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Transcranial Magnetic Stimulation of the Left Dorsolateral Prefrontal Cortex Decreases Cue-induced Nicotine Craving and EEG Delta Power

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ABSTRACT

Background: TMS has high potential as smoking cessation treatment. However, the neural mechanisms underlying TMS induced reduction of tobacco craving remain unclear. Electroencephalographic (EEG) delta frequency has been associated with the activity of the dopaminergic brain reward system, which is crucial for nicotine induced effects, and decreases after nicotine admission in smokers.
Objective: The aim of this study was to investigate EEG delta power changes induced by hf rTMS of the left dorsolateral prefrontal cortex (DLPFC) in nicotine deprived smokers and it's relation to cue-induced nicotine craving.
Methods: Fourteen healthy smokers meeting ICD-10 criteria for tobacco addiction participated in this within-subject sham controlled study. Participants had to abstain from smoking 6 h before the experiment. Effects of high-frequency repetitive TMS (hf rTMS) (10 Hz) for verum (left DLPFC) and sham (vertex) stimulations on cue-induced nicotine craving and resting state EEG delta power were assessed before and three times within 40 min after rTMS.
Results: Both craving ($P = 0.046$) and EEG delta power ($P = 0.048$) were significantly lower after verum stimulation compared to sham stimulation across the whole post stimulation time period assessed. However, changes of craving ratings and delta power did not correlate.
Conclusion: Hf rTMS applied to the left DLPFC reduces nicotine craving in short-term abstinent smokers. Changes in delta activity support the idea that stimulation induced effects are mediated by the dopaminergic brain reward system, which presumably plays a prominent, but probably not exclusive, role in this stimulation induced behavioral modulation, making this method a promising smoking cessation treatment candidate.

Introduction

Once established it is hard to quit smoking: the majority of smokers relapse after 6 months abstinence independent of the cessation therapy (for meta-analysis see Ref. [1]). Exposure to cues previously associated with smoking increases craving (for meta-analysis see Ref. [2]) and craving intensity predicts relapse to smoking [3]. Repetitive transcranial magnetic stimulation (rTMS) of the left dorsolateral prefrontal cortex (DLPFC) has been shown to modulate cigarette craving [4–7], suggesting that rTMS has potential to treat tobacco addiction (for review see Ref. [8]). However, the neural mechanisms underlying this effect of rTMS on craving remain unclear. One hypothesis [9] proposes that stimulation of the DLPFC by high-frequency repetitive TMS (hf rTMS) mimics nicotine's actions on brain reward systems. Indeed, studies in both animals [10,11] and humans [12] have shown that hf rTMS affects striatal dopaminergic activity. Furthermore, hf rTMS is effective in changing the power of EEG delta frequency [13–15] which is of high interest for two reasons: First, nicotine administration has been shown to result in a specific EEG profile mainly characterized by reduction in delta power (~1–4 Hz) (e.g. Refs. [16–25]), but only in smokers, indicating that delta power decreases after nicotine admission are specifically related to reduction of withdrawal symptoms [26]. Second, there is accumulating evidence that delta band EEG spectral power is associated with the activity of the

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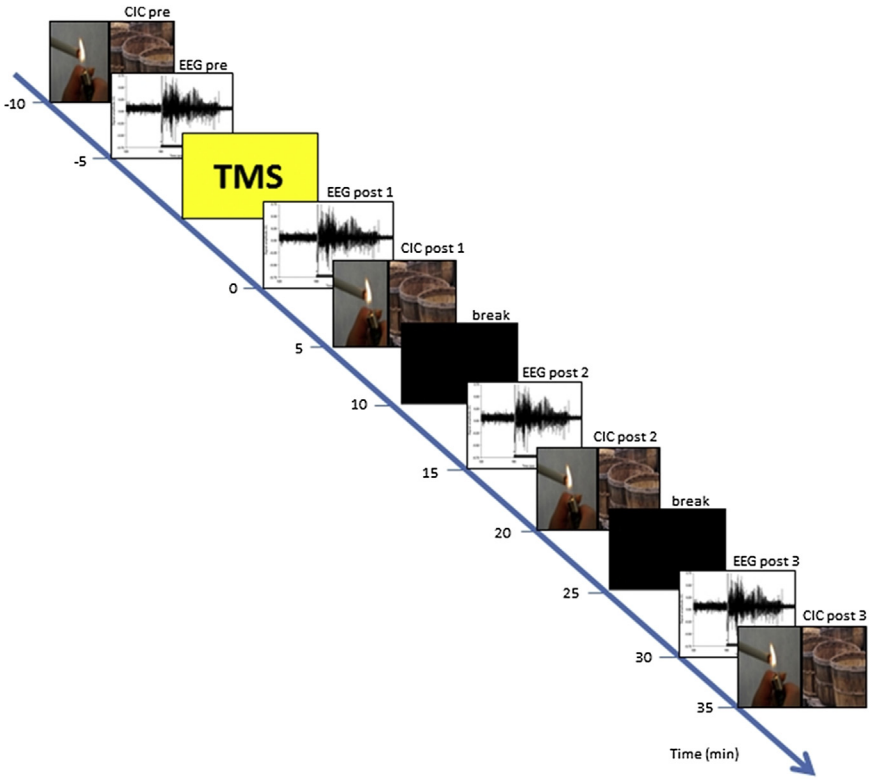

Figure 1. Timeline of experimental sessions. CIC = cue induced craving paradigm, EEG = resting state EEG recording.

dopaminergic reward system (for reviews, see Refs. [27,28]). More specifically, reduction of extracellular dopamine by using locally administered adenosine in the nucleus accumbens (NAc) of rats resulted in increased delta activity in the NAc [29]. Furthermore, a study in humans showed that delta EEG power correlates negatively with NAc activity responses to monetary gains, further supporting the assumption that the delta rhythm is associated with activity in the brain's reward circuit [30].

Based on these results from literature, we expected that hf rTMS of the left DLPFC reduces cue-induced craving and decreases resting state EEG delta power in short-term abstinent smokers. To assess the time course of the effect, cue-induced craving ratings and resting state EEG spectral power were sampled three times within 1 h after the stimulation.

Methods

Participants

Fourteen participants were included in the study. Analysis was performed on a final sample of 11 smokers (six females; mean age 29.2 years, S.D. = 5.5 years, range 21–38 years), as three participants had to be excluded due to strong contamination of EEG by motion artifacts. Participants met ICD-10 criteria for tobacco dependence (F17.2), had been smoking at least 10 cigarettes per day for at least one year and had a mean score of 3.64 ± 1.6 in the Fagerström Test for Nicotine Dependence (FTND [31]) which indicates a low level of dependence. Participants were all right handed as assessed by the Edinburgh Handedness Inventory [32], with normal or corrected-to-normal vision, and had been screened for the absence of present or past neurological or psychiatric conditions and use of psychoactive medication. Participants gave informed written consent and received monetary compensation for participation. The study was approved by the ethics committee of the Medical University of Vienna.

Experimental design

Each participant firstly joined a screening visit which included the acquisition of a structural MR image of the brain. Subsequently, each participant underwent two TMS treatment sessions (left DLPFC for verum and vertex for sham stimulation; within-subjects design) with at least one week between sessions. The sequence of stimulation conditions was counter-balanced across participants. Participants had to abstain from smoking at least 6 h before the TMS session started, as the level of craving intensifies over 3–6 h after the last cigarette [33]. To assure compliance participants were informed that a smoking sensitive urine drug test will be conducted. Urine samples were collected but actually no drug test was applied (not known by the participants). Participants were informed about this deception after the last session.

Before starting the experiment individual TMS motor thresholds were determined for each participant. Preceding the TMS stimulation baseline craving ratings ("CIC pre") were assessed with a cue induced craving (CIC) paradigm (see below) and baseline resting state EEG was recorded (subsequently referred to as "EEG pre"; see Fig. 1).

Immediately after TMS termination resting state EEG was recorded ("EEG post1") for 5 min instantaneously followed by the CIC task ("CIC post1"), lasting about 5 min and a few minutes break during which participants could relax but stayed seated. The break was also helpful to adjust for individual reaction time differences as these measurements were repeated starting 15 min ("EEG post2", "CIC post2") and 30 min after the stimulation ("EEG post3", "CIC post3"; see Fig. 1 for details). Previous studies have shown that the neural response to cigarette cues is strongly modulated by the

expectation to smoke a cigarette [34–36] and that craving is also intensified when drugs are available [37–40]. Participants had been instructed to be allowed to smoke immediately after the experiment to maximize craving and to minimize expectation induced variability in neuronal and behavioral craving processes.

Cue induced craving (CIC) task

Blocks of smoking images (S; e.g., hands holding lit cigarettes), neutral images (N; taken from the International Affective Picture Scale (IAPS) [41]) and a fixation cross (F) were presented in random order (6 blocks of each category) with blocks of the same category not being presented immediately one after the other. For each block four images were randomly selected without repetition within a block but with one repetition allowed between blocks from a pool of 12 images per category, i.e. each picture was presented twice. Presentation duration of each picture was 3 s, summing up to 12 s block duration for the S and N blocks, which was also the duration for the F blocks. After S and N blocks cigarette craving was assessed via a five-point rating scale ("How strong is your current desire to smoke?" ranging from "very weak" to "very strong"). Completion of the CIC task took about 5 min, depending on individual reaction times.

Transcranial magnetic stimulation and neuronavigation

Individual motor threshold (MT) was determined similar to the method described by Ref. [42], except that neuronavigation was used for initial coil positioning over the primary motor cortex (M1). More precisely, prior to experimental sessions, each participant underwent a T1-weighted anatomical MRI scan on a high-field 3T Tim Trio scanner (Siemens Medical, Germany) using a 32-channel head coil (magnetization prepared rapid gradient echo sequence; TR = 2.3 s, TE = 4.21 ms, 1.1 mm slice thickness, 900 ms inversion time, 9° flip angle) to acquire individual anatomical data for definition of individual DLPFC region. The localization of stimulation targets was accomplished by a computerized frameless stereotaxy system (Brainsight 2, Rogue Research Inc., Canada) which uses an infrared camera for monitoring head locations of the participant by tracking reflexive markers attached to the head of the participant. The head locations are then related to the structural MRI data of the participant so that precise positioning of the coil to previously defined MRI targets is enabled (for details see Supplementary material).

TMS intensity was varied using a descending staircase procedure (starting at 80% maximal stimulator output), and the motor evoked potential (MEP) of the abductor pollicis brevis muscle was assessed. Threshold was defined as the lowest stimulation intensity producing an MEP of a minimum of 50 μV in 5 out of 10 consecutive pulses.

Hf rTMS at 10 Hz (24 trains, 5 s per train, 25 s intertrain-interval, i.e. 1200 pulses within 11.6 min, 90% MT) was applied via a figure-eight coil with an outer winding of 70 mm connected to a Magstim Rapid2 stimulator (The Magstim Company Ltd, UK) targeting the left DLPFC (at Talairach coordinates $x = -42$, $y = 28$, $z = 21$ [43]) for verum stimulation (which was closely to electrode position F5 of the EEG 10–20 system in most subjects; for exact description of positions, see Supplementary material). Vertex stimulation was used in order to control for nonspecific effects of TMS because vertex TMS would not be expected to affect prefrontal or subcortical areas except by nonspecific means [44,45]. To target the vertex, we selected the intersection between the midline and the central sulci based on individual structural magnetic resonance images and using frameless stereotaxic neuronavigation. Note that vertex TMS is routinely used as control site in the TMS literature (e.g. Refs. [44,46–52]).

Resting state EEG recording and analysis

For the resting state EEG recordings participants were instructed to close their eyes and avoid mental activities as well as movements or muscular contractions during the recordings. EEG was recorded with a NEURO PRAX® DC-amplifier (neuroConn GmbH, Germany) from 9 scalp locations placed according to the international 10–20 system, i.e. F3, Fz, F4, C3, Cz, C4, P3, Pz and P4, and referenced to the right mastoid. Ag/AgCl electrodes were used mounted on an elastic cap (EasyCap GmbH, Germany). Skin preparation was performed according to procedures described in Ref. [53]. This method assured electrode impedance values of ≤ 3 kΩ as individually measured by an impedance meter (Ing. Zickler Ges.m.b.H., Pfaffstätten, Austria). The signal was analog filtered in the range of 0–150 Hz and sampled at 500 Hz and off-line down-sampled to 256 Hz. Artifact correction was performed according to Ref. [54]. Briefly, trials containing strong non-stereotype artifacts like movement or muscle-artifacts were rejected based on visual inspection followed by an independent component analysis (ICA) using the extended infomax algorithm [55,56]. Individual independent components were screened for time courses and maps reflecting artifacts and then removed by back-projecting only the remaining, non-artifact components to the voltage time series.

Resting EEG was recorded for 5 min. EEG power spectrum was calculated using a fast Fourier transform (4 s Hamming window with 50% window overlap) from the last minute as power values obtained at 4–5 min after hf rTMS have been shown to be higher than the earlier ones [15]. Mean spectral powers were calculated for the frequency bands δ (1–4 Hz), θ (4–8 Hz), α (8–13 Hz), β (13–30 Hz), and γ (30–40 Hz) [28,57]. While we only had specific hypotheses related to experimental effects in the delta band, alpha and gamma band analyses were included for reasons of better interpretability of the delta results [27]. Results for beta and theta power are reported in the Supplementary material. All off-line analyses of the EEG data were performed using EEGLAB 6.0.3b [58] integrated in Matlab 7.5.0 (The MathWorks).

Data analysis

The main outcome measures were CIC ratings and mean spectral power values for each frequency band. Linear mixed models with restricted maximum likelihood estimation were used to control for sphericity violations and to include the baseline as time-dependent covariate, which was necessary because of the within-subject repeated measurement design [59–61]. The baseline as covariate method was preferred to a change of baseline approach as this seems to be the most appropriate way to assess treatment effects of cross-over trials [62,63]. However, results for change of baseline analyses are reported in the Supplementary material.

Behavioral data were subjected to a statistical model with the repeated full-factorial fixed factors *stimulation* (verum, sham), *picture category* (S, N) and *time* (post1, post2, post3), the random factor *subjects* and the baseline craving ratings (CIC pre) as covariate. Similarly, for each EEG power spectrum (delta, alpha, and gamma) we evaluated the within-subjects factors *stimulation* (verum, sham), *time* (post1, post2, post3) and *electrode* (F3, Fz, F4, C3, Cz, C4, P3, Pz, P4) with baseline power spectrum (EEG pre) as covariate. Schwarz's Bayesian criteria [64] were used to determine the best-fitting variance-covariance structure, which was determined to be autoregressive [65]. Bonferroni corrected post hoc linear comparisons were used to examine interactions and omnibus main effects. Significance was evaluated at $P < 0.05$. All data are reported as means ± standard error of the mean (SEM).

Results

Behavioral data (CIC)

Analysis of the CIC ratings revealed a significant main effect of *picture category* ($F[1,39] = 5.313$, $P = 0.027$) and *stimulation* ($F[1,67] = 4.135$, $P = 0.046$). Smoking cues induced higher craving ratings than neutral pictures (mean difference ± SEM = 0.306 ± 0.133) and craving ratings were lower after verum stimulation than after sham stimulation (mean difference ± SEM = 0.242 ± 0.119) as can be seen in Fig. 2. *Time* had no significant effect on the rating ($F[2,78] = 0.704$, $P = 0.498$). We found no significant interaction effects of the independent variables (all *P*-values > 0.576).

EEG delta mean power

The analysis of EEG delta power revealed a significant main effect of *stimulation* ($F[1,138] = 3.975$, $P = 0.048$) with lower delta power after verum stimulation compared to sham stimulation (mean difference ± SEM = 0.807 ± 0.405 μV^2) shown in Fig. 3. Furthermore, a significant main effect of *electrode* ($F[8,222] = 2.568$, $P = 0.011$) was found with highest delta power at position Fz (mean difference ± SEM = 10.132 ± 0.762 μV^2) and lowest power at position P4 (mean difference ± SEM = 7.233 ± 0.765 μV^2). In general, delta power distribution followed a pattern with decreasing values from frontal to posterior and from midline to lateral electrode positions. However, neither the factor *time* nor any interaction did reach significance (all *P*-values > 0.097).

EEG alpha mean power

Mean values of EEG alpha power reached significance for the main effect of *stimulation* ($F[1,176] = 27.223$, $P < 0.001$). Alpha power was lower after verum stimulation than after sham stimulation (mean difference ± SEM = 1.957 ± 0.375 μV^2) as shown in Fig. 4. Furthermore the main effect of *time* showed a significant difference ($F[2,360] = 8.599$, $P < 0.001$) with alpha power of post3 (mean ± SEM 9.982 ± 1.028) being significantly lower ($P < 0.001$) as post2 (mean ± SEM 11.810 ± 1.028) and on a trend level ($P = 0.078$) lower compared to post1 (mean ± SEM 10.969 ± 1.028) as assessed by Bonferroni corrected post hoc linear contrasts. However, neither the factor *electrode* nor any interaction did reach significance (all *P*-values > 0.151).

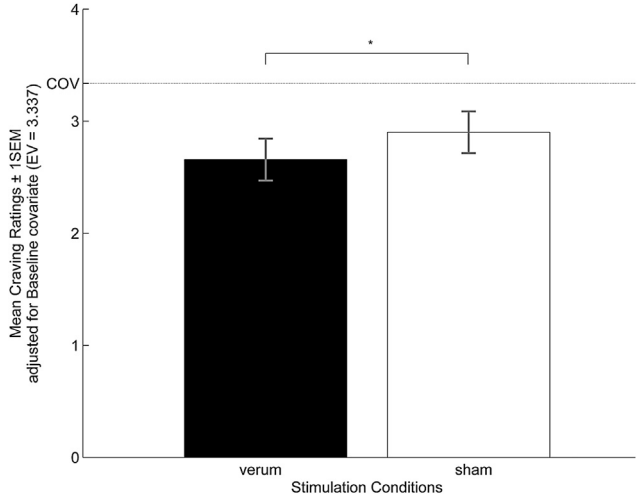

Figure 2. After verum stimulation craving ratings are lower than after sham TMS. COV: evaluated value (EV) of the covariate. Values below the dotted line indicate decreases and values above the dotted line increases in respect to the baseline (CIC pre).

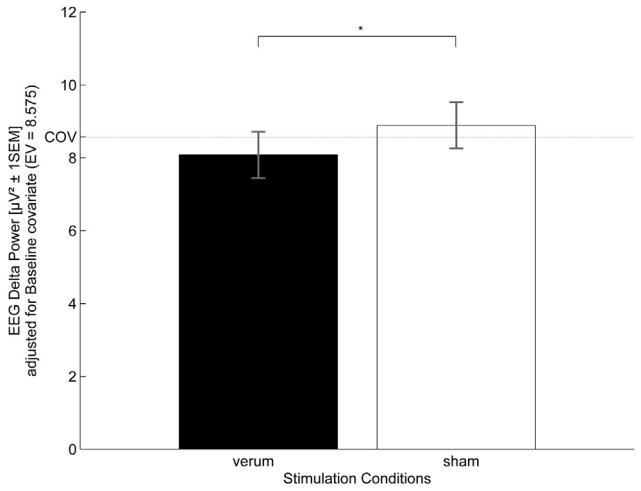

Figure 3. EEG delta power is decreased after verum TMS compared to sham TMS. COV: evaluated value (EV) of the covariate. Values below the dotted line indicate decreases and values above the dotted line increases in respect to the baseline (EEG pre).

EEG gamma mean power

Mean values of EEG gamma power reached significance for the main effect of *stimulation* ($F[1,166] = 19.616$, $P < 0.001$). Gamma power was higher after verum stimulation than after sham stimulation (mean difference ± SEM = 0.09 ± 0.020 μV^2) as shown in Fig. 5. Furthermore the main effect of *electrode* showed a significant difference ($F[8,259] = 3.824$, $P < 0.001$). However, neither the factor *time* nor any interaction did reach significance (all *P*-values > 0.071).

Correlation analysis for EEG delta power and cue-induced craving ratings

To assess if TMS induced modulations of delta power and craving ratings are correlated, we (i) subtracted for each post stimulation time point (post1, post2, post3) the baseline (pre) craving ratings (average ratings across smoking cues and neutral pictures because hf rTMS modulated craving ratings independent of picture categories) and delta power (average power across all 9 electrodes measured), respectively, and (ii) subsequently calculated the differences between verum and sham TMS for craving ratings and EEG delta power

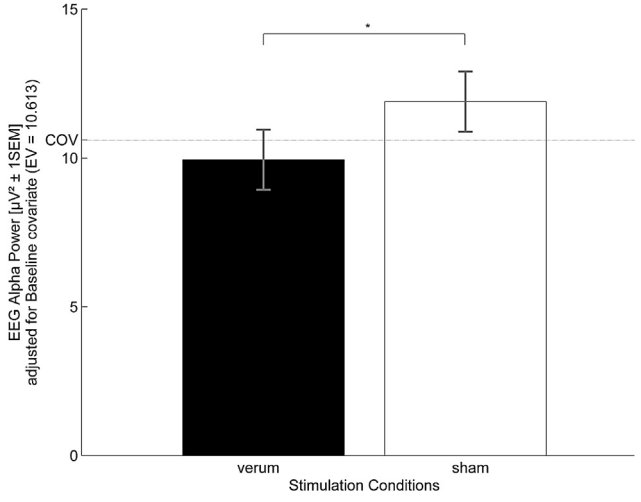

Figure 4. Verum TMS induces reduced EEG alpha power compared to sham TMS. COV: evaluated value (EV) of the covariate. Values below the dotted line indicate decreases and values above the dotted line increases in respect to the baseline (EEG pre).

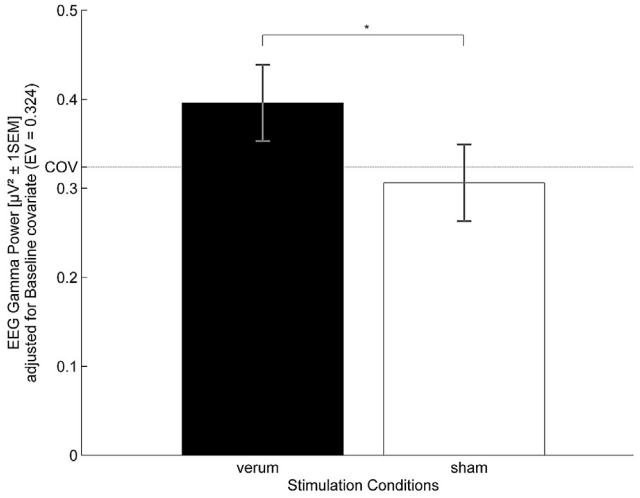

Figure 5. EEG gamma power is increased after verum TMS compared to sham TMS. COV: evaluated value (EV) of the covariate. Values below the dotted line indicate decreases and values above the dotted line increases in respect to the baseline (EEG pre).

[i.e., $post1_{Diff} = (pre_{verum} - post1_{verum}) - (pre_{sham} - post1_{sham})$; $post2_{Diff} = (pre_{verum} - post2_{verum}) - (pre_{sham} - post2_{sham})$; $post3_{Diff} = (pre_{verum} - post3_{verum}) - (pre_{sham} - post3_{sham})$]. These values were subjected to a Pearson correlation analysis, between craving ratings and EEG delta power for each time point. However, we did not find any significant correlations between delta power and craving ratings (all P-values > 0.102).

Discussion

In the present study, we used hf rTMS of the left DLPFC in order to assess its effects on cue-induced nicotine craving and EEG spectral power. As predicted based on previous findings showing that hf rTMS of the left DLPFC reduces smoking craving (e.g. Refs. [4–6]), craving ratings were significantly lower after verum stimulation compared to sham stimulation. Viewing smoking cues induced as expected higher self-reported craving ratings than viewing neutral pictures [2]. However, hf rTMS effects did not interact with picture categories, i.e., hf rTMS reduced craving after viewing smoking and neutral pictures in a similar way. Previous studies using high-frequency rTMS to examine the effects on smoking craving did either not use any cues to induce craving [4,9] or used them only during stimulation [66] and for pre-stimulation craving induction [5,67], respectively, but not for post stimulation craving assessment, which was done with a single question based visual analogue scale [5] or by tobacco craving questionnaires [66,67].

Only one study assessed cue-induced craving before and after craving [6]. The authors took the contrast (difference) between smoking cues and neutral cues in the pre- to post-experiment change in subjective craving as a primary measure of cue craving. They found that the effect of real TMS on cue craving was significantly greater than the effect of sham TMS, i.e. they observed a stronger reduction of craving ratings after viewing smoking cues compared to neutral cue craving ratings. However, the participants of that study [6] had to smoke before the TMS session took place (exhaled carbon monoxide (CO) levels $\geq$ 10 ppm), while our participants had to abstain from smoking for 6 h. This short term period of abstinence has been shown to intensify the level of craving after the last cigarette [33]. Hence, our participants had a higher level of general cigarette craving than the participants studied in Refs. [6], probably explaining the difference in behavioral results. Thus, our results extend those findings by showing a generalized effect of hf rTMS on craving of short-term deprived smokers, independently of whether post stimulation craving is assessed via smoking cues or neutral pictures.

Furthermore, the observed behavioral effect was stable over the time window assessed, i.e. up to 40 min post stimulation. This is the first study assessing acute effects of a single hf rTMS session over a period of consecutive craving and EEG measures. Thus, our results show that one session of hf rTMS can reduce cigarette craving for at least up to 40 min.

Our hypothesis concerning the hf rTMS influence on EEG delta power was confirmed. Delta power was significantly lower after verum stimulation compared to sham stimulation. In analogy to the behavioral data, this effect was stable over time, i.e. up to 40 min after stimulation.

This result supports the idea that hf rTMS of the left DLPFC leads to reduction of substance craving by mimicking nicotine's actions on the brain, probably mediated by modulations of dopaminergic activity [9]. This interpretation is supported by four lines of evidence: First, a decrease in delta power after nicotine intake has been consistently reported in nicotine admission studies (e.g. Refs. [16–25]). Second, delta power decrease has been linked to increased activity of the dopaminergic brain reward system (e.g. Ref. [30]), while increases in delta power have been associated with withdrawal (e.g. Refs. [23], for reviews see Refs. [27,28]). Third, the ascending dopaminergic pathways that originate in the VTA have been proposed to play a crucial role in the way nicotine affects the reward pathways of the brain (for review see Ref. [68]) and smoking induced ventral striatum (VST) dopamine release correlates with positive feeling states in smokers [69,70]. Fourth, hf rTMS over frontal regions increases dopamine activity in areas of the brain reward system in both animals (as shown by microdialysis [10,11]) and humans (as shown by [^{11}C]raclopride with positron emission tomography (PET) [12]). While these observations are all suggestive for hf rTMS induced modulation of the reward signaling dopaminergic system, they are necessarily speculative in the absence of direct measures of changes in dopamine release. Furthermore, it should be acknowledged that the interactions and mutual modulation between dopamine and nicotine are certainly highly complex (for review see Ref. [71]) and that the midbrain dopamine system has been suggested to be endowed not only in reward signaling, but also in other behavioral functions like motivation and cognition (for review see Ref. [72]). However, direct measures of dopaminergic processes were outside the scope of the methods we used, and need to be confirmed using methods such as receptor density PET.

Moreover, the missing correlation between individual EEG delta power and craving ratings points toward a complex picture of hf rTMS induced neuronal effects. It is reasonable that hf rTMS of the DLPFC leads to a cascade of modulations within the brain, with the effect on the dopamine system playing probably a prominent, but perhaps not exclusive, role in changing craving behavior. In addition, the DLPFC is involved in decision-making (for review see Ref. [73]), attentional control [74], and inhibitory control [75], which are all processes commonly impaired in people who suffer from addiction (for reviews see Refs. [76–78]). It has been proposed that hf rTMS of the DLPFC might alter these processes, leading to reduced impulsivity, reduced attentional biases, and enhanced inhibitory control, which might additionally contribute to reduced craving (for review see Ref. [79]). We used EEG gamma and alpha frequency bands to explore a possible contribution of cognitive inhibitory control processes to the observed craving reduction.

It has been demonstrated that inhibitory networks are largely responsible for the propagation of gamma activity in the cortex (e.g. Ref. [80]). GABA-ergic receptor mediated inhibitory post synaptic potentials (IPSPs) have a putative role in inhibition of gamma

oscillations (for review see Ref. [81]). Hf rTMS has been shown to reduce efficacy of intracortical GABA-ergic synapses (e.g. Ref. [82]). GABA activity in the PFC has been associated with cognitive control functions (e.g. Refs. [83,84]). Thus, if, as proposed, hf rTMS would increase cognitive inhibitory control, a decrease of gamma power after verum compared to sham stimulation should have been observed. However, in line with previous studies [85], we observed an increase of gamma power after verum compared to sham stimulation. Therefore, gamma activity measured in our study does not support the idea that hf rTMS induced craving reductions are mediated by cognitive inhibitory control processes.

The results of the EEG alpha power analyses which showed significantly lower alpha power after verum compared to sham stimulation further speak against the interpretation that hf rTMS induced increased cognitive inhibitory control processes. Instead, they lend further support to the interpretation that hf rTMS mimic nicotine's action on brain reward functions. Neural oscillations in the alpha band have been repeatedly associated with cognitive inhibitory control mechanisms [27,86]. Thus, the observed higher alpha power in the sham condition might indicate the higher need for cognitive inhibitory control of craving impulses. In contrast, after verum stimulation, which perhaps leads to similar effects in the dopamine system as induced by nicotine, cognitive inhibitory control is needed to a lesser extent because hf rTMS induced dopamine release dampens craving.

Taken together, hf rTMS effects on EEG indicators of inhibitory control, i.e. alpha and gamma power, do not support the idea that strengthening of cognitive inhibitory control contributes to the hf rTMS induced reduction of cigarette craving. We do not have any measures for the other processes (i.e. impulsivity or attentional control) suggested to play a role for TMS effects on craving (for review see Ref. [79]). Thus, further investigation are needed to determine which mechanisms, besides the empirically well supported hf rTMS induced modulation of the brain dopaminergic reward system, additionally contribute to the observed effect of hf rTMS on cigarette craving.

Certain limitations of the study should be kept in mind when interpreting the results. One important limitation is the small sample size. However, the use of a repeated-measures design in which the same subjects participated in all conditions allowed satisfactory control of the confounding variables. Furthermore, our results are in line with previous studies on the effects of hf rTMS on smoking craving [4–6], decreasing the possibility for statistical type I error. Another possible limitation of the study is that we do not have any objective measure of participant's nicotine abstinence starting at least 6 h before the experiment. Although compliance with abstinence criteria was self-reported by all participants, the possibility of non-compliance is existent. Another possible limitation represents the fact that we used vertex as a site for sham stimulation. Although vertex is consistently used as control condition in TMS studies (e.g. Refs. [44,46–52,87]), we cannot entirely rule out the possibility that vertex stimulation might have had an effect on brain activity. However, our behavioral results are in line with previous TMS studies showing a decrease in craving ratings after verum TMS compared to sham TMS. Furthermore, compared to the baseline, modulation of craving was only found after verum TMS, but not after sham TMS (see Supplementary material Table S1 and Table S2), indicating that for cue-induced craving paradigms, the vertex seems to be a reasonable site for a control TMS condition. Another issue that should be noted is that results of the few studies reporting hf rTMS effects on EEG power spectra are mixed, with differences which frequency bands are affected and in which direction (see Refs. [13–15]). Griskova et al. [14], for example, report an increase of mean delta power after 10 Hz rTMS stimulation but no effects in other frequency bands. Graf et al. [13] report a "somewhat enhanced" alpha activity and decreases of power in the delta, gamma and theta bands after both verum and sham rTMS stimulation with 20 Hz compared to recordings before the stimulation. Okamura et al. [38] observed a decrease of mean absolute alpha power at three to 4 min after stimulation with 10 Hz but an increase at four to 5 min (effects of other frequency bands are not reported for mean power). However, studies are difficult to compare due to differences in methodological approaches, study designs and the research questions focused on, which demonstrates the need for systematical research on the influence of these factors on neuronal activity and behavior. Our study is the first which introduced a cue-induced craving paradigm to a combined TMS-EEG study. Cue induced craving itself is known to influence EEG activity [88,89], and this further limits comparability with other studies. Finally, the sample used for the present study comprised short-time abstinent (6 h), low level dependent smokers expecting to have the possibility to smoke immediately after the experiment, thereby potentially limiting the generalizability of the results. It would be beneficial to study if neuronal and behavioral hf rTMS induced effects on cigarette craving are mediated by time of abstinence, level of cigarette dependence, and smoking expectation, as those factors have been shown to influence craving processes as well as PFC activity [36,90–93].

The present study demonstrates that hf rTMS applied to the left DLPFC has high potential to reduce cigarette craving. Furthermore, our results support the idea that stimulation induced effects are mediated by the dopaminergic brain reward system, which probably plays a prominent, but perhaps not exclusive role for this behavioral modulation. Hence, hf rTMS with the specific stimulation parameters used represents a promising nicotine cessation therapy candidate.

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.brs.2013.11.003.

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