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Reduced intra-individual reaction time variability during a Go-NoGo task in detoxified alcohol dependent patients after one right-sided dorsolateral prefrontal HF-rTMS session

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Abstract

Aims: As alcohol dependency is characterized by severe executive function deficits, we examined the influence of high-frequency (HF) - repetitive transcranial magnetic stimulation (rTMS) applied to the right dorsolateral prefrontal cortex (DLPFC) on executive functioning in recently detoxified alcohol dependent patients.

Methods: In this randomized, single blind, sham (placebo)-controlled crossover study we included fifty detoxified alcohol dependent patients. We examined the effect of a single right DLPFC HF-rTMS session on commission errors, mean reaction times (RT) and intra-individual reaction time variability (IIRTV) during a Go-NoGo task (50% Go / 50% NoGo condition) in 29 alcohol dependent patients. Patients completed this cognitive task immediately before and immediately after the stimulation session. In order to avoid carry-over effects between stimulation sessions, a one-week inter-session interval was respected. Because rTMS treatment has been shown to affect subjective craving all patients were also assessed with the Obsessive Compulsive Drinking Scale (OCDS).

Results: After both stimulation conditions we observed a significant decrease of commission errors, without differences between active and sham HF-rTMS stimulation. No significant difference was observed between active and sham stimulation on mean RT. However, only active stimulation resulted in a significant decrease in IIRTV. No effects of stimulation were found for the craving measurements.

Conclusion: Our findings suggest that in recently detoxified alcohol dependent patients, one right-sided HF-rTMS session stabilizes cognitive performance during executive control tasks, implying that active stimulation reduces patients' proneness to attentional lapses.

INTRODUCTION

Alcohol addiction is a chronic relapsing disorder. It gives rise to an important number of disability-adjusted live years (DALY's). Because of its chronicity, the disorder also has a major economic impact and is therefore considered a major health issue (World Health Organization (WHO), 2011). Alcohol consumption is the world's fifth largest risk factor for disease and disability. Biological, environmental and genetic factors can influence the development of addiction (Addolorato et al., 2005; Hillemacher et al., 2008). Although pharmacological treatments and psychotherapeutic interventions are available, alcohol addiction remains a difficult to treat mental disorder (Assanangkornchai & Srisurapanont, 2007).

Alcohol dependent patients have severe executive function deficits, characterized by abnormal response inhibition, difficulties in attentional control, planning, abstraction, mental flexibility, decision-making and problem solving (Noël et al., 2001). Alcohol dependent patients are found to be more impulsive and have difficulty to inhibit reward-driven behavior or prepotent responses (Courtney et al., 2012); they also have more difficulty keeping their attention and concentration on a specific task and consequently finalizing it (Noël et al., 2001; Davies et al., 2005). All these functions rely on adequate frontal lobe functioning (Chanraud et al., 2007) and possibly stimulation of the frontal lobe may improve these executive functions in alcohol-addicted patients. Furthermore, in addition to having executive function deficits, these patients frequently crave for alcohol, which often results in alcohol relapse (Wrase et al., 2008).

The application of high-frequency (HF) - repetitive transcranial magnetic stimulation (rTMS) treatment applied to the right dorsolateral prefrontal cortex (DLPFC) has already demonstrated a limited, but beneficial, anti-craving effect in

alcohol dependent patients (Mishra et al., 2010). The mechanism of action of HF-rTMS in alcohol dependence remains poorly understood. HF-rTMS is known to enhance cognitive functions, such as working memory, concentration, attention, memory and motor speed in subjects with neuropsychiatric disorders (Demirtas-Tatlidede et al., 2013). Of all executive functions, response inhibition in particular has been extensively investigated. The underlying neurobiology of response inhibition is complex and depends on task and imaging design (Mostofsky et al., 2003; Simmonds et al., 2008). Nonetheless, most studies observe a predominantly right-lateralized network in response inhibition. The regions implicated are the pre-supplementary motor area (pre-SMA), right/middle inferior frontal gyrus (IFG), parietal regions, occipital regions, putamen, left premotor cortex, bilateral insula, right DLPFC, right superior frontal sulcus (SFS), right inferior prefrontal cortex and anterior cingulate cortex (ACC) (Simmonds et al., 2008; Wager et al., 2005; Rubia et al., 2003; Garavan et al., 1999; konishi et al., 1999). Concerning attentional processes, the regions involved are the ACC, right DLPFC, right IFG, right middle frontal gyrus (MFG) and right temporal-parietal junction (TPJ) (Weissman et al., 2006; Prado et al., 2011). However, there are currently no neuroimaging studies investigating the laterality of these functions in alcohol dependent patients.

Because of the previously established anti-craving effects after right DLPFC HF-rTMS stimulation and because of the existing predominantly right-lateralized network in executive functioning, we wanted to assess the effect of one sham (placebo)-controlled HF-rTMS session applied to the right DLPFC on cognitive functioning in recently detoxified alcohol dependent patients. To do this we used a Go-NoGo task taken from the Test of Attentional Performance battery (TAP, Zimmermann & Fimm, 1992). This task triggers immediate impulsive responses and

subsequently tests the ability to suppress them, to evaluate response inhibition (a measure for inhibitory control) and the stability of cognitive performance. The errors to trials where a response needs to be inhibited (NoGo trials, i.e. commission errors) is a measurement of response inhibition (Zimmermann & Fimm, 1992). Reaction times (RT) to trials where a response is needed (Go trials) are an indication for the state of activation (Uebel et al., 2010). The stability of cognitive performance is assessed with the intra-individual reaction time variability (IIRTV), which is the dispersion or standard deviation of these RTs (Stuss et al., 2003). Fluctuations in cognitive performance, observed with simple reaction time tasks within the same subjects, reflect lapses of attention (Lövdén et al., 2013). The variability measured with more complex tasks indicate - next to lapses of attention - the search and application of new strategies by the subject to complete these tasks (Lövdén et al., 2013).

Consequently, in this study we evaluated the effect of one sham-controlled HF-rTMS session applied to the right DLPFC in alcohol dependent patients on response inhibition and on the stability of cognitive performance. Patients completed the Go-NoGo task just before and just after stimulation. To evaluate whether stimulation could influence subjective craving all patients were assessed with the Obsessive Compulsive Drinking Scale (OCDS) just before and just after the stimulation session (de Wildt et al., 2005).

We hypothesized that in recently detoxified alcohol dependent patients, one active HF-rTMS session would result in improved inhibitory control, defined as a reduction in commission errors. We expected that one active HF-rTMS session would also result in improved consistency of cognitive performance, displayed by a decrease of intra-individual reaction time variability. We did not expect any changes in these measurements after one sham (placebo) session. Based on our former work, we did not

expect that a single HF-rTMS session would influence subjective craving (Herremans et al., 2012).

METHODS

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

Participants

Fifty inpatients were randomized (flipping a coin) to receive one single blind, sham-controlled stimulation session. Intersession interval was set at one week. See also Fig 1. Four patients dropped out before stimulation because hospitalization was terminated prematurely. Six patients refused to undergo the second stimulation because they preferred not to prolong their hospitalization (Five patients received sham stimulation; one patient active stimulation). Five patients consumed alcohol after the first stimulation session and were considered dropout (three patients received active stimulation and two patients sham stimulation). One patient was stimulated under benzodiazepines and another patient was stimulated with an incorrect motor threshold (both were stimulated with active stimulation). In four stimulated patients there were registration errors; stimulation conditions could therefore not be verified. All these patients were considered dropouts.

Our final sample consisted of 29 participants, aged between 18 and 65 years (19 male and 10 female subjects; mean age= 48.15 years, *SD*= 9.32). Figure 1 shows the diagram of flow of participants through the study. Psychiatric disorders and alcohol dependence were assessed using the Mini-International Neuropsychiatric Interview (Mini: Sheehan et al., 1998). 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) <26 (Folstein et al., 1983)) were also exclusion criteria.

Detoxification

At admission patients received a diazepam substitution scheme, which was decreased progressively. When the substitution phase was completely terminated (mean duration= 14.24 days, SD= 9.55), patients were stimulated. Just before and after the stimulation session patients were asked to carry out the Go-NoGo task.

Go-NoGo task

The Go-NoGo from the "Test of Attentional Performance version 2.1, test form 1:2" (TAP, Zimmermann & Fimm, 1992) was used. This Go-NoGo task is a standardized cognitive test, which has been used in different patient population groups (Pflueger et al., 2007; Drechsler et al., 2008; Li et al., 2010; Schiffer et al., 2010). Patients completed this task just before and just after rTMS stimulation. The interval between the stimulation and the start of the task was merely a minute.

Participants viewed a series of two different symbols ('x','+'), which are easily distinguishable. In order to provoke a rapid reaction, the presentation of the stimulus is shortly depicted (200ms). Participants were instructed to continuously look at the center of the screen and to respond as quickly as possible and as accurately as possible when the "x" appeared (by pressing a button). When participants saw the NoGo stimulus ("+"), they had to suppress their reaction by not pressing the button.

Participants initially completed a 10 trial practice block, followed by 40 real trials in the experiment block. In accordance with other studies using a Go-NoGo task

in alcohol dependent patients (Kamarajan et al., 2005), the critical stimulus appeared in 50% of the time.

Commission errors (errors in the NoGo task), mean RT (mean reaction times on the Go task), and IIRTV were registered. To measure IIRTV, the intra-individual standard deviation (ISD) of the RTs was calculated for each Go task. ISD reflects the dispersion of all RT around the mean RT of each subject.

Craving assessment

Craving was measured with the obsessive compulsive drinking scale (OCDS), a 14-item self-report questionnaire (Schippers et al., 1997). It is developed to measure alcohol-related thoughts and compulsions (de Wildt et al., 2005). The minimum obtainable score is 0, while the maximum obtainable score is 56. The OCDS was administered at admission, just before and just after the termination of the Go-NoGo task.

rTMS procedure

For the stimulation sessions, 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. In order to accurately target 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 pollicis brevis muscle was determined using single pulse TMS in combination with motor evoked potentials

(MEP). The MT was considered as the lowest intensity to induce a visual MEP on electromyography (EMG). A stimulation intensity of 110 % of the subject's resting MT was used for the study. In each HF-rTMS session (20 Hz), 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 line with the current safety guidelines (Rossi et al., 2009).

Statistical analysis

All collected data were analyzed with SPSS 17 (Statistical Package for the Social Sciences). Significance was set $p<.05$, two-tailed for all analyses.

Extreme outliers (more than 6 times the standard deviation from the individual mean) (due to sneezing, external distractions etc.) were discarded (less than 1% of the data). No less severe outlier analysis was performed because we were also interested in the intra-individual variability of RT. Normality of commission errors, mean RT, ISD and OCDS was evaluated with the Kolmogorov-Smirnov test. Data with normal distributions were analyzed with ANOVA's and t-tests, non-normal distributed data were analyzed with the non-parametric Wilcoxon Signed Rank Test. In order to evaluate correlations, we used the Pearson Product-Moment Correlation for normal distributed data, while non-normal distributed data were evaluated with the Spearman's Rank Order Correlation.

The primary outcome measures of this study were commission errors (measurement of response inhibition) and mean RT. Secondary outcome measure was ISD (ISD and IIRTV can be seen as synonyms in this study). Because there was no

correlation between the standard deviation of reaction time and mean reaction time, and there were no group differences in mean reaction, we used SD as dependent variable, and not the coefficient of variation (CV = SD/mean) (Kaiser et al., 2008).

RESULTS

Overall, HF-rTMS stimulation was well tolerated. Only one patient suffered from a mild headache, which resolved after a single administration of paracetamol 500 mg, a common analgesic. An overview of the demographic data and craving is provided in table 1.

First of all, we observed no group differences (between the group receiving first active versus first sham HF-rTMS) in demographic data, such as age ($t(27)=0.41$, $p=.68$), motor treshold (MT) ($t(27)=0.83$, $p=.41$) and gender distribution (Fisher's Exact Test: $p=.45$). The duration of tapering off the benzodiazepines during hospitalization and the period without substitution therapy before the experiment did not differ between groups (duration of tapering off benzodiazepines: $t(27)=0.53$, $p=.60$; benzodiazepine-free period: $t(27)=3.59$, $p=.72$).

Commission errors (p's$<.01$), mean RT (mean RT after sham and active stimulation: $p<.05$) and ISD (ISD before and after sham stimulation, ISD after active stimulation: p's$<.05$) were not normally distributed. We therefore used the Wilcoxon Signed Rank Test, with a significance level of $p<.05$.

Accuracy rate before the active stimulation was 93%; before the sham stimulation it was 90.5%. No differences for commission error rate ($Z=-1.23$, $p=.22$) and mean RTs ($Z=-0.44$, $p=.66$) were found when comparing before active and before sham stimulation. Furthermore, there were no differences in ISD before active and before sham stimulation observed ($Z=-0.18$, $p=.86$).

Immediate HF-rTMS effect on commission errors, mean RT and IIRTV

Immediate HF-rTMS effect on commission errors

Both sham and active stimulation decreased commission error rate after stimulation (before versus after active stimulation: Z=-2.40, p=.02; before versus after sham stimulation: Z=-2.86, p<.01). No difference could be observed when commission errors after the active (accuracy rate 96.05%) and the sham (accuracy rate 95.55%) stimulation were compared (Z=-0.89, p=.37).

Immediate HF-rTMS effect on mean RT

No significant differences were found on mean RTs for both stimulation conditions (before versus after active HF-rTMS: Z=-1.42, p=.16; before versus after sham stimulation: Z=-0.40, p=.69). No difference could be observed when mean RT after the active and the sham stimulation were compared (Z= -0.81, p=.42).

Immediate HF-rTMS effect on IIRTV

The Wilcoxon Signed-Rank Test showed that one active session of HF-rTMS was able to decrease ISD (Z=-3.06, p<.01). Sham stimulation had no effect on ISD (Z=-1.03, p=.30). When ISD after the active and the sham stimulation was compared, a significant difference was found between the two stimulation modalities (Z=-2.24, p=.03).

Relationship between IIRTV and mean RT, commission errors and craving measurements

Relationship between IIRTV and commission errors

No significant correlation was found between Δ ISD and Δ commission errors for as well the active as the sham HF-rTMS stimulation (active stimulation: $r_s(27)=0.01$, p=.45; sham stimulation: $r_s(27)=-0.02$, $p=.90$).

Relationship between IIRTV and mean RT

No significant correlation was found between Δ ISD and Δ mean RT for as well the active as the sham HF-rTMS stimulation (active stimulation: $r_s(27)=0.15$, p=.45; sham stimulation: $r_s(27)=0.33$, $p=.08$).

Relationship between IIRTV and craving measurements

OCDS scores were normally distributed (p's>.05) and were therefore evaluated with a 2x2 ANOVA with OCDS as dependent variable; TIME (before and after HF-rTMS) and SESSION (active vs. sham HF-rTMS) were the within subjects factors.

The ANOVA showed a significant main effect for TIME ($F(1,28)=5.17$, $p=.03$). Only a tendency to significance was found for the main effect for SESSION ($F(1,28)=4.14$, $p=.052$). However, the ANOVA showed no significant interaction effect between TIME and SESSION ($F(1,28)=0.25$, $p=.62$).

No significant correlation between Δ ISD and Δ OCDS craving scores was found for as well the active as the sham HF-rTMS stimulation (active stimulation: $r_s(27)=-0.32$, p=.09; sham stimulation: $r_s(27)=0.17$, $p=.38$).

DISCUSSION

To our knowledge, this is the first study where the immediate effect of one sham-controlled HF-rTMS session on response inhibition in alcohol dependent patients was evaluated.

We expected to find that only the active HF-rTMS session would be able to improve inhibitory control (defined as a decrease in commission errors) and consistency in cognitive performance (defined as decreased IIRTV). However, both sham and active HF-rTMS decreased significantly commission error rates, and we found no difference when commission errors were compared after the active and the sham stimulation. Therefore, these findings may be attributed to learning mechanisms rather than the effect of HF-rTMS. The high accuracy rate on the Go-NoGo task before stimulation suggests that this task was too easy for our included patients. Therefore, a possible beneficial effect of HF-rTMS on response inhibition might have been missed. On the other hand, one HF-rTMS session significantly decreased IIRTV, measured with the intra-individual standard deviation (ISD). Sham (placebo) stimulation did not influence IIRTV measurements. Although no effect on mean RT was observed, one active HF-rTMS session stabilized the reaction times to the presented Go stimuli. Mean RT and the number of commission errors can influence IIRTV (Kaiser et al., 2008; Rentrop et al., 2010). Importantly, the marked change in IIRTV cannot be explained by alterations in mean RT and commission errors, because first, there was no change in mean RTs; second, there was a high accuracy rate; and third, there was no correlation between IIRTV, mean RTs and commission errors.

Until present, the underlying mechanism of action of rTMS in alcohol addiction is poorly understood. Our results show that when one session of right

DLPFC HF-rTMS is administered in these patients, the speed of responding to stimuli is not altered, but instead becomes more stable.

According to Bellgrove and colleagues (2004) damage to the right frontal lobe gives rise to diminished sustained attention. Further, lesions to the DLPFC and the superior medial frontal cortex results in increased IIRTV (Stuss et al., 2003). Therefore, our results may indicate that one active right DLPFC HF-rTMS session results in less lapses of attention in alcohol dependent patients. Indeed, it has been documented that HF-rTMS applied to the DLPFC positively affects attentional processes in healthy volunteers and psychiatric patients (Vanderhasselt et al., 2007; Demirtas-Tatlidede et al., 2013). Hence, the use of this brain stimulation technique in detoxified alcohol dependent patients points to an improvement of DLPFC functioning. This finding is of significance because this would mean that HF-rTMS is able to improve attentional processes in alcohol dependent patients. An important clinical implication could be that, because of a decrease in lapses of attention, detoxified alcohol dependent patients become less distracted by external alcoholic cues or stimuli. Assuming so, they may encounter less relapses in alcohol use. Interestingly, our current findings cannot be attributed to possible influences on craving, an observation in line with our former research (Herremans et al., 2012), because we didn't observe a correlation between subjective craving and IIRTV. In other words, it is not the decrease in alcohol craving that makes these patients less prone to attentional lapses.

Some limitations have to be discussed. As argued before, the Go-NoGo task might have been too easy for our detoxified alcohol dependent patients and therefore not suitable to evaluate response inhibition properly. On the other hand, according to Lövdén and colleagues (2013), variability in performance observed during an RT task

can be attributed to lapses of attention. This would be additional support for our results, indicating less attentional lapses after HF-rTMS stimulation. Although variability has mainly been investigated using simple RT tasks, our results indicate that variability using Go-NoGo tasks might also be a promising measure. Another limitation is that the severity of alcohol addiction was not taken into account. Possibly, daily alcohol dose and the duration of the existing alcohol addiction could both have an influence on response inhibition. Further, albeit all patients were alcohol-free for at least 14 days, the benzodiazepine substitution scheme was terminated only shortly before stimulation and could have had an influence on Go-NoGo task performance. However, since no group differences were found between the group receiving immediate active stimulation versus the group receiving real stimulation after one week, it is unlikely that the observed decrease in IIRTV may be explained by the benzodiazepine-free period before stimulation. Further, our results can be affected by an inclusion bias. Not all hospitalized patients were motivated to participate in or complete the study. The most important reasons for discontinuation of the study protocol or refusal to participate were lack of insight and longer duration of hospitalization. Concerning which rTMS parameters should be used to treat alcohol dependent patients, to date, there is no consensus. The few conducted studies differ in the choice of stimulation intensities, frequencies, and duration (Barr et al., 2008; Barr et al., 2011; Feil and Zangen, 2010). Further, different parameters may exert different modulatory effects on cortical excitability (Maeda et al., 2000 a,b).

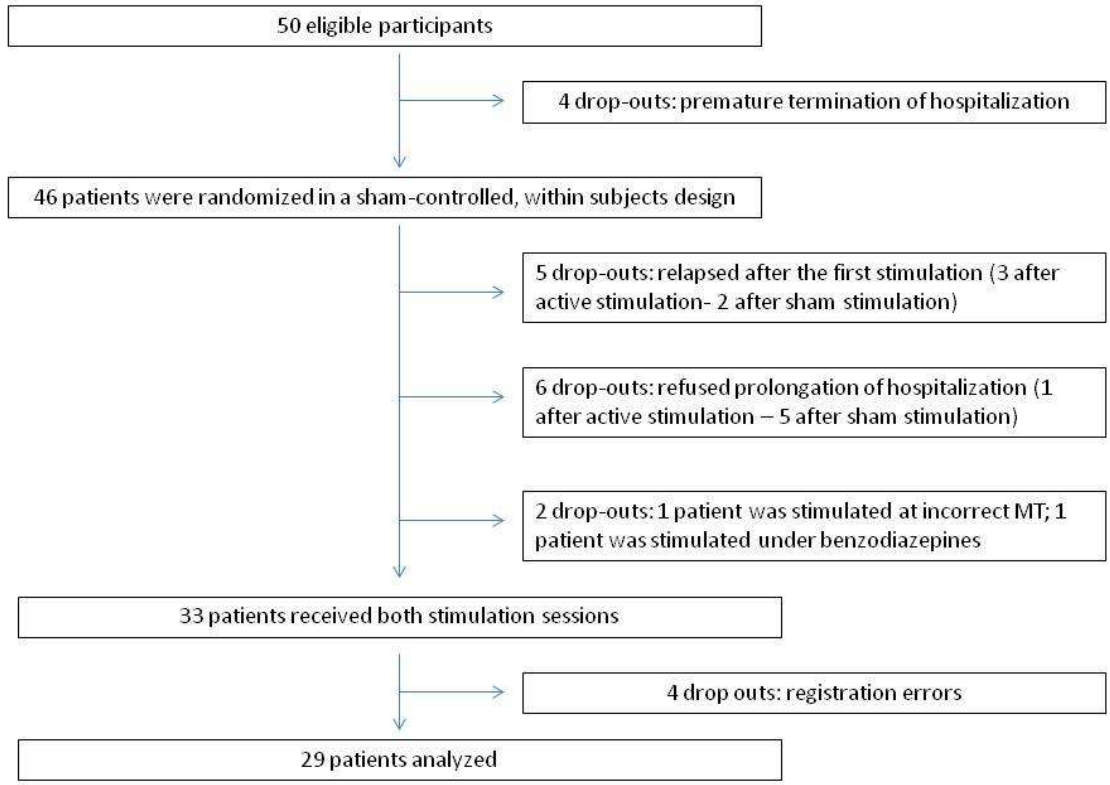
In short, it is possible that the effect of one HF-rTMS session on response inhibition could not be evaluated, because our Go-NoGo task was too simple. For future HF-rTMS and response inhibition research in alcohol addicted patients we suggest the use of a more complex Go-NoGo task, such as a Go-NoGo task with a

60% Go / 40% NoGo condition (Saunders et al., 2008) or an even higher Go/NoGo-ratio instead of a 50% Go / 50% NoGo condition; another task that could be used to evaluate response inhibition in alcohol addicted patients is a stop signal task (SST) (Lawrence et al., 2009). Further, it would be interesting to use a Go-NoGo task with alcohol related stimuli. Such a task could be more powerful in discovering a beneficial effect of HF-rTMS on response inhibition in detoxified alcohol dependent patients, because it is more specifically related to the inhibition problems of these patients.

On the other hand, the current results using the 50% Go / 50% NoGo task indicate that one HF-rTMS session applied to the right DLPFC decreases intra-individual variability in cognitive performance in recently detoxified alcohol dependent patients. These results suggest an improvement in the stability of attentional mechanisms. Since this is the first study evaluating the impact of HF-rTMS on executive functions in alcohol dependent patients, more research is necessary to confirm our current findings. As laterality differences have been proposed (Hwang et al., 2010), future studies should also evaluate stimulation of the left DLPFC. Functional imaging studies need to be conducted to examine the underlying mechanism of action of HF-rTMS on attentional processes in alcohol addiction. Further, the evaluation of IIRTV with more complex tasks in combination with neurostimulation could have greater clinical relevance, because task complexity is known to influence IIRTV measurements (Gorus et al., 2006).

Figures: headings and legends

Figure 1. Flowchart of the patients through the study.



Sarah C. Herremans. Reduced intra-individual reaction time in detoxified alcohol-dependent patients after one right-sided orsolateral prefrontal HF-rTMS session. Figure 1

Table 1: Overview of demographic data. MT= motor threshold.

	All subjects (N=29) mean	All subjects (N=29) Standard deviation
Age (years)	48.14	9.32
Gender (F:M)	10:19	
% comorbid nicotine dependence	86.2	
% comorbid drug dependence	10.3	
% comorbid narcotic analgesics dependence	3.2	
Duration tapering off benzodiazepines (days)	9.13	7.46
Benzodiazepine-free period before stimulation (days)	7.79	5.67
% MT	57.79	5.18
Craving before sham HF-rTMS	12.79	10.11
Craving after sham HF-rTMS	11.55	9.44
Craving before active HF-rTMS	9.45	7.68
Craving after active HF-rTMS	8.62	7.91

Conflict of interest statement

All authors declare no conflict of interest.

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