Alcohol 74 (2019) 113–124

Contents lists available at ScienceDirect

Alcohol

journal homepage: http://www.alcoholjournal.org/

Repetitive transcranial magnetic stimulation: Re-wiring the alcoholic human brain

Marco Diana [a, *], Corinna Bolloni [a], Mariangela Antonelli [b], Daniela Di Giuda [c], Fabrizio Cocciolillo [c], Liana Fattore [d], Giovanni Addolorato [b]

[a] Laboratory of Cognitive Neuroscience 'G. Minardi', Department of Chemistry and Pharmacy, University of Sassari, Sassari, Italy
[b] Alcohol Use Disorder Unit, Department of Internal Medicine, Gastroenterology and Hepatology, Catholic University of Rome, Italy
[c] Institute of Nuclear Medicine, Università Cattolica del Sacro Cuore, Rome, Italy
[d] CNR Institute of Neuroscience-Cagliari, National Research Council, Italy

ARTICLE INFO

Article history:
Received 18 February 2018
Received in revised form
15 May 2018
Accepted 28 May 2018

Keywords:
Alcohol
Transcranial magnetic stimulation
Alcohol intake
Abstinence

ABSTRACT

Alcohol use disorders (AUDs) are one of the leading causes of mortality and morbidity worldwide. In spite of significant advances in understanding the neural underpinnings of AUDs, therapeutic options remain limited. Recent studies have highlighted the potential of repetitive transcranial magnetic stimulation (rTMS) as an innovative, safe, and cost-effective treatment for AUDs. Here, we summarize the fundamental principles of rTMS and its putative mechanisms of action via neurocircuitries related to alcohol addiction. We will also discuss advantages and limitations of rTMS, and argue that Hebbian plasticity and connectivity changes, as well as state-dependency, play a role in shaping some of the long-term effects of rTMS. Visual imaging studies will be linked to recent clinical pilot studies describing the effect of rTMS on alcohol craving and intake, pinpointing new advances, and highlighting conceptual gaps to be filled by future controlled studies.

Introduction

Alcohol use disorder (AUD) represents a serious health concern that affects about 240 million people, i.e., almost 5% of the world's adult population (Gowing et al., 2015), with prevalence varying widely between countries and being significantly impacted by drinking cultures and social norms. Furthermore, AUD and alcohol-related impairments are among the most widespread psychiatric disorders (Alonso et al., 2004; Grant et al., 2015). Despite the great progress made in understanding the central mechanisms underlying alcohol addiction and in individuating associated risk factors, alcoholism remains a serious medical and social concern. Clinical research is evaluating different approaches for treating intoxicated patients and maintaining them alcohol-free, including acupuncture (Chen et al., 2018; Shin, Lim, Yang, & Kim, 2017), mindfulness-based interventions (Caselli, Gemelli, Spada, & Wells, 2016; Sancho et al., 2018), cognitive-behavioral therapy (CBT) (Carroll & Kiluk, 2017), and therapist-guided internet-based CBT (Sundström et al., 2017), motivational interviewing (Hettema et al., 2018; Morgenstern et al., 2017), yoga (Hallgren, Romberg, Bakshi, & Andréasson, 2014), and exercise intervention (Hallgren, Andersson, Ekblom, & Andréasson, 2018; Jensen, Nielsen, Ekstrøm, & Roessler, 2018).

At present, a number of pharmacological tools are available, among which are acamprosate and naltrexone, that proved to be more effective in promoting abstinence and reducing craving, respectively (Maisel, Blodgett, Wilbourne, Humphreys, & Finney, 2013), and disulfiram that acts as a deterrent by inhibiting aldehyde dehydrogenase, thus leading to acetaldehyde accumulation when alcohol is consumed (Krampe & Ehrenreich, 2010). Nalmefene (6-methylene naltrexone) and sodium oxybate (GHB) are also approved as relapse prevention medications in patients presenting with mild to moderate AUD (Caputo et al., 2016; Soyka, 2016). Finally, as off-label treatment, the GABA-B receptor agonist, baclofen, has been temporarily approved in France for treating AUD (Soyka & Müller, 2017), due to its ability to reduce alcohol intake in both humans (Addolorato et al., 2002, 2000; Pastor, Jones, & Currie, 2012) and laboratory animals (Holtyn, Kaminski, & Weerts, 2017; Maccioni et al., 2012). Yet, each of these pharmacological treatments include limitations (e.g., modest effect size, abuse liability)

* Corresponding author. 'G. Minardi' Laboratory of Cognitive Neuroscience Department of Chemistry and Pharmacy, via Muroni 23, 07100, University of Sassari, Italy.
E-mail address: dsfdiana@uniss.it (M. Diana).

https://doi.org/10.1016/j.alcohol.2018.05.011
0741-8329/

and side effects (Antonelli et al., 2018; Goh & Morgan, 2017), thus highlighting the need for exploring further possibilities. In this context, non-pharmacological approaches, such as deep brain stimulation (DBS) and transcranial magnetic stimulation (TMS), are beginning to be scrutinized systemically.

This review will focus on the use of the TMS technique, which has recently shown new potential applications in the treatment of different psychiatric disorders, such as depression (Filipčić et al., 2018; Wei et al., 2017), as well as in different forms of drug addiction (Diana et al., 2017; Hanlon et al., 2015). A growing body of evidence shows, for example, that TMS application is able to reduce cocaine intake (Bolloni et al., 2016; Martinez et al., 2018; Terraneo et al., 2016), craving for cocaine (Camprodon, Martínez-Raga, Alonso-Alonso, Shih, & Pascual-Leone, 2007; Rapinesi et al., 2016; Terraneo et al., 2016), and significantly reduces craving for heroin (Shen et al., 2016) and methamphetamine (Su et al., 2017) in long-term addicts. Moreover, TMS significantly reduces the number of cigarettes smoked (Dinur-Klein et al., 2014), attenuates nicotine craving in short-term abstinent smokers (Pripfl, Tomova, Riecansky, & Lamm, 2014), and reduces the risk of relapse in motivated abstinent patients (Sheffer et al., 2018). However, a single rTMS session targeting the dorsolateral prefrontal cortex (DLPFC) did not reduce cue-induced craving in heavy cannabis users (Sahlem, Baker, George, Malcolm, & McRae-Clark, 2018). Notably, TMS was found to significantly reduce gambling reinforcement in non-comorbid pathological gamblers (Zack et al., 2016) and to decrease cue-induced cravings among pathological gamblers seeking treatment (Sauvaget et al., 2018). Negative, when not opposite (Li et al., 2013), results have also been reported (Kozak et al., 2018), which pointed to the need of individuating the most appropriate experimental protocols and patient populations that could most benefit from TMS application.

TMS physiology

Transcranial magnetic stimulation (TMS) is a non-invasive method for injecting electric field (E-field) pulses into the brain, leading to neuronal action potential generation (Barker, Jalinous, & Freeston, 1985; Di Lazzaro, Ziemann & Lemon, 2008; Terao & Ugawa, 2002). Magnetic fields project virtually unimpeded through the electrically highly insulating skull, yielding strong and spatially focused intracranial currents. TMS is a remarkably flexible tool where different stimulation parameters engage different neuronal mechanisms. Each TMS pulse lasts only ~0.2 msec, which allows targeting of timing-dependent neuronal processes. Single pulses (spTMS) and paired pulses (ppTMS) have neuronal effects lasting only a fraction of a second. However, longer TMS pulse sequences may induce long-term neuroplastic changes, therefore producing enduring changes endowed with therapeutic potential.

A single magnetic pulse causes a local activation under the coil and distant/remote activations in connected cortical and subcortical areas (Bestmann, Baudewig, Siebner, Rothwell, & Frahm, 2004; Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005). Regardless of the various factors that influence its efficacy, the importance of the baseline cortical activation state on the impact of TMS is fundamental (Silvanto & Pascual-Leone, 2008). This state-dependency is key, as the neural impact of any external stimulus represents an interaction with the ongoing brain activity at the time of stimulation. The effects of external stimuli are thus not only determined by the properties of that stimulus, but also by the activation state of the brain. Accordingly, it was shown that baseline cortical activity determines whether TMS facilitates or impedes behavior (Silvanto, Cattaneo, Battelli, & Pascual-Leone, 2008).

It is important to note that TMS is unlikely to interfere with the physiological activities that are mediated by the targeted cortical areas only, since its effects may result from the combination of the effect on the targeted cortical area with those on the interconnected regions, as a function of the richness of the anatomical connectivity. Notably, cortical dysconnectivity among regions of the brain reward system in alcohol dependence has been reported (Kuceyeski, Meyerhoff, Durazzo, & Raj, 2013), being the microstructural integrity of white matter fiber networks, i.e., white matter connectivity, functionally compromised in patients with AUD. These patients also show significantly reduced gray matter volume as compared with healthy controls in several brain regions of the mesocorticolimbic system (Wang et al., 2016).

TMS effects at primary activation sites

Discharge of the TMS stimulator unit delivers a strong current pulse through the coil placed above the scalp (Barker et al., 1985). The resulting induced E-field drives electric currents in the brain. The shape of the intracranial E-field, and therefore the activated brain area, depends on the coil geometry and volume conductor properties of the head (Nummenmaa et al., 2013). For a more detailed description of the basic component of TMS equipment, we refer the reader to the elegant recent review of Valero-Cabréa, Amengual, Stengel, Pascual-Leone, & Coubard (2017). As a result, TMS primary E-fields are always strongest on the brain surface and rapidly attenuate toward depth (Deng, Lisanby, & Peterchev, 2013). The spatial accuracy and depth penetration depend on coil design; some coil geometries (8-shaped coil) project focal but quite superficial E-fields, whereas larger coils (circular, double-cone) can offer modest increases in depth penetration at the cost of reduced focality (Deng et al., 2013). The H-coil is unique in this respect, as it delivers deep, simultaneous bilateral stimuli (Roth, Zangen, & Hallett, 2002, 2007). Very recently, an atlas of optimized TMS coil orientations and positions has been developed (Gomez-Tames, Hamasaka, Laakso, Hirata, & Ugawa, 2018), which will hopefully lead in the near future to a personalized application of the TMS to obtain the most effective stimulation.

In the human brain, TMS physiology has been studied mainly with spTMS to the primary motor cortex (M1) while recording motor evoked potentials (MEPs) from peripheral muscles. Alternatively, TMS-evoked brain activity can be observed directly with electroencephalography (EEG) (Ilmoniemi et al., 1997), positron emission tomography (PET) (Paus et al., 1997), or functional magnetic resonance imaging (fMRI) (Bohning et al., 2000). More details have been revealed through *in vitro* (Pashut et al., 2014; Radman, Ramos, Brumberg, & Bikson, 2009) and *in vivo* animal studies (Edgley, Eyre, Lemon, & Miller, 1997; Mueller et al., 2014). Since the neuronal activations are driven by electric current pulses, TMS is merely an effective painless means of transporting them through the skull of a conscious subject and is therefore able to modulate brain activity without surgery, anesthesia, or induction of seizures.

RTMS long-term effects at the primary activation site

The frequency of rTMS is the major determinant in whether inhibitory or facilitatory long-term plasticity emerges (Chen et al., 1997; Huang et al., 2005; Pascual-Leone, Valls-Solé, Wassermann, & Hallett, 1994). For safety reasons (Rossi, Hallett, Rossini, & Pascual-Leone, 2009), most clinical trials use intensities <120% of motor threshold, which could limit the plasticity-inducing mechanisms. However, plastic changes do not require rTMS intensities that exceed pyramidal cell action potential thresholds; even subthreshold rTMS (~70–100% MT) can modulate cortical excitability, possibly by changing the synaptic strengths between interneurons and pyramidal cells. The interactions between frequency, intensity, and orientation in rTMS-induced plasticity have not been fully

characterized, and several studies have reported major inter-individual differences in the magnitude and direction of the plastic effects for both rTMS (Maeda, Keenan, Tormos, Topka, & Pascual-Leone, 2000; Ridding & Ziemann, 2010) and theta burst stimulation (TBS) (Hamada, Murase, Hasan, Balaratnam, & Rothwell, 2013; Vernet et al., 2014). Sources of variability (e.g., geometry, timing, and state-dependence) on the effect of rTMS on excitability and the other performance indicators have been previously discussed by Pell, Roth, and Zangen (2011).

TMS effects at secondary activation sites

Secondary activations rely on neurotransmitter release at the secondary target. Thus, the TMS timings and frequencies are critical. Secondary activations require efferent pyramidal cell action potential triggering at the primary site. Another mechanism for secondary activations is back-propagating (antidromic) action potentials from the primary activation site. Hence, rTMS of the frontal (and prefrontal) cortex can lead to the acute subcortical release of a wide variety of neurotransmitters (Baeken et al., 2011; Cho & Strafella, 2009; Strafella, Paus, Barrett, & Dagher, 2001; Strafella, Paus, Fraraccio, & Dagher, 2003). Secondary effects, such as connectivity-based spread from DLPFC to mesolimbic areas in major depressive disorder, are often therapeutically relevant (reviewed in Baeken & De Raedt, 2011).

Cellular-level mechanisms underlying rTMS long-term plasticity

Mechanisms underlying rTMS long-term plasticity are presently the focus of many research groups active in the field (reviewed in Fitzgerald, Fountain, & Daskalakis, 2006; Funke & Benali, 2011; Hoogendam, Ramakers, & Di Lazzaro, 2010; Müller-Dahlhaus & Vlachos, 2013; Pell et al., 2011; Tang, Thickbroom, & Rodger, 2015; Ziemann et al., 2008). RTMS cell culture and slice electrophysiology studies have identified mechanisms that require simultaneous activation of pre- and postsynaptic cells, reminiscent of the D-mechanism (Lenz et al., 2015; Müller-Dahlhaus & Vlachos, 2013; Vlachos et al., 2012) and of the classical NMDAR-dependent Hebbian plasticity. However, since the D-mechanism requires TMS intensities above the typical rTMS safety limits (Rossi et al., 2009), these mechanisms might not be engaged in clinical trials. As the intracortical interneurons are activated even at subthreshold TMS intensities (Fig. 1), modulation of GABAergic input to pyramidal neurons is likely to play a role in rTMS plasticity (Barr, Farzan, Davis, Fitzgerald, & Daskalakis, 2013; Daskalakis et al., 2006; Lenz et al., 2015). Yet, it is likely that multiple mechanisms, differing in the requirement for postsynaptic activation and its timing, coexist (Normann et al., 2000; Raymond, 2008).

Since 1 Hz (inhibitory) vs. 20 Hz (excitatory) rTMS produces opposing effects, the individual pulses must have neuronal interactions across time. For 20-Hz rTMS, Ca^{2+} accumulates in the postsynaptic dendrite, increasing the likelihood that the presynaptic axon and postsynaptic dendrite are simultaneously active, which potentiates the synapse (Hebbian plasticity). In contrast, for 1-Hz stimulation, Ca^{2+} does not accumulate and the presynaptic activation fails to evoke postsynaptic action potentials at intensities below the D-mechanism threshold, resulting in a weakened synapse (Yang, Tang, & Zucker, 1999). While this simple model can explain the difference between high- and low-frequency rTMS effects, the reaction cascade is likely more complex (Tigaret, Olivo,

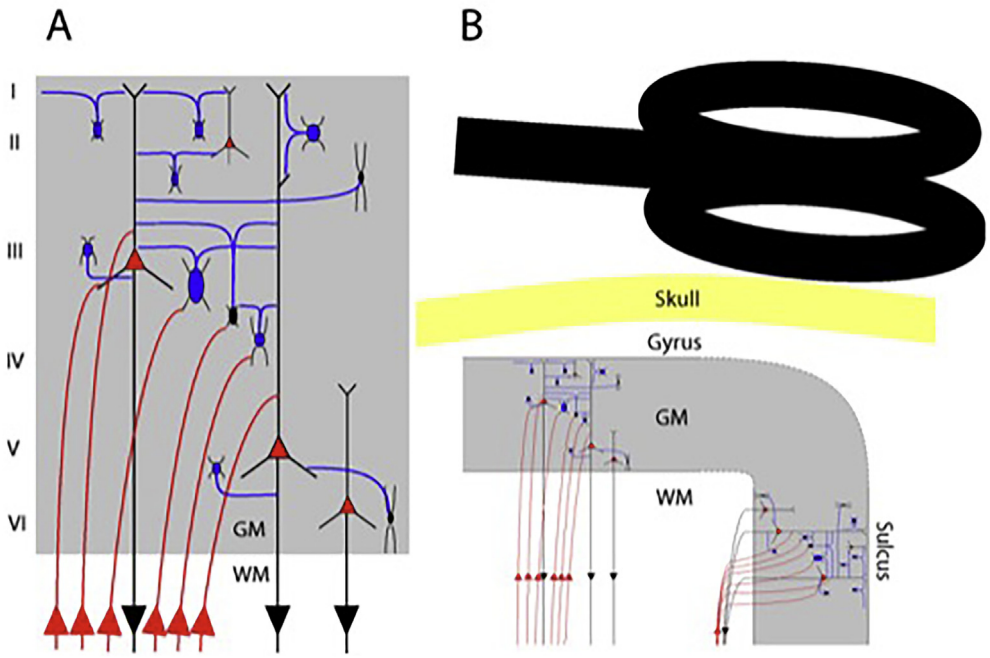

Fig. 1. The neuroanatomical bases for single-pulse TMS in humans. **A**. Cortical column in gray matter (GM). A column is an assembly of cells containing pyramidal cells (red triangular cell bodies), inhibitory interneurons (blue cell bodies), and a small number of excitatory interneurons (black cell bodies). Only pyramidal cells send outputs to white matter (WM). Cell types and connections vary depending on cortical layer I–VI. Dendrites have higher activation thresholds than axons, making axons preferred activation sites for TMS, particularly at the axon initial segment, synaptic terminals, and the places where they curve. Note that both afferent (red arrows) and efferent (black arrows) axons may be activated, leading to orthodromic and antidromic propagation to WM, respectively. Interneurons typically have lower activation thresholds than pyramidal neurons. **B.** Cortical columns in a gyrus and a sulcus. An 8-shaped TMS coil is shown above the skull (not to scale). The induced intracranial primary currents flow always tangential to the skull. Consequently, relative orientation between the currents and columns is ~90° rotated in gyri vs. sulci. Sulcal activations are sensitive to whether the currents flow orthogonal to the sulcal wall (parallel to the column) or parallel to it, whereas on gyri the primary currents always flow parallel to the cortex. Correspondingly, rotating the coil strongly influences sulcal activations, but has little effect in gyri. Note, also, that in sulci the afferent/efferent axons make sharp turns at the GM/WM border, making them preferred activation sites. (For interpretation of the references to color/colour in this figure legend, the reader is referred to the Web version of this article.)

Sadowski, Ashby, & Mellor, 2016). It also appears that the mechanisms for TBS are partially different from rTMS (Di Lazzaro, Pilato, et al., 2008; Huang et al., 2005; Huang, Rothwell, Chen, Lu, & Chuang, 2011; Larson & Munkácsy, 2015). Indeed, when continuous TBS (cTBS) was tested in comparison with different rTMS protocols, namely intermittent TBS (iTBS) and low-frequency (1 Hz) rTMS, in addition to common effects of low- (1 Hz) and high-frequency (TBS) stimulation on protein expression, significant differences in the quantity and time course of changes were reported (Trippe, Mix, Aydin-Abidin, Funke, & Benali, 2009). CTBS of M1 in humans has been shown to induce significant inhibition of synaptic transmission by increasing GABA concentration without any significant change in glutamate levels (Stagg, Wylezinska, et al., 2009), which could represent a mechanism through which TBS generates its long-lasting effects on corticospinal excitability.

The *synaptic* mechanisms discussed above may lead to changes via dendritic spine growth and receptor/neurotransmitter regulation, with possible contributions from presynaptic axonal sprouting and re-uptake modulation. In addition, *non-synaptic* mechanisms may be involved, such as metabotropic receptor activation, BDNF up-regulation (Cheeran et al., 2008; Zanardini et al., 2006), glial cell modulation (Chen et al., 2013; Letellier et al., 2016), and epigenetic changes (Etiévant et al., 2015).

RTMS neuroplastic effects on addiction circuitry

Compelling evidence from preclinical and clinical studies indicates that rTMS of some frontal brain regions produces adaptations of specific subcortical neural circuits, resulting in significant behavioral changes (Ceccanti et al., 2015; Cho & Strafella, 2009; Gesner, Schellenberg, Garside, George, & MacMillan, 2011; Keck et al., 2002; Löffler et al., 2012; Zangen & Hyodo, 2002). This effect may be mediated by modifications in the release of neurotransmitters and neuromodulators with effects on synaptic gain, signaling pathways, and gene transcription.

Chronic exposure to drugs of abuse typically induces reward-related behaviors by producing neurobiological adaptations of the mesocorticolimbic dopamine system (Baik, 2013; Ikemoto & Bonci, 2014), which is also involved in aversive effects of drug consumption (Matsui, Jarvie, Robinson, Hentges, & Williams, 2014; Pignatelli & Bonci, 2015; Volman et al., 2013) and represents negative motivation underlying the occurrence of relapses. Hence, the dopamine hypothesis of drug addiction (Melis, Spiga, & Diana, 2005), key in the brain disease model of addiction, has mainly focused attention on the dopamine pathway as a neural substrate of substance use disorders and drug action (Diana, 2011; Koob & Volkow, 2010; Lüscher, 2016; Melis et al., 2005; Volkow, Koob, & McLellan, 2016). Seminal preclinical studies have shown that increased AMPA receptor-mediated synaptic responses are associated with long-term potentiation (LTP) of glutamatergic synapses onto ventral tegmental area (VTA) dopamine neurons after both acute and chronic drug exposure (Argilli, Sibley, Malenka, England, & Bonci, 2008; Bellone & Lüscher, 2006; Chen et al., 2008; Good & Lupica, 2010; Kourrich, Calu, & Bonci, 2015; Mameli, Balland, Luján, & Lüscher, 2007; Saal, Dong, Bonci, & Malenka, 2003; Ungless, Whistler, Malenka, & Bonci, 2001). This form of synaptic plasticity, pivotal in memory and learning mechanisms, represents itself a portion of a '*drug engram*' (or drug memory trace), which precedes the subsequent specific and long-lasting neurocircuitry modifications resulting from chronic drug use in addicted individuals (Bock et al., 2013; Chen et al., 2013; Hsiang et al., 2014; Kasanetz et al., 2010, 2013).

Clinical data strongly support the hypothesis that brain dopaminergic neurotransmission is deeply altered in drug addiction (reviewed in Fattore & Diana, 2016), with lowered dopamine receptors and drug consumption triggering much smaller increases in dopamine levels (Martinez et al., 2005; Volkow et al., 2016, 2006; Wiers, Cabrera, Skarda, Volkow, & Wang, 2016). This state, which is characterized by anhedonia and is associated with a hypoactivity of the mesocorticolimbic dopaminergic system, increases the risk of drug use escalation and relapse, thus perpetuating the addiction cycle (Hatzigiakoumis, Martinotti, Giannantonio, & Janiri, 2011; Stein, 2008; Volkow et al., 2016). Neural changes associated with the addicted state are embedded within the mesocorticolimbic system, and spread to the circuit of the extended amygdala and the "anti-reward" system (George, Koob, & Vendruscolo, 2014; Koob & Le Moal, 2005) involving corticotropin-releasing factor (CRF) and glutamate. In particular, glutamate transmission has been shown to be tightly time-locked with dopamine signaling to promote spine enlargements (Yagishita et al., 2014), thus favoring Hebbian-learning mechanisms through spike timing dependent-plasticity (Dan & Poo, 2006). Consistent with a close interdependence between dopamine and glutamate transmission, alcohol-dependent rats show an impaired NMDA-dependent long-term potentiation (LTD), with a loss of long-thin dendritic spines (Spiga et al., 2014). Since these spines are fundamental learning sites (Kasai, Matsuzaki, Noguchi, Yasumatsu, & Nakahara, 2003), in which dopamine and glutamate converge to form the ventral striatal 'synaptic triad' (Freund, Powell, & Smith, 1984), their low dopamine tone dependent-loss may underlie learning deficits of alcoholism. It is important to note that rTMS promotes spine formation in the entorhino-hippocampal slice culture and that the effects of a magnetic field-induced electric current on spine size are predominantly seen in small spines, which suggests differential effects on specific subpopulations of spines (Vlachos et al., 2012). These experiments are particularly relevant as they indicate a direct action on spines, even when they are studied *in vitro* with afferents removed by the surgical procedure. In addition, the strengthening of the accumbal indirect pathway, as indexed by a potentiation of synapses upon dopamine D2 receptor- (D2) containing spiny neurons (SNs) of the nucleus accumbens (NAc), was associated with resilience toward compulsive cocaine seeking (Bock et al., 2013). Conversely, the weakening of the accumbal indirect pathway might be a synaptic marker required for the expression of compulsive behavior toward drugs such as cocaine and alcohol (Bock et al., 2013; Chen et al., 2013; Renteria et al., 2016). These findings provide the neurobiological underpinnings for a therapeutic role of rTMS-driven stimulation of the prefrontal cortex (PFC) on cocaine dependence. As a case in point, the optogenetic work on rats with compulsive cocaine self-administration (Chen et al., 2013) inspired a pilot open-label clinical study, where high frequency rTMS on DLPFC reduced cocaine use in patients with cocaine use disorder (Terraneo et al., 2016). This result is consistent with another pilot open-label study where high frequency rTMS on the DLPFC reduced spontaneous craving for cocaine (Politi, Fauci, Santoro, & Smeraldi, 2008). These findings have been recently confirmed by another sham-controlled pilot study in which bilateral rTMS of DLPFC resulted in a lasting (9 months) reduction in cocaine intake, as measured by hair analysis (Bolloni et al., 2016).

Visual imaging studies have shown that high frequency rTMS of PFC induces a sustained increase of dopamine levels in the human ventral striatal complex (Strafella et al., 2001), cortical areas (Cho & Strafella, 2009), and microdialysate dopamine efflux in rodent NAc (Keck et al., 2002; Löffler et al., 2012; Zangen & Hyodo, 2002). A direct stimulation of the NAc by the induced electric field appears to be unlikely because this latter increase sharply decays (Löffler et al., 2012), thus suggesting indirect effects of PFC stimulation on neurochemical changes occurring in NAc (George et al., 2002) through NAc-projecting dopamine neurons (see details in Diana, 2011). Remarkably, high frequency rTMS does not modify

glutamate levels in the rat NAc (Löffler et al., 2012), whereas low frequency rTMS does (Zangen & Hyodo, 2002). This effect is consistent with the notion that differences in rTMS frequency and pattern result in discrete short- and long-term effects on neural plasticity (Houdayer et al., 2008; Huang et al., 2005), although the ability of rTMS to induce long-term effects on plasticity remains unclear and controversial. In any case, the translational studies summarized above suggest that rTMS mechanisms of action may involve neuromodulation of subcortical areas, e.g., the NAc and the VTA, via its broader action to cortical areas like the DLPFC. In the addiction field, two sham-controlled and double-blind controlled studies support this notion. These studies indicated that deep rTMS resulted in a significant reduction in the number of drinks per day, in craving for alcohol in alcoholic patients (Ceccanti et al., 2015; Nardone et al., 2012), and in cigarette use and level of nicotine dependence in cigarette smokers (Dinur-Klein et al., 2014).

Another issue related to the clinical applications of rTMS in addiction is laterality, i.e., where rTMS can be applied. Some studies targeted the left DLPFC, while a smaller number of studies targeted the right DLPFC, but reported discrepant results as, for example, one study reported reduced spontaneous craving for cocaine after rTMS targeting the right, but not the left, side (Camprodon et al., 2007), while another study showed that daily sessions of TMS to the left DLPFC gradually reduce cocaine craving (Politi et al., 2008). Interestingly, Mishra and colleagues observed a significant reduction in the intensity of craving in patients receiving either right or left rTMS, but with no difference in anti-craving efficacy between the two groups (Mishra, Praharaj, Katshu, Sarkar, & Nizamie, 2015). However, none of these studies used a sham control group, the samples were small, and both used an H-coil, which is able to stimulate the DLPFC (and insula) bilaterally. In summary, the clinical work conducted until now does not provide a firm answer on whether left, right, or bilateral stimulation may be the most effective approach. Nonetheless, the issue of a potential laterality brings intriguing translational questions (Table 1).

Dopamine role in experience-dependent plasticity, which can be dynamically affected by both short- and long-term activity-dependent forms of plasticity, is well known. Nonetheless, investigation of whether this asymmetry takes part in the control of neuronal (e.g., D2-SNs) activity, whose re-wiring might contribute to the reduction in drug craving and taking in humans (Ceccanti et al., 2015; Terraneo et al., 2016), is still elusive. High frequency rTMS increases dopamine levels not only in the NAc, PFC, and anterior cingulate cortex (ACC), but also in the hippocampus, where activation of specific ensemble neurons is sufficient for engram retrieval (Liu, Liu, Zhang, & Yu, 2012). Accordingly, Hsiang et al. (2014) reported that a small portion of neurons in the amygdala is recruited to be part of the “cocaine engram”. This finding is particularly relevant because the amygdala is involved in those processes through which a neutral cue acquires conditioned rewarding properties, because of being paired with a rewarding stimulus, such as cocaine (Baxter & Murray, 2002; Tye, Stuber, de Ridder, Bonci, & Janak, 2008). Moreover, one might speculate that high frequency rTMS of left DLPFC might strengthen synaptic plasticity at excitatory synapses onto D2-SNs. As such, D2-SNs could be allocated as a critical component to a large compulsive drug taking memory engram. In fact, the weakening of excitatory synapses onto D2-SNs is associated with the expression of habitual and compulsive drug seeking (Bock et al., 2013; Corbit, Nie, & Janak, 2014; Renteria et al., 2016).

TMS in alcohol use disorder

Although the dopaminergic system plays a crucial role in the development of AUDs (Tupala, Hall, Halonen, & Tiihonen, 2004), at present the question remains whether alcohol dependence arises from a dysfunction of the dopaminergic system or whether chronic alcohol intake induces an alteration in dopamine circuits, or both.

It is well established that dopamine increases in the extracellular space after repeated alcohol intake by modulating the D2/D3 receptors (Ford, 2014; Grace, 2009), whereas a reduction of dopaminergic activation occurs in alcohol withdrawal syndrome or promotes an aberrant drinking behavior, as a result of the increased dopamine uptake due to the modification of presynaptic dopamine signaling (Karkhanis, Rose, Huggins, Konstantopoulos, & Jones, 2015; Melis et al., 2005; Siciliano, Calipari, Yorgason, Lovinger, et al., 2016; Siciliano, Calipari, Yorgason, Mateo, et al., 2016). Consequently, AUDs appear to be promoted by a deficit of dopamine availability (Budygin et al., 2007). Accordingly, neuroimaging studies reported a modification in striatal dopamine transporter (DAT) availability both in acute alcohol withdrawal and in chronic alcohol drinkers (Cosgrove et al., 2009; Laine, Ahonen, Räsänen, & Tiihonen, 1999; Volkow et al., 2006), therefore supporting a dopaminergic pathway dysfunction in the pathophysiology of AUDs. Different abnormalities have been described in alcohol-dependent patients, i.e., lower, higher, or unchanged DAT levels (Cosgrove et al., 2009; Laine et al., 1999; Volkow et al., 2006) in comparison with healthy subjects. Yet, they appear to be linked causally to a dopaminergic deficit caused by the alcohol consumption and succeeding withdrawal. Deep rTMS seems to be able to modify neuronal adaptations in chronic alcohol abusers by increasing the dopamine release through activation of pyramidal neurons impinging upon dopamine-containing neurons in the midbrain (Carr & Sesack, 2000; Diana, 2011; Frankle, Laruelle, & Haber, 2006). Different studies have shown the action of rTMS on the excitability of mesolimbic and mesostriatal dopaminergic pathways (Cho & Strafella, 2009; Strafella et al., 2001), which suggested a potential application to treat psychiatric disorders related to a dopaminergic activity dysfunction (Zyss et al., 2015). Notably, rTMS application may increase dopamine release in the striatal pathway and the cingulate and orbitofrontal cortices by directly stimulating the cortico-VTA axons and/or indirectly reducing GABA-mediated intracortical inhibition (Cho & Strafella, 2009; Strafella et al., 2001) or by activating the VTA (Ohnishi et al., 2004). RTMS may also be useful in AUDs for the reduction of aberrant neuroplasticity and impulsive choices due to a prefrontal cortical hypofunctioning (Goldstein & Volkow, 2011; Loheswaran et al., 2016). Finally, it should be kept into consideration that TMS application induces other neurochemical changes in terms of inhibitory or excitatory effects related to a reduction, respectively, in the excitatory glutamatergic neurotransmission and the inhibitory GABAergic one (Stagg, Best, et al., 2009).

Deep rTMS on the DLPC in AUD patients could represent a valid and non-invasive therapeutic option (Feil & Zangen, 2010; Gorelick, Zangen, & George, 2014) to reduce alcohol craving and intake (Addolorato et al., 2017; Ceccanti et al., 2015; De Ridder, Vanneste, Kovacs, Sunaert, & Dom, 2011; Del Felice et al., 2016; Höppner, Broese, Wendler, Berger, & Thome, 2011; Mishra, Nizamie, Das, & Praharaj, 2010). Noteworthy, in patients with impaired hepatic or renal function in which drugs should be used with caution (if not avoided), rTMS could represent a good alternative to reduce or prevent the consumption of alcohol. RTMS could also be used to either enhance the effects of sub-threshold doses of anti-craving drugs or in synergy with therapeutic doses of anti-craving medications. This latter hypothesis has been tested in tobacco addicts, in which a randomized controlled trial has shown an increased rate of abstinence in smokers after 10 sessions of TMS combined with nicotine replacement therapy (Trojak et al., 2015).

The first published study showing the potential therapeutic effect of rTMS in alcoholics is dated 2010 and showed that clinical

Table 1
Studies that implemented TMS in the treatment of alcohol addicts. ACC, anterior cingulate cortex; ACQ-Now, alcohol craving questionnaire; AUQ, alcohol urge questionnaire; cTBS, continuous theta burst stimulation; dACC, dorsal anterior cingulate cortex; DMAI, days of maximum alcohol intake; drTMS, deep repetitive transcranial magnetic stimulation; DLPFC, dorsolateral prefrontal cortex; F, female; HFrTMS, high frequency repetitive transcranial magnetic stimulation; M, male; mPFC, medial prefrontal cortex; N.I., not included; OCDS, obsessive compulsive drinking scale; rMT, resting motor threshold; rTMS, repetitive transcranial magnetic; VAS, visual analogic scale; vmPFC, ventromedial prefrontal cortex.

Study	REAL group (*n*)	SHAM group (*n*)	TMS	Sessions	Trains (pulses)	Coil	Frequency (Hz)	Intensity (% rMT)	Target Area	Assessment	Results (REAL vs. SHAM)
Addolorato et al., (2017)	5 (all M)	6 (all M)	rTMS	12 (3/week)	20 (50/train)	H-shaped coil	10	100%	DLPFC	OCDS	↓ alcohol intake
Del Felice et al., (2016)	10 (3 F)	10 (1 F)	HFrTMS	4 (2/week)	20 (50/train)	8-shaped coil	10	100%	left DLPFC	craving VAS, Symptom Check List-90-R (SCL), Numeric Stroop task (Stroop), Go/No-go task	VAS unchanged ↑ inhibitory control task and selective attention ↓ depressive symptoms
Herremans et al., 2016	19 (11M; 8F)	19 (11M; 8F)	Accelerated HF-rTMS	14 over 3 consecutive days (4/5/5)	40 (1.9 s/train, 12 s inter-train interval)	8-shaped coil	20	110%	right DLPFC	neuronal activation of vmPFC and ACC	dorsal ACC activation may serve as a protective mechanism regarding relapse
Herremans et al., 2015	13 (4F)	13 (5F)	Accelerated HF-rTMS	15 (spread over 4 consecutive days)	40 (1.9 s/train, 12 s inter-train interval)	8-shaped coil	20	110%	right DLPFC	AUQ and OCDS	↓ general craving ≈ cue-induced craving
Ceccanti et al., (2015)	9 (all M)	9 (all M)	drTMS	10 (5/week)	30 (50/train)	H-shaped coil	20	120%	mPFC	craving VAS; DMAI	↓ VAS ↓DMAI
Mishra et al., (2015)	10/group targeted at left vs right DLPFC (all M)	N.I.	rTMS	10	20 (4.9 s/train, 30 s inter-train interval)	8-shaped coil	10	110%	right and left DLPFC	ACQ-Now	↓ ACQ-NOW in patients receiving either right or left rTMS No significant differences between groups
Herremans et al., (2012)	15 (3F)	16 (7F)	HF-rTMS	1	40 (1.9 s/train, 12 s inter-train interval)	8-shaped coil	20	110%	right DLPFC	AUQ	≈ craving
De Ridder et al., (2011)	1 F	N.I.	rTMS	21	1 (600 pulses)	double-cone coil	1	50%	dACC	VAS	transient alcohol craving suppression
Mishra et al., (2010)	30 (M)	15 (M)	rTMS	10	20 (4.9 s/train, 30 s inter-train interval)	8-shaped coil	10	110%	right DLPFC	ACQ-Now	↓ ACQ-NOW

application of high-frequency rTMS for 10 daily sessions significantly reduced alcohol craving in AUDs (Mishra et al., 2010). In this pioneering study, 45 patients were randomly assigned to two treatments groups, REAL (n = 30) and SHAM (n = 15). The REAL stimulation on the right DLPFC was conducted at a frequency of 10 Hz at 110% of motor threshold, and each session generated 20 trains with a duration of 4.9 s, with a 30-sec inter-train interval. The evaluation of craving was based on the Alcohol Craving Questionnaire, which revealed a significant reduction of total scores in the REAL group only.

In addition, a case report found that low-frequency rTMS with a double cone coil applied on the dorsal anterior cingulated cortex led to a significant reduction of alcohol intake (De Ridder et al., 2011). A middle-aged AUDs woman was stimulated for 3 weeks at a frequency of 1 Hz. Both functional magnetic resonance imaging and electroencephalography were assessed before and after the treatment to register changes in brain activity, while alcohol craving was evaluated by Visual Analogue Scale (VAS). At the end of the treatment a significant reduction of craving and alcohol intake was observed, which lasted for 3 months.

On the contrary, application of high frequency (20 Hz) rTMS on the left DLPC did not reduce craving, as evaluated by the Obsessive Compulsive Drinking Scale (OCDS) in subjects submitted to real stimulation (Höppner et al., 2011). In particular, 19 AUD detoxified women were randomized in two groups, the REAL left rTMS (n = 10) and SHAM (n = 9), and treated for 10 days. At the end of the treatment, no significant differences in terms of craving were detected after REAL TMS compared to SHAM stimulation.

A subsequent prospective single-blind and sham-controlled study reported no effects after single rTMS stimulation on the right DLPFC (Herremans & Baeken, 2012). In particular, the treatment involved 36 AUD hospitalized subjects after detoxification, who underwent real high frequency (20 Hz) or sham stimulation. During the session, the real stimulation group was treated with 40 trains of 1.9 s with a 12-sec inter-train interval. Alcohol craving was evaluated by OCDS, and no changes were observed before and after a single-session stimulation. Yet, a reduction of craving and alcohol intake was subsequently reported after the use of H-coil TMS of the prefrontal cortex (Ceccanti et al., 2015). In this randomized double-blind placebo-controlled study, 18 AUD patients were randomly assigned to two groups, the REAL stimulation group (n = 9) and the SHAM stimulation group (n = 9). Ten sessions of high frequency (20 Hz) rTMS were conducted, showing a significant effect on craving (evaluated by VAS) and alcoholic consumption only in the real group.

Furthermore, Addolorato et al. (2017) have recently reported on the reduction or interruption of alcohol intake in AUDs treated with real rTMS for 4 weeks, in comparison with sham stimulation. Eleven AUD patients were randomized in a REAL (n = 5) or a SHAM group (n = 6), and 12 high-level (10 Hz) rTMS sessions with H-coil were conducted three times a week. Importantly, before stimulation, higher levels of DAT evaluated by single photon emission computed tomography (SPECT) were observed in AUDs active patients, in agreement with previous findings (Cosgrove et al., 2009; Mash et al., 1996). A reduction of DAT availability was detected after REAL rTMS only, which is probably related to a modulatory effect on the mesolimbic and mesostriatal dopamine system (Fig. 2). Importantly, alcohol intake underwent a significant reduction in the REAL group only, probably reflecting DAT changes and dopamine modulation, but alcohol craving (evaluated by OCDS) failed to reach a significant reduction, as compared with the SHAM group. However, subjects submitted to the real rTMS showed a reduction in terms of alcoholic units and an increase in the relapse time, suggesting the possibility to extend the timing of treatment or change the stimulation parameters (such as frequency [low or high], train duration, inter-train interval, etc.) to increase the chance of abstinence. At last, Makani, Pradhan, Shah, and Parikh (2017) have recently indicated a Level 2 study quality and class B strength of recommendation for rTMS in alcohol addiction, suggesting that future studies are needed to support the effectiveness of this technique in AUD treatment. Overall, data collected so far on the clinical application of the rTMS technique in alcohol dependence are still preliminary, obtained in small samples of patients only. Any definitive conclusion on the potential therapeutic use of rTMS in the treatment of AUDs is therefore hazardous at the moment, but the urgency of developing new effective approaches to treat alcohol addicts calls for future studies focusing on different stimulation protocols, e.g., theta burst, to maximize treating effects.

Future outlook

While the initial results from substance use disorders trials appear promising, rTMS long-term plastic effects are relatively weak and require weeks of stimulation sessions. The numerous gaps in the current knowledge of TMS physiology and large inter-individual differences hamper the clinical utility of current clinical regimens. Research aimed at understanding the interactions between rTMS frequency, intensity, and coil orientation, relative to anatomy, appears particularly useful. Importantly, development of

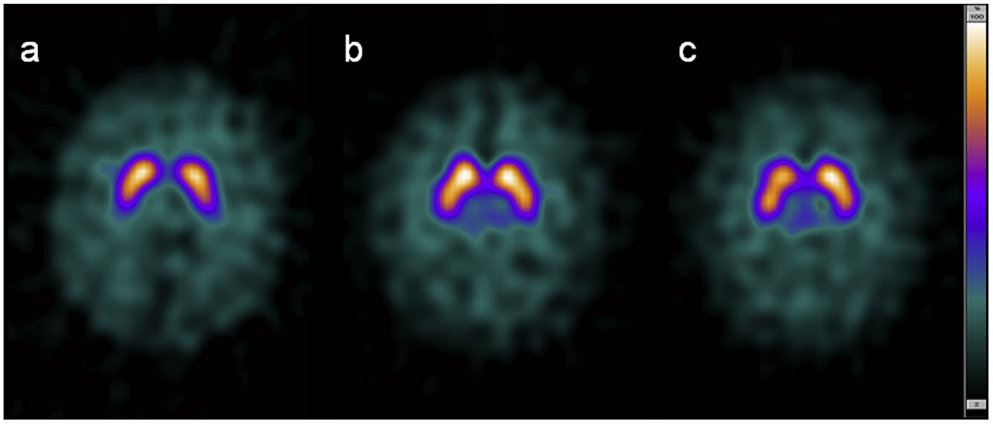

Fig. 2. Transaxial SPECT images (slice thickness: 3.9 mm) showing 123I-FP-CIT uptake in the bilateral striatum of an age-matched healthy subject **(a)** and an AUD patient before **(b)** and after **(c)** 1 month of real rTMS sessions. At baseline assessment, an increased radiotracer uptake (i.e., higher DAT availability) was observed in the bilateral striatum of the AUD patient as compared with the healthy subject. After rTMS treatment, a reduction of striatal radiotracer uptake was detected.

new TMS pulse sequences that result in stronger and more persistent long-term plasticity, and produce more consistent results across subjects, would also seem necessary. While TBS seems to be a step toward the right direction (Hanlon et al., 2017; Huang et al., 2005; Rachid, 2017; Zack et al., 2016), other patterning schemes using trains of two (known as "TMS at I-wave periodicity", iTMS) or four (known as "quadripulse stimulation", QPS) pulses (Hamada et al., 2008; Thickbroom, Byrnes, Edwards, & Mastaglia, 2006) should also be explored further to optimize current protocols aimed at reducing drug intake in the long term.

Since TMS activations critically depend on the relation between the E-fields and anatomy, clinical trials should utilize individual MRIs and TMS navigators. This information can be used during treatment planning, to precisely target the intended brain areas and networks in order to maximize the physiological effects, or during *post hoc* analysis to contribute to future treatment atlases that will (it is hoped) reveal cortical targets and networks responsible for the therapeutic effects.

Funding

This research was supported in part from a private fund-raising initiative from Gieffe Supermercati srl, Italy.

Acknowledgments

The authors wish to thank the AUD patients who dedicated their time and efforts to develop knowledge described in this paper.

References

Addolorato, G., Antonelli, M., Cocciolillo, F., Vassallo, G. A., Tarli, C., Sestito, L., et al. (2017). Deep transcranial magnetic stimulation of the dorsolateral prefrontal cortex in alcohol use disorder patients: Effects on dopamine transporter availability and alcohol intake. *European Neuropsychopharmacology, 27*, 450–461. https://doi.org/10.1016/j.euroneuro.2017.03.008.

Addolorato, G., Caputo, F., Capristo, E., Colombo, G., Gessa, G. L., & Gasbarrini, G. (2000). Ability of baclofen in reducing alcohol craving and intake: II–Preliminary clinical evidence. *Alcoholism: Clinical and Experimental Research, 24*, 67–71.

Addolorato, G., Caputo, F., Capristo, E., Domenicali, M., Bernardi, M., Janiri, L., et al. (2002). Baclofen efficacy in reducing alcohol craving and intake: A preliminary double-blind randomized controlled study. *Alcohol and Alcoholism, 37*, 504–508.

Alonso, J., Angermeyer, M. C., Bernert, S., Bruffaerts, R., Brugha, T. S., Bryson, H., et al. (2004). Prevalence of mental disorders in Europe: Results from the European study of the epidemiology of mental disorders (ESEMeD) project. *Acta Psychiatrica Scandinavica. Supplementum*, 21–27. https://doi.org/10.1111/j.1600-0047.2004.00327.x.

Antonelli, M., Ferrulli, A., Sestito, L., Vassallo, G. A., Tarli, C., Mosoni, C., et al. (2018). Alcohol addiction – the safety of available approved treatment options. *Expert Opinion on Drug Safety, 17*, 169–177. https://doi.org/10.1080/14740338.2018.1404025.

Argilli, E., Sibley, D. R., Malenka, R. C., England, P. M., & Bonci, A. (2008). Mechanism and time course of cocaine-induced long-term potentiation in the ventral tegmental area. *The Journal of Neuroscience, 28*, 9092–9100. https://doi.org/10.1523/JNEUROSCI.1001-08.2008.

Baeken, C., & De Raedt, R. (2011). Neurobiological mechanisms of repetitive transcranial magnetic stimulation on the underlying neurocircuitry in unipolar depression. *Dialogues in Clinical Neuroscience, 13*, 139–145.

Baeken, C., De Raedt, R., Bossuyt, A., Van Hove, C., Mertens, J., Dobbeleir, A., et al. (2011). The impact of HF-rTMS treatment on serotonin(2A) receptors in unipolar melancholic depression. *Brain Stimulation, 4*, 104–111. https://doi.org/10.1016/j.brs.2010.09.002.

Baik, J. H. (2013). Dopamine signaling in reward-related behaviors. *Frontiers in Neural Circuits, 7*, 152. https://doi.org/10.3389/fncir.2013.00152.

Barker, A. T., Jalinous, R., & Freeston, I. L. (1985). Non-invasive magnetic stimulation of human motor cortex. *Lancet, 1*, 1106–1107.

Barr, M. S., Farzan, F., Davis, K. D., Fitzgerald, P. B., & Daskalakis, Z. J. (2013). Measuring GABAergic inhibitory activity with TMS-EEG and its potential clinical application for chronic pain. *Journal of Neuroimmune Pharmacology, 8*, 535–546. https://doi.org/10.1007/s11481-012-9383-y.

Baxter, M. G., & Murray, E. A. (2002). The amygdala and reward. *Nature Reviews Neuroscience, 3*, 563–573. https://doi.org/10.1038/nrn875.

Bellone, C., & Lüscher, C. (2006). Cocaine triggered AMPA receptor redistribution is reversed in vivo by mGluR-dependent long-term depression. *Nature Neuroscience, 9*, 636–641. https://doi.org/10.1038/nn1682.

Bestmann, S., Baudewig, J., Siebner, H. R., Rothwell, J. C., & Frahm, J. (2004). Functional MRI of the immediate impact of transcranial magnetic stimulation on cortical and subcortical motor circuits. *European Journal of Neuroscience, 19*, 1950–1962. https://doi.org/10.1111/j.1460-9568.2004.03277.x.

Bock, R., Shin, J. H., Kaplan, A. R., Dobi, A., Markey, E., Kramer, P. F., et al. (2013). Strengthening the accumbal indirect pathway promotes resilience to compulsive cocaine use. *Nature Neuroscience, 16*, 632–638. https://doi.org/10.1038/nn.3369.

Bohning, D. E., Shastri, A., Wassermann, E. M., Ziemann, U., Lorberbaum, J. P., Nahas, Z., et al. (2000). BOLD-fMRI response to single-pulse transcranial magnetic stimulation (TMS). *Journal of Magnetic Resonance Imaging, 11*, 569–574.

Bolloni, C., Panella, R., Pedetti, M., Frascella, A. G., Gambelunghe, C., Piccoli, T., et al. (2016). Bilateral transcranial magnetic stimulation of the prefrontal cortex reduces cocaine intake: A pilot study. *Frontiers in Psychiatry, 7*, 133. https://doi.org/10.3389/fpsyt.2016.00133.

Budygin, E. A., Oleson, E. B., Mathews, T. A., Läck, A. K., Diaz, M. R., McCool, B. A., et al. (2007). Effects of chronic alcohol exposure on dopamine uptake in rat nucleus accumbens and caudate putamen. *Psychopharmacology, 193*, 495–501. https://doi.org/10.1007/s00213-007-0812-1.

Camprodon, J. A., Martínez-Raga, J., Alonso-Alonso, M., Shih, M. C., & Pascual-Leone, A. (2007). One session of high frequency repetitive transcranial magnetic stimulation (rTMS) to the right prefrontal cortex transiently reduces cocaine craving. *Drug and Alcohol Dependence, 86*, 91–94. https://doi.org/10.1016/j.drugalcdep.2006.06.002.

Caputo, F., Vignoli, T., Tarli, C., Domenicali, M., Zoli, G., Bernardi, M., et al. (2016). A brief up-date of the use of sodium oxybate for the treatment of alcohol use disorder. *International Journal of Environmental Research and Public Health, 13*. https://doi.org/10.3390/ijerph13030290. pii:E290.

Carroll, K. M., & Kiluk, B. D. (2017). Cognitive behavioral interventions for alcohol and drug use disorders: Through the stage model and back again. *Psychology of Addictive Behaviors, 31*, 847–861. https://doi.org/10.1037/adb0000311.

Carr, D. B., & Sesack, S. R. (2000). Projections from the rat prefrontal cortex to the ventral tegmental area: Target specificity in the synaptic associations with mesoaccumbens and mesocortical neurons. *The Journal of Neuroscience, 20*, 3864–3873.

Caselli, G., Gemelli, A., Spada, M. M., & Wells, A. (2016). Experimental modification of perspective on thoughts and metacognitive beliefs in alcohol use disorder. *Psychiatry Research, 244*, 57–61. https://doi.org/10.1016/j.psychres.2016.07.029.

Ceccanti, M., Inghilleri, M., Attilia, M. L., Raccah, R., Fiore, M., Zangen, A., et al. (2015). Deep TMS on alcoholics: Effects on cortisolemia and dopamine pathway modulation. A pilot study. *Canadian Journal of Physiology and Pharmacology, 93*, 283–290. https://doi.org/10.1139/cjpp-2014-0188.

Cheeran, B., Talelli, P., Mori, F., Koch, G., Suppa, A., Edwards, M., et al. (2008). A common polymorphism in the brain-derived neurotrophic factor gene (BDNF) modulates human cortical plasticity and the response to rTMS. *The Journal of Physiology, 586*, 5717–5725. https://doi.org/10.1113/jphysiol.2008.159905.

Chen, B. T., Bowers, M. S., Martin, M., Hopf, F. W., Guillory, A. M., Carelli, R. M., et al. (2008). Cocaine but not natural reward self-administration nor passive cocaine infusion produces persistent LTP in the VTA. *Neuron, 59*, 288–297. https://doi.org/10.1016/j.neuron.2008.05.024.

Chen, R., Classen, J., Gerloff, C., Celnik, P., Wassermann, E. M., Hallett, M., et al. (1997). Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. *Neurology, 48*, 1398–1403.

Chen, P., Li, J., Han, X., Grech, D., Xiong, M., Bekker, A., et al. (2018). Acupuncture for alcohol use disorder. *International Journal of Physiology Pathophysiology and Pharmacology, 10*, 60–69.

Chen, J., Tan, Z., Zeng, L., Zhang, X., He, Y., Gao, W., et al. (2013). Heterosynaptic long-term depression mediated by ATP released from astrocytes. *Glia, 61*, 178–191. https://doi.org/10.1002/glia.22425.

Cho, S. S., & Strafella, A. P. (2009). rTMS of the left dorsolateral prefrontal cortex modulates dopamine release in the ipsilateral anterior cingulate cortex and orbitofrontal cortex. *PLoS One, 4*, e6725. https://doi.org/10.1371/journal.pone.0006725.

Corbit, L. H., Nie, H., & Janak, P. H. (2014). Habitual responding for alcohol depends upon both AMPA and D2 receptor signaling in the dorsolateral striatum. *Frontiers in Behavioral Neuroscience, 8*, 301. https://doi.org/10.3389/fnbeh.2014.00301.

Cosgrove, K. P., Krantzler, E., Frohlich, E. B., Stiklus, S., Pittman, B., Tamagnan, G. D., et al. (2009). Dopamine and serotonin transporter availability during acute alcohol withdrawal: Effects of comorbid tobacco smoking. *Neuropsychopharmacology, 34*, 2218–2226. https://doi.org/10.1038/npp.2009.49.

Dan, Y., & Poo, M. M. (2006). Spike timing-dependent plasticity: From synapse to perception. *Physiological Reviews, 86*, 1033–1048. https://doi.org/10.1152/physrev.00030.2005.

Daskalakis, Z. J., Möller, B., Christensen, B. K., Fitzgerald, P. B., Gunraj, C., & Chen, R. (2006). The effects of repetitive transcranial magnetic stimulation on cortical inhibition in healthy human subjects. *Experimental Brain Research, 174*, 403–412. https://doi.org/10.1007/s00221-006-0472-0.

De Ridder, D., Vanneste, S., Kovacs, S., Sunaert, S., & Dom, G. (2011). Transient alcohol craving suppression by rTMS of dorsal anterior cingulate: An fMRI and

LORETA EEG study. *Neuroscience Letters, 496*, 5–10. https://doi.org/10.1016/j.neulet.2011.03.074.
Del Felice, A., Bellamoli, E., Formaggio, E., Manganotti, P., Masiero, S., Cuoghi, G., et al. (2016). Neurophysiological, psychological and behavioural correlates of rTMS treatment in alcohol dependence. *Drug and Alcohol Dependence, 158*, 147–153. https://doi.org/10.1016/j.drugalcdep.2015.11.018.
Deng, Z. D., Lisanby, S. H., & Peterchev, A. V. (2013). Electric field depth-focality tradeoff in transcranial magnetic stimulation: Simulation comparison of 50 coil designs. *Brain Stimulation, 6*, 1–13. https://doi.org/10.1016/j.brs.2012.02.005.
Di Lazzaro, V., Pilato, F., Dileone, M., Profice, P., Oliviero, A., Mazzone, P., et al. (2008). The physiological basis of the effects of intermittent theta burst stimulation of the human motor cortex. *The Journal of Physiology, 586*, 3871–3879. https://doi.org/10.1113/jphysiol.2008.152736.
Di Lazzaro, V., Ziemann, U., & Lemon, R. N. (2008). State of the art: Physiology of transcranial motor cortex stimulation. *Brain Stimulation, 1*, 345–362. https://doi.org/10.1016/j.brs.2008.07.004.
Diana, M. (2011). The dopamine hypothesis of drug addiction and its potential therapeutic value. *Frontiers in Psychiatry, 2*, 64. https://doi.org/10.3389/fpsyt.2011.00064.
Diana, M., Raij, T., Melis, M., Nummenmaa, A., Leggio, L., & Bonci, A. (2017). Rehabilitating the addicted brain with transcranial magnetic stimulation. *Nature Reviews Neuroscience, 18*, 685–693. https://doi.org/10.1038/nrn.2017.113.
Dinur-Klein, L., Dannon, P., Hadar, A., Rosenberg, O., Roth, Y., Kotler, M., et al. (2014). Smoking cessation induced by deep repetitive transcranial magnetic stimulation of the prefrontal and insular cortices: A prospective, randomized controlled trial. *Biological Psychiatry, 76*, 742–749. https://doi.org/10.1016/j.biopsych.2014.05.020.
Edgley, S. A., Eyre, J. A., Lemon, R. N., & Miller, S. (1997). Comparison of activation of corticospinal neurons and spinal motor neurons by magnetic and electrical transcranial stimulation in the lumbosacral cord of the anaesthetized monkey. *Brain, 120*, 839–853.
Etiévant, A., Manta, S., Latapy, C., Magno, L. A., Fecteau, S., & Beaulieu, J. M. (2015). Repetitive transcranial magnetic stimulation induces long-lasting changes in protein expression and histone acetylation. *Scientific Reports, 5*, 16873. https://doi.org/10.1038/srep16873.
Fattore, L., & Diana, M. (2016). Drug addiction: An affective-cognitive disorder in need of a cure. *Neuroscience and Biobehavioral Reviews, 65*, 341–361. https://doi.org/10.1016/j.neubiorev.2016.04.006.
Feil, J., & Zangen, A. (2010). Brain stimulation in the study and treatment of addiction. *Neuroscience and Biobehavioral Reviews, 34*, 559–574. https://doi.org/10.1016/j.neubiorev.2009.11.006.
Filipčić, I., Šimunović Filipčić, I., Gajšak, T., Milovac, Ž., Sučić, S., Ivezić, E., et al. (2018). Efficacy and safety of repetitive transcranial magnetic stimulation using an H1-coil or figure-8-coil in the treatment of unipolar major depressive disorder: A study protocol for a randomized controlled trial. *Psychiatria Danubina, 30*, 41–46. https://doi.org/10.24869/psyd.2018.41.
Fitzgerald, P. B., Fountain, S., & Daskalakis, Z. J. (2006). A comprehensive review of the effects of rTMS on motor cortical excitability and inhibition. *Clinical Neurophysiology, 117*, 2584–2596. https://doi.org/10.1016/j.clinph.2006.06.712.
Ford, C. P. (2014). The role of D2-autoreceptors in regulating dopamine neuron activity and transmission. *Neuroscience, 282*, 13–22. https://doi.org/10.1016/j.neuroscience.2014.01.025.
Frankle, W. G., Laruelle, M., & Haber, S. N. (2006). Prefrontal cortical projections to the midbrain in primates: Evidence for a sparse connection. *Neuropsychopharmacology, 31*, 1627–1636. https://doi.org/10.1038/sj.npp.1300990.
Freund, T. F., Powell, J. F., & Smith, A. D. (1984). Tyrosine hydroxylase-immunoreactive boutons in synaptic contact with identified striatonigral neurons, with particular reference to dendritic spines. *Neuroscience, 13*, 1189–1215.
Funke, K., & Benali, A. (2011). Modulation of cortical inhibition by rTMS – findings obtained from animal models. *The Journal of Physiology, 589*, 4423–4435. https://doi.org/10.1113/jphysiol.2011.206573.
George, O., Koob, G. F., & Vendruscolo, L. F. (2014). Negative reinforcement via motivational withdrawal is the driving force behind the transition to addiction. *Psychopharmacology, 231*, 3911–3917. https://doi.org/10.1007/s00213-014-3623-1.
George, M. S., Nahas, Z., Kozel, F. A., Li, X., Denslow, S., Yamanaka, K., et al. (2002). Mechanisms and state of the art of transcranial magnetic stimulation. *The Journal of ECT, 18*, 170–181.
Gesner, E. M., Schellenberg, M. J., Garside, E. L., George, M. M., & MacMillan, A. M. (2011). Recognition and maturation of effector RNAs in a CRISPR interference pathway. *Nature Structural & Molecular Biology, 18*, 688–692. https://doi.org/10.1038/nsmb.2042.
Goh, E. T., & Morgan, M. Y. (2017). Review article: Pharmacotherapy for alcohol dependence – the why, the what and the wherefore. *Alimentary Pharmacology & Therapeutics, 45*, 865–882. https://doi.org/10.1111/apt.13965.
Goldstein, R. Z., & Volkow, N. D. (2011). Dysfunction of the prefrontal cortex in addiction: Neuroimaging findings and clinical implications. *Nature Reviews Neuroscience, 12*, 652–669. https://doi.org/10.1038/nrn3119.
Gomez-Tames, J., Hamasaka, A., Laakso, I., Hirata, A., & Ugawa, Y. (2018). Atlas of optimal coil orientation and position for TMS: A computational study. *Brain Stimulation, 11*, 839–848. https://doi.org/10.1016/j.brs.2018.04.011.
Good, C. H., & Lupica, C. R. (2010). Afferent-specific AMPA receptor subunit composition and regulation of synaptic plasticity in midbrain dopamine neurons by abused drugs. *The Journal of Neuroscience, 30*, 7900–7909. https://doi.org/10.1523/JNEUROSCI.1507-10.2010.
Gorelick, D. A., Zangen, A., & George, M. S. (2014). Transcranial magnetic stimulation in the treatment of substance addiction. *Annals of the New York Academy of Sciences, 1327*, 79–93. https://doi.org/10.1111/nyas.12479.
Gowing, L. R., Ali, R. L., Allsop, S., Marsden, J., Turf, E. E., West, R., et al. (2015). Global statistics on addictive behaviours: 2014 status report. *Addiction, 110*, 904–919. https://doi.org/10.1111/add.12899.
Grace, A. A. (2009). The tonic/phasic model of dopamine system regulation and its implications for understanding alcohol and psychostimulant craving. *Addiction, 95*(Suppl 2), S119–S128.
Grant, B. F., Goldstein, R. B., Saha, T. D., Chou, S. P., Jung, J., Zhang, H., et al. (2015). Epidemiology of DSM-5 alcohol use disorder: Results from the national epidemiologic survey on alcohol and related conditions III. *JAMA Psychiatry, 72*, 757–766. https://doi.org/10.1001/jamapsychiatry.2015.0584.
Hallgren, M., Andersson, V., Ekblom, Ö., & Andréasson, S. (2018). Physical activity as treatment for alcohol use disorders (FitForChange): Study protocol for a randomized controlled trial. *Trials, 19*, 106. https://doi.org/10.1186/s13063-017-2435-0.
Hallgren, M., Romberg, K., Bakshi, A. S., & Andréasson, S. (2014). Yoga as an adjunct treatment for alcohol dependence: A pilot study. *Complementary Therapies in Medicine, 22*, 441–445. https://doi.org/10.1016/j.ctim.2014.03.003.
Hamada, M., Murase, N., Hasan, A., Balaratnam, M., & Rothwell, J. C. (2013). The role of interneuron networks in driving human motor cortical plasticity. *Cerebral Cortex, 23*, 1593–1605. https://doi.org/10.1093/cercor/bhs147.
Hamada, M., Terao, Y., Hanajima, R., Shirota, Y., Nakatani-Enomoto, S., & Furubayashi, T. (2008). Bidirectional long-term motor cortical plasticity and metaplasticity induced by quadripulse transcranial magnetic stimulation. *The Journal of Physiology, 586*, 3927–3947. https://doi.org/10.1113/jphysiol.2008.152793.
Hanlon, C. A., Dowdle, L. T., Austelle, C. W., DeVries, W., Mithoefer, O., Badran, B. W., et al. (2015). What goes up, can come down: Novel brain stimulation paradigms may attenuate craving and craving-related neural circuitry in substance dependent individuals. *Brain Research, 1628*, 199–209. https://doi.org/10.1016/j.brainres.2015.02.053.
Hanlon, C. A., Dowdle, L. T., Correia, B., Mithoefer, O., Kearney-Ramos, T., Lench, D., et al. (2017). Left frontal pole theta burst stimulation decreases orbitofrontal and insula activity in cocaine users and alcohol users. *Drug and Alcohol Dependence, 178*, 310–317. https://doi.org/10.1016/j.drugalcdep.2017.03.039.
Hatzigiakoumis, D., Martinotti, G., Giannantonio, M., & Janiri, L. (2011). Anhedonia and substance dependence: Clinical correlates and treatment options. *Frontiers in Psychiatry, 2*, 10. https://doi.org/10.3389/fpsyt.2011.00010.
Herremans, S. C., & Baeken, C. (2012). The current perspective of neuromodulation techniques in the treatment of alcohol addiction: A systematic review. *Psychiatria Danubina, 24*(Suppl 1), S14–S20.
Herremans, S. C., Van Schuerbeek, P., De Raedt, R., Matthys, F., Buyl, R., De Mey, J., et al. (2015 Aug 21). The impact of accelerated right prefrontal high-frequency repetitive transcranial magnetic stimulation (rTMS) on cue-reactivity: An fMRI study on craving in recently detoxified alcohol-dependent patients. *PLoS One, 10*(8), e0136182. https://doi.org/10.1371/journal.pone.0136182. eCollection 2015.
Herremans, S. C., De Raedt, R., Van Schuerbeek, P., Marinazzo, D., Matthys, F., De Mey, J., et al. (2016 Jan). Accelerated HF-rTMS protocol has a rate-dependent effect on dACC activation in alcohol-dependent patients: An open-label feasibility study. *Alcohol Clin Exp Res, 40*(1), 196–205. https://doi.org/10.1111/acer.12937.
Hettema, J. E., Cockrell, S. A., Reeves, A., Ingersoll, K. S., Lum, P. J., Saitz, R., et al. (2018). Development and differentiability of three brief interventions for risky alcohol use that include varying doses of motivational interviewing. *Addictive Science & Clinical Practice, 13*, 6. https://doi.org/10.1186/s13722-017-0102-0.
Holtyn, A. F., Kaminski, B. J., & Weerts, E. M. (2017). Baclofen and naltrexone effects on alcohol self-administration: Comparison of treatment initiated during abstinence or ongoing alcohol access in baboons. *Drug and Alcohol Dependence, 179*, 47–54. https://doi.org/10.1016/j.drugalcdep.2017.06.019.
Hoogendam, J. M., Ramakers, G. M., & Di Lazzaro, V. (2010). Physiology of repetitive transcranial magnetic stimulation of the human brain. *Brain Stimulation, 3*, 95–118. https://doi.org/10.1016/j.brs.2009.10.005.
Höppner, J., Broese, T., Wendler, L., Berger, C., & Thome, J. (2011). Repetitive transcranial magnetic stimulation (rTMS) for treatment of alcohol dependence. *The World Journal of Biological Psychiatry, 12*(Suppl 1), 57–62. https://doi.org/10.3109/15622975.2011.598383.
Houdayer, E., Degardin, A., Cassim, F., Bocquillon, P., Derambure, P., & Devanne, H. (2008). The effects of low- and high-frequency repetitive TMS on the input/output properties of the human corticospinal pathway. *Experimental Brain Research, 187*, 207–217. https://doi.org/10.1007/s00221-008-1294-z.
Hsiang, H. L., Epp, J. R., van den Oever, M. C., Yan, C., Rashid, A. J., Insel, N., et al. (2014). Manipulating a "cocaine engram" in mice. *The Journal of Neuroscience, 34*, 14115–14127. https://doi.org/10.1523/JNEUROSCI.3327-14.2014.
Huang, Y. Z., Edwards, M. J., Rounis, E., Bhatia, K. P., & Rothwell, J. C. (2005). Theta burst stimulation of the human motor cortex. *Neuron, 45*, 201–206. https://doi.org/10.1016/j.neuron.2004.12.033.
Huang, Y. Z., Rothwell, J. C., Chen, R. S., Lu, C. S., & Chuang, W. L. (2011). The theoretical model of theta burst form of repetitive transcranial magnetic stimulation. *Clinical Neurophysiology, 122*, 1011–1018. https://doi.org/10.1016/j.clinph.2010.08.016.
Ikemoto, S., & Bonci, A. (2014). Neurocircuitry of drug reward. *Neuropharmacology, 76*, 329–341. https://doi.org/10.1016/j.neuropharm.2013.04.031.

Ilmoniemi, R. J., Virtanen, J., Ruohonen, J., Karhu, J., Aronen, H. J., Näätänen, R., et al. (1997). Neuronal responses to magnetic stimulation reveal cortical reactivity and connectivity. *NeuroReport, 8*, 3537–3540.

Jensen, K., Nielsen, C., Ekstrøm, C. T., & Roessler, K. K. (2018). Physical exercise in the treatment of alcohol use disorder (AUD) patients affects their drinking habits: A randomized controlled trial. *Scandinavian Journal of Public Health*. https://doi.org/10.1177/1403494818759842, 1403494818759842. ([Epub ahead of print]).

Karkhanis, A. N., Rose, J. H., Huggins, K. N., Konstantopoulos, J. K., & Jones, S. R. (2015). Chronic intermittent ethanol exposure reduces presynaptic dopamine neurotransmission in the mouse nucleus accumbens. *Drug and Alcohol Dependence, 150*, 24–30. https://doi.org/10.1016/j.drugalcdep.2015.01.019.

Kasai, H., Matsuzaki, M., Noguchi, J., Yasumatsu, N., & Nakahara, H. (2003). Structure-stability-function relationships of dendritic spines. *Trends in Neurosciences, 26*, 360–368. https://doi.org/10.1016/S0166-2236(03)00162-0.

Kasanetz, F., Deroche-Gamonet, V., Berson, N., Balado, E., Lafourcade, M., Manzoni, O., et al. (2010). Transition to addiction is associated with a persistent impairment in synaptic plasticity. *Science, 328*, 1709–1712. https://doi.org/10.1126/science.1187801.

Kasanetz, F., Lafourcade, M., Deroche-Gamonet, V., Revest, J. M., Berson, N., Balado, E., et al. (2013). Prefrontal synaptic markers of cocaine addiction-like behavior in rats. *Molecular Psychiatry, 18*, 729–737. https://doi.org/10.1038/mp.2012.59.

Keck, M. E., Welt, T., Müller, M. B., Erhardt, A., Ohl, F., Toschi, N., et al. (2002). Repetitive transcranial magnetic stimulation increases the release of dopamine in the mesolimbic and mesostriatal system. *Neuropharmacology, 43*, 101–109.

Koob, G. F., & Le Moal, M. (2005). Plasticity of reward neurocircuitry and the 'dark side' of drug addiction. *Nature Neuroscience, 8*, 1442–1444. https://doi.org/10.1038/nn1105-1442.

Koob, G. F., & Volkow, N. D. (2010). Neurocircuitry of addiction. *Neuropsychopharmacology, 35*, 217–238. https://doi.org/10.1038/npp.2009.110.

Kourrich, S., Calu, D. J., & Bonci, A. (2015). Intrinsic plasticity: An emerging player in addiction. *Nature Reviews Neuroscience, 16*, 173–184. https://doi.org/10.1038/nrn3877.

Kozak, K., Sharif-Razi, M., Morozova, M., Gaudette, E. V., Barr, M. S., Daskalakis, Z. J., et al. (2018). Effects of short-term, high-frequency repetitive transcranial magnetic stimulation to bilateral dorsolateral prefrontal cortex on smoking behavior and cognition in patients with schizophrenia and non-psychiatric controls. *Schizophrenia Research*, (18), 30089–30096. https://doi.org/10.1016/j.schres.2018.02.015. pii:S0920–9964([Epub ahead of print]).

Krampe, H., & Ehrenreich, H. (2010). Supervised disulfiram as adjunct to psychotherapy in alcoholism treatment. *Current Pharmaceutical Design, 16*, 2076–2090.

Kuceyeski, A., Meyerhoff, D. J., Durazzo, T. C., & Raj, A. (2013). Loss in connectivity among regions of the brain reward system in alcohol dependence. *Human Brain Mapping, 34*, 3129–3142. https://doi.org/10.1002/hbm.22132.

Laine, T. P., Ahonen, A., Räsänen, P., & Tiihonen, J. (1999). Dopamine transporter availability and depressive symptoms during alcohol withdrawal. *Psychiatry Research, 90*, 153–157.

Larson, J., & Munkácsy, E. (2015). Theta-burst LTP. *Brain Research, 1621*, 38–50. https://doi.org/10.1016/j.brainres.2014.10.034.

Lenz, M., Platschek, S., Priesemann, V., Becker, D., Willems, L. M., Ziemann, U., et al. (2015). Repetitive magnetic stimulation induces plasticity of excitatory postsynapses on proximal dendrites of cultured mouse CA1 pyramidal neurons. *Brain Structure and Function, 220*, 3323–3337. https://doi.org/10.1007/s00429-014-0859-9.

Letellier, M., Park, Y. K., Chater, T. E., Chipman, P. H., Gautam, S. G., Oshima-Takago, T., et al. (2016). Astrocytes regulate heterogeneity of presynaptic strengths in hippocampal networks. *Proceedings of the National Academy of Sciences of the United States of America, 113*, E2685–E2694. https://doi.org/10.1073/pnas.1523717113.

Li, X., Malcolm, R. J., Huebner, K., Hanlon, C. A., Taylor, J. J., Brady, K. T., et al. (2013). Low frequency repetitive transcranial magnetic stimulation of the left dorsolateral prefrontal cortex transiently increases cue-induced craving for methamphetamine: A preliminary study. *Drug and Alcohol Dependence, 133*, 641–646. https://doi.org/10.1016/j.drugalcdep.2013.08.012.

Liu, Z., Liu, X. D., Zhang, J. J., & Yu, L. C. (2012). Increases in αCaMKII phosphorylated on Thr286 in the nucleus accumbens shell but not the core during priming-induced reinstatement of morphine-seeking in rats. *Neuroscience Letters, 526*, 39–44. https://doi.org/10.1016/j.neulet.2012.07.042.

Löffler, S., Gasca, F., Richter, L., Leipscher, U., Trillenberg, P., & Moser, A. (2012). The effect of repetitive transcranial magnetic stimulation on monoamine outflow in the nucleus accumbens shell in freely moving rats. *Neuropharmacology, 63*, 898–904. https://doi.org/10.1016/j.neuropharm.2012.06.045.

Loheswaran, G., Barr, M. S., Rajji, T. K., Blumberger, D. M., Le Foll, B., & Daskalakis, Z. J. (2016). Alcohol intoxication by binge drinking impairs neuroplasticity. *Brain Stimulation, 9*, 27–32. https://doi.org/10.1016/j.brs.2015.08.011.

Lüscher, C. (2016). The emergence of a circuit model for addiction. *Annual Review of Neuroscience, 39*, 257–276. https://doi.org/10.1146/annurev-neuro-070815-013920.

Maccioni, P., Zaru, A., Loi, B., Lobina, C., Carai, M. A., Gessa, G. L., et al. (2012). Comparison of the effect of the GABAB receptor agonist, baclofen, and the positive allosteric modulator of the GABAB receptor, GS39783, on alcohol self-administration in 3 different lines of alcohol-preferring rats. *Alcoholism: Clinical and Experimental Research, 36*, 1748–1766. https://doi.org/10.1111/j.1530-0277.2012.01782.x.

Maeda, F., Keenan, J., Tormos, J. M., Topka, H., & Pascual-Leone, A. (2000). Modulation of corticospinal excitability by repetitive transcranial magnetic stimulation. *Clinical Neurophysiology, 111*, 800–805.

Maisel, N. C., Blodgett, J. C., Wilbourne, P. L., Humphreys, K., & Finney, J. W. (2013). Meta-analysis of naltrexone and acamprosate for treating alcohol use disorders: When are these medications most helpful? *Addiction, 108*, 275–293. https://doi.org/10.1111/j.1360-0443.2012.04054.x.

Makani, R., Pradhan, B., Shah, U., & Parikh, T. (2017). Role of repetitive transcranial magnetic stimulation (rTMS) in treatment of addiction and related disorders: A systematic review. *Current Drug Abuse Reviews, 10*, 31–43. https://doi.org/10.2174/1874473710666171129225914.

Mameli, M., Balland, B., Luján, R., & Lüscher, C. (2007). Rapid synthesis and synaptic insertion of GluR2 for mGluR-LTD in the ventral tegmental area. *Science, 317*, 530–533. https://doi.org/10.1126/science.1142365.

Martinez, D., Gil, R., Slifstein, M., Hwang, D. R., Huang, Y., Perez, A., et al. (2005). Alcohol dependence is associated with blunted dopamine transmission in the ventral striatum. *Biological Psychiatry, 58*, 779–786. https://doi.org/10.1016/j.biopsych.2005.04.044.

Martinez, D., Urban, N., Grassetti, A., Chang, D., Hu, M. C., Zangen, A., et al. (2018). Transcranial magnetic stimulation of medial prefrontal and cingulate cortices reduces cocaine self-administration: A pilot study. *Frontiers in Psychiatry, 9*, 80. https://doi.org/10.3389/fpsyt.2018.00080.

Mash, D. C., Staley, J. K., Doepel, F. M., Young, S. N., Ervin, F. R., & Palmour, R. M. (1996). Altered dopamine transporter densities in alcohol-preferring vervet monkeys. *NeuroReport, 7*, 457–462.

Matsui, A., Jarvie, B. C., Robinson, B. G., Hentges, S. T., & Williams, J. T. (2014). Separate GABA afferents to dopamine neurons mediate acute action of opioids, development of tolerance, and expression of withdrawal. *Neuron, 82*, 1346–1356. https://doi.org/10.1016/j.neuron.2014.04.030.

Melis, M., Spiga, S., & Diana, M. (2005). The dopamine hypothesis of drug addiction: Hypodopaminergic state. *International Review of Neurobiology, 63*, 101–154. https://doi.org/10.1016/S0074-7742(05)63005-X.

Mishra, B. R., Nizamie, S. H., Das, B., & Praharaj, S. K. (2010). Efficacy of repetitive transcranial magnetic stimulation in alcohol dependence: A sham-controlled study. *Addiction, 105*, 49–55. https://doi.org/10.1111/j.1360-0443.2009.02777.x.

Mishra, B. R., Praharaj, S. K., Katshu, M. Z., Sarkar, S., & Nizamie, S. H. (2015). Comparison of anticraving efficacy of right and left repetitive transcranial magnetic stimulation in alcohol dependence: A randomized double-blind study. *Journal of Neuropsychiatry and Clinical Neurosciences, 27*, e54–e59. https://doi.org/10.1176/appi.neuropsych.13010013.

Morgenstern, J., Kuerbis, A., Houser, J., Levak, S., Amrhein, P., Shao, S., et al. (2017). Dismantling motivational interviewing: Effects on initiation of behavior change among problem drinkers seeking treatment. *Psychology of Addictive Behaviors, 31*, 751–762. https://doi.org/10.1037/adb0000317.

Mueller, J. K., Grigsby, E. M., Prevosto, V., Petraglia, F. W., 3rd, Rao, H., Deng, Z. D., et al. (2014). Simultaneous transcranial magnetic stimulation and single-neuron recording in alert non-human primates. *Nature Neuroscience, 17*, 1130–1136. https://doi.org/10.1038/nn.3751.

Müller-Dahlhaus, F., & Vlachos, A. (2013). Unraveling the cellular and molecular mechanisms of repetitive magnetic stimulation. *Frontiers in Molecular Neuroscience, 6*, 50. https://doi.org/10.3389/fnmol.2013.00050.

Nardone, R., Bergmann, J., Christova, M., Locher, P., Tezzon, F., Golaszewski, S., et al. (2012). Non-invasive brain stimulation in the functional evaluation of alcohol effects and in the treatment of alcohol craving: A review. *Neuroscience Research, 74*, 169–176. https://doi.org/10.1016/j.neures.2012.08.003.

Normann, C., Peckys, D., Schulze, C. H., Walden, J., Jonas, P., & Bischofberger, J. (2000). Associative long-term depression in the hippocampus is dependent on postsynaptic N-type Ca2+ channels. *The Journal of Neuroscience, 20*, 8290–8297.

Nummenmaa, A., Stenroos, M., Ilmoniemi, R. J., Okada, Y. C., Hämäläinen, M. S., & Raij, T. (2013). Comparison of spherical and realistically shaped boundary element head models for transcranial magnetic stimulation navigation. *Clinical Neurophysiology, 124*, 1995–2007. https://doi.org/10.1016/j.clinph.2013.04.019.

Ohnishi, T., Hayashi, T., Okabe, S., Nonaka, I., Matsuda, H., Iida, H., et al. (2004). Endogenous dopamine release induced by repetitive transcranial magnetic stimulation over the primary motor cortex: An [11C]raclopride positron emission tomography study in anesthetized macaque monkeys. *Biological Psychiatry, 55*, 484–489. https://doi.org/10.1016/j.biopsych.2003.09.016.

Pascual-Leone, A., Valls-Solé, J., Wassermann, E. M., & Hallett, M. (1994). Responses to rapid-rate transcranial magnetic stimulation of the human motor cortex. *Brain, 117*, 847–858.

Pashut, T., Magidov, D., Ben-Porat, H., Wolfus, S., Friedman, A., Perel, E., et al. (2014). Patch-clamp recordings of rat neurons from acute brain slices of the somatosensory cortex during magnetic stimulation. *Frontiers in Cellular Neuroscience, 8*, 145. https://doi.org/10.3389/fncel.2014.00145.

Pastor, A., Jones, D. M., & Currie, J. (2012). High-dose baclofen for treatment-resistant alcohol dependence. *Journal of Clinical Psychopharmacology, 32*, 266–268. https://doi.org/10.1097/JCP.0b013e31824929b2.

Paus, T., Jech, R., Thompson, C. J., Comeau, R., Peters, T., & Evans, A. C. (1997). Transcranial magnetic stimulation during positron emission tomography: A new method for studying connectivity of the human cerebral cortex. *The Journal of Neuroscience, 17*, 3178–3184.

Pell, G. S., Roth, Y., & Zangen, A. (2011). Modulation of cortical excitability induced by repetitive transcranial magnetic stimulation: Influence of timing and geometrical parameters and underlying mechanisms. *Progress in Neurobiology, 93*, 59–98. https://doi.org/10.1016/j.pneurobio.2010.10.003.

Pignatelli, M., & Bonci, A. (2015). Role of dopamine neurons in reward and aversion: A synaptic plasticity perspective. *Neuron, 86*, 1145–1157. https://doi.org/10.1016/j.neuron.2015.04.015.

Politi, E., Fauci, E., Santoro, A., & Smeraldi, E. (2008). Daily sessions of transcranial magnetic stimulation to the left prefrontal cortex gradually reduce cocaine craving. *The American Journal of Addiction, 17*, 345–346. https://doi.org/10.1080/10550490802139283.

Pripfl, J., Tomova, L., Riecansky, I., & Lamm, C. (2014). Transcranial magnetic stimulation of the left dorsolateral prefrontal cortex decreases cue-induced nicotine craving and EEG delta power. *Brain Stimulation, 7*, 226–233. https://doi.org/10.1016/j.brs.2013.11.003.

Rachid, F. (2017). Safety and efficacy of theta-burst stimulation in the treatment of psychiatric disorders: A review of the literature. *The Journal of Nervous and Mental Disease, 205*, 823–839. https://doi.org/10.1097/NMD.0000000000000742.

Radman, T., Ramos, R. L., Brumberg, J. C., & Bikson, M. (2009). Role of cortical cell type and morphology in subthreshold and suprathreshold uniform electric field stimulation in vitro. *Brain Stimulation, 2*, 215–228. https://doi.org/10.1016/j.brs.2009.03.007.

Rapinesi, C., Del Casale, A., Di Pietro, S., Ferri, V. R., Piacentino, D., Sani, G., et al. (2016). Add-on high frequency deep transcranial magnetic stimulation (dTMS) to bilateral prefrontal cortex reduces cocaine craving in patients with cocaine use disorder. *Neuroscience Letters, 629*, 43–47. https://doi.org/10.1016/j.neulet.2016.06.049.

Raymond, C. R. (2008). Different requirements for action potentials in the induction of different forms of long-term potentiation. *The Journal of Physiology, 586*, 1859–1865. https://doi.org/10.1113/jphysiol.2008.151035.

Renteria, R., Jeanes, Z. M., Mangieri, R. A., Maier, E. Y., Kircher, D. M., Buske, T. R., et al. (2016). Using in vitro electrophysiology to screen medications: Accumbal plasticity as an engram of alcohol dependence. *International Review of Neurobiology, 126*, 441–465. https://doi.org/10.1016/bs.irn.2016.02.018.

Ridding, M. C., & Ziemann, U. (2010). Determinants of the induction of cortical plasticity by non-invasive brain stimulation in healthy subjects. *The Journal of Physiology, 588*, 2291–2304. https://doi.org/10.1113/jphysiol.2010.190314.

Rossi, S., Hallett, M., Rossini, P. M., & Pascual-Leone, A. (2009). Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clinical Neurophysiology, 120*, 2008–2039. https://doi.org/10.1016/j.clinph.2009.08.016.

Roth, Y., Amir, A., Levkovitz, Y., & Zangen, A. (2007). Three-dimensional distribution of the electric field induced in the brain by transcranial magnetic stimulation using figure- 8 and deep H-coils. *Journal of Clinical Neurophysiology, 24*, 31–38. https://doi.org/10.1097/WNP.0b013e31802fa393.

Roth, Y., Zangen, A., & Hallett, M. (2002). A coil design for transcranial magnetic stimulation of deep brain regions. *Journal of Clinical Neurophysiology, 19*, 361–370.

Saal, D., Dong, Y., Bonci, A., & Malenka, R. C. (2003). Drugs of abuse and stress trigger a common synaptic adaptation in dopamine neurons. *Neuron, 37*, 577–582.

Sahlem, G. L., Baker, N. L., George, M. S., Malcolm, R. J., & McRae-Clark, A. L. (2018). Repetitive transcranial magnetic stimulation (rTMS) administration to heavy cannabis users. *The American Journal of Drug and Alcohol Abuse, 44*, 47–55. https://doi.org/10.1080/00952990.2017.1355920.

Sancho, M., De Gracia, M., Rodríguez, R. C., Mallorquí-Bagué, N., Sánchez-González, J., Trujols, J., et al. (2018). Mindfulness-based interventions for the treatment of substance and behavioral addictions: A systematic review. *Frontiers in Psychiatry, 9*, 95. https://doi.org/10.3389/fpsyt.2018.00095.

Sauvaget, A., Bulteau, S., Guilleux, A., Leboucher, J., Pichot, A., Valrivière, P., et al. (2018). Both active and sham low-frequency rTMS single sessions over the right DLPFC decrease cue-induced cravings among pathological gamblers seeking treatment: A randomized, double-blind, sham-controlled crossover trial. *Journal of Behavioral Addictions, 7*, 126–136. https://doi.org/10.1556/2006.7.2018.14.

Sheffer, C. E., Bickel, W. K., Brandon, T. H., Franck, C. T., Deen, D., Panissidi, L., et al. (2018). Preventing relapse to smoking with transcranial magnetic stimulation: Feasibility and potential efficacy. *Drug and Alcohol Dependence, 182*, 8–18. https://doi.org/10.1016/j.drugalcdep.2017.09.037.

Shen, Y., Cao, X., Tan, T., Shan, C., Wang, Y., Pan, J., et al. (2016). 10-Hz repetitive transcranial magnetic stimulation of the left dorsolateral prefrontal cortex reduces heroin cue craving in long-term addicts. *Biological Psychiatry, 80*, e13–e14. https://doi.org/10.1016/j.biopsych.2016.02.006.

Shin, N. Y., Lim, Y. J., Yang, C. H., & Kim, C. (2017). Acupuncture for alcohol use disorder: A meta-analysis. *Evidence-based Complementary & Alternative Medicine, 2017*, 7823278. https://doi.org/10.1155/2017/7823278.

Siciliano, C. A., Calipari, E. S., Yorgason, J. T., Lovinger, D. M., Mateo, Y., Jimenez, V. A., et al. (2016). Increased presynaptic regulation of dopamine neurotransmission in the nucleus accumbens core following chronic ethanol self-administration in female macaques. *Psychopharmacology, 233*, 1435–1443. https://doi.org/10.1007/s00213-016-4239-4.

Siciliano, C. A., Calipari, E. S., Yorgason, J. T., Mateo, Y., Helms, C. M., Lovinger, D. M., et al. (2016). Chronic ethanol self-administration in macaques shifts dopamine feedback inhibition to predominantly D2 receptors in nucleus accumbens core. *Drug and Alcohol Dependence, 158*, 159–163. https://doi.org/10.1016/j.drugalcdep.2015.10.031.

Silvanto, J., Cattaneo, Z., Battelli, L., & Pascual-Leone, A. (2008). Baseline cortical excitability determines whether TMS disrupts or facilitates behavior. *Journal of Neurophysiology, 99*, 2725–2730. https://doi.org/10.1152/jn.01392.2007.

Silvanto, J., & Pascual-Leone, A. (2008). State-dependency of transcranial magnetic stimulation. *Brain Topography, 21*, 1–10. https://doi.org/10.1007/s10548-008-0067-0.

Soyka, M. (2016). Nalmefene for the treatment of alcohol use disorders: Recent data and clinical potential. *Expert Opinion on Pharmacotherapy, 17*, 619–626. https://doi.org/10.1517/14656566.2016.1146689.

Soyka, M., & Müller, C. A. (2017). Pharmacotherapy of alcoholism – an update on approved and off-label medications. *Expert Opinion on Pharmacotherapy, 18*, 1187–1199. https://doi.org/10.1080/14656566.2017.1349098.

Spiga, S., Talani, G., Mulas, G., Licheri, V., Fois, G. R., Muggironi, G., et al. (2014). Hampered long-term depression and thin spine loss in the nucleus accumbens of ethanol-dependent rats. *Proceedings of the National Academy of Sciences of the United States of America, 111*, E3745–E3754. https://doi.org/10.1073/pnas.1406768111.

Stagg, C. J., Best, J. G., Stephenson, M. C., O'Shea, J., Wylezinska, M., Kincses, Z. T., et al. (2009). Polarity-sensitive modulation of cortical neurotransmitters by transcranial stimulation. *The Journal of Neuroscience, 29*, 5202–5206. https://doi.org/10.1523/JNEUROSCI.4432-08.2009.

Stagg, C. J., Wylezinska, M., Matthews, P. M., Johansen-Berg, H., Jezzard, P., Rothwell, J. C., et al. (2009). Neurochemical effects of theta burst stimulation as assessed by magnetic resonance spectroscopy. *Journal of Neurophysiology, 101*, 2872–2877. https://doi.org/10.1152/jn.91060.2008.

Stein, D. J. (2008). Depression, anhedonia, and psychomotor symptoms: The role of dopaminergic neurocircuitry. *CNS Spectrums, 13*, 561–565.

Strafella, A. P., Paus, T., Barrett, J., & Dagher, A. (2001). Repetitive transcranial magnetic stimulation of the human prefrontal cortex induces dopamine release in the caudate nucleus. *The Journal of Neuroscience, 21*, RC157.

Strafella, A. P., Paus, T., Fraraccio, M., & Dagher, A. (2003). Striatal dopamine release induced by repetitive transcranial magnetic stimulation of the human motor cortex. *Brain, 126*, 2609–2615. https://doi.org/10.1093/brain/awg268.

Sundström, C., Kraepelien, M., Eék, N., Fahlke, C., Kaldo, V., & Berman, A. H. (2017). High-intensity therapist-guided internet-based cognitive behavior therapy for alcohol use disorder: A pilot study. *BMC Psychiatry, 17*, 197. https://doi.org/10.1186/s12888-017-1355-6.

Su, H., Zhong, N., Gan, H., Wang, J., Han, H., Chen, T., et al. (2017). High frequency repetitive transcranial magnetic stimulation of the left dorsolateral prefrontal cortex for methamphetamine use disorders: A randomised clinical trial. *Drug and Alcohol Dependence, 175*, 84–91. https://doi.org/10.1016/j.drugalcdep.2017.01.037.

Tang, A., Thickbroom, G., & Rodger, J. (2015). Repetitive transcranial magnetic stimulation of the brain: Mechanisms from animal and experimental models. *The Neuroscientist, 23*, 82–94. https://doi.org/10.1177/1073858415618897.

Terao, Y., & Ugawa, Y. (2002). Basic mechanisms of TMS. *Journal of Clinical Neurophysiology, 19*, 322–343.

Terraneo, A., Leggio, L., Saladini, M., Ermani, M., Bonci, A., & Gallimberti, L. (2016). Transcranial magnetic stimulation of dorsolateral prefrontal cortex reduces cocaine use: A pilot study. *European Neuropsychopharmacology, 26*, 37–44. https://doi.org/10.1016/j.euroneuro.2015.11.011.

Thickbroom, G. W., Byrnes, M. L., Edwards, D. J., & Mastaglia, F. L. (2006). Repetitive paired-pulse TMS at I-wave periodicity markedly increases corticospinal excitability: A new technique for modulating synaptic plasticity. *Clinical Neurophysiology, 117*, 61–66. https://doi.org/10.1016/j.clinph.2005.09.010.

Tigaret, C. M., Olivo, V., Sadowski, J. H., Ashby, M. C., & Mellor, J. R. (2016). Coordinated activation of distinct Ca(2+) sources and metabotropic glutamate receptors encodes Hebbian synaptic plasticity. *Nature Communications, 7*, 10289. https://doi.org/10.1038/ncomms10289.

Trippe, J., Mix, A., Aydin-Abidin, S., Funke, K., & Benali, A. (2009). θ burst and conventional low-frequency rTMS differentially affect GABAergic neurotransmission in the rat cortex. *Experimental Brain Research, 199*, 411–421. https://doi.org/10.1007/s00221-009-1961-8.

Trojak, B., Meille, V., Achab, S., Lalanne, L., Poquet, H., Ponavoy, E., et al. (2015). Transcranial magnetic stimulation combined with nicotine replacement therapy for smoking cessation: A randomized controlled trial. *Brain Stimulation, 8*, 1168–1174. https://doi.org/10.1016/j.brs.2015.06.004.

Tupala, E., Hall, H., Halonen, P., & Tiihonen, J. (2004). Cortical dopamine D2 receptors in type 1 and 2 alcoholics measured with human whole hemisphere autoradiography. *Synapse, 54*, 129–137. https://doi.org/10.1002/syn.20071.

Tye, K. M., Stuber, G. D., de Ridder, B., Bonci, A., & Janak, P. H. (2008). Rapid strengthening of thalamo-amygdala synapses mediates cue-reward learning. *Nature, 453*, 1253–1257. https://doi.org/10.1038/nature06963.

Ungless, M. A., Whistler, J. L., Malenka, R. C., & Bonci, A. (2001). Single cocaine exposure in vivo induces long-term potentiation in dopamine neurons. *Nature, 411*, 583–587. https://doi.org/10.1038/35079077.

Valero-Cabré, A., Amengual, J. L., Stengel, C., Pascual-Leone, A., & Coubard, O. A. (2017). Transcranial magnetic stimulation in basic and clinical neuroscience: A comprehensive review of fundamental principles and novel insights. *Neuroscience and Biobehavioral Reviews, 83*, 381–404. https://doi.org/10.1016/j.neubiorev.2017.10.006.

Vernet, M., Bashir, S., Yoo, W. K., Oberman, L., Mizrahi, I., Ifert-Miller, F., et al. (2014). Reproducibility of the effects of theta burst stimulation on motor cortical plasticity in healthy participants. *Clinical Neurophysiology, 125*, 320–326. https://doi.org/10.1016/j.clinph.2013.07.004.

Vlachos, A., Müller-Dahlhaus, F., Rosskopp, J., Lenz, M., Ziemann, U., & Deller, T. (2012). Repetitive magnetic stimulation induces functional and structural plasticity of excitatory postsynapses in mouse organotypic hippocampal slice

cultures. *The Journal of Neuroscience, 32*, 17514–17523. https://doi.org/10.1523/JNEUROSCI.0409-12.2012.

Volkow, N. D., Koob, G. F., & McLellan, A. T. (2016). Neurobiologic advances from the brain disease model of addiction. *The New England Journal of Medicine, 374*, 363–371. https://doi.org/10.1056/NEJMra1511480.

Volkow, N. D., Wang, G. J., Begleiter, H., Porjesz, B., Fowler, J. S., Telang, F., et al. (2006). High levels of dopamine D2 receptors in unaffected members of alcoholic families: Possible protective factors. *Archives of General Psychiatry, 63*, 999–1008. https://doi.org/10.1001/archpsyc.63.9.999.

Volman, S. F., Lammel, S., Margolis, E. B., Kim, Y., Richard, J. M., Roitman, M. F., et al. (2013). New insights into the specificity and plasticity of reward and aversion encoding in the mesolimbic system. *The Journal of Neuroscience, 33*, 17569–17576. https://doi.org/10.1523/JNEUROSCI.3250-13.2013.

Wang, J., Fan, Y., Dong, Y., Ma, M., Ma, Y., Dong, Y., et al. (2016). Alterations in Brain Structure and Functional Connectivity in Alcohol Dependent Patients and Possible Association with Impulsivity. *PloS One, 11*, e0161956. https://doi.org/10.1371/journal.pone.0161956.

Wei, Y., Zhu, J., Pan, S., Su, H., Li, H., & Wang, J. (2017). Meta-analysis of the efficacy and safety of repetitive transcranial magnetic stimulation (rTMS) in the treatment of depression. *Shanghai Archives of Psychiatry, 29*, 328–342. https://doi.org/10.11919/j.issn.1002-0829.217106.

Wiers, C. E., Cabrera, E., Skarda, E., Volkow, N. D., & Wang, G. J. (2016). PET imaging for addiction medicine: From neural mechanisms to clinical considerations. *Progress in Brain Research, 224*, 175–201. https://doi.org/10.1016/bs.pbr.2015.07.016.

Yagishita, S., Hayashi-Takagi, A., Ellis-Davies, G. C., Urakubo, H., Ishii, S., & Kasai, H. (2014). A critical time window for dopamine actions on the structural plasticity of dendritic spines. *Science, 345*, 1616–1620. https://doi.org/10.1126/science.1255514.

Yang, S., Tang, Y. G., & Zucker, R. S. (1999). Selective induction of LTP and LTD by postsynaptic [Ca2+]i elevation. *Journal of Neurophysiology, 81*, 781–787. https://doi.org/10.1152/jn.1999.81.2.781.

Zack, M., Cho, S. S., Parlee, J., Jacobs, M., Li, C., Boileau, I., et al. (2016). Effects of high frequency repeated transcranial magnetic stimulation and continuous theta burst stimulation on gambling reinforcement, delay discounting, and stroop interference in men with pathological gambling. *Brain Stimulation, 9*, 867–875. https://doi.org/10.1016/j.brs.2016.06.003.

Zanardini, R., Gazzoli, A., Ventriglia, M., Perez, J., Bignotti, S., Rossini, P. M., et al. (2006). Effect of repetitive transcranial magnetic stimulation on serum brain derived neurotrophic factor in drug resistant depressed patients. *Journal of Affective Disorders, 91*, 83–86. https://doi.org/10.1016/j.jad.2005.12.029.

Zangen, A., & Hyodo, K. (2002). Transcranial magnetic stimulation induces increases in extracellular levels of dopamine and glutamate in the nucleus accumbens. *NeuroReport, 13*, 2401–2405. https://doi.org/10.1097/01.wnr.0000048021.74602.f2.

Ziemann, U., Paulus, W., Nitsche, M. A., Pascual-Leone, A., Byblow, W. D., Berardelli, A., et al. (2008). Consensus: Motor cortex plasticity protocols. *Brain Stimulation, 1*, 164–182. https://doi.org/10.1016/j.brs.2008.06.006.

Zyss, T., Rachel, W., Datka, W., Dudek, D., Zięba, A., Gorczyca, P., et al. (2015). Transcranial magnetic stimulation in psychiatric therapy. *Przeglad Lekarski, 72*, 371–375.