Original article

Repetitive transcranial magnetic stimulation in anorexia nervosa: A pilot study

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ABSTRACT

The search for new treatments to improve outcome in people with anorexia nervosa continues. This pilot study investigated whether one session of high frequency repetitive transcranial magnetic stimulation (rTMS) delivered to the left dorsolateral prefrontal cortex reduces eating disorder related symptoms following exposure to visual and real food stimuli. Safety and tolerability were also assessed. Ten right-handed people with anorexia nervosa underwent one session of rTMS. Subjective experiences related to the eating disorder (e.g. urge to restrict, feeling full etc.) were assessed before and after rTMS. Non-parametric repeated measures tests were used. rTMS was safe and well-tolerated, and resulted in reduced levels of feeling full, feeling fat and feeling anxious. Thus, rTMS may reduce core symptoms of anorexia nervosa. Future research should establish the therapeutic potential of rTMS in anorexia nervosa.

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1. Introduction

Anorexia nervosa (AN) is a serious mental disorder. Core symptoms of AN are severe food restriction, intense fear of gaining weight or becoming fat, and disturbance in the way one's body weight or shape are experienced. AN is associated with high levels of morbidity and mortality, and impaired quality of life [13]. Management of AN is a major challenge and better understanding of its pathophysiology is needed to aid the development of improved treatments [13]. In this respect, neuromodulatory techniques that directly alter brain functioning are a promising avenue to explore [9]. Repetitive transcranial magnetic stimulation (rTMS) is one such technique that is non-invasive. It is increasingly used as a research tool and has clinical applications [18], for example, it is an FDA-approved treatment for treatment-resistant depression [17].

The use of rTMS in eating disorders is in its infancy. A pilot study in people with bulimia nervosa did not detect any clinical improvement following a 3-week course of high frequency (HF) rTMS delivered to the left dorsolateral prefrontal cortex (DLPFC) [27]. In contrast, a recent study showed reduced food craving [24] and stress reactivity (i.e. salivary cortisol concentration) [4] in people with a bulimic eating disorder following a single session of HF rTMS to the left DLPFC. This was not mediated by changes in mood, tension or hunger. This research underlines the potential of rTMS to improve our understanding of the aetiology of eating disorders and to aid in the development of new treatments.

 Provisional support for the use of rTMS in AN comes from a case report where rTMS was successfully used to treat comorbid depression in a patient with AN [10]. Importantly, an increase in body mass index (BMI) also occurred [10]. Brain imaging data also provide a rationale for the use of brain modulation techniques such as rTMS to reduce AN symptoms. Imaging research has identified a range of brain structures that are likely to be involved in the pathophysiology of eating disorders; these include the (dorsol)ateral prefrontal cortex (DLPFC) (for review see [25,26]). The lateral prefrontal cortex has been proposed to be part of dysfunctional fronto-striatal circuitry that underlies the impaired capacity for self-regulation seen in eating disorders. In AN this is, inter alia, illustrated by preoccupations with food and body [15]. In addition, problems in dorsal neural circuits (which include the DLPFC) may contribute to symptoms of AN as a result of an impaired balance between interoceptive and reward processing [11]. Finally, increased lateral prefrontal cortex activity during the processing of visual food stimuli in recovered AN patients, suggests that this may be associated with good outcome [20].

Based on the data described above and on the ability of HF rTMS to stimulate underlying cortical areas, we conducted a pilot study on the effect of one session of HF rTMS delivered to the left DLPFC in people with AN. We hypothesised that rTMS would:

1) improve self-regulation and reduce preoccupation with food and body, i.e. result in a decreased urge to restrict food intake or to exercise;

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2) improve interoception, i.e. result in feeling less full and less fat;
3) have no immediate effect on mood, tension or hunger;
4) be a safe and acceptable intervention;
5) reduce stress reactivity and thus lower salivary cortisol concentrations.

2. Subjects and methods

2.1. Participants

Ten people with a Diagnostic and Statistical Manual for Mental Disorders (DSM-IV-TR) diagnosis of AN (restricting and binge-purging type) were recruited from the Eating Disorders Outpatients department at the South London and Maudsley NHS Foundation Trust, London, and by email advertisement in King’s College London. Diagnosis was established with the eating disorders module of the Structured Clinical Interview for DSM-IV–axis I Disorders/Patient version [6].

Contraindications to rTMS were checked with the Adult Safety Screen Questionnaire [12]. Exclusion criteria were: being on a dose of psychotropic medication that had not been stable for at least 14 days prior to enrolment, pregnancy, nicotine use exceeding the equivalent of more than 15 cigarettes/day and substance dependence. In addition, we only recruited right-handed people because handedness (and hence lateralisation of some brain functions) may play a role in the outcome of rTMS research [22]. Local ethical committee approval was obtained and written informed consent was obtained from all participants.

2.2. Procedures and outcomes

For this pilot study, we did not opt for an open-label study. Participants were informed that they would be randomised to sham or real rTMS; however, all received real rTMS. This “blinding” procedure was unveiled at the end of the study protocol. We have used this approach previously [22].

The rTMS was delivered to the left DLPFC using a Magstim Rapid device and figure-eight coil (Magstim, UK), with the same real rTMS procedure and parameters applied as in our previous research [21,22,24]. Following mapping of the abductor pollicis brevis site in the left motor cortex, the participant’s motor threshold was established as the minimum stimulus required to induce contraction of the right thumb at least five out of 10 times. The site for the left DLPFC stimulation was 5 cm anterior to the point of maximal abductor pollicis brevis stimulation, in a parasagittal plane. Twenty trains of 5 seconds with 55-second inter-train intervals were administered with a frequency of 10 Hz and intensity of 110% of the individual’s motor threshold, providing 1000 pulses over 20 min.

Baseline measures consisted of the Eating Disorder Examination – Questionnaire (EDE–Q) version 6 [5] and Depression Anxiety Stress Scale (DASS) [21–items] [14].

2.2.1. Eating disorder related symptoms

Given the exploratory nature of this pilot study, we employed several outcome measures (described below) using 10-cm visual analogue scales (VAS). For some of these outcomes we collected data at four time points (TP1: at baseline (i.e. start of the study; TP1), pre-rTMS (TP2), post-rTMS (TP3) and at the end of the study (TP4) (urge to restrict; urge to exercise; feeling full; feeling fat; anxiety). These measures assess aspects of behavioural self-regulation and interoceptive awareness. For other outcomes, we collected data only pre- (TP2) and post-rTMS (TP3) (urge to eat; tension; hunger; mood). At TP2 and TP3, participants were exposed to a “Food Challenge Task (FCT)”; this included watching a short film clip of young people eating high calorie foods and the presentation of real food (biscuits, chocolate, nuts and crisps). Participants were asked to rate the appearance, the smell and taste of these foods, as well as their urge to eat them [24].

2.2.2. Hormonal stress response

To assess whether the rTMS intervention had an effect on the hypothalamus-pituitary-adrenal axis stress response, we collected salivary cortisol samples at the four time points described above (using Salivettes®). We did not adhere to fixed time points as this was not practically feasible. As time of the day constitutes a significant confounding factor in research on cortisol concentrations, for the analysis of this measure, we selected a subgroup of participants who were assessed in the afternoon (n = 6). After collection, samples were stored at −20°C where they are stable for several months [7].

2.2.3. Cardiac safety

To assess cardiac safety, we measured – using A&D Medical UA-767 Plus Digital Blood Pressure Monitor – participants’ blood pressure and pulse at baseline, and after every fifth rTMS train.

2.2.4. Tolerability

To evaluate the tolerability and acceptability of the intervention, we asked participants at the end of the protocol whether they had side-effects. During the rTMS procedure, level of “discomfort” was repeatedly assessed using a 10-cm VAS. Finally, participants were asked whether, if rTMS proved to be efficacious, they would consider participating in a 3-week study with 5 rTMS sessions per week.

2.2.5. Blinding success

After the completion of the post-rTMS assessments and before the “unblinding” they were asked to guess whether they had received real or sham rTMS.

2.3. Statistical analyses

To investigate changes, we used two-tailed non-parametric repeated measures tests: signed rank and Friedman tests. First, we investigated the effect of rTMS by comparing the measures at TP2 and TP3. Secondly, we investigated whether the exposure to food stimuli resulted in an increase in eating disorder related experiences and symptoms (TP1 vs TP2). The final assessment was conducted to see whether the effect of rTMS was sustained. However, as the time between TP3 and TP4 was relatively short (10–15 minutes), TP4 was not included in any analysis.

3. Results

3.1. Demographic and clinical variables

One patient discontinued the study prematurely after four trains of rTMS due to discomfort related to the intervention. Her data were not included in the analyses. The demographic and clinical characteristics of the sample were as follows (median [range]): age: 25 (18–44) years; BMI: 15.7 (13.8–17.8) kg/m²; duration of illness: 10 (3–30) years, EDE–Q total score: 4.1 (3.8–5.6) and DASS total score 63 (10–104). The EDE–Q scores indicate severe eating disorder psychopathology: they are higher than the cut-off (> 2.80) for clinical significance when the EDE–Q is used as a screening instrument [16] and they are in the same range as reported by others [19]. For the DASS, normative data indicate a median score of 13 [8]; thus, the scores in our sample can be considered in the moderate-severe range. Seven participants had AN-restrictive type, and two the AN-binge-purging type. Seven participants had amenorrhea. Three were on psychotropic medication (fluoxetine n = 1; paroxetine n = 1; venlafaxine n = 1).
Table 1
Baseline (TP1), pre-rTMS (TP2), post-rTMS (TP3) and final assessment (TP4) scores for the VAS measures and cortisol concentrations.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Baseline assessment TP1</th>
<th>FCT pre-rTMS TP2</th>
<th>P-value</th>
<th>FCT post-rTMS TP3</th>
<th>P-value</th>
<th>Final assessment TP4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urge to restrict</td>
<td>3.3 (1.5–8.5)</td>
<td>9.1 (2–10.0)</td>
<td>&lt; 0.01</td>
<td>7.3 (4.1–10)</td>
<td>0.19</td>
<td>6.2 (1.5–10)</td>
</tr>
<tr>
<td>Urge to exercise</td>
<td>3 (1.3–6.5)</td>
<td>4.1 (1.2–8.6)</td>
<td>0.16</td>
<td>2.8 (1.0–8.0)</td>
<td>0.09</td>
<td>3.0 (0.2–8.2)</td>
</tr>
<tr>
<td>Feeling fat</td>
<td>7 (1.8–10)</td>
<td>9.0 (1.2–10.0)</td>
<td>0.15</td>
<td>6.3 (1.0–10.0)</td>
<td>&lt; 0.01</td>
<td>6.1 (0.4–10)</td>
</tr>
<tr>
<td>Feeling full</td>
<td>5.3 (1.8–8)</td>
<td>7.1 (1.0–9.7)</td>
<td>0.02</td>
<td>5.9 (1.7–9.3)</td>
<td>0.05</td>
<td>3.8 (0.5–9.5)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>3.5 (0.2–8)</td>
<td>5.7 (1.5–9.4)</td>
<td>0.25</td>
<td>3.4 (0.3–8.9)</td>
<td>&lt; 0.01</td>
<td>1.5 (0.4–6.5)</td>
</tr>
<tr>
<td>Stress</td>
<td>6.4 (1–8.2)</td>
<td>5.8 (0.7–9.4)</td>
<td>1.00</td>
<td>2.9 (1.1–9.5)</td>
<td>0.14</td>
<td>2.4 (0.3–7.5)</td>
</tr>
<tr>
<td>Mood</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Tension</td>
<td>NA</td>
<td>5.7 (0.5–9.1)</td>
<td>NA</td>
<td>4.3 (1.1–9.2)</td>
<td>0.17</td>
<td>NA</td>
</tr>
<tr>
<td>Hunger</td>
<td>NA</td>
<td>3.7 (0.3–6.7)</td>
<td>NA</td>
<td>3.6 (2.2–7.0)</td>
<td>0.60</td>
<td>NA</td>
</tr>
<tr>
<td>Urge to eat</td>
<td>NA</td>
<td>2.5 (0.2–8.7)</td>
<td>NA</td>
<td>2.7 (0.0–9.4)</td>
<td>0.30</td>
<td>NA</td>
</tr>
<tr>
<td>Cortisol concentration (n=6)</td>
<td>5.52 (2.04–13.18)</td>
<td>5.75 (1.45–11.93)</td>
<td>0.68</td>
<td>4.16 (1.41–12.18)</td>
<td>1.00</td>
<td>5.41 (1.50–12.30)</td>
</tr>
<tr>
<td>Cortisol assessment time (minutes)</td>
<td>Reference=0</td>
<td>24 (20–33)</td>
<td>NA</td>
<td>82.5 (75–100)</td>
<td>NA</td>
<td>97.5 (84–105)</td>
</tr>
</tbody>
</table>

FCT: Food Challenge Task. Results are reported as median (range). NA: not applicable. TP: time point.

3.2. Eating disorders related symptoms

The data from the VAS outcome measures are presented in Table 1. Compared to pre-rTMS (TP2), post-rTMS (TP3) sensations of “feeling fat” (P = 0.007) and “feeling full” (P = 0.05) were decreased. There was also a significant decrease in “anxiety” (P = 0.009). There was a statistical trend for a decrease in the “urge to exercise” (P = 0.09); however, no difference was observed on the measures “urge to restrict” or “urge to eat”.

3.3. Additional measures

There were no changes in mood, tension or hunger following rTMS.

3.4. Food Challenge Task (FCT)

We also investigated the “salience” of the food exposure (comparison between TP1 and TP2). The FCT resulted in an increase in the “urge to restrict” (P = 0.007) and the sensation of “feeling full” (P = 0.02). There was no significant change on the measures “urge to exercise”, “feeling fat”, “anxiety” or “stress”.

3.5. Tolerability and safety

There were no differences in pulse (P = 0.10) or diastolic (P = 0.66) and systolic (P = 0.33) blood pressure over time. Eight participants reported no side-effects post-rTMS; one described having a “slight buzzing in the head”. However, all participants reported a significant degree of discomfort during the trains. This appeared to gradually reduce during the course of the rTMS. The median (range) discomfort score after the 1st and 20th train was 6.5 (0.9–8.2) and 5.0 (2.5–7.3), respectively (detailed information is available upon request from the authors). The participant who discontinued the research prematurely, reported high levels of discomfort and described the effect of rTMS as “a very intense and painful tapping”.

3.6. Hormonal stress response

Cortisol concentrations did not alter from before (TP2) to after (TP2) the delivery of rTMS (Table 1).

3.7. Success of blinding procedures

All participants correctly guessed their allocation to real rTMS; the median (range) score of “how sure they were” was 7.3 (1.8–8).

4. Discussion

The results from this pilot study indicate that HF rTMS delivered to the left DLPFC may reduce feelings of fullness and fatness, and anxiety in people with AN. The effect on more complex behaviours such as urge to restrict or urge to exercise is less clear. Clinically undesirable effects such as reduced urge to eat were not observed. In line with previous research, one rTMS session did not alter subjective mood, tension or hunger levels [1,24]. Finally, we did not replicate findings of reduced cortisol levels following HF rTMS to the left DLPFC [1,4].

Overall, rTMS was well tolerated. All but the one participant who discontinued the study prematurely, would agree to rTMS treatment. In accordance with the findings in people with bulimic disorders [23], rTMS proved to be cardiac safe (as assessed with blood pressure and pulse).

The FCT appeared to be salient. Overall, the FCT accentuated the aspects of AN psychopathology under study and the effect of rTMS was investigated in this context. It is possible that rTMS may not lead to similar results in baseline conditions without exposure to salient stimuli.

Together with the lack of a sham group, the study’s small sample size constitutes its main limitation. In light of the exploratory character of this study, we did not perform a sample size calculation or correct for multiple comparisons. We cannot rule out that non-significant findings are due to a lack of power. In addition, despite being told that they would be randomised to either real or sham rTMS, all participants guessed their allocation to real rTMS. Such a high proportion is in line with our and others’ findings [3,22,24]. Although this may affect the outcome, the observation that some measures (including mood) did not change indicates that this does not explain our findings. In addition, we used the “5 cm anterior” method; the use of localisation techniques based on individual imaging data may prove more accurate to determine the DLPFC. Finally, it is possible that delivery of a higher number of rTMS pulses might have resulted in a significant improvement on measures (e.g. the urge to restrict) where these were not found with the current 1000 pulses.

5. Conclusion

rTMS, as applied in this study appears to be a safe and well-accepted brain modulation technique that may have an effect on core symptoms of anorexia nervosa such as feelings of fullness and fatness, and anxiety. Larger studies are required to establish whether this is accompanied by reduced food restriction and, ultimately, will facilitate weight gain. In this context, rTMS could
be – as, for example, in depression [2] – investigated as an augmentation strategy.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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