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Weight loss induced by deep transcranial magnetic stimulation in obesity: A randomized, double-blind, sham-controlled study

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Abstract

Aim: To test the hypothesis that deep transcranial magnetic stimulation (dTMS) reduces food craving and causes weight loss via neuromodulation.

Materials and methods: This pilot study was designed as a randomized, double-blind, sham-controlled study. A total of 33 obese people (nine men, 24 women, mean age 48.1 ± 10.6 years, body mass index [BMI] 36.9 ± 4.7 kg/m^2) were randomized and completed the study: 13 participants underwent a 5-week treatment with high-frequency (HF) dTMS (18 Hz; HF group), 10 were treated with low-frequency (LF) dTMS (1 Hz; LF group), and 10 were sham-treated (sham group). Food craving, and metabolic and neuro-endocrine variables were evaluated at baseline, after the 5-week treatment, and at follow-up visits (1 month, 6 months, 1 year after the end of treatment).

Results: The mixed-model analysis for repeated measures showed a significant interaction of time and groups for body weight ($P = 0.001$) and BMI ($P = 0.001$), with a significant body weight (−7.83 ± 2.28 kg; $P = 0.0009$) and BMI (−2.83 ± 0.83, $P = 0.0009$) decrease in the HF versus the sham group. A decreasing trend in food craving in the HF versus the LF and sham groups ($P = 0.073$) was observed. A significant improvement of metabolic and physical activity variables was found ($P < 0.05$) in the HF group.

Conclusions: We demonstrated the safety and efficacy of dTMS, in addition to physical exercise and a hypocaloric diet, in reducing body weight for up to 1 year in obese people. We hypothesize that a possible mechanism of HF dTMS treatment is modulation of the dopaminergic pathway and stimulation of physical activity.

KEYWORDS
appetite control, obesity therapy, randomised trial, weight control

1 | INTRODUCTION

Obesity has reached epidemic proportions, becoming a global health concern.[1,2] Current approaches to treating obesity include lifestyle interventions (diet and physical activity programmes), supported by psychological and behavioural interventions to overcome the clinical problems faced by obese people undergoing such dietary and exercise programmes (eg, the "yo-yo effect").[3] To improve patients' adherence,

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pharmacological treatment forms part of a comprehensive strategy for the management of obesity.[3] Currently, bariatric surgery represents the most effective treatment for morbid obesity in terms of long-term weight loss; however, this is considered a major surgical intervention that carries significant risk of peri-operative mortality.[4] In addition, the emergence or re-emergence after bariatric surgery of a binge-eating disorder, and the loss of eating control, can result in reduced weight loss and/or increased weight regain.[5]

Obesity is a heterogeneous condition not classified as an eating disorder, but which may be both a risk factor for, and a consequence of the latter. Considering several shared behavioural and neurobiological mechanisms, there is increasing interest in the conceptualization of disordered eating as craving for food. Several brain regions appear to be involved in the mechanisms of food craving. Neuroimaging studies in obesity showed a consistent lower postprandial activation in the dorsolateral prefrontal cortex (PFC), a sub-region of the PFC. This suggests a dysfunctional inhibitory control and decision-making ability over food consumption,[6] indicating that this brain region is a potential target for intervention in obesity.

Altered activities in the reward circuitry, similar to those found in drug addiction, have also been reported in obese individuals.[7] Several studies suggest that eating palatable food increases activation in reward regions and causes dopamine release in the dorsal striatum,[8] while in other studies reduced striatal dopamine D2 receptor availability,[9] and an inferior striatal responsivity to the taste of high-calorie beverages[10] were observed in obese adults compared to lean adults. This led to the hypothesis that obese people have lower sensitivity of dopamine-based regions of the brain and overeat to compensate for this deficiency.[9]

A complex and highly coordinated system of peripheral appetite hormones and centrally mediated neuronal regulation is also involved in body weight homeostasis.[11] Peptide hormones (eg, leptin, ghrelin, insulin) act in the central nervous system by affecting brain pathways that regulate food intake. Specific peptide hormone receptors (eg, leptin and insulin receptors) are expressed on dopaminergic neurons both in brain regions regulating "homeostatic hunger" (eg, the hypothalamus), and in the reward areas linked to "hedonic hunger" (eg, the substantia nigra and the ventral tegmental area [VTA]), releasing signals to the cortical, limbic and striatal regions involved in motivational and behavioural responses to the rewarding food stimuli.[12]

A methodology that was proven to be effective in inducing long-lasting changes in cortical excitability and dopamine release is repetitive transcranial magnetic stimulation (TMS),[13] a novel, non-invasive technique, based on the principle of electromagnetic induction.[14] When applied at a low frequency (LF; ≤ 1 Hz), TMS suppresses cortical excitability, while high-frequency (HF) TMS (≥5 Hz) enhances cortical excitability.[13] Repetitive TMS has been found to have therapeutic benefits for several neuropsychiatric disorders, and has recently been proposed as a potential treatment in addiction disorders.[15-17] To stimulate deep brain regions, Zangen et al[18] developed the H-coil. Compared to conventional coils, the H-coil contains an array of elements which are contoured to the shape of the skull, allowing deeper (up to 4.5–5.5 cm from the skull vs. 1.5 cm of the standard coils) and larger volumes of brain stimulation, affecting both cortical and subcortical regions. Promising results have been obtained by the application of deep TMS (dTMS) in reducing nicotine dependence,[19] alcohol craving[20,21] and cocaine abuse.[22] dTMS (H-coil) can generate an electric field which can penetrate the cortex up to 4 cm, noticeably increasing the penetration depth of the traditional TMS systems.[23]

Consistent with the dysregulation of the PFC inhibitory control and brain reward system in obese people and with the dTMS modulatory effect on the reward system, we hypothesized a potential role of repetitive dTMS in reducing food craving. The present pilot study was designed primarily to investigate the safety and the efficacy of a 5-week treatment with dTMS in reducing food craving and body weight in obese subjects, comparing HF (18 Hz) with LF (1 Hz) stimulation, and with sham treatment (primary outcome). Secondary aims of the study were to identify chronic modifications of neuro-endocrine pathways related to food craving in response to dTMS and to investigate chronic effects of dTMS treatment on metabolic variables and body energy homeostasis.

2 | MATERIALS AND METHODS

2.1 | Trial design

2.1.1 | Study setting

The present study was performed in the Endocrinology and Metabolic Diseases Department, of the *IRCCS Policlinico San Donato* (San Donato Milanese, Italy) and was a double-blind, sham-controlled, randomized clinical trial, designed to investigate the effects of 5 weeks' treatment with dTMS in reducing food craving and body weight in obese subjects, comparing HF with LF stimulation and with sham treatment. Additionally, we explored the chronic effects on neuroendocrine pathways related to appetite/satiety balance, metabolic variables and body energy homeostasis.

2.1.2 | Randomization and masking

Patients fulfilling all inclusion/exclusion criteria were randomized to one of three experimental groups: 18 Hz dTMS (HF group); 1 Hz dTMS (LF group) or sham treatment (sham group). The range of stimulatory (18 Hz) and inhibitory (1 Hz) frequencies were based on previous evidence in the literature on addiction disorders.[19,22] Participants were randomized in a 1:1:1 allocation ratio. The study design is shown in the Figure 1. Allocation to the three groups was performed according to a randomization sequence generated by a computer program. The randomization code was only given to the treating investigator at the first treatment session by an independent investigator not involved with any other aspect of the trial. The independent investigator could be contacted at any time to unblind the randomization code in the case of serious adverse events. Participants and other investigators were unaware of the type of treatment to which they were assigned. The magnetic stimulation coil for active and sham treatments (dTMS sessions) was the same. Magnetic cards encoding for real or sham stimulation were used to activate the dTMS device or not, according to the

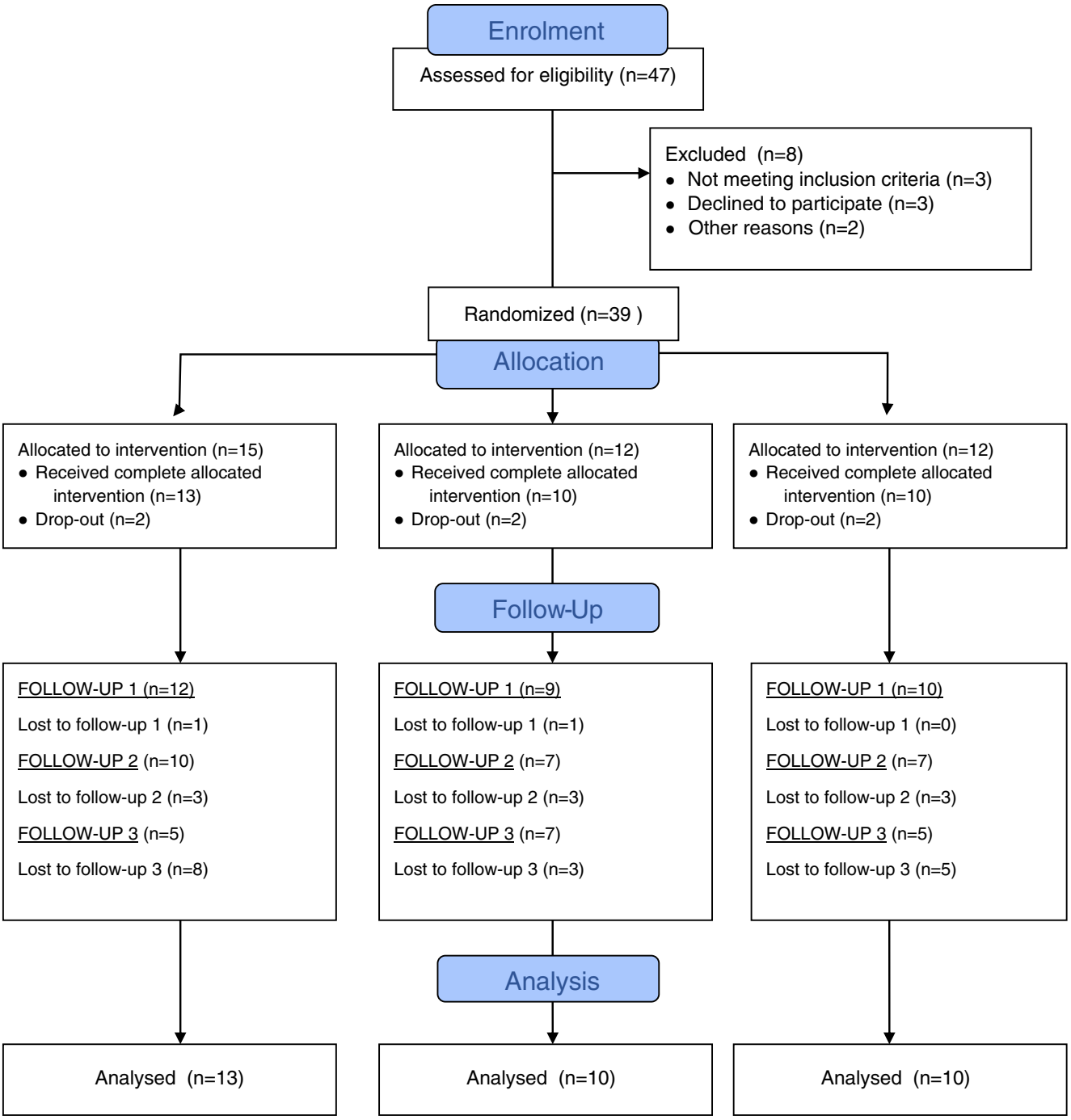

FIGURE 1 CONSORT diagram showing the flow of patients through each stage of the randomized, controlled trial

randomization sequence. Both real and sham stimulation produced identical sounds and scalp sensations during the sessions.

2.2 | Study approval

This study was conducted in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments; it received approval from the local institutional review board (Ethics Committee of San Raffaele Hospital, Milan, Italy). All participants provided written informed consent before participating in any study procedures. The trial was registered with ClinicalTrials.gov (NCT03009695).

2.3 | Study participants

Adult men and women (aged 22–65 years, inclusive), who were referred to the Endocrinology and Metabolic Diseases outpatient clinic for overweight/obesity treatment from January 2017 until July 2017, were screened by a short interview to determine eligibility. Patient recruitment strategy involved only direct interviews. No paper

or web advertisements were used. Inclusion and exclusion criteria are shown in Table 1.

2.4 | Intervention

Each participant received a total of 15 treatments, three times per week over 5 weeks (visits 1–15). Prior to stimulation, the obese participants were either shown a series of palatable food images (cue) or not (no cue). Participants were not administered any drugs or psychological or psychiatric therapy during the study period (1 year duration). dTMS was the only treatment allowed. Participants could discontinue the study treatment for no more than three non-consecutive dTMS sessions for a valid reason.

Follow-up visits were planned 1 month (FU1), 6 months (FU2), and 1 year (FU3) after the end of the treatment.

2.4.1 | Repetitive dTMS

The dTMS was performed by a trained physician using a Magstim Rapid^{2}TMS stimulator (Magstim Co. Ltd, Whitland, UK) equipped with an H-shaped coil (H-ADD), specifically designed to bilaterally stimulate the PFC and the insula.[18,24] This H-coil allows direct stimulation of deeper brain regions such as the insula (3 cm vs. 1.5 cm from the skull). Details of the stimulation procedure are reported in the Supporting Information in File S1.

2.4.2 | Diet and lifestyle recommendations

Throughout the entire study, all participants were prescribed a hypocaloric diet. Details of the diet prescription are provided in the Supporting Information in File S1. The participants were also instructed to engage in moderate-intensity physical activity (eg, 30 minute walking every day) during the study.

TABLE 1 Inclusion and exclusion criteria for participants

Inclusion criteria	Exclusion criteria
Age 22–65 years	Personal or a family history of seizures
BMI 30–45 kg/m^2	Psychotic and/or organic brain disorders
Willingness to reduce body weight	Implanted metal devices
	Fasting blood glucose level > 8.33 mmol/L
	Abuse of substances other than nicotine
	Weight variation (>3%) <3 months prior the screening visit
	Current or recent (<6 months prior the screening visit) treatment with anti-obesity medications or other medications for weight reduction
	Medications associated with lowered seizure threshold
	Type 1 diabetes or insulin-treated type 2 diabetes

Abbreviation: BMI, body mass index.

2.5 | Measurements

2.5.1 | Evaluation of food craving

The Food Craving Questionnaire-Trait (FCQ-T), a self-report inventory, was used to assess food craving.[25] It is a multidimensional questionnaire consisting of 39 items selected from the literature on addiction and eating disorders. The total score was considered for evaluation in this study. FCQ-T was administered at baseline, at the end of the 5-week treatment, and then at FU1, FU2, and FU3.

2.5.2 | Anthropometric values and blood pressure

Anthropometric measurements were recorded at baseline, at the last dTMS session (visit 15), and at FU1, FU2 and FU3. They included: body weight and height, to calculate body mass index (BMI; kg/m^2).

Systolic (SBP) and diastolic blood pressure (DBP) were measured at each dTMS session, and at the follow-up visits.

2.5.3 | Resting energy expenditure and respiratory quotient

Metabolism analysis was performed by measuring the resting energy expenditure (REE) and the respiratory quotient (RQ) with indirect calorimetry.[26,27] Indirect calorimetry was performed at baseline visit, at visit 15, and at FU2.

Details of indirect calorimetry procedure are reported in the Supporting Information in File S1.

2.5.4 | Activity energy expenditure

During the entire 5-week treatment period, participants underwent an evaluation of activity energy expenditure (AEE) using actigraph technology. Physical activity was recorded with accelerometers during the initial 5-week period. During the additional follow-up, it was monitored via phone calls. Details of the actigraph technology used are provided in the Supporting Information in File S1.

2.5.5 | Laboratory measurements

Blood tests were carried out at the first and last dTMS sessions, and at FU1, FU2 and FU3. The metabolite assessment included: glucose, glycated haemoglobin (HbA1c), cholesterol and triglycerides. The hormonal and neuroendocrine marker assessment included: insulin, leptin, total ghrelin, β-endorphins, epinephrine and norepinephrine. Details of laboratory measurement procedures are reported in the Supporting Information in File S1.

2.6 | Statistical methods

Descriptive statistics (means, SDs, counts and percentages) were used to describe the study populations. To evaluate the intervention effect on food craving, body weight and neuro-endocrine

variables related to appetite/satiety balance, repeated-measures regression models (PROC MIXED; SAS Institute) with type of treatment (between-participant factor with three levels), time (within-participant factor with five levels), and the respective interaction as independent variables, were used. Variables were reported as least squares means (±SE). Mixed modelling is a useful tool for analysing repeated measures over time, and a main advantage is its ability to retain cases with missing data points. A post hoc *t*-test comparing the variation of the investigated variables at 1 year, when the interaction is significant, has been evaluated. Specifically, we evaluated if there was a significant difference between treatments when comparing the change from baseline: (FU3 – baseline) in the HF versus the sham group, and in the LF group versus the sham group. A Bonferroni adjustment for multiple testing was considered as 17 variables were investigated.

The Kolmogorov–Smirnov test was used to check if the sample distributions were normal. Whenever the variables did not meet the normality assumptions, a log transformation was successful in normalizing the data.

Changes in median concentrations (from baseline to 5 weeks of treatment) of physical activity variables in the three experimental groups were analysed using the non-parametric Kruskal–Wallis test. For body weight and BMI a simple analysis of variance (ANOVA) to evaluate the difference among groups when considering the change at 1 year from baseline, was performed.

Statistical analysis was performed using SAS version 9.4 (SAS Institute, Cary, North Carolina). A two-sided *P* value ≤0.05 was deemed to be statistically significant.

3 | RESULTS

3.1 | Participant characteristics

Out of the 39 initially randomized participants (15 in the HF, 12 in the LF and 12 in the sham group), 33 completed the study as per protocol. Six participants dropped out from the study and were excluded from the statistical analysis. The mean age of the analysed sample group was 48.1 ± 10.6 years and the mean BMI was 36.9 ± 4.7 kg/m^2. Of these 33 participants, 13 were allocated to the HF group, 10 to the LF group, and 10 to the sham group.

Thirty-one of the 33 participants underwent FU1; 24 underwent FU2; 17 underwent FU3 (Figure 1).

Baseline characteristics for the three groups are reported in Table 2. At baseline, no significant differences were observed for the examined variables between the three groups (*P* > 0.05).

3.2 | Drop-out rate

Of the 39 enrolled participants, six dropped out from the study: four decided to withdraw from the study for personal reasons other than side effects (HF group, n = 1; LF group, n = 1; sham group, n = 2), one participant (LF group) accidentally fell, reporting a shoulder fracture, and only one participant (HF group) discontinued the treatment for a possible treatment side effect (high blood pressure). These participants were excluded from the statistical analysis because of missing outcome data.

3.3 | Food craving

Figure 2A illustrates the FCQ-T score levels in the three treatment groups over time throughout the treatment period. The mixed-model analysis revealed a trend toward a significant interaction between intervention group and time (*P* = 0.073). At 1 year of follow-up there was a decrease in FCQ-T score in the HF group (120.7 ± 10 at baseline vs. 81.8 ± 12.7, at 1 year).

3.4 | Body weight and BMI

Mixed-model analyses showed a significant interaction between intervention group and time for body weight and BMI (*P* = 0.001; Figure 2B,C).

At the end of the follow-up, there was a significant decrease in body weight and BMI in the HF group (103.6 ± 4.2 kg at baseline vs. 94.9 ± 4.4 kg after 1 year for body weight [difference − 7.83, *P* = 0.0009], and 36.8 ± 1.0 at baseline vs. 33.6 ± 1.4 at 1 year for BMI [difference − 2.83, *P* = 0.0009]).

Cohen's d, evaluated using a one-way ANOVA model, was 0.21 (95% confidence interval 0.00–0.55) for weight and 0.22 (95% confidence interval 0.00–0.55) for BMI.

No significant differences between cue and no cue subgroups was found in either food craving or body weight variations (*P* > 0.05).

3.5 | REE and RQ

With regard to the metabolic variables evaluated by indirect calorimetry (Table 3), the mixed-model analysis revealed a trend toward a significant interaction between intervention group and time for RQ (*P* = 0.061), but no interaction was shown for REE (*P* = 0.279).

3.6 | Blood pressure

No significant differences in SBP over time between treatment groups were found (*P* = 0.236). The mixed-model analysis revealed a trend interaction between intervention group and time for DBP (*P* = 0.079; Table 3).

3.7 | Activity energy expenditure

Of the 33 enrolled participants, 28 (HF group, n = 12; LF group, n = 8; sham group, n = 8) underwent an evaluation of the AEE during the 5 weeks of treatment. A significant increase in AEE was found in the HF group compared to other groups (*P* = 0.049). Consequently, in the same group, a trend toward an increase in TEE was observed (*P* = 0.078). After 5 weeks of treatment, a trend toward an increase

TABLE 2 Baseline characteristics of participants, stratified by study group

Characteristic	HF dTMS group	LF dTMS group	Sham treatment group
	n = 13	n = 10	n = 10
Women, n (%)	8 (33.33)	7 (29.17)	9 (37.5)
Age, years	47.46 ± 10.13	46.50 ± 11.73	50.60 ± 10.52
FCQ-T score	120.69 ± 38.05	115.50 ± 44.99	106.7 ± 32.23
BMI, kg/m^2	36.78 ± 5.24	37.51 ± 5.92	36.33 ± 2.12
Body weight, kg	103.61 ± 17.21	102.61 ± 17.35	97.38 ± 8.19
SBP, mmHg	122.55 ± 13.34	118.33 ± 19.36	124.00 ± 8.43
DBP, mmHg	80.33 ± 8.21	75.00 ± 15.00	76.50 ± 11.07
Glucose, mmol/L	5.28 (4.28–6.11)	4.83 (4.56–6.61)	4.58 (4.5–4.89)
Insulin, pmol/L	119.3 (72.7–280.5)	158.4 (94.9–210.8)	90.8 (65.8–92.6)
HbA1c, mmol/mol	37 (34–40.50)	37 (33–38)	32.5 (32–34.5)
Triglycerides, mmol/L	1.4 (1.04–2.08)	1.75 (1.24–3.18)	1.23 (1.06–1.54)
Cholesterol, mmol/L	5.26 ± 0.98	5.32 ± 1.46	4.95 ± 0.47
Leptin, μg/L	72.49 (45.49–87.52)	72.44 (20.9–127.59)	59.47 (22.3–77.95)
Epinephrine, pmol/L	2886.45 (705.95–4852.06)	4040.55(3277.07–5063.74)	2719.42 (1126.63–4901.19)
Ghrelin, pmol/L	1924 (1408.9–306.9)	3152.4 (2693.6–5624)	1681.3 (1006.4–2859.4)
Norepinephrine, nmol/L	25.44 ± 10.32	28.86 ± 15.3	20.4 ± 14.64
β-endorphin, ng/mL	0.45 (0.33–0.52)	0.48 (0.34–0.59)	0.48 (0.43–0.52)
RQ	0.88 ± 0.05	0.88 ± 0.06	0.86 ± 0.06
REE	0.96 ± 0.13	0.93 ± 0.12	0.92 ± 0.12
TEE, kcal/d	2006.00 (1865.5–2315.0)	2107.50 (1946.0–2241.0)	1890.50 (1778.0–1921.0)
AEE, kcal/d	273.50 (153–284)	224.50 (169–298)	242.50 (156–315.5)
METs	1.55 (1.40–1.75)	1.45 (1.30–1.75)	1.60 (1.45–1.85)
Steps/d	6743.5 (3543.50–7547.50)	5013.5 (3829.00–8070.50)	6004.5 (3934–8055.5)
Distance, km/d	4.25 (2.55–4.95)	3.60 (2.70–5.35)	4.25 (2.65–5.4)

Data are mean ± SD, number (%) or median (Q1–Q3).
Abbreviations: AEE, activity energy expenditure; BMI, body mass index; DBP, diastolic blood pressure; dTMS, deep transcranial magnetic stimulation; FCQ-T, Food Cravings Questionnaire-Trait; HF, high frequency; LF, low frequency; MET, metabolic equivalent of task; REE, resting energy expenditure; RQ, respiratory quotient; SBP, systolic blood pressure; TEE, total energy expenditure.

was observed in the HF group for metabolic equivalent of tasks (METs), steps, and travelled kilometres (Table S1 and Figure S1).

3.8 | Metabolic and neuro-endocrine assessments

Chronic variations of laboratory measurements are presented in Table 3.

With regard to neuroendocrine markers, a significant effect of interaction between intervention group and time on logarithmized leptin (Figure 2D; $P = 0.002$) and on logarithmized epinephrine (Figure S2; $P = 0.004$) was found, with a significant change in the HF vs. sham group (difference = −1.11, $P = 0.0014$ and 1.44, $P = 0.0020$, respectively). The mixed-model analysis showed a trend effect of time by group interaction on β-endorphin ($P = 0.078$; Figure S3).

As to metabolic variables, the same analysis revealed a borderline significant time by group interaction on logarithmized HbA1c ($P = 0.007$; Figure S4).

3.9 | Adverse events and safety

No serious or severe side effects were observed. Participants in the HF group experienced more frequent headaches (6/13) than those in the LF (4/10) and sham groups (3/10). This side effect resolved spontaneously within 1 to 2 days from the beginning of treatment. There were no significant differences among the groups in the frequency and intensity of other adverse events: drowsiness (HF group, 2/13; LF group, 4/10; sham group, 1/10), neck pain (HF group, 2/13; LF group, 1/10; sham group, 2/10), temporary hypertension (HF group, 1/13; LF group, 1/10; sham group, 1/10). Only one participant enrolled in the HF group discontinued the treatment because of high blood pressure.

4 | DISCUSSION

This is the first clinical pilot study using dTMS in obese people that demonstrates a decrease in body weight with an indication for a long-

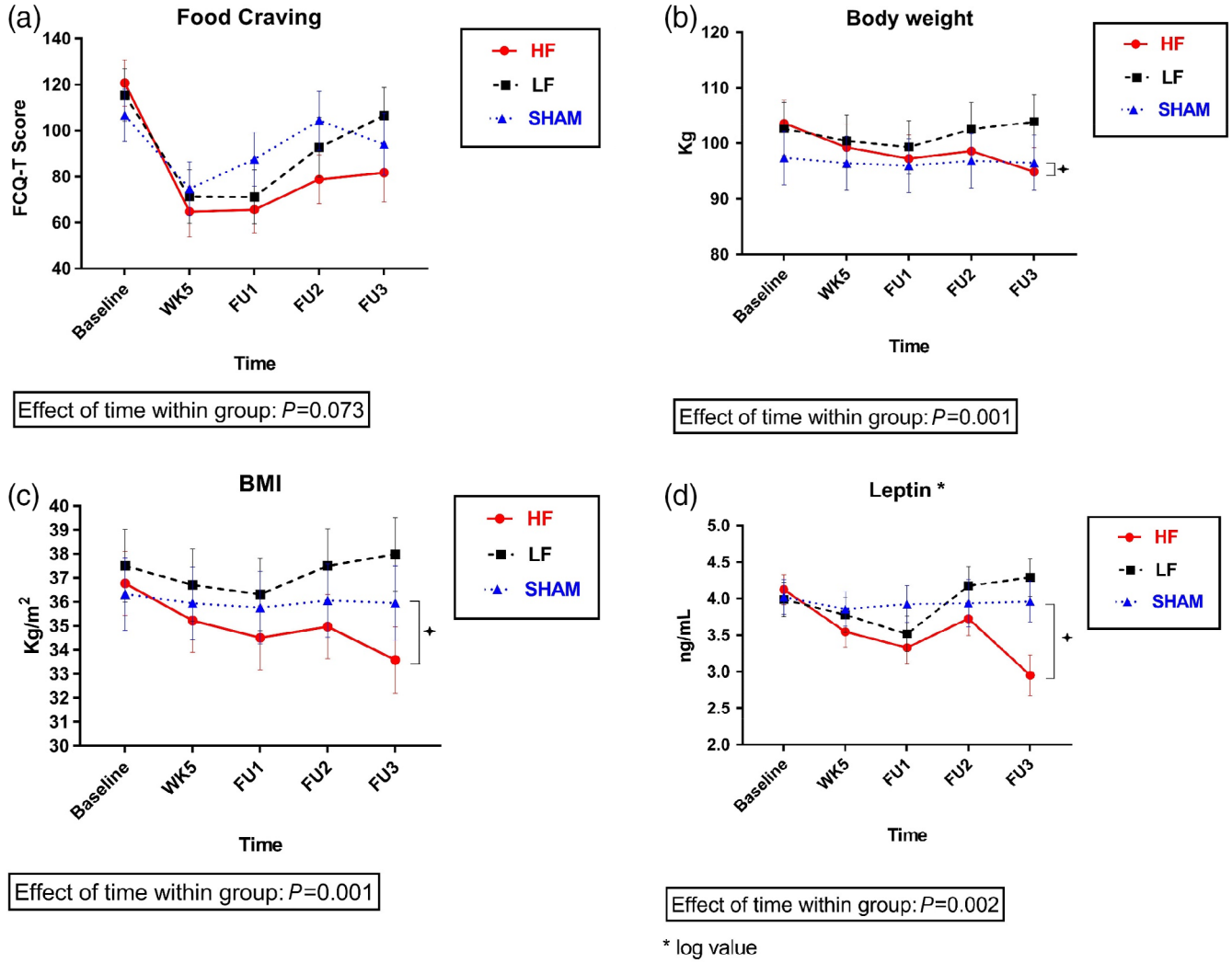

FIGURE 2 Effects of deep transcranial magnetic stimulation (dTMS) on food craving, body weight, body mass index (BMI) and leptin levels in the three groups during the treatment and follow-up period. A, Food craving, evaluated by the Food Cravings Questionnaire-Trait (FCQ-T), in the three treatment groups over time throughout the treatment and follow-up period. A trend interaction between intervention group and time on food craving was revealed by the mixed-model analysis (P = 0.073). B, Body weight and C, BMI in the three treatment groups over time throughout the treatment and follow-up period. At baseline, no significant differences were observed between the three groups for either body weight or BMI (P > 0.05). Mixed-model analyses showed a significant interaction between intervention group and time for body weight and BMI (P = 0.001). D, Leptin levels in the three treatment groups over time throughout the treatment and follow-up period. Mixed-model analysis showed a significant interaction between intervention group and time for leptin (P = 0.002). Leptin is expressed as logarithmised values. + The symbol shows if there is a significant difference between groups when comparing the change from baseline: (FU3 – baseline) in group HF vs sham, (FU3 – baseline) in group LF vs sham. Abbreviations: FU, follow-up; HF, high-frequency treatment group; LF, low-frequency treatment group; SHAM, sham treatment group; WK5, week 5

lasting weight control effect (up to 1 year). This effect occurred in participants receiving a total or 15 sessions over 5 weeks of HF stimulation. Several mechanisms could be involved in the pronounced weight-lowering effects produced by the HF stimulation.

The first mechanism is an effect on the PFC, which is centrally implicated in inhibitory control processes and linked to self-control in the dietary context. In fact, an impaired activation of PFC, specifically of the left dorsolateral PFC, has been reported in response to a meal in obese individuals.[28] This suggests a weakened ability to control feeding behaviour. Our findings build on previous evidence that excitatory stimulation of the dorsolateral PFC via repetitive TMS enhances its inhibitory capacity and thereby alters habits in both substance- and food-addicted subjects.[28] Currently, excitatory repetitive TMS, targeting the left dorsolateral PFC, has been found to be effective in reliably reducing food cravings.[29,30] However, changes in food intake have been inconsistent with a single session of repetitive TMS. Application of multi-session repetitive TMS to eating disorders has also yielded promising, but ultimately controversial, results, especially in relation to bulimia nervosa and binge-eating disorder.[31] In the present study neuromodulation was specifically applied to obese subjects for the first time, and was performed by dTMS (H-coil),

TABLE 3 Effects of treatment on dependent variables over time assessed by a mixed-modelling approach

BMI						*P*			FCQ-T score						*P*		
	Baseline	Wk 5	FU1	FU2	FU3	Time × group	Post hoc	STD effect		Baseline	Wk 5	FU1	FU2	FU3	Time × group	Post hoc	STD effect
HF	36.78 ± 1.32	35.23 ± 1.32	34.51 ± 1.33	34.98 ± 1.34	33.58 ± 1.39		−2.83 ± 0.83 p = 0.0009	−3.41	HF	120.69 ± 9.99	64.86 ± 10.87	65.71 ± 10.17	78.89 ± 10.61	81.83 ± 12.72		−26.32 ± 15.97	−1.65
LF	37.51 ± 1.51	36.71 ± 1.51	36.32 ± 1.51	37.51 ± 1.53	37.99 ± 1.53	**0.001(*)**	0.85 ± 0.79 p = 0.2862	1.08	LF	115.5 ± 11.39	71.36 ± 11.71	71.25 ± 11.71	92.75 ± 12.85	106.5 ± 12.39	**0.073**	3.54 ± 15.34	0.23
Sham	36.33 ± 1.51	35.95 ± 1.51	35.78 ± 1.51	36.07 ± 1.53	35.97 ± 1.55		REF		Sham	106.7 ± 11.39	74.83 ± 11.71	87.61 ± 11.71	104.45 ± 12.87	94.16 ± 13.49		REF	
Body weight						*P*			Glucose[a]						*P*		
	Baseline	Wk 5	FU1	FU2	FU3	Time × group	Post hoc	STD effect		Baseline	Wk 5	FU1	FU2	FU3	Time × group	Post hoc	STD effect
HF	103.60 ± 4.23	99.26 ± 4.23	97.22 ± 4.24	98.59 ± 4.26	94.89 ± 4.38		−7.83 ± 2.28 p = 0.0009	−3.43	HF	4.53 ± 0.05	4.51 ± 0.05	4.52 ± 0.05	4.52 ± 0.06	4.56 ± 0.06		0.04 ± 0.07	0.57
LF	102.61 ± 4.82	100.40 ± 4.82	99.32 ± 4.83	102.51 ± 4.87	103.92 ± 4.87	**0.001(*)**	2.20 ± 2.19 p = 0.3152	1.00	LF	4.61 ± 0.06	4.53 ± 0.06	4.61 ± 0.06	4.55 ± 0.06	4.67 ± 0.06	**0.745**	0.06 ± 0.07	0.86
Sham	97.38 ± 4.82	96.40 ± 4.82	95.97 ± 4.82	96.86 ± 4.87	96.49 ± 4.93		REF		Sham	4.47 ± 0.06	4.45 ± 0.06	4.46 ± 0.06	4.44 ± 0.07	4.47 ± 0.07		REF	
Insulin[a]						*P*			HbA1c[a]						*P*		
	Baseline	Wk 5	FU1	FU2	FU3	Time × group	Post hoc	STD effect		Baseline	Wk 5	FU1	FU2	FU3	Time × group	Post hoc	STD effect
HF	2.90 ± 0.20	2.51 ± 0.20	2.61 ± 0.20	2.78 ± 0.21	3.08 ± 0.24		0.43 ± 0.28	1.54	HF	3.64 ± 0.05	3.57 ± 0.05	3.54 ± 0.05	3.56 ± 0.05	3.55 ± 0.05		−0.03 ± 0.06	−0.05
LF	3.12 ± 0.22	2.79 ± 0.22	2.82 ± 0.23	2.98 ± 0.24	3.10 ± 0.24	**0.761**	0.24 ± 0.27	0.88	LF	3.58 ± 0.06	3.59 ± 0.06	3.59 ± 0.06	3.59 ± 0.06	3.73 ± 0.06	**0.007**	0.21 ± 0.06	3.5
Sham	2.70 ± 0.23	2.46 ± 0.22	2.47 ± 0.23	2.43 ± 0.26	2.45 ± 0.26		REF		Sham	3.55 ± 0.05	3.51 ± 0.05	3.54 ± 0.06	3.49 ± 0.07	3.49 ± 0.06		REF	
Triglycerides[a]						*P*			Cholesterol						*P*		
	Baseline	Wk 5	FU1	FU2	FU3	Time × group	Post hoc	STD effect		Baseline	Wk 5	FU1	FU2	FU3	Time × group	Post hoc	STD effect
HF	4.89 ± 0.15	4.81 ± 0.15	4.88 ± 0.15	4.95 ± 0.16	4.99 ± 0.19		0.02 ± 0.24	0.08	HF	5.27 ± 2.27	5.01 ± 2.7	5.2 ± 2.75	5.56 ± 2.92	5.24 ± 3.4		−3.26 ± 16.25	−0.20
LF	5.04 ± 0.17	4.80 ± 0.17	4.65 ± 0.17	4.79 ± 0.18	4.98 ± 0.18	**0.572**	−0.13 ± 0.23	−0.56	LF	5.33 ± 3.08	4.63 ± 3.08	4.98 ± 3.15	5.02 ± 3.33	5.09 ± 3.33	**0.753**	−11.26 ± 15.59	−0.73
Sham	4.70 ± 0.17	4.72 ± 0.17	4.68 ± 0.17	4.77 ± 0.19	4.78 ± 0.20		REF		Sham	4.96 ± 3.08	4.57 ± 3.08	4.81 ± 3.15	4.72 ± 3.45	5.01 ± 3.61		REF	
SBP						*P*			DBP						*P*		
	Baseline	Wk 5	FU1	FU2	FU3	Time × group	Post hoc	STD effect		Baseline	Wk 5	FU1	FU2	FU3	Time × group	Post hoc	STD effect
HF	122.0 ± 3.74	117.31 ± 3.67	117.22 ± 3.75	123.35 ± 4.71	120.77 ± 5.03		3.78 ± 7.06	0.53	HF	80.52 ± 2.82	76.15 ± 2.76	78.94 ± 2.82	82.44 ± 3.56	80.35 ± 3.81		−1.85 ± 5.39	−0.34
LF	118.07 ± 4.30	112.23 ± 4.30	114.7 ± 4.90	129.55 ± 5.22	127.23 ± 4.90	**0.2359**	14.17 ± 6.97	2.03	LF	74.80 ± 3.24	70.38 ± 3.24	71.37 ± 3.70	82.45 ± 3.95	83.96 ± 3.70	**0.0794**	7.48 ± 5.32	1.41
Sham	124 ± 4.17	112.53 ± 4.33	116.28 ± 4.68	116.23 ± 5.23	118.99 ± 5.23		REF		Sham	76.5 ± 3.14	76.63 ± 3.24	77.60 ± 3.52	72.44 ± 3.94	78.18 ± 3.95		REF	
Leptin[a]						*P*			Ghrelin[a]						*P*		
	Baseline	Wk 5	FU1	FU2	FU3	Time × group	Post hoc	STD effect		Baseline	Wk 5	FU1	FU2	FU3	Time × group	Post hoc	STD effect
HF	4.13 ± 0.21	3.55 ± 0.21	3.33 ± 0.22	3.73 ± 0.23	2.95 ± 0.28		−1.11 ± 0.33 p = 0.0014	−3.36	HF	1.97 ± 0.24	2.10 ± 0.26	2.28 ± 0.27	2.50 ± 0.28	2.17 ± 0.35		−0.08 ± 0.56	−0.14
LF	3.99 ± 0.24	3.78 ± 0.24	3.52 ± 0.24	4.18 ± 0.27	4.30 ± 0.26	**0.002(*)**	0.36 ± 0.31	1.16	LF	2.42 ± 0.26	1.97 ± 0.26	2.44 ± 0.27	1.59 ± 0.33	2.12 ± 0.30	**0.286**	0.57 ± 0.54	1.06

(Continues)

TABLE 3 (Continued)

BMI						*P*			FCQ-T score						*P*		
	Baseline	**Wk 5**	**FU1**	**FU2**	**FU3**	**Time × group**	**Post hoc**	**STD effect**		**Baseline**	**Wk 5**	**FU1**	**FU2**	**FU3**	**Time × group**	**Post hoc**	**STD effect**
							p = 0.2440										
Sham	4.02 ± 0.24	3.86 ± 0.24	3.93 ± 0.25	3.94 ± 0.32	3.96 ± 0.28		REF		Sham	1.83 ± 0.26	2.03 ± 0.26	2.38 ± 0.27	2.43 ± 0.35	2.10 ± 0.35		REF	
Epinephrine[a]						*P*			Norepinephrine						*P*		
	Baseline	**Wk 5**	**FU1**	**FU2**	**FU3**	**Time × group**	**Post hoc**	**STD effect**		**Baseline**	**Wk 5**	**FU1**	**FU2**	**FU3**	**Time × group**	**Post hoc**	**STD effect**
HF	5.99 ± 0.29	6.16 ± 0.29	6.44 ± 0.30	6.09 ± 0.32	6.66 ± 0.38		1.44 ± 0.45 p = 0.0020	3.2	HF	25.44 ± 5.28	20.64 ± 5.28	21.36 ± 5.58	16.68 ± 6.24	18.12 ± 8.04		−0.64 ± 1.83	−0.35
LF	6.52 ± 0.33	6.37 ± 0.33	6.44 ± 0.33	6.69 ± 0.35	5.37 ± 0.35	**0.004**	−0.37 ± 0.41 p = 0.3780	−0.90	LF	28.86 ± 6.06	25.2 ± 6.06	31.86 ± 6.24	22.68 ± 6.78	10.32 ± 7.62	**0.178**	−2.51 ± 1.77	−1.42
Sham	6.14 ± 0.33	6.43 ± 0.33	6.50 ± 0.34	6.23 ± 0.41	5.37 ± 0.38		REF		Sham	20.4 ± 6.06	21.96 ± 6.24	41.46 ± 6.54	24.12 ± 8.34	16.92 ± 7.68		REF	
β-Endorphin[a]						*P*											
	Baseline	**Wk 5**	**FU1**	**FU2**	**FU3**	**Time × group**	**Post hoc**	**STD effect**									
HF	−0.85 ± 0.13	−0.90 ± 0.13	−0.70 ± 0.13	−0.66 ± 0.15	−0.10 ± 0.18		0.56 ± 0.22	2.54									
LF	−0.76 ± 0.15	−0.89 ± 0.15	−0.87 ± 0.15	−0.57 ± 0.16	−0.56 ± 0.16	**0.078**	−0.00 ± 0.20	0.00									
Sham	−0.73 ± 0.15	−0.77 ± 0.15	−0.48 ± 0.15	−0.54 ± 0.17	−0.54 ± 0.17		REF										
RQ				*P*					REE				*P*				
	Baseline	**Wk 5**	**FU2**	**Time × group**	**Post hoc**	**STD effect**				**Baseline**	**Wk 5**	**FU2**	**Time × group**	**Post hoc**	**STD effect**		
HF	0.88 ± 0.02	0.82 ± 0.02	0.90 ± 0.02		0.01 ± 0.04	0.25			HF	0.96 ± 0.03	0.85 ± 0.03	0.94 ± 0.04		0.02 ± 0.06	0.33		
LF	0.88 ± 0.018	0.82 ± 0.02	0.90 ± 0.02	**0.061**	0.01 ± 0.04	0.25			LF	0.93 ± 0.04	0.88 ± 0.04	0.90 ± 0.04	**0.279**	0.12 ± 0.06	2		
Sham	0.86 ± 0.02	0.88 ± 0.02	0.87 ± 0.02		REF				Sham	0.92 ± 0.04	0.92 ± 0.04	0.89 ± 0.05		REF			

A mixed-modelling approach was used to assess the effect of treatment on dependent variable over time [5-week (WK5), 1 month (FU1), 6 months (FU2), and 1 year (FU3)]. Data are expressed with LS means ± SD. P-values for the interaction of time with treatment groups (time*group), and for the difference between HF or LF vs Sham after 1 year compared to baseline (post-hoc) are reported only when the interaction was statistically significant. After Bonferroni correction, $P < 0.0029$ was deemed to be statistically significant (*).

Standardized mean difference scores for all comparisons are reported (STD effect).

Abbreviations: AEE, activity energy expenditure; BMI, body mass index; DBP, diastolic blood pressure; dTMS, deep transcranial magnetic stimulation; FCQ-T, Food Cravings Questionnaire-Trait; FU, follow-up; HbA1c, glycated haemoglobin; HF, high frequency; LF, low frequency; REE, resting energy expenditure; REF, reference; RQ, respiratory quotient; SBP, systolic blood pressure.

[a]Log-transformed variable.

increasing the penetration depth of the traditional TMS systems used in the previous studies.[23]

An additional pathway, potentially explaining the therapeutic effect of HF dTMS in obesity, is modulation of the cortico-mesolimbic dopamine system, or "reward system", which is implicated in the regulation of hedonic eating behaviour.[32] In fact, dopamine signalling is involved in the "wanting" or desire for certain types of food, which underlies food craving.[33]

Considering its prominent role in interpreting internal and external cues, the insula is increasingly recognized as being a critical neural substrate for both drug and food addiction by mediating cue reactivity and processes related to decision-making[34]; therefore, modulating the insular cortex function was considered a novel therapeutic strategy to treat addiction. This was made possible by the advent of the H-coil, targeting deeper brain structures, which was not previously feasible. A previous study targeting dTMS to the PFC and insula bilaterally demonstrated the efficacy of HF stimulation in reducing nicotine addiction.[19] The activation of deeper brain regions can take place directly or indirectly; namely, mediated by activation of dorsolateral PFC.

The number of human studies using repetitive TMS to manipulate craving is growing.[35] In the present study, an enduring decreasing trend in food craving was observed in the HF group compared to the other two groups, although the interaction effect between time and treatment was found to be more pronounced on body weight. Food craving is influenced not only by the intended experimental intervention, but also by environmental context, individual's psychological state (including mood, focus of attention and expectancy), and treatment-seeking status.[36] Furthermore, food craving evaluation was performed by using a self-administered questionnaire; although the FCQ-T is considered a reliable tool to detect food craving, like almost all self-reported questionnaires, it is a subjective measurement and could be influenced by several variables.

A more pronounced decrease in leptin levels was found in the HF group compared with the other two groups. Leptin is a peptide hormone produced by adipocytes in proportion to their triglyceride content; leptin plasma levels link changes in fat stores to adaptive responses in the central control of energy balance, and correlate with adipose tissue amount. Leptin receptors are expressed on dopaminergic neurons both in brain regions regulating "homeostatic hunger" (e.g. hypothalamus) and in areas of the reward network linked to "hedonic hunger" (eg, the substantia nigra and VTA). A neuroimaging study highlighted that higher plasma leptin levels correlate with hyper-responsiveness of reward brain areas to high-calorie food cues in obesity, suggesting that dysfunctional leptin signalling may lead to overconsumption of these foods.[12] A potential relationship between plasma leptin concentrations and craving was also recently reported in cocaine-addicted subjects.[37] The leptin reduction observed in the HF group indicates that dTMS could exert control on food craving also via the modulation of neuro-endocrine pathways.

In addition to dopamine, endogenous opioid compounds are also involved in the "reward system", mainly in the pleasurable feeling ("liking") associated with the food rewarding stimuli.[29] Particularly, the β-endorphins secreted by the proopiomelanocortin neurons in the hypothalamic arcuate nucleus, inhibit further proopiomelanocortin activation, leading to a decreased appetite and increased energy expenditure.[32] In this study, a trend toward a significant interaction effect was found between time and treatment on β-endorphin level. The increase in β-endorphins during the 1-year study period with HF dTMS are in line with our recent work, demonstrating that HF dTMS acutely increases β-endorphins.[38]

Finally, we found a significant and enduring effect of HF dTMS in increasing epinephrine. Few studies have investigated the modulation produced by repetitive TMS on the sympathetic nervous system. In animal behavioural models of depression, repetitive TMS of the brain was found to significantly upregulate β-adrenergic receptors in the frontal cortex, after only 10 days of treatment,[39] suggesting a possible involvement of the adrenergic system in the mechanisms of action of the dTMS. A dysregulation of the autonomic nervous system also plays a role in the pathophysiology of obesity, being involved in the modulation of the appetite/satiety signal and energy expenditure.[40] On one hand, the observed increase of epinephrine after 5 weeks of HF dTMS in obese people could affect the food craving associated with obesity, although the underlying mechanisms of action need to be clarified. On the other hand, the stimulation of the sympathetic system plays a role in increasing physical activity. Physical activity is normally lacking in obese people. Nonetheless a lifestyle intervention beyond dietary counselling is mandatory to achieve and maintain weight reduction. Voluntary contractions of skeletal muscle fibres are regulated by effective cortical areas, including motor areas and the PFC. Sympathetic activation increases frequency, intensity and strength of skeletal muscle contractile activity.[41] Intracerebral administration of dopamine agonists,[42] or of dopamine antagonists[43] respectively activates and inhibits locomotor activity in rats. More recently, Beeler et al[44] demonstrated in the D2R knockdown mouse model that low dopamine D2 receptor increases vulnerability to obesity via reduced physical activity rather than via increased appetitive motivation. Our present data demonstrate that HF dTMS increases locomotor activity over a 5-week period. Since several reports suggested that HF dTMS increases the concentration of endogenous dopamine in the striatum,[33] and in the Broadmann area 11 of the medial orbitofrontal cortex,[44] it is conceivable that at least part of the weight-lowering effect of our treatment was related to direct activation of locomotor activity in the obese participants. In addition, the observed increase of epinephrine after 5 weeks of HF dTMS treatment suggests a role of stimulation-induced sympathetic system activation in increasing physical activity.

The reduction in HbA1c levels during the 1-year study period in the HF group is interesting. At present, the most likely explanation for HbA1c reduction is related to the decrease in body weight. Future studies are needed to directly assess a potential role of TMS in the treatment of type 2 diabetes.

The present study has some limitations. The low number of obese people enrolled did not allow us to adjust the analysis for possible confounding factors, for example, for the cue/no-cue information. In addition, the loss to follow-up led to missing outcome data, which did

not allow us to perform a proper intention-to-treat analysis. Although statistical significance was reached for the main outcomes, the effect size, when calculated for this study population, was small to moderate. Future multicentre studies are needed to confirm the findings of this pilot study.

In conclusion, the present study indicates that HF dTMS over the lateral PFC and insula reduces body weight, with significant and long-lasting effects via several mechanisms. It is conceivable that the main mechanism is the increased dopaminergic activity in the mesolimbic and mesostriatal pathways. Our data suggest a potential role for β-endorphins and epinephrine increase during HF dTMS treatment to be additional mechanisms. Reduction of body weight is obtained via both a decrease of craving for food and an increase of physical activity. Future studies should determine whether this promising technique, associated with lifestyle intervention, may become an established obesity treatment, alone or in combination with weight-lowering drugs or after failure of bariatric surgery.

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CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

L.L., A.F. and I.T. contributed to designing the research study. L.L., A.F. and C.M. conducted experiments; specifically, L.L. provided research conduct oversight; A.F. contributed to performing dTMS after a specific training, and to providing medical supervision; C.M. and S.M. contributed to performing instrumental tests (indirect calorimetry, body plethysmography, accelerometer) and collecting blood samples. A.F. and M.A. contributed to acquiring data; F.A. and V.M. performed statistical analysis. A.F., L.L., F.A. and V.M. contributed to writing and editing the manuscript. L.L. had full access to all the data in the study and had final responsibility for the decision to submit for publication.

PRIOR PRESENTATION

The preliminary results of this study were presented as an oral presentation at the 53rd European Association for the Study of Diabetes (EASD) Annual Meeting, Lisbon, Portugal, 11–15 September 2017.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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