upon cocaine (Abuse N.I.O.D, 2010) and short-term cocaine relapse rates can reach 75% [25]. Advances in understanding the neurobiological underpinnings of cocaine use disorders have unraveled that chronic cocaine use causes damage and changes in the PFC [26], including significant

brain volume reduction [27,28], cortical hypoactivity [5,29,30], impairment in executive functions, and dysregulation of neurotransmitters systems [31-33]. Thus, targeting the PFC via TMS appears to be a promising intervention. An open label study with a sample of 36 subjects, analysed the effect of high-frequency TMS (15 Hz) on the LDLPFC with a low number of pulse (600 pulses; 100% RMT) per session. This study lead to a significative reduction in intensity of craving for cocaine [34]. However, one of the first studies strongly highlighting these evidences is the one conducted by Terraneo and collaborators. In this work the LDLPFC was stimulated with rTMS (15 Hz, 2400 pulses / session, 40 trains of 60 pulses each) for two consecutive weeks. This treatment lead to an improvement in cocaine assumption (traceable on urine control tests) and craving [35]. In more recent time, the works of Zhang and coll. [36] and Pettorruso and coll. [37] offered more evidences on the efficacy of TMS to treat CUD. In the last of these studies, nine of sixteen patient stimulated with the same parameter of Terraneo and coll. [35] did not report any cocaine assumption after 4 treatment weeks. Also other psychiatric dimensions (depressive symptoms, anhedonia, and anxiety) improved after TMS stimulation.
The stimulation of right DLPFC (RDLPFC) was investigated in a study conducted in 2007 by Camprodon and coll. [38]. This randomized crossover trial offered a first insight on the efficacy of the RDLPFC stimulation (10 Hz; 90% RMT) with a population of six male patient underwent two session of rTMS, one per week. In addition to the craving for the substance as assessed with the VAS scale, other variables (e.g. anxiety, happiness, sadness) were also evaluated

Opioid Use Disorder

Recent increases in opioid addiction, opioid-related morbidity, and opioid-related mortality have been reported in both USA and Europe. While the number of opioid prescriptions doubled in Europe during the last 10 years, nowadays every day 130 patients die from an overdose of prescription opioids each day in USA [39]. Treatment for opioid use disorder typically requires acute detoxification and/or opioid maintenance treatment. The two primary treatments for opioid use disorder (methadone, buprenorphine) are designed for long term opioid maintenance therapy. Methadone is a mu-opioid receptor agonist whereas buprenorphine is a partial mu-opioid receptor agonist (mu agonist-K antagonist).
In the field of Opioid Use Disorder (OUD), the investigation around the effectiveness of TMS is difficult and susceptible of major side effects. Given that opioid withdrawal increases brain sensitivity to TMS induced seizures, this device has not been deeply examined in opioids-dependent patients [40].
Few studies have investigated the anti-craving efficacy of TMS by stimulating LDLPFC. A case report of a heroin-dependent subject conducted on 2020 [41], showed that seven rTMS session in 3 weeks (10Hz rTMS, 100% RMT) can significantly reduce craving. In another sham-controlled study [42], the efficacy of high frequency rTMS (10 Hz, 100% RMT) was studied on 20 subjects (10 for each group) after five session and then after other four days of stimulation. A significative improvement in craving symptomatology was highlighted .
Moreover, it may be interesting to notice that Nucleus Accumbens (NAcc) stimulation with Deep Brain Stimulation (DBS) has been reported to significantly reduced heroin consumption and/or craving in single cases [43-45].

Alcohol Use Disorder

There are currently four FDA-approved pharmacotherapies for alcohol use disorder – disulfiram, oral naltrexone, extended release injectable naltrexone, and acamprosate. These pharmacotherapies have been approved based on their effects in increasing abstinence more than placebo. Although these pharmacotherapies, also in combination with psychotherapies, have shown some positive findings, relapse rate are still high in patients with Alcohol Use Disorder (AUD) [46]. One of the first brain stimulation of subject with AUD was conducted in 2010 by Mishra and coll. and reported a significative anti-craving action of a 10 Hz rTMS protocol. In this sham-controlled trial 45 subjects underwent 10 daily stimulation on RDLPFC [47].
Some anti-craving effect was also showed by the stimulation of the dorsal anterior cingulate cortex using a double-cone coil [48]. A recent study conducted in 2017, analyzed the availability of DAT after four weeks of rTMS sessions in a sham controlled study. In this work, only the patients receiving active stimulation had a modulation in DAT availability, suggesting a potential role of rTMS as anti-craving tool [49].
However, there are several studies that do not show efficacy of the rTMS treatment for AUD. In 2011, Höppner and coll., investigated the efficacy of rTMS (20 Hz) on LDLPFC. In this sham-controlled trial, 19 subjects were enrolled (10 active and nine sham stimulation) and underwent rTMS stimulation for 10 days. No signifivative improvenment in craving levels for alchol was showed [50]. In the sham-controlled single-blind study of Herremans and coll. in 2012, 36 alcohol-dependent inpatients, underwent a single rTMS stimulation (20 Hz, 110% RMT, 40 train with a 12 s inter-train interval) above the RDLPFC before the discharge from a community for the weekend. Also in this study there was no significant effect of rTMS on craving for alcohol [51].

Cannabis Use Disorder

Cannabis is the most recreationally used drug worldwide: recreational users were approximately 3.8% of the world population in 2017. As the number of cannabis users has increased, the potency of cannabis expressed as the amount of THC increased as well. At the same time, legalization policies lead to decreased risk perception.

The risk to develop a Cannabis Use Disorder is around 10% for recreational users and is linked to increased risk of psychiatric and neurological illnesses [52].
Only one recent open label study investigated the efficacy of rTMS in Cannabis Use Disorder (CaUD) [53]. Nine patients underwent 20 sessions (two weeks) of rTMS stimulation (10 Hz, 120% of RMT, 4000 pulses 5s-on,10s-off) above the LDLPFC. Only three patients completed the entire protocol, and no significant improvement in craving symptomatology was highlighted in this study [53].

Gambling disorder

Non-substance-related addictive disorders are frequently comorbid and share some neurobiological substrates and behavioral manifestations of substance-related addictive disorders. This is particularly true for gambling disorder. It is thus an important question whether neuromodulation could change these neurobiological vulnerabilities, and thereby have clinical value for non-substance addictive behaviors as well [54].
Gambling disorder (GD) was recognized as the first behavioral addiction, and as such was reclassified within the category of "Substance-related and Addictive Disorders", in the Diagnostic and Statistical Manual of psychiatric disorders (DSM-5) in 2013. In the ICD-11, gambling disorder was classified within the same super-category of disorders due to substance use or addictive behaviors. In the DSM-5, gaming disorder was placed in the Appendix as a condition requiring more research. There is abundant evidence on similarities between GD and SUDs regarding genetics, neurobiology, psychological processes, and effectiveness of psychological treatment [55]. In GD, a neurocognitive profile showing diminished executive functioning compared to healthy controls (e.g. diminished response inhibition, cognitive flexibility) was related to differential functioning of the DLPFC and anterior cingulate cortex (ACC), both part of the cognitive control circuitry [56,57]. Moreover, increased neural cue reactivity and associated self-reported craving are present in the striatum, orbitofrontal cortex and insular cortex in gambling disorder compared to healthy controls. These abnormalities in frontostriatal functioning in GD warrant the question of whether NIBS may be a promising add-on treatment for gambling disorder and other non-substance-related addictive disorders [58]. Currently, a very limited number of studies explored TMS correlates in GD. For instance, in a single session pilot study in nine problematic gamblers, high frequency rTMS reduced desire to gamble, whereas cTBS reduced blood pressure, but had no effects on gambling desire [59]. Furthermore, the authors reported no effects on impulsive behavior (delay discounting) and Stroop interference were evident. Also in a sham-controlled cross-over high-frequency rTMS study (left DLPFC), a single session active rTMS diminished craving compared to sham rTMS [60]. Yet in another trial, low-frequency rTMS over the right DLPFC had similar effects as sham stimulation on craving, thus suggesting the occurrence of placebo effect [61]. Recently, a sustained effect (six months) was described in a GD subject [62], along with a modulation in dopaminergic pathways. In addition, a reduction in gambling-related symptoms has been observed also in GD-CUD comorbid patients [63]. Although preliminary, rTMS shows promise in restoring gambling-related pathophysiological alterations, deserving further investigations in well-powered controlled studies. Moreover, rigorously conducted clinical trials are needed to investigate optimal rTMS protocols with the potential to improve cognitive functioning, to diminish craving, and/or to reduce gambling behaviors/relapses in GD. Finally, if we consider GD as a disorder characterized by loss of control with respect to striatal drives such as craving, urgency for gambling and reward-seeking behaviors, then neuromodulation could be utilized as an intervention aimed at enhancing both cognitive control and the regulation of the reactivity to natural rewards.

Safety of rTMS in SUDs

The major concern about TMS safety in the treatment of SUDs is related to the risk of inducing seizures [64]. Currently, no evidence supports a TMS-related increased risk of serious or non-serious adverse events in the treatment of addictive disorders [64]. Nonetheless, increased vigilance is always warranted when theoretical concerns exist or in specific patient subgroups with limited prior data. From a safety standpoint, while rTMS has been recently established as a safe therapeutic tool, it is important to take into account that the application of rTMS in addiction is still a nascent field. Some concerns regard the possibility to induce seizures, an event that is frequently described in SUDs. Any medical and pharmacological factor independently increasing the risk of a seizure (e.g., stimulant use, alcohol use/withdrawal, benzodiazepine/barbiturate use/withdrawal, opioid use, tramadol use, bupropion in nicotine treatment, other psychopharmacological treatments used for comorbid psychiatric disorders) can in theory synergistically increase brain sensitivity to TMS induced seizures and should be taken into account.

Discussion and Conclusion

Building on data from major depression and OCD (for which TMS is currently FDA approved), we are now beginning to build a foundation of knowledge regarding rTMS utility as a tool to change smoking, drinking, and cocaine use behavior. These data provide a summary of the use of rTMS in the field of addiction. While for OUD and CaUD there are few studies in the literature reporting the efficacy of TMS protocols, for AUD the studies show controversies. Probably these results are affected by the concerns of stimulating these patients, given the increased risk to have seizures with TMS during the alcohol detoxification

phases, for which particular attention is required [65]. Many of the studies regarding the treatment of SUD deal with cocaine addiction. In this field rTMS can be classified as useful anti-craving tool, with promising effect size for high frequency rTMS stimulation protocol of the LDLPFC. Also, in the treatment of GD, TMS treatment could be considered as an innovative and promising technique.

One of the main evidences highlighted in this review is the high heterogeneity of the parameters used and in particular: frequency of stimulation (high vs. low frequency); intensity; number of stimulations; stimulation area and laterality; typology of coil; concurrent psychopharmacology; specific days of treatment. This high variability makes very hard to detect a specific protocol that could guarantee a better outcome [58]. These concerns about laterality 66 are highlighted by the difference in anti-craving efficacy considering CUD and AUD: in the former, the greatest benefits are obtained by stimulating the LDLPFC, in the latter the RDLPFC.

Moreover, the number of days of stimulation play a crucial role in the efficacy of rTMS. In general, repeating stimulation over multiple days has demonstrated efficacy in various clinical applications, as happen for the treatment of depression [67]. In addition, there are few study with a long follow up period; this is a serious limitation, given that addiction is a chronically relapsing disorder [58].

"When to stimulate" is another issue that need to be better defined. As suggested in a recent consensus paper [58] there are four distinct time intervals at which rTMS/tDCS interventions were administered: (1) before the participant sought standard treatment, (2) while the subject was treatment seeking but before undergoing standard treatment, (3) within the first month of standard treatment (mainly detoxification and stabilization) and (4) after the initial recovery period (more than one month). If the definition of these time intervals appears to be clear, we are still far to know which intervention would benefit the most in terms of efficacy. For safety reason it is of course advisable to avoid the intoxication phase and the early detoxification, specifically alcohol and opiates withdrawals.

The role of "Outcome Measures" is also of high relevance [58]. Most of the studies used craving as their primary outcome measure. Self-report on a visual analogue scale (VAS) was the most frequently used craving measure whereas few studies used objective measures such as urine drug tests or breath analyzers. Although a reduction or elimination of the consumption of the drug is the ultimate endpoint for clinical trials research, there are also many other behavioral and biologic variables that have been studied extensively and are considered meaningful surrogate endpoints for patients seeking treatment for SUDs (e.g. heightened reactivity to predictive drug cues, perseverative responding, delayed discounting for the drug, response to stress, narrowing of the behavioral repertoire) [68].

Neuromodulatory treatments have also been used for comorbidities with SUDs [58]. Overlapping neurobiological substrates between SUDs and psychiatric disorders (Dunlop et al., 2017) have been widely reported. One group studying smokers with schizophrenia demonstrated that rTMS reduced cigarette cravings compared to sham 69. Another group using rTMS for comorbid dysthymia and alcohol use disorder, showed decreased alcohol consumption with rTMS 70. Perhaps a dual benefit of brain stimulation treatments targeting underlying neurobiological factors in SUDs may also extend to deficiencies found in other psychiatric disorders (i.e., nicotinic acetylcholine receptor deficits found in schizophrenia patients, associated with both higher smoking rates and cognitive dysfunction) [71].

The outcome observed is still far to be considered fully satisfactory. Variability in cortical excitability may also be linked to genetic characteristics, in the same way that responses to medications can be influenced by genetic variability [72]. A research domain criteria approach able to identify the specific endophenotype that could be better benefit from rTMS is going to be the goal of NIBS in the next years.

This summary of the literature on rTMS treatment of SUDs, although bringing very interesting clinical potentials, highlights the need to identify potential parameters of stimulation in order to produce reliable efficacy data to the already well-investigated safety of TMS [73].

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