IS REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION (RTMS) A PROMISING THERAPEUTIC INTERVENTION FOR EATING DISORDERS AND OBESITY? CLINICAL CONSIDERATIONS BASED ON A META-ANALYTIC REVIEW

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Abstract

Objective: Repetitive Transcranial Magnetic Stimulation (rTMS) has been introduced to treat eating disorders (EDs), especially Anorexia, Bulimia Nervosa (AN and BN) and other EDs not otherwise specified (NOS). Provisional rTMS single-case studies and clinical trials have been carried out for the treatment of binge eating disorder (BED) and obesity. However, it is still unclear whether and to what extent rTMS might be considered an effective intervention for these conditions.

Method: This meta-analysis includes 15 independent studies examining the clinical effects of rTMS among different EDs and obesity (N = 402 patients). Several primary and secondary treatment outcomes have been considered. Cohen's d was used as an effect size measure. The analyses estimate heterogeneity across findings, sources of variability and publication bias together with an assessment of the quality of the studies.

Results: The analyses show that rTMS induced large improvements in body mass index (BMI) among obese individuals. Null clinical effects have been detected for primary outcomes (i.e., BMI, binge eating and compensatory behaviors; urge to binge and to eat; severity of EDs symptoms) among individuals with AN, BN and other EDs-NOS. rTMS shows moderate therapeutic effects on the affective functioning (i.e., negative affectivity, depressive and anxious symptoms) of individuals with EDs. rTMS should be considered a promising intervention for the treatment of obesity.

Conclusions: This evidence might provisionally support the hypothesis on the implementation of rTMS for BED. Furthermore, rTMS could be included as an ancillary intervention for the other EDs, especially considering secondary treatment outcomes. Future controlled trials are needed to clarify the clinical effects of rTMS for EDs.

Key words: eating disorders, obesity, rTMS, clinical efficacy, behavioral outcomes, symptomatic outcomes, affective functioning

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Introduction

Several burden of diseases studies have clearly shown that eating disorders (EDs), especially Anorexia and Bulimia Nervosa (AN and BN, respectively), are responsible for both disability and mortality (Erskine et al., 2016; Sminket al., 2012). The worldwide prevalence of EDs varies significantly across countries and across the spectrum of EDs. Epidemiological studies have shown modest prevalence rates of AN among the general population (.10% – 1.05%) and significantly higher prevalence rates of BN (0.87% – 2.98%), binge

eating disorder (BED) and other EDs not otherwise specified (NOS) (1.98% – 4.45%) (e.g., Hoek, 2016). According to this evidence, clinicians have developed different treatment approaches for these clinical conditions, both pharmacological (Sysko et al., 2019) and psychological (Abbate-Daga, Marzola, Amianto, & Fassino, 2016; Pisetsky, Schaefer, Wonderlich, & Peterson, 2019). However, it is well-recognized that a significant proportion of individuals with EDs who receive different treatments do not make a full, lasting recovery (Kim, & Kim, 2019).

Regarding treatment-resistant and relapsing psychiatric disorders (e.g., mood disorders; addictive disorders; post-traumatic stress disorder), there is a growing body of empirical research that has investigated the efficacy of neuromodulation techniques for the treatment of such conditions (Kim et al., 2009). Among available neuromodulation approaches, repetitive transcranial magnetic stimulation (rTMS) is noninvasive and one of the most widely used interventions for several mental disorders (Lefaucheur et al., 2020). rTMS uses a pulsed magnetic field to alter the activity of specific neural circuits through the local induction of an electrical current in the cortex of the brain, inducing neuronal depolarization about 3 cm in depth from the coil surface, with an active area estimated to be 2 cm^2 (Barker, 1999). Several empirical studies among heathy subjects have demonstrated two main effects of rTMS on stimulated brain regions. On the one hand, the inhibitory effect is produced using a low-frequency stimulation ($\leq$ 1 Hz), and on the other hand, the excitatory effect is sustained through the administration of a high-frequency stimulation ($\geq$ 5 Hz), with a size of effect that is linked to the number of stimulations delivered and their intensity (Siebner & Rothwell, 2003). From a clinical perspective, the main interest in applying rTMS resides in the long-term persistence of clinical changes beyond the time of stimulation (e.g., Gangitano et al., 2002), based on evidence concerning long-term synaptic plasticity induced by TMS (e.g., Ziemann, 2004).

The application of rTMS for the treatment of psychiatric conditions has shown promising results, especially for mood disorders and, provisionally for substance use disorders (SUDs). Several meta-analyses have found large and consistent improvements in depressive symptoms among patients with major depressive disorder and bipolar disorder (e.g., Berlim, et al., 2014; Brunoni et al., 2017 Couturier, 2005; McGirr et al., 2016). Similarly, a growing body of empirical evidence has demonstrated the efficacy of rTMS in reducing craving and substance-use behaviors among individuals with SUDs (Zhang et al., 2019).

Starting from this evidence, rTMS has been introduced as an alternative treatment for the spectrum of EDs. The clinical application of these procedures among EDs is based on the hypothesis that the core maladaptive features of these conditions could be explained by an altered balance between neural mechanisms related to reward and cognitive control/inhibitory systems (O'Hara, Campbell, & Schmidt, 2015; Wierenga et al., 2014). The growing interest in carrying out clinical trials that apply rTMS for the treatment of EDs led Dalton and colleagues (2018) to conduct a qualitative systematic review on the topic. According to this review, the authors concluded that "*neurostimulation has potential for altering disordered eating behaviors, food intake and body weight*" (p. 1184). However, this study had several limitations. Specifically, the qualitative approach did not clarify the extent of the clinical efficacy of rTMS for EDs. Furthermore, this

systematic review did not quantitatively test whether rTMS might have differential effects on several primary and secondary treatment outcomes routinely considered within clinical research on EDs. Ultimately, it is still unclear whether rTMS might be a promising treatment for the full spectrum of EDs or, whether it could be more effective for specific conditions.

The present study

Therefore, the current study aims at testing the efficacy of rTMS for the treatment of EDs using a meta-analytic approach. Specifically, this study assessed several primary and secondary treatment outcomes according to previous systematic reviews and meta-analyses on the efficacy of different therapeutic interventions for EDs (e.g., Vocks et al., 2010). Considering primary treatment outcomes (e.g, frequency of binge eating and other compensatory behaviors, severity of ED symptoms), the analyses aggregated results of studies evaluating the effects of rTMS among individuals with AN, BN and other EDs-NOS, according to well-documented overlaps between these conditions (e.g., Bulik et al., 2010; Gleaves et al., 2000; Tozzi et al., 2005; Yao et al., 2019). On the contrary, the current meta-analysis separately considered the results of primary treatment outcomes among individuals affected by overweight-associated conditions, namely BED and obesity (body mass index [BMI] $\geq$ 25; World Health Organization criteria). This approach is validated for several reasons. First of all, both conditions share the same primary therapeutic goal of weight/ BMI reduction. Although obesity is not considered an ED, several empirical studies have demonstrated that these conditions show common latent psychopathological dimensions and overt behavioral manifestations (e.g., Davis, 2017; Lavagnino et al., 2016), suggesting a possible independent spectrum from the other EDs (Giel et al., 2017). Consistently, well-validated evidence has robustly linked BED and obesity to addictive disorders, taking into account similar phenomenological manifestations and neurobiological alterations (e.g., Schulte, Grilo, & Gearhardt, 2016; Smith, & Robbins, 2013). These considerations support a provisional hypothesis regarding the greater efficacy of rTMS for the treatment of BED and obesity compared to AN and BN. This hypothesis was sustained in the light of consistent and promising effects of rTMS in addressing core clinical targets of SUDs, namely craving and substance intake (Zhang et al., 2019). With respect to secondary outcomes, mainly the affective functioning of individuals with EDs and obesity, this study assumed a transdiagnostic approach consistently with empirical findings demonstrating common difficulties with emotion regulation across the spectrum of EDs (e.g., Dingemans et al., 2017; Lavender et al., 2015; Mallorquí-Bagué et al., 2018; Svaldi et al., 2012) and obesity (Leehr et al., 2015). Consistently, this meta-analysis did not expect significantly different effects of rTMS among these clinical conditions on the improvement of this domain of functioning.

Method

Criteria for selecting studies

The current meta-analytic review was conducted in line with the Meta-Analysis Reporting Standards (MARS) of the *American Psychological Association*

Table 1. *Characteristics of studies included (N = 15)*

Study	Research design	Country	Sample size	Sample characteristics	Gender	Mean of age	rTMS interventions	Number of rTMS sessions; period of evaluation	Outcomes
Alvarado-Reynoso, & Ambriz-Tututi, 2019	RCT	Mexico	37 (real rTMS = 18; sham rTMS = 19)	Obesity	M ; W	39.95	The coil was oriented at 45° from the mid-sagittal plane to induce currents to the left primary sensory-motor cortex hand area (M1/S1). The motor threshold is defined as the minimum intensity to evoke five consecutive motor evoked potentials. The stimulation was applied over the DLPFC. The stimulation parameters had a frequency of 10 Hz, and a field intensity of 90% of the MT. Stimuli were provided in 10 trains of100 pulses, with inter-train intervals of 10 s.	10 (5 times a week) 2-weeks treatment 28-week follow-up	SF-36 emo-tional role subscale
Dalton et al., 2018	RCT	UK	32 (real rTMS = 16; sham rTMS = 16)	AN-P; AN-BP	W	27.4	Each session lasted 30–60 minutes, including preparation time, 20 minutes of rTMS. Magstim Rapid device with a real TMS figure-of-eight coil was used to determine participants' motor threshold (MT). Using the motor-evoked potential method, the MT was established by determining the minimum stimulator output intensity required to obtain 5 out o 10 motor-evoked potentials. Participants in the real group received 20 sessions of high-frequency (10 Hz) rTMS at 110% of their individual MT, consisting of 20 5 s trains with 55 s inter-train intervals delivered to the left DLPFC	20 (5 times a week) 4-week treatment 16-week follow-up	BMI EDE-Q DASS-21 PANAS
Dalton et al., 2020	RCT	UK	26 (real rTMS = 13; sham rTMS = 13)	AN-SE	W	26.0	See Dalton et al., 2018	20 (5 times a week) 4-week treatment 16-week follow-up	BMI EDE-Q DASS-21
Dunlop et al., 2015	Pre-post no control group	Canada	28	AN-BP BN	M ; W	31.0	Stimulation of the DMPFC was delivered at 120% resting motor threshold, at 10 Hz, 5 s on, 10 s off, 3000 pulses/ hemisphere, with left then right lateralized coil orientation	20 (once a week) 20-week treatment 4-week follow-up	EDE binge and purge frequency

Table 1. *Continued*

Study	Design	Country	N	Diagnosis	Sex	BMI	Protocol	Sessions	Outcomes
Encarnacion et al., 2020	RCT	Philippines	29 (real rTMS = 15; sham rTMS = 14)	Obesity	M ; W	41.2	The site for stimulation of the left DLPFC was 5 cm anterior to and in the same parasagittal plane as the site of maximal abductor pollicis brevis stimulation. Twenty trains of 5 seconds with 55-second intertrain intervals were given at a frequency of 10 Hz and intensity of 110% of the participant's motor threshold, providing a total of 1000 pulses over 20 minutes	4 (twice a week) 2-week treatment 12-week follow-up	BMI, Urge to eat
Kim et al., 2018	RCT	Korea	57 (real rTMS = 29; sham rTMS = 28)	Obesity	M ; W	40.99	The rTMS was delivered to the left DLPFC. 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. Twenty trains of 5 s with 55-s inter-train intervals were administered at a frequency of 10 Hz and an intensity of 110% of the individual's motor threshold, providing 1000 pulses over 20 min.	8 (4 times a week) 2-week treatment 2-week follow-up	BMI
Kim et al., 2019	RCT	Korea	43 (real rTMS = 21; sham rTMS = 22)	Obesity	M ; W	53.4	See Kim et al., 2018	8 (4 times a week) 2-week treatment 2-week follow-up	BMI
Knyahnytska et al., 2019	Pre-post no control group	Canada	8	AN	W	33.00	dTMS session included stimulation with 18 Hz, 2 s on, 20 s off, number of pulses 36, number of trains 80, over 20 mins. Stimulation intensity was determined relative to the patient's resting motor threshold according to previously published protocols	30 (5 times a week) + 12 (twice a week) 12-week treatment 24-week follow-up	YBC-EDS, BAI, HDRS
McClelland et al., 2016a	RCT experimental paradigm	UK	49 (real rTMS = 21; sham rTMS = 28)	AN-R; AN-BP	M ; W	26.48	TMS coil to the l-DLPFC using Talaraich co-ordinates, (x = -45, y = 45, z= 35). MT was defined as the minimum stimulation required to evoke 5 out of 10 motor evoked potentials greater than 50μV. 5 second trains/55 second intertrain intervals, 10Hz, 110% MT, delivering 1000 pulses over 20 minutes to the l-DLPFC.	1 No treatment No follow-up	VAS Scales: Anxiety, Stress, Mood, Urge to binge, Urge to sick/purge, Urge to eat

Table 1. *Continued*

| Study	Design	Country	N	Diagnosis	Gender	BMI	Intervention	Sessions / Follow-up	Outcome measures
McClelland et al., 2016b	Pre-post no control group	UK	5	AN	W	35.6	TMS coil to the l-DLPFC using Talaraich co-ordinates (x = 45, y=45, z = 35). MT was defined as the minimum stimulus required to produce 5/10 motor-evoke potentials greater than 50 μV. This was repeated weekly to ensure rTMS dose was accurate The Magstim device was used to deliver 20 × 5 s trains/55 s inter-train interval at a frequency of 10 Hz, intensity of 110% MT, delivering 1000 pulses over 20min within each session.	20 (4 times a week) 5-week treatment 12-month follow-up	BMI bingeing/ vomiting/ laxative use-behaviors EDE-Q DASS-21
Sutoh et al., 2016	Pre-post no control group experimental paradigm	Japan	8	BN	W	24.28	The stimulations were placed at 5 cm anterior in the same parasagittal plane from the site of maximal abductor pollicis brevis stimulation, which was projected on the left DLPFC. Stimulation was delivered at a frequency of 10 Hz and an intensity of 110% of the individual motor threshold. Fifteen trains of 5 s, with 55-s inter-train intervals, were performed. A total of 1000 pulses were provided over 20 min.	1 No treatment No follow-up	EDE-Q HADS Anxiety and Depression subscale
Van den Eynde et al., 2012	Pre-post no control group experimental paradigm	UK	7	BN and other EDs-NOS	W	22.9	Following mapping of the abductor pollicis brevis site in the left motor cortex, each participant's motor threshold was established as the minimum stimulus required to induce contraction of the right thumb at least five of 10 times. The site for the left DLPFC stimulation was 5 cm anterior to the point of maximal abductor pollicis brevis stimulation. Twenty trains of 5 seconds with 55-seconds intertrain intervals were administered with a frequency of 10 Hz and intensity of 110% of the individual's motor threshold, providing 1000 pulses over 20 minutes.	1 No treatment No follow-up	VAS Scale: Urge to eat Urge to binge Mood Tension
Van den Eynde et al., 2009	RCT experimental paradigm	UK	49 (real rTMS = 21; sham rTMS = 28)	BN and other EDs-NOS	M ; W	30.00	The site for stimulation of the left DLPFC was 5 cm anterior to and in the same parasagittal plane as the site of maximal abductor pollicis brevis stimulation. Twenty trains of 5 sec with 55-sec intertrain intervals were administered with a frequency of 10 Hz and intensity 110% of the individual's motor threshold, providing a total of 1000 pulses over 20 min.	1 No treatment No follow-up	VAS Scale Urge to binge Mood Tension

Table 1. *Continued*

Study	Study design	Country	N	Diagnosis	Sex	Value	rTMS protocol	Sessions	Outcome measures
Van den Eynde et al., 2013	Pre-post no control group experimental paradigm	UK	10	AN-P; AN-BP	W	25.00	The rTMS was delivered to the left DLPFC. 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. The site for the left DLPFC stimulation was 5 cm anterior to the point of maximal abductor pollicis brevis stimulation, in a parasagittal plane. Twenty trains of 5 seconds with 55-second inter-train intervals were administered with a frequency of 10 Hz and intensity of 110% of the individual's motor threshold, providing 1000 pulses over 20 min.	1 No treatment No follow-up	VAS Scale Urge to eat Mood Anxiety Tension
Walpoth et al., 2008	RCT	Austria	14 (real rTMS = 7; sham rTMS = 7)	BN	W	25.00	Stimulation was placed over left DLPFC. Stimulation was delivered with an intensity of 120% motor threshold using 20 Hz, in one session a day. Ten trains of 10 s, with a train interval of 60 s, were performed per session. Patients got an amount of 2,000 stimuli per session summing up to a total	15 (5 times a week) 3-week treatment No follow-up	Binge eating behaviors Vomiting behaviors BDI

AN-BP = Anorexia Nervosa Binge-Purge subtype; AN-P= Anorexia Purge subtype; AN-R = Anorexia Nervosa Restrictive subtype; AN-SE = Anorexia Nervosa Severe Enduring; BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; BMI = Body Mass Index; BN = Bulimia Nervosa; DASS-21 = Depression, Anxiety and Stress Scale – 21 item; DLPFC = Dorso-Lateral Prefrontal Cortex; DMPFC = Dorso-Medial Prefrontal Cortex; EDE = Eating Disorder Examination Rating Scale; EDE-Q = Eating Disorder Examination Interview; EDs-NOS = Eating Disorders Not Otherwise Specified; HDRS = Hamilton Depression Rating Scale; M = Men; PANAS = Positive Affect and Negative Affect Scale; SF-36 = Short Form General Health Survey; RCT = Randomized Controlled Trial; UK = United Kigdom; VAS = Visual Analogue Scale; YBC-EDS = Yale-Brown-Cornell Eating Disorder Scale; W = Women;

(APA, 2008; 2010) and PRISMA guidelines (Moher et al., 2009). **Figure 1** summarizes the inclusion process of the studies. In order to consider studies of comparable quality, the analysis only included studies that were published in scientific journals. PsychINFo, Pubmed, ISI Web of Knowledge and Scopus online databases were used to generate potentially relevant articles. The online search was conducted for the period between January 1993 and 31st July 2021. The starting point was 1993 because this was the year when the first studies on the therapeutic effects of rTMS were published (for a review:

Wassermann, & Lisanby, 2001). The online research was based on the following keywords: "transcranial magnetic stimulation", "rTMS", "TMS" AND "eating disorders", "anorexi*", "bulimi*", "binge eating disorder", "obesity", "food craving". The references of a review article were used as additional sources of information (Dalton et al., 2018a). M.C. and A.S. conducted the online research. The screening process was double-checked in order to produce a reliable initial sample of articles. Cohen's k was estimated for inter-rater reliability of study selection (Cohen, 1960).

Figure 1. *CONSORT flow chart of studies inclusion process*
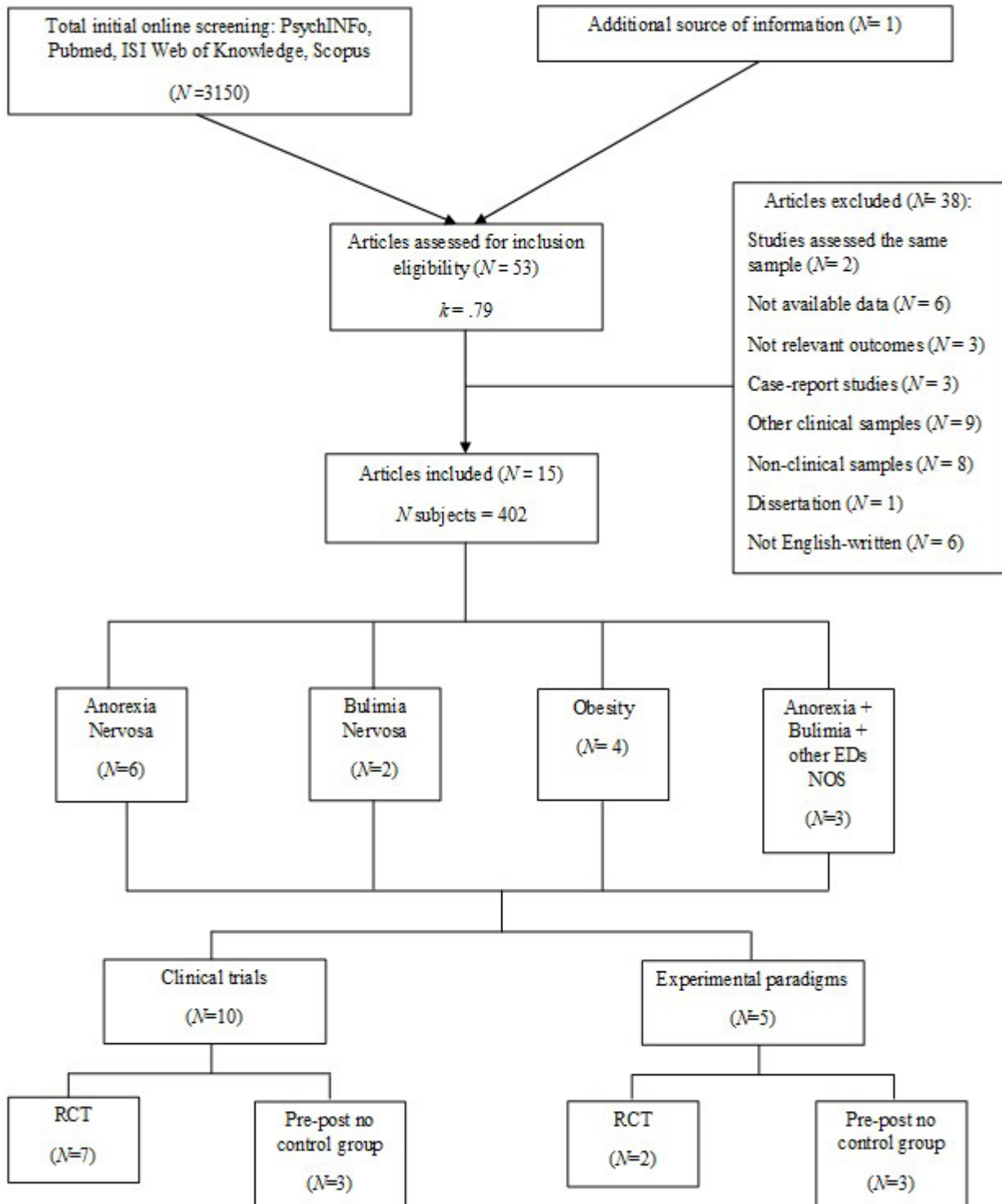
In order to be included in the current meta-analytic review, the studies met the following inclusion criteria to support the validity and reliability of results: a) all studies assessed the effects of rTMS protocols among clinical samples of individuals with EDs according to DSM criteria; b) given the lack of adequate clinical trials among patients with BED (i.e., single-case studies), the current meta-analysis included results from research on the clinical effects of rTMS among individuals affected by obesity, according to common latent psychopathological dimensions and overt behavioral manifestations (e.g., Davis, 2017, Lavagnino et al., 2016); c) all studies assessed primary outcomes (e.g., BMI, frequency and urge of dysfunctional eating behaviors, ED symptoms) and secondary outcomes (e.g., negative affectivity, depressive and anxious symptoms) routinely evaluated for the efficacy of different therapeutic approaches for EDs (e.g., Linardon et al., 2017; Vall & Wade, 2015); d) all studies referred to valid, reliable instruments for the assessment of primary outcomes— the Eating Disorder Examination Interview (EDE; Cooper & Fairburn, 1987); the Eating Disorder Examination Questionnaire (EDE-Q; Fairburn & Beglin, 2008); The Yale-Brown-Cornell eating disorder scale (Mazure et al., 1994); Visual Analogue Scales (VASs) for estimating the intensity of urges to engage in maladaptive eating behaviors — and secondary outcomes — the Beck Depression Inventory (BDI; Beck et al., 1961), the Beck Anxiety Inventory (BAI; Fydrich et al., 1992); the Hamilton Depression Rating Scale (HDRS; Williams, 1988); the Depression, Anxiety and Stress Scale-21 (DASS-21; Lovibond & Lovibond, 1995); the Positive Affect and Negative Affect Scale (PANAS; Watson et al., 1988); the Short-Form health survey (SF-36; Ware & Sherbourne, 1992); VASs evaluating feeling of anxiety, tension, stress and quality of mood. Case-reports and animal studies, together with dissertations were excluded from the meta-analysis. The research design (i.e., clinical trial vs experimental paradigms) and sex were not considered exclusion criteria. However, these aspects were considered as possible moderators of effect sizes when there was significant heterogeneity of findings across studies.

Data analysis

Cohen's *d* (Cohen, 1988) was used as a measure of effect size. It was primarily calculated using descriptive statistics reported in the Results section of each study. The suitable procedures proposed by Morris (2008) were used to estimate Cohen's *d* for the pretest-posttest-control group design. Specifically, the Cohen's *d* computation was based on pre-post score differences, the pooled pre- and posttest standard deviation and the application of a bias correction factor. In the case of multiple comparisons over time performed by the original authors, the analyses calculated *d* for each contrast and obtained a single pooled coefficient, consistently with procedures provided by Borenstein and colleagues (2011). Values of Cohen's *d* greater than or equal to .20, .50, and .80 were interpreted as small, moderate, and large effect sizes, respectively (Cohen, 1988).

The overall pooled effect sizes (d_w) for each treatment outcome were estimated using the weighted mean of *d* value for each study (Borenstein et al., 2011; Hedges & Olkin, 1985). The 95% confidence interval (CI) was computed, as was its significance according to the ratio of pooled effect size to the standard error (Borenstein et al., 2011; Hedges & Olkin, 1985). Pooled effect sizes were estimated whenever at least three

independent studies yielded data.

Heterogeneity in effect sizes was computed using the *Q* statistic (Hedges & Olkin, 1985) and I^2 index (Higgins et al., 2003; Huedo-Medina et al., 2006). Despite the small number of studies for each outcome, Egger's regression (i.e., the standard normal deviate [SND] is regressed against the estimate's precision, defined as the inverse of the standard error; SND = a + *b* × precision; Egger et al., 1997) was performed to detect publication bias. Furthermore, in order to control for possible sources of variability across studies, the analysis tested the effects of sample size, age of participants, year of publications, number of rTMS session, length of treatment and follow-up period of evaluation on meta-analytic results. Specifically, Spearman's correlations (ρ) between these potential sources of variability and effect sizes were estimated. Given the small number of available studies, a bootstrap methodology (bias corrected and accelerated; Davison, 1997) was applied to compute the significance of the previous parameters. A total of 1000 bootstrap independent samples were used with *p* < .05 (2-*tailed*).

Orwin's (1983) fail-safe procedure was estimated to assess the number of studies with null results needed to overturn our conclusions. For Orwin's fail-safe *N*, the critical level was set at .20. Furthermore, using procedures proposed by Rosenthal (1991), the critical value (5*k* + 10; *k* = number of studies) of Orwin's fail-safe *N* was computed to assess the power of our conclusions. Ultimately, the quality of studies included in this meta-analysis was screened using adequate assessment instruments. According to the systematic review proposed by Olivo and colleagues (2008), the Jadad scale (Jadad et al., 1996) was used as the most valid and reliable tool for assessing the quality of randomized controlled trials. On the contrary, the quality of nonrandomized trials was evaluated using the Newcastle-Ottawa Scale (Well et al., 2009), consistently with well-accepted guidelines for this research design (Stang, 2010). M.C. and A.S. independently assessed the quality of studies included. Cohen's *k* was estimated for inter-rater reliability of quality of studies evaluation. The discrepancies were resolved by a third reviewer (A.O.)

Results

Figure 1 shows the inclusion process of studies, and summarizes the characteristics of the studies considered for meta-analytic procedures. The analysis showed a good inter-rater reliability value (Cohen's *k* = .79) for the screening of articles. Thirty-eight studies were excluded. Two studies were excluded because they published data from the same sample. Nine studies were not included due to incomplete data presentation for computing effect sizes, and to the investigation of non-pertinent outcomes for testing the hypotheses of the current study. Fifteen independent studies were included for a total of 402 individuals with EDs and obesity. **Table 2** reports the results of meta-analytic procedures for each primary and secondary treatment outcome. With respect to primary treatment outcomes, the current meta-analytic review computed pooled effect sizes and related metrics for the BMI of individuals affected by obesity (*N*=3) and AN (*N*=3), frequency of binge eating (*N* = 3) and other compensatory behaviors (*N*=3), intensity of urge to binge (*N*=3) and to eat (*N*=4) and severity of EDs symptoms (*N* = 5). Considering secondary outcomes, the analyses estimated pooled effect sizes for overall negative affectivity (*N* = 7) and

Table 2. *Meta-analytic results for each outcome*

Outcome	Sample	N subjects	N studies	d_w (95%CI)	Q (df)	I^2	Egger's coefficient (95% bootstrap CI)
BMI	Obesity	129	3	-.85 (-1.14 – -.56)***	23.35 (2)***	91.44%	-9.02 (NE); ns
BMI	AN	63	3	.07 (-.21 – .34)	1.66 (2)	0.00%	-4.77 (NE); ns
Binge eating behaviors	AN; BN	47	3	-.14 (-.42 – .15)	.04 (2)	0.00%	-.31 (NE); ns
Urge to binge	AN; BN; EDs-NOS	93	3	.01 (-.35 – .39)	1.29 (2)	0.00%	-5.17 (NE); ns
Urge to eat	AN; BN ; EDs-NOS	95	4	-.09 (-.35 – .16)	.54 (3)	0.00%	-2.79 (NE); ns
Compensatory behaviors	AN; BN	47	3	0.00 (-29 – .29)	.89 (2)	0.00%	-1.41 (NE); ns
Severity of EDs symptoms	AN; BN; EDs-NOS	79	5	-.13 (-.36 – .10)	6.38 (4)	37.29%	-2.5 (-45.49 – 5.74); ns
Overall negative affectivity	AN; BN; EDs-NOS; obesity	177	7	-.47 (-.68 – -.26)***	28.17 (6)***	78.70%	-4.86 (-11.99 – .53); ns
Severity of depressive symptoms	AN; BN	30	5	-.42 (-.92 – -.07)	5.53 (4)	27.75%	3.13 (-11.38 – 11.44); ns
Severity of anxious symptoms	AN; BN	133	6	-36 (-.80 – .08)	3.03 (5)	0.00%	.10 (-17.78 – 50.01); ns

**p<.01; ***p<.001; AN = Anorexia Nervosa; BN = Bulimia Nervosa; CI = Confidence Interval; EDs-NOS = Eating Disorders Not Ot

severity of both depressive (*N* = 5) and anxious (*N* = 6) symptoms. **Tables 3** and **4** show the screening of the quality of studies included in the current meta-analysis.

Primary treatment outcomes

Considering effects of rTMS on BMI, the analyses showed a large improvement (d_w = -.85 [-1.14 – -.56]; *p* < .001) among individuals with obesity, even though the heterogeneity of findings across studies was large (I^2 = 91.44%) and significant ($Q_{(2)}$ = 23.35; *p* < .01). However, the sample size, age of participants, years of publication, number of rTMS sessions, length of treatment and follow-up period of evaluation were not related to effect sizes. The robustness of this pooled effect size (Orwin's fail-safe *N* = 9.78) prevented us from drawing definitive conclusions concerning the efficacy of rTMS for reducing BMI in this clinical population (Rosenthal's critical value *N* = 25). However, the analysis did not detect publication bias.

On the contrary, null and consistent effects (d_w = .07 [-.21 – .34], *ns; $Q_{(2)}$* = 1.66; *ns*) of rTMS were detected considering individuals with AN. Egger's regression did not highlight publication bias. Considering the other primary outcomes — frequency of binge eating and other compensatory behaviors, urge to binge and eat, severity of EDs symptoms — investigated among individuals with AN, BN and other EDs-NOS, the analyses showed null therapeutic effects of rTMS for all these dimensions. Furthermore, findings were consistent across studies. Ultimately, the analyses did not show publication bias.

Secondary treatment outcomes

Meta-analytic procedures showed that rTMS had a moderate therapeutic effect (d_w = -.47 [-.68 – -.26]; *p* < .001) on the improvement of overall negative affectivity among different EDs. However, the heterogeneity of results across studies was large (I^2 = 78.70%) and significant ($Q_{(6)}$ = 28.17; *p* < .01). Excluding an outlier

Table 3. *Quality of randomized controlled trials (Jadad scale)*

Study	Was the study described as randomized (this includes the use of words such as randomly, random, and randomization)?	Was the study described as double blind?	Was there a description of withdrawals and dropouts?
Alvarado-Reynoso, & Ambriz-Tututi, 2019	Yes	Yes	No
Dalton et al., 2018	Yes	Yes	Yes
Dalton et al., 2020	Yes	No	Yes
Encarnacion et al., 2020	Yes	No	not applicable
Kim et al., 2018	Yes	No	Yes
Kim et al., 2019	Yes	No	Yes
McClelland et al., 2016a	Yes	Yes	Yes
Van den Eynde et al., 2009	Yes	No	not applicable
Walpoth et al., 2008	Yes	No	not applicable

Table 4. *Quality of nonrandomized controlled trials (Newcastle-Ottawa Scale)*

Study	Selection			
	Is the case definition adequate?	**Representativeness of the cases**	**Selection of Controls**	**Definition of Controls**
Dunlop et al., 2015	yes, with independent validation	consecutive	not applicable	not applicable
Knyahnytska et al., 2019	yes, with independent validation	potential for selection biases	not applicable	not applicable
McClelland et al., 2016b	yes, with independent validation	potential for selection biases	not applicable	not applicable
Sutoh et al., 2016	yes, with independent validation	potential for selection biases	not applicable	not applicable
Van den Eynde et al., 2012	yes, with independent validation	potential for selection biases	not applicable	not applicable
Van den Eynde et al., 2013	yes, with independent validation	potential for selection biases	not applicable	not applicable

of the distribution (Alvarado-Reynoso & Ambriz-Tututi, 2019: d = -1.93 [-2.71 – -1.15]), the analyses highlighted consistent results across the remaining studies ($Q_{(5)}$ = 4.70; *ns*; I^2 = 0.00%) and small to moderate improvements (d_w = -.37 [-.58 – -.16]; *p* < .001). However, this pooled effect was not robust enough to draw definitive conclusions (Orwin's fail-safe N = 5.07; critical value N = 40). Similar findings were detected for both depressive (d_w = -.42 [-.92 – .07]; *ns*; $Q_{(4)}$ = 5.53; *ns*; I^2 = 27.75%) and anxious symptoms (d_w = -.36 [-.80 – .00]; *ns*; $Q_{(5)}$ = 3.03; *ns*; I^2 = 0.00%), even though the effects of rTMS on these dimensions were not significant. Overall, the analyses did not find publication bias for these secondary treatment outcomes.

Quality of studies

The analysis showed a good inter-rater reliability value (Cohen's k = .83) for the quality of studies assessment. Considering randomized controlled trials (N = 9; see **table 3**), only 3 studies (33.3%) were described as double-blind. The remaining 6 studies were carried out as single-blind protocols. Five studies (55.5%) provided an adequate description of subjects who dropped out of clinical trials and comparisons between them and individuals who completed the treatments. This item of the Jadad scale was inapplicable for 3 studies. The maximum total mean score of the Jadad scale assigning a score of 1 to "Yes" responses and 0 to "No" responses is 1. The mean score of randomized controlled trials included in this meta-analysis on the Jadad scale was .71, suggesting an overall good quality.

With respect to nonrandomized controlled trials (N = 6; see **table 4**), the Newcastle-Ottawa Scale showed that the most recurrent strengths of the studies included referred to a valid and reliable identification of individuals with EDs (100%; *selection domain*) and the *ascertainment of exposure* to rTMS protocols (100%; *exposure domain*). On the contrary, the remaining items of the scale highlighted limitations for all the studies included, suggesting a low quality of findings.

Discussion

This study sought to provisionally test the efficacy of rTMS for the treatment of EDs using a meta-analytic approach. Accordingly, this meta-analysis aggregated results considering several primary and secondary treatment outcomes that are well-validated in clinical research on EDs. Furthermore, the current study sought to investigate whether this clinical approach might have comparable effects for the full spectrum of EDs or whether it could be more effective for specific conditions, namely BED or obesity. This was hypothesized considering empirical evidence that shows overlaps between these conditions and addictive disorders, for which rTMS protocols have highlighted promising therapeutic effects in addressing the core features of SUDs, namely craving and substance-use behaviors.

Consistently with the hypotheses of the study, meta-analytic procedures showed that rTMS had large therapeutic effects in sustaining the reduction of BMI among individuals with obesity. This result is consistent with evidence demonstrating fronto-striatal alterations linked to inhibitory control found among patients with obesity (Lavagnino et al., 2016). Specifically, rTMS at a high frequency might reinforce the activity of 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) (Lefaucheur et al., 2020) involved in the regulation of reward-based behaviors (Volkow et al., 2017). On the contrary, rTMS showed consistent null impacts on the improvements of BMI among individuals with AN. These findings might provisionally support the claim that rTMS should be specifically carried out for the treatment of patients with obesity, rather than for the other EDs. This consideration might also be sustained by empirical evidence showing that core neural alterations related to AN involved attentional and perceptual mechanisms, instead of inhibitory control processes (Reville et al., 2016). These differential neural mechanisms underlying EDs might also explain the null therapeutic effects of rTMS for the other primary treatment outcomes assessed among individuals with AN, BN and other EDs-NOS. Specifically, it could be possible that binge eating and other compensatory behaviors among these conditions reflect other core features of the disorders, such as cognitive overcontrol (e.g., King et al., 2019) and cognitive inflexibility (e.g., Roberts et al., 2007), which could be insensitive to rTMS procedures.

Contrary to primary outcomes, rTMS seems to show significant and moderate therapeutic effects in reducing negative affectivity. This result is partially consistent with results of previous meta-analyses that demonstrated clinically significant impacts of rTMS in the treatment of depressive symptoms (e.g., Berlim et al., 2014; Gross et al., 2007; Teng et al., 2017).

However, excluding the results of Alvarado-Reynoso & Ambriz-Tututi's (2019) study carried out among individuals with obesity, the effects of rTMS on the affective functioning of individuals with the other EDs was small, especially considering depressive and anxious symptoms. Therefore, rTMS procedures should be considered an ancillary intervention for the treatment of AN, BN and other EDs-NOS with modest effects on the improvement of affective functioning.

On the contrary, rTMS seems to largely improve the negative affectivity of individuals with obesity, even though this consideration is based on only one study (Alvarado-Reynoso & Ambriz-Tututi, 2019). Taken together this finding and the results linked to rTMS effects on BMI reduction, it is possible to provisionally conclude that these procedures are promising for the treatment of obesity and, likely also for patients with BED as reported by a single case study (Pires Baczynski et al., 2014). However, future randomized controlled trials are needed to further support this hypothesis, especially considering individuals with BED.

Although the current study showed consistent results across studies included for meta-analytic procedures, some limitations must be discussed. First of all, the number of studies considered for the computation of pooled effect size for each outcome was small. Moreover, the systematic assessment of study quality showed that results from nonrandomized controlled trials might be biased due to several methodological limitations. Therefore, additional randomized controlled trials on the therapeutic effects of rTMS for the treatment of EDs are recommended in order to replicate the evidence provided in the current meta-analysis.

Second, several issues might limit conclusions regarding the efficacy of rTMS for reducing BMI among individuals with obesity. Specifically, the heterogeneity of findings was large and unexplained, also Orwin's fail-safe number suggested that the pooled effect size was not robust enough to draw definitive conclusions on the efficacy of this clinical approach in reaching this primary therapeutic goal. Moreover, the stability over time of the therapeutic effects of rTMS on the BMI of individuals with obesity should be considered as an additional critical issue. Although the analysis did not detect a significant association between length of follow-up and effect sizes, the study with a longer follow-up (i.e., 12 weeks) (Encarnacion et al., 2020) showed a small to moderate effect size ($d = -.45$ [$-.82 – -.08$]) contrary to the other two remaining studies (Kim et al., 2018, 2019), assessing the effects of rTMS treatment over a 4-week follow-up period and highlighted large effect sizes ($d = -.92$ [$-1.47 – -.38$]; $d = -2.67$ [$-3.49 – -1.85$]). Hence, future studies should be carried out considering the long-term effects of rTMS on BMI reduction among individuals affected by obesity. Another limitation concerning the therapeutic effects of rTMS among individuals with obesity is the fact that two (Kim et al., 2018, 2019) out of three studies were conducted by the same research group among individuals coming from the same culture. Accordingly, further replication studies carried out by different research groups and conducted among different cultures are needed to corroborate the provisional evidence concerning the therapeutic effects of rTMS for this condition. Furthermore, speculations on the efficacy of rTMS for the treatment of BED should be empirically demonstrated through several clinical trials in this population, since the current meta-analytic procedures have not found any adequate studies to be included.

Third, the studies included in the current meta-analysis are very heterogeneous considering the characteristics of each rTMS protocol. Specifically, the length of rTMS sessions ranged from 10 to 20 minutes and differed greatly in inter-train intervals (i.e., 10 – 60 seconds). Furthermore, rTMS protocols varied significantly with respect to the number of pulses provided in each session (i.e., 1000 – 3000), especially considering how the trains of pulses were administered. Some studies delivered twenty trains of 5 seconds (e.g., Dalton et al., 2018; McClelland et al., 2016b; Van den Eynde et al., 2009) while others performed ten trains of 10 seconds (Walpoth et al., 2008) or eighty trains of 2 seconds (Knyahnytska et al., 2019). Some inconsistencies were also detected regarding the frequency of trains of pulses. Although most of the research provided pulses with a 10 Hz frequency, other protocols used different frequencies, such as 20 Hz (Walpoth et al., 2008) or 18 Hz (Knyahnytska et al., 2019). Therefore, future research on the effects of rTMS for the treatment of EDs should move toward a more rigorous consensus on common guidelines to provide this clinical intervention as is done for other conditions, such as major depression disorder (Perera, George, Grammer, Janicak, Pascual-Leone, & Wirecki, 2016).

Ultimately, an additional limitation may be linked to self-report measures used to assess primary and secondary treatment outcomes, which might partially explain the small therapeutic effects of rTMS. Therefore, future research on the efficacy of rTMS should include the evaluation of other objective indexes of brain functioning (e.g., functional magnetic resonance imaging, electroencephalography) in order to clarify the short and long-term effects of these procedures at a neurobiological level among individuals with EDs.

However, this is the first meta-analysis that has attempted to clarify the efficacy of rTMS for the treatment of EDs. The current provisional findings have suggested that this clinical approach shows encouraging results for obese individuals and might be promising for patients with BED. Furthermore, rTMS could represent an ancillary treatment for the other EDs, especially considering secondary treatment outcomes. Further research is needed to provide additional support for these hypotheses and to clarify mechanisms of action of rTMS among different populations of EDs.

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