

Commentary:

Repetitive Transcranial Magnetic Stimulation (rTMS) in the Management of Alcohol Dependence and other Substance Abuse Disorders – Emerging Data and Clinical Relevance

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Article info:

Received: 19 January 2013

First Revision: 20 June 2013

Accepted: 25 June 2013

Key Words:

rTMS,
Substance Use Disorders,
Alcohol Dependence,
Nicotine Dependence,
Opiate,
Heroin,
Amphetamine.

A B S T R A C T

Repetitive transcranial magnetic stimulation (rTMS) has been used widely in various psychiatric disorders like depression and schizophrenia. There have been some reports of its usefulness in alcohol dependence and substance use disorders. The present paper reviews the studies done using rTMS in substance use disorders including alcohol and nicotine dependence. Various studies done have been reviewed including the proposed mechanisms of action are outlined with the future research needs and need for further clinical data

Introduction

Substance abuse is a major health problem worldwide and has been linked to several neuropsychiatric disorders, gastrointestinal diseases, cancer, cardiovascular diseases, fetal alcohol syndrome, pre-term birth complications and diabetes mellitus (Chesher et al., 2011). Genetic, biological and environmental factors could all together influence the development of alcohol and substance abuse (Tarter, 2002). Substance abuse disorders are often difficult to treat and relapse rates are high, even when successful detoxification is followed by pharmacotherapeutic or psychotherapeutic interventions (Garner, 2009).

Critical Aspects of Drug and Alcohol Dependence

A recent important paper on the neurobiology of alcohol dependence (Koob, 2011) describes an Addiction Cycle in alcohol dependent patients, which consists of three phases, namely the binge/intoxication phase, the withdrawal/negative affect phase and the preoccupation/anticipation phase. Further, before becoming dependent, this cycle is usually repeated multiple times. Although other neurotransmitter systems can be involved as well, the dopaminergic system is the key player in all these phases (Kalsi et al., 2009). Alcohol addicted patients display a deregulated dopaminergic system, which results in stronger alcohol orientation and loss in interest for natural rewards. Because of this malfunctioning dopa-

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minergic system alcoholic patients encounter difficulties in learning new reward associated stimuli and they lack motivation to seek new rewarding stimuli (Heinz et al., 2009). Once 'addiction' is established, the cycle is characterized by impulsivity and compulsivity (Koob & Volkow 2010).

Main Cognitive Targets For Therapeutic Interventions In Drug And Alcohol Dependence

Impulsivity is characterized by non planned reactions to external and internal stimuli and it is associated with positive reinforcement (Zhang et al. 2012). The underlying neurobiology of impulsivity in alcohol dependency is complex (Potenza and Taylor, 2009). The prefrontal cortical network, and in particular the dorsolateral prefrontal cortex (DLPFC) and the orbitofrontal cortex (OFC) play an important role in inhibitory control mechanisms when patients are confronted with addictive substances (Bechara 2005; Schoenbaum et al., 2009). Increasing the activity of the PFC and thus cognitive control could decrease automatic impulses and therefore reduce substance abuse behavior (Houben et al., 2011). Next to the deregulation of the dopaminergic system, the hypothalamus-pituitary-adrenal (HPA) axis is dysfunctional (Koob & Volkow 2010, Sinha et al., 2011).

Recently, neuromodulation techniques, such as transcranial magnetic stimulation (TMS) have been applied to substance abuse and alcohol dependent patients (Barr et al., 2008). However, to date no clear guidelines in alcohol addiction are at hand to determine when such interventions can be applied. Therefore, the purpose of this review is to critically evaluate the efficacy of TMS in the treatment of alcohol dependence and other substance abuse disorders.

Method of Conducting this Review

We conducted a broad search on electronic databases such as PubMed and the Cochrane Library. We used PubMed search terms were alcohol dependence, craving, addiction, cocaine abuse, nicotine dependence and transcranial magnetic stimulation. Only articles written in English were taken into account. Systematic reviews and meta-analysis were also analysed and relevant articles were chosen for this study.

Repetitive Transcranial Magnetic Stimulation (Rtms) in The Treatment of Alcohol Dependence

rTMS can alter cortical excitability, and hence induce changes in neuronal circuits (Fitzgerald et al., 2009, Cho & Strafella, 2009). rTMS is also able to influence the HPA-axis (Baeken et al., 2011). With this technique, the DLPFC is the preferred stimulation place for the rTMS application in alcohol dependency (Bechara, 2005, Mishra et al., 2010). rTMS has the capacity to modulate decision-making in healthy individuals and it is hypothesized that this neuromodulation technique can change impulsivity in addicted individuals (Fecteau et al., 2010).

In a recent study authors (Heremans et al., 2012) stimulated thirty-six recently detoxified alcohol-dependent patients with one sham-controlled high-frequency (HF)-rTMS session delivered on the right DLPFC. Alcohol craving was evaluated and measured with the Obsessive Compulsive Drinking Scale (OCDS). Immediate effects were registered in the lab setting without cue exposure, while long-term effects were evaluated in patients' natural environment. The lack of effect in subjective craving measurements was explained by the absence of cue reactivity and because not all alcoholic patients do experience craving when confronted with alcohol cues (Ooteman et al., 2006).

In a case report, a 48-year-old woman with a treatment-resistant alcohol dependence problem was stimulated with low-frequency (LF)-rTMS during an active drinking period (De Ridder et al., 2011). The frontal cortex was stimulated with a double cone coil. A double cone coil is able to modulate both dorsal and subcallosal ACC, both important in craving. The patient was stimulated during 5 weeks. During the treatment craving measurements were suppressed and remained so until three months after stimulation. Authors (Mishra et al., 2010) have performed a sham-controlled study with ten daily sessions of HF-rTMS on the right DLPFC in forty-five alcohol-dependent patients. Craving was evaluated before the first and after the last stimulation session with the Alcohol Craving Questionnaire (ACQ-NOW). Real rTMS was significantly superior in decreasing craving measurements compared to sham stimulation. Craving measurements were evaluated until 4 weeks after stimulation. After four weeks however, there were no significant differences between the active and the sham group, which might imply that the effects are waning after a couple of weeks.

Höppner et al. (2011) stimulated nineteen detoxified alcohol-dependent female patients at the left DLPFC during 10 days with HF-rTMS in a sham-controlled design. Although no differences were found in craving measurements with the OCDS, they found an alteration in the attentional blink (AB) paradigm. According to the authors this alteration in the AB could be a physiological parable for craving reduction. However, patients did not acknowledge a decrease in subjective craving. Research on rTMS in alcohol dependence is still relatively scarce and over the different studies there is a considerable variability in methodology. Therefore it is difficult to draw firm conclusions. Stimulation parameters, such as frequency, % of motor threshold, train duration, inter-train interval and laterality of stimulation differ significantly among studies. Until now, there are no fixed stimulation protocols in alcohol addiction. Research on the effect of rTMS on impulsivity is inconclusive and as to which hemisphere needs to be stimulated remains to be determined. The use of multiple sessions may prove to be more effective in decreasing craving. We suggest the evaluation of multiple rTMS sessions in larger, randomized, sham controlled population samples. Studies should also be done to evaluate whether patients need stimulation with high or low frequency.

Repetitive Transcranial Magnetic Stimulation in other Substance Abuse Disorders

Recently, Camprodon and colleagues (2007) examined rTMS as a potential treatment for the cravings experienced by cocaine-dependent individuals. In this randomized cross-over design, two sessions of 10 Hz rTMS was administered to the right and left DLPFC at 90% RMT. Visual analogue scales were administered to obtain level of cocaine cravings 10 minutes before, immediately, and 4 hours following rTMS treatment. RTMS applied to the right, but not the left DLPFC, was found to decrease subjects' level of cravings for cocaine with these differences existing between baseline and immediately after rTMS session, and baseline and 4 hours post rTMS session.

Moreover, as rTMS applied to the DLPFC has been shown to induce DA release in the subcortical structures and the caudate nucleus (Strafella et al., 2001), these findings provide a possible mechanism through which the cravings associated with chronic use of cocaine are reduced (Goldstein and Volkow, 2002).

Although several treatments including bupropion, varenicline, nicotine chewing gum, nicotine skin patch, nicotine nasal spray and lozenges and psychosocial as well as behavior therapy, are proven to be approx-

imately double to triple the rate of smoking cessation (Siu and Tyndale, 2007), an effective treatment is still needed to target the altered neurotransmission resulting from chronic nicotine dependence. In this regard, rTMS applied to frontal regions has been shown to increase the release of DA in rats (Keck et al., 2000) and in humans (Strafella et al., 2001) associated with enhanced GABA-B receptor activity (Daskalakis et al., 2006). Repetitive TMS applied to the DLPFC, therefore, shows promise as an effective treatment in nicotine dependence. The Eichhammer group (Hoffmann et al., 2003) were the first to examine the efficacy of rTMS as a potential treatment in nicotine dependence. In the first pilot double-blind cross-over study, 11 smoking dependent individuals who hoped to stop smoking were administered either active or sham rTMS over the left DLPFC at 90% of RMT. In the individuals who received active high-frequency rTMS over the DLPFC reported significantly reduced levels in smoking cravings 30 minutes following the treatment as compared to those who received sham stimulation. These findings, therefore, motivated further examination of rTMS' potential in the treatment of nicotine dependence in smokers with aims to reduce not only the level of cravings but also smoking consumption. In the second double-blind cross-over design study, 14 individuals who wished to stop smoking were administered 2 active, and 2 placebo-control sham rTMS in a randomized order for 4 consecutive days. High-frequency (20 Hz) rTMS was applied to the left DLPFC at an intensity of 90% RMT, and smoking cravings were measured at baseline and 30 minutes after the rTMS session using a 100-point visual analogue scale. During this 6 hour time period, the number of cigarettes smoked following rTMS applied to the left DLPFC was significantly decreased, with no change in the level of cravings. Treatment with high-frequency rTMS was, therefore, found to reduce the level of cravings for cigarettes in the pilot study, although this finding was not replicated in the second study. A similar out patient study stimulating the DLPFC with HF-rTMS has also shown to attenuate nicotine craving (Amiaz et al., 2009).

Limitations of Studies and Future Directions

Repetitive TMS has been shown to induce cortical changes in preclinical and clinical investigations through its effects on neurotransmission (Daskalakis et al., 2006). The treatment studies that examined the efficacy of rTMS in the treatment of cocaine and nicotine dependence in are the first in this field. Although the reviewed work represents promise in the use of rTMS in the treatment of substance abuse, certain limitations must be ad-

Table 1. Summary of major studies of rTMS in Substance Abuse and Alcohol Dependence

STUDY DETAILS	METHODS	RESULTS
Alcohol Dependence		
Bechara 2005	DLPFC 10 sessions HF-rTMS	Decreased craving
Mishra et al., 2010 Hoppner et al., 2011 Heremans et al., 2012	DLPFC 10 sessions HF-rTMS	Decreased craving Attenuates Attentional Blink
Substance Abuse		
Camprodon et al., 2007	Cocaine dependence HF DLPFC stimulation	Decreased cocaine craving
Hoffman et al., 2003 Amiaz et al., 2009	Nicotine dependence HF DLPFC stimulation	Attenuates nicotine craving

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dressed. First, the use of larger sample sizes in the examination of rTMS as a potential treatment in persons with substance abuse with aims to reduce the level of cravings and consumption would strengthen this preliminary evidence with increased statistical power. Second, the studies reviewed here are limited to the short-term effects of rTMS on the level of cravings and consumption, and fail to examine the efficacy of rTMS' long-term effects and its potential to achieve abstinence. In addition, preclinical studies using animal models to examine the efficacy of rTMS in the treatment of substance abuse represents an area that needs to be further explored.

Conclusions

Transcranial magnetic stimulation has provided a safe and non-invasive method to evaluate the neurophysiology of the human cortex. Moreover, TMS has shown promise in the diagnosis of several patient populations, including SUDs. Although, this research remains in its infancy, TMS paradigms have demonstrated alterations in cortical excitation in chronic cocaine, nicotine, and alcohol users. Moreover, rTMS has been reported to modulate neurotransmission, and early studies suggest that it may be a promising treatment for a number of substance abuse disorders.

References

- Amiaz, R., Levy, D., Vainiger, D., Grunhaus, L., Zangen, A. (2009). Brain stimulation in the study and treatment of addiction. *Addiction*, 104(4), 653-660.
- Baeken, C., Vanderhasselt, M.A., De Raedt, R. (2009). Baseline 'state anxiety' influences HPA-axis sensitivity to one sham controlled HF-rTMS session applied to the right dorsolateral prefrontal cortex. *Psychoneuroendocrinology*, 36, 60-67.
- Barr, M.S., Fitzgerald, P.B., Farzan, F., George, T.P., Daslakis, Z.J. (2008). Transcranial magnetic stimulation to understand the pathophysiology and treatment of substance use disorders. *Current Drug Abuse Reviews*, 1, 328-339.
- Bechara, A. (2005). Decision making, impulse control and loss of willpower to resist drugs: a neurocognitive perspective. *Nature Neuroscience*, 8, 1458-1463.
- Camprodon, J.A., Martinez-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(1), 91-94.
- Chesher, N.J., Bousman, C.A., Gale, M., Norman, S.B., Twamley, E.W., Heaton, P.K., et al. (2011). Chronic illness history of adults entering into treatment for co-occurring substance use disorders and other mental illnesses. *American Journal on Addiction*, 21, 1-4.
- Cho, S.S., Strafella, A.P. (2009). rTMS on the left dorsolateral prefrontal cortex modulates dopamine release in the ipsilateral anterior cingulate cortex and orbitofrontal cortex. *PLoS One*, 4, e6725.
- Daskalakis, 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. Toronto: University of Toronto.

- De Ridder, D., Vanneste, S., Kovacs, S., Sunaert, S., Dom, G. (2011). Transient alcohol craving suppression by rTMS of dorsolateral anterior cingulate: an fMRI and LORETA EEG study. *Neuroscience Letters*, 496, 5-10.
- Fecteau, S., Fregni, F., Boggio, P.S., Camprodon, J.A., Pascual-Leone, A. (2010). Neuromodulation of decision-making in the addictive brain. *Substance Use and Misuse*, 45, 1766-1786.
- Fitzgerald, P.B., Maller, J.J., Hoy, K., Farzan, F., Daskalakis, Z.J. (2009). GABA and cortical inhibition in motor and non-motor regions using combined TMS-EEG: a time analysis. *Clinical Neurophysiology*, 120, 1706-1710.
- Garner, B. (2009). Research on the diffusion of evidence based therapies with substance abuse treatments : a systematic review. *Journal of Substance Abuse Treatment*, 36(4), 376-399.
- Goldstein, R.Z., Volkow, N.D. (2002). Drug addiction and its underlying neurobiological basis: neuroimaging evidence for the involvement of the frontal cortex. *American Journal of Psychiatry*, 159(10), 1642-1652.
- Heinz, A., Beck, A., Grüsser, S.M., Grace, A.A., Wrase, J. (2009). Identifying the neural circuitry of alcohol craving and relapse vulnerability. *Addiction Biology*, 14, 108-118.
- Herremans, S.C., Baeken, C., Vanderbruggen, N., Vanderhaselt, M.A., Zeeuws, D., Santermans, L., et al. (2012). No influence of one right-sided prefrontal HF-rTMS session on alcohol craving in recently detoxified alcohol dependent patients: results of a naturalistic study. *Drug and Alcohol Dependence*, 120, 209-213.
- Hoffman, R.E., Hawkins, K.A., Gueorguieva, R., Boutros, N.N., Wu, Y.T., Carroll, K., et al. (2003). Transcranial magnetic stimulation of left temporoparietal cortex and medication resistant auditory hallucinations. *Archives of General Psychiatry*, 60(1), 49-56.
- 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, 57-62.
- Houben, K., Nederkoorn, C., Wiers, R.W., Jansen, A. (2011). Resisting temptation: decreasing alcohol-related affect and drinking behavior by training response inhibition. *Drug and Alcohol Dependence*, 116, 132-136.
- Jones, S., Gutlerner, J.L. (2002). Addictive drugs modify excitatory synaptic control of midbrain dopamine cells. *Neuroreport*, 13(2), A29-33.
- Kalsi, G., Prescott, C.A., Kendler, K.S., Riley, B.P. (2009). Unravelling the molecular mechanisms of alcohol dependence. *Trends in Genetics*, 25(1), 49-55.
- Keck, M.E., Sillaber, I., Ebner, K. (2000). Acute transcranial magnetic stimulation of frontal brain regions selectively modulates the release of vasopressin, biogenic amines and amino acids in the rat brain. *European Journal of Neuroscience*, 12(10), 3713-3720.
- Koob, G.F. (2013). Theoretical frameworks and mechanistic aspects of alcohol addiction: alcohol addiction as a reward deficit disorder. *Current Topics in Behavioural Neuroscience*, 13, 3-30.
- Koob, G.F., Volkow, N.D. (2010). Neurocircuitry of addiction. *Neuropsychopharmacology*, 35, 217-238.
- Mishra, B.R., Nizamie, S.H., Das, B., Praharai, S.K. (2010). Efficacy of repetitive transcranial magnetic stimulation in alcohol dependence: a sham-controlled study. *Addiction*, 105, 49-55.
- Ooteman, W., Koester, M.W., Verheul, R., Schippers, G.M., van den Brink, W. (2006). Measuring craving: an attempt to connect subjective craving with cue reactivity. *Alcoholism Clinical and Experimental Research*, 30, 57-69.
- Potenza, M.N., Taylor J.R. (2009). Found in translation : understanding impulsivity and related constructs through integrated pre-clinical and clinical research. *Biological Psychiatry*, 66(8), 714-716.
- Schoenbaum, G., Roesch, M.R., Stalnaker, T.A., Takahashi, Y.K. (2009). A new perspective on the role of the orbitofrontal cortex in adaptive behaviour. *Nature Reviews Neuroscience*, 10(12), 885-892.
- Sinha, R., Fox, H.C., Hong, K.I., Hansen, J., Tuit, K., Kreek, M.J. (2011). Effects of adrenal sensitivity, stress- and cue-induced craving, and anxiety on subsequent alcohol relapse and treatment outcomes. *Archives of General Psychiatry*, 68, 942-952.
- Siu, E.C., Tyndale, R.F. (2007). Non-nicotinic therapies for smoking cessation. *Annual Reviews of Pharmacology and Toxicology*, 47, 541-564.
- 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. *Journal of Neuroscience*, 21(15), RC157.
- Tarter, R.E. (2002). Etiology of adolescent substance abuse : a developmental perspective. *American Journal on Addiction*, 11(3), 171-191.
- Zhang, X.L., Wang, G.B., Zhao, L.Y., Sun, L.L., Wang, J., Wu, P., et al (2012). Clonidine improved laboratory-measured decision-making performance in abstinent heroin addicts. *PLoS One* e29084.