Transcranial Magnetic Stimulation: From Basic Mechanisms to Clinical Application for Addiction Medicine

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Glossary

Deep rTMS Delivery of rTMS pulses by using a unique type of coil (H-coil) able to generate a deeper electric field.

Excitatory rTMS protocols Conventional or patterned protocols of rTMS (i.e., high-frequency rTMS and iTBS), which usually result in increase of excitability/response facilitation.

High-frequency rTMS Conventional protocol of rTMS, in which TMS pulses are delivered with a frequency rate equal or superior to 5 Hz.

Inhibitory rTMS protocols Conventional or patterned protocols of rTMS (i.e., low-frequency rTMS and cTBS), which usually result in suppression of excitability/response inhibition.

Low-frequency rTMS Conventional protocol of rTMS, in which TMS pulses are delivered with a frequency rate inferior or equal to 1 Hz.

Motor threshold (MT) The minimal intensity at which TMS of motor cortex produces a response in the 'target' muscle. It is considered the simplest biomarker of individual excitability levels and is used to compare intensity levels across participants or studies. In clinical and research practice, the intensity of TMS is individually adjusted to the MT (usually set at 100%–120% of MT) also when TMS is applied to other cortical areas.

Paired-pulse TMS (ppTMS) The application of pairs of pulses separated by a variable interval.

Repetitive TMS (rTMS) The application of regularly repeated single TMS pulses at a certain frequency, usually defined as "trains" of stimulation.

Single pulse TMS (spTMS) The delivery of a single TMS pulse.

Theta burst stimulation (TBS) Patterned protocols of rTMS, in which short rTMS bursts at a high inner frequency (50 Hz) are applied at a rate of 5 Hz, in a continuous (cTBS) or intermittent (iTBS) modality.

Principles and Mechanisms of Action

Transcranial magnetic stimulation (TMS) is a noninvasive brain stimulation technique widely used from over 30 years to interact with the brain activity of healthy volunteers as well as of patients with brain illness (Burke et al., 2019; Lefaucheur et al., 2020). TMS relies on the physical principles of electromagnetic induction discovered by Michael Faraday in 1931. The passage of a brief and large current in a copper wire coil generates a magnetic field, which, in turn, passes the cranium with marginal attenuation and induces an electric field in the underlying neural tissue. Whether the current flow is sufficiently strong to depolarize the membrane potential, TMS gives rise to local excitation by triggering action potentials in those susceptible neurons lying within the induced electric field (Wassermann et al., 2008). Because the electromagnetic field decays with increasing distance from the coil, TMS pulse reaches a limited depth of penetration into the brain. To generate a deeper electric field, higher TMS intensity or specifically designed coils for deep stimulation may be used (e.g., double-cone coils, H-coils) (Zangen et al., 2005). In any case, a trade-off between focality and depth of penetration exists: the ability to directly stimulate deeper brain structures is obtained at the expense of inducing a wider electric field spread (Deng et al., 2013).

In addition to the local effects, TMS produces also long-distance excitatory and inhibitory effects. The action potentials directly induced by TMS spread *trans*-synaptically along cortico-cortical and cortico-subcortical projections to distant sites, resulting in a propagation of neuronal activation to the connected cortical and subcortical areas (Bestmann et al., 2004; Bohning et al., 1998; Fox et al., 1997; Ilmoniemi et al., 1997; Ruff et al., 2009; Siebner et al., 2009).

The overall outcomes of TMS at local and long-distance sites are dependent on several parameters, which contribute to determine the geometry of the induced electric field and the relative modulated neural structures. Besides the intensity of the magnetic field, the most relevant factors include the type and orientation of TMS coil, the waveform of the magnetic pulse, the direction of the current induced in the brain and the state of activity of the stimulated areas (Groppa et al., 2012; Silvanto and Pascual-Leone, 2008; Valero-Cabré et al., 2017).

TMS was first introduced by Barker and colleagues in the mid-1980s, for the pain-free stimulation of the motor cortex (Barker et al., 1985). At that time, indeed, high-voltage electrical stimulation (TES) was being used to excite the motor cortex, but it generated high pain in the scalp (Merton and Morton, 1980). In his seminal communication, Barker showed that a single TMS pulse applied over the primary motor cortex (M1) activates corticospinal tract and associated circuits, and thus induces responses in the muscles that receive input from the targeted area (Barker et al., 1985). The effects induced by TMS on the motor system could be easily detected by measuring the evoked motor responses (MEPs) of the contralateral muscles. For this reason, TMS has been extensively used to investigate the motor system functioning (Hallett, 2007), quickly becoming a diagnostic tool in clinical neurophysiology to assess the integrity of corticospinal and corticobulbar motor pathways in a wide range of neurological and psychiatric disorders (Groppa et al., 2012; Lefaucheur et al., 2020; Rossini and Rossi, 2007). Soon TMS began to be employed to stimulate cortical areas beyond the motor system in order to improve the understanding of brain–behavior relations. The peculiar ability of TMS to interact with the ongoing brain functioning with an extremely high temporal resolution and a fair spatial accuracy allowed to draw causal inferences between the role of the targeted cortical area and the resulting behavior. For the first time, cognitive neuroscientists could directly assess in a painless and noninvasive manner how experimentally induced changes in a cortical area affected behavior, emulating the intriguing approach followed by Penfield and coworkers almost 50 years before (Penfield and Jasper, 1954). The use of TMS in the functional brain mapping began to provide important complementary information to the growing evidence obtained with neuroimaging methods, which, conversely, permitted to establish purely correlative relations. In this context, the visual cortex gained special attention in the field because its stimulation induced the perception of subjective sparking lights, the so-called phosphenes, which were used as a direct measure of TMS-induced effects. Amassian and collaborators (Amassian et al., 1989) were the first to show that TMS pulses applied over the primary visual cortex at a specific latency from the onset of alphabetical characters (i.e., 80–100 ms) induced the suppression of the visual perception of the stimuli. Similarly, disruptive effects resulted also with higher order cortical areas. For instance, TMS pulses produced speech arrest when applied over the cortical areas involved in language production during a task requiring participants to count aloud (Pascual-Leone et al., 1991). This evidence directed researchers to equate TMS-induced effects to the consequences of a "virtual lesion" (Pascual-Leone et al., 1999; Walsh and Cowey, 1998; Walsh and Rushworth, 1998). In comparison to real lesion studies, however, TMS had the advantages to be time limited, reversible and repeatable. In this theoretical frame, TMS was applied to a brain region believed to be implicated in the function of interest (e.g., based on previous neuroimaging or lesion studies), while participants were involved in the performance of the cognitive/behavioral task (Burke et al., 2019). TMS pulses were thought to effectively act as an electrical interference with ongoing neuronal processes, enabling to study the temporal dynamics of brain function with high temporal resolution (Walsh and Pascual-Leone, 2003). This virtual-lesion approach to investigate causal brain−behavior relations has been widely used in several domains, including sensorimotor processing and higher cognitive functions such as memory, attention, counting and decision making (Jahanshahi et al., 1998; Kosslyn et al., 1999; Muellbacher et al., 2002; Oliveri et al., 2001; Philiastides et al., 2011; Rossi et al., 2001; Silvanto et al., 2005).

Afterward, a host of evidence showed that TMS not only could disrupt but also enhance performance on some tasks (Fecteau et al., 2006; Töpper et al., 1998; Wang et al., 2014), partly invalidating the virtual lesion concept (Miniussi et al., 2010; Ziemann, 2010). How could TMS lead to enhancements rather than deficits, if it acted as a virtual lesion by disrupting organized neural firings? At the beginning, the facilitatory effects induced by TMS were referred to as "paradoxical," but later the virtual lesion metaphor was partially left behind. The signal to noise ratio framework was introduced to explain TMS effects on behavior (Miniussi et al, 2010, 2013). The idea was that TMS artificially induces neural noise in the entire targeted region, affecting both neurons coding for the task under investigation (signal) and neurons generating background activity (noise). Depending on the amount of noise introduced on the existing signal strength, TMS can be detrimental to behavior, or it can improve performance on a task by pushing weak subthreshold signals beyond the threshold (i.e., stochastic resonance; Stocks, 2000). Other attempts to modeling TMS effects on behavior have been recently suggested (Silvanto and Cattaneo, 2017).

Rationale for the Therapeutic Use of rTMS in Neurological and Psychiatric Disorders

With technological evolution, new TMS stimulators have been introduced, enabling to generate single pulses with different configurations and repetition rates (up to 50 Hz) (Wassermann et al., 2008). In addition to the delivery of a single pulse (spTMS), TMS can be applied in pairs of pulses separated by a variable interval (i.e., paired-pulse TMS - ppTMS) or in trains of pulses in "conventional" or "patterned" protocols (Rossi et al., 2009). Conventional protocols refer to the application of regularly repeated single TMS pulses (i.e., repetitive TMS - rTMS), that, according to the frequency rate are considered low-frequency (1 Hz or less) or high-frequency

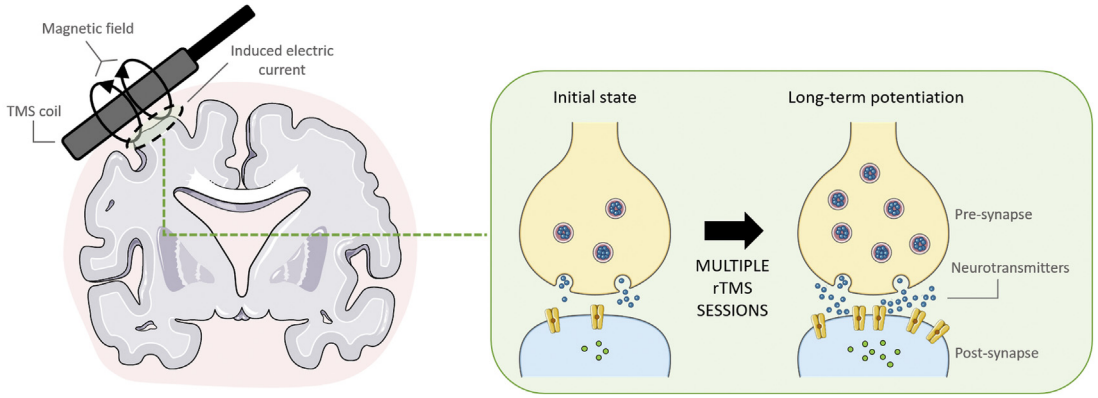

Fig. 1 A schematic representation of one of the supposed neurophysiological mechanisms (i.e., long-term potentiation – LTP) subtending lasting effects of multiple rTMS sessions.

(5 Hz or greater) rTMS protocols (Siebner and Rothwell, 2003). Patterned protocols describe the repetitive application of short rTMS bursts at a high inner frequency, interleaved by short pauses of no stimulation. The most used are the theta burst stimulation (TBS) protocols, which combine theta and gamma wave patterns: short bursts of 50 Hz rTMS are repeated at a rate of 5 Hz in a continuous (cTBS) or intermittent (iTBS) modality (Di Lazzaro et al., 2008; Huang et al., 2005).

Consistent evidence has widely shown that rTMS and TBS protocols can produce effects on brain activity, cognition or behavior that outlast the duration of stimulation itself (Thut and Pascual-Leone, 2010). These after-effects, also called offline effects in contraposition to the online effects occurring during stimulation, are critically dependent on many specific stimulation variables. For instance, low-frequency rTMS and cTBS usually result in suppression of excitability/response inhibition, while high-frequency rTMS and iTBS tend to result in facilitatory aftereffects (Aydin-Abidin et al., 2006; Chen et al., 1997; Fitzgerald et al., 2006; Romero et al., 2002; Suppa et al., 2016). On these bases, excitatory or inhibitory rTMS protocols have been alternatively applied to specific disorders according to their characteristic dysfunction of brain excitability (e.g., Wassermann and Lisanby, 2001).

Interestingly, when multiple rTMS sessions are delivered, usually with a daily frequency, cumulative effects are obtained, reflecting long-term effects of rTMS intervention (Bäumer et al., 2003; May et al., 2007). These phenomena have been ascribed to neuroplastic changes affecting the synaptic properties via long-term potentiation (LTP)- or long-term depression (LTD)-like mechanisms (Huang et al., 2017) (**Fig. 1**). Pharmacological interventions, targeting ion channels, or neurotransmitters, allowed asserting that rTMS acts on the strength of glutamatergic synapses via NMDA receptor, AMPA receptor and calcium channel (Huang et al., 2007; Nitsche et al., 2012). In addition, inhibitory GABAergic neurons and non-synaptic mechanisms, including alterations in epigenetic mechanisms as well as in molecules related to neuroplasticity such the neurotrophin Brain-Derived Neurotrophic Factor (BDNF), and the genetic variability, have been suggested as possible mediators of long-term effects (Chervyakov et al., 2015; Fidalgo et al., 2014; Müller-Dahlhaus and Vlachos, 2013; Tang et al., 2015). Though these explanations are based on indirect evidence at system level, supported by similarities with cellular mechanisms, the possibility to modulate cortical plasticity mechanisms has raised great interest in the use of rTMS as therapeutic intervention in neurology, psychiatry and rehabilitation medicine (Lefaucheur et al., 2014; Miniussi et al., 2008).

Current Evidence on Therapeutic Efficacy of rTMS

Scientific literature counts a massive proliferation of studies applying rTMS as a therapeutic tool in a wide range of neurological and psychiatric conditions. In order to establish evidence-based recommendations for the therapeutic use of rTMS, a group of European experts (Lefaucheur et al., 2014, 2020) took into account all the published rTMS studies up to 2018 considering a comprehensive range of psychiatric and neurological disorders (i.e., neuropathic and chronic pain syndromes, movement disorders, stroke, multiple sclerosis, epilepsy, disorders of consciousness, mild cognitive impairment and Alzheimer's disease, tinnitus, depression, schizophrenia, anxiety disorders, autism spectrum disorders, attention deficit hyperactivity disorders, mental retardation, functional neurological disorders and addiction). Definite efficacy of rTMS intervention has been demonstrated for neuropathic pain, major depression disorder and for hand motor recovery at the post-acute stage of stroke, whereas a probable level of efficacy was reached to improve several symptoms in fibromyalgia, Parkinson's disease, spasticity in multiple sclerosis, post-traumatic stress disorder and chronic post-stroke fluent aphasia (Lefaucheur et al., 2020). Alongside, in 2008 the US Food and Drug Administration (FDA) approved rTMS for treating major depressive disorder patients who have failed to receive satisfactory improvement from antidepressant medications. More recently, deep TMS (i.e., a further development of rTMS that delivers stimuli by using a unique type of coil called H-coil) received clearance from the FDA for the treatment of obsessive-compulsive disorder.

Rationale for the Application of rTMS in Addiction Medicine

Prompted by promising results of specific reversal approaches obtained with pharmacological or optogenetic methodologies in animal models (Diana et al., 2017; Lüscher, 2016), there is currently a growing interest in the application of rTMS treatment for addiction with the aim of reducing drug craving and associated addictive behaviors (Ekhtiari et al., 2019; Feil and Zangen, 2010).

Addiction is a chronic and relapsing condition, which is considered among the most prevalent psychiatric disorders in the world and is responsible for a devastating multifaceted economic, health and social burden. Addiction (i.e., Substance Use Disorder - SUD, as defined in DSM-5) refers to a class of diseases characterized by a compulsive use of a substance, craving (i.e., strong desire or urge to consume to substance), persevering intention to desist from substance use and by considerable amount of time spent to obtain, assume, or recover from the effects of the substance, that result in a significant social, occupational or recreational impairment (Diagnostic and Statistical Manual of Mental Disorders, Fifth edition. Arlington, VA, American Psychiatric Association, 2013). Diagnosis of SUD pertain to 10 different classes of drugs that are alcohol, caffeine, cannabis, hallucinogens, inhalants, opioids, sedative, hypnotic, stimulants and tobacco. In addition to substance-related disorders, DSM-5 includes also a behavioral addiction, i.e., gambling disorder.

Despite drugs of abuse have very different mechanisms of action and pharmacological effects, considerable evidence indicates that all of them converge on common circuitries in the brain's limbic system (Koob and Le Moal, 2005; Nestler, 2005; Volkow et al., 2011). The mesolimbic dopamine (DA) pathway, which includes neurons in ventral tegmental area of the midbrain projecting to the striatum, especially to the nucleus accumbens, is the most crucial for drug reward (Nestler, 2005). Other DA pathways, as those subtending conditioning, motivation and executive functions (e.g., inhibitory control, salience attribution and decision making) are also involved in addiction (Volkow et al., 2011; Wise, 2009). In general, this complex meso-cortico-limbic DA pathway promotes behavioral drives, which might then translate into actual behaviors, or being inhibited, based on the interplay with the mechanisms of executive control (Bechara, 2005; Schultz, 2000). Chronic exposure to drugs of abuse typically induces neurobiological adaptations of these circuits (Lüscher, 2016). Patients with substance dependence, indeed, normally show reduced levels of DA transmission in striatum (including NAc), but drug exposures or substance-related cues exaggerate DA function, in association with self-reports of drug craving. In addition, several regions of frontal cortex, such as dorsolateral prefrontal cortex (DLPFC), orbitofrontal cortex, and anterior cingulate gyrus, show hypofunctionality (Goldstein and Volkow, 2011). This altered pattern points to an imbalance between the separate, but interacting, DA circuits involved in reward and those underling executive function, with compulsivity and impulsivity as final result (Bechara, 2005; Koob and Volkow, 2016).

The rationale for rTMS treatment of addiction is grounded on the possibility of restoring the normal functioning of the meso-cortico-limbic DA pathway, through repeated stimulation protocols (rTMS and TBS) able to produce long-lasting modulations of cortical excitability (Diana et al., 2017; Gorelick et al., 2014). Given the pathophysiology of addiction, two frontal-striatal pathways (i.e., dorsolateral or ventro-medial systems) may be distinctively targeted by rTMS, in both cases with a direct access from the superficial frontal nodes of the networks. Therapeutic potential of this approach should be driven by excitability modulations of both the local stimulated sites and of the connected subcortical areas, where TMS effects spread along cortico-subcortical projections. Accordingly, strengthening the hypofunctional PFC with excitatory rTMS protocols is expected to enhance DA release in the meso-cortico-limbic circuitry (Diana et al., 2017; Hanlon et al., 2015).

Compelling evidence from preclinical studies and from single sessions of rTMS in healthy subjects support this theoretic reasoning (Gorelick et al., 2014). Strafella and colleagues (Strafella et al., 2001) assessed the effects of excitatory/high frequency rTMS on DA transmission, using positron emission tomography (PET). They found that rTMS of the left mid-DLPFC induced release of striatal DA, specifically in the caudate nucleus. Consistently, an inhibitory stimulation protocol (cTBS) applied to the same frontal area reduced striatal DA release during the performance of an executive task (Ko et al., 2008). Interestingly, it was shown with the same methodology, that high-frequency rTMS of the left DLPFC induced a focal increase of DA release also in the ipsilateral medial prefrontal cortex (i.e., anterior cingulate cortex and orbitofrontal cortex) (Cho and Strafella, 2009). When medial prefrontal cortex was instead directly stimulated with an excitatory rTMS protocol, DA release was observed mainly in the dorsal striatum, in relation with behavioral changes to a reward task (Cho et al., 2015).

rTMS to Treat Addiction

Even though the knowledge acquired from basic neuroscience studies and preclinical investigations may endorse rTMS as a promising tool to modulate the neural circuits specifically impaired in addiction, an important gap has to be bridged to translate available findings into effective clinical interventions. Notably, rTMS effects occurring in healthy brains might be different from what happens in damaged brains. For example, in an outstanding study, Kearney-Ramos and colleagues (Kearney-Ramos et al., 2018) demonstrated that in cocaine-dependent individuals the subcortical activation induced by frontal spTMS was dependent upon the structural integrity of white and gray matter of the meso-cortico-limbic pathway.

A growing number of clinical studies has been conducted with the attempt to investigate the effects of rTMS treatment on craving and substance consumption. The most targeted substances have been nicotine, alcohol, stimulants (i.e., cocaine and methamphetamine), cannabis, opioid, together with gambling disorder (for recent reviews, please refer to Coles et al., 2018; Ekhtiari et al., 2019; Spagnolo and Goldman, 2017; Zhang et al., 2019). Here we summarize the current body of findings on rTMS treatment for two of the most studied addiction related disorders: alcohol and cocaine use disorders (**Tables 1** and **2**; for recent reviews, please refer to Bolloni et al., 2018; Philip et al., 2020; Rachid, 2018).

Table 1 Summary of the clinical studies on the therapeutic use of TMS in Alcohol Use Disorder (AUD)

									Measures		Finding	
Study	*Design*	*Control*	*Sample*	*Treatment-seeking*	*TMS protocol*	*Frequency and intensity*	*Target*	*Number of sessions*	*Craving*	*Consumption*	*Craving*	*Consumption*
Mishra et al. (2010)	Parallel	Sham	45 (30/15)	NR	rTMS	10 Hz, 110% rMT	Right DLPFC	10	ACQ-NOW	NA	Active rTMS significantly reduced craving as compared to sham	
Hoppner et al. (2011)	Parallel	Sham	19 (10/9)	NR	rTMS	20 Hz, 90% rMT	Left DLPFC	10	OCDS	NA	Reduction of craving after both active and sham rTMS, with no significant differences between groups	
Mishra et al. (2015)	Parallel	Active comparator	20 (10/10)	NR	rTMS	10 Hz, 110% rMT	Left/right DLPFC	10	ACQ-NOW	NA	Significant reduction of craving after both left and right DLPFC rTMS	
Herremans et al. (2015)	Open label	None	23	NR	rTMS	20 Hz, 110% rMT	Right DLPFC	15	AUQ; OCDS	NA	Reduction of craving after rTMS protocol	
Ceccanti et al. (2015)	Parallel	Sham	18 (9/9)	NR	dTMS	20 Hz, 120% rMT	Bilateral mlPFC (left pref.)	10	VAS	Blood sample/ self report	Significant reduction of craving after active dTMS as compared to sham	Active rTMS but not sham reduced cortisol levels and prolactinemia; reduction of alcohol intake in both groups
Girardi et al. (2015)	Parallel	SDT	20 (10/10)	NR	dTMS	20 Hz, 120% rMT	Bilateral mlPFC (left pref.)	20	OCDS	NA	Greater reduction of craving in patients receiving dTMS as compared to SDT alone	
Rapinesi et al. (2015)	Open label	None	11	NR	dTMS	20 Hz, 120% rMT	Bilateral mlPFC (left pref.)	20	OCDS	NA	Significant reduction of craving after dTMS protocol	
Del Felice et al. (2016)	Parallel	Sham	20 (10/10)	Yes	rTMS	10 Hz, 100% rMT	Left DLPFC	4	VAS	Toxicological tests/self report	No significant effect of rTMS on craving	No significant effect of rTMS on alcohol intake
Addolorato et al. (2017)	Parallel	Sham	11 (5/6)	Yes	dTMS	10 Hz, 100% rMT	Bilateral mlPFC (left pref.)	12	OCDS	Breath alcohol content/TLFB	No significant effect of rTMS on craving	Significant decrease of alcohol intake after active dTMS only
Perini et al. (2019)	Parallel	Sham	56 (29/27)	Yes	dTMS	10 Hz, 120% rMT	Bilateral insular cortex	15	AUQ; PACS	Blood sample/ TLFB	Reduction of craving after both active and sham dTMS, with no significant differences between groups	Reduction of alcohol use after both active and sham dTMS, with no differences between groups

ACQ, Alcohol Craving Questionnaire; *DLPFC*, dorsolateral prefrontal cortex; *dTMS*, deep TMS; *mlPFC*, medial and lateral prefrontal cortex; *NA*, not assessed; *NR*, not reported; *OCDS*, Obssessive Compulsive Drinking Scale; *PACS*, Penn Alcohol Craving Scale; *rMT*, resting motor threshold; *rTMS*, repetitive TMS; *SDT*, Standard detoxification treatment; *TLFB*, Timeline Followback interview; *VAS*, Visual Analog Scale.

Table 2 Summary of the clinical studies on the therapeutic use of TMS in Cocaine Use Disorder (CUD)

									Measures		Finding	
Study	*Design*	*Control*	*Sample*	*Treatment-seeking*	*TMS protocol*	*Frequency and intensity*	*Target*	*Number of sessions*	*Craving*	*Consumption*	*Craving*	*Consumption*
Politi et al. (2008)	Open label	None	36	NR	rTMS	15 Hz, 100% rMT	Left DLPFC	10	VAS	NA	Reduction of craving after rTMS	
Terraneo et al. (2016)	Parallel	Routine pharmacological treatment	32 (16/16)	Yes	rTMS	15 Hz, 100% rMT	Left DLPFC	8	VAS	Urine drug test	Lower craving scores in the rTMS group compared to control	Higher number of cocaine-free drug tests in the rTMS group compared to control
Rapinesi et al. (2016)	Open label	None	7	NR	dTMS	15 Hz, 100% rMT	Bilateral mlPFC (left pref.)	12	VAS	NA	Significant reduction of craving after dTMS protocol	
Bolloni et al. (2016)	Parallel	Sham	10 (6/4)	Yes	dTMS	10 Hz, 100% rMT	Bilateral mlPFC (left pref.)	12	NA	Hair analysis		Significant reduction of cocaine intake after both active dTMS and sham, with no difference between groups
Martinez et al. (2018)	Parallel	Active comparator (high vs low frequency)/Sham	18 (6/6/6)	No	dTMS	10 Hz-1 Hz; 90%–110% rMT	Bilateral mPFC and ACC	15	VAS	Cocaine self-administration	Craving was not affected by any dTMS condition	Significant reduction of cocaine choices after high frequency dTMS only
Cardullo et al. (2019)	Open label	None	7	Yes	rTMS	15 Hz, 100% rMT	Left DLPFC	26	CCQ	Urine drug test/ self report	Significant reduction of craving scores after rTMS	Five out of 7 patients did not use cocaine for the entire duration of the study

Pettorruso et al. (2019)	Open label	None	16	Yes	rTMS	15 Hz, 100% rMT	Left DLPFC	24	CSSA	Urine drug test	Significant reduction of craving scores after rTMS treatment	Nine out of 16 patients had a negative urine drug test after rTMS
Sanna et al. (2019)	Parallel	Active comparator	47 (22/25)	Yes	dTMS/ iTBS	dTMS: 15 Hz, 100% rMT; iTBS: 80% aMT	Bilateral PFC and insula	20	CCQ	Urine drug test/ self report	Significant reduction of craving scores after both dTMS and iTBS, with no difference between groups	Significant reduction of cocaine intake after both dTMS and iTBS, with no difference between groups
Steele et al. (2019)	Open label	None	19	No	iTBS	100% rMT	Left DLPFC	30	CCQ; CCS	Urine drug test/ TLFB	Significant reduction of craving scores after iTBS	Significant reduction of the amount of money spent for cocaine consumption and of the number of days of use; change in the relationship with cocaine with a reduced compulsivity
Mahoney et al. (2020)	Single case	None	1	NR	rTMS	10 Hz; 100% rMT	Left DLPFC	7	VAS	NA	Reduction of craving after rTMS; the patient remained abstinent for 1 month after treatment	

ACC, Anterior cingulate cortex; *aMT*, active motor threshold; *CCQ*, Cocaine Craving Questionnaire; *CSS*, Cocaine Craving Scale; *CSSA*, Cocaine Selective Severity Assessment; *DLPFC*, dorsolateral prefrontal cortex; *dTMS*, deep TMS; *iTBS*, intermittent Theta Burst Stimulation; *mlPFC*, medial and lateral prefrontal cortex; *NA*, not assessed; *NR*, not reported; *rMT*, resting motor threshold; *rTMS*, repetitive TMS; *TLFB*, Timeline Followback interview; *VAS*, Visual Analog Scale.

rTMS in Alcohol Use Disorders (AUD)

The first study that adopted rTMS as a therapeutic tool in AUD was the one by Mishra and colleagues, which reported a significant reduction of alcohol craving after 10 sessions of right DLPFC 10 Hz rTMS (Mishra et al., 2010). In a subsequent study, the same research group demonstrated that the stimulation of the left DLPFC was equally effective in reducing craving scores (Mishra et al., 2015). A decrease in craving was further corroborated by other studies, particularly when adopting an accelerated rTMS protocol, which consisted in the delivery of 14 sessions of 20 Hz right DLPFC stimulation over 3 consecutive days (Herremans et al., 2015), and also when deep TMS was preferred (Ceccanti et al., 2015; Girardi et al., 2015; Rapinesi et al., 2015).

In contrast, several studies failed to support the anti-craving effect of rTMS. Höppner et al. (2011) did not report a significant decrease of craving after 10 sessions of 20 Hz rTMS targeting left DLPFC. Similarly, 4 sessions of 10 Hz rTMS over the same brain region did not induce any modification over time in alcohol craving (Del Felice et al., 2016). Of note, the lack of a significant effect of rTMS in craving has also been replayed in deep TMS studies (Addolorato et al., 2017; Perini et al., 2019).

Regarding substance consumption, reduced alcohol intake after multiple sessions of deep high frequency rTMS targeting bilateral prefrontal cortices has been demonstrated by two studies measuring cortisolemia and prolactinemia in blood sample and collecting a self-report alcohol intake questionnaire, respectively (Addolorato et al., 2017; Ceccanti et al., 2015). However, as for craving, other studies did not replicate these findings. In particular, Perini et al. (2019) applied daily sessions of 10 Hz deep rTMS (by means of an H-coil) for 3 weeks and reported that alcohol decrease was not significant neither when analyzing objective biomarkers nor when estimated by self-report results. In line with craving results, Del Felice et al. (2016) did not find any modification in alcohol intake (measured with toxicological testing and self-report) after 4 sessions of left DLPFC 10 Hz rTMS.

rTMS in Cocaine Use Disorders (CUD)

Following the preliminary evidence on the ability of high frequency rTMS applied over the left DLPFC to transiently reduce craving in cocaine dependent patients (Camprodon et al., 2007), Politi et al. (2008) were the first to investigate the potential of 10 daily sessions of 15 Hz rTMS over the left DLPFC in reducing cocaine craving. Authors reported a reduction of craving levels as assessed by a Visual Analog Scale (VAS). An anti-craving effect of 15 Hz left DLPFC rTMS in CUD was further corroborated by two later studies (Pettorruso et al., 2019; Terraneo et al., 2016) and replicated in studies adopting deep TMS protocols (Rapinesi et al., 2016; Sanna et al., 2019) or intermittent Theta Burst Stimulation (Sanna et al., 2019; Steele et al., 2019). In contrast, a randomized controlled trial comparing the anti-craving effect of 3 weeks of daily sessions of high frequency (10 Hz), low frequency (1 Hz) or sham dTMS failed to yield a significant effect (Martinez et al., 2018).

Considering substance consumption as the main outcome, a reduction of cocaine intake verified by toxicological testing was reported after multiple sessions of both high frequency rTMS over the left DLPFC (Pettorruso et al., 2019; Terraneo et al., 2016) and bilateral prefrontal cortex 15 Hz rTMS and iTBS when using an H-coil (Sanna et al., 2019). Bolloni et al. (2016) randomized 10 treatment-seeking CUD patients to receive 12 sessions of either 10 Hz deep TMS or sham stimulation over the bilateral prefrontal cortex. In contrast to previous findings, the latter study failed to endorse rTMS as an effective tool to limit substance consumption since the reported reduction effect was observed after both active and sham rTMS with no significant difference between groups.

Furthermore, the therapeutic effects of rTMS have been investigated in polysubstances abuse. Cardullo et al. (2019) explored the effect of rTMS treatment in patients with a diagnosis of CUD in comorbidity with gambling disorder, reporting an amelioration in craving scores and a reduction of cocaine consumption. Finally, a single-case report on cocaine and opioid use disorder recently showed a reduction of craving and a 1-month lasting abstinence following 7 sessions of left DLPFC 10 Hz rTMS (Mahoney et al., 2020).

Critical Overview

Results of clinical studies investigating the effects of rTMS treatment in addiction appear promising but cannot reveal conclusive evidence neither on craving nor on substance consumption. Reliefs induced by rTMS treatment are reported in all the open-label studies, which are biased by the lack of a control condition. In parallel design studies, significant reductions of craving or substance abuse are sometimes equally found after both real rTMS intervention and control condition. Curiously, positive effects are achieved mostly with excitatory rTMS protocols, irrespective of the targeted frontal area (DLPFC vs. medial PFC; left vs. right hemisphere). Importantly, the role played by patients' expectations about the efficacy of treatment has yet to be scrutinized, especially when the recruited patients are treatment-seeking individuals who failed to respond to other treatments. Even though expectations-related placebo effects are inherent to any type of rTMS intervention, as well as medical or pharmaceutical clinical trials (Price et al., 2008), this issue assumes a stronger importance when testing treatments for addiction. Indeed, the neural mechanisms generating and updating the expectations that shape our choices and behaviors (Schultz, 2013) rely on the same fronto-striatal pathways impaired in SUD. For instance, the meso-cortico-limbic network underlying reward anticipation is also involved in the anticipation of placebo-induced pain relief, which is the mere expectation of clinical benefits despite no actual treatment (Benedetti, 2014; De la Fuente-Fernández et al., 2001). Therefore, it might be argued that the patient's positive expectations with regard to rTMS treatment may endogenously activate the same pathway exogenously stimulated by rTMS intervention, contributing to the results. Similar additive effects have been reported between expectations and methylphenidate

pharmacological effects in cocaine abusers (Volkow et al., 2003). A greater increase of glucose metabolism was detected when patients expected to receive the drug than when they did not, proving that expectation amplifies the effects of the stimulant drug in the brain, reinforcing its final outcome.

Besides the mere consideration that medical devices, such as rTMS, might produce enhanced placebo effects compared with standard interventions (Kaptchuk et al., 2000), some studies have empirically disentangled placebo contribution during rTMS. In 2006, Strafella et al. (2006) tested whether the expectation of therapeutic benefit from rTMS induced striatal DA modulations in Parkinson's disease patients. Using the same PET methodology as in the studies previously described (e.g., Strafella et al., 2001), they found that placebo rTMS induced a significant DA increase in dorsal and ventral striatum. More recently, a systematic review and meta-analysis revealed a large placebo response in rTMS trials for major depressive disorder, thus emerging as a possible component of therapeutic response to rTMS in this psychiatric disease (Razza et al., 2018).

To conclude, available evidence is not sufficient to firmly demonstrate that rTMS effects on craving and substance consumption are solely ascribed to the physiological mechanisms driven by the magnetic fields. At the same time, considering the promising results obtained by some clinical studies and the strong theoretical rationale behind the use of rTMS in substance use disorders, rTMS treatments may represent a concrete chance to develop innovative treatment options in addiction medicine beyond available conventional therapies.

Future research should aim at elucidating all the factors that contribute to rTMS response and their interaction. A proper insight of these mechanisms, along with a better definition of patient's susceptibility to neurostimulation, will be crucial to design rTMS treatments with stronger and more persistent effects. In this framework, the development of predictive indices of treatment success, such as biological markers, could account for the high inter-individual differences in the response to rTMS treatment and, therefore, pave the way for tailoring treatment strategies to individual profiles toward a personalized addiction medicine approach.

Acknowledgment

D.B. was supported by the Italian Ministry of Health (Ricerca Corrente).

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