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## **Effects of repetitive transcranial magnetic stimulation of the right inferior parietal lobe on the body image perception in anorexia nervosa: A pilot randomized controlled study**

Nathalie Chastan, Najate Achamrah, Olivier Etard, Clément Nathou, Marie-astrid Piquet, Sébastien Guillaume, Jérôme Attal, André Gillibert, Pierre Dechelotte, Olivier Guillin, et al.

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**Effects of repetitive transcranial magnetic stimulation of the right inferior parietal lobe on the body image perception in anorexia nervosa: a pilot randomized controlled study.**

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Search Terms:	trans cranial magnetic stimulation, eating disorders
Keywords:	
Abstract:	<p>Introduction Restrictive anorexia nervosa (AN) is associated with distorted perception of body shape, previously linked to hypoactivity and reduced excitability of the right inferior parietal lobe (rIPL). Here, we investigated the impact of high-frequency repetitive transcranial magnetic stimulation (HF rTMS) of the rIPL on body shape perception in patients with AN.</p> <p>Methods Seventeen patients with AN (median [Q1_Q3] age, 35 [27_39] yrs; disease duration, 12 [6_18] yrs) were randomly assigned to receive real or sham HF (10 Hz) rTMS of the rIPL over a 2 week-period, comprising 10 sessions. The primary outcome measure was the Body Shape Questionnaire (BSQ). Secondary outcomes included eating disorder symptoms, body mass index, mood, anxiety, and safety. Data collection were done at baseline, post-rTMS, and at 2 weeks and 3 months post-rTMS.</p> <p>Results Following both real and sham rTMS of the rIPL, no significant differences were observed in body shape perception or other parameters. Both real and sham rTMS interventions were deemed safe and well tolerated. Notably, serious adverse events were associated with the underlying eating and mood disorders, resulting in hospitalization for undernutrition (5 patients) or suicidal attempts (2 patients).</p> <p>Conclusion This pilot study does not support the use of rTMS of the rIPL</p>

	<p>as an effective method for improving body shape perception in individuals with the restrictive form of AN. Further research is warranted to comprehensively explore both the clinical and neurophysiological effects of HF rTMS in this population.</p>

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## Comments to the Author

Thank you very much for inviting me to review the paper titled “Effects of repetitive transcranial magnetic stimulation of the right inferior parietal lobe on the body image perception in anorexia nervosa: a pilot randomized controlled study.” This study focuses on an emerging and important area for the treatment of AN. I would like to make some suggestions for the improvement of the manuscript.

We thank the reviewer for this very positive comment.

1. **Abstract : Consider substituting "reduced excitability" for "under excitability."**

This has been corrected.

2. **Introduction**

**Further elaboration is warranted regarding the rationale and mechanistic underpinnings of utilizing high-frequency repetitive transcranial magnetic stimulation (rTMS) on the right inferior parietal lobe (rILP) to potentially to enhance excitability and to ameliorate body image distortions in individuals with AN.**

We thank reviewer 1 for this insightful comment, which has allowed us to clarify our main hypothesis. High-frequency rTMS (> 5 Hz) has been demonstrated to increase cortical excitability. In AN patients, hypoactivation of the right inferior parietal lobe has been observed and linked to body image distortion. Building upon these previous findings, our aim was to enhance the cortical excitability of the rIPL in order to improve body image distortion in individuals with restrictive forms of AN.

In accordance with this comment and to better articulate our primary objective and hypothesis, we have restructured the Introduction section and included the following sentences :

- Page 6, lines 4-7: ***“In addition to food restriction, AN involves an intense fear of gaining weight or becoming fat, persistent behaviors that interfere with weight gain, and a distorted body image or lack of recognition of the seriousness of low body weight. This body image distortion significantly contributes...”*** and the reference to DSM-IV added.

- Page 6, line 17: “**Regarding body image distortion, anormal activation has been observed...**”
- Page 7, line 2: “**Repetitive transcranial magnetic stimulation (rTMS) has shown potential in modulating cortical excitability, with low-frequency (<5 Hz) rTMS decreasing and high-frequency ( $\geq$  5Hz) rTMS increasing cortical excitability. High-frequency rTMS targeted at the dorsolateral...**”
- Page 6, line 15: “**In this study, considering the reduced rIPL activity observed in AN patients and its link to body image distortion, we hypothesized that enhancing the excitability of the rIPL through high-frequency rTMS could potentially ameliorate body image distortions in individuals with AN.**”

### 3. Method

- a. **Please give some examples for contraindications to transcranial magnetic stimulation – exclusion criteria section.**

We have added contraindications to TMS, as noted in the protocol: page 7, line 13: “...transcranial magnetic stimulation or MRI (**pace-maker, neurostimulation, metallic implants anywhere in the body...**), pregnancy, lactation, a history of seizures....”

- b. **Before recruiting patients, were there any safety and suitability assessments conducted by a clinician (e.g., psychiatrist, psychologists etc)?**

Before inclusion, all patients were previously followed in the local recruiting center within the psychiatry departments, with interviews conducted by their treating psychiatrist and psychologist. They were screened to ensure they met inclusion and exclusion criteria and underwent a thorough baseline examination, including a complete general medical exam, and additional interviews to identify any potential contraindications or safety issues.

- c. **Were any stratification criteria used for randomisation?**

We did not include a stratification criteria in our study. In line with this comment, we have modified the “Randomization” section as follows (page 9, line 22): “... *and conducted by the Rouen University Clinical Research Unit, **without stratification***”.

**d. Procedure: It's unclear what informs the decision to offer 10 sessions over a 2-week period. Any relevant literature? Also, it is not clear how authors decided to use “10 Hz frequency at 90% of their individual MT”.**

In this study, we utilized 10 Hz for the frequency, consistent with other rTMS studies conducted in AN patients. Regarding the number of sessions, very few studies have reported the effects of high-frequency rTMS in AN patients, and none applied it to the rIPL.

Previous literature on the effects of rTMS applied over the motor cortex suggests that a minimum of 750 pulses is necessary to induce changes in cortical excitability (see Lefaucheur et al, 2011). In our study, AN patients received a total of 20,000 stimulations over a 2-week period, thus exceeding this minimum requirement.

Although a limited number of studies have examined the effects of rTMS in AN patients and no validated protocol has been established thus far, previous research has typically involved 20 sessions of 10 Hz rTMS with 600 to 1000 stimulations per session. Consequently, this resulted in a total number of 12,000 to 20,000 pulses delivered over a 2 or 3-week period, which aligns closely with the parameters utilized in our study.

Additionally, to minimize side-effects and the potential for subjects to discern the the randomization, we utilized 90% of each individual’s motor threshold.

In line with this comment, we have modified the Methods section as follows: page 10, line 21: “***In line with previous published trials, each session consisted of 20 trains..***”

**e. Did authors conducted any checking to see if the blinding was successful?**

In this study, we did not directly assess whether patients had any intuitions about their randomization. However, the fact that both groups reported similar numbers of serious adverse events, and that only patients from the sham group reported rTMS-

related side effects, does not support the hypothesis that patients were aware of their group assignment.

- f. **Manuscript states that this is “a double-blind parallel group trial”, however, it is also stated that “the neurologist responsible for administering the rTMS sessions.” These appear to be contradictory.**

The neurologist in charge of the rTMS sessions was indeed aware of the randomization but did not perform the assessments of the patients. Patients were assessed by an investigator blinded of the rTMS condition that did clinical assessments at baseline and during the follow-up visits.

In line with this comment, and to prevent confusion, we have modified the Methods section as follows: pages 9-10 : *“Both the patients and the investigators remained blinded to the treatment allocation throughout the study. **The neurologist responsible for administering the rTMS sessions was not involved in patient assessments.**”*

#### 4. Outcomes

- a. **Please replace the word of considered to used/applied. (page 10, paragraph 1)**

This has been corrected.

- b. **This section would benefit from more details about the outcome measures, particularly about the Body Shape Questionnaire.**

We apologize for these insufficient details on the outcome measures.

In line with this comment, we have modified this section as follows: page 11, lines 5-18:

*“The primary outcome measure was the Body Shape questionnaire 24 (BSQ-34). **This is a one-dimensional questionnaire consisting of 34 items to assess concerns about body weight and shape. Responses are rated on a 6-point Likert scale (“never”, “rarely”, “sometimes”, “often”, “very often”, “always”), with the total scores ranging from 34 (no body image concerns) to 204 (severe concerns).**”*

Several secondary outcomes were assessed, including the Eating Attitude test (EAT-40), a 40-item self-report questionnaire measuring dieting behavior, oral control, food preoccupation, and body intake; the Bulimia test (BULIT),<sup>22</sup> a 36-item self-report questionnaire assessing signs of bulimia; the Eating Disorder Inventory (EDI-2),<sup>23</sup> a 91-item self-report questionnaire evaluating the presence of an eating disorders through 11 subscales: “drive for thinness”, “bulimia”, “body dissatisfaction”, “ineffectiveness”, “perfectionism”, “interpersonal distrust, interoceptive awareness”; “maturity fears”, “asceticism”, “impulse regulation” and “social insecurity”; and the Hamilton Anxiety and Depression Rating Scales (HARS, HDRS)<sup>24,25</sup> to assess symptoms of anxiety and depression.”

The references to these different scales were also added.

**c. How were safety and tolerability assessed?**

Safety and tolerability were assessed after each rTMS session and at each visit. This is now clearly stated in the “Outcomes section”: page 12, line 1: *“The safety and tolerability were also assessed after each rTMS session and at each visit.”*

**5. Result**

**a. The subtitle "Cohort analysis" might be better replaced with "Sample description."**

This has been corrected.

**b. Were there any reasons for withdrawal from the study? Did these three participants reported any reason?**

Three patients withdrew from the study before randomization because two of these patients withdrew their approval and one was hospitalized for a medical issue before randomization, resulting in premature dropout.

This is now clearly stated in the Results section: page 13, line 6: *“Three patients withdrew from the study before randomization: two of these patients withdrew their approval, and one was hospitalized for a medical issue before randomization, resulting in premature dropout.”*

- c. **Page 11, paragraph 1, line 7 – please indicate “patients assigned to the sham condition”**

We thank the reviewer to have pointed out this error. This has been corrected (page 11, line 10).

- d. **Please provide more detail regarding both the within-group and between-group statistical differences in the result section.**

**Currently, these are not clearly stated.**

We apologize for this unclarity in the Results section. We thank the reviewer for this comment allowing us to improve this part.

In line with it, we have modified the Results section to clearly dissociate between and within-groups effects: page 13: ***“Effects of real or sham rTMS on AN symptoms”***.

***“Comparing the scores between the real and sham rTMS groups post-rTMS, no significant differences in BSQ-34, EAT-40, EDI-2, HARS and HDRS scores, or BMI values (Table 1). The BULIT score remained significantly higher in the sham group compared to the real rTMS group (Table 1).***

***Within-group analysis revealed no significant changes in the BSQ-34, EAT-40, EDI-2, HARS and HDRS scores, or BMI values, after either sham or real rTMS (Table 1). The changes in the BSQ-34 score from baseline to post-rTMS was also not significantly different between the two groups with a mean effect of real vs sham rTMS of +5.6 points (linear model, 95% CI: -21.3 to +32.6, p=0.66).”***

## 6. Discussion

- a. The first sentence is a bit misleading and confusing. I recommend revising it to succinctly underscore the study's aims.

We thank reviewer for this comment, and we have modified the text as follows: page 15-line 2: ***“This pilot controlled study is the first to examine the effects of high-frequency rTMS targeting the right IPL on body image distortion in AN patients.”***

- b. Please make sure about stating “statistically significant” term when talking about changes.

This has been corrected.

- c. Given the BMI levels and illness durations, within the sample, it appears that the severity of the ED is pronounced. Based on research evidence and clinical experiences, we would expect that mood and eating behaviours would improve first, body image improvements would come after.

We thank reviewer 1 for this comment and we fully agree with it. In line with it, we have modified the discussion as follows: page16, lines 1-14:

***“Due to the complex fronto-parietal neural network disruptions involved in AN, prior research suggests that targeting the prefrontal cortical areas might be more effective in modulating these functional networks. This approach has shown a more favorable impact on clinical and behavioral components (BMI, food avoidance),<sup>16</sup> and IPL activity modulation.<sup>29</sup> When applied over the DMPFC, rTMS induced significant improvements in mood, anxiety, and some core domains of AN pathology, including shape and weight concerns. This improvement was correlated with lower baseline functional connectivity between the DMPFC, right inferior pole and left angular gyrus, parts of the ‘salience network’.<sup>17</sup> This was interpreted as a lesser capacity for cognitive control over perseverance or negative self-referential thinking in responsive AN patients. When applied over the DLPFC, rTMS also induced significant improvements in anxiety and mood, but no changes in body image distortion or BMI. Overall, these data could suggest that improvements in mood, anxiety, and eating behaviors may precede improvements in body image distortion.”***

We also added this sentence: page 15-line 21: ***“Unlike previous rTMS studies targeting the DLPFC, we observed no significant changes in anxiety or mood. In fact, mood worsened in two patients who attempted suicide after rTMS, one in each patients group, with no clear relationship to the intervention. However, our protocol targeting the rIPL did not aim to improve these psychiatric comorbidities.”***

- d. Also, the differences between patients who were allocated to sham and real rTMS at baseline are non-negligible, particularly for an experimental treatment study. This aspect needs to be better discussed.

We thank reviewer 1 for this comment and we fully agree with it. In line with it, we have modified the discussion as follows:

- page 15, lines 8-13: *“the patients **randomized to the real rTMS group** had a very severe disease profiles, with significant body image distortion, **extremely low BMI (mean <14)**, long disease duration and resistance to previous interventions. **In prior therapeutics trials assessing the effects of rTMS in AN patients, the average BMI was around 16, whereas it was 13.6 in our patients randomized to real rTMS. This severe baseline condition might have limited the potential benefits of our approach.**”*
- page 15, line 16: *“This study also acknowledges several limitations. First, the small cohort size limits the generalizability of the findings. **Second, the two groups exhibited significant differences in AN severity at baseline, which could have affected the statistical comparison of the effects of rTMS between groups. Additionally, the absence...**”*
- e. I think not finding any effect of HF-rTMS of the right IPL can be explained by several factors: severity of sample, target location, outcome measure and intensity/frequency of the treatment. Further elaboration on these factors is necessary.

Once again, we fully concur with this comment, and have adjusted the discussion accordingly, in addition to the aforementioned changes: page 15, lines 14-16:

*“**Although previous studies that tested HF rTMS of the DMPFC used similar protocols, with a 10 Hz frequency and a total number of pulses of 20,000 delivered over a 2 or 3-week period,<sup>14-17</sup> this might not have been optimally designed to modulate the targeted brain area’s excitability. A longer treatment period might be necessary for substantial changes,<sup>16</sup> rather than focusing solely on the total number of pulses administered.**”*

1 **Effects of repetitive transcranial magnetic stimulation of the right inferior parietal lobe on**  
2 **the body image perception in anorexia nervosa: a pilot randomized controlled study.**

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3

4 **Running title:** IPL rTMS for body image distortion in AN

5

6 **Statistics:** Word count: Abstract: 235 words, Text 2507 words, 2 Figures/Tables, 29

7 References, Running title: 40 characters

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9

#### 10 **Author Contribution Statement**

11 Conceptualization : N Chastan, N Achamrah, O Guillin; Data curation: A. Gillibert;

12 Formal analysis: A. Gillibert; Funding acquisition: N Chastan, O Guillin; Investigation: N

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14 Guillin, ML Welter; Methodology : N Chastan, A Gillibert, ML Welter; Project administration: N

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17 Welter; Validation: A Gillibert; Visualization: N Chastan, A Gillibert, ML Welter; Writing

18 original draft: N Chastan, A Gillibert, ML Welter; Writing – review & editing: N Chastan, N

19 Achamrah, O Etard, C Nathou, MA Piquet, S Guillaume, J Attal, A Gillibert, P Dechelotte, O

20 Guillin, ML Welter.

21

#### 22 **Acknowledgments**

23 We thank all the participants in this study. We also thank the administrative staff of the

24 Clinical Research Department of the CHU Rouen.

1

2 **Data availability statement**

3 All relevant data are within the article. Requests for anonymized data should be sent to M.L.

4 Welter at the CHU Rouen, 76000 Rouen, France

5

6 **Funding**

7 This study was supported by the French Ministry of Health

8

9 **Financial disclosure/Conflict of interest relative to research**

10 The authors declare to have no conflict of interest relative to research

11

12 **Ethics approval/Clinical trial registration**

13 This study was done in accordance with the Declaration of Helsinki and good clinical practice

14 guidelines. It was approved by the local ethics committee and was registered on

15 ClinicalTrials.gov (NCT01717079).

16

## 1 **Abstract**

2 **Introduction** Restrictive anorexia nervosa (AN) is associated with distorted perception of  
3 body shape, previously linked to hypoactivity and **reduced** excitability of the right inferior  
4 parietal lobe (rIPL). Here, we investigated the impact of high-frequency repetitive  
5 transcranial magnetic stimulation (HF rTMS) of the rIPL on body shape perception in patients  
6 with AN.

7 **Methods** Seventeen patients with AN (median [Q1\_Q3] age, 35 [27\_39] yrs; disease  
8 duration, 12 [6\_18] yrs) were randomly assigned to receive real or sham HF (10 Hz) rTMS of  
9 the rIPL over a 2 week-period, comprising 10 sessions. The primary outcome measure was  
10 the Body Shape Questionnaire (BSQ). Secondary outcomes included eating disorder  
11 symptoms, body mass index, mood, anxiety, and safety. Data collection were done at  
12 baseline, post-rTMS, and at 2 weeks and 3 months post-rTMS.

13 **Results** Following both real and sham rTMS of the rIPL, no significant differences were  
14 observed in body shape perception or other parameters. Both real and sham rTMS  
15 interventions were deemed safe and well tolerated. Notably, serious adverse events were  
16 associated with the underlying eating and mood disorders, resulting in hospitalization for  
17 undernutrition (5 patients) or suicidal attempts (2 patients).

18 **Conclusion** This pilot study does not support the use of rTMS of the rIPL as an effective  
19 method for improving body shape perception in individuals with the restrictive form of AN.  
20 Further research is warranted to comprehensively explore both the clinical and  
21 neurophysiological effects of HF rTMS in this population.

22

23

1 **Key words:** Anorexia Nervosa; repetitive transcranial magnetic stimulation; body image;  
2 right inferior parietal lobe.

3

4 **Key points:**

5 • Distorted body shape perception in AN is associated with abnormal activity in the  
6 right inferior parietal lobe (rIPL).

7 • High-frequency rTMS of the rIPL did not significantly modified body shape perception  
8 in individuals with severe AN

9 • High-frequency rTMS of the rIPL is well tolerated

10

Pre-Review Only

## 1 Introduction

2 Anorexia nervosa, a prevalent eating disorder among adolescents, manifests through severe  
3 food restriction leading to undernutrition, and is associated with significant morbidity,  
4 including mood disorders, and an almost sixfold increase in mortality rates (Arcelus et al.,  
5 2011; van Eeden, van Hoeken and Hoek, 2021). In addition to food restriction, AN involves  
6 an intense fear of gaining weight or becoming fat, persistent behaviors that interfere with  
7 weight gain, and a distorted body image or lack of recognition of the seriousness of low body  
8 weight (Dobrescu et al., 2020). This body image distortion significantly contributes to the  
9 perpetuation of food restriction and refusal to acknowledge thinness (Dobrescu et al., 2020).  
10 Current treatments, such as pharmacological and cognitive behavioral therapies, have  
11 shown limited effectiveness, resulting in a chronic course of the disorder in about 20% of  
12 cases (Dobrescu et al., 2020).

13 The intricate pathophysiology of AN remains poorly understood. Recent research has  
14 identified various structural and functional brain anomalies, including decreased grey matter  
15 volume in the anterior and median cingulate cortex, left middle occipital gyrus, and inferior  
16 parietal lobe (IPL) (Joos et al., 2010; Titova et al., 2013; Su et al., 2021). Additionally,  
17 disruptions in resting state functional connectivity in the anterior and median cingulate  
18 cortex (Su et al., 2021), as well as white matter alterations within the thalamo-cortical and  
19 occipital-parietal-temporal-frontal tracts, have been reported (Gaudio et al., 2019).

20 Regarding body image distortion, abnormal activation has been observed in the lateral  
21 temporo-occipital, precuneus, and inferior parietal cortices (Gaudio et al., 2019), with a  
22 positive correlation of 'drive for thinness' and grey matter volume of the right IPL (Joos et al.,  
23 2010). Hypoactivation of the rIPL during tasks involving the visualization of one's body  
24 relative to others (Vocks et al., 2010), coupled with increased amygdala activity during

1 visualization of others' bodies or one's own body being inflated (Wagner et al., 2003; Vocks  
2 et al., 2010) were also reported in AN patients, and linked to heightened emotional  
3 sensitivity and social comparison awareness (Gaudio and Quattrocchi, 2012).

4 In line with these recent advances, non-invasive brain stimulation has emerged as a  
5 potential therapeutic option for treating AN. Repetitive transcranial magnetic stimulation  
6 (rTMS) has shown potential in modulating cortical excitability, with low-frequency (<5 Hz)  
7 rTMS decreasing and high-frequency ( $\geq 5$ Hz) rTMS increasing cortical excitability (Fitzgerald,  
8 Fountain and Daskalakis, 2006). High-frequency rTMS targeted at the dorsolateral prefrontal  
9 cortex (DLPFC) has shown promise in alleviating certain clinical symptoms, such as reducing  
10 subjective feelings of being 'fat' or 'full' (Van den Eynde et al., 2013) and fat avoidance  
11 (Muratore et al., 2021). However, controlled studies performed on larger cohorts have  
12 produced mixed results (McClelland, Bozhilova, Campbell, et al., 2013; McClelland,  
13 Bozhilova, Nestler, et al., 2013; Dalton et al., 2018), indicating varying effects on mood and  
14 anxiety (Dalton et al., 2018). A recent open-label study found that 20-30 sessions of high-  
15 frequency rTMS targeted at the dorsomedial PFC in AN patients with comorbid depression  
16 improved functional scales of eating disorders and comorbid anxiety (Woodside et al., 2021).  
17 A meta-analysis suggested only moderate therapeutic effects on depressive and anxiety  
18 symptoms, with no impact on body mass index (BMI) (Cavicchioli et al., 2022). This highlights  
19 the heterogeneous nature of rTMS protocols, including targeted brain areas, sessions  
20 durations, inter-train interval, and the number and frequency of train pulses (Cavicchioli et  
21 al., 2022).

22 In this study, considering the reduced rIPL activity observed in AN patients and its link  
23 to body image distortion, we hypothesized that enhancing the excitability of the rIPL through

- 1 high-frequency rTMS could potentially ameliorate body image distortions in individuals with
- 2 AN.
- 3

For Review Only

## 1 **Patients and Methods**

### 2 **Study design and Patients**

3 In this randomized double-blind parallel group trial, patients were assigned to receive either  
4 real or sham 10 Hz rTMS across 10 sessions. The recruitment of participants was carried out  
5 at the Psychiatry and Nutrition departments at the Rouen, Caen and Montpellier University  
6 Hospitals. Inclusion criteria were: right-handed adults (age  $\geq 18$  years old), diagnosed with  
7 AN of the restricting subtype, as per the Diagnostic and Statistical Mental Disorders (Call,  
8 Walsh and Attia, 2013). Additionally, individuals were required to have a disease duration of  
9 over 1 year, a BMI of  $\leq 18.5$  kg/m<sup>2</sup> sustained for minimum of 3 months, and a stable medical  
10 drug regimen maintained for more than 3 months. To be eligible for the study, patients  
11 willingly consented and provided informed written consent, and were affiliated with a social  
12 security scheme. Non-inclusion criteria comprised: contraindications to transcranial  
13 magnetic stimulation or MRI (pace-maker, neurostimulation, metallic implants anywhere in  
14 the body...), pregnancy, lactation, a history of seizures or an increased risk thereof, prior  
15 exposure to rTMS, or the presence of any brain lesion. This study was done in accordance  
16 with the Declaration of Helsinki and good clinical practice guidelines. It was approved by the  
17 local ethics committee and was registered on ClinicalTrials.gov (NCT01717079).

18

### 19 **Randomization and masking**

20 Patients were randomly assigned to either real or sham rTMS group, with a ratio of 1:1  
21 between the two trial arms. Randomization was overseen and conducted by the Rouen  
22 University Clinical Research Unit, without stratification. Both the patients and the  
23 investigators remained blinded to the treatment allocation throughout the study. The

1 neurologist responsible for administering the rTMS sessions was not involved in patient  
2 assessments.

3

#### 4 **Procedures**

5 Patients underwent a comprehensive assessment at the inclusion before TMS (baseline, D0),  
6 followed by the first rTMS session (Figure). Over the course of a 2-week period, a total of ten  
7 rTMS sessions were administered. The 10<sup>th</sup> rTMS session was followed by a second  
8 assessment (Figure). Subsequently, two follow-up visits were scheduled at 2 weeks and 3  
9 months post-treatment (Figure).

10 Before the rTMS sessions, every patient underwent a structural MRI scan to precisely  
11 localize the right inferior parietal lobe (IPL, Brodmann area 40, supramarginalis gyrus) for  
12 neuronavigation purposes (Nexstim, eXimia NBS, Helsinki, Finland). Each rTMS session  
13 commenced by determining the patients' motor threshold (MT) through the recording of the  
14 left thumb adductor muscle using surface EMG electrodes and using a real TMS figure-of-  
15 eight coil applied over the right primary motor cortex. The motor threshold was defined as  
16 the minimum stimulator output intensity required to obtain a peak-to-peak amplitude of the  
17 motor-evoked potentials > 50  $\mu$ V for half of a series of 10-20 stimulations.

18 The Magstim Rapid device and the Magstim 70-mm air-cooled real and sham coils  
19 were employed to perform rTMS sessions (Whitland, UK). Patients allocated to the real  
20 group received 10 sessions of 10 Hz frequency at 90% of their individual MT. In line with  
21 previous published trials, (McClelland, Bozhilova, Campbell, et al., 2013; Dalton et al., 2018)  
22 each session consisted of 20 trains of 10 seconds with 50-second inter-train intervals,  
23 resulting in a total of 2000 pulses per session, all precisely targeted at the right IPL. In the  
24 sham group, a similar stimulation protocol was applied, using a sham coil designed to

1 replicate the sensory experience of the active coil without delivering actual stimulation to  
2 the brain, ensuring the integrity of the masking procedure.

3

#### 4 **Outcomes**

5 The primary outcome measure was the Body-shape questionnaire-34 (BSQ-34). This is a one-  
6 dimensional questionnaire consisting of 34 items to assess concerns about body weight and  
7 shape. Responses are rated on a 6-point Likert scale ("never", "rarely", "sometimes",  
8 "often", "very often", "always"), with the total scores ranging from 34 (no body image  
9 concerns) to 204 (severe concerns) (Cooper et al., 1987; Rousseau et al., 2005).

10 Several secondary outcomes were assessed, including the Eating Attitude test (EAT-  
11 40), a 40-item self-report questionnaire measuring dieting behavior, oral control, food  
12 preoccupation, and body intake (Garner and Garfinkel, 1979); the Bulimia test (BULIT), a 36-  
13 item self-report questionnaire assessing signs of bulimia (Thelen et al., 1996); the Eating  
14 Disorder Inventory (EDI-2), a 91-item self-report questionnaire evaluating the presence of an  
15 eating disorders through 11 subscales: "drive for thinness", "bulimia", "body dissatisfaction",  
16 "ineffectiveness", "perfectionism", "interpersonal distrust, interoceptive awareness";  
17 "maturity fears", "asceticism", "impulse regulation" and "social insecurity" (Garner, D. M.,  
18 1991); and the Hamilton Anxiety and Depression Rating Scales (HARS, HDRS) to assess  
19 symptoms of anxiety and depression (Hamilton, 1959, 1967).

20 Physical indicators such as the Body Mass Index (BMI=body mass, kg/[height, cm]<sup>2</sup>),  
21 percentage of fat mass and lean mass measured via Dual Energy X-ray Absorptiometry  
22 (DEXA) using a Lunar Prodigy device (GE Medical Systems Lunar, Madison, USA) were also  
23 included.

1 Safety and tolerability were also assessed after each rTMS session and at each visit.

2 Any new symptom was considered an adverse event and classified as serious if it resulted in  
3 hospital admission, persisted as sequelae, or were deemed critical by the attending clinician.

4

## 5 **Statistics**

6 To evaluate the impact of the intervention, we utilized non-parametric Mann-Whitney tests  
7 to compare scores for the BSQ, EAT-40, BULIT, EDI-2, HARS, HDRS, SF-36, and BMI  
8 measurements between the patients' groups at both baseline and after the rTMS. The  
9 analysis was conducted in an intention-to-treat (ITT) manner, with all randomized patients  
10 included in the primary analysis and data imputed using the 'last observation carried  
11 forward' (LOCF) method for missing data pertaining to the primary outcome. For imputation,  
12 median values of both randomization groups at baseline were employed. Additionally, a post  
13 hoc analysis was conducted, considering differences at baseline, utilizing a linear model to  
14 explain immediate post-stimulation BSQ (primary endpoint) by the baseline BSQ and by the  
15 ITT randomization group, with LOCF, mirroring the approach in the main analysis. All  
16 statistical analyses were conducted with the R statistical software (the R Foundation for  
17 Statistical Computing, Vienna, Austria), with a significance set at 0.05.

18

19

## 1 Results

### 2 Sample description

3 A screening of twenty patients with AN resulted in the enrollment and randomization of 17  
4 participants, with a median age of 35 years (range:27-39), a disease duration of 12 years  
5 (range: 6-18), and a BMI of 16 kg/m<sup>2</sup> (range: 14-17) (Table 1). Three patients withdrew from  
6 the study before randomization: two of these patients withdrew their approval, and one was  
7 hospitalized for a medical issue before randomization, resulting in premature dropout.

8 Among the randomized patients, seven were allocated to the real rTMS group and ten to the  
9 sham rTMS group. Baseline analysis showed significant differences between the groups, with  
10 higher scores for the EDI-2 and BULIT scales, as well as BMI in patients assigned to the sham  
11 rTMS group compared to those in the real rTMS group (Table 1).

12

### 13 Effects of real or sham IPL rTMS on AN symptoms

14 Comparing the scores between the real and sham rTMS groups post-rTMS, we found no  
15 significant differences in BSQ-34 (Figure 1), EAT-40, EDI-2, HARS and HDRS scores, or BMI  
16 values (Table 1). The BULIT score remained significantly higher in the sham group compared  
17 to the real rTMS group (Table 1).

18 Within-group analysis revealed no significant changes in the BSQ-34, ETA40, EDI2,  
19 HARS and HDRS scores, or BMI values, after either sham or real rTMS (Table 1). The changes  
20 in the BSQ-34 score from baseline to post-rTMS were also not significantly different between  
21 the two groups, with a mean effect of real versus sham rTMS of +5.6 points (linear model,  
22 95% CI: -21.3 to +32.6, p=0.66).

23

### 24 Follow-up period

1 During the follow-up period, assessments at 2 weeks and 3 months post-rTMS sessions were  
2 conducted for 16 patients. No significant changes were observed in BSQ-34 or other scores,  
3 nor in the proportion of lean and fat masses in both groups (not shown). The BULIT score  
4 continued to exhibit significant differences between groups, with persistently higher scores  
5 in patients assigned to the real rTMS group (Table 1).

6

### 7 **Adverse events**

8 Throughout the rTMS sessions, a total of 30 non-serious adverse events were reported, with  
9 20 occurring in the sham group and 10 in the real group. Cephalalgia and twitching of the  
10 eyelid were reported during sham rTMS, while no rTMS related side-effects were reported  
11 during real IPL rTMS sessions. During the randomized period, eight serious adverse events  
12 were documented, involving three patients assigned to the sham rTMS group and four in the  
13 real rTMS group. These events included five cases of exacerbated undernutrition and  
14 deteriorated general status, leading to hospitalizations in the psychiatry department for two  
15 patients, and enteral nutrition for one patient. Additionally, two patients committed a  
16 suicidal attempt through drug intoxication, requiring intensive care hospitalization and  
17 subsequent withdrawal from the study in one patient. Another patient developed a  
18 pulmonary infection, which resolved with appropriate antibiotic therapy.

19

## 1 Discussion

2 This pilot controlled study is the first to examine the effects of high-frequency rTMS  
3 targeting the right IPL on body image distortion in AN patients. Our results indicated that HF-  
4 rTMS of the rIPL failed to statistically significant improvements in body image distortion or  
5 other related AN symptoms. Severe adverse events were observed across patient groups,  
6 primarily due to AN severity, with a good tolerance of the rTMS protocol.

7 The lack of observable effects on body shape distortion, but also BMI, anxiety or  
8 depression, in our AN patients could be attributed to several factors. First, the patients  
9 randomized to the real rTMS group had a very severe disease profiles, with significant body  
10 image distortion, extremely low BMI (mean <14), long disease duration and resistance to  
11 previous interventions. In prior therapeutics trials assessing the effects of rTMS in AN  
12 patients, the average BMI was around 16 (Dalton et al., 2018; Muratore et al., 2021;  
13 Woodside et al., 2021), whereas it was 13.6 in our patients randomized to real rTMS. This  
14 severe baseline condition might have limited the potential benefits of our approach. Another  
15 factor could be the chosen protocol. Although previous studies that tested HF rTMS of the  
16 DMPFC used similar protocols, with a 10 Hz frequency and a total number of pulses of  
17 20,000 delivered over a 2 or 3-week period (McClelland, Bozhilova, Campbell, et al., 2013;  
18 McClelland, Bozhilova, Nestler, et al., 2013; Dalton et al., 2018; Woodside et al., 2021), this  
19 might not have been optimally designed to modulate the targeted brain area's excitability. A  
20 longer treatment period might be necessary for substantial changes (Dalton et al., 2018),  
21 rather than focusing solely on the total number of pulses administered. Unlike previous  
22 rTMS studies targeting the DLPFC, we observed no significant changes in anxiety or mood. In  
23 fact, mood worsened in two patients who attempted suicide after rTMS, one in each  
24 patients group, with no clear relationship to the intervention. However, our protocol

1 targeting the rIPL did not aim to improve these psychiatric comorbidities. Overall, these  
2 data indicate that targeting the rIPL alone may not suffice for significant changes in body  
3 perception, despite its involvement in self-other discrimination and self-perception  
4 processes (Uddin et al., 2006; Karhson, Mock and Golob, 2015). Due to the complex fronto-  
5 parietal neural network disruptions involved in AN, prior research suggests that targeting the  
6 prefrontal cortical areas might be more effective in modulating these functional networks.  
7 This approach has shown a more favorable impact on clinical and behavioral components  
8 (BMI, food avoidance) (Dalton et al., 2018), and IPL activity modulation (Ćurčić-Blake, Kos  
9 and Aleman, 2022). When applied over the DMPFC, rTMS induced significant improvements  
10 in mood, anxiety, and some core domains of AN pathology, including shape and weight  
11 concerns. This improvement was correlated with lower baseline functional connectivity  
12 between the DMPFC, right inferior pole and left angular gyrus, parts of the 'salience  
13 network' (Woodside et al., 2021). This was interpreted as a lesser capacity for cognitive  
14 control over perseverance or negative self-referential thinking in responsive AN patients.  
15 When applied over the DLPFC, rTMS also induced significant improvements in anxiety and  
16 mood, but no changes in body image distortion or BMI. Overall, these data could suggest  
17 that improvements in mood, anxiety, and eating behaviors may precede improvements in  
18 body image distortion.

19 This study also acknowledges several limitations. First, the small cohort size limits the  
20 generalizability of the findings. Second, the two groups exhibited significant differences in  
21 AN severity at baseline, which could have affected the statistical comparison of the effects of  
22 rTMS between groups. Additionally, the absence of an assessment of the neurophysiological  
23 effects of the HF-rTMS protocol hinders a comprehensive understanding of its impact on  
24 local and network brain excitability and functional connectivity.

1

2 **Conclusions**

3 This small cohort study does not advocate for the use of HF-rTMS of the right IPL to

4 ameliorate body image distortion in patients with severe AN. Further studies are necessary

5 to optimize protocols, considering less severe cases and identifying the most effective target

6 areas for intervention in AN. Future research Incorporating neurophysiological markers will

7 provide insights into the relationship between brain activity changes and symptom

8 improvement, advancing more effective therapeutic approaches for AN patients.

9

10

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**Table 1. Baseline characteristics and effects of real and sham rTMS of the right IPL in 17 patients with Anorexia nervosa**

	Baseline		P-value	Post-rTMS		P-value
	Real	Sham		Real	Sham	
Age (yrs)	36 (29_39)	29 (27_36)				
Disease duration (yrs)	18 (7_21)	11 (7_12)				
BSQ-34	93 (67_142)	154 (130_164)	0.055	85 (54_90)	120 (95_151)	0.073
EAT-40	42 (34_55)	72 (61_78)	0.082	44 (33_50)	65 (48_70)	0.28
EDI-2	81 (47_88)	130 (110_141)	0.016	69 (40_85)	108 (76_115)	0.057
BULIT	68 (55_76)	100 (92_114)	0.003	67 (59_73)	90 (83_114)	0.001
HARS	16 (8_23)	16 (14_30)	0.46	10 (6_16)	12 (6_16)	0.96
HDRS	16 (14_18)	16 (13_20)	0.96	12 (11_13)	12 (10_14)	1.0
BMI	13.6 (13.2_15.5)	16.5 (15.6_17.1)	0.025	14 (13_16)	16 (15_18)	0.073

Values are median (Q1\_Q3); P-value: between-group comparison at baseline and post-rTMS sessions.

BSQ-34=Body-shape questionnaire-34 (BSQ-34) ; EAT-40=Eating Attitude test (EAT-40); BULIT=Bulimia test; EDI-2=Eating Disorder Inventory;

HARS and HDRS=Hamilton Anxiety and Depression Rating Scales; BMI=Body Mass Index.

## Figure legends

### **Figure 1. Study design and effects of real and sham high-frequency rTMS of the right IPL on the body shape questionnaire in patients with Anorexia Nervosa.**

Study design (left panel) and body shape questionnaire scores obtained in AN patients randomized in the real (blue) or sham (red) groups. Each line represents one individual patient. rTMS = repetitive transcranial magnetic stimulation.

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1 **Effects of repetitive transcranial magnetic stimulation of the right inferior parietal lobe on**  
2 **the body image perception in anorexia nervosa: a pilot randomized controlled study.**

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1

2 **Data availability statement**

3 All relevant data are within the article. Requests for anonymized data should be sent to M.L.

4 Welter at the CHU Rouen, 76000 Rouen, France

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9 **Financial disclosure/Conflict of interest relative to research**

10 The authors declare to have no conflict of interest relative to research

11

12 **Ethics approval/Clinical trial registration**

13 This study was done in accordance with the Declaration of Helsinki and good clinical practice

14 guidelines. It was approved by the local ethics committee and was registered on

15 ClinicalTrials.gov (NCT01717079).

16

1 **Abstract**

2 **Introduction** Restrictive anorexia nervosa (AN) is associated with distorted perception of  
3 body shape, previously linked to hypoactivity and reduced excitability of the right inferior  
4 parietal lobe (rIPL). Here, we investigated the impact of high-frequency repetitive  
5 transcranial magnetic stimulation (HF rTMS) of the rIPL on body shape perception in patients  
6 with AN.

7 **Methods** Seventeen patients with AN (median [Q1\_Q3] age, 35 [27\_39] yrs; disease  
8 duration, 12 [6\_18] yrs) were randomly assigned to receive real or sham HF (10 Hz) rTMS of  
9 the rIPL over a 2 week-period, comprising 10 sessions. The primary outcome measure was  
10 the Body Shape Questionnaire (BSQ). Secondary outcomes included eating disorder  
11 symptoms, body mass index, mood, anxiety, and safety. Data collection were done at  
12 baseline, post-rTMS, and at 2 weeks and 3 months post-rTMS.

13 **Results** Following both real and sham rTMS of the rIPL, no significant differences were  
14 observed in body shape perception or other parameters. Both real and sham rTMS  
15 interventions were deemed safe and well tolerated. Notably, serious adverse events were  
16 associated with the underlying eating and mood disorders, resulting in hospitalization for  
17 undernutrition (5 patients) or suicidal attempts (2 patients).

18 **Conclusion** This pilot study does not support the use of rTMS of the rIPL as an effective  
19 method for improving body shape perception in individuals with the restrictive form of AN.  
20 Further research is warranted to comprehensively explore both the clinical and  
21 neurophysiological effects of HF rTMS in this population.

22

23

1 **Key words:** Anorexia Nervosa; repetitive transcranial magnetic stimulation; body image;  
2 right inferior parietal lobe.

3

4 **Key points:**

5 • Distorted body shape perception in AN is associated with abnormal activity in the  
6 right inferior parietal lobe (rIPL).

7 • High-frequency rTMS of the rIPL did not significantly modified body shape perception  
8 in individuals with severe AN

9 • High-frequency rTMS of the rIPL is well tolerated

10

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## 1 Introduction

2 Anorexia nervosa, a prevalent eating disorder among adolescents, manifests through severe  
3 food restriction leading to undernutrition, and is associated with significant morbidity,  
4 including mood disorders, and an almost sixfold increase in mortality rates (Arcelus et al.,  
5 2011; van Eeden, van Hoeken and Hoek, 2021). In addition to food restriction, AN involves  
6 an intense fear of gaining weight or becoming fat, persistent behaviors that interfere with  
7 weight gain, and a distorted body image or lack of recognition of the seriousness of low body  
8 weight (Dobrescu et al., 2020). This body image distortion significantly contributes to the  
9 perpetuation of food restriction and refusal to acknowledge thinness (Dobrescu et al., 2020).  
10 Current treatments, such as pharmacological and cognitive behavioral therapies, have  
11 shown limited effectiveness, resulting in a chronic course of the disorder in about 20% of  
12 cases (Dobrescu et al., 2020).

13 The intricate pathophysiology of AN remains poorly understood. Recent research has  
14 identified various structural and functional brain anomalies, including decreased grey matter  
15 volume in the anterior and median cingulate cortex, left middle occipital gyrus, and inferior  
16 parietal lobe (IPL) (Joos et al., 2010; Titova et al., 2013; Su et al., 2021). Additionally,  
17 disruptions in resting state functional connectivity in the anterior and median cingulate  
18 cortex (Su et al., 2021), as well as white matter alterations within the thalamo-cortical and  
19 occipital-parietal-temporal-frontal tracts, have been reported (Gaudio et al., 2019).

20 Regarding body image distortion, abnormal activation has been observed in the lateral  
21 temporo-occipital, precuneus, and inferior parietal cortices (Gaudio et al., 2019), with a  
22 positive correlation of 'drive for thinness' and grey matter volume of the right IPL (Joos et al.,  
23 2010). Hypoactivation of the rIPL during tasks involving the visualization of one's body  
24 relative to others (Vocks et al., 2010), coupled with increased amygdala activity during

1 visualization of others' bodies or one's own body being inflated (Wagner et al., 2003; Vocks  
2 et al., 2010) were also reported in AN patients, and linked to heightened emotional  
3 sensitivity and social comparison awareness (Gaudio and Quattrocchi, 2012).

4 In line with these recent advances, non-invasive brain stimulation has emerged as a  
5 potential therapeutic option for treating AN. Repetitive transcranial magnetic stimulation  
6 (rTMS) has shown potential in modulating cortical excitability, with low-frequency (<5 Hz)  
7 rTMS decreasing and high-frequency ( $\geq 5$ Hz) rTMS increasing cortical excitability (Fitzgerald,  
8 Fountain and Daskalakis, 2006). High-frequency rTMS targeted at the dorsolateral prefrontal  
9 cortex (DLPFC) has shown promise in alleviating certain clinical symptoms, such as reducing  
10 subjective feelings of being 'fat' or 'full' (Van den Eynde et al., 2013) and fat avoidance  
11 (Muratore et al., 2021). However, controlled studies performed on larger cohorts have  
12 produced mixed results (McClelland, Bozhilova, Campbell, et al., 2013; McClelland,  
13 Bozhilova, Nestler, et al., 2013; Dalton et al., 2018), indicating varying effects on mood and  
14 anxiety (Dalton et al., 2018). A recent open-label study found that 20-30 sessions of high-  
15 frequency rTMS targeted at the dorsomedial PFC in AN patients with comorbid depression  
16 improved functional scales of eating disorders and comorbid anxiety (Woodside et al., 2021).  
17 A meta-analysis suggested only moderate therapeutic effects on depressive and anxiety  
18 symptoms, with no impact on body mass index (BMI) (Cavicchioli et al., 2022). This highlights  
19 the heterogeneous nature of rTMS protocols, including targeted brain areas, sessions  
20 durations, inter-train interval, and the number and frequency of train pulses (Cavicchioli et  
21 al., 2022).

22 In this study, considering the reduced rIPL activity observed in AN patients and its link  
23 to body image distortion, we hypothesized that enhancing the excitability of the rIPL through

- 1 high-frequency rTMS could potentially ameliorate body image distortions in individuals with
- 2 AN.
- 3

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## 1 **Patients and Methods**

### 2 **Study design and Patients**

3 In this randomized double-blind parallel group trial, patients were assigned to receive either  
4 real or sham 10 Hz rTMS across 10 sessions. The recruitment of participants was carried out  
5 at the Psychiatry and Nutrition departments at the Rouen, Caen and Montpellier University  
6 Hospitals. Inclusion criteria were: right-handed adults (age  $\geq 18$  years old), diagnosed with  
7 AN of the restricting subtype, as per the Diagnostic and Statistical Mental Disorders (Call,  
8 Walsh and Attia, 2013). Additionally, individuals were required to have a disease duration of  
9 over 1 year, a BMI of  $\leq 18.5$  kg/m<sup>2</sup> sustained for minimum of 3 months, and a stable medical  
10 drug regimen maintained for more than 3 months. To be eligible for the study, patients  
11 willingly consented and provided informed written consent, and were affiliated with a social  
12 security scheme. Non-inclusion criteria comprised: contraindications to transcranial  
13 magnetic stimulation or MRI (pace-maker, neurostimulation, metallic implants anywhere in  
14 the body...), pregnancy, lactation, a history of seizures or an increased risk thereof, prior  
15 exposure to rTMS, or the presence of any brain lesion. This study was done in accordance  
16 with the Declaration of Helsinki and good clinical practice guidelines. It was approved by the  
17 local ethics committee and was registered on ClinicalTrials.gov (NCT01717079).

18

### 19 **Randomization and masking**

20 Patients were randomly assigned to either real or sham rTMS group, with a ratio of 1:1  
21 between the two trial arms. Randomization was overseen and conducted by the Rouen  
22 University Clinical Research Unit, without stratification. Both the patients and the  
23 investigators remained blinded to the treatment allocation throughout the study. The

1 neurologist responsible for administering the rTMS sessions was not involved in patient  
2 assessments.

3

#### 4 **Procedures**

5 Patients underwent a comprehensive assessment at the inclusion before TMS (baseline, D0),  
6 followed by the first rTMS session (Figure). Over the course of a 2-week period, a total of ten  
7 rTMS sessions were administered. The 10<sup>th</sup> rTMS session was followed by a second  
8 assessment (Figure). Subsequently, two follow-up visits were scheduled at 2 weeks and 3  
9 months post-treatment (Figure).

10 Before the rTMS sessions, every patient underwent a structural MRI scan to precisely  
11 localize the right inferior parietal lobe (IPL, Brodmann area 40, supramarginalis gyrus) for  
12 neuronavigation purposes (Nexstim, eXimia NBS, Helsinki, Finland). Each rTMS session  
13 commenced by determining the patients' motor threshold (MT) through the recording of the  
14 left thumb adductor muscle using surface EMG electrodes and using a real TMS figure-of-  
15 eight coil applied over the right primary motor cortex. The motor threshold was defined as  
16 the minimum stimulator output intensity required to obtain a peak-to-peak amplitude of the  
17 motor-evoked potentials > 50  $\mu$ V for half of a series of 10-20 stimulations.

18 The Magstim Rapid device and the Magstim 70-mm air-cooled real and sham coils  
19 were employed to perform rTMS sessions (Whitland, UK). Patients allocated to the real  
20 group received 10 sessions of 10 Hz frequency at 90% of their individual MT. In line with  
21 previous published trials,(McClelland, Bozhilova, Campbell, et al., 2013; Dalton et al., 2018)  
22 each session consisted of 20 trains of 10 seconds with 50-second inter-train intervals,  
23 resulting in a total of 2000 pulses per session, all precisely targeted at the right IPL. In the  
24 sham group, a similar stimulation protocol was applied, using a sham coil designed to

1 replicate the sensory experience of the active coil without delivering actual stimulation to  
2 the brain, ensuring the integrity of the masking procedure.

3

#### 4 **Outcomes**

5 The primary outcome measure was the Body-shape questionnaire-34 (BSQ-34). This is a one-  
6 dimensional questionnaire consisting of 34 items to assess concerns about body weight and  
7 shape. Responses are rated on a 6-point Likert scale (“never”, “rarely”, “sometimes”,  
8 “often”, “very often”, “always”), with the total scores ranging from 34 (no body image  
9 concerns) to 204 (severe concerns) (Cooper et al., 1987; Rousseau et al., 2005).

10 Several secondary outcomes were assessed, including the Eating Attitude test (EAT-  
11 40), a 40-item self-report questionnaire measuring dieting behavior, oral control, food  
12 preoccupation, and body intake (Garner and Garfinkel, 1979); the Bulimia test (BULIT), a 36-  
13 item self-report questionnaire assessing signs of bulimia (Thelen et al., 1996); the Eating  
14 Disorder Inventory (EDI-2), a 91-item self-report questionnaire evaluating the presence of an  
15 eating disorders through 11 subscales: “drive for thinness”, “bulimia”, “body dissatisfaction”,  
16 “ineffectiveness”, “perfectionism”, “interpersonal distrust, interoceptive awareness”;  
17 “maturity fears”, “asceticism”, “impulse regulation” and “social insecurity” (Garner, D. M.,  
18 1991); and the Hamilton Anxiety and Depression Rating Scales (HARS, HDRS) to assess  
19 symptoms of anxiety and depression (Hamilton, 1959, 1967).

20 Physical indicators such as the Body Mass Index ( $BMI = \text{body mass, kg} / [\text{height, cm}]^2$ ),  
21 percentage of fat mass and lean mass measured via Dual Energy X-ray Absorptiometry  
22 (DEXA) using a Lunar Prodigy device (GE Medical Systems Lunar, Madison, USA) were also  
23 included.

1 Safety and tolerability were also assessed after each rTMS session and at each visit.  
2 Any new symptom was considered an adverse event and classified as serious if it resulted in  
3 hospital admission, persisted as sequelae, or were deemed critical by the attending clinician.  
4

## 5 **Statistics**

6 To evaluate the impact of the intervention, we utilized non-parametric Mann-Whitney tests  
7 to compare scores for the BSQ, EAT-40, BULIT, EDI-2, HARS, HDRS, SF-36, and BMI  
8 measurements between the patients' groups at both baseline and after the rTMS. The  
9 analysis was conducted in an intention-to-treat (ITT) manner, with all randomized patients  
10 included in the primary analysis and data imputed using the 'last observation carried  
11 forward' (LOCF) method for missing data pertaining to the primary outcome. For imputation,  
12 median values of both randomization groups at baseline were employed. Additionally, a post  
13 hoc analysis was conducted, considering differences at baseline, utilizing a linear model to  
14 explain immediate post-stimulation BSQ (primary endpoint) by the baseline BSQ and by the  
15 ITT randomization group, with LOCF, mirroring the approach in the main analysis. All  
16 statistical analyses were conducted with the R statistical software (the R Foundation for  
17 Statistical Computing, Vienna, Austria), with a significance set at 0.05.  
18  
19

## 1 **Results**

### 2 **Sample description**

3 A screening of twenty patients with AN resulted in the enrollment and randomization of 17  
4 participants, with a median age of 35 years (range:27-39), a disease duration of 12 years  
5 (range: 6-18), and a BMI of 16 kg/m<sup>2</sup> (range: 14-17) (Table 1). Three patients withdrew from  
6 the study before randomization: two of these patients withdrew their approval, and one was  
7 hospitalized for a medical issue before randomization, resulting in premature dropout.  
8 Among the randomized patients, seven were allocated to the real rTMS group and ten to the  
9 sham rTMS group. Baseline analysis showed significant differences between the groups, with  
10 higher scores for the EDI-2 and BULIT scales, as well as BMI in patients assigned to the sham  
11 rTMS group compared to those in the real rTMS group (Table 1).

12

### 13 **Effects of real or sham IPL rTMS on AN symptoms**

14 Comparing the scores between the real and sham rTMS groups post-rTMS, we found no  
15 significant differences in BSQ-34 (Figure 1), EAT-40, EDI-2, HARS and HDRS scores, or BMI  
16 values (Table 1). The BULIT score remained significantly higher in the sham group compared  
17 to the real rTMS group (Table 1).

18 Within-group analysis revealed no significant changes in the BSQ-34, ETA40, EDI2,  
19 HARS and HDRS scores, or BMI values, after either sham or real rTMS (Table 1). The changes  
20 in the BSQ-34 score from baseline to post-rTMS were also not significantly different between  
21 the two groups, with a mean effect of real versus sham rTMS of +5.6 points (linear model,  
22 95% CI: -21.3 to +32.6, p=0.66).

23

### 24 **Follow-up period**

1 During the follow-up period, assessments at 2 weeks and 3 months post-rTMS sessions were  
2 conducted for 16 patients. No significant changes were observed in BSQ-34 or other scores,  
3 nor in the proportion of lean and fat masses in both groups (not shown). The BULIT score  
4 continued to exhibit significant differences between groups, with persistently higher scores  
5 in patients assigned to the real rTMS group (Table 1).

6

### 7 **Adverse events**

8 Throughout the rTMS sessions, a total of 30 non-serious adverse events were reported, with  
9 20 occurring in the sham group and 10 in the real group. Cephalalgia and twitching of the  
10 eyelid were reported during sham rTMS, while no rTMS related side-effects were reported  
11 during real IPL rTMS sessions. During the randomized period, eight serious adverse events  
12 were documented, involving three patients assigned to the sham rTMS group and four in the  
13 real rTMS group. These events included five cases of exacerbated undernutrition and  
14 deteriorated general status, leading to hospitalizations in the psychiatry department for two  
15 patients, and enteral nutrition for one patient. Additionally, two patients committed a  
16 suicidal attempt through drug intoxication, requiring intensive care hospitalization and  
17 subsequent withdrawal from the study in one patient. Another patient developed a  
18 pulmonary infection, which resolved with appropriate antibiotic therapy.

19

## 1 Discussion

2 This pilot controlled study is the first to examine the effects of high-frequency rTMS  
3 targeting the right IPL on body image distortion in AN patients. Our results indicated that HF-  
4 rTMS of the rIPL failed to statistically significant improvements in body image distortion or  
5 other related AN symptoms. Severe adverse events were observed across patient groups,  
6 primarily due to AN severity, with a good tolerance of the rTMS protocol.

7 The lack of observable effects on body shape distortion, but also BMI, anxiety or  
8 depression, in our AN patients could be attributed to several factors. First, the patients  
9 randomized to the real rTMS group had a very severe disease profiles, with significant body  
10 image distortion, extremely low BMI (mean <14), long disease duration and resistance to  
11 previous interventions. In prior therapeutics trials assessing the effects of rTMS in AN  
12 patients, the average BMI was around 16 (Dalton et al., 2018; Muratore et al., 2021;  
13 Woodside et al., 2021), whereas it was 13.6 in our patients randomized to real rTMS. This  
14 severe baseline condition might have limited the potential benefits of our approach. Another  
15 factor could be the chosen protocol. Although previous studies that tested HF rTMS of the  
16 DMPFC used similar protocols, with a 10 Hz frequency and a total number of pulses of  
17 20,000 delivered over a 2 or 3-week period (McClelland, Bozhilova, Campbell, et al., 2013;  
18 McClelland, Bozhilova, Nestler, et al., 2013; Dalton et al., 2018; Woodside et al., 2021), this  
19 might not have been optimally designed to modulate the targeted brain area's excitability. A  
20 longer treatment period might be necessary for substantial changes (Dalton et al., 2018),  
21 rather than focusing solely on the total number of pulses administered. Unlike previous  
22 rTMS studies targeting the DLPFC, we observed no significant changes in anxiety or mood. In  
23 fact, mood worsened in two patients who attempted suicide after rTMS, one in each  
24 patients group, with no clear relationship to the intervention. However, our protocol

1 targeting the rIPL did not aim to improve these psychiatric comorbidities. Overall, these  
2 data indicate that targeting the rIPL alone may not suffice for significant changes in body  
3 perception, despite its involvement in self-other discrimination and self-perception  
4 processes (Uddin et al., 2006; Karhson, Mock and Golob, 2015). Due to the complex fronto-  
5 parietal neural network disruptions involved in AN, prior research suggests that targeting the  
6 prefrontal cortical areas might be more effective in modulating these functional networks.  
7 This approach has shown a more favorable impact on clinical and behavioral components  
8 (BMI, food avoidance) (Dalton et al., 2018), and IPL activity modulation (Ćurčić-Blake, Kos  
9 and Aleman, 2022). When applied over the DMPFC, rTMS induced significant improvements  
10 in mood, anxiety, and some core domains of AN pathology, including shape and weight  
11 concerns. This improvement was correlated with lower baseline functional connectivity  
12 between the DMPFC, right inferior pole and left angular gyrus, parts of the 'salience  
13 network' (Woodside et al., 2021). This was interpreted as a lesser capacity for cognitive  
14 control over perseverance or negative self-referential thinking in responsive AN patients.  
15 When applied over the DLPFC, rTMS also induced significant improvements in anxiety and  
16 mood, but no changes in body image distortion or BMI. Overall, these data could suggest  
17 that improvements in mood, anxiety, and eating behaviors may precede improvements in  
18 body image distortion.

19 This study also acknowledges several limitations. First, the small cohort size limits the  
20 generalizability of the findings. Second, the two groups exhibited significant differences in  
21 AN severity at baseline, which could have affected the statistical comparison of the effects of  
22 rTMS between groups. Additionally, the absence of an assessment of the neurophysiological  
23 effects of the HF-rTMS protocol hinders a comprehensive understanding of its impact on  
24 local and network brain excitability and functional connectivity.

1

2 **Conclusions**

3 This small cohort study does not advocate for the use of HF-rTMS of the right IPL to  
4 ameliorate body image distortion in patients with severe AN. Further studies are necessary  
5 to optimize protocols, considering less severe cases and identifying the most effective target  
6 areas for intervention in AN. Future research Incorporating neurophysiological markers will  
7 provide insights into the relationship between brain activity changes and symptom  
8 improvement, advancing more effective therapeutic approaches for AN patients.

9

10

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**Table 1. Baseline characteristics and effects of real and sham rTMS of the right IPL in 17 patients with Anorexia nervosa**

	Baseline		P-value	Post-rTMS		P-value
	Real	Sham		Real	Sham	
Age (yrs)	36 (29_39)	29 (27_36)				
Disease duration (yrs)	18 (7_21)	11 (7_12)				
BSQ-34	93 (67_142)	154 (130_164)	0.055	85 (54_90)	120 (95_151)	0.073
EAT-40	42 (34_55)	72 (61_78)	0.082	44 (33_50)	65 (48_70)	0.28
EDI-2	81 (47_88)	130 (110_141)	0.016	69 (40_85)	108 (76_115)	0.057
BULIT	68 (55_76)	100 (92_114)	0.003	67 (59_73)	90 (83_114)	0.001
HARS	16 (8_23)	16 (14_30)	0.46	10 (6_16)	12 (6_16)	0.96
HDRS	16 (14_18)	16 (13_20)	0.96	12 (11_13)	12 (10_14)	1.0
BMI	13.6 (13.2_15.5)	16.5 (15.6_17.1)	0.025	14 (13_16)	16 (15_18)	0.073

Values are median (Q1\_Q3); P-value: between-group comparison at baseline and post-rTMS sessions.

BSQ-34=Body-shape questionnaire-34 (BSQ-34) ; EAT-40=Eating Attitude test (EAT-40); BULIT=Bulimia test; EDI-2=Eating Disorder Inventory;

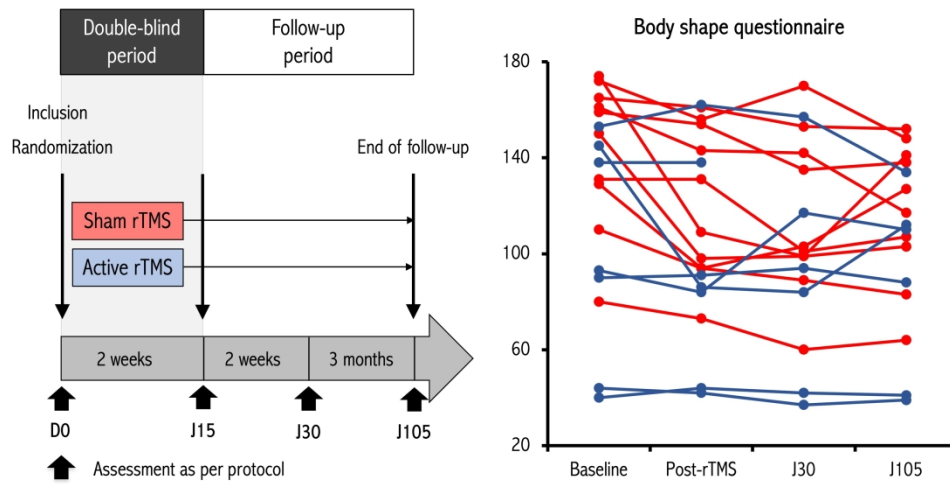
HARS and HDRS=Hamilton Anxiety and Depression Rating Scales; BMI=Body Mass Index.

## Figure legends

### **Figure 1. Study design and effects of real and sham high-frequency rTMS of the right IPL on the body shape questionnaire in patients with Anorexia Nervosa.**

Study design (left panel) and body shape questionnaire scores obtained in AN patients randomized in the real (blue) or sham (red) groups. Each line represents one individual patient. rTMS = repetitive transcranial magnetic stimulation.

For Review Only



275x190mm (369 x 369 DPI)