Brain Stimulation 12 (2019) 1556–1564

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: http://www.journals.elsevier.com/brain-stimulation

The effects of repetitive transcranial magnetic stimulation on body weight and food consumption in obese adults: A randomized controlled study

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ARTICLE INFO

Article history:
Received 23 October 2018
Received in revised form
14 July 2019
Accepted 23 July 2019
Available online 25 July 2019

Keywords:
Obesity
Repetitive transcranial magnetic stimulation (rTMS)
Food intake
Body weight

ABSTRACT

Background: Although some studies have reported significant reductions in food cravings following the single-session of repetitive transcranial magnetic stimulation (rTMS), there is little research on the effects of multi-session of rTMS on food consumption and body weight in obese subjects.
Objective: We conducted 4-week randomized, sham-controlled, single-blind, parallel-group trial to examine the effect of rTMS on body weight in obese adults.
Methods: Forty-three obese patients (body mass index [BMI] $\geq$25 kg/m^2) aged between 18 and 70 years were randomized to the sham or real treatment group (21 in the TMS group and 22 in the sham treatment group). A total of 8 sessions of rTMS targeting the left dorsolateral prefrontal cortex (DLPFC) was provided over a period of 4 weeks. The primary outcome measure was weight change in kilograms from baseline to 4 weeks. Secondary endpoints included changes in anthropometric measures, cardiovascular risk factors, food intake, and appetite.
Results: Participants in the rTMS group showed significantly greater weight loss from baseline following the 8 session of rTMS (-2.75 ± 2.37 kg vs. 0.38 ± 1.0 kg, $p < 0.01$). Consistent with weight loss, there was a significant reduction in fat mass and visceral adipose tissue at week 4 in the rTMS group compared with the control group ($p < 0.01$). After the 8 sessions of rTMS, the TMS group consumed fewer total kilocalories and carbohydrates per day than the control group ($p < 0.05$).
Conclusions: 8 sessions of HF rTMS delivered to the left DLPFC were effective in inducing weight loss and decreasing food intake in obese patients.
Trial registration: Clinical trial registered with the Clinical Trials Registry at http://cris.cdc.go.kr (**KCT0002548**).

Introduction

The prevalence of obesity has increased dramatically worldwide over recent decades and has reached epidemic proportions [1]. It has been reported that one-third of the adult population in most developed countries is obese [2], resulting in an increasing number of people with type 2 diabetes, cardiovascular disease, stroke, cancer, metabolic syndrome, liver disease, and other conditions [3]. Although the first-line strategy for the treatment of obesity is lifestyle modifications, the success rate in the long term is low [4–6]. When lifestyle changes alone do not achieve the desired

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https://doi.org/10.1016/j.brs.2019.07.020
1935-861X/

weight loss, pharmacotherapy or bariatric surgery provides an applicable option for patients meeting eligible criteria. However, current pharmacologic treatments have so far been limited because of the adverse effects and difficulties with tolerability, and bariatric surgery is limited to selected participants with complicated or severe obesity due to the risks of invasive procedures [7]. Thus, there is a need for additional non-surgical, non-pharmacologic weight loss therapies for obesity.

There is a growing body of evidence suggesting a role of brain mechanisms underlying food-cravings in obesity [8]. Obesity may be considered as a type of psychological disease that is related to deranged eating behaviors, which results from dysfunctional fronto-striatal circuitry [9,10]. In particular, the lateral prefrontal cortex has been considered an important part of fronto-striatal circuits and plays a major role in the regulation of eating behavior; neuroimaging studies in obese participants demonstrated impaired inhibitory control from lateral prefrontal circuits [11–14]. Thus, it is possible that a lack of regulatory influence from the dorsolateral prefrontal cortex (DLPFC) in obesity might lead to uncontrolled eating, suggesting that this area as a potential target for intervention in obesity.

Repetitive transcranial magnetic stimulation (rTMS) is a safe and non-invasive neuromodulation technique that may reduce the food craving levels in obese patients by changing cortical brain activity [9]. rTMS at high frequency has the potential to directly activate the immediately underlying cortex (e.g., the dorsolateral prefrontal cortex), while inhibiting neural activity in more remote areas (e.g., the orbitofrontal and anterior cingulate cortex) [15,16]. This pattern of action directly counterbalances neural processes associated with food cravings. Accordingly, rTMS might be an effective modality for patients with obesity by modulating cortico-limbic connectivity. Indeed, some initial findings have suggested that the single-session of high-frequency (HF) rTMS to the left DLPFC may reduce acute craving in patients with eating disorders [17–19]. However, there is little research on the effects of rTMS on food consumption in obese subjects. Moreover, changes in body composition with multi-session rTMS beyond the immediate changes in food cravings after a single session of rTMS remain unexplored.

In previous 2-week trial in obese subjects, we demonstrated that, compared to sham rTMS, 4 sessions of real HF rTMS applied to the left DLPFC reduced food intake and body weight [20]. The present study was designed to further investigate the longer-term efficacy, safety and tolerability of 8 sessions of rTMS for an additional 2 weeks intervention (a total treatment duration of 4 weeks) in obese subjects. We speculated that 8 sessions of rTMS delivered to the left DLPFC would result in significantly more reduction of food consumption and body weight than would 4 sessions of rTMS.

Materials and methods

Study design and randomization

We performed a 4-week randomized, sham-controlled, single-blind, parallel-group trial that compared the effects of rTMS on body weight. The trial was conducted at St. Vincent's Hospital in South Korea with approvals from the Institutional Review Boards of the Catholic University of Korea (no. VC17DNSI0132, approved August 2017). After reviewing the potential benefits, risks, and adverse effects of the TMS and sham stimulations, written informed consent was obtained. Eligible participants were randomly allocated (1:1) to either real TMS stimulation (intervention group) or sham stimulation (control group) via sealed randomization envelopes.

Participants

Obese men and women (body mass index [BMI] $\geq$25 kg/m^2) aged between 18 and 70 years were recruited from the outpatient clinics at St. Vincent's Hospital in South Korea between October 2017 and March 2018 (Clinical Trial Registry: KCT0002548). All participants were naive to rTMS and continued their daily routines without any instructions for diet and physical activity during the study period. They were weight stable (±5%) for 3 months prior to their study participation.

The exclusion criteria included (1) past history of head injury or epilepsy; (2) body metallic implants, pacemaker and any other contraindication to MRI or rTMS; (3) current psychiatric illness or psychotropic medication; (4) recent use of weight-loss drugs or very-low-calorie diet; (5) pregnancy or breast feeding; (6) history of an eating disorder or substance dependence; and (7) the presence of uncontrolled diabetes or an unstable cardiovascular disease. Additionally, participants showing abnormal findings in brain MRI were excluded from the study.

Assessment of study outcomes

The primary outcome measure was weight change in kilograms from baseline to 4 weeks. Secondary end points included changes in anthropometric measures, body mass index, cardiovascular risk factors, visceral fat assessed by CT, food intake, appetite and adverse events; cardiovascular risk factors were evaluated by changes in fasting lipid concentrations total cholesterol, high-density lipoprotein [HDL] cholesterol, low-density lipoprotein [LDL] cholesterol, and triglycerides [TG], glucose, insulin, and C-reactive protein.

Body composition and cardiovascular risk factors

Anthropometric, clinical and laboratory investigations were performed on all participants at baseline and after the 4 week of intervention, as previously described in detail [20]. Blood samples were drawn in the morning hours after a 12-h overnight fast. The HOMA-IR that was used as a marker of insulin sensitivity was calculated using Matthews' method: fasting insulin (in microunits per milliliter) $\times$ fasting blood glucose (in millimoles per liter)/22.5 [21].

The cross-sectional areas of visceral adipose tissue were measured using a CT scanner (LightSpeed, GE Healthcare, Milwaukee, WI). Body fat mass (kg) and skeletal muscle mass (kg) were estimated using a multi-frequency BIA device with a body composition analyzer (InBody 720, Biospace Co., Seoul, Korea).

Diet

Dietary intake was assessed by a 3-day food record at baseline and after the 4 week of intervention. Each participant was asked to record all foods and beverages consumed over 3 non-consecutive days, including one weekend day or holiday. Dietitians reviewed unclear descriptions, errors, omissions, or doubtful entries in food records and asked the participants to clarify them during study visits. Total energy and macronutrient intakes were calculated by a computer-aided nutrient analysis program (CAN-Pro 5.0, APAC Intelligence, Seoul, South Korea).

Appetite, physical activity, and mood state

Questionnaires related to physical activity and mood states were completed by all participants at baseline (week 0) and at week 4. Subjective sense of appetite was assessed in the 2-h fasted state using 10-cm visual analogue scale (VAS) of “Fullness”, “Hunger,”

"Desire to eat" and "Prospective food consumption" on day 0 (baseline) and at each visit for rTMS session (see Supplemental Fig. 1). VAS had questions such as 'How hungry do you feel?' (Hunger), 'How full do you feel?' (Fullness), 'Would you like to eat something?' (Desire to eat), 'How much do you think you can eat?' (Prospective food consumption) [22]. We examined physical activity using the Korean version of International Physical Activity Questionnaire (IPAQ-K) [23]. To screen for eating disorders, eating behavior was assessed by the Korean eating attitude test (KEAT-26) [24]. To assess whether the rTMS intervention had an effect on mood state, we evaluated depression and anxiety symptoms using the Hospital Anxiety and Depression Scale (HADS) [25].

rTMS intervention

Real rTMS

A total of 8 sessions of rTMS were provided for 2 non-consecutive days per week for 4 weeks. The rTMS was delivered to the left DLPFC using an ALTMS device and a figure-eight coil (REMED, Daejeon, Korea). After mapping the abductor pollicis brevis site in the left motor cortex, the participant's motor threshold was established as the minimum stimulus required to induce contraction of the right thumb at least five out of 10 times [26]. The site for the left DLPFC stimulation was 5 cm anterior to the point of maximal abductor pollicis brevis stimulation in the parasagittal plane. Forty trains of 5 s with 25-s inter-train intervals were administered at a frequency of 10 Hz and an intensity of 110% of the individual's motor threshold, providing 2000 pulses over 20 min.

Sham rTMS

For sham stimulation, the coil was placed over the interhemispheric fissure on the vertex at 90° to the scalp, and stimulation with low intensity (10% resting motor threshold) was given to elicit similar skin sensations as real stimulation [27,28].

Statistical analysis

The sample size for the present study was estimated using data from our previously published study, which demonstrated the effects of rTMS on body weight in obese patient [20]. Applying these data, we calculated that 20 participants in each group would give 80% power to detect a significant ($p < 0.05$) difference between the groups. We conducted an intent-to-treat analysis of patients as randomized. The results are expressed as the mean ± standard deviation (SD), and independent *t*-tests or Fisher's exact tests were used to compare characteristics at baseline between the TMS and control groups. Between-group differences on outcome variables that were measured at baseline and after 4 week were analyzed using an ANCOVA with treatment group as factors and baseline values as covariates. Effect sizes (partial eta-squared, η^2) were calculated for the statistically significant differences between-group. Within-group differences were estimated by using a paired samples *t*-test or the mixed linear model. VAS scores for subjective appetite were analyzed using two-way repeated measures ANOVA and multiple comparisons with Bonferroni corrections. The data were analyzed using the Statistical Package for the Social Sciences version 21 (SPSS Inc., Chicago, IL, USA), and a two-tailed *p*-value <0.05 was considered statistically significant.

Results

Participants

Of the 45 volunteers, 2 who failed to meet the inclusion criteria were excluded, and 43 participants were randomized to the sham or real treatment group. One participant who was randomized to the TMS group dropped out due to withdrawal from participation, and two participants in the sham treatment group were lost to follow-up due to poor adherence and withdrawal from participation. Thus, 40 participants completed the 4 weeks of follow-up, and the primary analysis was conducted on 43 obese adults who were received allocated intervention (21 in the TMS group and 22 in the sham treatment group; Fig. 1).

Table 1 summarizes the baseline characteristics of the study participants. Baseline demographic, anthropometric, and clinical characteristics were similar between the two groups; we found no significant between-group difference in age, gender, BMI, weight (kg), WC, glucose, insulin, HOMA-IR, or lipid profile. The physical activity level, KEAT-26 score, subjective sense of appetite and HADS subtest scores were also not significantly different between groups.

Weight loss

While there were no differences in weight change during the 4 weeks for those who received sham stimulation, participants in the rTMS showed significantly greater weight loss from baseline following the 8 sessions of rTMS (−2.75 ± 2.37 kg vs. 0.38 ± 1.0 kg; $p < 0.01$, Table 2). Consistent with weight loss, there was a statistically significant reduction in BMI, fat mass, skeletal muscle mass, waist circumference and visceral adipose tissue at week 4 in the rTMS group compared with the control group ($p < 0.01$).

Appetite and food intake

Fig. 2 shows the results of the VAS measures for Hunger, Fullness, Desire to eat and Prospective food consumption. There was no significant difference between the two groups in Prospective food consumption and Fullness. However, the real rTMS group showed a significant reduction in Desire to eat ($F = 5.450$; $p = 0.025$, $\eta^2 = 0.125$) and Hunger sense ($F = 6.964$; $p = 0.012$, $\eta^2 = 0.155$), compared with the sham group.

The characteristics of energy intake are shown in Table 3. After the 8 sessions of rTMS, participants who received real stimulation consumed fewer total kilocalories per day than the control group (−262.99 ± 161.41 kcal/day vs. −13.83 ± 362.61 kcal/day, $p = 0.011$). In addition, the rTMS group showed significantly less carbohydrates intake compared with the sham stimulated group at week 4 (−47.56 ± 42.01 vs. −9.80 ± 34.75 g/day, $p = 0.003$). However, there were no differences in fat ($p = 0.487$), protein ($p = 0.835$), and fiber ($p = 0.723$) intake between the two groups.

Changes in the cardiometabolic risk factors

Consistent with the weight loss, rTMS treatment was associated with beneficial effects on glucose metabolism at 4 week (Table 4). Compared with the sham stimulated group, rTMS treatment reduced fasting insulin concentration (−3.81 ± 8.46 μU/mL vs. 4.73 ± 13.03, $p = 0.014$) and HOMA-IR (−1.14 ± 2.51 vs. 2.23 ± 7.03, $p = 0.044$), which is indicative of an improvement in insulin sensitivity. Contrary to improvements in glucose metabolism, rTMS had no effect on C-reactive protein, liver enzymes, and lipid profiles.

Blinding

After the completion of the study, we asked participants to guess whether they thought they had received real or sham stimulation. Most (18 of 22 in the sham group, 19 of 21 in the real group) believed that they had received real stimulation (Fisher's exact test, $p = 0.108$).

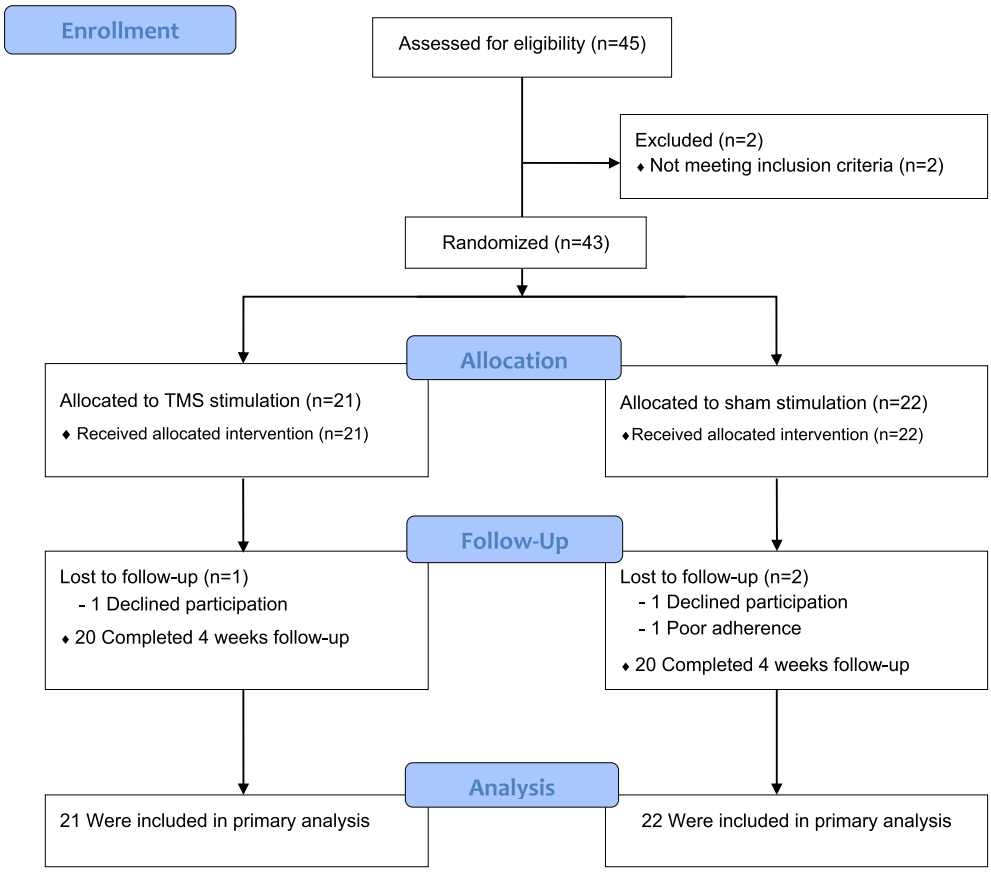

Fig. 1. Screening, enrollment, randomization, and follow-up of study participants.

Table 1
General characteristics at baseline.

	TMS group (n = 21)	Sham group (n = 22)	*p*-value*
Age (years)	55.81 ± 10.55	51.00 ± 10.81	0.148
Sex (n)			
Male	5 (23.8%)	8 (36.4%)	0.510
Female	16 (76.2%)	14 (63.6%)	
BMI (kg/m2)	31.01 ± 3.35	29.24 ± 3.13	0.081
WC (cm)	101.93 ± 9.14	95.72 ± 9.82	0.068
Weight (kg)	79.92 ± 12.69	79.04 ± 14.25	0.831
VAT (cm2)	154.88 ± 38.14	143.37 ± 38.94	0.333
Glucose (mg/dl)	104.29 ± 18.46	102.05 ± 21.30	0.662
Insulin (μU/mL)	12.80 ± 9.50	12.22 ± 10.09	0.886
HOMA-IR	3.38 ± 2.67	3.35 ± 3.41	0.852
Total cholesterol (mg/dl)	202.05 ± 29.21	202.55 ± 32.38	0.923
Triglyceride (mg/dl)	144.67 ± 54.00	159.70 ± 85.76	0.081
HDL cholesterol (mg/dl)	48.33 ± 5.32	53.05 ± 11.53	0.626
LDL cholesterol (mg/dl)	124.78 ± 24.25	117.56 ± 31.72	0.473
Physical activity (METs·min/wk)	2771.5 ± 3566.9	2198.2 ± 2067.5	0.526
HADS-A	5.52 ± 3.19	4.80 ± 3.16	0.473
HADS-D	8.24 ± 3.27	6.30 ± 3.48	0.074
VAS for subjective appetite			
Hunger	2.31 ± 2.63	2.59 ± 3.02	0.767
Fullness	4.19 ± 2.84	3.33 ± 3.29	0.371
Desire to eat	2.83 ± 2.64	1.98 ± 2.85	0.318
Food consumption	4.02 ± 2.72	3.47 ± 2.07	0.494
KEAT-26	11.95 ± 6.94	10.30 ± 6.14	0.425

Abbreviations: BMI, body mass index; WC, waist circumference; VAT, visceral adipose tissue; HOMA-IR, homeostasis model assessment of insulin resistance; HADS-A, Hospital Anxiety and Depression Scale-anxiety subscale; HADS-D, Hospital Anxiety and Depression Scale-depression subscale; VAS, visual analogue scale; KEAT, Korean eating attitude test. Values are mean ± SD.
* Statistical significance was tested using independent *t*-test or $\chi 2$ test.

Table 2
Changes in body composition.

	TMS group (n = 21)			Sham group (n = 22)			F	Effect size (η^2)	*P* for change
	Baseline	Post	Change	Baseline	Post	Change			
Weight (kg)	79.92 ± 12.69	77.17 ± 11.28	−2.75 ± 2.37*	79.04 ± 14.25	79.41 ± 14.25	0.38 ± 1.00	36.431	0.477	< 0.01
BMI (kg/m^2)	31.01 ± 3.35	29.88 ± 3.18	−1.14 ± 0.74*	29.24 ± 3.13	29.39 ± 3.09	0.15 ± 0.38	44.768	0.528	< 0.01
Skeletal muscle mass (kg)	26.10 ± 5.39	25.48 ± 5.29	−0.61 ± 0.43*	26.97 ± 6.55	27.01 ± 6.44	0.04 ± 0.45	21.229	0.352	< 0.01
Fat mass (kg)	32.30 ± 7.77	30.79 ± 7.09	−1.50 ± 2.09*	30.34 ± 7.93	30.60 ± 8.05	0.25 ± 0.97	19.196	0.330	< 0.01
Waist circumference (cm)	101.93 ± 9.14	96.42 ± 7.82	−5.52 ± 4.63*	95.72 ± 9.82	97.35 ± 10.40	1.63 ± 2.71*	30.093	0.429	< 0.01
VAT (cm^2)	154.88 ± 38.14	143.33 ± 36.23	−11.55 ± 11.16*	143.37 ± 38.94	150.51 ± 41.61	7.15 ± 8.92*	34.617	0.464	<0.01

Values are mean ± SD.
p values correspond to between-group comparisons by using an analysis of covariance (ANCOVA) with baseline value as covariates.
*: $p < 0.05$ for within group comparison by paired *t*-test.

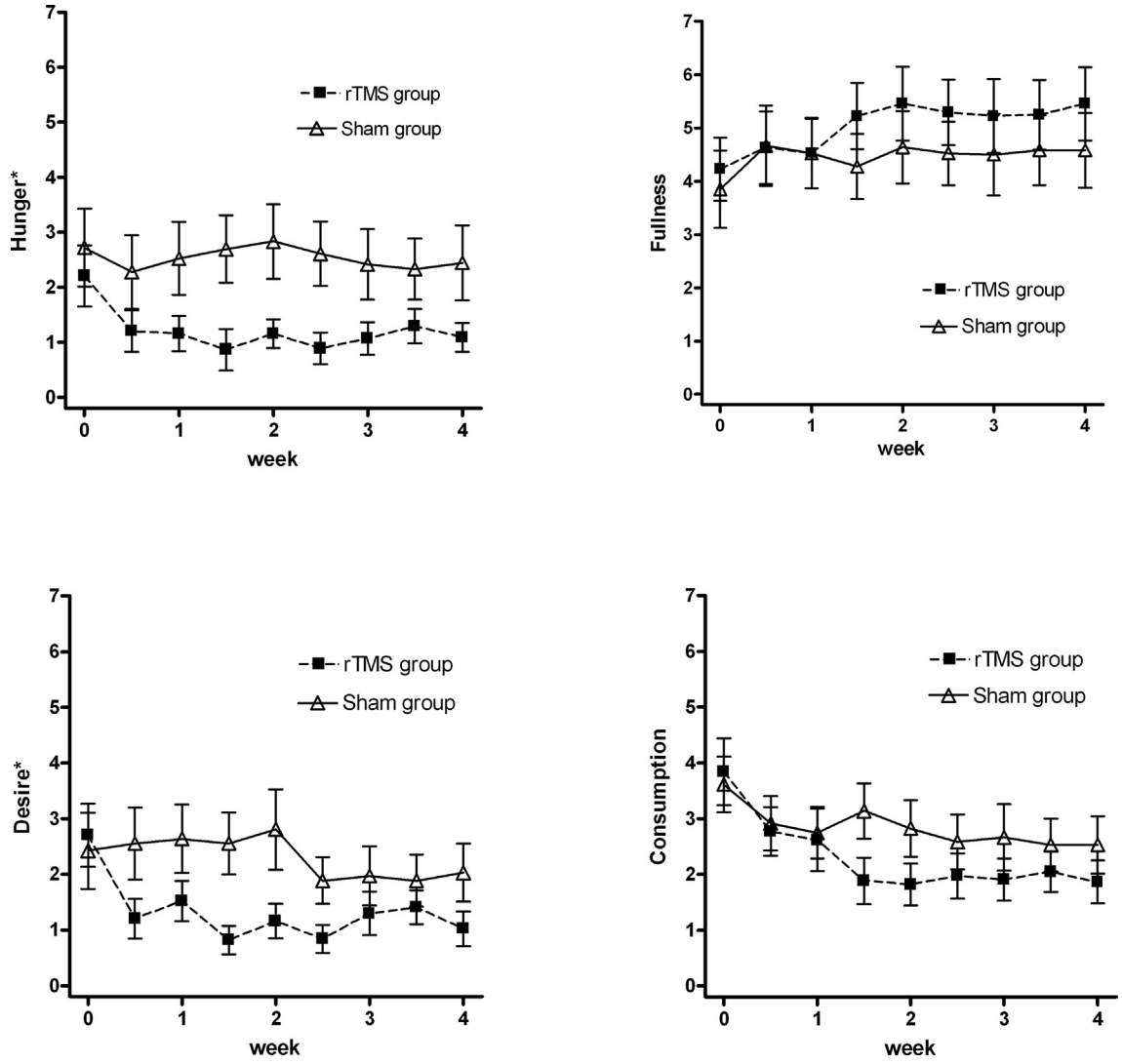

Fig. 2. VAS score for subjective appetite in the rTMS group and the sham stimulation group. Values are expressed as mean ± standard error of the mean(SEM) for Hunger, Fullness, Desire to eat and Prospective food consumption. All analyses were conducted using two-way repeated measures ANOVA. *p < 0.05 for between group changes.

Safety and tolerability

rTMS was well tolerated during the 8 sessions. Consistent with previous experience [20], the most common adverse event with TMS was a transient mild headache; 3 participants (2 participants in rTMS group and 1 participant in sham stimulation group) reported slight headache immediately after the rTMS session. Besides, transient tinnitus (1 participant in sham stimulation group) and mild dizziness (1 participant in rTMS stimulation group) were reported, however no participant dropped out due to discomfort during the trial. The profile of mood states by HADS questionnaire did not show any effect of rTMS on anxiety or depression compared with sham group (data not shown).

Table 3
Changes in food intake from baseline to week 4.

	TMS group (n = 21)			Sham group (n = 22)			F	Effect size (η^2)	*P* for change
	Baseline	Post	Change	Baseline	Post	Change			
Total energy intake (kcal/day)	1881.46 ± 340.64	1618.47 ± 340.68	−262.99 ± 161.41*	1827.88 ± 365.40	1814.05 ± 470.44	−13.83 ± 362.61	7.129	0.162	0.011
Carbohydrate (g/day)	269.47 ± 59.91	221.90 ± 58.17	−47.56 ± 42.01*	269.27 ± 64.53	259.47 ± 66.94	−9.80 ± 34.75	10.275	0.217	0.003
Fat (g/day)	48.13 ± 21.02	42.00 ± 16.94	−6.13 ± 16.85	51.00 ± 11.56	47.08 ± 18.71	−3.92 ± 15.17	0.493	0.013	0.487
Protein (g/day)	72.94 ± 18.30	68.68 ± 23.03	−4.27 ± 19.56	70.52 ± 13.12	68.50 ± 13.20	−2.03 ± 16.55	0.044	0.001	0.835
Fiber (g/day)	23.75 ± 7.25	21.56 ± 6.58	−2.19 ± 8.09	21.34 ± 6.40	19.83 ± 5.90	−1.51 ± 4.76	0.127	0.003	0.723

Values are mean ± SD.
p values correspond to between-group comparisons by using ANCOVA with baseline value as covariates.
*: $p < 0.05$ for within group comparison by paired *t*-test.

Table 4
Changes in cardiovascular and metabolic risk factors.

	TMS group (n = 21)			Sham group (n = 22)			F	Effect size (η^2)	P for change
	Baseline	Post	Change	Baseline	Post	Change			
CRP (mg/dL)	0.22 ± 0.31	0.23 ± 0.38	0.01 ± 0.37	0.26 ± 0.44	0.23 ± 0.18	−0.04 ± 0.43	0.081	0.002	0.777
AST (IU/L)	31.43 ± 13.52	28.67 ± 11.28	−2.76 ± 9.43	32.15 ± 15.05	33.75 ± 14.50	1.60 ± 11.61	2.521	0.062	0.121
ALT (IU/L)	32.05 ± 20.43	29.19 ± 19.56	−2.86 ± 9.13	41.30 ± 26.26	42.30 ± 26.10	1.00 ± 17.20	1.808	0.045	0.187
Total cholesterol (mg/dl)	202.05 ± 29.21	203.33 ± 23.32	1.29 ± 26.95	202.55 ± 32.38	199.20 ± 38.68	−3.35 ± 21.83	0.383	0.010	0.540
HDL cholesterol (mg/dl)	48.33 ± 5.32	49.57 ± 7.46	1.24 ± 6.20	53.05 ± 11.53	52.65 ± 12.10	−0.40 ± 5.99	0.335	0.009	0.566
Triglyceride (mg/dl)	144.67 ± 54.00	135.90 ± 61.40	−8.76 ± 36.09	159.70 ± 85.76	158.70 ± 97.21	−1.00 ± 55.76	0.357	0.009	0.554
LDL cholesterol (mg/dl)	124.78 ± 24.25	126.58 ± 19.15	1.80 ± 24.15	117.56 ± 31.72	114.81 ± 33.25	−2.75 ± 21.81	1.237	0.032	0.273
Glucose (mg/dl)	104.29 ± 18.46	104.19 ± 13.19	−0.10 ± 20.27	102.05 ± 21.30	110.95 ± 35.45	8.90 ± 23.26	1.623	0.040	0.210
Insulin (μU/mL)	12.80 ± 9.50	8.98 ± 5.31	−3.81 ± 8.46*	12.22 ± 10.09	16.95 ± 16.13	4.73 ± 13.03	6.632	0.145	0.014
HOMA-IR	3.38 ± 2.67	2.24 ± 1.17	−1.14 ± 2.51*	3.35 ± 3.41	5.58 ± 9.12	2.23 ± 7.03	4.312	0.100	0.044

Abbreviations: CRP, C-reactive protein; AST, aspartate aminotransferase; ALT, alanine aminotransferase. Values are mean ± SD.
P values correspond to between-group comparisons by using ANCOVA with baseline value as covariates.
*: $p < 0.05$ for within group comparison by paired *t*-test.

Discussion

In the present study, we found that 8 sessions of HF rTMS delivered to the left DLPFC produced clinically significant weight loss and improvements in insulin resistance. The results from this study suggest that rTMS may reduce cardiometabolic risks associated with obesity, and could be an effective treatment option for obesity.

Decreased food intake due to decreased appetite is the probable mechanism of weight loss by rTMS. In the present study, VAS measures for the subjective appetite revealed that the rTMS group showed the reduction in desire to eat and hunger sense compared to the sham group. These findings confirm and extend our previous observations of 2 weeks rTMS increasing the satiety [20]. Consistent with our finding, some previous studies have reported reduced food cravings by rTMS [17,29]. However, the effect of rTMS on food craving was inconsistent in randomized controlled studies; Barth et al. reported that prefrontal rTMS did not inhibit food cravings compared to sham stimulation [30]. In that study, however, the heterogeneity of study participants (several overweight or healthy lean participants were included) may have limited the sensitivity to detect differences in food craving. In addition, rTMS was administered at 100% of the motor threshold, whereas other studies have used rTMS at 110% MT. The effect of rTMS may depend on subtle differences in the parameters of stimulation, and the relatively weak stimulation power might lead to decreased effectiveness on food cravings by rTMS.

Although there is growing evidence for a significant reduction in acute food cravings following short-term rTMS [18,19], little is known regarding the effect of rTMS on body weight and food intake beyond immediate changes in food cravings. To our knowledge, only one randomized controlled trial has so far assessed the effects of multi-session rTMS on food consumption and body weight in obese populations; we previously examined the effects of high frequency (10 Hz) rTMS to the left dlPFC at a frequency of 2 times per week for 2 weeks on body weight in 60 obese individuals [20]. In previous 2-week trial, 4 sessions of rTMS produced average weight loss of 1.35 ± 2.31 kg/4 week. In the present study, we observed that treatment with the 8 sessions of rTMS reduced body weight by 2.75 ± 2.3 kg during 4 weeks, which is almost two times greater weight reduction when compared with our previous 2-week trial. Several methodological variations might have contributed to this difference in weight loss, including inter-train interval (55 s vs. 25 s), the number of stimuli per session (1000 pulses vs. 2000 pulses), and protocol (4 sessions vs. 8 sessions).

In rTMS treatment, one of the important considerations is the parameters of stimulation (i.e. number of stimulation sessions, frequency, intensity and site of stimulation). Although the ideal protocol of rTMS has yet to be established for obesity, the therapeutic benefit in addiction and eating disorder was found to be higher for a higher number of sessions or for a suprathreshold intensity (110–120% of resting motor threshold) [31,32]. The protocol of the present study was very close to that of our previous study, with 20-min sessions of 10 Hz rTMS of the left DLPFC at an intensity of 110% of the individual's motor threshold. However, the number of pulses and sessions (2000 pulses, 8 sessions) was higher than our previous study (1000 pulses, 4 sessions). One issue with rTMS-protocols is the question of whether the intensity of stimulation would affect the therapeutic response of rTMS. Regarding the intensity of stimulation, we used a suprathreshold intensity (110% of resting motor threshold), in line with most studies in the field of addictive disorders [31,33,34]. Another factor that might need to be considered is the number of sessions. Previously, we performed only 4 sessions of rTMS. However, increasing the total number of sessions might offer advantages as they might induce longer-lasting modulation of cortical excitability with cumulative effect. Thus, in this study, we investigated the effects of a higher dose of rTMS on weight loss, given the positive effects found in a previous

trial [20]. In agree with previous observations [32,35], eight rTMS sessions in this study appear to have a cumulative benefit for weight reduction, suggesting that the amount of weight loss might be dose dependent. Further refinement of the parameters of stimulation may have important impact on responses to rTMS in the management of obesity, as has been the case with TMS for other clinical conditions such as depressive disorders [36].

In the present study, daily caloric intake was decreased by approximately 260 kcal after the 8 sessions of rTMS. Moreover, differential analyses showed that this effect was mainly attributable to reduced carbohydrate intake, suggesting that rTMS may influence the preference for specific macronutrient beyond reducing appetite. These findings are in line with previous observations of transcranial direct current stimulation (tDCS) diminishing the desire to eat [37] as well as cravings for carbohydrates [38]. In contrast to our findings, Uher et al. concluded that the difference in subjective craving did not translate into differential food consumption after a single session of rTMS [29]. This inconsistency may be explained by the heterogeneity of study participants and the relatively short duration of this trial. Furthermore, the food intake preceding the study was not standardized, and there was no baseline measure of food intake.

For the changes in body composition, there was a significant reduction in waist circumference, fat mass and visceral adipose tissue after the 8 sessions of rTMS. These findings indicate that rTMS could be effective for improving the body composition and decreasing the risk for cardiovascular diseases in obese patients. Although skeletal muscle mass was decreased, it may have been related to a decrease in daily physical activity and the age of subjects; the majority of the participants were recruited during the winter, and relatively older subjects (who comprised the majority of the participants) might have tended to be less motivated to maintain physical activity during the winter weather. In fact, reports on seasonal variation of physical activity and body weight have been relatively consistent; at temperate latitudes, physical activity has been found to decrease in the winter [39].

Obesity increases the risk of cardiovascular disease, such as hypertension, diabetes, and hyperlipidemia. In the present study, we observed significant changes in glucose metabolism after rTMS; the mean values of fasting insulin concentration and HOMA-IR index were decreased in the TMS group, suggesting an improvement in insulin sensitivity. In contrast to the beneficial effects of rTMS on glucose metabolism, C-reactive protein and lipid profiles did not significantly change compared to the control group. A possible explanation for this negative finding could have been that the present study included mild obese patients with fairly normal C-reactive protein and lipid profiles. In addition, it seems possible that the duration of the study was too short to induce any effects on blood lipid profile.

The precise mechanisms for the reduced food intake and weight loss by rTMS are only partly understood, but rTMS may have an important role in the treatment of deranged eating behaviors by increasing cognitive control. In particular, the dorsolateral prefrontal cortex (dlPFC), has been consistently implicated as an important cortical node underlying both effortful self-control of eating behavior and dietary restraint [40,41]. Considering that excessive food cravings in obesity may be explained by decreased activation in the dorsolateral prefrontal area [11,42], resetting of reward thresholds may be a potential therapeutic options for treatment of obesity [14,43]. rTMS, as a type of non-invasive brain stimulation technique, was shown to decreases food cravings by modulating the neural networks closely related to eating behavior and obesity [9,18]. In fact, rTMS applied to the prefrontal cortex has been shown to increase dopamine excretion from the ventral tegmental area to striatum, which is associated with reward processing [44]. Interestingly, the result of our study showed that the mood states assessed by HADS questionnaire did not show any effect of rTMS on anxiety or depression. These findings suggest that the rTMS effect was specific to food craving and was not mediated by a reduction in an improvement in mood.

The present study has some limitations. First, we did not consider the menstrual cycle of female participants, although food cravings are highest during the premenstrual period. Second, given the small sample size in this preliminary study, the generalizability of our findings to larger populations of obese persons should be approached with caution. Third, sham stimulation in this study was given to the interhemispheric fissure on the vertex at 90° to the scalp with very low intensity. Although low intensity rTMS to the DLPFC might produce more similar scalp sensations of real stimulation, the possibility of unintentional cortical activation cannot be excluded [28]. Moreover, an effective sham might not need to feel identical to active TMS in order for TMS naïve participants to be blind to condition. All patients in this trial were naive to rTMS, and patient blinding was rigorous; most participants believed that they had received real stimulation after the completion of the study. Fourth, although we defined obesity as a BMI $\geq$25 kg/m^2 according to the obesity guideline for a Korean population [45], this BMI category is classified as overweight in other countries. This may have resulted in relatively lower VAS scores for appetite in this study. However, the subjective ratings of appetite are usually influenced by fasting duration rather than body weight; we assessed subjective sense of appetite in the 2-h fasted state, therefore there was a trend toward lower VAS at baseline compared with previous studies with longer fasting durations (>4 h) [46]. Fifth, several potential sources of bias need to be considered in interpreting our data. In the present study, while daily caloric intake was decreased by approximately 260 kcal after the 8 sessions of rTMS, the magnitude of weight loss was above what we expected: participants in this study showed a weight loss of about 1.51 pounds per week. In general, the clinical practice guidelines recommend calorie intake reductions of 500–1000 kcal/day, providing a weight loss of about 1–2 pounds per week [3]. A common preconception for this recommendation is that one pound of fat can produce 3500 kcal of calories, so a reduction of 500 kcal per day will result in approximately 1 pound of fat loss per week. However, this is the theoretical calculation for fat tissue loss and it is necessary to consider the additional loss of lean body mass. Another possible explanation for this discrepancy between estimated daily calorie intake and weight loss may be that self-reported dietary measures could have been subject to reporting biases. In particular, obese people are likely to underreport their dietary intake, which has been observed mainly in 24 h dietary recalls [47,48]. Indeed, participants of the present study appeared to have a daily caloric intake within normal range at baseline. In addition, 24-h dietary recall may not reflect daily variations in the nutrient intakes of the individual subjects. Although 3 non-consecutive days, including one weekend day or holiday are sufficient for 24-h recalls to assess dietary intake accurately [49], more than three days of records might better capture fluctuating intakes [50]. In addition to accuracy issues related to the measurement of food intake, weight change may have been confounded by uncontrolled factors such as physical activity. Lastly, although understanding the ideal stimulation target within the DLPFC may be important to improve the effectiveness of stimulation, the ideal stimulation location of rTMS has not yet been standardized for obese subjects. While most controlled rTMS studies on food craving and eating disorder targeted the right or left DLPFC at 5 cm anterior to the primary motor cortex, this “standard 5 cm method” does not account for structural and functional variations between individuals. Moreover, a function of specific parts of the DLPFC

remains still unclear, because the DLPFC is a large region, heterogenous in both cytoarchitecture and anatomical connectivity [51]. Thus, several studies on depression have proposed that more anterior and lateral site is more likely to be effective [52]. However, before proposing the clinical adoption of any other method for targeting the DLPFC, it is important to question whether we really understand the optimal site of stimulation. Previous studies applying rTMS in food craving and eating disorder demonstrated the evidence showing that 5 cm method is an acceptable option for targeting DLPFC [18,19,32]. Indeed, rTMS applied with functional imaging or a more anterior location for targeting the DLPFC did not show superior efficacy compared to the standard 5 cm method [53,54]. Furthermore, some studies reported an important role of the posterior part of the DLPFC (Brodmann Area 9) in obese subjects; the negative association of BMI and the body fat percentage with the metabolism of Brodmann Area 9 was shown in the obese subjects [55,56]. In addition, considering the relatively small head size in the Korean population [57], more posterior and medial site such as 5 cm method might have been the optimal option for targeting DLPFC. Until more research can reveal the optimally targeting location within the DLPFC, a conservative conclusion may be to target the traditionally used location. Therefore, stimulating the posterior areas of DLPFC by the standard 5 cm method would seem to be a logical and relatively practical choice in this perspective. However, we cannot rule out that the absence of neuronavigation for targeting the exact location of the DLPFC had an impact on our results. Even if we assume that the posterior part of DLPFC is the optimal stimulation target for obesity, further studies combining neuronavigation and functional imaging is necessary for more specific on the exact stimulation location within the DLPFC. Despite these limitations, our study design has strengths in allowing for an exact analysis of body composition and dietary intake. Moreover, we included healthy obese persons without eating disorders or psychiatric problems by performing a comprehensive clinical evaluation, providing robust evidence for the therapeutic use of rTMS in obesity. To date, our previous and the present studies are the only two studies applying rTMS in obese patients. Our results, in combination with previous work, support the use of rTMS as potential therapeutic options for body weight regulation. Further studies to evaluate the effect of various types of rTMS, including stimulation location, intensity, frequency, and duration, on weight reduction are needed to verify the improvements observed in the present study.

In summary, the current study demonstrated that rTMS was effective in inducing weight loss and decreasing food intake in obese patients. The observed magnitude of weight loss in the present study was greater than our previously published findings of 4 sessions rTMS [20]. Furthermore, the 8 sessions of rTMS were well tolerated, suggesting that further weight loss may be possible with continued rTMS. In light of the growing number of patients suffering from obesity, our data suggest that the implementation of rTMS for the treatment of obesity may be an effective and promising means of weight reduction.

Disclosure statement

The authors have nothing to disclose.

Conflicts of interest

None.

Acknowledgements

This research was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number: HI17C1234).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2019.07.020.

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