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Effects of Repetitive Transcranial Magnetic Stimulation (rTMS) Treatment in Comorbid Nicotine Addiction with Major Depressive Disorder and Obsessive-Compulsive Disorder

Major Depresif Bozukluk ve Obsesif-Kompulsif Bozukluğa Eşlik Eden Nikotin Bağımlılığında Tekrarlayan Transkraniyal Manyetik Stimülasyon (rTMS) Tedavisinin Etkileri

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Abstract

Objective: Nicotine addiction is a common health problem in psychiatric disorders. The aim of this study was to analyze the effects of rTMS on comorbid nicotine addiction in patients receiving recurrent Transcranial Magnetic Stimulation (rTMS) therapy for major depressive disorder (MDD) and obsessive-compulsive disorder (OCD).

Method: Data of 32 patients (23 MDD, 9 OCD) were evaluated retrospectively. We compared the Hamilton Depression Rating Scale (HAM-D), Beck Anxiety Inventory (BAS), Yale-Brown Obsession Compulsion Scale (Y-BOCS), and Fagerström Test for Nicotine Dependence (FTND) scores at three time points (before treatment "0th week", at the end of treatment "6th week", and 12 weeks after this assessment "18th week").

Results: The patients' mean age was 40.47±10.20, 13 (40.6%) were women. A significant reduction was found in HAM-D, BAS, FTND at weeks 6 ($p<0.001$ for all) and 18 ($p<0.001$ for all) compared to baseline scores. A binary logistic regression showed that changes in depression and anxiety symptoms were not associated with the changes in FTND ratings at weeks 6 and 18 ($p=0.158$, $p=0.251$, respectively).

Conclusion: In this study, it can be said that rTMS treatment reduces the severity of nicotine addiction accompanying MDD and OCD, independent of the recovery of the psychiatric disease. This study suggests that rTMS can be an effective treatment for nicotine addiction comorbid with psychiatric disorders. We recommend placebo-controlled randomized double-blind studies.

Keywords: Neuromodulation, nicotine addiction, psychiatric disorders, transcranial magnetic stimulation, rTMS

Öz

Amaç: Psikiyatrik bozukluklarda nikotin bağımlılığı çok sık eşlik eden bir sağlık sorunudur. Bu çalışmanın amacı, majör depresif bozukluk (MDB) ve obsesif-kompulsif bozukluk (OKB) için tekrarlayan Transkraniyal Manyetik Stimülasyon (rTMS) tedavisi alan hastalarda, rTMS'nin komorbid nikotin bağımlılığı üzerindeki etkilerini analiz etmektir.

Yöntem: rTMS tedavisi alan 32 hastadan (23 MDB, 9 OKB) elde edilen verilere dayanan retrospektif bir kohort yaptık. Hamilton Depresyon Derecelendirme Ölçeği (HAM-D), Beck Anksiyete Envanteri (BAS), Yale-Brown Obsesyon Kompulsiyon Ölçeği (Y-BOCS) ve Fagerström Nikotin Bağımlılığı Testi (FTND) puanlarını üç zaman noktasında karşılaştırdık (tedaviden önce "0. hafta", tedavinin sonunda "6. hafta" ve bu değerlendirmeden 12 hafta sonra "18. hafta").

Bulgular: Hastaların yaş ortalaması 40,47±10,20, 13'ü (%40,6) kadındı. HAM-D, BAS, FTND'de 6. haftalarda (tümü için $p<0,001$) ve 18. haftada (tümü için $p<0,001$) başlangıç puanlarına göre anlamlı bir azalma bulundu. İkili bir lojistik regresyon, depresyon ve anksiyete semptomlarındaki değişikliklerin 6. ve 18. haftalarda FTND puanlarındaki değişikliklerle ilişkili olmadığını gösterdi (sırasıyla $p=0,158$, $p=0,251$).

Sonuç: Bu çalışmada rTMS tedavisinin psikiyatrik hastalığın iyileşmesinden bağımsız olarak MDB ve OKB'ye eşlik eden nikotin bağımlılığının şiddetini azalttığı söylenebilir. Bu çalışma, rTMS'nin psikiyatrik bozukluklarla birlikte görülen nikotin bağımlılığı için etkili bir tedavi olabileceğini düşündürmektedir. Plasebo kontrollü randomize çift kör çalışmaları öneriyoruz.

Anahtar kelimeler: Nöromodülasyon, nikotin bağımlılığı, psikiyatrik bozukluklar, transkraniyal manyetik stimülasyon, rTMS

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Introduction

Nicotine addiction is a significant health problem affecting approximately %23 of the adult population worldwide (1). 68.0% of adult smokers in the United States reported they wanted to quit smoking (2), and 55.1% have made a quit attempt in the past year, but success in these attempts seems to be relatively low, with a rate of 7.5% (3). Nicotine addiction is more of a problem when it is comorbid with psychiatric disorders. Smoking prevalence is higher among psychiatric patients compared to the general population (4), and the risk of morbidity and mortality from tobacco-related conditions is elevated in this patient group (5).

Repetitive Transcranial Magnetic Stimulation (rTMS) is a safe and non-invasive brain stimulation method using repetitive magnetic waves to induce a depolarizing current in a localized region of the cerebral cortex. Depending on the frequency of the magnetic pulses, rTMS has either excitatory (>5 Hz) or inhibitory effects on the cortical activity (6). rTMS has a long-lasting impact on the brain through mechanisms such as affecting gene expression and neural plasticity, modulating neural circuits, and changing connectivity, all of which are suggested to have therapeutic effects in various neuropsychiatric disorders (7,8). Today, rTMS is an United States Food and Drug Administration-approved treatment method in major depressive disorder (MDD) and obsessive compulsive disorder (OCD).

In recent years, research findings regarding the use of rTMS in addiction disorders have been added to the literature, including nicotine addiction. Preliminary studies investigating the effects of rTMS in nicotine addiction have been promising (9-11). But the participants in a majority of these studies are "healthy" smokers in the sense that they are not psychiatric patients. rTMS effects on comorbid nicotine addiction with psychiatric illness have been investigated only for schizophrenia and proved to be effective (12). However, until now, no other comorbid psychiatric disorder has been investigated in this regard.

In this retrospective study, we aimed to analyze the effects of rTMS treatment on nicotine addiction in a group of patients who got this treatment primarily for MDD and OCD and were smokers at the same time. The hypotheses of our study are that MDD and OCD symptoms will improve with rTMS treatment, and the severity of nicotine addiction will decrease regardless of the improvement of the psychiatric diseases.

Methods

Sample

This study is a retrospective study that analyzed data from the medical records of 32 patients treated with rTMS at the Trancranial Magnetic Stimulation (TMS) unit of Akdeniz University Medical Faculty, Psychiatry Department. The data were collected between June 1, 2019 and March 1, 2020. Twenty-three patients had a MDD diagnosis, whereas 7 had OCD. Two patients were diagnosed as having comorbid MDD and OCD. All patients were also cigarette smokers. The diagnosis of the patients was evaluated by the same psychiatrist with a detailed psychiatric examination according to DSM 5 diagnostic criteria. Written informed consent was obtained from all patients. The study design is a retrospective cohort. Inclusion criteria for the study; According to DSM-5, receiving rTMS treatment with a diagnosis of MDD or OCD, being an active smoker between the ages of 18-70, and being at least a primary school graduate. Exclusion criteria were the presence of a metal implant in the body, a history of neurological disease, a history of head trauma, being younger than 18 years of age, being mentally retarded, and using alcohol and psychoactive substances. During the study period, 94 patients were reached, but only 32 patients were included in the study. Some of the excluded patients refused to fill the scales, some did not fill the scales at all three-time points.

Procedure

Written ethical approval was obtained for this study from the Akdeniz University Clinical Research Ethics Committee with the decision number KAEK-328 on 13.05.2020. This study was conducted in accordance with the Declaration of Helsinki..

The Neuro-MS/D magnetic stimulator device with figure-of-eight coil is used for rTMS treatments (Neurosoft, Ivanovo, Russia). After determining the resting motor threshold (MT) of the patient, BEAM method is used to localize the left dorsolateral prefrontal cortex (L-DLPFC) which is the stimulation site used for both MDD and OCD treatments. After the coil is positioned over the stimulation site and fixed, stimulation is started by selecting the appropriate protocol for the patient's diagnosis via computer software.

The rTMS parameters of MDD and OCD protocols applied in our clinic are listed in Table 1. MDD protocol comprising of high-frequency rTMS (HF-rTMS) on the left DLPFC was applied in 27 (78.1%) patients, two of whom had a comorbid diagnosis of OCD and MDD, while five (21.9%) got low-frequency rTMS (LF-rTMS) again on the left DLPFC according to the OCD protocol. The average number of total rTMS sessions applied to the patients was 34±5 (range=23-46, median=36). While the number of patients who received rTMS on the left DLPFC was 31 (96.9%), the number of patients who received rTMS on the right DLPFC was only one (3.1%).

The patients who receive rTMS treatment in our clinic are followed with clinical rating scales at regular time points, which are generally every third week. Hamilton Depression Rating Scale (HDRS) and Beck Anxiety Scale (BAS) are used to rate depression and anxiety severity in every patient, while The

Yale-Brown Obsessive Compulsive Scale (Y-BOCS) is used only in OCD patients. Patients who also have comorbid substance use are followed with the scales specific for the disorder. As such, Fagerström Test for Nicotine Dependence (FTND) is used in smoking patients. Follow-up for every patient continues for up to 18 weeks after the treatment is completed. The data analyzed in this study included sociodemographic characteristics, comorbid diagnosis, medication data, rTMS parameters in addition to clinical ratings of HDRS, BAS, Y-BOCS, and FTND at three time points; immediately before and after the treatment (week 0, week 6) and at the end of the following 12 weeks (week 18).

Data Collection Tools

Hamilton Depression Rating Scale (HDRS)

HDRS is a 17-item scale developed by Hamilton to evaluate the severity of depression in patients diagnosed with depression (13). Turkish validity and reliability study was conducted by Akdemir et al. Cronbach's alpha coefficient was 0.75. It is scored between 0-52 points and above 7 points is considered depression. (14).

Beck Anxiety Scale (BAS)

BAS is a 4-point Likert-type scale consisting of 21 items. It is scored between 0 and 3 and a maximum of 63 points can be obtained from the scale (15). Turkish validity and reliability study was conducted. Cronbach's alpha coefficient was 0.75 (16).

The Yale-Brown Obsessive Compulsive Scale (Y-BOCS)

This scale was developed by Goodman et al to rate the type and severity of OCD symptoms. It consists of 19 items in total, but only the first 10 items are used to determine the total score. The first 5 items evaluate obsessions and the next 5 items evaluate compulsions. The score of each question ranges from 0 to 4. The maximum score is 40 (17). Turkish validity and reliability study was conducted. Cronbach's alpha coefficient was 0.94 (18).

Fagerström Test for Nicotine Dependence (FTND)

This scale consists of 6 questions and aims to measure the nicotine addiction level of smokers. Three of the questions consist of two answer options, "yes no". Three of them consist of four options and are scored between 0-3. A maximum of 10 and a minimum of 0 points are taken from the test. High scores from the test indicate high levels of nicotine addiction, while low scores indicate low levels of nicotine addiction (19). The Turkish validity and reliability study was conducted in 2003 and the Cronbach's alpha coefficient was found to be 0.56 (20).

Statistical Analysis

The assumption of normality was checked by using the Shapiro–Wilk test, skewness and kurtosis values, and q-q plot graphs. Descriptive statistics were calculated as frequency and percentage for categorical variables. Mean (± standard deviation) was used in cases where continuous variables conformed to the normal distribution, and median (minimum-maximum) was used when they did not comply with the normal distribution. The Friedman test was used for the analysis of differences between dependent measurements whenever the measurements did not conform to the normal distribution. Friedman test was used to compare repeated measurements and post hoc analysis was performed using Wilcoxon signed-rank with a Bonferroni correction ($p<0.017$). Binary logistic regression analysis was used to examine the relationship between the independent variables and the binary dependent variables. Statistical significance level (p-value) was set at 0.05 in the analyses. SPSS version 23 was used for statistical analysis.

Results

The sociodemographic characteristics and clinical data of the study group including primary and comorbid diagnoses, symptom severity, pharmacotherapy and history and the present status of smoking are presented in table 2.

When we compared the results obtained from the scales evaluating smoking behavior in our study, we observed a significant change after rTMS treatment compared to the baseline, so we wanted to understand whether this change is related to the change in the psychiatric symptoms of the patients. To see if the changes in nicotine dependence at weeks 6 and 18 were related to any change in symptom severity in depression and anxiety with the rTMS treatment, a binary logistic regression was run for each of these two conditions. For this aim, a new binary grouping of patients was made as to whether each participant showed a

Table 1. The rTMS parameters used in the study group

The rTMS method	Pulse mode	Frequency (Hz)	Total trains	Pulses per train	Inter-train intervals (seconds)	Pulses per session	Total time per session (minutes)
HF-rTMS	Single pulse	≥10	60	50	25	300	30
LF-rTMS	Single pulse	≤1	1	1200	0	1200	20

*rTMS: Repetitive Transcranial Magnetic Stimulation, LF: Low-frequency, HF: High frequency

Table 2. Sociodemographic and clinical characteristics of the study group

		n	%
Sex	Female	13	40.6
	Male	19	59.4
Marital status	Single	13	40.6
	Married	14	43.8
	Divorced	5	15.6
Education status	Primary school	4	12.5
	Secondary school	4	12.5
	High school	11	34.4
	University	13	40.6
Employment status	Employed	14	43.8
	Unemployed	9	28.1
	Retired	8	25.0
	Student	1	3.1
Primary diagnosis	Major depressive disorder	23	71.9
	Obsessive compulsive disorder	9	28.1
Pharmacotherapy (some patients were using 2 or more drugs at the same time)	Serotonin reuptake inhibitor	23	71.9
	Serotonin noradrenaline reuptake inhibitor	16	50.0
	Tricyclic antidepressant	4	12.5
	Noradrenaline dopamine reuptake inhibitor	2	6.3
	Atypical antipsychotic	19	59.4
	Mood stabilizer	3	9.4
Age (years) (mean ± SD) (min-max)	40.47±10.20 (23-59)		
Duration of illness (years) (mean ± SD) (min-max)	6.88±5.55 (1-20)		
Age of starting smoking (years) (mean ± SD) (min-max)	19.16±4.85 (11-37)		
Cigarette consumption (n/day) (mean ± SD) (min-max)	21.00±9.33 (4-40)		
Duration of smoking (years)) (mean ± SD) (min-max)	20.97±9.36 (4-40)		
Number of quit attempts (mean ± SD) (min-max)	1.09±1.49 (0-6)		
Total duration of past abstinence from nicotine (months) (mean ± SD) (min-max)	9.19±15.11 (0-60)		

decrease in FTND or not for each condition. This was done by subtracting the scores obtained from the FTND at weeks 6 and 18 from the score at week 0 (baseline) separately. Thus participants who improved in nicotine dependence (difference <0) comprised one group, whereas those who did not (difference ≤0) comprised the other. Accordingly, 23 (71.88%) patients improved in their nicotine dependence at week 6 whereas 18 (56.25%) were observed to have improved at the end of the 18th week. The independent variables were defined as the differences of ratings (changes in scores) for HDRS and BAS with the same method used to determine the dependent variable. Thus, the mean differences in HDRS score at week 6 and 18 were 6.34±6.67, 5.69±6.00, respectively, and the mean differences in BAS score at week 6 and 18 were 6.53±9.33, 6.78±9.09, respectively. In the model we applied, those with and without a decrease in FTND scores were the dependent variables, while the others were independent variables. Both of the binary logistic models with the dependent and independent variables as defined above were not significant. That is to say; changes in the severity of both depression and anxiety symptoms were not significantly associated with the changes in nicotine dependence both at the end of week 6 ($\chi^2(2)=3.69$, $p=0.158$) and week 18 ($\chi^2(2)=2.76$, $p=.251$) (Table 3).

Discussion

The primary finding of this study is the significant decrease in comorbid nicotine dependence in a group of patients treated with rTMS primarily either for MDD or OCD. The decrease was most evident immediately after the rTMS treatment (i.e., at the 6th week). Although no more decrease was observed at the end of the following 12 weeks (18th week), and there was even an upward

Table 3. Analysis of the relationship between changes in nicotine dependence and in symptoms of depression and anxiety

	Week 6					Week 18				
Variable	B	SE	$\chi 2$	p	OR	B	SE	$\chi 2$	p	OR
(Intercept)	1.374	0.663	4.295	0.038		0.408	0.551	0.549	0.551	
HAM-Ddif[1]	0.039	0.066	0.355	0.552	1.040	0.058	0.067	0.744	0.067	1.059
BASdif[2]	-0.089	0.050	3.165	0.075	0.915	-0.070	0.047	2.231	0.057	0.932

[1]HAM-Ddif: Difference between Hamilton Depression Rating Scale scores

[2]BASdif: Difference between Beck Anxiety Scale scores

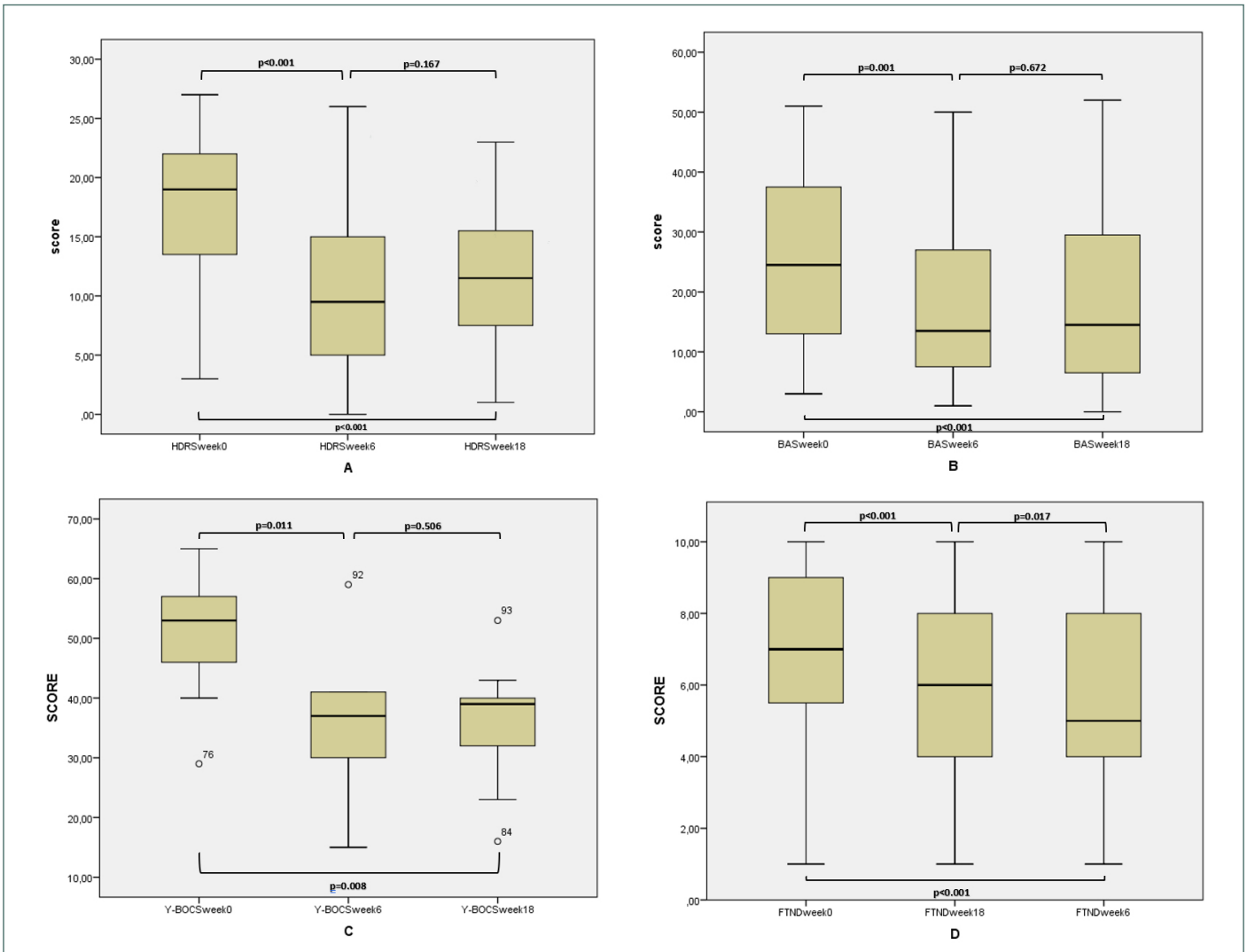

Figure 1. Box-plot visualisation and comparisons of the scores obtained from the four rating scales at weeks 0,6 and 18. a) Hamilton Depression Rating Scale (HAM-D scores. b) Beck Anxiety Scale (BAS) scores, c) Yale-Brown Obsession Compulsion Scale (Y-BOCS) scores, d) Fagerström Nicotine Dependence Test (FTND) scores

trend in nicotine dependence, the level of nicotine dependence remained significantly lower than the baseline (pre-treatment) severity. Furthermore, this decrease in nicotine dependence was not related to the improvement either in depression or anxiety symptoms. To our knowledge, this is the first study to analyze the effects of rTMS on nicotine addiction with comorbid MDD and OCD.

There is a well-established relationship between nicotine addiction and MDD or anxiety disorders. For instance, a patient with MDD might smoke to relieve his/her complaints such that an improvement in MDD might also lead to a decrease in smoking (21). Therefore, we also wanted to examine the relationship between changes in depressive and anxiety symptoms and the decrease in nicotine addiction in this study. As a result, we found no relationship at all the time points of observation (6th and 18th weeks). In a recently published double-blind, randomized study reported very similar findings to our study (22). They observed a significant decrease in nicotine dependence in a group of male chronic smokers (n=62) who got rTMS treatment (10 sessions of (20 Hz) HF-rTMS with 2000 pulses/session over the L-DLPFC), and this effect was sustained in the following three months. The authors also reported a significant decrease in both HDRS and Hamilton Anxiety Rating Scale (HARS) scores immediately after the completion of the treatment protocol, which had a significant positive correlation with the improvement in FTND. Conversely, no relationship was observed between the decrease in nicotine dependence and the improvement in depression and anxiety symptoms in our study. Suffice it to say that one common implication of these two studies is the effectiveness of HF-rTMS on the left DLPFC in simultaneously reducing the symptoms of nicotine dependence and MDD and/or anxiety, either independently or in a correlated manner.

The decrease in nicotine dependence after the rTMS treatment observed in this study is by and large in line with the findings obtained from a limited number of studies on TMS use in nicotine addiction. Owing partly to the novelty of rTMS as a treatment method in nicotine addiction, studies so far have been performed with a small sample size and widely heterogeneous in terms of both having different protocols and efficacy measures. One of the preliminary studies is a double-blind crossover study by Eichhammer et al. (11) in which fourteen smokers were included. Compared to sham stimulation, the authors found out that an active HF stimulation of the left DLPFC significantly reduced smoking in a 6-hour follow-up period, but there was not a significant change in craving. However, craving was found to decrease 30 minutes after a single session of HF-rTMS (90% MT, 20 Hz) applied to the DLPFC region in another randomized double-blind sham-controlled study (n=11) (23). What is common in these single-session studies is the immediate observation of the positive effects of rTMS on different aspects of nicotine dependence. Subsequent studies were trials with multisession rTMS protocols which also reported findings supportive of TMS efficacy (10). Nevertheless, to understand the efficacy of TMS treatment in a particular disease, it is essential to figure out the optimal dose-response pattern and the durability of this pattern, both of which involve the description of an optimal rTMS treatment. A recent meta-analysis of studies investigating the effects of non-invasive brain stimulation [transcranial Direct Current Stimulation (tDCS)] and high-frequency rTMS on the DLPFC made a comparative analysis of single vs. multisession excitatory stimulation protocols in a variety of addiction disorders, including nicotine (24). The results showed that multisession protocols of HF-rTMS on the DLPFC were more effective than single session protocols in reducing craving and consumption, and the effect was a linear dose-response effect such that both the number of sessions and the total number of pulses showed a positive linear relationship with the reduction in craving level. In our study, stimulation parameters were 120% MT, 10 Hz, and 3000 pulses for the high-frequency, and 100% MT, 1 Hz, 1200 for the low-frequency rTMS protocols, whereas the average number of sessions applied was 34 (range=23-46, median=36). Overall this is the highest average total dose applied so far, and the significant decrease in nicotine dependence was sustained 12 weeks after the end of the whole protocol. However, it was not possible to determine either the least effective dose or a saturation dose for such a durable effect from this study because of the protocols used. In a recent study, Li et al. (25) used MRI guided rTMS on the left DLPFC in a randomized sham-controlled study to investigate its effect on smoking (100% rMT, 10 Hz with 3000 pulses/session) for ten days and observed a decrease in craving and cigarette consumption which was sustained for the following three months similar to our study. This data obtained from Li's study, together with our observations, suggest that at least 10 sessions of HF-rTMS on the DLPFC might provide the decisive smoker a period of decreased nicotine dependence long enough to keep away from smoking. However, the dampening of nicotine dependence observed by the end of the 18th week in our study is worth considering since it may predict the extinction of the positive effects of rTMS over time. Thus for a longer duration of the therapeutic effect -at least in certain cases, maintenance protocols may be put to work.

Other parameters which might be significant in the efficacy of TMS are the application region, mode of administration in terms of being either excitatory or inhibitory, and the method used (i.e., regular, theta-burst, or deep rTMS) (26). In our study, L-DLPFC was the application site in all, but one of the patients and HF-rTMS was applied to 25 patients, whereas the remaining 7 got LF-rTMS. In a meta-analysis; most of the studies of rTMS treatment in nicotine addiction have used excitatory stimulation as the mode of administration and the L-DLPFC as the target area. In the same meta-analysis, the authors did not find a

significant effect of targeting the left versus the right hemisphere (24). Yet, another meta-analysis by Zhang et al. (27) showed that the left but not right DLPFC stimulation is superior to sham stimulation. Furthermore, inhibitory stimulation protocols and deep TMS (dTMS) had no significant effects on craving, whereas consumption was reduced immediately after excitatory left DLPFC rTMS and dTMS of the bilateral DLPFC and insula (24).

Overall, significant improvements were observed in the severity of depression and anxiety symptoms in the whole study group (n=32). Improvement in depression severity is in accordance with the majority of the published evidence so far (28). In a more recent meta-analysis of 19 RSCSs investigating the efficacy of HF-rTMS on the left DLPFC a significant reduction in depression severity after 10 sessions was found in all studies (29). Another finding consistent with earlier evidence is the duration of depressive symptom improvement during the 12-week follow-up period after rTMS treatment. In a comprehensive meta-analytic study regarding the durability of the antidepressant effects of rTMS treatment, Senova et al. (30) observed that 66.5% of MMD patients maintained response after three months; however, these rates decreased progressively to 46.3% 1 year after induction treatment. The observed decline in anxiety severity is also concordant with the findings from previous studies. rTMS has been shown to reduce anxiety symptoms not only in primary anxiety disorders (31) but also in other psychiatric disorders as was the case in our study (32, 33). Hence simultaneous improvement of anxiety symptoms with rTMS may make it a desirable option for various psychiatric disorders associated with anxiety.

In our study, a significant decrease was observed in the YBOCS scores of OCD patients (n=9) with rTMS treatment which was evident by the time it was completed and persisted till the 18th week. In the study in which the total number of sessions ranged between 20 and 40, two of the patients got HF-rTMS since they also had comorbid MDD and the other seven got LF-rTMS, and the application site was left DLPFC in all the patients. Studies with different protocols report different findings as to the efficacy of rTMS treatment in OCD. There are short-duration (approximately ten sessions) studies that have not found a significant finding in favor of the effectiveness of low or high-frequency rTMS treatment targeting DLPFC (34, 35). However, some other studies show that as the dose increases, a positive treatment response can be observed with longer durations. Sachdev et al. (36) found out that Y-BOCS scores improved significantly after the protocol was extended to 20 sessions in OCD patients who did not show any significant change with ten sessions. In another randomized single-blind sham-controlled study in which 21 resistant OCD patients were included, high-frequency rTMS was applied on bilateral DLPFC, and improvement in OCD symptoms was shown in the group receiving active rTMS (37). The findings of our study, in which long-duration protocols were applied, are in line with the findings of these last two studies. Moreover, in our study, the improvement in OCD symptoms was durable in the following 12 weeks.

One of the strongest aspects of our study is the evaluation of smoking frequency in people who received rTMS treatment primarily for MDD or OCD; thus they did not have a motivation to quit smoking before. Other strengths of our study are that it has a higher mean total dose than all studies conducted so far and that follow-up is carried out for an additional 12-weeks period.The study has several limitations. The first is the relatively small sample. Another significant limitation is that the study is retrospective and does not include a control group. Another limitation of our study is that the scales for evaluating cigarette addiction are based on self-report.

In conclusion, This study shows that rTMS treatment might be an effective treatment in comorbid nicotine addiction with MDD and OCD regardless of the severity of psychiatric illness. Considering that nicotine addiction is an important public health problem, we can say that rTMS is a promising treatment. In order to observe the effectiveness of rTMS, randomized and placebo (sham) controlled studies are required with larger samples consisting of participants without psychiatric comorbidity.

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