No influence of one right-sided prefrontal HF-rTMS session on alcohol craving in recently detoxified alcohol-dependent patients: results of a naturalistic study.

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Abstract

Background: Prior research in substance dependence has suggested potential anti-craving effects of repetitive transcranial magnetic stimulation (rTMS) when applied to the dorsolateral prefrontal cortex (DLPFC). However, no single sham-controlled session studies applied to the right DLPFC have been carried-out in recently detoxified alcohol-dependent patients. Furthermore, no studies examined the effect of a single HF-rTMS session on craving in these patients' natural habitat.

Methods: To further investigate the effect of high-frequency (HF)-rTMS of the right DLPFC on alcohol craving, we performed a prospective, single-blind, sham-controlled study involving 36 hospitalized patients with alcohol dependence syndrome. After successful detoxification, patients were allocated receiving one active or one sham HF-rTMS session. The obsessive-compulsive drinking scale (OCDS) was administered to evaluate the extent of craving just before and after the HF-rTMS session (on Friday), on Saturday and Sunday during the weekend at home, and on Monday when the patient returned to the hospital.

Results: One single blind sham-controlled HF-rTMS session applied to the right DLPFC did not result in changes in craving. Not immediately after the stimulation session, nor in patients' natural environment during the weekend.

Conclusions: One HF-rTMS stimulation session applied to the right DLPFC had no significant effects on alcohol craving in alcohol dependent patients. One such a session could have been too short to alter alcohol craving in a sample of alcohol dependent patients.

Key words: Alcohol dependence, Craving, HF-rTMS

1.0 Introduction

Alcohol abuse and alcohol dependence are important major health issues in our modern society (Saddichha et al., 2010). Alcohol dependency is considered to be a chronic disease and relapse rates are high (Feltenstein et al., 2008). Alcohol craving represents an irresistible urge to drink and is characterized by anticipation and preoccupation with the needed product (Koob and Volkov, 2010) and might be an important factor as to why patients relapse (Wrase et al., 2008). Craving appears stronger when confronted with drugs or drug-related stimuli or when confronted with an acute stressor and/or a residual negative emotional state (Koob and Volkov, 2010). Because uncontrolled craving could be an important reason for relapse after a period of abstinence, interventions that could reduce craving in alcohol dependent patients are needed. Although anti craving medication is available, not all patients benefit (Johnson et al., 2008).

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive technique with a treatment potential for a variety of neuropsychiatric illnesses (George et al., 2002; Simons and Dierick, 2005). Research has revealed the potential anti-craving effects of rTMS in substance dependence such as nicotine, cocaine and alcohol dependence (Barr et al., 2008, De Ridder et al., 2011). Neuroimaging studies showed that the dorsolateral prefrontal cortex (DLPFC) is a major component of the neural substrate for craving associated with various psychoactive substances (Mishra et al., 2010).

Amiaz et al., 2009 found a decrease in nicotine craving after ten consecutive days of stimulating the left dorsolateral prefrontal cortex (DLPFC) with high frequency (HF)-rTMS, while Eichhammer et al., 2003 found no reduction in nicotine craving after two left DLPFC stimulations. One HF-rTMS session on the right DLPFC temporarily reduced craving symptoms in cocaine dependent patients (Camprodon et al., 2007). Mishra et al (2010)

reported on beneficial HF-rTMS treatment after 10 consecutive sessions applied to the right DLPFC in alcohol-dependent patients. Except for the Eichammer et al (2003) study, none of the other studies evaluated craving in patients' natural environment, where an increase in craving could be anticipated (Juliano and Brandon, 1998). It has been suggested that the right prefrontal cortex plays a crucial role in the inhibition of action when a patient is confronted with a specific cue (Crockford et al., 2005). In drug abuse or non-substance addictions some studies suggests a preferential right-hemispheric impairment of decision-making concerning these control processes (Knoch et al., 2006 a, Camus et al., 2009). Exposure to alcohol-related stimuli might enhance the need for substance use and therefore result in enhanced risk for relapse (Rohsenow et al., 1990-1991). However, not all studies were consistent in finding strong correlations between craving measurements and cue-reactivity (Ooteman et al., 2006).

Because no studies examined the effect of one HF-rTMS session on craving in alcohol-dependence, in this study we wanted to examine the effect on craving of one such a HF-rTMS session applied to the right DLPFC in a sample of hospitalized alcohol dependent patients. After successful detoxification, patients were randomized into two groups, with one group receiving active stimulation, the other sham. The right DLPFC was located with 3D-MRI, correcting for individual cortical anatomical differences. Craving was assessed with the obsessive-compulsive drinking scale (OCDS), a well validated self-report questionnaire (Anton and Latham, 1996). We only used those five OCDS items representing reliably craving in alcohol dependent patients (de Wildt et al., 2005). In a first part of the study, immediate HF-rTMS effects on craving measurements were evaluated on Friday just after stimulation. In a second part, delayed HF-rTMS effects on craving were measured on Saturday, Sunday and Monday when patients were allowed to leave the hospital. We separated this second part from the first as we assumed that in their natural environment they were most likely to be confronted with their individual alcohol-related cues influencing

craving. Importantly, besides the Eichhammer et al (2003) study on nicotine craving, no current studies examined possible single session HF-rTMS effects on alcohol craving in patients' natural environment.

Because patients were hospitalized and therefore not optimally confronted with alcohol-related cues, we might expect no or only limited immediate stimulation effects on Friday. Albeit nearly no former HF-rTMS studies examined possible delayed effects on craving in alcohol-dependent patients, we hypothesized that only the active stimulation session would result in reduced craving measurements when patients were in their natural habitats (on Saturday and Sunday), while sham stimulation should not affect craving measurements at all.

2.0 Materials and Methods

The study was approved by the ethical committee of our University hospital (UZBrussel). Written informed consent was obtained from all participants.

2.1 Participants

539 patients were admitted in our psychiatric service during the duration of the study (1/2/2010 – 9/3/2011). 132 were diagnosed with alcohol dependence. Exclusion criteria included old age (≥65y), the use of anti-craving medication at admission, any personal or familial history of epilepsy, a recent neurosurgical condition, the presence of pacemakers or other electronic implants, metal or magnetic objects in the brain, unstable medical condition, and pregnancy. Psychotic episodes, delirium, disorientation and severe cognitive deterioration (Mini Mental State Examination; MMSE (Folstein et al., 1983) were also exclusion criteria. 52 patients of those diagnosed with an alcohol dependence problem were excluded.

80 patients fulfilled the criteria for the study. 11 patients refused to participate due to anxiety for the application. 33 patients terminated hospitalization prematurely before they were asked to participate. Finally 36 alcohol dependent patients gave informed consent for the current study. Three patients dropped out before stimulation (1 consumed alcohol before stimulation and 2 were discharged), while two patients dropped out after stimulation (stimulation under benzodiazepines and invalid completion of the OCDS). Our final sample consisted of 31 participants. In the active group 2 patients were considered drop-out because of relapse on Sunday and on Monday. In the sham group one patient was considered drop-out on Saturday because of not completing the OCDS and another was dropped-out from the study because of a relapse on Sunday.

All participants, aged between 18 and 65 years (21 male and 10 female subjects; mean age= 49 year, SD= 9.96), were current inpatients. Psychiatric disorders and alcohol dependence were assessed using the Mini-International Neuropsychiatric Interview (Mini) (Sheehan et al., 1998).

2.2 Detoxification

At admission patients were asked to complete the obsessive-compulsive drinking scale (OCDS) to evaluate their alcohol craving (Anton and Latham, 1996) and they received a diazepam substitution scheme, which was decreased progressively. When the substitution phase was completely terminated (mean duration= 12.03 days, SD= 7.05), patients were stimulated just before the weekend on a Friday afternoon.

2.3 Craving assessment

Craving was evaluated by the OCDS, which is a 14-item self-report questionnaire developed to measure alcohol-associated thoughts and compulsions to drink (de Wildt et al., 2005). It is supposed to have a higher validity than visual analogue scales (Schippers et al., 1997). The lowest attainable total score is 0, while the highest total score is 56. Because the OCDS contains items that do not represent the core concept of craving but instead are indicators for the consequences of craving, we used only those items related to subjective craving. These items were 1, 2, 4, 5, and 13 (de Wildt et al., 2005). The lowest attainable total score is 0, while the highest total score is 20.

Patients were asked to complete the questionnaire in the week of admission, just before and after the HF-rTMS session on Friday, and on Saturday, Sunday and Monday after stimulation. During the weekend the patients were allowed to leave the hospital in order to get exposed to their habitual ‘alcohol related cues’. On Saturday and on Sunday, patients rated

themselves once they were at home. All patients were also stimulated in a cross-over design the following Friday with OCDS assessment during the following weekend. [1]

2.4 rTMS procedure

In this single blind sham-controlled between-subjects design, we used a Magstim high-speed magnetic stimulator (Magstim Company Limited, Wales, UK), connected to a figure-of-eight-formed double 70mm coil held tangentially to the skull. Participants were randomized (tossing a coin) into two groups: an active HF-rTMS group and a sham group.

In order to accurately target the middle of the right DLPFC (Brodmann area 9/46), taking into account individual anatomical brain differences, the precise stimulation site and position of the coil was determined using MRI non-stereotactic guidance (Peleman et al., 2010). Perpendicular to this point the precise stimulation site on the skull was marked and stimulated. The individual motor threshold (MT) for the right abductor pollicisbrevis muscle was determined using single pulse TMS in combination with motor evoked potentials (MEP). A stimulation intensity of 110 % of the subject's resting MT was used for the study. In each high-frequency (20 Hz) rTMS session, subjects received forty trains of 1.9 seconds duration, separated by an intertrain interval of 12 seconds (1560 pulses per session). For the sham condition, the coil was held at an angle of 90°, only resting on the scalp with one edge. Subjects were kept unaware of the type of stimulation they received; they wore earplugs and were blindfolded. The study was conducted in conformity with the current safety guidelines (Rossi et al., 2009).

[1] Because of the one-week time interval and possible carry-over effects these measurements are not considered as primary outcome results.

2.5 Statistical analysis

All collected OCDS data were analyzed with SPSS 17 (Statistical Package for the Social Sciences). To examine the immediate effects of one HF-rTMS session on Friday, a mixed 2 X 2 ANOVA was performed with the OCDS score as dependent variable, Time as within subjects factor (before and after HF-rTMS) and Group (active vs. SHAM) as between subjects factor. To investigate possible delayed effects of one stimulation session on craving another 3 X 2 ANOVA was performed with the OCDS craving scores as dependent variable, Test Moment (Saturday, Sunday, Monday) as within subjects factor and Group (active vs. SHAM) as between subjects factor. The significance level was set at $p < .05$, two-tailed for all analyses.

3.0 Results

First of all, we observed no group differences (between the group receiving real versus sham HF-rTMS) in age ($t(29)=.97$, $p=.34$), MT ($t(29)=1.52$, $p=.14$) or gender distribution ($X^2(1)=2.00$, $p=0.16$). The duration of tapering off the benzodiazepines during hospitalization and the period without substitution therapy before the experiment did not differ between groups (duration: ($t(29)=.73$, $p=.47$); substitution: ($t(29)=.14$, $p=.89$)).

Because OCDS craving values were not normally distributed, square root transformation was used for data normalization. Craving scores measured with the 5 sub items of the OCDS (items 1, 2, 4, 5, and 13) also did not show group differences at admission ($t(29)=.28$, $p=.78$) nor just before the first stimulation session ($t(29)=.88$, $p=0.39$).

A paired t-test comparing the craving scores at admission versus just before stimulation showed that after detoxification craving significantly decreased over all patients, ($t(30)=3.68$, $p<.01$).

3.1 Immediate HF-rTMS effects on craving

The ANOVA with Time (before and after HF-rTMS) as within subjects factor and Group (active vs. Sham) as between subjects factor showed a significant main effect of Time ($F(1,29)=5.70$, $p=0.02$). However, we found no main effect for Group ($F(1,29)=0.91$, $p=.35$) nor was there a significant interaction effect between Time and Group ($F(1,29)=.21$, $p=.65$). [2]

[2] All patients were also stimulated in a cross-over design on the next Friday and assessed with the OCDS before and after HF-rTMS. This did not result in a significant HF-rTMS effects on craving measurements (p's>.05). When taking into account poly-drug use, excluding these patients from analyses, this did not affect outcome results.

3.2 Delayed HF-rTMS effects on craving

Due to relapses in the weekend, two in the active HF-rTMS group and one in the sham group, the analyses examining delayed effects were performed in 28 patients.

The ANOVA to investigate the delayed effects of one stimulation session on craving analysis showed no main effects for Test Moment (Saturday, Sunday, Monday) ($F(2,52)= 2.26$, $p=0.14$) or for Group ($F(1,26)= .27$, $p=0.61$). The interaction effect between Test Moment and Group also did not reach significance ($F(2,52)=.38$, $p=0.69$).[3]

[3] Consequently, all patients were stimulated again in a cross-over design on the second Friday and were further assessed with the OCDS on the second Saturday, Sunday and Monday. Again, by using the alcohol dependent patients as their own control, this did not result in any HF-rTMS effects on craving measurements (p's>.05). When taking into account poly-drug use, excluding these patients from analyses, this did not affect outcome results.

4.0 Discussion

In this study, we examined the effect of one HF-rTMS session applied to the right DLPFC on subjective craving in a sample of alcohol dependent patients after successful detoxification in a hospital environment. This is to our knowledge the first study in recently detoxified alcohol-dependent patients in which not only the immediate effects of one sham-controlled HF-rTMS session applied to the right DLPFC on craving was examined, but this is also be the first investigation examining the effect of such a single session in these kinds of patients' natural habitat. The rTMS application was well tolerated and no side-effects were observed. One active HF-rTMS session had no subjective impact on any of the craving measurements. As could be expected, no immediate HF-rTMS effects were observed after stimulation on Friday during hospitalization. In contrast to our initial hypothesis, no delayed HF-rTMS on craving were reported during the weekend, when patients were exposed to their habitual alcohol-related cues. Furthermore, no changes in craving were observed when patients returned to the hospital on Monday. Importantly, demographical analyses did not show group differences in age, gender, duration of tapering off substitution therapy, nor the duration of benzodiazepine-free period before stimulation.

First of all, our results are not in line with the Camprodon et al (2007) study where an immediate effect on craving was found in cocaine dependent inpatients after one right-sided DLPFC HF-rTMS session. Although cocaine craving might not directly compare to alcohol craving, only six participants were studied and no sham condition was included. In this study, subjects received active stimulation over the right and left DLPFC. HF-rTMS sessions (90% MT, 10Hz, 20 trains of 10s duration) were separated by at least a week. Stimulation of the right, but not the left DLPFC, brought about a transient reduction in craving scores measured with visual analogue scales (VAS). Furthermore, because no sham was used and right-sided

stimulation also resulted in anxiety decreases, it is possible that the reduced craving reports reflect some kind of stress reduction, because the neurobiological modulation of stress-regulatory systems such as the HPA-system are predominantly regulated by the right prefrontal cortex (Sullivan and Gratton, 2002; Cerqueira et al., 2008). In our design, patients were hospitalized for at least two weeks before they were stimulated, and their craving scores decreased significantly during admission. During the admission patients were not confronted with their specific alcoholic context, reflected by the relatively low OCDS scores the day of stimulation on Friday. The absence of a cue-related exposure in the hospital environment could explain the lack of change on the craving measurements on Friday (Addolorato et al., 2005).

Secondly, one right-sided HF-rTMS session did not result in delayed reduced craving measurements when patients were back in their natural environment. At this point, we can only conclude that one HF-rTMS session delivered on the right DLPFC has no delayed effects on craving measurements. Nevertheless, as only limited former research examined possible delayed effects, this assumption should be interpreted cautiously. Further, it has to be noted that at this moment the number of stimulation sessions needed to have an effect on craving remains unclear. It might well be possible that to detect changes on subjective craving scales, a larger number of stimulations sessions is necessary, conform to the treatment effects found in other psychiatric conditions after multiple sessions (Gershon et al., 2003). In short, one such a right DLPFC HF-rTMS session could have been too short to alter alcohol craving in a sample of recently detoxified alcohol dependent patients. In line with these assumptions, Mishra et al (2010) did report a significantly greater reduction in craving when alcohol dependent patients were stimulated during 10 consecutive HF-rTMS sessions applied to the right DLPFC. In addition, it has also been suggested that a larger number and left-sided prefrontal stimulation sessions would be needed to subjectively decrease craving (Amiaz et

al., 2009). These authors reported a significant reduction in nicotine craving after ten left-sided stimulation sessions whereas Eichhammer et al (2003) found no significant effects on cigarette craving after 2 left-sided stimulation sessions.

From a neurophysiological point of view, the few conducted studies investigating the effect of high frequency stimulation on craving measurements not only differed in population (cocaine, nicotine, alcohol dependent patients), but they also differed in the choice of stimulation intensities (sub- and suprathreshold), durations (from one to 10 daily sessions) and in frequencies (10 to 20 Hz). From the four cited HF-rTMS studies only Eichammer and co-workers (2003) used a frequency of 20 Hz as we did (but they applied two sessions and subthreshold) and they also observed no effects on craving. Although 10 and 20 Hz frequencies are positioned in the high frequency range (5 to 20 Hz), it might be possible that different frequencies in this range exert different modulatory effects on cortical excitability (Maeda et al., 2000 a, b). Another important methodological issue could be the effect of lateralization (Knoch et al., 2006 b). Although all cited studies stimulated the dorsolateral prefrontal cortices, the neurophysiological and behavioral effects on craving might not be the same when stimulating left or right. Concerning the pathophysiology of alcohol addiction and craving, the dopaminergic system is known to be a key system (Heinz et al., 2005). However, current data indicate that in addiction the dopaminergic system is rather affected by left-sided rTMS instead of stimulating the right DLPFC (Cho &Strafella, 2009; Strafella et al., 2001; Ko et al., 2008). Therefore the lack of craving effects in our current alcohol dependent patient study may partially be explained by not affecting the dopaminergic system. However, as we did dot perform concomitant brain imaging techniques to support this hypothesis, this assumption should be interpreted with caution.

It is important to point out that our study is the first that used 3D-MRI to locate the DLPFC before stimulation in these kinds of patients. As the accuracy of rTMS stimulation

becomes more and more important, we can state that we accurately stimulated the right DLPFC and not other cortical areas such as premotor or ventrolateral cortices (Peleman et al., 2010). In spite of the lack of effect found on craving, another advantage of our study was that patients were evaluated post-stimulation in their natural habitat, where they were confronted with a context where they used to consume alcohol. Although we expected that cue exposure in patients' usual environment was necessary to provoke significant craving, we found no support for this assumption. The craving scores remained unchanged during the weekend, both in the rTMS and Sham condition. It is known that the correlation between craving and cue reactivity is limited and that only a subgroup of alcoholic patients experiences craving when confronted with alcohol cues (Ooteman et al., 2006). Although, both studied groups did not differ in demographic features, examining two groups could have introduced more variability into our data.[4]

Some limitations have to be discussed; the most important is the restricted number of participants. Although all patients were alcohol abstinent for at least 14 days and in spite that no group differences were observed, the benzodiazepine substitution scheme was terminated only shortly before the HF-rTMS experiment. This could have influenced patients' craving measurements. Another limitation could be the lack of control on craving assessment during the weekend. Patients were asked to complete the OCDS when they arrived at their homes. As a consequence, we lacked a certain control whether patients were confronted or not with their specific alcohol related environment. Further, not all patients were motivated to participate. Lack of insight, fear of stimulation and longer duration of hospitalization were the most important factors for participation refusal. Therefore, it could be possible that our patient sample was influenced by inclusion bias.

[4] On the other hand, the cross-over part of the study did also not reveal effects on immediate or delayed craving when patients were used as their own control.

In conclusion, in recently detoxified alcohol dependent patients one HF-rTMS session applied to the right DLPFC did not influence subjective craving. No immediate or delayed changes on OCDS scores were found. Therefore, one such a session might not be enough to subjectively change craving in these kinds of patients. Larger sham-controlled groups treated with multiple HF-rTMS sessions could be needed to optimize clinical response. As it is not clear whether left or right DLPFC stimulation is superior in alcohol-dependent patients one might consider to replicate such an experiment when HF-rTMS is applied to the left DLPFC. However, we advocate the use of 'cue-exposure' experiments with co-registration of subjective craving questionnaires. When doing so, one should include a control mechanism in patients' natural environment to properly check whether or not they are confronted with their specific alcohol-related cues when assessing craving questionnaires.

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	All	Active HF-rTMS	SHAM HF-rTMS
Age	*49 (9.96)*	*47.20 (11.28)*	*50.69 (8.56)*
Gender (F:M)	*10:21*	*3:12*	*7:9*
% Nicotine	*80.6*	*68.8*	*93.3*
% Drug abuse	*12.9*	*20*	*6.2*
% Benzodiazepines	*9.7*	*13.3*	*6.2*
% Narcotic analgesics	*3.2*	*6.7*	*0*
Duration tapering off benzodiazepines (days)	*12.03 (7.05)*	*11.07 (6.86)*	*12.94 (7.33)*
Benzodiazepine-free period before stimulation (days)	*6.94 (5.25)*	*6.80 (5.23)*	*7.06 (5.44)*
Total OCDS admission	*29.10 (11.87)*	*28.67 (10.28)*	*29.50 (13.53)*
OCDS admission	*8.77 (4.85)*	*8.27 (4.67)*	*9.25 (5.12)*
OCDS before stimulation	*5.26 (3.29)*	*4.67 (3.04)*	*5.81 (3.51)*
OCDS after stimulation	*4.68 (3.51)*	*4.33 (3.72)*	*5.00 (3.39)*
OCDS Saturday	*3.68 (2.76)*	*4.00 (2.42)*	*3.36 (3.13)*
OCDS Sunday	*3.36 (2.92)*	*3.36 (2.47)*	*3.36 (3.41)*
OCDS Monday	*3.14 (3.16)*	*3.29 (3.91)*	*3.00 (2.32)*
% MT	*56.62 (5.74)*	*58.20 (5.49)*	*55.13 (5.73)*

Table 1. Demographic data of the stimulated group of hospitalized alcohol-dependent patients.