2024, Retos, 60, 1036-1048

Repetitive transcranial magnetic stimulation (rTMS) in the treatment and diagnosis of eating disorders in athletes and patients: a systematic review

Estimulação magnética transcraniana repetitiva (EMTr) no tratamento e diagnóstico de transtornos alimentares em atletas e pacientes: uma revisão sistemática

Estimulación magnética transcraneal repetitiva (EMTr) en el tratamiento y diagnóstico de trastornos alimentarios en atletas y pacientes: una revisión sistemática

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Abstract. Repetitive Transcranial Magnetic Stimulation (rTMS) is a non-invasive technique used to treat and diagnose eating disorders (EDs) by targeting brain regions like the dorsolateral prefrontal cortex, which is involved in impulse control and emotion regulation. Particularly beneficial for athletes, rTMS can reduce symptoms of EDs. Therefore, this study aimed to carry out a systematic review of the scientific literature on the therapeutic or diagnostic use of rTMS in athletes and patients with EDs, with an emphasis on binge eating disorder (BED), anorexia nervosa (AN), and bulimia nervosa (BN). A literature survey was carried out in the Directory of Open Access Journals (DOAJ), Medline, Directory of Open Access Scholarly Resources (ROAD), Academic Search Premier, Wiley-Blackwell Full Collection, Nature Open Access, BioMed Central Open Access, and Cumulative Index to Nursing and Allied Health Literature (CINAHL). A total of 26 original papers published until November 21, 2021, were included. The selected studies were grouped for each respective protocol: total number of patients or athletes, sociodemographic aspects of the participants, parameters performed in rTMS: type of coil, intensity, frequency, number of pulses, stimulation site, preliminary results, and incidence of adverse effects. Recent evidence suggests a low rate of side effects with the technique and a substantial high frequency rTMS response in both the dorsolateral prefrontal cortex and the ventromedial region, especially in studies where internal comparison was performed. The great tolerance and safety of neuromodulatory treatment with rTMS encourage the application of the technique, especially in patients with refractory eating disorders. In addition to the therapeutic potential, rTMS is an essential diagnostic tool in elucidating the complex neurobiology of eating disorders. A more significant increase in publications on the subject is expected in a controlled, blind, and randomized manner, leading to a homogenization of results and generalization of its potential use.
Keywords: Eating disorders, Neurology, Neuromodulation, Psychology, Psychiatry, Noninvasive brain stimulation.

Resumo. A Estimulação Magnética Transcraniana Repetitiva (EMTr) é uma técnica não invasiva utilizada para tratar e diagnosticar transtornos alimentares (TAs) ao direcionar regiões do cérebro como o córtex pré-frontal dorsolateral, envolvido no controle dos impulsos e na regulação das emoções. Particularmente benéfica para atletas, a EMTr pode reduzir os sintomas dos TAs. Portanto, este estudo teve como objetivo realizar uma revisão sistemática da literatura científica sobre o uso terapêutico ou diagnóstico da EMTr em atletas e pacientes com TAs, com ênfase no transtorno de compulsão alimentar periódica (TCAP), anorexia nervosa (AN) e bulimia nervosa (BN). Foi realizada uma pesquisa bibliográfica no Directory of Open Access Journals (DOAJ), Medline, Directory of Open Access Scholarly Resources (ROAD), Academic Search Premier, Wiley-Blackwell Full Collection, Nature Open Access, BioMed Central Open Access e Cumulative Index to Nursing and Allied Health Literature (CINAHL). Um total de 26 artigos originais publicados até 21 de novembro de 2021 foram incluídos. Os estudos selecionados foram agrupados para cada respectivo protocolo: número total de pacientes, aspectos sociodemográficos dos participantes, parâmetros realizados na EMTr: tipo de bobina, intensidade, frequência, número de pulsos, local de estimulação, resultados preliminares e incidência de efeitos adversos. Evidências recentes sugerem uma baixa taxa de efeitos colaterais com a técnica e uma resposta substancial de EMTr de alta frequência tanto no córtex pré-frontal dorsolateral quanto na região ventromedial, especialmente em estudos onde foi realizada comparação interna. A grande tolerância e segurança do tratamento neuromodulador com EMTr incentivam a aplicação da técnica, especialmente em pacientes com transtornos alimentares refratários. Além do potencial terapêutico, a EMTr é uma ferramenta diagnóstica essencial na elucidação da complexa neurobiologia dos transtornos alimentares. Espera-se um aumento significativo nas publicações sobre o assunto de forma controlada, cega e randomizada, levando à homogeneização dos resultados e à generalização de seu potencial uso.
Palavras-chave: Transtornos alimentares, Neurologia, Neuromodulação, Psicologia, Psiquiatria, Estimulação cerebral não invasiva.

Resumen. La Estimulación Magnética Transcraneal Repetitiva (EMTr) es una técnica no invasiva utilizada para tratar y diagnosticar trastornos alimentarios (TAs) al dirigir regiones del cerebro como la corteza prefrontal dorsolateral, involucrada en el control de los impulsos y la regulación de las emociones. Particularmente beneficiosa para los atletas, la EMTr puede reducir los síntomas de los TAs. Por lo tanto, este estudio tuvo como objetivo realizar una revisión sistemática de la literatura científica sobre el uso terapéutico o diagnóstico de la EMTr en atletas y pacientes con TAs, con énfasis en el trastorno por atracón (TA), anorexia nerviosa (AN) y bulimia nerviosa (BN). Se realizó una búsqueda bibliográfica en el Directory of Open Access Journals (DOAJ), Medline, Directory of Open Access Scholarly Resources (ROAD), Academic Search Premier, Wiley-Blackwell Full Collection, Nature Open Access, BioMed Central Open Access y Cumulative Index to Nursing and Allied Health Literature (CINAHL). Se incluyeron un total de 26 artículos originales publicados hasta el 21 de noviembre de 2021. Los estudios seleccionados se agruparon para cada protocolo respectivo: número total de pacientes, aspectos sociodemográficos de los participantes, parámetros realizados en la EMTr: tipo de bobina, intensidad, frecuencia, número de pulsos, lugar de estimulación, resultados preliminares e incidencia de efectos adversos. La evidencia reciente sugiere una baja tasa de efectos secundarios con la técnica y una respuesta sustancial de EMTr de alta frecuencia tanto en la corteza prefrontal dorsolateral como en la región ventromedial, especialmente en estudios donde se realizó comparación interna. La gran tolerancia y seguridad del tratamiento neuromodulador con EMTr fomentan la aplicación de la técnica, especialmente en pacientes con trastornos alimentarios refractarios. Además del potencial terapéutico, la EMTr es una herramienta diagnóstica esencial para dilucidar la compleja neurobiología de los trastornos alimentarios. Se espera un aumento significativo en las publicaciones sobre el tema de manera controlada, ciega y aleatorizada, lo que llevará a una homogeneización de los resultados y a la generalización de su uso potencial.
Palabras clave: Trastornos alimentarios, Neurología, Neuromodulación, Psicología, Psiquiatría, Estimulación cerebral no invasiva.

Fecha recepción: 31-05-24. Fecha de aceptación: 28-08-24
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Introduction

Eating disorders (EDs) such as anorexia nervosa (AN), bulimia nervosa (BN), and binge eating disorder (BED) are serious health concerns that affect individuals across all demographics, including athletes (de Souza et al., 2022; Gallop et al., 2022). These disorders significantly impact physical health, mental well-being, and overall performance. For athletes, the pressures related to body image, performance, and weight management can further increase the risk of developing EDs (de Souza et al., 2022). These conditions are recognized as severe mental health disorders that drastically reduce the quality of life for patients and their families (Gay et al., 2016). Conventional treatment for EDs typically includes nutritional

therapy, which aims to achieve optimal nutrition, impact body mass index (BMI), and influence mood through the serotonergic system (Dalton et al., 2018). Psychotherapy, particularly cognitive-behavioral therapy, is another primary treatment method, alongside pharmacological interventions such as anticonvulsants and serotonin reuptake inhibitor antidepressants (Mitchell et al., 2024; Gallop et al., 2022). Despite these treatments, only about one-third of patients with AN and BN achieve symptom remission, indicating a need for more effective therapeutic approaches (Gallop et al., 2022).

Athletes often experience EDs that mirror those found in the general population but can be exacerbated by the unique demands of competitive sports. For example:

AN is characterized by an intense fear of gaining weight and a distorted body image, leading to severe food restriction. Athletes, particularly those in sports emphasizing leanness, might adopt extreme diets and exercise regimes to maintain a lower weight for performance or aesthetic reasons (Ghazzawi et al., 2024).

BN involves cycles of binge eating followed by purging, such as vomiting or excessive exercise, to prevent weight gain. Athletes may use these behaviors to control weight while still consuming sufficient calories to meet their energy demands (de Souza et al., 2022; Ghazzawi et al., 2024).

BED is marked by recurrent episodes of consuming large quantities of food in a short period, often leading to discomfort but without compensatory behaviors seen in bulimia (de Souza et al., 2022). In athletes, binge eating may serve as a coping mechanism for stress, or emotional issues related to sport.

Orthorexia, although not officially recognized as a distinct eating disorder, involves an unhealthy obsession with eating foods considered healthy and avoiding those deemed unhealthy to an extreme degree that affects well-being. Athletes, especially those in sports where diet is crucial for performance or appearance, may be particularly susceptible to orthorexia (Ghazzawi et al., 2024; Mitchell et al., 2024).

In recent years, Repetitive Transcranial Magnetic Stimulation (rTMS) has emerged as a promising neuromodulatory strategy that may offer new treatment avenues for EDs. rTMS involves applying magnetic stimuli at regular intervals to induce electrical currents in specific cortical regions, thereby modulating brain activity. This technique has been shown to impact various neural processes, including long-term potentiation (LTP), long-term depression (LTD), cerebral blood flow, enzyme activity, and gene expression (Chervyakov et al., 2015). These changes are believed to underlie the therapeutic effects of rTMS in treating various neurological and psychiatric disorders, including EDs (Chervyakov et al., 2015; Gay et al., 2016).

The primary TMS techniques include Single-pulse and Paired-pulse TMS, which are used to map the cerebral cortex and assess its excitability, helping researchers understand the brain's functional connectivity (McClelland et al., 2013). rTMS, which involves a series of magnetic pulses delivered in succession. The frequency of these pulses determines the effects on neuronal activity, for instance, Low-frequency rTMS (≤ 1 Hz) reduces neuronal excitability and inhibits cortical activity, and High-frequency rTMS (> 1 Hz, up to 60 Hz) increases neuronal excitability and stimulates cortical activity (S. Song et al., 2019). Another variant, Theta-burst Stimulation (TBS), delivers three consecutive 50 Hz stimuli every 200 ms, offering a shorter session time of about 3 minutes compared to traditional rTMS sessions, which last 15 to 30 minutes (Dunlop et al., 2016; Val-Laillet et al., 2015). Despite its potential, the outcomes of rTMS, including TBS, in treating EDs are not yet fully established.

The type of coil used in rTMS also plays a crucial role in determining the focus and depth of cortical activation. For example, figure-eight or butterfly coils provide a more focal action, targeting specific cortical areas with precision (Gallop et al., 2022). Circular coils have a more diffuse activation cone, affecting a broader cortical area (Gay et al., 2022). Specialized coils, such as the 120 double cone or H-shaped coils, can reach deeper brain regions, like the ventromedial cortex or the cingulate and insula regions, making them suitable for targeted neuromodulation (Duriez et al., 2020).

According to the European Guidelines on the therapeutic efficacy of rTMS, this therapy has achieved Level A evidence for conditions such as neuropathic pain, depression, and motor recovery post-acute stroke. It also has Level B evidence for fibromyalgia, Parkinson's disease, and spasticity in multiple sclerosis (Lefaucheur et al., 2020). While generally safe, rTMS is contraindicated for individuals with metallic hardware near the stimulation site due to the risk of device malfunction. The most significant risk associated with rTMS is the potential for inducing a seizure, although this is rare when following established safety guidelines (Gay et al., 2022).

Emerging research indicates that high-frequency rTMS targeting the left dorsolateral prefrontal cortex (dlPFC) can effectively reduce ED symptoms, including anxiety, stress, compulsive behaviors, purging episodes, and food cravings in BN and BED, as well as the desire to restrict food intake in AN (Baczynski et al., 2014; Gay et al., 2022; Gay et al., 2016). Modulating this brain region is expected to alter cortical excitability and brain activity patterns, leading to improved cognitive control and reduced ED symptoms (Lurati, 2022; Claudino et al., 2011).

Given the growing interest in rTMS as a treatment and diagnostic tool for EDs, particularly among athletes, this systematic review aims to synthesize the current scientific literature on the use of rTMS in these populations. By examining the therapeutic and diagnostic potential of rTMS across different protocols and patient groups, this review seeks to provide a comprehensive understanding of its efficacy, safety, and future applications in clinical practice.

Material and Methods

The study's protocol was registered in PROSPERO, and the data are available on the Open Science Framework via the provided link. We adhered to the PRISMA guidelines for organizing systematic reviews (Page et al., 2021). Our research focused on participants with EDs.

Research strategy

First, a search was conducted in the Directory of Open Access Journals (DOAJ), Medline, ROAD (Directory of Open Access Scholarly Resources), Academic Search Premier, Wiley-Blackwell Full Collection, Nature Open Access, BioMedCentral Open Access, and Cumulative Index to Nursing and Allied Health Literature (CINAHL) to collect the majority of studies relevant to the review objectives. The descriptors of the respective Medical Subject Headings (MeSH) and Descriptors in Health Sciences (DeCS) were consulted and combined with the Boolean operators AND and OR. The following search terms were used: "binge eating" OR "binge eating disorder" OR "binge eating disorders" OR "eating behavior" OR "eating disorder" OR "disorders of eating" OR "anorexia" OR "bulimia" AND "Transcranial Magnetic Stimulation" OR "TMS" OR "Theta burst" OR "rTMS" AND "patients" OR "athletes." From 487 studies, 88 articles were selected from the databases mentioned above and published in English, describing the role of rTMS in patients with eating disorders (ED). Of these, 52 were excluded for the reasons described in Diagram 1: 31 were review articles without original data or did not meet the inclusion criteria (n=31): (1) patients diagnosed with one of the specific EDs—binge eating disorder, anorexia nervosa (AN), or bulimia nervosa (BN); (2) human studies; (3) reports of patients with EDs who received rTMS as an experimental treatment or intervention.

Study selection

Two authors conducted the research independently. The Mendeley software was used to screen the articles. First, we included all published articles with study designs that applied rTMS to reduce ED by reading the titles and abstracts. In the next step, we used the Rayyan software, duplicates were removed, articles were read, and those that did not have enough information to apply the eligibility criteria were excluded. After the evaluation, the two authors plus a judge (a third author) met to reach a consensus regarding the inclusion and exclusion criteria for each article, and disagreements were discussed. A consensus was reached for all included articles. The agreement between raters was 95%. The description of the selection of studies is shown in Figure 1.

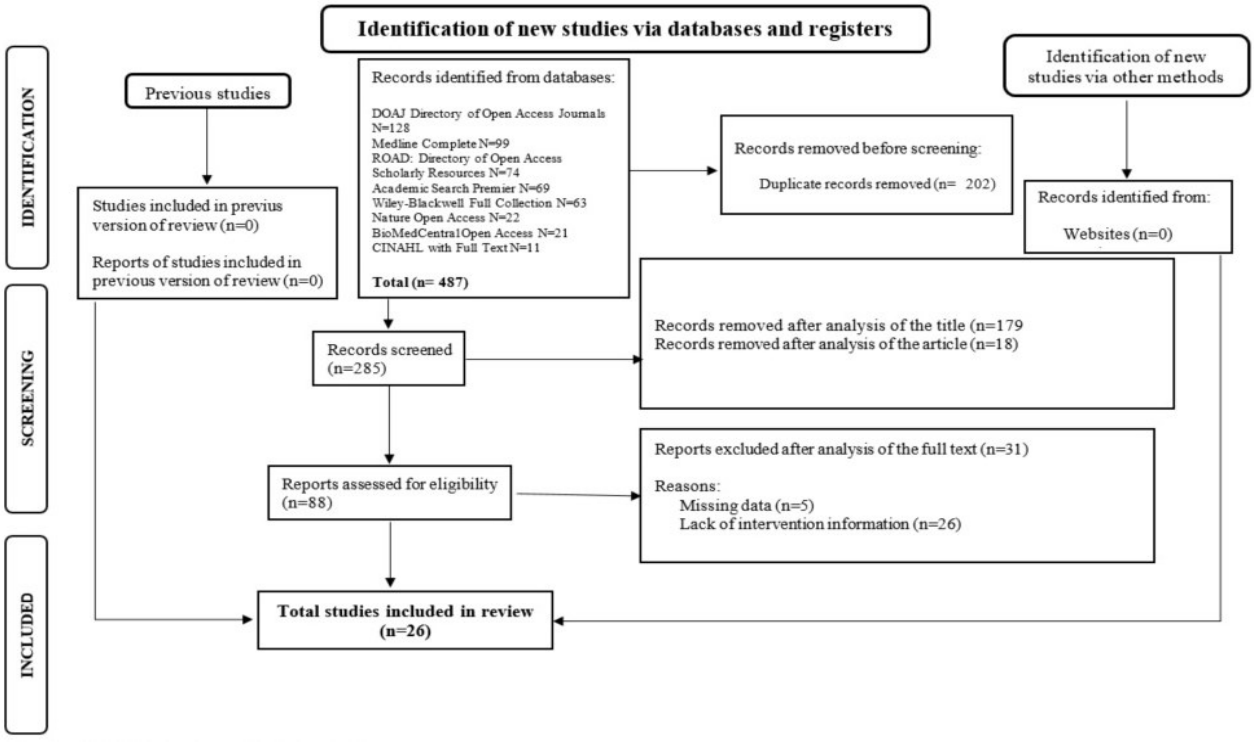

Figure 1. PRISMA flow diagram for study selection.

Data extraction and analysis

For articles that met the eligibility criteria, we extracted

the following information for qualitative analysis: authors and year of publication; participant characteristics (e.g., sample size, age, gender, medication responsiveness, diagnosis, and duration of the eating disorder); study characteristics (e.g., intervention, type of protocol used, evaluation and measurements performed, brain regions targeted); and outcomes.

Inclusion criteria

Articles in English were selected based on the following criteria: primary studies involving adults (>18 years old); case reports, case series, blind studies, double-blind research, non-randomized controlled, and randomized rTMS studies. Included studies involved patients who were clinically nonresponsive, without psychotropic medications, or using neuroleptic agents, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, trazodone, lithium, or benzodiazepines. Studies were also included if they involved patients whose medications had not changed for at least four weeks before baseline and patients without neurological disorders, comorbid conditions, suicidal ideation, or severe medical problems that could limit the application of rTMS.

Exclusion criteria

This study employed the aforementioned search strategy, initially retrieving 487 articles from the databases. We excluded studies that lacked sufficient information about the type of intervention, had incomplete statistical data, or involved participants with chronic diseases or medications such as anticonvulsants, slimming drugs, and psychostimulants. Additionally, studies were excluded if they involved patients with contraindications to rTMS (e.g., epilepsy, craniocerebral injury, or positive pregnancy tests). Of the total, 202 duplicates were identified and removed, and 197 titles and abstracts were subsequently excluded. Of the 88 remaining articles, only 26 met the final eligibility criteria according to PRISMA, as shown in Figure 1.

Quality and Evidence Assessment

Regarding the quality of evidence for clinical recommendations, the present study used the Physiotherapy Evidence Database (PEDro) scale (Moseley, Herbert, Sherrington, & Maher, 2002) to identify which of the known or suspected randomized clinical trials archived in the PEDro database are likely to be internally valid (criteria 2–9) and which studies provide sufficient statistical information to make their results interpretable (criteria 10–11). The assessment included the following criteria: (1) eligibility criteria were specified; (2) subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received); (3) allocation was concealed; (4) the groups were similar at baseline regarding the most important prognostic indicators; (5) there was blinding of all subjects; (6) there was blinding of all therapists who administered the therapy; (7) there was blinding of all assessors who measured at least one key outcome; (8) measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups; (9) all subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome were analyzed by "intention to treat"; (10) the results of between-group statistical comparisons were reported for at least one key outcome; and (11) the study provided both point measures and measures of variability for at least one key outcome.

Additional considerations include an analysis using GRADEpro GDT (2022) as the basis for selecting evidence (Table 2), which considered the following assessments: (1) Is the problem a priority?; (2) How accurate is the evaluation?; (3) How substantial are the desirable anticipated effects?; (4) How substantial are the undesirable anticipated effects?; (5) What is the overall certainty of the evidence of test accuracy?; (6) What is the overall certainty of the evidence for any critical or essential direct benefits, adverse effects, or burden of the test?; (7) What is the overall certainty of the evidence of effects of the management guided by the test results?; (8) How certain is the link between test results and management decisions?; (9) What is the overall certainty of the evidence of effects of the test?; (10) Is there substantial uncertainty about or variability in how much people value the primary outcomes?; (11) Does the balance between desirable and undesirable effects favor the intervention or the comparison?; (12) How large are the resource requirements (costs)?; (13) What is the certainty of the evidence of resource requirements (costs)?; (14) Does the cost-effectiveness of the intervention favor the intervention or the comparison?; (15) What would be the impact on health equity?; (16) Is the intervention acceptable to key stakeholders?; and (17) Is the intervention feasible to implement?

GRADEpro GDT is an easy-to-use, all-in-one web solution for summarizing and presenting information for healthcare decision-making in Cochrane systematic reviews (Nowak & Schünemann, 2017).

Results

Table 1 presents the results of all included studies along with the quality analysis based on the PEDro scale.

All studies had a score of ≥6, with 42.3% (n=11) achieving a score of ≥8. The quality analysis indicated a significant body of high-level external evidence from randomized controlled trials that can be used to support decision-making regarding rTMS treatment in eating disorders (ED). Table 2 illustrates the quality of the evidence. The selected studies were grouped by each respective protocol, including the total number of patients, sociodemographic characteristics of the

participants, rTMS parameters (e.g., type of coil, intensity, frequency, number of pulses, stimulation site), main results, and incidence of adverse effects, as summarized in Table 3.

Quality analysis of the included studies performed using the PEDro scale.

Study	1	2	3	4	5	6	7	8	9	10	11	Score
Baczynski et al. (2014)	y	n	n	y	n	n	n	y	y	y	y	6
Choudhary et al. (2017)	y	n	n	y	n	n	n	y	y	y	y	6
Claudino et al. (2011)	y	y	y	y	n	n	n	y	y	y	y	8
Dalton et al. (2018)	y	y	y	y	y	y	y	y	y	y	y	11
Dalton, Foerde, et al. (2020)	y	y	y	y	y	n	n	y	y	y	y	9
Dalton, Lewis, et al. (2020)	y	y	y	y	y	n	n	y	y	y	y	9
Downar et al. (2012)	y	n	n	y	n	n	n	y	y	y	y	6
Dunlop et al. (2015)	y	n	n	y	n	n	n	y	y	y	y	6
Gay et al. (2016)	y	y	y	y	y	n	n	y	y	y	y	9
Guillaume et al. (2018)	y	y	y	y	n	n	n	y	y	y	y	8
Hausmann et al. (2004)	y	n	n	y	n	n	n	y	y	y	y	6
Jassova et al. (2018)	y	n	n	y	n	n	n	y	y	y	y	6
Kamolz et al. (2008)	y	n	n	y	n	n	n	y	y	y	y	6
Khedr et al. (2014)	y	n	n	y	n	n	n	y	y	y	y	6
Knyahnytska et al. (2019)	y	n	n	y	n	n	n	y	y	y	y	6
McClelland et al. (2013)	y	n	n	y	n	n	n	y	y	y	y	6
McClelland et al. (2016)	y	y	y	y	y	n	n	y	y	y	y	9
McClelland et al. (2016)	y	n	n	y	n	n	n	y	y	y	y	6
Sutoh et al. (2016)	y	n	n	y	n	n	n	y	y	y	y	6
Van den Eynde et al. (2012)	y	n	n	y	n	n	n	y	y	y	y	6
Van den Eynde, Claudino, Campbell, Horrell, et al. (2011)	y	y	y	y	y	y	y	y	y	y	y	11
Van den Eynde, Claudino, Campbell, and Schmidt (2011)	y	y	y	y	y	y	y	y	y	y	y	11
Van den Eynde et al. (2010)	y	y	y	y	y	y	y	y	y	y	y	11
Van den Eynde et al. (2013)	y	n	n	y	n	n	n	y	y	y	y	6
Walpoth et al. (2008)	y	y	y	y	y	y	y	y	y	y	y	11
Woodside et al. (2017)	y	n	n	y	n	n	n	y	y	y	y	6

Table 1.

Table 2.
GRADE analysis on the rating quality of evidence.

Criteria	Summary of judgements						Importance of decision
Problem	No	Probably no	Probably yes	Yes	Varies	Don't know	High
Desirable effects	Trivial	Small	moderate	Large	Varies	Don't know	High
Undesirable effects	Large	Moderate	Small	Trivial	Varies	Don't know	High
Certain of evidence	Very low	Low	Moderate	High	No included studies		High
Values	Important uncertainty of variability	Possible important uncertainty of variability	Probably no important uncertainty of variability	No important uncertainty of variability			High
Balance of effects	Favors the comparison«	Probably favors the comparison ◄	Does not favor either the intervention or the comparison •	Probably favors the intervention ►	Favor the intervention»	Varies	Don't know	High
Acceptability	No	Probably no	Probably yes	Yes	Varies	Don't know	High
feasibility	No	Probably no	Probably yes	Yes	Varies	Don't know	High

Table 3.
Summary of the main findings from studies involving patients or athletes with ED and TMS/rTMS included in the review.

Study	Mean age	BMI actives patients on baseline	N° of patients (actives)	Profile of patients	Gender (n)	laterality	Type of study	N° of sessions to RTMS	Coil	Place of application	N° total of pulses/ sessions	Interval/session	threshold motor	Freq. (Hz)	Stem of target point	Stem of placebo	Evaluation uses	Results	EA
Baczynski et al. (2014)	24	28	0	BED and Dep	F	NR	RC	20	8	dlPFC	2400	5 s by 4/W	110%	10	B	N	BES BDI	↓ BES from 38 to 27 ↓ BDI from 42 to 23	NR
Choudhary et al. (2017)	23	14.74	1	SE-NA	F	NR	RC	21	8	dlPFC	1000	7s/ W	110%	10	B	N	Evaluation of mental state and evolution	↓ Abuse of laxatives/ abuse of diuretics ↑ BMI to 18.55	NR
Claudino et al. (2011)	28.2	26.8	11	BU	F	NR	CR	1	8	dlPFC	100	5 s by 4/W	110%	10	E	S	FCQ-S; VAS; CCC; (FCQ-S and VAS 'urge to eat'; EDE-Q; HADS; FCQ-T; FCQ-S	↓ cortisol on active group ↓ greed for food	NR
Dalton, Bartholdy, Campbell, et al. (2018)	28.5	16	17	SE-NA	F	R	CRDC	20	8	dlPFC	1000	5 s by 4/W	110%	10	A	S	BMI; (DASS-21),5-level EQ-5D version; EQ-5D-5L)	TEP for the BMI and symptoms of eating disorder TEM for quality of live TEG for humor	SEA
Dalton, Foerde, et al. (2020)	27	15.90 ± 1.40	13	SE-NA	F	R	CR	20	8	dlPFC	1000	5 s by 4/W	110%	10	A	S	FCQ-T; EDE-Q; DASS-21	↑ control and ↑ food more health and less flavor; TEP for BMI TEP for the symptoms of eating TEM for the anxiety TEG for follow-up, on active group	SEA
Dalton, Lewis, et al., (2020)	>18	12	12	SE-NA	F	R	CR	20	8	dlPFC	1000	5 s by 4/W	110%	10	A	S	EDE-Q; CIA; DASS-21	TEM on BMI	SEA

Downar et al. (2012)	46	12.9	1	BU severe	F	R	RC	20	DC120	vmPFC	3000 D/3000 E	5 s by 4/W	120%	10	A	N	HamD17; BDI-II	↓ BDI-II scores from 28 to 7 (after 11 sessions) ↓ HamD17 from 26 to 0 (at the end of treatment) Cessation of purgative episodes All results lasted for two months	CEF
Dunlop et al. (2015)	31	14.5–28.8	28	BU and AN	26F; 2M	NR	CR	20	DC120	vmPFC	3000 D/3000 E	5 s by 4/W	120%	10	A	N	EDE-Q; (HamD17), BDI-II; BAI	Respondents: ↓ functional connectivity (CFS) in dmPFC to side orbitofrontal cortex and right posterior insula, and from dACC to right posterior insula and hippocampus. ↓ dACC to the ventral striatum and previous insula In non-responders: ↑ CFS in dmPFC and frontostriatal circuit CFS suppressed HR with worsening symptoms	CEF
Gay et al. (2016)	27	BMI>18.5	24	BU	F	R	CR	10	8	dlPFC	1000	5 s by 2/W	110%	10	D	S	MADRS	Ø	CEF
Guillaume et al. (2018)	NR	BMI>18.5	17	BU	F	R	CR	10	8	dlPFC	1000	5 s by 2/W	110%	10	D	S	Going-go task and BIS and IGT and assessment of sustained attention with the attention test	Ø in quest of neuropsychological. ↑ sustained Warning between before and after-rTMS on both groups ↑ inhibitory control after rTMS on group rTMS active	SEA
Hausmann et al. (2004)	28	18	1	Patient at 17 with AN and at 21 with BU	F	R	RC	10	8	dlPFC	2000	5 s by 2/W	80%	20	NR	N	HDRS; BDI., YBOCS, Binge–Purge Diary	↓ 10 points in HAM ↓ compulsives and purgatives symptoms	SEA
Jassova et al. (2018)	29	11.98	1	AN/TAG/Dep	F	R	RC	10	8	dlPFC	1500	5 s by 2/W	100%	10	NR	N	IMC and Zung self-rating scale	↑ BMI of 11.98 to 13.15 Ø on scale Zung	CEF
Kamolz et al. (2008)	24	12.4	1	AN and Dep	F	R	RC	10	8	dlPFC	2400	5 s by 2/W	110%	10	B	N	IMC and Hamd17	↓10 points in HAM Remission of symptoms (after 8 weeks) ↑ BMI from 12.4 to almost 16	NR
Khedr et al. (2014)	21.3	14-18.5	13	NA	12F1M	NR	CR	1 (Only pulse)	8	Mt	PU	PU	NR	PU	C	N	EDI, EAT, (BDI-II); LM at rest and active; PS; IT; PEM, Esophageal PEM Cortical Latency	↓ The onset latency of LMR and PEM anorexic patients Ø in AML] ↓BDI, EDI, EAT PSC between patients and controls Negative correlations between EAT and MRL scores and ITC duration	NR
Knyahnytska et al. (2019)	33	16.6	8	AN-SE	F	NR	RC	54	H	Insula	2880	5s/W by 6 W. followed by TMS 2s/W to 6 W	100%	18	A	N	IMC, MOCA, YBC-EDS, HamD17, MADRS, BDI-II. BAI.	↓ YBC-EDS from 23.4 to 18.8 (after 12 weeks), and to 19.76 (after 6 months) ↓ HDRS to 5.5 (after 12 weeks) to 10.25 (after 6 months) ↓MADRS from 17.88 and to 11 (after 12 weeks) and to 15 (after 6 months) ↓ BDI from 24.66 to 10 (after 12 weeks) and to 13.25 (after 6 months) ↓ BAI from 15.44 to 7 (after 12 weeks) and to 6.25 (after 6 months) ↓ BMI from 16.7 to 16.3 and to 16.98 (after 6 months)	NR
McClelland et al. (2013)	23; 52	15.76; 16.40	2	AN-SE	F	NR	RC	20; 19 (n=1)	8	dlPFC	1000	3 s/W by 2 W; after 5s/W	110%	10	A	N	(h), weight, EDE-Q, DASS-21; Before and after each rTMS session, AN patients were exposed to FCT. VAS for "anxiety levels", "desire to restrict", "feeling full/Wtuffed", "feeling fat".	↓ VAS scale from 6-8/10 to 1/10 Ø differences in weight (after 20 rTMS sessions) ↓DASS from 23 to 11 (after 20 rTMS sessions) in A ↓ DASS from 40 to 23 (after 19 rTMS sessions) in B patients ↓ Of induction of emesis and use of laxatives (10 for seven x/month- vomiting; 15 for nine laxatives)	SEA
McClelland et al. (2016)	25;29	16.73	21	13 AN	F	NR	CR	1	8	dlPFC	1000	1 session	110%	10	A	S	EDE-Q, DASS-21, VAS for: levels of need for food restriction, feeling of satiety, feeling of being fat, stress and anxiety and impulsiveness in spending money; TD task (TDpre); Salivary cortisol measurement (before FCT, Before rTMS, just after rTMS and 24 h after rTMS, PA, HR.	Ø among the main symptoms of A, salivary cortisol level ↓ TDT after active rTMS	SEA
McClelland et al. (2016)	23;30;32;41; 52	9.8 - 16.2	5	3 AN	F	NR	SC	20	8	dlPFC	1000	3 s/W by 2 W; after 5s/W	110	10	A	N	BMI; EDE-Q, DASS-21, VAS for need for food restriction, feeling of satiety, feeling of being fat, after exposure to a 2-minute film.	↓ VAS scores on all levels of stress, anxiety levels, desire to restrict, feelings of satiety, and post-rTMS fat feeling levels Ø BMI	CEF

Sutoh et al. (2016)	24.8	19.54	8	BU	F	R	CR	1	8	dlPFC	1000	1 session	110%	10	E	N	HADS, GAF, Task performance and NIRS: food photo task, VAS; EDE-Q; BITE; CGIS; RPST;	↓HADS ↑ GAF scale score ↓ subjective rate of "want to eat", "desire to eat", "feeling hungry" by photo stimulation with high-calorie foods ↓ NIRS during RPST in [oxyHb] in the dlPFC	NR
Van den Eynde et al. (2012)	L: 22.9+/-2.9 R: 28.5 + /-9.8	L: 22.2 +/-2.7 H: 25.4 +/-11.9	7	6 BU; 1 TANE	F	7 C; 1 4 R	CNR	1	8	dlPFC	1000	1 session	110%	10	E	N	BMI, EDE-Q; FCQT); (HADS); VAS for (eating craving, mood, tension, anger, binge eating)	↑ VAS on mood and desire to eat ↓ Of food craving by FCQ-S scale	NR
Van den Eynde, Claudino, Campbell, Horrell, et al. (2011)	NR	NR	18	Majority BU and TANE	33 F; 5 M	R	CRDC	1	8	dlPFC	1000	1 session	110%	10	E	S	PA. FC	Ø heart rates accessed through BP and HR after rTMS	CEF
Van den Eynde, Claudino, Campbell, & Schmidt (2011)	29.3	26.7±12.0	15	BU and TANE	28 F; 5 M	R	CRDC	1	8	dlPFC	1000	1 session	110%	10	E	S	SCWT	Ø in the stroop test between groups as well as Ø pos rTMS between SCWT and food cravings (FCQ-S), eating disorder symptoms (EDE-Q), anxiety and depression HADS	CEF
Van den Eynde et al. (2010)	30.5	25.8	17	BN (10) TANE (7)	33 F; 5 M	R	CRDC	1	8	dlPFC	1000	1 session	110%	10	E	S	HADS/FCQ-S in the pre-intervention. VAS for "desire to eat"; VAS for "hunger", "tension", "mood" and "compulsive overeating".	↓ in the VAS in the desire to eat. Ø of FCQ-S (comparison between) ↓ FCQ-S score (before and after rTMS) in GA After 24 hours, 4 PG reported binge eating and no compulsive event	CEF
Van den Eynde et al. (2013)	25	15.7 (13.8–17.8)	10	AN	F	R	ECN	1	8	dlPFC	1000	1 session	110%	10	E	N	EDE-Q; DASS (21-items); (VAS) for "desire to restrict food", "desire to exercise"; "feeling full", "feeling fat", "anxiety"; FCQT; Salivary cortisol level; BP and HR; VAS for discomfort level during rTMS.	↓ significant of "feeling stuffed" and "feeling fat" assessed through the VAS. Ø for anxiety and a slight difference for "need to exercise" Ø for "desire to restrict" or "desire to eat" Ø in mood, tension or hunger	CEF
Walpoth et al. (2008)	27.5	19.682.4	7	BU	F	NR	CRDC	15	8	dlPFC	2000	5s/W, interval 2 day by 3 W	120%	20	E	S	HDRS, BMI and YBOCS	↓compulsions/BDI and YBOCs in both groups Ø purgative behavior Ø in BDI, HDRS scales	SEA
Woodside et al. (2017)	39.8	20.81 +/-4.54	14	EPT with BU or AN	F	NR	SC	20-30	8	vmPFC	10 p=3000; 3 p=the taburst 600 bilat.; 1 p=1500 bilat.	20-30 s; NR period of treatment	11 patients 120%	10 (N=10); 20 (N=1); TBI (N=3)	A	N	PCL-C; DERS.	↓PCL-C (57%) showed >50% reduction in PCL-C scores ↓DERS	CEF

ACRONYMS: ↓ - Decrease; ↑ - Increase; Ø - No statistically significant difference; A - Neuronavigation; B - System 10-20; 8 - Eight-shaped coil; BAI - Beck Anxiety Index; BDI - Beck Depression Inventory; BDI-II - Beck Depression Inventory-II; BES - Binge Eating Scale; BIS - Barratt Impulsivity Scale; BITE - Bulimic Investigatory Test; BU - Bulimia; CCA - Anterior Cingulate Cortex; CCC - Cortisol Concentration Changes; CGIS - Clinical Global Impression of Disease Severity; D - 6 cm anterior to the motor cortex hotspot; DAS 21 - Depression, Anxiety, and Stress Scale – 21 items; Dep - Depression; DERS - Difficulties with Emotional Regulation Scale; E - 5 cm before the motor hotspot; EAT - The Eating Attitude Test; EDE-Q - Eating Disorder Examination Questionnaire; EDI-2 - Eating Disorder Inventory 2; HR - Heart Rate; FCQ-S - Food Craving Questionnaire State; EQ-5D-5L - EuroQol Quality of Life Scale, 5-level EQ-5D version; FCQ-T - Food Craving Questionnaire Trait; GA - Active Group; PG - Placebo Group; GAF - Global Assessment of Functioning; HADS - Hospital Anxiety and Depression Scale; HamD17 - Hamilton Depression Rating Scale; PTSD - Post-Traumatic Stress Disorder; h - Height; IGT - Decision Making with the Iowa Gambling Task; BMI - Body Mass Index; IT - Transcallosal Inhibition; Mt - Motor Threshold; dlPFC - Left Dorsolateral Prefrontal Cortex; vmPFC - Ventromedial Prefrontal Cortex; NR - Not Reported; BP - Blood Pressure; HR - Heart Rate; PCL-C - Checklist-Civilian Version; MEP - Motor Evoked Potential; PS - Cortical Silent Period; PU - Single Pulse; S - Sham Coil; MADRS - Montgomery–Åsberg Depression Rating Scale; RPST - Rock-Paper-Scissors Task; SCWT - Stroop Color Word Task; SEA - No Adverse Effects; SE-AN - Severe Anorexia Nervosa; SFC - Seed-Based Functional Connectivity; s/W - Sessions/Week; W - Week; TAG - Generalized Anxiety Disorder; TEP - Small Effect Size; TEM - Medium Effect Size; TEG - Large Effect Size; TANE - Eating Disorder Not Otherwise Specified; TDT - Temporal Discounting Task; TBI - Theta-Burst Intermittent; Tdtask/tdpro - Temporal Discount Task (Decision-making task involving choosing between a smaller immediate reward or a larger delayed reward); TFCT - The Food Challenge Task (patients watch a 2-minute movie showing people eating palatable, caloric foods such as chocolates, cookies, hamburgers, and nuts); VAS - Visual Analogue Scale; YBC-EDS - Yale-Brown-Cornell Eating Disorder Scale; YBOCS - Yale–Brown Obsessive Compulsive Scale; EA - Adverse Effect; CEF - Headache and Discomfort; RC - Case Report; SC - Case Series; CR - Randomized Controlled; DC - Double-Blind, Non-Randomized Controlled; R - Right-Handed; L - Left-Handed; F - Female; M - Male; DC 120 - Double Cone 120; TMS - Transcranial Magnetic Stimulation; rTMS - Repetitive Transcranial Magnetic Stimulation.

Discussion

The present review provides crucial insights into the diagnostic and therapeutic applications of TMS in EDs, with a particular focus on AN, BN, and BED. Notably, this review identifies a significant scarcity of studies that exclusively involve athletes. Most existing research does not distinguish between athletes and non-athletes, highlighting a critical gap in the literature. It is essential to investigate the effects of rTMS on athletes due to the unique physiological and psychological demands placed on this population. Athletes often experience high levels of stress, both physically from intensive training and psychologically from performance pressures (de Souza et al., 2022; Mitchell et al., 2024), which can affect their mental health and cognitive functions (Ghazzawi et al., 2024). rTMS, a non-invasive brain stimulation technique, has shown potential in treating various psychiatric disorders and enhancing cognitive functions. Our results demonstrated diverse rTMS parameters applicable to AN, BED, and BN. Figure 2 summarizes the principal brain areas associated with ED and the corresponding rTMS treatments.

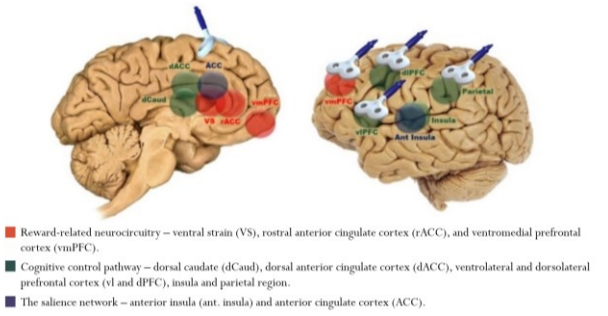

Figure 2. Cognitive control pathway, reward-related neurocircuitry, and salience network as the principal parts affected by ED and considered in the rTMS treatment.

rTMS in Anorexia Nervosa (AN)

The cause of AN and other EDs is multifactorial (Salvadó, Casanova, Fernández-Iglesias, Arola, & Bladé, 2015). AN is characterized by self-induced weight loss, distortion of body image or altered perception of one's own body, and an intense fear of gaining weight (Gallop et al., 2022). Patients may engage in inappropriate compensatory behaviors such as excessive exercise, fasting, and the use of appetite suppressants, as well as purging methods like self-induced vomiting, and the use of laxatives and diuretics, as a way to lose weight (Gay et al., 2022).

Changes in neural circuits involving the gratification system, negative affect, stress, appetite regulation, self-regulatory control systems (cognition), and socio-emotional processes may be related to the cause and maintenance of AN (Dalton, Bartholdy, Campbell, et al., 2018; Dunlop et al., 2015; Jassova et al., 2018; Khedr et al., 2014; J. McClelland et al., 2013). These symptoms are associated with critical brain areas involved in mood regulation and cognition, such as the dorsolateral prefrontal cortex (dlPFC), ventromedial prefrontal cortex (vmPFC), and other subcortical regions such as the thalamus, insula, and cingulate regions (Val-Laillet et al., 2015). These regions are implicated in the pathogenesis of AN through their roles in emotion control and the regulation of feeding behaviors (Tsai, 2005). An increase in cortical motor excitability was observed in some studies using single-pulse TMS (Khedr et al., 2014; Val-Laillet et al., 2015). For example, Khedr et al. (2014) reported a reduction in the latency of motor evoked potentials (MEP) in patients with AN, with uptake in the 1st dorsal interosseous muscle and esophagus, a reduction in resting motor threshold (RMT), and a decrease in the duration of transcallosal inhibition (TCI) in patients compared to healthy controls.

Pharmacological and non-pharmacological treatments for AN and severe AN (SE-AN) have shown modest results (Kotilahti et al., 2020); in this context, rTMS can be considered a promising non-invasive neuromodulatory treatment tool (Dalton, Bartholdy, Campbell, et al., 2018). Many studies have employed rTMS protocols targeting the dlPFC region (Dalton, Bartholdy, Campbell, et al., 2018; Dalton, Foerde, et al., 2020; Dalton, Lewis, et al., 2020; Jessica McClelland et al., 2016; Van den Eynde, Claudino, Campbell, & Schmidt, 2011; Walpoth et al., 2008). Few protocols have targeted the vmPFC (Dunlop et al., 2015) or the insula region (Sankar et al., 2022). The lack of studies targeting these areas may be due to the need for advanced and more expensive equipment, such as double-cone and H-shaped coils (Gersner et al., 2016). All studies included in the present review used high-frequency rTMS, mostly at 10Hz (Baczynski et al., 2014; Gay et al., 2016), except for one study (Hausmann et al., 2004), which used a frequency of 20Hz (Baczynski et al., 2014). rTMS treatment showed considerable tolerability, with few reports of adverse effects (Table 1) (Baczynski et al., 2014; Dunlop et al., 2015; Jassova et al., 2018; Jessica McClelland et al., 2016; Van den Eynde et al., 2013). In this context, rTMS was presented as a safe technique, with only mild transient headaches reported. In only one study, a patient abandoned treatment due to discomfort (headache) (Van den Eynde et al., 2013).

As summarized in Table 1, recent evidence suggests that high-frequency rTMS has shown promising results in reducing the main symptoms of AN, such as the desire to restrict food intake and anxiety (Dalton, Bartholdy, Campbell, et al., 2018; Choudhary et al., 2017; Dalton, Bartholdy, McClelland, et al., 2018; Dalton, Foerde, et al., 2020; Kamolz et al., 2008; Knyahnytska et al., 2019; J. McClelland et al., 2013). Most protocols among these studies with positive results used a 10Hz protocol in the dlPFC region, except for the study by Hausmann et al. (2004) with 20Hz, and the study by Knyahnytska et al. (2019) with an 18Hz stimulus frequency. Additionally, these authors stimulated the vmPFC and insula regions, respectively, using double-cone and H-shaped coils instead of the figure-eight type, as these targets are in deeper brain regions (Hausmann et al., 2004; Knyahnytska et al., 2019).

Fewer studies involving patients with AN were randomized and controlled (Dalton, Bartholdy, McClelland, et al., 2018; Dalton, Foerde, et al., 2020; Dalton, Lewis, et al., 2020; Jessica McClelland et al., 2016). Dalton, Bartholdy, McClelland, et al. (2018) demonstrated significant effects of rTMS in randomized AN Research, with the active rTMS group showing better outcomes than the placebo group in terms of Body Mass Index (BMI), eating disorder symptoms, quality of life, and mood state. Dalton, Foerde, et al. (2020) evaluated food choice behavior, comparing individuals with AN to healthy individuals. A "food choice task" was applied, consisting of three phases: evaluating the healthiness of the food, the taste of the food, and the participants' specific food choices. Compared to healthy individuals, patients with SE-AN, after rTMS, showed increased positive effects in food choice tasks. Initially, SE-AN patients demonstrated that they (a) chose foods rated as less healthy; (b) chose foods rated as less palatable, especially those with high-fat content; (c)

showed a preference for foods with higher calories and made fewer choices of high-fat foods; and (d) exercised greater self-control during the trial, choosing healthier, less palatable foods and fewer unhealthy foods (Dalton, Foerde, et al., 2020). These differences indicate that rTMS can promote behavioral and cognitive modifications. In contrast, Dalton, Lewis, et al. (2020) found a small effect size for BMI and eating disorder symptoms, such as anxiety and a reduction in self-control in food choice in the active rTMS group among AN patients; however, similar to other studies, a change in the pattern of food item choices was observed. These results were attributed to increased flexibility in attitudes towards food, which may be associated with neuroplastic changes in the dlPFC and related neurocircuits.

Interventions with SE-AN patients from the TIARA study, conducted in London (Dalton, Bartholdy, McClelland, et al., 2018; Dalton, Lewis, et al., 2020), involved rTMS treatment and were followed for 18 months. There was a significant mood improvement in the first four months post-randomization between the active and placebo groups, favoring the active rTMS group. The mood improvement in the active group remained stable at follow-up up to 18 months post-randomization, while there was a convergence effect in the group that initially received a placebo (Dalton, Bartholdy, McClelland, et al., 2018; Dalton, Lewis, et al., 2020). This result is logical, as most participants who initially received a placebo later began receiving real rTMS. Consequently, there was a small difference in effect between the group that received real rTMS early on and the group that received rTMS later. Although both the placebo and active groups showed improvements in BMI, the change in BMI was greater in the active group. These effects resulted in a moderate between-group effect, combined with an increase in weight gain in the real rTMS group compared to the placebo group (46% versus 9%). These findings suggest that weight gain in AN patients is a gradual process related to eating symptoms and psychosocial impairment (Dalton, Foerde, et al., 2020).

However, results from the fourth randomized controlled trial were non-significant (Jessica McClelland et al., 2016). This study evaluated the effect of a single session of rTMS applied to the dlPFC in 45 patients with severe AN. Although the results were not significant for the main symptoms of AN, and no differences were found in salivary cortisol levels after the rTMS session, there was a trend towards more reflective choice behavior between the groups. This evaluation was conducted using the computerized monetary Temporal Discounting task (TDpre), which involves decision-making based on choosing between receiving a smaller amount of money sooner or a larger amount later (McClelland et al., 2016). The heterogeneity of protocols could partly explain the conflicting results. It is evident that protocols with fewer sessions and pulses have a lesser effect on reducing AN symptoms. The treatment duration in the research is shorter than the potential plateau at maximum observed improvement. Only one study with SE-AN included 54 sessions (Knyahnytska et al., 2019), indicating improvement in EDs symptoms across different scales and BMI. From this, we suggest that more longitudinal studies are needed. A study that supports this postulation (Kamolz et al., 2008) described a SE-AN patient with a BMI of 12.4 kg/m² and a Hamilton depression scale score of 28 points, who showed partial improvement in both eating and depressive symptoms after ten sessions of 10Hz rTMS in the dlPFC, and achieved remission of symptoms after 16 more sessions. The authors noted that the improvements were maintained, with the patient increasing her BMI to 16 and returning to work. Additionally, patient selection can affect results, as seen in case studies (Jassova et al., 2018; Nowak & Schünemann, 2017), which, unlike other uncontrolled studies, did not show a satisfactory clinical response. In this case report, the patient had several comorbidities (depression, anxiety, OCD) and a very low BMI.

rTMS in Binge Eating Disorder (BED)

BED was included in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) as an eating disorder characterized by excessive food consumption, known as binge eating episodes (BEE), which occur at least once a week for three consecutive months (Downar et al., 2012). This disorder affects about 2% to 20% of the population in different studies and is often associated with obesity (Gay et al., 2016). BED shares similarities with the neuropathological mechanisms of drug craving, including increased activity in the orbitofrontal cortex and anterior cingulate, as well as a decrease in the regulatory influence of the lateral prefrontal cortex circuit (Maranhão et al., 2015).

In a previous study, 38 patients with EDs were evaluated, 33 of whom were right-handed women. Some participants had BED, BN (bulimia nervosa), or unspecified ED (ANE) (Van den Eynde et al., 2010). The Hospital Anxiety and Depression Scale (HADS) and the Food Craving Questionnaire (FCQ-S) were administered before a single 10Hz rTMS session in the dlPFC region. Other outcomes were measured before and after rTMS, including the Visual Analog Scale (VAS) for "desire to eat" and FCQ-S (primary outcomes), as well as VAS for "hunger," "tension," "mood," and "compulsive overeating" (secondary outcomes). Secondary data were collected through a phone call 24 hours after rTMS to assess how many binge eating episodes occurred. Participants watched a 2-minute film showing people eating palatable foods to stimulate food cravings. They were then presented with a buffet of the same foods and asked to rate their appearance, smell, and taste. Finally, participants were asked to rank the five VAS and complete the FCQ-S. There was a significant difference between the placebo and real rTMS groups in the reduction of VAS scores for the desire to eat (i.e., primary outcome). In contrast, VAS scores for the secondary outcomes

did not show a significant difference between the groups. The FCQ-S scores showed no difference between the active and placebo groups. After the 24-hour follow-up, four placebo participants reported binge eating, while none in the real rTMS group experienced a BEE. This same research group studied the impact of 10Hz rTMS on the dlPFC in left-handed patients (six with BN and one with BED/Unspecified Feeding or Eating Disorder – UFED) (Van den Eynde et al., 2012). Unlike the results obtained in right-handed patients, the VAS scores for the desire to eat worsened. This result reinforces the need to establish optimized protocols based on neurobiological knowledge tailored to each group, and perhaps each individual (J. McClelland et al., 2016).

Patients with six binge eating crises in 28 days were classified as UFED using the Eating Disorder Examination–Questionnaire (EDE-Q). In the study by Van den Eynde, Claudino, Campbell, & Schmidt (2011), about half of the patients had BN, and the other half had unspecified ED. The authors compared the results of the Stroop Color-Word Task (SCWT), levels of food cravings (FCQ-T, FCQ-S), and eating disorder symptoms (EDE-Q: Eating Disorder Examination–Questionnaire; HADS: Hamilton Depression and Anxiety Scale; FCQ-T: Food Craving Questionnaire–Trait; FCQ-S: Food Craving Questionnaire–State) before and after a single rTMS session. The authors found no significant changes in SCWT cognitive assessment scores. Furthermore, no cognitive changes were observed, and no changes in heart rate or blood pressure were detected in this same group of patients (Van den Eynde, Claudino, Campbell, Horrell, et al., 2011). Therefore, the absence of negative effects on selective attention and cardiac alterations can be considered an important indicator of the technique's safety.

Most of the studies mentioned above include patients with BED, but only a few focus exclusively on BED patients. This scarcity makes it difficult to understand the neurobiological factors involved specifically in BED. Table 2 demonstrates that in a case report involving a patient with BED and depression, there was a significant therapeutic response after 20 sessions of rTMS in the dlPFC, reducing the Binge Eating Scale (BES) index from 38 to 27 and the Beck Depression Inventory score from 42 to 23.

rTMS in Bulimia Nervosa (BN)

BN is an eating disorder characterized by recurrent episodes of binge eating associated with compensatory behaviors, including purging methods, to prevent weight gain or promote weight loss after binge episodes (Hall, Vincent, & Burhan, 2018). Despite the severity of EDs, therapeutic options are still limited (Gay et al., 2016; Maranhão et al., 2015). Traditional approaches often do not yield satisfactory outcomes, and new diagnostic tools are needed to better understand the neurobiological mechanisms. Additionally, new treatments such as TMS and rTMS are needed (Duriez et al., 2020; Val-Laillet et al., 2015). When exposed to high-calorie foods, people with BN experience increased cravings, subjective stress, and elevated salivary cortisol levels (Claudino et al., 2011). Craving/desire is a precipitating factor in binge eating. Proposed mechanisms underlying the "irresistible urge" to consume include hyperactivity of the orbitofrontal cortex and anterior cingulate, along with impaired inhibitory control of the prefrontal cortex (Gay et al., 2016; Maranhão et al., 2015; Val-Laillet et al., 2015). In a study using near-infrared spectroscopy (NIRS), a non-invasive technique used to measure changes in blood oxygen concentration (OxyHb), Sutoh et al. (2016) observed a significant decrease in cerebral oxygenation in the dlPFC of eight BN patients following a 110% 10Hz rTMS session. This reduction in OxyHb concentration is inconsistent with other findings from excitatory brain stimulation (i.e., rTMS with frequencies >1Hz). The author hypothesizes that BN patients have inferior and inefficient autoregulatory function in the prefrontal cortex, which was modulated by rTMS, consequently requiring less blood in response to tasks. Despite the study's limitations, such as the lack of a control group and a small sample size (n=8), there was a significant reduction in compulsion, desire for food, and anxiety. Nevertheless, it was concluded that NIRS is a technique with high temporal resolution and could be an efficient strategy for monitoring the effectiveness of the cortical response to rTMS. In the therapeutic field, it is known that rTMS targeting the vmPFC region has promising effects in reducing compulsive and purgative symptoms in patients with EDs (Dunlop et al., 2015; Dunlop et al., 2016). As with depression, these effects are associated with increased functional connectivity in frontostriatal circuits, detectable by fMRI before rTMS treatment (Dunlop et al., 2015).

Recurrent episodes of binge eating and purging behavior occur in AN (the compulsive-purging subtype) and patients with BN (Claudino et al., 2011). This review identified six studies exclusively involving patients with BN (Claudino et al., 2011; Downar et al., 2012; Sutoh et al., 2016; Walpoth et al., 2008), four of which were randomized controlled trials (Claudino et al., 2011; Gay et al., 2016; Guillaume et al., 2018; Walpoth et al., 2008). In one study (Claudino et al., 2011), 22 patients underwent a single session of high-frequency rTMS applied to the dlPFC, resulting in significantly reduced cortisol levels and craving in the active group. Whether rTMS acts directly or indirectly on the subcortical pathway or structures within the hypothalamic-pituitary-adrenal (HPA) system is still unknown; however, these findings may suggest an interaction between the HPA axis and the dopaminergic reward system.

In another randomized controlled study involving 14 women with BN, Walpoth et al. (2008) observed a reduction in the mean number of compulsions per day, BDI, and YBOCS scores in both groups through internal comparison. However, there was no significant difference when comparing the active and placebo groups. In another study (Gay et

al., 2016), although rTMS was well tolerated by the 24 patients with BN undergoing active rTMS, there was no significant benefit in response compared to placebo in terms of binge eating episodes, food cravings, or mood. This difference in results may be attributed to the lower number of rTMS sessions—ten in this case—compared to most protocols that involve 20 or more sessions (Claudino et al., 2011; Downar et al., 2012; Dunlop et al., 2015). However, studies by Gay et al. (2016) and Guillaume et al. (2018) evaluated the impact of rTMS on cognitive performance. As in the study by Walpoth et al. (2008), analyses between the groups did not reveal differences in the final neuropsychological examination. However, there was an improvement in sustained attention, inhibitory control as assessed by the go-no-go test, decision-making as evaluated by the Iowa Gambling Task, and impulsivity as assessed by the Barratt Impulsivity Scale, from subject-to-subject analysis (comparison within the control and active groups). The author suggests that these changes could impact the clinical response of patients and could be used as a marker of rTMS response (Guillaume et al., 2018).

Regarding safety and tolerability, most studies reported few adverse effects related to the rTMS technique. The few adverse effects reported included discomfort in the head and headache, which were temporary (Downar et al., 2012; Dunlop et al., 2015; Gay et al., 2016; Van den Eynde et al., 2010; Woodside et al., 2017). Analyzing the available studies, most observed a significant response in reducing compulsive behavior and craving in internal comparisons. However, a statistically significant response was not observed when external active-placebo comparisons were made. Therefore, increasing the number of research participants would be valuable for drawing more significant conclusions (Walpoth et al., 2008), and greater homogenization of study protocols is necessary to establish more robust conclusions.

Conclusion

Research on the use of rTMS in patients or athletes with EDs is an emerging field, reflecting a broader interest in both the mental health challenges faced by athletes and the potential of rTMS as a therapeutic tool. Given the relative novelty of this specific application, the body of literature remains limited but promising. The number of articles on the use of rTMS in EDs compared to those published on depression is still small. Managing the treatment of EDs remains challenging, with few effective treatments available. The high tolerance and safety of neuromodulatory treatment with rTMS encourage its application, particularly in patients with refractory ED. In addition to its substantial therapeutic potential, rTMS is an important diagnostic tool for elucidating the complex neurobiology of EDs. A significant increase in publications on this subject, conducted in a controlled, blind, and randomized manner, is expected, which will likely lead to the homogenization of results and the generalization of its potential use.

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