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ARTICLE

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Efficacy and acceptability of noninvasive brain stimulation interventions for weight reduction in obesity: a pilot network meta-analysis

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Abstract

Background/Objectives: Obesity has recently been recognized as a neurocognitive disorder involving circuits associated with the reward system and the dorsolateral prefrontal cortex (DLPFC). Noninvasive brain stimulation (NIBS) has been proposed as a strategy for the management of obesity. However, the results have been inconclusive. The aim of the current network meta-analysis (NMA) was to evaluate the efficacy and acceptability of different NIBS modalities for weight reduction in participants with obesity.

Methods: Randomized controlled trials (RCTs) examining NIBS interventions in patients with obesity were analyzed using the frequentist model of NMA. The coprimary outcome was change in body mass index (BMI) and acceptability, which was calculated using the dropout rate.

Results: Overall, the current NMA, consisting of eight RCTs, revealed that the high-frequency repetitive transcranial magnetic stimulation (TMS) over the left DLPFC was ranked to be associated with the second-largest decrease in BMI and the largest decrease in total energy intake and craving severity, whereas the high-frequency deep TMS over bilateral DLPFC and the insula was ranked to be associated with the largest decrease in BMI.

Conclusion: This pilot study provided a "signal" for the design of more methodologically robust and larger RCTs based on the findings of the potentially beneficial effect on weight reduction in participants with obesity by different NIBS interventions.

Introduction

Obesity has become an important issue that has been reported to affect one-third of adults in most developed countries [1]. It is associated with a high risk of diabetes, stroke, and cardiovascular disease [1]. Reports estimate that the increasing prevalence of obesity will achieve nearly 60% of the worldwide population in 2030 [2].

Obesity is a complex condition influenced by genetic predisposition and multifactorial environmental risk factors [3]. Dysfunction in eating behavior regulation is a key risk factor for obesity [4], which is controlled by homeostatic and hedonic processes. Homeostatic hunger, which is controlled by the hypothalamus and the brainstem, is the result of the natural response to nutritional needs in balance of matching energy intake and daily expenditure [5, 6]. Hedonic hunger increases human eating behavior to the palatable and energy-dense. Hedonic hunger is mainly based on the dopaminergic mesocorticolimbic pathway (so-called reward system), which consists of the ventral tegmental area, the nucleus accumbens, and the dorsolateral prefrontal cortex (DLPFC) [5, 6]. Several

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lines of evidence based on neuroimaging studies have shown hypoactivity in the DLPFC in participants with obesity and the consequent reduced inhibitory control and increased attentional bias to food, which could lead to maladaptive eating behaviors [7–9]. Therefore, taking the aforementioned information together, obesity has been understood as a neurocognitive disorder [10].

Noninvasive brain stimulation (NIBS) was been introduced to alter human brain function in a safe, tolerable, and convenient way [11]. It includes repetitive transcranial magnetic stimulation (rTMS) [12, 13], transcranial direct current stimulation (tDCS) [8, 14], and a variant of TMS (i.e., deep transcranial magnetic stimulation (dTMS)) [15]. The various NIBSs could exert different effects on the targeted brain cortex. For example, high-frequency rTMS (HF-rTMS) induces increased brain excitability, whereas low-frequency rTMS (LF-rTMS) decreases it [16]. Likewise, anodal and cathodal tDCS generally increase and decrease cortical excitability, respectively [17, 18] although the suppressing or enhancing effect, which is due to the polarity of tDCS, is still debated [19, 20]. The neuromodulation of the hypoactive DLPFC [21] or other associated brain regions, such as the reward system, is considered a reasonable NIBS method in the management of obesity [8, 12, 13, 15, 22].

Previous traditional pairwise meta-analyses have indicated significant efficacy of rTMS but not tDCS [23] in improving craving severity. However, this pairwise meta-analysis included not only randomized controlled trials (RCTs) but also other non-RCTs, which might bias the results. In addition, the primary outcome was changes in craving severity but not body mass index (BMI), which is the main target of many weight-reduction programs. In addition, traditional pairwise meta-analyses cannot provide further information about the relative efficacy of interventions that have not been directly compared in head-to-head trials, which is an essential aspect when judging the therapeutic value of an intervention.

Considering the aforementioned shortage of conventional pairwise meta-analyses, a network meta-analysis (NMA) of relevant RCTs enables the estimation of comparative efficacy or acceptability and the understanding of the relative merits of multiple interventions [24, 25]. To the best of our knowledge, no NMA has yet been performed on this important topic. Therefore, we conducted a pilot NMA to compare the efficacy and acceptability of different NIBS for weight reduction in participants with obesity.

Methods

General guidelines of the study

The current NMA was performed according to the preferred reporting items for systematic reviews and meta-analyses extension guidelines (eTable 1) [26] and a priori defined unpublished protocol (Appendix: study protocol), which had been approved by the Institutional Review Board of the Tri-Service General Hospital, National Defense Medical Center (TSGHIRB No. B-109-29).

Search strategy and selection criteria

We conducted a systematic review using PubMed, Embase, ClinicalKey, Cochrane CENTRAL, ProQuest, ScienceDirect, Web of Science, and ClinicalTrials.gov databases from inception to September 15, 2020. The detailed keyword used in each database had been listed in eTable 2. No language restriction was applied. In addition, manual searches were performed for potentially eligible articles selected from the reference lists of review articles and pairwise meta-analyses [7, 27–30].

Inclusion and exclusion criteria

We included only RCTs with either sham-controlled or active-controlled designs conducted in human subjects and with published articles. The targets of the comparison arms were set to be the NIBS method used in patients with a diagnosis of obesity. The NIBS methods were rTMS, tDCS, and dTMS. The detailed categorization of the treatment arms is listed in the node definition section. Because the diagnosis of obesity varied with ethnicity, country, and criteria, we allowed the diagnosis of obesity to have a BMI of at least 25 kg/m^2 for the acceptable lowest limit diagnostic criteria of obesity [31].

The exclusion criteria were (1) not a clinical trial, (2) not an RCT, (3) not reporting the target outcomes (BMI changes, craving severity, or total energy intake), (4) not related to the NIBS methods mentioned earlier, and (5) did not include patients with a diagnosis of obesity. In cases of duplicated usage of data (i.e., different articles based on the same sample sources), we included only the article with the most informative and largest sample source.

Data extraction

Two authors (YW Chen and BY Zeng) independently screened the studies, extracted the relevant information from the manuscripts, and evaluated the risk of bias in the included studies. In cases of discrepancy, the corresponding author (PT Tseng) was involved. If manuscript data were not available, the corresponding authors or coauthors were contacted to obtain the original data. We only extracted data on NIBS, not including data on peripheral stimulation, and we followed the flowchart used in previous NMAs [32–38].

Outcomes

Coprimary outcome

The coprimary outcomes were the changes in BMI and acceptability. We did not choose body weight as our primary outcome because BMI was the direct diagnostic measurement in the diagnosis of obesity in most studies. When there were at least two primary outcome data points in different follow-up periods, we mainly extracted data from the longest follow-up period because we intended to focus on the long-lasting effects of NIBS. The acceptability was calculated using the dropout rate, which was defined as the percentage of patients leaving the study before the end of study for any reason.

Secondary outcomes and safety profile

The secondary outcomes were changes in total energy intake and changes in craving severity. The safety profile was calculated using the rate of any local discomfort, including headache, itching, swelling, or local erythematous change.

Node definition

Because the NIBS method varied widely between the studies, we categorized the methods into three major subgroups: (i) rTMS modalities, which were HF-rTMS (≥5 Hz) and LF-rTMS (<5 Hz); (ii) deep TMS (dTMS) modalities; and (iii) tDCS modalities, which were specifically categorized according to the anodal/cathodal placement position (for example, a-tDCS over F3 or c-tDCS over F3). We further categorized the treatment arms on the basis of the stimulation position according to the electroencephalogram brain map.

Cochrane risk-of-bias tool

Two independent authors (YW Chen and BY Zeng) evaluated the risk of bias (interrater reliability, 0.85) for each domain described in the Cochrane risk-of-bias tool [39].

Statistical analysis

NMA was performed using STATA version 16.0 (StataCorp Statistics/Data Analysis, StataCorp LLC, College Station, TX, USA). We estimated the standardized mean difference (SMD) with a 95% confidence interval (CI) for continuous variables (i.e., the primary outcome and secondary outcome). For the categorical variables, we evaluated them with the odds ratio (OR) and 95% CI (i.e., the safety profile and acceptability) and applied a 0.5-zero-cell correction during the meta-analysis procedure. However, in the case that zeroes were present in both the intervention and control arms of one study, we did not apply such a correction procedure because of the risk of increasing bias; instead, such studies were excluded from our analysis [40, 41]. We used the frequentist model of NMA to compare the effect sizes of studies with similar interventions. All comparisons were performed using a two-tailed *t*-test, and $p < 0.05$ was considered significant. Heterogeneity among the included studies was evaluated using the tau value, which is the estimated standard deviation of the effect across the included studies.

Regarding the meta-analysis procedure employed in this study, we used mixed comparisons with generalized linear mixed models to make direct and indirect comparisons [42]. Specifically, indirect comparisons were conducted using transitivity in which the differences between treatments A and B could be calculated from their comparisons with a third treatment, C. To compare multiple treatment arms, we combined the direct and indirect evidence from the included studies [43]. STATA was used in our NMA with the mvmeta command [44]. The restricted maximum likelihood method was used to evaluate between-study variance [45].

To provide additional information for clinical applications, we calculated the relative ranking probabilities of treatment effects of all treatments for the target outcomes. In brief, the surface under the cumulative ranking curve (SUCRA) indicates the percentage of the mean rank of each treatment relative to an imaginary intervention that is the best without uncertainty [46]. Finally, we evaluated potential inconsistencies between the direct and indirect evidence within the network by using the loop-specific approach. The design-by-treatment model was used to evaluate global inconsistencies across the entire NMA [47]. Finally, per the rationale of a previous NMA study [48], we additionally assessed the effectiveness of the different sham interventions to justify our assumption of transitivity. Specifically, we computed the changes in BMI for tDCS sham therapy and rTMS sham therapy using comprehensive meta-analysis (version 3; Biostat, Englewood, NJ, USA). When we obtained significant evidence of different effects from a given sham therapy [49], we conducted a sensitivity test to remove trials that employed that specific sham therapy, and we then recalculated the main NMA results.

Results

After the initial screening procedure, 34 articles were considered for full-text review (Fig. 1), and 26 were excluded for various reasons (eTable 3). Finally, 8 articles were included in the current study (eTable 4) [4, 8, 10, 12–15, 22]. Figure 2 depicts the entire geometric distribution of the treatment arms.

Characteristics of the included studies

A total of 267 participants were included. The mean age of the participants was 43.5 years (range = 31.4–54.1 years; interquartile range [IQR] = 41.0–48.1 years), and 70.0% (range = 33.3–100.0%; IQR = 58.6–77.8%) were women. The mean treatment duration of NIBS treatment was 3.5 weeks (range = 2–5 weeks; IQR = 2.0–4.0 weeks), and the mean follow-up duration was 12.6 weeks (range = 2–52 weeks; IQR = 3.0–4.0 weeks). The mean baseline BMI was 33.6 kg/m^2 (range = 29.3–42.6; IQR = 31.7–38.0). Among the included RCTs, the cutoff points of BMI varied from at least 25 kg/m^2 [12, 13], at least 30 kg/m^2 [14, 22], at least 35 kg/m^2 [4], between 25–35 kg/m^2 [8], between 30-35 kg/m^2 [10], and between 30-45 kg/m^2 [15]. Most RCTs did not specifically restrict their time of intervention except for the situation mentioned below. Three RCTs performed their intervention in the morning under fasting conditions[10, 14, 22]. Four of the included RCTs excluded concomitant medication with an effect on body weight;[12, 13, 15, 22] the other RCTs did not specifically restrict concomitant medication use during their studies [4, 8, 10, 14]. The investigated NIBS included tDCS [4, 8, 10, 14, 22], rTMS [12, 13], and dTMS [15]. The rating scales for the measurement of craving severity included a visual analog scale for craving or food craving questionnaires. Five of the included RCTs also introduced a diet program during the treatment duration [8, 10, 14, 15, 22] and only three RCTs did not apply any diet program during the treatment duration [4, 12, 13].

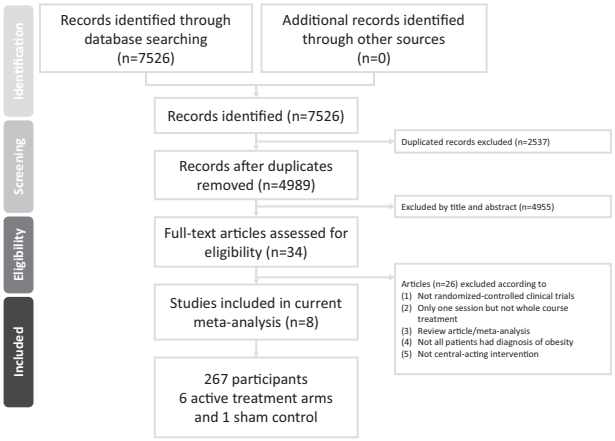
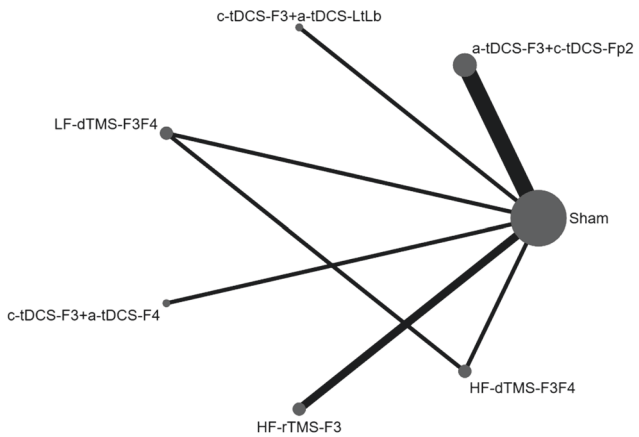


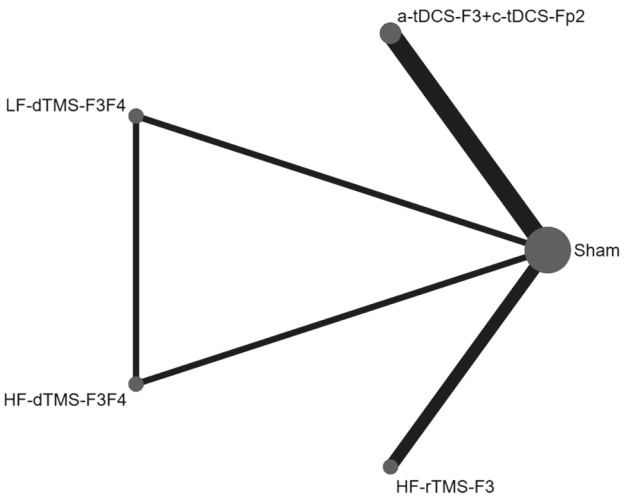
Fig. 1 Flowchart of the current network meta-analysis. Depicts the entire flowchart of the current network meta-analysis.

Coprimary outcome: changes in BMI

NMA revealed that in comparison to the sham control, only high-frequency dTMS over the bilateral DLPFC and the insula (F3F4) (HF-dTMS-F3F4) (SMD = −1.57 [95% CI = −2.99 to −0.15]) and high-frequency rTMS over the left DLPFC (F3) (HF-rTMS-F3) (SMD = −1.34 [95% CI = −2.24 to −0.43]) were associated with a significant decrease in BMI (Table 1A, Fig. 2A, and Fig. 3A). The associations between NIBS methods and changes in BMI were ranked according to the SUCRA. In brief, HF-dTMS-F3F4 was associated with the largest decrease in BMI, followed by HF-rTMS-F3 and anodal tDCS of the left DLPFC and cathodal tDCS over the right supraorbital region (a-tDCS-F3 + c-tDCS-Fp2) (SMD = −0.14 [95%



A network structure of NMA of BMI change



B network structure of NMA of acceptability in aspect of drop-out rate

Fig. 2 The network structure of coprimary outcome: (2A) changes in BMI after individual NIBS intervention and (2B) acceptability, reflected by the dropout rate. Depicts the overall network structure of the current network meta-analysis of (2A) changes in BMI after individual NIBS intervention and (2B) acceptability with respect to dropout rate. The lines between nodes represent direct comparisons in various trials, and the size of each circle is proportional to the size of the population involved in each specific treatment. The thickness of the lines is proportional to the number of trials connected to the network.

Table 1A League table of the changes of BMI.

HF-dTMS-F3F4			***−1.57 (−2.49, −0.65)**			***−2.90 (−4.02, −1.78)**
−0.24 (−1.92, 1.45)	HF-rTMS-F3		***−1.34 (−2.26, −0.42)**			
−1.43 (−3.00, 0.15)	***−1.19 (−2.32, −0.06)**	a-tDCS-F3 + c-tDCS-Fp2	−0.14 (−0.84, 0.55)			
***−1.57 (−2.99, −0.15)**	***−1.34 −2.24, −0.43)**	−0.14 (−0.82, 0.54)	Sham	−0.16 (−1.48, 1.16)	−0.25 (−1.18, 0.68)	***−1.33 (−2.27, −0.39)**
−1.73 (−3.95, 0.48)	−1.50 (−3.43, 0.43)	−0.30 (−2.14, 1.53)	−0.16 (−1.87, 1.54)	c-tDCS-F3 + a-tDCS-LtLb		
−1.82 (−3.83, 0.19)	−1.58 (−3.27, 0.10)	−0.39 (−1.97, 1.19)	−0.25 (−1.67, 1.18)	−0.09 (−2.31, 2.13)	c-tDCS-F3 + a-tDCS-F4	
***−2.90 (−4.46, −1.35)**	***−2.66 (−4.36, −0.97)**	−1.47 (−3.06, 0.12)	−1.33 (−2.76, 0.11)	−1.17 (−3.39, 1.06)	−1.08 (−3.10, 0.94)	LF-dTMS-F3F4

A: Pairwise (upper-right portion) and network (lower-left portion) meta-analysis results are presented as estimate effect sizes for the outcome of changes of BMI in patients with obesity. Interventions are reported in order of mean ranking of decrease in BMI, and outcomes are expressed as standardized mean difference (SMD) (95% confidence intervals). For the pairwise meta-analyses, SMD of less than 0 indicate that the treatment specified in the row got more decrease than that specified in the column. For the network meta-analysis (NMA), SMD of less than 0 indicate that the treatment specified in the column got more decrease than that specified in the row. Bold results marked with * indicate statistical significance.

Table 1B League table of the acceptability in aspect of drop-out rate.

HF-rTMS-F3			0.49 (0.03, 9.68)	
0.51 (0.02, 14.12)	HF-dTMS-F3F4	0.77 (0.09, 6.45)	0.77 (0.09, 6.45)	
0.39 (0.01, 11.01)	0.77 (0.06, 9.28)	LF-dTMS-F3F4	1.00 (0.12, 8.56)	
0.39 (0.04, 3.53)	0.77 (0.06, 9.28)	1.00 (0.08, 12.28)	Sham	0.82 (0.24, 2.77)
0.33 (0.02, 5.05)	0.65 (0.04, 11.36)	0.84 (0.05, 15.00)	0.84 (0.21, 3.46)	a-tDCS-F3 + c-tDCS-Fp2

B: Pairwise (upper-right portion) and network (lower-left portion) meta-analysis results are presented as estimate effect sizes for the outcome of acceptability in aspect of drop-out rate in patients with obesity. Interventions are reported in order of mean ranking of acceptability, and outcomes are expressed as odds ratio (OR) (95% confidence intervals). For the pairwise meta-analyses, OR of less than 1 indicate that the treatment specified in the row got better acceptability than that specified in the column. For the network meta-analysis (NMA), OR of less than 1 indicate that the treatment specified in the column got better acceptability than that specified in the row. Bold results marked with * indicate statistical significance.

a-tDCS-F3 + c-tDCS-Fp2 anodal tDCS of the left DLPFC and cathodal over right supraorbital region, *BMI* body mass index, *CI* confidence interval, *c-tDCS-F3 + a-tDCS-F4* cathodal tDCS of the left DLPFC and anodal over right, DLPFC, *c-tDCS-F3 + a-tDCS-LtLb* cathodal tDCS of the left DLPFC and anodal over left forearm, *DLPFC* dorsolateral prefrontal cortex, *dTMS* deep TMS, *EHF-rTMS* extreme high-frequency rTMS, *HF-dTMS-F3F4* 18 Hz dTMS over bilateral DLPFC and the insula, *HF-rTMS* high-frequency rTMS, *HF-rTMS-F3* 10 Hz rTMS over left DLPFC, *IQR* interquartile range, *LF-dTMS-F3F4* 1 Hz dTMS over bilateral DLPFC and the insula, *LF-rTMS* low-frequency rTMS, *MF-rTMS* medium-frequency rTMS, *NIBS* noninvasive brain stimulation, *NMA* network meta-analysis, *OR* odds ratio, *PRISMA* preferred reporting items for systematic reviews and the meta-analysis, *RCT* randomized controlled trial, *rTMS* repetitive transcranial magnetic stimulation, *Sham* sham control, *SMD* standardized mean difference, *SUCRA* surface under the cumulative ranking curve, *TBS* theta-burst stimulation, *tDCS* transcranial direct current stimulation.

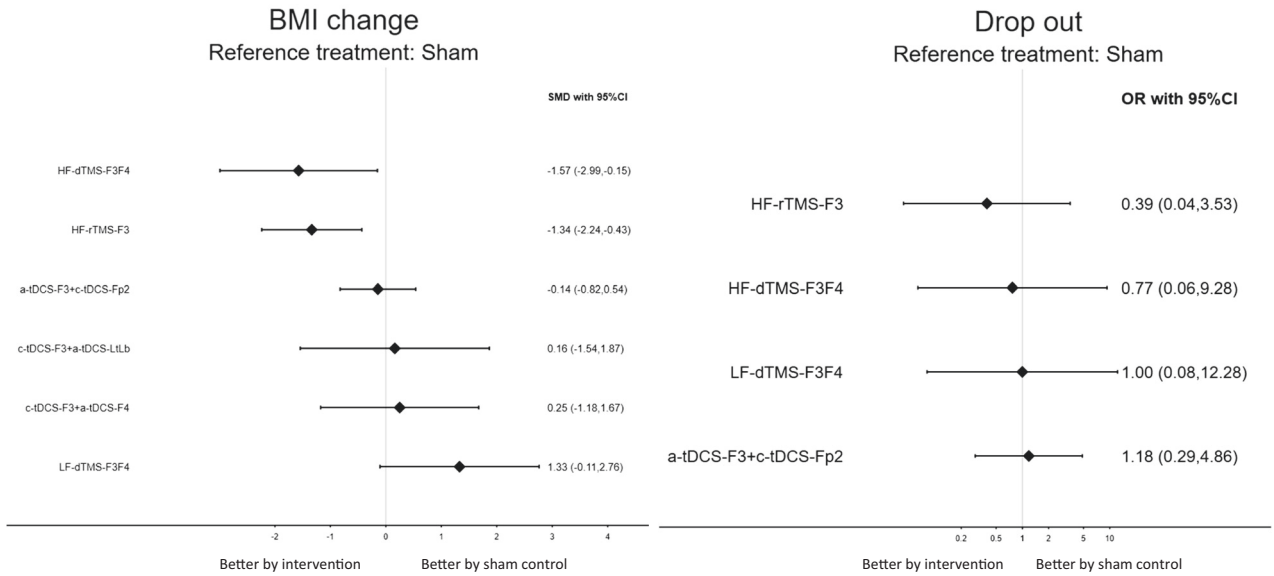


Fig. 3 Forest plot of the coprimary outcome: (3A) changes in BMI after individual NIBS intervention and (3B) acceptability with respect to dropout rate. indicates that (3A) when the effect size was less than zero, it indicated that the specified treatment was associated with a higher decrease in BMI than the sham controls, or (3B) when the effect size was less than one, it indicated that the specified treatment was associated with a lower dropout rate than the sham controls. Abbreviation: a-tDCS-F3 + c-tDCS-Fp2 anodal tDCS of the left DLPFC and cathodal over right supraorbital region, BMI body mass index, CI confidence interval, c-tDCS-F3 + a-tDCS-F4 cathodal tDCS of the left DLPFC and anodal over right DLPFC, c-tDCS-F3 + a-tDCS-LtLb: cathodal tDCS of the left DLPFC and anodal over left forearm, DLPFC dorsolateral prefrontal cortex, dTMS deep TMS, EHF-rTMS extreme high-frequency rTMS, HF-dTMS-F3F4 18 Hz dTMS over bilateral DLPFC and the insula, HF-rTMS high-frequency rTMS, HF-rTMS-F3 10 Hz rTMS over left DLPFC, IQR interquartile range, LF-dTMS-F3F4 1 Hz dTMS over bilateral DLPFC and the insula, LF-rTMS low-frequency rTMS, MF-rTMS medium-frequency rTMS, NIBS noninvasive brain stimulation, NMA network meta-analysis, OR odds ratio, PRISMA preferred reporting items for systematic reviews and the meta-analysis, RCT randomized controlled trial, rTMS repetitive transcranial magnetic stimulation, Sham sham control, SMD standardized mean difference, SUCRA surface under the cumulative ranking curve, tDCS transcranial direct current stimulation.

CI = −0.82 to 0.54] compared to the sham control) (eTable 6A).

The assumption of transitivity was verified according to the rationale of previous NMA [48]. We noted that the sham therapy effect did not significantly differ between rTMS/dTMS sham therapy and tDCS sham therapy ($p = 0.284$). Additionally, there was no significant placebo effect noticed in the rTMS/dTMS sham therapy and tDCS sham therapy groups ($p = 0.855$ and $p = 0.261$, respectively, eFigure 1).

Coprimary outcome: acceptability reflected by dropout rate

The NMA revealed that in comparison to the sham control, none of the investigated NIBS was associated with a significantly different dropout rate (Table 1B, Fig. 2B, Fig. 3B, and eTable 6B).

Secondary outcome: changes in total energy intake

NMA revealed that in comparison to the sham control, HF-rTMS-F3 (SMD = −0.85 [95% CI = −1.27 to −0.42]) was associated with a significant decrease in total energy intake (eTable 5A, eFigure 2A, and eFigure 3A). The associations between a NIBS method and the changes in total energy intake were ranked according to the SUCRA. In brief, HF-rTMS-F3 was associated with the largest decrease in total energy intake, followed by cathodal tDCS of the left DLPFC (F3) and anodal over the right DLPFC (F4) (c-tDCS-F3 + a-tDCS-F4) (SMD = −0.38 [95% CI = −1.32 to 0.55] compared to sham control) and cathodal tDCS of the left DLPFC and anodal over left forearm (c-tDCS-F3 + a-tDCS-LtLb) (SMD = −0.09 [95% CI = −1.41 to 1.22] compared to sham control) (eTable 6C).

Secondary outcome: changes in craving severity

NMA revealed that in comparison to the sham control, HF-rTMS-F3 (SMD = −0.97 [95% CI = −1.83 to −0.12]) was associated with a significant decrease in craving severity (eTable 5B, eFigure 2B, and eFigure 3B). Associations between the NIBS method and changes in craving severity were ranked according to the SUCRA. In brief, HF-rTMS-F3 was associated with the largest decrease in craving severity, followed by anodal tDCS of the left DLPFC and cathodal tDCS over the right supraorbital

region (a-tDCS-F3 + c-tDCS-Fp2) (SMD = −0.38 [95% CI = −0.93 to 0.16] compared to the sham control) and HF-dTMS-F3F4 (SMD = −0.34 [95% CI = −1.75 to 1.07] compared to the sham control) (eTable 6D).

Safety profile of rate of any local discomforts

The NMA revealed that in comparison to the sham control, none of the investigated NIBS was associated with a significantly different rate of any adverse events (eTable 5C, eFigure 2C, eFigure 3C, and eTable 6E).

Risk of bias, publication bias, and inconsistency

We found that 73.2% (41/56 items), 21.4% (12/56 items), and 5.4% (3/56 items) of the included studies had, overall, a low, unclear, and high risk of bias, respectively. Unclear reporting of the allocation procedure further contributed to the risk of bias (eFigure 4A-4B). Funnel plots of the publication bias revealed general symmetry, and the results of Egger's test indicated no significant publication bias among the articles included in the NMA (eFigure 5A–5J). In general, the NMA did not demonstrate inconsistencies in terms of either local inconsistencies, as assessed using the loop-specific approach or global inconsistencies, as determined using the design-by-treatment method except for the situation mentioned below. There were significant inconsistencies in the changes in BMI and craving severity by design-by-treatment ($p = 0.0037$ and 0.0261, respectively) and loop inconsistency method ($p = 0.0037$ and 0.0261, respectively) (eTable 7-8).

Discussion

To our knowledge, the present study is the first comprehensive NMA performed to investigate the efficacy and safety of different NIBS interventions in patients with obesity. Evidence from this NMA revealed that in comparison to sham, both HF-rTMS-F3 and HF-dTMS-F3F4 were associated with a significant decrease in BMI. In comparison to the sham control, HF-rTMS-F3 was associated with a significant decrease in total energy intake, whereas in comparison to the sham control, only HF-rTMS-F3 was associated with a significant decrease in craving severity. Furthermore, HF-rTMS-F3 was ranked to be associated with the second-largest decrease in BMI and the largest decrease in total energy intake and craving severity, whereas in comparison to the sham control, HF-dTMS-F3F4 was ranked to be associated with the largest decrease in BMI but was not associated with a significant decrease in craving severity. In addition, there were no significant placebo effects noticed in the rTMS/dTMS sham therapy and tDCS sham therapy groups for the primary outcome. Finally, most of the investigated NIBS methods were suggested to be well tolerated in regards to the safety profile of the rate of any local discomfort and acceptability reflected by the dropout rate, which indicated that most of the investigated NIBS methods were generally well-acceptable and well-tolerable.

The first main finding of this study was that in comparison to the sham control, HF-rTMS-F3 was associated with a significant decrease in BMI and was ranked to be associated with the second-largest decrease in BMI and the largest decrease in total energy intake and craving severity. In a previous study using resting-state fMRI, obese participants were found to have decreased functional connectivity in their DLPFC, which is part of the frontoparietal network, and its deficiency indicated a top-down deficiency in inhibitory control [50, 51]. This deficient inhibitory control could serve as one of the possible links between obesity and self-control, which is decreased in obese participants [51]. HF-rTMS increases brain activity [16] so that the application of HF-rTMS over the left DLPFC could theoretically enhance patients' control over the intake of tempting foods [52]. The hypothesis of the enhancing effect of HF-rTMS on the left DLPFC and the frontoparietal network could be supported by a previous RCT applying HF-rTMS over the left DLPFC, which revealed a significant interaction of treatment (real rTMS vs. sham) and time (pre vs. post) in the frontoparietal network [13]. Additionally, compared to sham, the significant decrease in craving severity and total energy intake by HF-rTMS-F3 in the current NMA would support a beneficial effect of HF-rTMS-F3 in reducing energy intake. Another potential mechanism to explain why HF-rTMS could help in weight reduction was that rTMS was shown to improve brain-derived neurotrophic factor (BDNF) and cholecystokinin (CCK) expression in the rat brain [53], which are deficient in obesity[54]. Therefore, through the restoration of such neuroendocrine factors, HF-rTMS might exert its weight-controlling effect in participants with obesity. However, because of insufficient human studies on the alteration of BDNF and CCK by HF-rTMS in participants with obesity, future RCTs targeting this topic should be warranted.

Another important finding of the current NMA was that in comparison to the sham control, HF-dTMS-F3F4 was ranked to be associated with the largest decrease in BMI but was not associated with a significant decrease in craving severity. The possible mechanism to explain the weight-controlling effect of HF-dTMS is the resetting of reward thresholds [12, 55]. Indeed, a previous neuroimaging study revealed that the abnormally hyperactive reward system was associated with obesity [56]. This abnormally elevated connectivity in reward circuits had been found to have gender-dependent increased brain metabolism in the

orbitofrontal cortex, which was especially high in female obese patients [57]. The orbitofrontal cortex had been found to play an important role in taste reward [58]. The application of HF-dTMS could modulate the reward system, the so-called dopaminergic mesocorticolimbic pathway [15]. Another RCT addressing HF-dTMS to the bilateral PFCs and insula revealed the efficacy of HF-dTMS in reducing nicotine addiction but marginal effects on craving [59]. However, in the current NMA, compared to the sham control, HF-dTMS-F3F4 was not associated with a significant change in craving severity (SMD = −0.34 [95% CI = −1.75 to 1.07]). Therefore, there might be some other potential mechanism between HF-dTMS-F3F4 and the weight-reducing effect. In the report of Ferrulli (2019), the authors found that compared to 1 Hz dTMS over bilateral DLPFC and the insula (LF-dTMS-F3F4) and sham control, HF-dTMS-F3F4 significantly decreased leptin levels. Leptin mainly targets leptin receptors, which are located on dopaminergic neurons in both the hypothalamus, which regulates homeostatic hunger, and the reward network system, which consisted of the substantia nigra and the ventral tegmental area and have been linked to hedonic hunger [15]. Therefore, the activation of leptin receptors might modulate the motivational and behavioral responses to rewarding stimuli by specific food [60]. A previous neuroimaging study demonstrated the potential association between hyperactive leptin signaling and overconsumption of foods [60]. Therefore, the decreased leptin after application of HF-dTMS-F3F4 might exert its reducing effect on food craving via the modulation of neuroendocrine pathways [15]. In addition to the leptin hypothesis, Ferrulli et al. had demonstrated that a single 18 Hz dTMS session could significantly increase the levels of blood beta-endorphin compared to the other treatment groups (1 Hz dTMS and sham control groups), which indicated an activation of the reward pathway [61]. However, because there was insufficient evidence about the effect of HF-dTMS-F3F4 on the alteration of leptin and beta-endorphin levels, future RCTs targeting this topic are needed.

Another important issue of the main result of current NMA was the insignificant effects by tDCS in weight reduction. Among the included RCTs, Fassini et al. found that over time, the tDCS group showed a tendency to lose less weight than the sham group [10]. This controversial finding could be supported by the dopamine hypothesis associated with tDCS application to DLPFC. To be specific, the application of tDCS to the DLPFC would increase dopamine-release in the striatum [62], which might facilitate over-eating and hinder weight loss efforts [10].

In the inconsistency evaluation, there were significant inconsistencies in the changes in BMI and craving severity by design-by-treatment and loop inconsistency methods. When we re-examined the evidence of the individual treatment arm, we found that immediately after the completion of the NIBS 2-4 week course there was a potentially weight-reducing effect and improvement in craving severity by sham control by either tDCS or rTMS/dTMS sham control, which was not significant, and that was also not significant in the original studies [10, 12, 15]. The potentially different changes in BMI or craving severity between the active NIBS and sham control groups have achieved significance during a longer follow-up duration (i.e., 4–52 weeks) [12, 15]. Although in the current study, we tried to reduce the potential time-effect by extracting data in the final follow-up, there were only three RCTs providing data immediately after the completion of the NIBS course and those data of follow-up duration [10, 12, 15]. Additionally, the relatively shorter follow-up duration (mean follow-up duration was 12.6 weeks) still might be confounded with the potential time-effect. Therefore, future RCTs with longer follow-up durations are warranted.

Several potential limitations should be underscored for the current NMA. First, this NMA may have been underpowered because of the heterogeneity of the participants (e.g., comorbidities, concomitant medication with effect on body weight, baseline BMI, type of machine used in each study, timing of NIBS intervention, and follow-up duration). Second, although all the RCTs included a sham control in their study design, the blindness of those RCTs may not have been complete because of the limitation of the commercial machine employed. Although there was no significant placebo effect noticed in the rTMS/dTMS sham therapy and tDCS sham therapy groups ($p = 0.855$ and $p = 0.261$, respectively, eFigure 1), the psychologic effect might impose a potential bias on the patients with obesity. Third, given the relatively small number of patients and RCTs, the main results of this NMA should perhaps be conservatively applied in clinical practice. Specifically, the evidence of potentially beneficial effects of HF-rTMS-F3 and HF-dTMS-F3F4 on weight reduction in the current NMA mainly came from two RCTs [12, 13] and one RCT [15], respectively. Fourth, the most included RCTs provided comparisons between NIBS and sham controls, but only one of them provided comparisons between different NIBS [15]. Therefore, the geometric structure of the current NMA was relatively weak (Fig. 2). Fifth, only four RCTs excluded concomitant medication with a potential effect on body weight [12, 13, 15, 22], which medication might impose an unwanted bias on the results of the current NMA. Six, in the previous report, there might be gender-dependent difference in the abnormally elevated connectivity in reward circuits between male and female genders [57]. However, we could not make further subgroup analysis because there had not been RCTs addressing the different NIBS effect on weight reduction in different genders. Seventh, because of the natural limitation of NMA, we could observe the

phenomenon (the result) but not over-state its physiopathology behind the result. Although insignificant, we found that the effect of LF-dTMS-F3F4 was different from the other NIBS (Fig. 3A). We would recommend future RCTs addressing potentially clinical application of this different effect by LF-dTMS-F3F4 in other clinical situations. Finally, there were significant inconsistencies detected in some of the outcomes (i.e., changes in BMI and craving severity). Clinicians should consider these issues when delivering these results in clinical practice.

This pilot study provided a "signal" for the design of more methodologically robust and larger RCTs based on the findings that HF-rTMS-F3 might be ranked to be associated with the second-largest decrease in BMI and the largest decrease in total energy intake and craving severity based on currently available evidence, whereas HF-dTMS-F3F4 was ranked to be associated with the largest decrease in BMI. Finally, most of the investigated NIBS methods were suggested to be well tolerated in regards to the safety profile of the rate of any local discomfort and acceptability reflected by the dropout rate. However, because there were not enough RCTs performing direct head-to-head comparisons between NIBS techniques, the development of RCTs investigating direct head-to-head comparisons between different NIBSs should be encouraged.

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Compliance with ethical standards

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