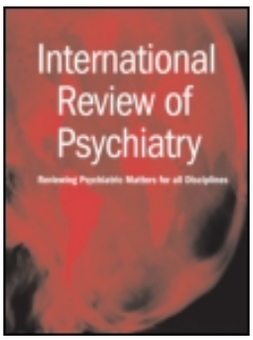

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Repetitive transcranial magnetic stimulation and drug addiction

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Abstract

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation technique that is now being tested for its ability to treat addiction. This review discusses current research approaches and results of studies which measured the therapeutic use of rTMS to treat tobacco, alcohol and illicit drug addiction. The research in this area is limited and therefore all studies evaluating the therapeutic use of rTMS in tobacco, alcohol or illicit drug addiction were retained including case studies through NCBI PubMed (http://www.ncbi.nlm.nih.gov) and manual searches. A total of eight studies were identified that examined the ability of rTMS to treat tobacco, alcohol and cocaine addiction. The results of this review indicate that rTMS is effective in reducing the level of cravings for smoking, alcohol, and cocaine when applied at high frequencies to the dorsolateral prefrontal cortex (DLPFC). Furthermore, these studies suggest that repeated sessions of high frequency rTMS over the DLPFC may be most effective in reducing the level of smoking and alcohol consumption. Although work in this area is limited, this review indicates that rTMS is a promising modality for treating drug addiction.

Introduction

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation technique that has been proven to be an efficacious treatment for neuropsychiatric disorders including depression (Bortolomasi et al., 2007; Fitzgerald et al., 2003), schizophrenia (Hoffman et al., 2003), and now potentially drug addiction. Repetitive TMS uses alternating magnetic fields applied at the same frequency to induce electric currents in the cortical tissue (Burt et al., 2002). Low frequency (≤ 1 Hz) rTMS is believed to cause inhibition of neuronal firing in a localized area and is used to induce virtual lesions to examine a brain region's role in different tasks. High frequency rTMS (>1 Hz) is believed to be excitatory in nature and can result in neuronal depolarization under the stimulating coil (Haraldsson et al., 2004). Moreover, the effect of rTMS is not limited to the targeted brain region as changes can also occur at distant interconnected sites of the brain. That is, the application of rTMS over cortical brain regions may provide a possible mechanism through which to influence subcortical regions that regulate emotion and behaviour (Ben-Shachar et al., 1997; Burt et al., 2002; Conca et al., 1996; Gershon et al., 2003; A. Post & Keck, 2001). The interest in rTMS as a potential treatment in addiction rests on its ability to induce changes in brain function.

Cortical changes induced by rTMS have been shown in both animal models and in humans. In the rat brain, rTMS has been shown to induce significant changes in neuronal circuits evidenced by changes in behaviour and an attenuation of the hypothalamic–pituitary–adrenocortical system (Fleischmann et al., 1995; Keck et al., 2002). Furthermore, it has been demonstrated that rTMS increases dopamine in the dorsal hippocampus (Keck et al., 2002) and the nucleus accumbens (Erhardt et al., 2004; Keck et al., 2002) using microdialysis in rodents. Repetitive TMS in the rat has also been shown to change the expression of proteins reflected by the synthesis of γ-aminobutyric acid (GABA) by two isoforms of GAD (Trippe et al., 2009). That is, Trippe et al. demonstrated that 1 Hz rTMS in the rat reduced expression of GAD67 and increased the expression of GAD65 and GABA transporter (GAT-1) compared to sham stimulation (Trippe et al., 2009). In humans, rTMS has been shown to induce changes in

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cortical inhibition. For example, increased rTMS frequency up until 20 Hz applied to the motor cortex has been shown to enhance neurophysiological indices of $GABA_B$ receptor mediated inhibitory neurotransmission (Daskalakis et al., 2006) but with 25 Hz stimulation a reduction in $GABA_B$ receptor mediated inhibitory neurotransmission has also been shown (Khedr et al., 2007). Repetitive TMS has also been shown to induce changes in indexes of $GABA_A$ receptor mediated inhibitory neurotransmission applied at 5 Hz (Takano et al., 2004) and 10 Hz over the motor cortex (Jung et al., 2008). In addition, combined rTMS/PET studies in healthy subjects demonstrated that 10 Hz rTMS over the dorsolateral prefrontal cortex (DLPFC) resulted in increased levels of extracellular dopamine (Cho & Strafella, 2009; Strafella et al., 2001), while 1 Hz rTMS resulted in increased regional blood flow in the stimulation site (DLPFC) and in the ventrolateral prefrontal cortex (Eisenegger et al., 2008). Taken together, animal and human studies demonstrate that rTMS has the potential to alter cortical excitability through the modulation of different neurotransmitters including dopamine and GABA that may have therapeutic effects on addiction.

According to the World Health Organization (WHO), use of tobacco, alcohol and illicit drugs contribute significantly to the global burden of disease (WHO, 2004). It is estimated that the number of individuals who smoke in developing countries continues to rise with 50% of men and 9% of women compared to 35% of men and 22% of women in developed countries (WHO, 2004). The level of alcohol consumption also is increasing in developing countries compared to a decrease in consumption over the past 20 years in developed countries. An approximated 200 million people use illicit drugs, translating to 3.1% of the global population and 4.3% of the population aged 15 years or older (WHO, 2004). Considered together, tobacco, alcohol and illicit drug use are implicated in over 12% of mortality worldwide and are also the leading cause of preventable death (WHO, 2009a, 2009b). However, these statistics describe a minority of individuals who develop abuse or dependence to substances and represent the majority of the morbidity and mortality rate. As such, the development of efficacious treatments for drug and alcohol addiction remains an important global priority.

The aim of this review was to report on studies which evaluated rTMS in the treatment of drug addiction. Due to the limited amount of research in this area, all studies evaluating the therapeutic use of rTMS in tobacco, alcohol or other illicit drug addiction were retained including case studies as identified through NCBI PubMed (http://www.ncbi.nlm.nih.gov) and manual searches. The search terms: rTMS, TMS and 7 drug classifications (e.g. sedatives-hypotics-anxiolytics, cannabis, stimulants, opioids, cocaine, hallucinogents, and other) according to the DSM-IV were initially used to identify the studies included in this review. Next, a narrower search using the search terms of specific drugs including street names within the drug classes (i.e. MDMA, ecstasy) and rTMS and TMS was conducted. Studies examining alcohol treatment with rTMS were also examined with the search terms: alcohol and rTMS and TMS. A total of eight studies were identified. Prior to the review of these studies, a discussion of the pathophysiology of the drug will be provided. In addition, the possible mechanism in which rTMS exerts its therapeutic effects will be examined.

Nicotine addiction

Pathophysiology of nicotine addiction

Nicotine dependence is characterized by both the tolerance and withdrawal symptoms in relation to nicotine use. From the first use of nicotine, the chances of repeated nicotine consumption are increased. The subjective and physiological effects of smoking are caused by the central actions of nicotine (Jarvik et al., 2000), the primary psychoactive constitute of tobacco. A significant amount of research has been focused on nicotine's action on the brain. Neuroimaging studies have demonstrated reductions in global brain activity particularly in the prefrontal cortex, thalamus, and visual systems following acute administration of nicotine. At the cellular level, nicotine binds to nicotinic receptors (acetylcholine receptors; nAChRs), which are ligand-gated ion channels consisting of five different subunits (Dani & Bertrand, 2007; Quattrocki et al., 2000). Moreover, postmortem studies demonstrate that nAChRs are present throughout the brain with highest to lowest distribution being: thalamus, basal ganglia, cerebral cortex, hippocampus, and cerebellum (Brody et al., 2004).

Chronic nicotine use generates tolerance to the drug, and like cocaine abuse, cravings and withdrawal symptoms result when the drug use is terminated. Unlike most neurotransmitter receptors, nAChRs are up-regulated in both animals and humans from chronic nicotine exposure (Wonnacott, 1990), thereby increasing the number of nicotine receptors (Benwell et al., 1988; Sabbagh et al., 2002). Moreover, an increase in nAChRs results in an influx of calcium ions which in turn increase the levels of dopamine, serotonin, acetylcholine, GABA, and glutamate levels in the brain (Dani & Bertrand, 2007; Quattrocki et al., 2000). Nicotine receptors, thus, are considered neuromodulators of other neurotransmitter pathways. For example, animal studies collectively show that nicotine: 1) enhances GLU transmission in cortical pyramidal neurons (Vidal & Changeux, 1993); 2) increases the levels of norepinephrine in

striatal neurons to activate the release of GABA from hippocampal neurons (Alkondon et al., 1997); and 3) releases serotonin from the dorsal raphe neurons (Li et al., 2004) and of striatal neurons in rat brain slices (Westfall et al., 1989) through activation of nicotinic receptors. In addition to the ability of nicotine to modulate other neurotransmitter systems, they also propagate fast ACh neurotransmission in certain areas of the rat brain, including hippocampal interneurons (McGehee & Role, 1995). Finally, chronic exposure can also lead to oxidative stress. For example, chronic smokers have more than 25% lower circulating concentrations of antioxidants, as compared to healthy individuals (Alberg, 2002), which has been associated with enhanced levels of glutamate leading to neurotoxicity, and ultimately, cell death (Butterfield & Pocernich, 2003).

Together these studies indicate that nicotine acts on several neurotransmitters and their associated neuromodulators, thereby changing brain activity associated with nicotine addiction and withdrawal. There are three classes of approved treatments for nicotine addiction, including nicotine replacement therapies (e.g. gum, patch, inhaler and nasal spray), sustained release bupropion and varenicline, which have been proven to increase rates of smoking cessation 2–3-fold compared to placebo treatments (Hughes, 2000; Le Foll & George, 2007; Siu & Tyndale, 2007). However, an effective treatment is still needed to target the altered neurotransmission resulting from chronic nicotine dependence.

Treatment of nicotine addiction with rTMS

Our search identified four studies which investigated the ability of rTMS to treat nicotine dependence (Table I), none of which reported negative results. In a double-blind, placebo-controlled cross-over pilot study, Johann et al. (2003) tested 11 smoking dependent individuals who wished to stop smoking. Subjects received a single session of both active and sham 20 Hz rTMS delivered to the left DLPFC at 90% resting motor threshold. Smoking cravings were measured with the 100-point visual analogue scale (VAS) 30 min prior to and following the treatment of rTMS. Active rTMS was found to significantly reduce the level of smoking craving 30 min following the treatment as compared to sham stimulation. This was the first study to demonstrate reduced levels of smoking cravings following a single session of rTMS over the DLPFC. The findings of this study were then extended by the same research group to investigate whether repeated sessions of rTMS would also result in reduced smoking consumption (Eichhammer et al., 2003).

In a similar double-blind cross-over design study, Eichammer et al. (2003) tested 14 individuals who smoked an average of 16.8 (±) 10 cigarettes per day and wished to stop smoking. Two sessions of both active and sham 20 Hz rTMS (90% resting motor threshold in 20 trains, 50 pulses per train, 42.5 s inter-train interval) were delivered over the left DLPFC in a randomized order for four consecutive days. Smoking cravings were measured at baseline and 30 min after the rTMS session using a 100-point VAS. Following rTMS, the number of cigarettes freely smoked in a 6-h time period was also measured. Active rTMS was found to significantly decrease the number of cigarettes smoked over the 6-h time period but no change in the level of cravings was observed. Together the findings of the Eichhammer group indicate that repeated sessions of 20 Hz rTMS may be effective in reducing smoking consumption, however, the second study was not able to replicate the findings of the first demonstrating reduced levels of smoking cravings with rTMS.

More recently, Amiaz et al. (2009) investigated the effect of repeated high frequency rTMS combined with the presentation of smoking cues on cigarette consumption, dependence and cravings. In a randomized double-blind placebo controlled design, 48 subjects who smoked at least 20 cigarettes per day were allocated to receive either active or sham 10 Hz rTMS for 10 sessions (100% resting motor threshold in 20 trains, 50 pulses per train, 15 s inter-train interval) applied over the left DLPFC. Within each rTMS group, subjects were randomized to receive either the

Table I. Review of studies evaluating the ability of rTMS to treat drug addiction.

Drug	Study	Subject status	N	rTMS parameters	Findings
Nicotine	Johanne et al., 2003	12 h abstinence	11	20 Hz rTMS left DLPFC	↓cravings
	Eichhammer et al., 2003	12 h abstinence	14	20 Hz rTMS left DLPFC	↓consumption
	Amiaz et al., 2009	Use continued	48	10 Hz rTMS left DLPFC	↓cravings and consumption
	Wing et al., 2011	30 min abstinence	15	20 Hz rTMS bilateral DLPFC	↓ cravings
Alcohol	Mishra et al., 2010	≥10 day abstinence	45	10 Hz rTMS right DLPFC	↓ cravings
	De Ridder et al., 2011	Use continued	1	50% intensity of rTMS to dorsal anterior cingulated cortex	↓cravings and consumption
Cocaine	Camprodon et al., 2007	Use continued	6	10 Hz bilateral DLPFC	↓cravings with right DLPFC rTMS
	Politi et al., 2008	Detoxified	36	15 Hz left DLPFC	↓cravings

presentation of smoking or neutral visual cues for a total of four different groups. A series of 14 pictures were presented to the subjects immediately before the administration of the rTMS. Cigarette consumption was measured both subjectively through self-report and objectively through urine samples at the beginning of each week. The level of cravings was assessed with the VAS prior to and following the presentation of the visual cues every day and with the short version of the Tobacco Craving Questionnaire (sTCQ) before and after the rTMS treatment course. Nicotine dependence was also measured before and after the rTMS treatment course with the Fagerstrom Test for Nicotine Dependence (mFTND). Subjects also participated in a maintenance phase of rTMS that was administered on alternate days for the first week and once a week for the following three weeks. Urine samples were provided and the mFTND and the sTCQ were measured at each maintenance session. Finally, long-term effects of rTMS on nicotine addiction were evaluated through telephone surveys 6 months following the completion of the rTMS course. Active rTMS was found to significantly reduce both cigarette consumption and nicotine dependence compared to sham stimulation. Repetitive TMS also reduced cue-induced cigarette craving induced by repeated presentation of smoking-related pictures over the 10 days. These effects were, however, found to decrease during the maintenance phase, thereby suggesting that longer daily treatment courses may be needed for complete cessation of smoking (Amiaz et al., 2009).

We have recently examined the efficacy of high frequency rTMS for smoking cessation in treatment-seeking individuals with comorbid schizophrenia (Wing et al., 2010). In a randomized double-blind placebo controlled design, 15 subjects with a diagnosis of schizophrenia or schizoaffective disorder who smoked at least 10 cigarettes per day were allocated to receive either active (n = 6) or sham (n = 9) 20 Hz rTMS for 4 weeks (100% resting motor threshold, 25 trains per hemisphere, 30 pulses per train, 30 second inter train interval for a total of 20 sessions) applied bilaterally over the DLPFC. Cravings were assessed once a week immediately before and after rTMS treatment with the Tiffany Questionnaire for Smoking Urges (TQSU). A significant change in the level of cravings was found after 1 week of active stimulation compared to sham. No differences were found on cravings in the following 3 weeks. Smoking consumption was unchanged. These preliminary findings indicate that rTMS should be evaluated further in smokers with schizophrenia, a population of smokers who are typically highly nicotine-dependent and are less likely to quit with currently available tobacco treatments (Morisano et al., 2009).

Importantly, these studies were conducted in a double-blind design with two studies administering a separate placebo group condition. The findings of these four studies provide early evidence supporting the therapeutic effects of repeated sessions of rTMS on cigarette craving, dependence and consumption when applied at high frequency over the DLPFC. More specifically, these studies suggest that rTMS applied at frequencies of 10 Hz (Amiaz et al., 2009) and 20 Hz ((Johann et al., 2003) Hz applied to the DLPFC reduces the level of cigarette cravings regardless of whether subjects were abstinent or continued cigarette use. Decreased consumption was also observed with 10 Hz (Amiaz et al., 2009) and 20 Hz (Eichhammer et al., 2003) rTMS when administered in repeated sessions, thereby suggesting that longer treatment courses are needed for complete cessation of smoking (Amiaz et al., 2009). Finally, the review of these studies indicates that the DLPFC is a reasonable brain region to target with rTMS in the treatment of the nicotine addiction.

Although it is unclear how rTMS exerts its effects on smoking, it has been suggested that rTMS increases the availability of striatal dopamine (Pogarell et al., 2006; Strafella et al., 2001), which may reduce the level of craving (de la Fuente-Fernandez et al., 2002; Ernst, 2007; Perkins et al., 2003). Withdrawal symptoms may even be improved with transient increases in dopamine secretion (Amiaz et al., 2009). It has also been suggested that rTMS may modulate the neuroadaptations in the reward system involved in nicotine addiction provided that rTMS has been shown to induce changes in cortical excitability (Daskalakis et al., 2006; Pascual-Leone et al., 1994), which could lead to changes in cortical plasticity through mechanisms such as long-term potentiation (Cooke & Bliss, 2006; Frantseva et al., 2008; Huang et al., 2005). Future replication studies are needed in order to optimize the parameters of rTMS in the treatment of nicotine addiction through a reduction in the levels of cravings, dependence and its consumption.

Alcohol addiction

Pathophysiology of alcohol addiction

Alcohol dependence or alcoholism is a condition characterized by impaired control over drinking, compulsive drinking, pre-occupation with drinking, tolerance to alcohol and/or withdrawal symptoms. That is, with alcohol dependence, there is a persistent use of alcohol despite problems related to the use of the substance. According to the DSM-IV, alcohol abuse is characterized by failure to fulfil major role obligations at work, school or home, involving interpersonal social and legal problems and/or drinking in hazardous situations.

Ethanol, the active ingredient in alcoholic beverages, acts as a central nervous system depressant even with acute administration (Conte et al., 2008). At present, there is no one specific neurotransmitter binding site for ethanol. That is, alterations in the GABAergic, glutamatergic, dopaminergic neurotransmitter systems (Davidson & Wilce, 1998; Harris et al., 2003; Koob, 2006a; Koob & Le Moal, 2008; Rossetti et al., 1999; Rudolph et al., 1997) have been implicated in the pathophysiology of ethanol abuse. An immense number of animal studies have examined the effect of ethanol on GABAergic neurotransmission. For example, *in vitro* actions of ethanol exert its most potent effects on the $GABA_A$ receptor even with low doses of 1–3 mM and alter GABA-gated current measures (Sundstrom-Poromaa et al., 2002). It is suggested that ethanol modulates the GABA receptor complex allosterically to open the chloride channel and hyperpolarize cells or potentiate the hyperpolarization by GABA (Koob, 2006b). The specific effects of ethanol on $GABA_A$ receptors produce anti-conflict actions and motor impairment (Frye & Breese, 1982; Liljequist & Engel, 1982) which has been shown to be reversed with $GABA_A$ antagonists. Other modulators of GABAergic system may not only act through the modulation of $GABA_A$ receptors but also through the interaction with $GABA_B$ receptors inducing the release of GABA (Koob, 2004). For example, baclofen, a $GABA_B$ agonist, has been shown to decrease both alcohol self-administration in non-dependent rats (Janak & Michael Gill, 2003) and ethanol deprivation effects in alcohol-preferring rats (Colombo, 2003a; Colombo, 2003b). Importantly, clinical studies have also demonstrated the efficacy of baclofen on reducing ethanol craving, consumption and withdrawal (Addolorato et al., 2002a; Addolorato et al., 2002b).

Several studies have also demonstrated the involvement of glutamate in the mediation of ethanol. For example, functional studies have demonstrated that acute exposure to ethanol can inhibit cellular events including *N*-methyl *D*-aspartate (NMDA) receptor-mediated increasing intracellular Ca^{2+} levels (Dildy & Leslie, 1989), long-term potentiation (Blitzer et al., 1990), excitotoxicity (Chandler et al., 1993), and nitric oxide formation (Lovinger et al., 1990). In contrast, with chronic ethanol administration, NMDA-mediated excitotoxicity potentiates NMDA-mediated intracellular Ca^{2+} influx (Ahern et al., 1994) and nitric oxide formation (Chandler et al., 1997). Studies *in vivo* suggest that NMDA receptors are modulated during the development of tolerance and dependence to alcohol which may reflect increased sensitivity to such NMDA cellular events (Rudolph et al., 1997). That is, when MK-801 (a non-competitive antagonist of NMDA receptor) is chronically administered with ethanol, tolerance and dependence to ethanol is abolished (Khanna, Kalant, Shah & Chau, 1992a; Khanna, Kalant, Weiner, Chau & Shah, 1992b). Together both *in vivo and in vitro* studies indicate that NMDA receptor sensitivity is involved in the development of ethanol tolerance and dependence.

Alterations in dopamine have also been implicated in the pathophysiology of alcoholism particularly with the involvement of cravings associated with the brain reward centre in the medial forebrain bundle comprising the meso-cortico-limbic pathway (Park et al., 2007). Specifically, ethanol has been shown to stimulate the release of dopamine and the down-regulation of striatal D_2 receptors (Volkow et al., 1996). Longitudinal studies have demonstrated that the down-regulation of D_2 receptors is most pronounced immediately following detoxification and recovers during abstinence (Dettling et al., 1995; Heinz et al., 1996). If the recovery of the central dopaminergic neurotransmission system is delayed this is predictive of a higher chance of relapse in detoxified alcoholics (Dettling et al., 1995; George et al., 1999; Heinz et al., 1996).

Neuroimaging studies have identified alterations in the orbitofrontal cortex (Koob & Le Moal, 2008), anterior and posterior cingulated cortex (Koob & Le Moal, 2008; Lingford-Hughes et al., 2006; Sinha & Li, 2007; Tapert et al., 2004) and amygdala (Koob & Le Moal, 2008) are associated with alcohol craving, dependency and relapse. Moreover, electrophysiology studies examining oscillatory activity have demonstrated alterations in the beta frequency band during alcohol craving (De Ridder et al., 2011), while changes in the alpha, theta and delta bands has been associated with alcohol consumption (Ehlers et al., 1989; Lehtinen et al., 1985; Lukas et al., 1986). In spite of the availability of several anti-craving medications (e.g. acamprosate and naltrexone) the efficacy of these drugs is limited for alcohol dependence (Mishra et al., 2010). Similar to the lines of evidences for the potential of rTMS to treat nicotine dependence, such as its action on the neurotransmitter systems including dopamine and GABA, rTMS has also been examined for its ability to treat alcohol dependence.

Treatment of alcoholism with rTMS

Our search revealed two recent studies which tested the efficacy of rTMS to treat alcohol addiction (Table I). First, in a single blind prospective sham-controlled study, Mishra et al. (2010) examined the ability of high frequency rTMS to treat patients with alcohol dependence, determined by the ICD-10, with Clinical Institute of Withdrawal (CIWA-Ar) scores ≤ 10. In their study, 45 patients were randomized to receive either active or sham

stimulation in a 2:1 ratio whereby 30 patients received active stimulation and 15 patients received sham applied at 10 Hz rTMS (110% resting motor threshold in 20 trains, 50 pulses per train, 30 s inter-train interval) to the right DLPFC for 10 sessions. The level of alcohol craving was assessed with the Alcohol Craving Questionnaire (ACQ-NOW) before and after rTMS treatment, and 1 month following. The results of the study demonstrated a significant reduction in the level of craving scores in patients who received active compared to sham rTMS (Mishra et al., 2010). Although this study was single blind and by extension susceptible to rater bias, it provides support for the ability of high frequency rTMS over the right DLPFC to reduce alcohol cravings.

The second study was a recent case-report on a 48-year-old woman with a 23-year heavy drinking history and current severe intractable alcohol cravings in a combined rTMS neuroimaging study (De Ridder et al., 2011). One Hz rTMS (50% of the machine's intensity, total of 600 pulses) was delivered for 3 weeks to the medial frontal cortex using a double cone. Functional magnetic resonance imaging (fMRI) and resting electroencephalography (EEG) were measured before and after rTMS treatments. Blood alcohol volumes were acquired on random days during the treatment course using a breathalyser test. Alcohol cravings were measured daily with the VAS. Repetitive rTMS reduced alcohol consumption for the duration of the treatment. Symptoms of withdrawal and cravings were also reduced for up to 3 months. This reduction was also reflected with the change in fMRI and EEG activity. After 3 months, the patient relapsed and was treated with 1 week of rTMS. These effects lasted for 3 weeks until the patient relapsed again and the patient became unresponsive to the rTMS treatment. While no studies with negative results were revealed through our search, these two studies provide early positive support for the use of rTMS in treating alcoholism. Since ethanol acts on several neurotransmitter systems, it is difficult to hypothesize how rTMS exerted its therapeutic effects on the level of alcohol cravings observed in both studies. Furthermore, interpretation of these findings is further complicated by the difference in brain targets (e.g. DLPFC, medial frontal cortex) used for treatment, rTMS stimulators, number of subjects tested and overall design of the study. In spite of these differences, these studies suggest that repeated sessions may be needed to reduce alcohol cravings. The positive results of these studies underscore the need to further examine the ability of rTMS in treating alcoholism with randomized, double-blind placebo-controlled experimental designs in large subject samples.

Cocaine addiction

Pathophysiology of cocaine addiction

Exposure to cocaine acts as a biological stimulus, which is mediated by the neostriatal dopamine projection pathway, releasing dopamine (Peris et al., 1998). Cocaine binds to dopamine transporters and blocks the re-uptake of synaptic dopamine thereby increasing its lifetime in the synaptic cleft and allowing dopamine to diffuse more efficiently between synapses (Kalivas, 2007). Repeated increases in dopamine transmission in chronic cocaine exposure lead to cellular alterations that are involved in learning behaviours relevant to biological stimuli (i.e. cocaine) (Kalivas, 2007) thought to, in part, underlie drug addiction.

The effect of chronic cocaine exposure is less clear. Conceptually, it has been suggested that cocaine addiction increases excitatory glutamatergic activity at the expense of GABA inhibitory neurotransmission (Kalivas, 2007) leading to altered cortical excitability. In this regard, cues associated with cocaine are reported to activate a circuit involving the cortico-limbic brain regions, notably between the prefrontal cortex, amygdala and ventral striatum (nucleus accumbens) in cocaine-dependent patients (Garavan et al., 2000). Moreover, the outputs from the prefrontal cortex to the nucleus accumbens are glutamatergic, and from the nucleus accumbens to the ventral pallidum is GABAergic and peptidergic (Kalivas, 2007). That is, GABA is involved in dopamine projections from prefrontal cortex to the ventral pallidum where neuropeptides that regulate GABA are co-localized (Zahm et al., 1996). Therefore, drugs that target either GABA or peptide transmission are potential targets in pharmacological therapies in cocaine addiction. In this regard, both $GABA_A$ and $GABA_B$ receptors have been implicated in cocaine exposure in preclinical investigations. For example, a significant correlation has been found between the decrease in striatal $GABA_A$ receptor function and the degree of cocaine-sensitized behaviour in rats, strongly implicating GABAergic neurotransmission in the development of cocaine sensitization (Peris et al., 1998). In addition, gamma-vinyl GABA (GVG), an irreversible inhibitor of GABA transminase, which is the primary enzyme involved in GABA metabolism, has been shown to elevate GABA levels in the rat brain (Kushner et al., 1999). Moreover, GVG dose-dependently decreases cocaine self-administration independent of the feeding regime, thereby suggesting that GVG attenuates the reward value of cocaine.

There is also evidence for $GABA_B$ receptor activity in the mediation of cocaine. For example, baclofen has been shown to inhibit cocaine administration in a dose-dependent fashion (Brebner et al., 2002).

Consistent with this finding, CGP56433A, a $GABA_B$ antagonist also attenuates baclofen's effect on cocaine self-administration in rats under a number of different feeding regimes. Further, $GABA_B$ receptors are believed to be critical in the reward properties of cocaine, as baclofen decreases extracellular dopamine in the ventral tegmental area and other structures of the dopaminergic system (Brebner et al., 2002). In addition to preclinical evidence, clinical trials have also demonstrated a reduction in cocaine cravings and cocaine use following the administration of baclofen (Haney et al., 2006; Ling et al., 1998; Shoptaw et al., 2003), thus strengthening the consideration of $GABA_B$ as a therapeutic target in the treatment of cocaine addiction.

In addition to GABA, glutamate is also a major neurotransmitter in the mediation of cocaine exposure. As previously noted, repeated cocaine exposure leads to alterations in glutamate and metabotropic glutamate receptors (mGluRs) (Kalivas, 2007), which have been investigated as therapeutic targets in preclinical studies. For example, glutamate antagonists (i.e. selective NMDA antagonists) block the locomotor stimulant effects of cocaine (Witkin, 1993), and decrease the incidence of cocaine-induced convulsions and mortality in mice (Rockhold et al., 1991). In addition, Shoji et al. (1997) examined both acute and chronic cocaine exposure on inhibitory and excitatory transmission in rats, and reported that cocaine's mechanism of action influences GABA and glutamate, as well as biogenic amines. Amine transport sites which uptake biogenic amines are reportedly inhibited with chronic cocaine exposure, thereby elevating the actions of endogenous neuromodulators, such as dopamine, serotonin, and norepinephrine (Shoji et al., 1997). Although several mechanisms of glutamate transmission have been targeted with pharmacological therapies in animal models in the treatment of cocaine addiction, clinical studies in patients still need to be investigated.

Chronic cocaine exposure typically results in the sensitization to the drug, implying that an individual may demonstrate an increase in response to cocaine over time. Cocaine sensitization is believed to be related to its intense euphoria (Gawin & Ellinwood, 1988), a process dependent on the activity of glutamate receptors (Pierce et al., 1996), and is paralleled by an increase in sensitivity to the proconvulsant effects of cocaine (Post, 1977). It is clear that cocaine abuse can result in alterations of cortical excitability through its influence on both GABA and glutamate neurotransmitters, and their associated neuromodulators. The interplay between these elements is thought to be involved in the sensitization of cocaine that underlies the cravings for the drug. Furthermore, the hypothesis that cravings for cocaine involves a distributed neural network including the amygdala, anterior cingulate, orbitofrontal, and DLPFC is starting to emerge (Wilson et al., 2004). To this end, the DLPFC may serve as a suitable target for the treatment of cocaine addiction because of its connections to the limbic brain areas (i.e. the ventral pallidum) mediated by both GABAergic and peptidergic transmission.

To date, there is no approved treatment for cocaine abuse despite the number of pharmacotherapy regimes proposed (Sofuoglu & Kosten, 2006). An effective treatment for cocaine users, which targets the neural mechanisms associated with chronic cocaine administration and sensitization, is therefore needed. rTMS applied to the DLPFC may represent a potential treatment in cocaine addiction given that rTMS has been shown to enhance $GABA_B$'s neurotransmission (McDonnell et al., 2006) through increased cortical inhibitory activity (Daskalakis et al., 2006).

Treatment of cocaine addiction with rTMS

Our search revealed two positive studies which examined rTMS as a potential treatment for the cravings experienced by cocaine-dependent individuals (Table I), while no study with a negative finding was found. In the first study, Camprodon et al. (2007) administered two sessions of 10 Hz rTMS to the right or left DLPFC at 90% resting motor threshold in a randomized cross-over design in six subjects. The level of cocaine cravings were assessed with VAS 10 min before, immediately following, and 4 h following rTMS. Repetitive TMS applied to the right, but not the left DLPFC; decreased the level of cravings for cocaine immediately and 4 h following rTMS administration compared to baseline levels.

Politi et al. (2008) also administered high frequency rTMS over the DLPFC to examine its ability to modulate cravings in cocaine-dependent individuals. Thirty-six detoxified subjects received 15 Hz rTMS (20 trains, inter train interval 30 seconds at 100% resting motor threshold) over the left DLPFC for 10 sessions. The level of cocaine cravings were measured each day with the psychopathological symptoms related to cravings were acquired each day of the stimulation. Cravings were found to decrease gradually with each rTMS session with the greatest reduction observed following the seventh session.

Although only two studies have evaluated the ability of rTMS to treat cocaine cravings, the results are positive. Together they indicate that high frequency rTMS over the DLPFC may be effective in treating cocaine cravings; however, the most optimal hemisphere to target remains unclear. That is, the first study by Camprodon et al. (2007) found that only the right and not the left DLPFC resulted in a reduction of cocaine cravings. In contrast, the later study by Politi et al. (2008) found left targeting of the

DLPFC reduced cocaine levels. The inconsistent results following stimulation to the left DLPFC may be attributed to differences in subjects, as cocaine use was allowed in the Camprodon study while subjects in the Politi study were detoxified. It is also possible that a greater number of rTMS sessions results in greater therapeutic effects in the left hemisphere. Further examination of the optimal rTMS parameters and site of stimulation are greatly needed, particularly with the addition of a placebo sham controlled condition.

Discussion

The studies reviewed in this paper provide positive support for the ability of rTMS to reduce the level of cravings in tobacco, alcohol and cocaine addicted patients with the potential to reduce consumption. Review of these studies indicates that repeated administration of high frequency rTMS over brain regions involved in the pathophysiology of addiction (e.g. DLPFC and the medial frontal cortex) show promise in treating drug cravings and consumption. Given the positive results of this review, future studies are needed to replicate and further examine how rTMS can be optimized for the treatment of drug addiction.

Most studies, with the exception of one, targeted the DLPFC with rTMS to examine its effect on drug addiction. Several lines of evidence suggest that rTMS over the DLPFC may influence the brain regions involved in drug addiction. First, the DLPFC is connected to the meso-fronto-limbic dopaminergic system (Boggio et al., 2008), the brain reward system that is associated with cravings that lead to addiction (Park et al., 2007). Second, rTMS has been demonstrated to induce dopamine release in subcortical and cortical areas and therefore may remediate the dopamine dysfunction associated with addiction. In rodents, rTMS resulted in dopamine released in the hippocampus and the nucleus accumbens measured by intracerebral microdialysis in the hippocampus and the nucleus accumbens (Keck et al., 2002; Zangen & Hyodo, 2002). Similarly in humans, high frequency rTMS over the DLPFC has been shown to stimulate dopamine release in the caudate nucleus (Strafella et al., 2001) and the ipsilateral anterior cingulate cortex and orbitofrontal cortex (Cho & Strafella, 2009). Third, the level of cravings for food, alcohol, and nicotine in the presence of visual cues has been shown to be reduced with stimulation of the DLPFC with rTMS (Amiaz et al., 2009; Uher et al., 2005) and direct current stimulation (Boggio et al., 2008; Fregni et al., 2008), respectively. Fourth, the DLPFC has been shown to be involved with decision-making processes which may be altered in addicted patients who are more likely to be more impulsive with risk-taking behaviour (Rorie & Newsome, 2005). Fifth, low frequency rTMS over the right DLPFC induces risk-taking behaviours (Knoch et al., 2006) and it is possible then that application of rTMS may result in decreased impulsivity through increased inhibitory control (Amiaz et al., 2009). In this regard, finally, high frequency rTMS over the motor cortex has been shown to increase cortical inhibition in healthy human subjects (Daskalakis et al., 2006). Taken together, these lines of evidence suggest that high frequency rTMS over the DLPFC may have a beneficial effect on drug cravings and dependence to ultimately reduce consumption.

Due to the limited number of studies reviewed in this paper, it is difficult to comment on the optimal hemisphere and rTMS parameters to treat drug addiction to guide future investigations. With that being said, it appears that left DLPFC stimulation is beneficial for treating nicotine addiction, right DLPFC stimulation may reduce addiction to alcohol; however, the hemisphere site remains unclear for cocaine addiction. Regardless of the stimulation site, this review indicates that high frequency rTMS is promising in treating drug addiction, although lower frequencies (<10 Hz) were not examined. Nevertheless, the results of this review are positive, warranting future examination of how best to optimize rTMS for the treatment of drug addiction.

A critical limitation to these studies is the evaluation of the mechanism in which rTMS exerts its effects. Although we speculate that rTMS acts on several neurotransmitter systems, future studies should consider evaluating the therapeutic mechanisms of rTMS with TMS diagnostic measures or neuroimaging techniques. For example, De Ridder et al. (2011) identified alterations in beta and gamma oscillatory activities associated with craving and relapse, suggesting that oscillatory activity is involved in addiction and modulation of this activity through rTMS may have therapeutic effects in treating addiction. In line with this suggestion, high frequency rTMS over the DLPFC has been shown to modulate gamma oscillation in healthy human subjects (Barr et al., 2009). A multi-method approach may therefore provide the best way in which to understand and optimize the ability of rTMS to treat addiction.

The conceptualization of addiction has changed from the traditional drug-centred model that aims to understand the neurobiological changes induced by drug exposure towards an individual-centred approach which attempts to characterize vulnerabilities to understand individual differences in the propensity to addiction (Swendsen & Le Moal, 2011). Support for the later model comes from epidemiology studies which have shown that demographic factors such as gender and age contribute to the development of

addiction (Crum et al., 2005; Grant et al., 2001; Hasin et al., 2007; Kessler et al., 2005a; Warner et al., 1995). Similarly, clinical studies have correlated specific personality traits and comorbid mental disorders to drug addiction (Conway et al., 2002; Kessler et al., 1997, 2005b; Merikangas et al., 1998; Swendsen et al., 2002), while basic neuroscientific research implicates biological and genetic factors that may underlie an individual's propensity to drug addiction (Gelernter & Kranzler, 2009; Koob & Zorrilla, 2010). In this regard, another limitation to these studies is the assessment of other comorbidities associated with the patient population. For example, alcoholism is associated with individuals suffering from anxiety and may serve as a negative reinforcement in the motivation to consume alcohol (Koob & Le Moal, 2008) and tobacco addiction is more prevalent in those with a comorbid psychiatric disorder such as schizophrenia. Further, the adoption of the individual-centred model may help to uncover potential mediators and moderators of alcohol addiction for the development of relapse prediction indices.

The studies reviewed typically used VAS to determine the efficacy of rTMS on the level of cravings. However, objective measures including urine and breathalyser tests provided convincing evidence for the ability of rTMS to reduce drug consumption (Amiaz et al., 2009; De Ridder et al., 2011). In this regard, future studies should consider using both objective and subjective measures to evaluate the potential of rTMS to treat addiction.

Conclusion

Although the research in this area is in its early days, there is positive and compelling evidence for the ability of rTMS to treat addiction. The work available has examined addiction to nicotine, alcohol and cocaine, but these studies show promise in treating addiction to other illicit drugs such as 3, 4-methylenedioxymethamphetamine (MDMA) and opiates as well as gambling and gaming addictions. The development of efficacious treatments for addiction continue to be an area of important research as addiction contributes significantly to the global burden of disease and mortality.

Take-home points

- Repetitive TMS shows promise in reducing drug and alcohol cravings.
- Review of the literature demonstrates that high frequency rTMS administered repeatedly to the DLPFC has a beneficial effect on the level of cravings. The optimal frequency, number of sessions and hemisphere targeted may vary with the drug or alcohol addiction and needs further investigation.
- Although the results of this review are favourable, the number of studies is limited. At this point, we cannot recommend rTMS as a treatment for drug or alcohol addiction without further investigation of its efficacy.

Future directions

- Further evaluation of rTMS parameters is needed to optimize treatment for drug addiction.
- To further examine the how rTMS exerts its therapeutic effects on drug cravings and addiction.

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