Original research

Effects of repetitive transcranial magnetic stimulation in combination with a low-carbohydrate diet in overweight or obese patients. A randomized controlled trial.

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ABSTRACT

Aims: The present study evaluated the effects of repetitive Transcranial Magnetic Stimulation (rTMS) in combination with a low-carbohydrate diet on body weight, food craving, auto-perception, general health, depression and anxiety, in overweight or obese patients.
Methods: Thirty-seven eligible patients were randomly allocated in two groups: rTMS group (low-carbohydrate diet plus rTMS, n = 18) and sham group (low-carbohydrate diet plus sham rTMS, n = 19). A total of 17 rTMS (10 Hz, left dorsolateral prefrontal cortex) or sham sessions were applied (10 sessions during two weeks, then, patients received 7 sessions over the next 28 weeks). Patients were evaluated before and after treatment with the following tests: short form 36 health survey (SF-36), food craving inventory, Beck's depression inventory, Beck's anxiety inventory and, body shape questionnaire.
Results: In the rTMS-treated group, but not in the sham group, we observed: a reduction in body weight, anxiety, and food craving ($P < .001$); in the general health survey were improved the aspects of physical functioning, emotional role, and vitality ($P < .001$), a significant improvement in the body shape questionnaire ($P < .001$).
Conclusion: We conclude that long-term rTMS treatment in combination with a low-carbohydrate diet is a promising approach for the management of overweight and obese patients.

1. Introduction

Overweight and obesity are defined as abnormal or excessive fat accumulation that may impair health. Overweight is when the body mass index (BMI) is greater or equal to 25 kg/m^2; and obesity is a BMI greater or equal to 30 kg/m^2 (WHO, 2018). The main cause of overweight and obesity is an energy imbalance between calories consumed and calories expended, often accompanied by abnormal eating habits, and food cravings. Moreover, high BMI is a major risk for cardiovascular diseases, musculoskeletal disorders, and some cancers (Brown et al., 2000; Aune et al., 2016). Additional to the physical implications of obesity, patients may suffer from other psychological afflictions as body distortion, anxiety, and depression (Dixon et al., 2013). Current treatments for obesity include diet, exercise, medication or bariatric surgery (Brown et al., 2000; Hainer et al., 2008). However, the success of these treatments has been considered low because of economic or psychological factors, added to the difficulty of long-term weight loss due to noncompliance and high dropout rate (Mann et al., 2007; Powell

et al., 2007; Hainer et al., 2008).

The utilization of brain stimulation techniques, such as, deep brain stimulation (DBS) and repetitive transcranial magnetic stimulation (rTMS), has been recently explored for several mental conditions, including depression, anxiety, chronic pain, obsessive-compulsive disorder and obesity (Roh et al., 2012; Kennedy et al., 2011; Ambriz-Tututi et al., 2016; Lee et al., 2017, 2018; Dilkov et al., 2017). The rTMS involves placing a copper wire coil on the scalp, which causes cortical neurons just below the skull, to depolarize in response to a short pulse of electric. This pulse generates an electromagnetic field reaching the cortex (Barker et al., 1985). Previous studies have reported that high-frequency rTMS promotes weight loss and reduction of food intake in people with obesity (Jansen et al., 2013; McClelland et al., 2013; Kim et al., 2018).

Studies have reported the role of the dorsolateral prefrontal cortex (DLPFC) on craving, which is related to obesity (Uher et al., 2005; Kekic et al., 2014; Jauregui-Lobera and Martínez-Quiñones, 2018). Interestingly, obese individuals have less DLPFC activation after a meal
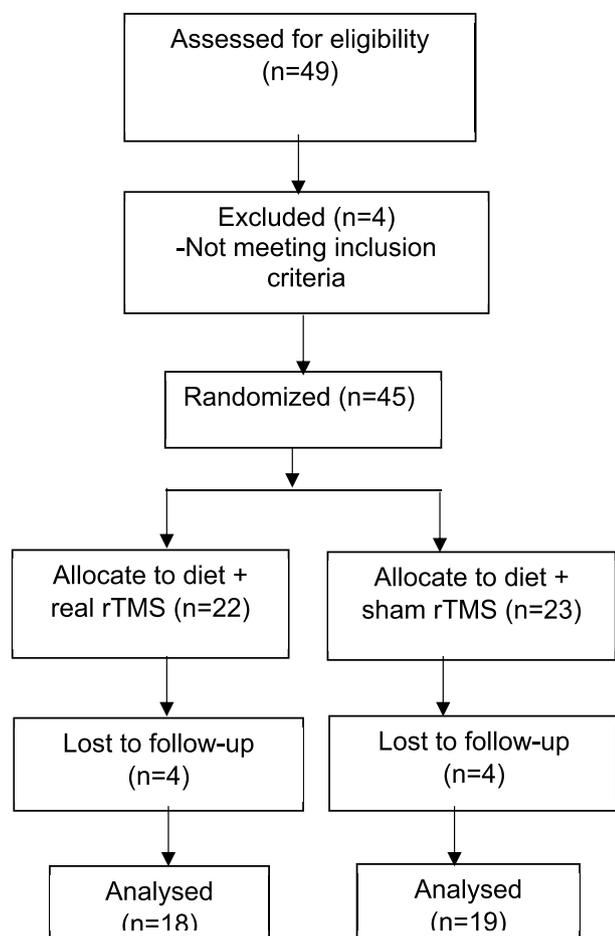
Fig. 1. Consort. Enrollment, randomization and, follow-up of patients in the study.

compared with lean individuals, suggesting possible unregulated inhibitory mechanisms that influence eating behavior (Le et al., 2006, 2007). Also, decreasing the excitability of the DLPFC with rTMS increases the consumption of snack food (Lowe et al., 2014). In contrast, patients with obesity who received transcranial direct current stimulation (tDCS) at the DLPFC, tended to consume fewer kcal (less fat and soda intake) (Gluck et al., 2015). This evidence suggests the pivotal role of DLPFC in food intake and body weight regulation. Hence, we hypothesized that high-frequency rTMS applied over the DLPFC might reduce body weight and food craving in overweight or obese patients, and it will allow them to follow a low carbohydrate diet in the long-term.

2. Material and methods

2.1. Subjects

Forty-nine patients were recruited from the Hospital Ajusco Medio between October 2017 and May 2018, being October 2018 the date of the final follow-up. The flow chart of the trial is presented in Fig. 1 as we followed the CONSORT 2010. All patients read and signed the informed consent and were informed that the data obtained from the study would be submitted for publication. Following, they completed the TMS adult safety questionnaire (Keel et al. 2001). We included patients with overweight (BMI $\geq 25 \, kg/m^2$) or obesity (BMI $\geq 30 \, kg/m^2$) aged 18–40 years. We excluded subjects with epilepsy, body metallic implants, pacemaker, hypertension, diabetes or major circulatory conditions, use of anti-obesity drugs, and pregnancy. Patients were asked not to concurrently use an other weight loss program during the

study. It is important to remark that none of the participants had received any form of magnetic stimulation before. The BMI was calculated as the ratio between the patient's weight in kilograms (kg) divided by the square of its height in meters.

2.2. Study design

We conducted a unicenter, double-blind, randomized, placebo-controlled trial. It conformed to the Declaration of Helsinki and was approved by the institutional Medical Research Ethics Committee with number 211-91-001-17. The protocol ID assigned at *clinicaltrials.gov* was NCT03345368. Patients were divided by stratified randomization 1:1 in two groups: group 1 received rTMS treatment + low-carbohydrate diet, while group 2 sham treatment + low-carbohydrate diet. Stratification was done by BMI to classify in overweight or obesity rank. This was necessary in order not to underestimate changes in weight. Allocation was done using sized two random permuted blocks. Whereas the physician who applied treatment was aware of the assignment of the participant, patients and data analyst were kept blinded to the allocation.

Treatment with rTMS or sham stimulation was applied from Monday to Friday during two weeks. After this period, all patients were asked to assist once per week for additional sessions (in the 3rd, 4th, 6th, 8th, 12th, 20th and 28th week). We ended the trial according to the schedule of the clinicians.

2.3. Repetitive transcranial magnetic stimulation (rTMS)

A Magstim Stimulator (Magstim Company, UK) was used to stimulate the DLPFC. Subjects sat comfortably in a chair. An eight-shaped coil was placed over the scalp. The coil was oriented at 45° from the mid-sagittal plane to induce currents to the left primary sensory-motor cortex hand area (M1/S1) (Sakai et al. 1997). The motor threshold (MT) was determined in each patient, each session. MT is defined as the minimum intensity to evoke five consecutive motor evoked potentials (MEPs). The stimulation was applied over the DLPFC (BA 9/46, Beam et al., 2009). The stimulation parameters had a frequency of 10 Hz, and a field intensity of 90% of the MT. Stimuli were provided in 10 trains of 100 pulses, with inter-train intervals of 10 s. Sham rTMS was administered with the coil held in contact with the head but 180° from the scalp with reduced field intensity. We followed the guidelines for the safe use of rTMS (Wassermann, 1998).

2.4. Dietary intervention

A qualified dietician explained the diet to all subjects during an individual visit. A written menu containing permitted and non-permitted foods was provided to each participant. Diet consisted in reducing carbohydrates intake (bread, rice, pasta, beans, and potatoes) to 20 g/day during the first 8 weeks and allowing patients to eat meat, fish, eggs, vegetables and natural fats (Halton and Hu, 2004). Then, it was permitted that individuals added fats or carbohydrates back to their diets but in controlled increments (5–15 g per week) (Stanton et al., 2017). Patients were asked to record their meals.

2.5. Tests

2.5.1. Short form general health survey

Patients were tested with a Spanish translation of the SF-36 survey authorized by the International Quality of Life Assessment Project (Alonso et al., 1995). This survey consists of 36 questions, which evaluate eight dimensions of health: physical functioning, physical role, emotional role, social functioning, mental health, vitality, pain, and general health perception. Each feature is directly transformed into a 0–100 scale on the assumption that each question carries equal weight. A test score of zero is equivalent to maximum disability and a test score

of 100 is equivalent to no disability.

2.5.2. Food craving inventory

The food-craving inventory (FCI, Spanish version: Jauregui-Lobera et al., 2010) was used to assess food cravings and consumption of craved food. The FCI consists of 28 food items distributed across four factors (high-fats, sweets, starches/carbohydrates, and fast-food). Each item is scored from 0 to 4 (where 0 = never, 1 = rarely, 2 = sometimes, 3 = often, and 4 = always/almost every day) according to the strength of the craving. A total score was also calculated. The definition of food craving was given to patients. They were asked to indicate how often craved each food item during the past 30 days and how often they have eaten the craven food.

2.5.3. Beck depression and anxiety tests

Beck depression inventory is a 21 item self-reported inventory designed to assess the presence and severity of depressive symptoms. Each item is rated on a 4-point scale ranging from 0 to 3, based on the severity in the last two weeks. The total score ranges from 0 to 63. Scores ranging from 0 to 13 indicate minimal depression, 14 to 19 mild depression, 20 to 28 moderate depression and, 29 to 63 severe depression. The Beck anxiety inventory is a short list describing 21 anxiety symptoms. Respondents are asked to rate how much each of these symptoms bothered them in the two past weeks. The test has a scale ranging from 0 to 3 and raw scores ranging from 0 to 63. The scores are classified as minimal anxiety (0–7), mild anxiety (8–15), moderate anxiety (16–25), and severe anxiety (30–63).

2.5.4. Body shape questionnaire

Body shape questionnaire is a self-report measure of the body shape preoccupations (Cooper et al., 1987). The questions refer to the patient' state over the past four weeks. Each item is scored 1 to 6 with "never" = 1 and "always" = 6 and the overall score is the total across the 34 items. Less than 80 points is taken as evidence of no dissatisfaction, 80 to 110 represents slight dissatisfaction, 111 to 140 moderate dissatisfaction and a score higher than 140 indicates serious dissatisfaction.

2.6. Statistical analysis

Analyses were done with Sigma Stat 4.0 (SigmaStat for Windows, Systat Software Inc. San Jose, CA, USA). The effect of the treatment was assessed using one-way repeated-measures ANOVA followed by Dunnett's test. Body measurements were weekly registered. Paired t-test was used to evaluate the pre-versus post-changes in questionnaires. Data are expressed as mean ± standard deviation. $P < .05$ was considered significant.

3. Results

Of the initially screened 49 volunteers, four did not meet inclusion criteria; seven were excluded due to poor compliance, and one for medical problems, thus leaving 37 to randomize. Subject demographics characteristics for both, rTMS and sham stimulation groups, are shown in Table 1. We did not find significant differences between these two groups. BMI was calculated to differentiate between overweight and obesity, 17 patients were classified with overweight (mean BMI, 27.7), and 20 were obese (mean BMI, 34.31). Nineteen patients were allocated to group 1 (sham + diet) and, 18 patients to group 2 (rTMS + diet).

After the first two weeks of the treatment, we found a reduction in weight in both groups, sham + diet, and rTMS + diet (Fig. 2). However, three weeks after treatment, the difference between groups was significantly different ($P < .05$). This was observed in obese (Fig. 2A) and overweight (Fig. 2B) patients. In obese patients treated with sham + diet, there was a weight decrease after two weeks. However, it stabilized with no further significant changes at the end of the study. We observed a slight but significant weight reduction in overweight

Table 1
Baseline characteristics and demographics.

	Diet + sham rTMS N = 19	Diet + real rTMS N = 18	P
Age (mean ± SD, years)	37.8 ± 3.358	42.1 ± 3.256	0.2615
Sex (n, %)			
Male	2, 10.53%	1, 5.5%	
Female	17, 89.47%	17, 94.5%	
BMI category (mean ± SD, Kg)			
Overweight	28.56 ± 0.43 (n = 9)	28.22 ± 0.35 (n = 8)	0.52
Obesity	37.26 ± 1.59 (n = 10)	36.25 ± 1.16(n = 10)	0.34
Body weight (mean ± SD, Kg)	82.655 ± 8.03	83.23 ± 6.18	0.32
High (mean ± SD, m)	1.57 ± 0.016	1.59 ± 0.012	0.47

BMI, body mass index, Statistical significance was tested using unpaired t-test, $P < .05$ was considered significant.

patients during the last few weeks. In the rTMS group, there was a slow but significant decrease with no signs of weight increase over the course of the study ($P < .05$). The mean decrease in body weight for patients with obesity in the rTMS group was 8.37% compared with 0.32% in sham-treated patients. In overweight patients treated with rTMS, the mean decrease was 9.94%, whereas in the sham group, the decrease was approximately 2.19%.

For the questionnaires, we applied two evaluations, before treatment and at the end of the study. The SFQ-36 showed an improvement on physical functioning, vitality, and emotional role (Table 2).

Patients who received rTMS, but not sham stimulation, also scored lower on the anxiety test (Fig. 3A). No changes were observed in the depression test (Fig. 3B). Furthermore, mean scores of the Food Craving Inventory showed a significant reduction after rTMS plus diet. Interestingly, participants showed an improvement at resisting cravings; some patients even reported not feeling any cravings during the week after rTMS. On the other hand, the sham group showed an increase in craving for some foods (Table 3). In the body shape questionnaire, we found a significant reduction on the score of patients treated with rTMS (94.84 ± 4.87 to 67.05 ± 4.17, $P < .001$), but not in the sham group (97.94 ± 6.08 to 80.22 ± 3.9, $P = .064$). This means that after rTMS treatment, patients scored "no dissatisfaction".

4. Discussion

The main finding of our research is that rTMS applied in the DLPFC plus a low-carbohydrate diet helps to reduce the weight in patients with overweight and obesity more efficiently than diet plus sham rTMS in the long term. In addition, we also observed a reduction in food craving, anxiety, corporal dissatisfaction, and a significant improvement on measures of general health in rTMS group compared to the sham group.

It is accepted that high-frequency (2–30 Hz) rTMS stimulation increases cortical excitability whereas low-frequency (0.3–1 Hz) stimulation, decreases it (Hallett, 2007). Accordingly, targeting the left DLPFC with 10 Hz rTMS induces increased cortico-spinal excitability (Oliveira-Maia et al., 2017). In order to activate this area we applied several high-frequency rTMS sessions, since clinical benefits generally emerges around 2–3 weeks of treatment (Roh et al., 2012; Lee et al., 2018). Our study shows a reduction of body weight and food cravings in obese and overweight patients after two weeks of 10 Hz rTMS. We applied sessions of rTMS along of seven months to maintain the effects of the treatment. However, the interval between sessions was longer each time, and we did not observe weight regain; this could suggest a cumulative effect of rTMS.

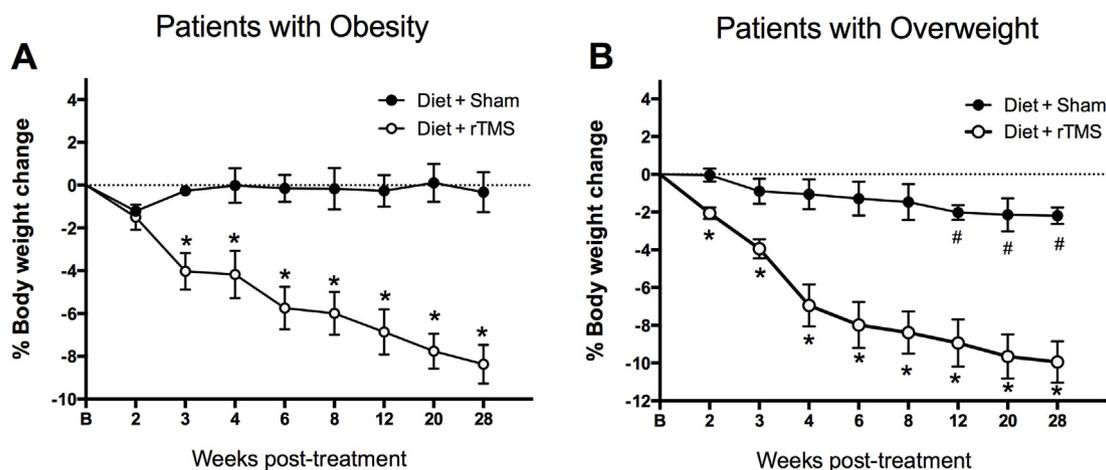A study reported that four sessions with rTMS over the left DLPFC

Fig. 2. Percentage body weight change over time. A) % Body weight change in patients with obesity. B) % Body weight change in patients with overweight. B: baseline before diet + sham or, diet + rTMS treatment. *$P < .05$ vs. B, #$P < .05$ vs. B. Two-way ANOVA followed by Dunnet's test.

Table 2
Short form general health survey.

	Sham + diet group		P	rTMS + diet group		P
	Before	After		Before	After	
General health	56.38 ± 2.68	62.59 ± 2.31	0.18	69.00 ± 3.45	74.47 ± 2.88	0.15
Physical functioning	68.83 ± 4.09	75.23 ± 6.60	0.21	68.10 ± 2.51	80 ± 1.74	< .01*
Physical role	76.77 ± 5.02	81.47 ± 5.32	0.18	78.47 ± 2.95	83.42 ± 2.38	0.23
Somatic pain	71.36 ± 6.49	70.88 ± 4.39	0.35	69.04 ± 4.34	73.68 ± 3.97	0.54
Emotional role	73.16 ± 5.77	78.82 ± 4.67	0.28	67.26 ± 2.96	80.94 ± 2.56	< .01*
Social functioning	66.5 ± 3.45	70.52 ± 2.78	0.16	71.32 ± 4.84	75.47 ± 3.02	0.12
Vitality	56.12 ± 3.37	60 ± 3.03	0.18	57.39 ± 3.45	73.42 ± 2.24	< .01*
Mental health	65.33 ± 2.77	65.94 ± 3.01	0.35	70.47 ± 3.21	74.26 ± 2.36	0.31

* Statistical significance was tested using paired t-test, $P < .05$ was considered significant.
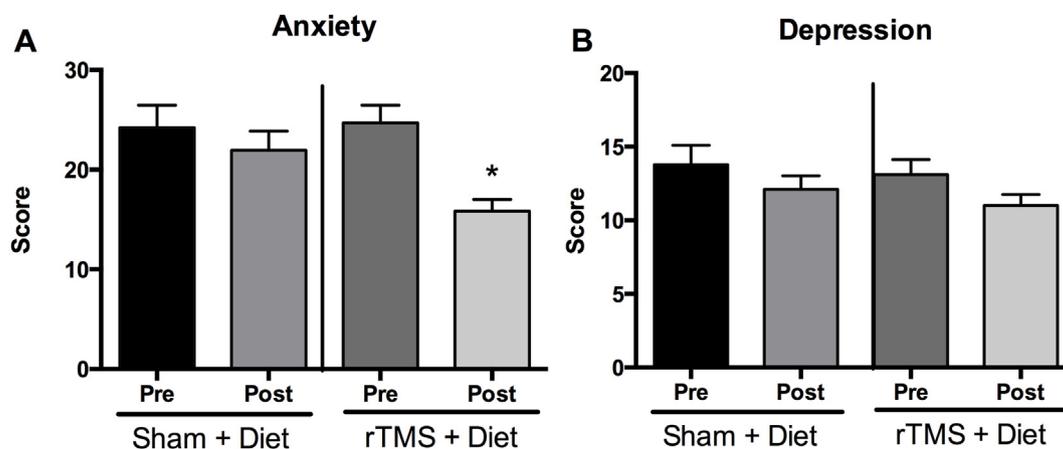

Fig. 3. Mean score in Beck's anxiety and depression tests before and after treatment. Bars represent mean ± S.E.M. of the group. * Significantly different from corresponding sham group. ($P < .05$), determined by paired t-test.

Table 3
Food craving inventory.

	Sham group		P	rTMS group		P
	Before	After		Before	After	
FCT	36.72 ± 2.17	53.22 ± 1.08	< .001*	39.26 ± 1.14	26.84 ± 1.25	< .001*
FC1 (sweets)	11.66 ± 0.62	15.16 ± 1.07	0.05	11.73 ± 0.50	7.15 ± 0.54	< .001*
FC2 (starches/carbohydrates)	10.55 ± 0.74	13.88 ± 0.79	< .05*	9.63 ± 0.65	7.42 ± 0.81	< .001*
FC3 (high fats)	13.33 ± 1.29	15.83 ± 1.14	0.06	10.36 ± 0.57	7.42 ± 0.81	< .001*
FC4 (Fast food)	8.5 ± 0.89	8.33 ± 0.62	0.89	7.52 ± 0.56	3.26 ± 0.25	< .001*

* Statistical significance was tested using paired t-test, $P < .05$ was considered significant.

induces weight loss and reduces food intake in people with obesity (Kim et al., 2018). In agreement, we found similar result but in a long-term effect. Furthermore, we identified favorable effects on anxiety, food-cravings and general health.

Uher et al. (2005) showed that the application of rTMS to the left DLPFC prevents the increase of craving during food exposition. However, no significant differences were observed in food consumption. They applied a single session of rTMS that would explain the difference with our study. We speculate that rTMS therapy should be applied for a longer time in order to achieve a therapeutic effect in patients. In the present study, rTMS treatment led to significant food craving reduction in the patients, this probably allowed to achieve and maintain the diet since food cravings can precipitate eating behavior (Weingarten and Elston, 1990; Hill and Heaton-Brown, 1994). During controlled feeding studies, patients frequently reported food craving as the reason for failing to adhere to diet (Teixeira et al., 2004; Hall and Most, 2005; Wadden et al., 2011).

In this regard, the DLPFC has been targeted as a key role in self-regulatory control mechanisms and now it is a common target for neuromodulatory interventions (Jáuregui-Lobera and Martinez-Quiñones, 2018). In our study, patients reported that they did not feel food craving at night and felt satisfied after rTMS treatment. Also, rTMS-treated patients scored better than sham in the anxiety test, from moderate to mild anxiety. This result is significant since moderate anxiety can become more severe and overwhelming, making feel more nervous.

On the other hand, in the SF-36 questionnaire we found an improvement on several aspects in rTMS-treated patients, but not in the sham-treated group. SF-36 is the most robustly standardized and widely used test to evaluate the quality of life. It is essential in deciding if an intervention is worth adopting (Contopoulos-Ioannidis et al., 2009). We observed a significant improvement on physical functioning, emotional role, and vitality. These changes, in addition to the weight reduction, result in a promising combination (rTMS plus diet) as an obesity treatment.

A suggested mechanism behind rTMS long-term effects is that rTMS changes the synaptic plasticity through long-term potentiation/depression (LTP/LTD) of excitatory synaptic transmission (Ma et al., 2014). Furthermore, depending on the intrinsic properties and geometrical orientation of the neural fibers confined in the cortical region, the magnetic stimulus could modify fibers of distant brain structures (Peng et al., 2018). The DLPFC plays an important role in several cognitive, affective and sensory networks, for that reason it has been a recurrent target for numerous disorders. For example, low-frequency rTMS delivered to right and left DLPFC alleviated anxiety symptoms in patients and elevated serum concentration of BDNF and serotonin (Lu et al., 2018). Also, it was reported that individuals with effective dietary self-control had increased activity in the DLPFC when making food choices (Hare et al., 2009). Our study targets the DLPFC considering that previous studies showed its role in the regulation of eating behavior (Le et al. 2007). Heinitz et al. (2017) suggested that stimulating the left DLPFC would enhance dietary self-control and, as a result, reduce over-consumption. This agrees with our study, patients reported a decrease in the consumption of food.

In the self-image reported test, we found an improvement in patients who received rTMS, but not in sham-treated. Similarly, it was reported that after applying 20 rTMS trains, the perception of feeling fat was decreased in patients with anorexia nervosa (Van den Eynde et al., 2013). Body dissatisfaction is correlated to poor self-esteem and unhealthy food habits, and it has been suggested that both are mediated by similar psychological issues (Cruz-Sáez et al., 2018). Moreover, body image might be affected by obesity through psychological distress, which has an impact on quality of life (Schwartz and Brownell, 2004). A meta-analysis showed that body dissatisfaction is more severe among patients with obesity than in normal-weight individuals (Weinberger et al., 2017). This is a preliminary study; we consider that a major

number of patients must be included in the future, and mostly it would be important to develop a study that evaluates structural and functional changes after rTMS in obese and overweight patients, which was a limitation in our study.

Our study suggests that rTMS may help as adjuvant therapy in obesity with long-term effects reducing food-cravings and anxiety Furthermore, rTMS improves some aspects of general health and auto-perception.

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Conflicts of interest

The authors declare no conflict of interest.

Declarations of interest

None.

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