Repetitive Transcranial Magnetic Stimulation in Addiction

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11.1 The Addicted Brain: From Neurotransmitters to Neural Circuits

Drug addiction, currently included in the field of Substance-Use Disorders (SUDs), can be defined as a chronically relapsing disorder, characterized by compulsive drug seeking and taking, loss of control over drug use, behavioral inflexibility, and emergence of negative emotional states (e.g., dysphoria, anxiety, irritability, anhedonia) [1]. Preclinical investigations, human neuroimaging and clinical studies have provided extensive evidence that these manifestations result from long-lasting neuroadaptations in several brain circuits, including basal ganglia, extended amygdala, and prefrontal cortex circuits [1].

Specifically, a central feature in the framework of causation of SUDs and other addictive disorders is represented by neuroadaptations in the reward neural circuitry (i.e., mesocorticolimbic dopamine (DA) system) and in the glutamatergic corticolimbic circuitry, in which the dopamine projections are embedded [2–5]. Although having diverse primary neurocircuitry and neurotransmitters targets, all addictive agents initially act by enhancing reward via increased dopamine release in the nucleus accumbens (NAc) [6] and other areas of the limbic forebrain, including the amygdala and prefrontal cortex [7]. According to the incentive-sensitization theory proposed by Robinson and Berridge [4], a sensitization of the mesolimbic dopaminergic system is critically implicated in the development of drug addiction and in the emergence of craving. Craving is a multifaceted construct, known is shown to be one of the most important contributors to relapse, thus representing an important treatment target [1].

The repeated stimulation of DA pathways, induced by exposure to addictive agents, evokes plastic changes in the reward neural circuitry, which leads to hypersensitivity to drugs, as well as to drug-associated cues [4]. Indeed, preclinical studies have shown that with repeated drug exposure neutral stimuli paired with the drug (conditioned stimuli) start to increase dopamine by themselves [8–12]. Brain imaging studies confirm that drug-associated cues induce dopamine increases, particularly in the dorsal striatum (region implicated in habit learning and action initiation). Thus, cue-induced conditioning plays a critical role in strengthening habitual responding in drug-seeking behavior, which reflects a transition from prefrontal cortical to striatal control over responding, and a transition from ventral striatal to more dorsal striatal subregions ([13, 14]). Indeed, studies using positron emission tomography (PET) reported reduced ventral striatal D2 receptors and diminished dopamine release in patients with substance dependence [15].

The changes in striatal dopamine function are accompanied by decreased activity in several prefrontal and associated regions. Alterations and dysfunction in prefrontal circuits have been shown to underlie the loss of inhibitory control, behavioral inflexibility, and impairment in executive functioning commonly observed in individuals with SUDs. The dorsal prefrontal cortex (PFC) network, including the dorsolateral prefrontal cortex (DLPFC) and the dorsal anterior cingulate cortex (dACC), controls executive functioning, including decision making and self-control, while the ventral PFC network, including the medial prefrontal cortex (MPFC), orbitofrontal cortex (OFC), and ventral anterior cingulate cortex (vACC), governs limbic arousal and emotion processing [16]. An imbalance of these two systems, specifically a

hyperactive emotional processing and hypoactive executive functioning system, has been hypothesized as one of the main factors contributing to the transition to compulsive drug seeking and taking [17]. Indeed, hyperactivation of the ventral PFC network has been associated with craving [18], resulting in substance use [19], whereas hypoactivity of the left [20], as well as the right DLPFC [21], has been described in drug addicts while performing cognitive tasks, indicating impairments in executive functioning, which is modulated by the DLPFC network.

In addition to the alterations in reward neural circuitry and prefrontal circuits, SUDs are also characterized by neuroadaptations in the circuitry of the extended amygdala (central nucleus of the amygdala, bed nucleus of the stria terminalis, and NAc shell) and also in the lateral habenula. These changes are associated with abnormalities in neurotransmitter systems involved in stress response (e.g., corticotropin-releasing factor, CRF; neuropeptide 1, NK1; norepinephrine; and dynorphin). Engagement of these circuits and neurotransmitters leads to the emergence of negative affective states, which are manifest when the drug is removed during acute withdrawal but also during protracted abstinence [22]. Thus, negative states may powerfully motivate drug seeking via negative reinforcement and may trigger relapse even after prolonged periods of abstinence.

Taken together, these findings demonstrate that SUDs, as well as other addictive disorders rather than being expressions of a single brain region or neurotransmitter system, are mediated and maintained by alterations in multiple, integrated neural circuits, and allostatic alterations in the expression of their related neurotransmitters and molecular mediators. Therefore, effective treatments should be ideally able to address such complexity, by targeting and remodeling impaired circuits. In this perspective, an integrated, multidisciplinary approach based on combining pharmacotherapies, behavioral and cognitive interventions, and neurocircuitry-based interventions, such as transcranial magnetic stimulation and transcranial direct current stimulation, may represent a safe, effective, and feasible therapeutic option for patients with SUDs. As a neuroscientific, transdiagnostic-based approach has been proposed also for addictive disorders, including behavioral addictions [23–25], intermediate phenotypes of addiction, and their underlying neurobiological underpinnings, are being characterized. This can further fuel the development and use of interventions targeting these common underlying mechanisms.

11.2 The Rationale for Repetitive Transcranial Magnetic Stimulation (rTMS) for Addictive Disorders

Although in the last two decades important advances have been made in understanding the neurobiological underpinnings of ADs, this knowledge has not yet been translated into effective treatments for these disorders. Psychosocial interventions and currently FDA-approved pharmacotherapies for alcohol- and substance-use disorders (AUD and SUDs) have been shown to improve clinical outcomes. However, not all patients respond to these treatments, and relapse rates remain high. For example, SUDs present with disturbingly high recidivism rates, estimated between 40–60%, but in some instances exceeding 90%, depending on the primary substance being abused and how one measures the time frame of the treatment outcome (www.drugabuse.gov). This has prompted the investigation of novel pharmacotherapeutic

targets, mostly with unsuccessful results [26–29]. Despite all these efforts, still there are no FDA-approved pharmacotherapies for cocaine- or amphetamine-use disorders, whose treatment relies mainly on behavioral and cognitive interventions, with variable success rates [30]. Furthermore, it is important to consider that pharmacotherapies such as methadone and buprenorphine, for opioid-use disorders, and naltrexone, for alcohol-use disorders, have been shown to modulate neural circuits implicated in ADs, but they lack spatial and temporal specificity of action.

Recent findings have indicated that brain stimulation techniques can be effective in reducing craving and consumption across different substances, and may also be efficacious for behavioral addictions, given their ability to induce neuroplasticity and modulate brain activity and connectivity. The rationale for the application of rTMS in the treatment of SUDs and other behavioral addictions lies in preclinical investigations. In a seminal optogenetic study, in vivo stimulation of prelimbic cortex (PLC) reversed cocaine-induced prefrontal hypofunction, and blocked drug-seeking behaviors [31, 32] in compulsive cocaine-seeking rats. The PLC in rats is the closest functional homologue of the DLPFC and the anterior cingulate cortex (ACC) in humans [33–35]. Consensus on this matter is still missing, due to the relevant large anatomical diversity between the rodent and the human frontal/anterior cortices, but both DLPFC and ACC play a major role in top-down inhibitory control and reward mechanisms. Thus, the aforementioned preclinical findings may be translated in humans by noninvasive stimulation of homologous areas (e.g., the DLPFC) [31] to test whether this intervention may reduce cocaine craving and consumption. This hypothesis has been preliminarly tested using transcranial magnetic stimulation (TMS).

The rationale of targeting the DLPFC is based also on the key role that this brain region plays in decision-making processes [36]. Addiction is associated with increased impulsivity and impaired risky decision making [37]. 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 with it.

The complex trajectory of addiction development from impulsive to compulsive substance use is thought to be reflected in changes in various cognitive constructs and their underlying networks, including reward processing [38], salience detection [39], executive control [39], and internal ruminations [40], with cycling phases, including binge/intoxication (i.e., reward seeking), withdrawal (negative affect) and drug-craving brain circuits and networks [1, 41]. The hypothesis of an imbalance between drive state and reward processing (so-called "Go-circuits") and executive control ("Stop-circuits") processes [16, 42–46] is a manifestation of such dysregulation. As reported by Hanlon et al. [47]) in their recent studies, two neurobehavioral systems may be targeted by TMS in order to treat substance-use disorders: an executive control system, namely, the *dorsal-lateral* frontal-striatal, likely involved in resisting drug use, and an impulsive system, namely, the *ventral-medial* frontal-striatal, likely involved in craving and use. Under this framework, a *Stop* system would inhibit the *Go*-craving system and stress system. It may therefore be useful to either increase activity in the DLPFC-dorsal striatal circuit or to decrease the activity

in the ventral medial prefrontal cortex-caudate circuit using an inhibitory rTMS (1 Hz or continuous Theta Burst Stimulation, cTBS) [47]. It is therefore a possibility that the stimulation of the DLPFC could be less associated with a direct anticraving effect, probably exerting its action in terms of relapse prevention, increasing the possibility to control craving and to cope with it through a top-down mechanism.

A further aspect to consider is that targeting prefrontal areas via TMS also affects dopaminergic neurotransmission. Strafella and colleagues [48] found that high-frequency rTMS on the prefrontal cortex in humans induces subcortical release of dopamine in caudate nucleus, whereas Cho and Strafella [49] showed that rTMS over the left DLPFC modulates the release of dopamine in anterior cingulated cortex and orbitofrontal cortex in the same hemisphere. These findings have been recently confirmed in a longitudinal study investigating alcohol intake and dopamine transporter (DAT) availability in the striatum before and after deep rTMS. With respect to sham stimulation, active stimulation significantly reduced both alcohol craving and intake and DAT availability, suggesting a modulatory effect on dopaminergic terminals [50].

Also in the long-term perspective, in addicted brain where a repeated exposure to drugs has determined long-term neural adaptations, rTMS can exert its effect reverting the process of neuroadaptation. These neuroadaptations are partly associated with altered dopamine activity in the mesocorticolimbic circuitry [51] and lead to an alteration of cortical excitability [52], which have been implicated in the persistence of drug-seeking behaviors and in an increased likelihood of relapse. Repeated applications of rTMS can affect cortical excitability and increase the release of dopamine in the mesolimbic dopaminergic system, affecting neuroadaptation induced by the chronic use of substances [48, 53].

In addition to dopaminergic signaling, some of the TMS-induced effects depend on glutamatergic transmission [31, 54]. Different preclinical studies have clearly demonstrated that rTMS induced-LTP/LTD are strictly dependent on NMDA and AMPA receptor signaling [55, 56] within glutamatergic synapses within addiction-related brain areas [56, 57]. Additionally, rTMS has been shown to enhance GABA neurotransmission [58] through increased cortical inhibitory activity [59]. GABA neurotransmission is relevant in SUDs, and its modulation showed to have some potentials in terms of treatment outcomes [60–62].

Finally, rTMS could also exert its effects modulating the expression of neurotrophic factors, such as BDNF, an active regulator of synaptic plasticity, within cortical and subcortical areas [55]. More recently, nonsynaptic events have been suggested as mediators of rTMS long-term effects, including plasticity-related gene expression and neurogenesis [63, 64]. The role of BDNF should be also better explored, given its role in ADs [65, 66]. Whether these mechanisms are involved in rTMS-mediated effects in SUDs remains to be explored.

11.3 rTMS as a Therapeutic Tool in the Treatment of Addictive Disorders (ADs)

Repetitive transcranial magnetic stimulation (rTMS), including theta burst stimulation (TBS) and deep TMS (dTMS), has emerged as a potential treatment for ADs due to its promising results in terms of craving reduction [56, 67]. Most studies

target the DLPFC by means of excitatory stimulation in order to strengthen executive functions and cognitive control [68].

A recent meta-analysis, including data from 748 patients with SUDs, showed that left DLPFC stimulation had a significant anticraving effect with medium effect size compared with sham stimulation [67]. However, this effect was limited in duration, as indicated by a nonsignificant treatment effect at follow-up. Meta-regression indicated an association between stimulation dosage (i.e., total number of stimulation pulses) and anticraving effect, whereas the number of sessions, pulse per session, frequency, and intensity was not significant [67]. This analysis yielded a large effect size for illicit drug dependence (including cocaine, opiates, methamphetamine, and cannabis), followed by a medium effect size for nicotine dependence and a small effect size for alcohol dependence [67]. Conversely, meta-analysis, including all studies for right DLPFC stimulation, showed no significant anticraving effect compared to sham stimulation [67]. Inhibitory stimulation protocols as well as dTMS had no significant effects on craving. Deep TMS is performed using a group of coils, called H coils, whose geometry and configuration allow to reach deeper brain regions [69], at the expense of focality. With regard to drug consumption, the analysis revealed that both excitatory rTMS of the left DLPFC and excitatory dTMS of the bilateral DLPFC and insula resulted in a significant reduction of substance consumption, compared with sham stimulation. Recently, other brain targets have been tested. For example, Hanlon and colleagues used continuous theta burst stimulation to attenuate MPFC activity during cue exposure [70, 71]. However, results were not supportive of an anticraving effect using this protocol.

The following sections describe trials exploring the experimental evidence for rTMS in SUD and other addictive behaviors.

11.3.1 rTMS in Nicotine-Use Disorder

There are three FDA-approved medications for smoking cessation, all of which promote abstinence: nicotine replacement therapies, bupropion, and varenicline. However, the outcomes are still far from satisfactory and there is ground for developments in the area of noninvasive brain stimulation (NIBS).

The first to investigate the efficacy of rTMS for smoking addiction were Johann and colleagues [72], who examined whether rTMS of the DLPFC could modulate tobacco craving. Following a 12-hour period of abstinence, 11 treatment-seeking smokers received either one active or one sham session of 20 Hz rTMS over the left DLPFC at 90% of MT. The session consisted of 20 trains of stimuli of 2.5 seconds. The levels of tobacco craving were assessed using a 100-point visual analogue scale (VAS) both 30 minutes prior to and following the rTMS treatment. rTMS significantly reduced the level of tobacco craving at 30 minutes post-treatment [72]. These findings, therefore, motivated further investigation on the efficacy of rTMS as a potential treatment in nicotine addiction, with the aim to test also whether this intervention could reduce cigarette consumption. Following this pilot study, the same research group [73] investigated the effects of two sessions of active and sham rTMS at the same parameters with a double-blind crossover design study. The second study demonstrated reduced smoking consumption following rTMS session,

thus contributing to the preliminary evidence of the utility of rTMS treatment in nicotine dependence [74]. Based on these findings, the authors proposed that high-frequency rTMS could have potential therapeutic value in the treatment of nicotine dependence by reducing the levels of craving [72] and its consumption [73].

Amiaz and colleagues were also interested in evaluating the effects of high-frequency rTMS of the left DLPFC, combined with either smoking or neutral cues exposure, on cigarette consumption, dependence, and craving. Thus, there were four experimental groups: active TMS with smoking pictures, active TMS with neutral pictures, sham TMS with smoking pictures, and sham TMS with neutral pictures. The authors assessed the effects of 10 days of treatment with either active or sham 10 Hz rTMS treatment applied to the left DLPFC. Stimulation included 20 trains/day at 100% of MT and each train consisted of 50 pulses at 10 Hz. rTMS, independent of exposure to smoking pictures, reduced subjective and objective measures of cigarette consumption and nicotine dependence. However, these effects reduced gradually after completing the rTMS sessions and the reduction in cigarette use was not significant 6 months after treatment termination, although in the group of smokers who received active rTMS-smoking picture cigarette consumption was lower at 6-month follow-up compared to the other treatment groups. Overall, results from this study suggested that high-frequency rTMS over the DLPFC could reduce cigarette consumption and nicotine dependence [75].

Consistent with findings in nonpsychiatric smokers, some studies [72, 76] showed that treatment with rTMS significantly reduced craving in treatment-seeking individuals with schizophrenia, a population of smokers who are typically highly nicotine dependent. While there was a robust increase in craving following the rTMS session in the sham group (due to abstinence from smoking), post-treatment craving levels in the active group were the same or lower than the pretreatment assessment. Despite attenuation of tobacco craving, rTMS did not increase abstinence rates, thus suggesting that the number of rTMS sessions could be a critical factor modulating rTMS efficacy [76]. Rose et al. [77], instead, tested whether either excitatory and inhibitory stimulation of superior frontal gyrus (SFG) had anti-craving effects, with promising results. In one of the largest studies carried out to date, Dinur-Klein et al. [78] enrolled 115 smokers to either receive, in a randomized order, 13 sessions of high-frequency, low-frequency, or sham stimulation to the lateral PFC and insula bilaterally. This stimulation was done using an H-coil for deep TMS designed to target the DLPFC and insula, crucially involved in cigarette craving [79]. High-frequency deep TMS (10 Hz), in association with smoking cues during the stimulation procedure, was found to significantly reduce cigarette consumption, as well as nicotine dependence.

While other types of brain stimulation techniques (transcranial direct current stimulation, cranial electrostimulation, and deep brain stimulation) have been evaluated in the treatment of nicotine addiction, there is more evidence to support rTMS' potential to treat nicotine dependence. According to the criteria suggested by Brainin et al. [80], research on the therapeutic use of rTMS for nicotine dependence has one study in class II, three studies in class III, and one study in class IV that showed reduction in craving, consumption, and dependence [68]. Thus, according to the available evidence, rTMS falls within the level B recommendation as probably effective in the treatment of nicotine addiction [68].

11.3.2 rTMS in Alcohol-Use Disorder (AUD)

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 rates are still high in patients with AUD [81]. The first brain stimulation study to test the anticraving efficacy of rTMS was carried out by Mishra and colleagues, who administered high-frequency (10 Hz) rTMS of the right DLPFC in a single-blind, sham-controlled fashion, in 45 patients with AUD [82]. The authors reported that 10 daily sessions of high-frequency rTMS over right DLPFC significantly reduced craving. This study supports the therapeutic potential of rTMS. Hoppner et al. [83] investigated the effect of high-frequency rTMS of the left DLPFC compared to sham stimulation on craving and mood in alcohol-dependent women. Nineteen female detoxified participants were randomized either to a high-frequency rTMS (20 Hz) over the left DLPFC ($N = 10$) or sham stimulations ($N = 9$) for 10 days. There were no significant differences in clinical parameters such as alcohol craving or mood after active rTMS compared to sham stimulation.

Herremans et al. [84] performed a sham-controlled, prospective, single-blind study in order to investigate the effect of single high-frequency rTMS session of the right DLPFC on alcohol craving in the community. Participants ($N = 36$) were alcohol-dependent inpatients. After successful detoxification, participants were allocated to receive one active or one sham rTMS session. The rTMS session (40 trains of 1.9 s at 20 Hz, 110% of MT with a 12-s intertrain interval) was administered the day prior to discharge patients for the weekend. One high-frequency rTMS session delivered to the right DLPFC did not lead to changes in craving (neither immediately after the stimulation session nor in participants' natural environment during the weekend). This study found that application of a single rTMS session had no significant effect on alcohol craving [84]. In another study, repetitive rTMS targeting the dACC using a double cone coil reduced immediate alcohol craving and consumption [85]. In a recent study [50], a small cohort of patients was treated by bilateral dTMS. Clinical and SPECT evaluations were then carried out after 4 weeks of rTMS sessions. Patients that received the real stimulation revealed a reduction in DAT availability at T1, whereas the sham-treated group did not suggest a modulatory effect of deep rTMS on dopaminergic terminals and a potential clinical efficacy in reducing alcohol intake in AUD patients.

Based on these findings, Herremans and Baeken [86] suggested the evaluation of multiple rTMS sessions in larger, randomized, and sham-controlled population samples. Furthermore, randomized controlled studies should be done to evaluate whether patients need stimulation with high or low frequency [86].

Taken together, data regarding the efficacy of rTMS in AUD are still partial and not conclusive. According to the criteria suggested by Brainin et al. [80], there is inadequate evidence to confer a level of recommendation for its effectiveness in the treatment of AUD.

11.3.3 rTMS in Cocaine- and Stimulant-Use Disorder

Cocaine-use disorder (CUD) is a major public health concern, associated with high relapse rates, significant disability, and substantial mortality [87]. 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 and short-term cocaine relapse rates can reach up to 75% [88]. Unfortunately, no unequivocally effective pharmacological or psychological therapies have been identified to date. At the moment, there are currently no FDA-approved pharmacotherapies for cocaine- and amphetamine-use disorders.

Advances in understanding the neurobiological underpinnings of cocaine-use disorders have unraveled that chronic cocaine use causes damage and changes in the prefrontal cortex (PFC), [89], including significant brain volume reduction [90, 91], cortical hypoactivity [16, 92, 93], impairment in executive functions, and dysregulation of neurotransmitters systems [94–96]. Thus, targeting the PFC via TMS appears to be a promising intervention. In the first, open-label study testing this hypothesis, high-frequency rTMS of the right (but not left) DLPFC was linked to a reduction of craving in cocaine-addicted subjects [97]. The authors investigated whether a single session of rTMS over DLPFC could reduce cocaine craving among six male participants with CUD, and also assessed effects on mood. Participants received two sessions of high-frequency (10 Hz) rTMS at 90% of MT, to the right and left DLPFC, separated by 1 week. Patients were asked to complete a set of 15 visual analogue scales (VAS) ranging from "not at all" to "more than ever." Each VAS evaluated one of the primary or secondary endpoints on three occasions: 10 min before the intervention and immediately after and 4 h after rTMS session. This research provided the first demonstration that high-frequency rTMS applied over the right DLPFC could reduce craving associated with chronic use of cocaine.

In 2008, Politi and colleagues also performed an open-label study showing that in cocaine users ($n = 36$), 10 sessions of 15-Hz TMS to the left DLPFC (600 pulses, 100% resting MT, rTMT) led to a significant reduction in self-reported craving [98].

Other open-label studies confirmed these preliminary data, suggesting that rTMS of the PFC may determine a reduction in cocaine use and minimize the risk of relapse [97, 99–102, 103]. In a recent open-label study, Pettorruso et al. [104] confirmed the efficacy of high-frequency rTMS of the DLPF in CUD, showing a reduction in psychiatric symptoms that contribute to the overall clinical burden. rTMS appears to elicit its more notable effects on depressive and anxiety symptoms, confirming previous data by the same group, according to which the prohedonic effect of rTMS is crucial and directly related to the reduction of cocaine craving [100]. Future studies that assess cocaine intake after treatment are also required. According to the criteria suggested by Brainin et al. [80], there is still inadequate evidence to confer a level of recommendation for the effectiveness of this treatment.

Methamphetamine (METH) is a psychostimulant of the phenethylamine and amphetamine class of psychoactive drugs and is a widely used illicit drug, also available on the cybermarket [105, 106]. Neurotoxic effects and potentially irreversible loss of neurons and axons have been linked to the repeated exposure to moderate-to-high levels of METH [107]. Moreover, cognitive functioning under

methamphetamine administration is linked to cognitive deficits and alteration of fronto-striatal and limbic pathways [107]. At the same time, METH users showed impaired cortical plasticity induced by TMS [108]. Nowadays, available treatments are limited psychosocial interventions and no medications have been approved by the FDA. NIBS have been evaluated as a potential treatment for Methamphetamine-Use Disorder (MUD) in few sham-controlled trials. High-Frequency rTMS on the left DLPFC has been proven to reduce craving [109, 110] and sleep disturbances [111] and to improve cognitive performance [112] in both male [111, 112] and female METH users [109]. At the same time, low-frequency rTMS transiently increased craving when applied on the same site [113]. Interestingly, both high- and low-frequency rTMS applied on both right and left DLPFC showed a significant effect on craving when compared to a control stimulation site (P3, of 10–20 EEG system) [114]. Unfortunately, given the high variability across studies, no recommendation may be highlighted.

11.3.4 rTMS in Opiate-Use Disorder

Recently, 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 in the USA [115]. 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). Given that opioid withdrawal increases brain sensitivity to TMS-induced seizures, TMS has not been deeply examined in opioid-dependent patients. However, it is important to note that currently more than 15 different studies evaluating the effects of TMS in OUD have been registered in clinical trial.gov. Moreover, it may be interesting to notice that Nucleus Accumbens (NAcc) stimulation with Deep Brain Stimulation (DBS) was reported to significantly reduce heroin consumption and/or craving in single cases [116–118].

11.3.5 rTMS in Other SUDs

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 has increased as well. At the same time, legalization policies led 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 [119]. As for Stimulants, available treatments for Cannabis-Use Disorders are limited to few effective psychosocial interventions and no medications have been approved. Even if rTMS has been shown to be safe in cannabis-dependent

individuals, one single 10-Hz rTMS session on the left DLPFC did not exert any significant changes in craving when compared to sham stimulation [120].

11.3.6 rTMS in Gambling Disorder and Other Behavioral Addictions

Nonsubstance-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 (GD). It is thus an important question whether neuromodulation could change these neurobiological vulnerabilities, and thereby have clinical value for nonsubstance addictive behaviors as well [121].

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 supercategory 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 [122]. 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 [123, 124]. Moreover, increased neural cue reactivity and associated self-reported craving are present in the striatum, orbitofrontal cortex, and insular cortex in GD patients 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 GD and other nonsubstance-related addictive disorders [125]. Currently, a very limited number of studies have explored TMS correlates in GD. For instance, in a single-session pilot study in nine men pathological gamblers, high-frequency rTMS over MPFC reduced desire to gamble, whereas cTBS over right DLPFC reduced blood pressure, but had no effects on gambling desire [126]. Furthermore, the authors reported that rTMS and cTBS had no effect on impulsive behavior (delay discounting) while both active stimulation protocols improved Stroop interference. Also in a sham-controlled crossover high-frequency rTMS study (left DLPFC), a single session active rTMS diminished craving compared to sham rTMS [127]. 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 [128]. Recently, a sustained effect (6 months) was described in a GD subject [129], along with a modulation in dopaminergic pathways. In addition, a reduction in gambling-related symptoms has been observed also in GD-CUD comorbid patients [131]. Although preliminary, rTMS shows promise in restoring gambling-related pathophysiological alterations [130], 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.

11.4 Safety of rTMS in SUDs

The major concern about TMS safety in the treatment of SUDs is related to the risk of inducing seizures [132]. Currently, no evidence supports a TMS-related increased risk of serious or nonserious adverse events in the treatment of addictive disorders. 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. SUD patients may present with long-lasting adaptations and changes in brain circuits and given that rTMS treatment results in functional changes in brain activity, establishing the safety of rTMS protocols in SUDs patients is a relevant issue and deserves further investigation. 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.

11.5 Current Limitations and Future Perspectives

Based on the rationale we exposed and on the current evidence, rTMS can be classified as probably effective in the treatment of addiction, with a promising effect size for high-frequency rTMS stimulation protocol of the DLPFC mainly in nicotine- and cocaine-use disorders. However, as recently reported by a consensus of experts [125], different points need to be better explored in order to understand which specific protocol could guarantee a better outcome: (1) frequency of stimulation (high vs. low frequency); (2) laterality of stimulation; (3) area of stimulation and the role of neuronavigation; (4) number of stimulations; (5) duration of repetition interval; (6) typology of coil; (7) should TMS be administered in "resting state" or during an "induced state" such as during cue-induced craving inhibition; (8) how should the clinical efficacy of TMS be determined (e.g., drug use behavior, self-reports of craving, cognitive constructs like working memory or executive control, alterations in brain circuits and networks); (9) the role of psychiatric comorbidities other than addiction; (10) should TMS be thought of as a monotherapy or combined with pharmacotherapy and/or behavioral interventions; (11) the relevance of placebo effect and sham stimulations; (12) duration of the positive effect on the long term and the role of long-term sessions (as a relapse prevention strategy); (13) how to phenotypically subtype individuals most likely to benefit from TMS.

Stimulation parameters, such as duration, number of stimulation sessions, stimulation frequency, intensity, target brain region, and interval between treatments, should be investigated to define the dose response of rTMS. Few of these parameters have been systematically investigated for addiction treatment [125]. Among TMS studies, most of them applied 10-Hz or 20-Hz pulses, whereas a minority performed 1 Hz and intermittent and continuous TBS stimulations. Evidence from depression rTMS studies suggest that longer treatment duration and/or higher number of rTMS sessions could contribute to faster clinical improvement and better outcomes [133]. Moreover, the use of multiple rTMS sessions per day may also be a promising therapeutic development, as recently shown in depression samples [134].

Another relevant issue is that of treatment duration. There were only two studies with 1-year follow-up, six studies with 6 months' follow-up, and four studies with 3 months' follow-up. Twelve studies had less than 3 months' follow-up [125]. This is a serious limitation, given that addiction is a chronically relapsing disorder.

There is very little information available from empirical studies to help guide the selection of left- or right-sided targets for neuromodulation approaches in SUDs. Most rTMS studies in SUDs have targeted the left DLPFC (following the pathway that was forged by depression researchers) [125]. In alcohol research, however, there has been a unique emphasis on stimulating the right DLPFC. Thus, the question on laterality in the treatment of addictive disorders should be put in a wider perspective, and be approached from a network perspective, where not only laterality, but also the target location is relevant. However, it has also been assumed that the left DLPFC processes reward-based motivation, whereas the right DLPFC is more involved in withdrawal-related behaviors and self-inhibition [135].

In order to establish protocols for clinically relevant long-lasting effects, an ongoing effort of research has been dedicated to exploring the effects of repeating stimulation, either by applying stimulation daily over several days or weeks, or repeating stimulation within a single daily session, separated by a critical time window [125]. In general, repeating stimulation over multiple days has demonstrated efficacy in various clinical applications, such as treatment of depression using rTMS [136, 137]. With regard to addiction studies, positive evidence also exists for lasting effects of repeated stimulation for smokers [78, 138]. However, even with these promising results, systematic or face-to-face studies comparing different repetition intervals are missing, and are crucially needed in order to determine effective repetition rates and durations. The importance of this issue also underlies the need for determining the optimal repetition intervals between sessions. In studies using TMS, the duration of the repetition interval has been found to be critical in modulating plasticity, while also avoiding homeostatic mechanisms that may limit or counteract plasticity [139–142]. For example, in a study on depression, repeating rTMS twice daily with a 15-min interval between stimulation blocks resulted in superior effects compared to a once daily application with the same number of pulses [143]. In case of addictive disorders, the number of studies investigating the effect of interval timings remains scarce. In summary, although there is promising evidence for persisting and long-lasting effects with repeated stimulation sessions, the relatively large heterogeneity of these studies with regard to stimulation technique, timing, repetition, and montage precludes a clear understanding of how repetition may

affect therapeutic outcomes in SUD, warranting a need for systematic research designs [144].

The role of placebo effects and sham stimulations in rTMS is another issue specifically relevant in addiction. Participants and patients typically receive considerable information in advance about TMS and they inevitably speculate about its effects [145]. The occurrence of a placebo effect is therefore at least plausible and should be considered when evaluating rTMS efficacy, especially in light of a recent study reporting that sham rTMS has itself differential effects on neuronal activity on an individual-by-individual basis [146]. Placebo effects have been observed in different psychiatric disorders with a strong neurobiological component, including major depression [147] and obsessive-compulsive disorder (OCD) [148]. SUDs and behavioral addictions are conditions that can be easily complicated by abnormal personality, with histrionic features that can enhance the possibility to observe a placebo effect. Moreover, the external locus of control, a typical cognitive psychological disposition frequently reported in SUDs [149], might emphasize the possibility to see in an external aid (the use of rTMS) the resolution of their disorders. Adequate sham stimulation protocols are therefore a critical factor in clinical trials to ensure that effects can be ascribed specifically to TMS. Sham TMS approaches require further development but may be sufficient in clinical settings in which patients are generally naïve to TMS [145]. There are ongoing efforts by the TMS community to evaluate and revise sham protocols in order to increase rigor across the field [150], "When to stimulate" is another issue that needs to be better defined. As suggested in a recent consensus paper [125], 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 1 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 [125]. 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 biological 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) [151].

Neuromodulatory treatments have also been used for comorbidities with SUDs [152]. One group studying smoking patients with schizophrenia demonstrated that rTMS reduced cigarette cravings compared to sham [153]. Another group using rTMS for comorbid dysthymia and AUD showed decreased alcohol consumption with rTMS [154]. 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) [155]. Actually, overlapping neurobiological substrates between SUDs and psychiatric disorders [19, 156] have been widely reported.

While neuromodulatory techniques are a promising interventional approach in the treatment of SUDs, most responses are partial and even the well-documented anti-craving effects of rTMS do not necessarily translate into reduced drug use or abstinence [153]. Combining neuromodulation with behavioral and pharmacotherapeutic interventions may ultimately mitigate these shortcomings [157]. Indeed, coupling pharmacological treatments with brain stimulation methods has an advantage of reversing plasticity induced by drugs of abuse by targeting the neurocircuits that maintain addictive behaviors [158]. For instance, nearly 50% of patients become abstinent from cigarettes after treatment with rTMS and concomitant nicotine replacement therapy [159]. Future studies will define optimal augmentation strategies, in order to determine possible rationales to combine neuromodulation and pharmacological interventions. Promising strategies seem to be represented by the simultaneous interaction with glutamate and GABA neurotransmissions [160, 161].

At present, the gap between the knowledge we have about the neurobiology of addiction and the translation in effective treatments remains substantial. Bridging this gap could help increase the efficacy of treatments for those patients who suffer from the serious consequences of these disorders, as well as for their families. The implementation of neuromodulation techniques offers a chance to remodel dysfunctional neural circuits. Moreover, combining these actions with synergistic pharmacological modulation could determine more pronounced and long-lasting effects. Furthermore, also behavioral interventions (i.e., motivational interviewing (MI); cognitive behavioral therapy (CBT); contingency management (CM)) can be used in combination to NIBS. Given that neuromodulation can improve cognitive control/functioning, it may (in part) diminish the risk for relapse by strengthening cognitive control [162, 163], favoring the psychotherapeutic and rehabilitation process in absence of craving perturbations [164].

11.6 Conclusions

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.

At the moment, the best level of effectiveness of rTMS is in the treatment of nicotine and cocaine/stimulant-use disorders. The effects of rTMS sessions on drug craving and consumption provide evidence and support for further TMS studies in the field of addiction research. It is important to note that none of these studies demonstrated complete abstinence from substance use and few studies [73, 83] evaluated craving in real-life scenarios. The outcome observed is still far from being 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 [165]. 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 [166, 167].

Future research should identify potential parameters (i.e., duration, number of stimulation treatments, stimulation frequency, intensity, brain region of target, and proximity between treatments) of stimulation in rTMS studies for the most effective and safe treatment of drug addiction. Optimal stimulation parameters are still far from being defined. Rigorous preclinical TMS-dosing studies in various addiction models are needed to comprehensively evaluate the full parameter space of dosing variables.

The data presented in this chapter demonstrate that whereas most of the efforts for rTMS in addiction have been focused on increasing activity in the DLPFC, decreasing activity in the MPFC and ventral striatum may also be a feasible and fruitful target to consider [47]. It seems plausible that either increasing neural firing in the executive control circuit (perhaps via 10-Hz TMS in the DLPFC) or decreasing firing in the limbic circuit in the presence of cues (perhaps via cTBS TMS in the MPFC) may be valuable strategies for decreasing vulnerability to drug-related cues among patients. Convincing evidence also leads to the idea of the insula being a promising brain region to target for addiction with dTMS stimulation [168].

Promising therapeutic development is represented by the use of multiple rTMS sessions per day, as shown in depression studies for accelerated rTMS protocols [134], by the use of appropriate add-on pharmacotherapy [160, 161], and by the concomitant use of other NIBS (tDCS) in the long term, also in terms of cost effectiveness [160, 161].

Future studies should focus on the personalization of the rTMS treatment, as well as on the optimization of stimulation protocols.

Conflict of Interest None.

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