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ORIGINAL RESEARCH

Insula H-coil deep transcranial magnetic stimulation in severe and enduring anorexia nervosa (SE-AN): a pilot study

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Introduction: Anorexia nervosa (AN) is a complex disorder of unknown etiology, characterized by obsessions and compulsions around body shape, weight, and calorie intake. In the course of AN, 10%–30% will recover, while the rest will develop a treatment-resistant course with a high mortality rate due to AN-related complications. The insula is a region in the brain of considerable interest to its role in gustatory modulation, feeding behavior, and processing of interoceptive stimuli.

Objective: Recent advances in the neurophysiology of AN suggest insula dysfunction as a potential biomarker for people with severe and enduring AN (SE-AN). Deep transcranial magnetic stimulation (dTMS) is of particular interest in SE-AN because of its ability to target deep areas of the brain.

Design: We conducted a pilot study to investigate the feasibility and safety of insula dTMS in subjects with SE-AN.

Results: We found that dTMS is a safe and well-tolerated treatment. We also found a reduction in AN-related obsessions and compulsions, as well as depression and anxiety scores from baseline to the end of the trial. Due to small sample size, the results of this study should be interpreted with great caution.

Discussion: The results suggest that dTMS is safe and well tolerated and may be of some clinical interest in patients with SE-AN. However, to determine the true efficacy of dTMS for SE-AN, there is a need to conduct a randomized controlled trial comparing real versus sham dTMS in a larger number of AN subjects.

Keywords: severe and enduring anorexia nervosa, deep transcranial magnetic stimulation, repetitive transcranial magnetic stimulation, insula

Introduction

Anorexia nervosa (AN) is a complex disorder of unknown etiology that is characterized by severely low weight and significant obsessions and compulsions in relation to body shape, weight, and calorie intake. It has the highest mortality rate of all psychiatric disorders, with exceptionally high relapse rates, where only 10–30% recover with the best available psychotherapies, as pharmacological interventions are largely ineffective and have low acceptability.[1,2]

Amongst multiple etiology models, recent advances in understanding the neurobiology of AN point toward neurobiological functioning as a potential explanatory model in AN psychopathology.[3–5] Brain areas, such as the dorsomedial and the dorsolateral prefrontal cortex have been shown to play an important role in the

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regulation of mood and affect in people with AN.[4,6] Current research also points to deeper prefrontal and subcortical areas as being implicated in eating disorders.[7] Neuroimaging studies have identified deeper brain structures and limbic regions as critical in the modulation of eating behavior and self-awareness.[7,8] Current studies demonstrate that deep prefrontal (subcallosal and cingulate gyrus) and subcortical areas (thalamus and insula) played a role in the pathophysiology of AN.[3–8] Specifically, functional MRI studies have shown that when emaciated and malnourished AN individuals are shown pictures of food they display abnormal activity in the insula.[7–9] The insula has also been identified as a potentially important region in AN pathophysiology due to its role in gustatory modulation and feeding behavior, as well as in the processing of interoceptive stimuli and self-awareness.[8,9] According to Nunn et al (2008), the insula plays a predominant role in orchestrating the balance between areas of the brain responsible for adaptation to the environment and those responsible for internal homeostasis.[8] The authors proposed that the clinical phenomenon of AN may be explained by insula dysfunction, specifically the restricted capacity to operate effectively in the integration of visual and body perceptions with feelings/emotions and the inhibition of higher cognitive processes. The experience of disgust has also been described as a dominant trait in the aberrant eating behaviors of AN.[9] A number of investigations show that, among other structures, the insula and the amygdala are activated when subjects are exposed to disgusting odors or tastes.[10] It has been also demonstrated that insular cortex is active in a wide variety of tasks involving subjective awareness of both positive and negative feelings and is believed to play a domain-general role in identifying the most salient among several internal and extrapersonal stimuli in guiding eating behaviors.[11]

Achieving recovery in AN can be difficult. AN continues to be among the most pernicious of psychiatric disorders, demonstrating a mortality rate 6 times greater than the general population and a crude mortality rate of 5–6%.[12] At a 10-year follow-up, more than 30% of the patients were found to have AN that was refractory to treatment (SE-AN), while 10% of the patients died from disease.[13,14] Even though there is evidence to support the effectiveness of family based treatment for young adolescents with a short duration of illness, no evidence-based treatments for adults with SE-AN are currently available, and therefore new approaches are constantly sought.[15] Recent research points out that treatment for this population should be aimed toward a better understanding of the underlying neurobiological mechanisms, along with the development of interventions able to mitigate and address these abnormalities.[15]

Repetitive transcranial magnetic brain stimulation (rTMS) is of particular interest as a treatment. It is a non-invasive intervention method that modulates brain activity through magnetic fields applied to different parts of the brain. rTMS has demonstrated its efficacy in a range of psychiatric conditions, such as unipolar depression[16,17] including treatment-resistant cases,[18–20] anxiety conditions,[21,22] psychosis,[23] and addictions.[24] The overall symptom reduction following rTMS is reported to be approximately 40%, with studies demonstrating its effectiveness in treatment-resistant depression.[25] New studies on rTMS in people with AN are promising and report some clinical response, specifically a decrease in preoccupations around weight, shape, and calorie intake.[26,27] However, these studies have employed conventional rTMS where its functional capacity is limited to the stimulation of only the superficial cortical regions of the brain,[28] such as the dorsolateral prefrontal cortex (DLPFC) and some subcortical areas. This conventional rTMS does not reach deeper areas of the brain, such as the insula, as the intensity of the electric field decreases rapidly as a function of tissue depth.[28–31]

In this study, we used a Hesed coil (H-coil), a novel transcranial magnetic stimulation (TMS) device, to target the insula in patients with SE-AN, referred to as deep transcranial magnetic stimulation (dTMS). Compared to a regular rTMS coil, the H-coil is capable of inducing a magnetic field with a deeper and wider distribution and can reach the insula bitemporally to a depth of 5–6 cm.[30,31] However, even though it is difficult to conclude that we are actually stimulating the insula cortex with the H-coil and not the surrounding tissue and/or structures, it is generally accepted that TMS-induced excitation of one region will likely influence other areas.[32]

Objectives

Here we report the results of a pilot study investigating the feasibility, safety, tolerability, and clinical effects of the H-coil in targeting the insula in patients with SE-AN. We hypothesized that 42 sessions of dTMS to the insula would be both safe and well tolerated, as measured by the absence of adverse events such as seizures and drop in weight (eg, BMI).

Design

Patient and public involvement

Patients and/or public were not involved in the development of the research question and/or outcome measures.

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Participants

Eight females with a diagnosis of AN (restricting and binge-purging type), confirmed by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), were recruited from the community from November 2012 to September 2016. The diagnosis was established with the eating disorder module for the Structured Clinical Interview for DSM-IV-axis I Disorders (SCID), performed by a trained clinician. Patients with a lifetime diagnosis of schizophrenia or bipolar disorders, unstable medical conditions, or active substance use disorder in past 3 months were all excluded. Contraindications to TMS were checked with the adult safety screen questionnaire. Patients with a personal/family history of epilepsy, neurodevelopmental disorders, and ongoing pregnancy were excluded.

Ethics

This study was approved by the research ethics board at Centre for Addiction and Mental Health, and informed consent was obtained from each participant. Participant consent was written informed consent, and this study was conducted in accordance with the Declaration of Helsinki.

Intervention

The treatment involved a total of 42 sessions applied daily for 20 mins, 5 days per week over the first 6 weeks, followed by twice per week for 6 more weeks. Multiple assessments were performed bi-weekly, followed by 1- and 6-month follow-ups to ensure frequent and regular check-in points were in place, given the high risk of this population and the novelty of the procedure.

Each treatment session was composed of two steps: cue provocation and dTMS. Participants in this study received no concurrent treatments and did not to initiate any new treatments during both the acute and maintenance phases.

Cue provocation

We used a cue provocation technique before administering dTMS treatment. The main purpose was to activate relevant brain circuitries, a technique previously used in different studies and referred to as priming.[33,34] The stimuli material was developed by the first author through adopting the technique from Brooks et al[35] and consisted of 32 professional color images of high calorie, sweet and savory food presented in one block on a computer screen against a neutral background. Each image was shown for 5 s followed by a blank screen for 1 s.

dTMS procedure

The treatment trial included two stages: (1) an acute and (2) a maintenance course, for a total of 42 dTMS sessions per subject applied using a Brainsway H-Coil device. Each dTMS session included stimulation with 18 Hz, 2 s on, 20 s off, number of pulses 36, number of trains 80, over 20 mins; the protocol was developed in collaboration with the study's co-investigators, who are experts in brain stimulation interventions. Stimulation intensity was determined relative to the patient's resting motor threshold according to previously published protocols.[36] The acute course included daily sessions, 5 days per week for 6 weeks, for a total of 30 sessions. The maintenance course included 2 sessions per week for 6 weeks, for a total of 12 sessions.

Primary and secondary outcome measures

The primary outcomes were safety and feasibility. Safety was assessed by the (1) absence of any adverse events, especially seizures; and (2) the subject's medical stability, as measured by the patient's body mass index (eg, no decrease in BMI), and cognition (eg, no decrease in scores as measured by Montreal Cognitive Assessment Scale (MOCA)). Feasibility was assessed by the subject's adherence to the research protocol and attrition rate from the trial.

The secondary outcomes were the clinical responses to the treatment evaluated by the symptomatic improvement in AN-specific psychopathology, specifically (1) AN-related compulsions and obsessions as measured by Yale-Brown-Cornell Eating Disorder Scale (YBC-EDS) mean score; followed by the improvement in (2) symptoms of depression and anxiety as measured by Hamilton Depression Rating Scale (HDRS) and Montgomery–Asberg Depression Rating Scale (MADRS), administered by a trained clinician; and (3) Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI), collected through each patient's self-reports.

Statistical analyses

We used descriptive statistics calculated at each time point, specifically distributions of continuous variables described using means (M) and standard deviations (SD); categorical variables were described by the use of percentages. We used non-parametric Mann–Whitney U *t*-test to assess whether within-group differences in key parameters were statistically significant (see Table 1). Given the very small

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sample size and to understand the clinical significance of the observed clinical responses, we calculated Cohen's *d* – a measure of the effect size as the difference in the two groups' means divided by the average of their SDs (Becker, 2000).

Results

Demographic and clinical variables

Eight subjects diagnosed with SE-AN were enrolled and received dTMS treatment with the same protocol. All subjects were women with a mean age of 33±11.56 years, mean years of education of 16.9±2.2 years, and a mean BMI of 16.6±0.9. All were unemployed at the time of assessment; the majority identified as Caucasian and one identified as a person of color. Six patients met the criteria for Anorexia restrictive type and two for binge-purging type. Even though no criteria for judging refractoriness to treatment or defined gradations of medical seriousness or psychological morbidity in anorexia nervosa exist,[28] we based our definition of treatment resistance on both duration and the number of failed treatment trials. All subjects met the criteria for treatment resistance, which was defined in this study as the persistence of anorexia symptoms for over 5 years with failure to respond to at least 2 trials of intensive treatment interventions.

All 8 participants completed daily treatments of dTMS for the first 6 weeks as a part of an acute course. Four participants completed the remaining 6 weeks of twice weekly, followed by 2 follow-up assessments a month, and 6 months after the completion of this trial.

Tolerability and safety

All participants tolerated treatments well. Apart from the occasional mild headache/discomfort associated with dTMS (which we did not calculate due to low occurrence rates), there were no significant adverse events reported. For the duration of this trial, the BMI remained stable, as evident from no statistically significant change in BMI score (see Table 1 for details), and there was no change in cognition, as measured by MOCA. The study demonstrated that dTMS was safe and well tolerated.

Eating disorder-related symptoms

The results in this pilot study demonstrated changes in scores in AN-related obsessions and compulsions, depression, and anxiety from baseline to 6-week (eg, completion of the acute course), 12-week (completion of the full trial, including maintenance course), and a 6-month follow-up (see Table 1). Due to the limited number of subjects included in this trial, results were not statistically significant (see Table 1 for details).

Our findings indicate that the severity of AN-related obsessions and compulsions around food, shape, and weight as measured by YBC-EDS decreased by 0.6 following the first 6 weeks of treatment with dTMS as compared to pre-treatment (M=23.4; SD=3.4; Cohen's *d*=0.21). This decrease in severity continued and was sustained after the completion of a full trial of 12 weeks (M=18.8; SD=5.9, Cohen's *d*=0.96) and was further sustained over the period of 6 months post-treatment (M=19.75; SD=3.76; Cohen's *d*=1.02) (see Figure 1 for details).

Next, we found a reduction in depressive scores as measured by the HDRS (HDRS-17) (see Figure 2) following the completion of the first 6 weeks (acute phase) of the dTMS course (M=6.8; SD=5.4) compared to the baseline (M=12.2; SD=5.05) (Cohen's d=1.99). A reduction in depressive and anxiety symptoms was also reflected in a reduction in depression and anxiety scores as measured by MADRS after 6 weeks of dTMS treatment compared to the baseline (Cohen's *d*=0.85) (see Figure 3). These improvements sustained at 12 weeks (completion of the full trial) as measured by HDRS (M=5.5; SD=4.7; Cohen's *d*=1.31) and MADRS (M=11; SD=7.9; Cohen's *d*=1.02) compared to baseline. Interestingly enough, depressive scores increased over the next 6 months as measured by HDRS (M=10.25; SD=5.11; Cohen's *d*=0.37) and MDRS (M=15; SD=5; Cohen's *d*=0.56) compared to baseline; however, they did not return to their pre-treatment levels.

These results mirrored those analyzed from self-reports, indicating a decrease in depression scores as measured by BDI (see Figure 4). Specifically, there was a decrease in depression scores in the post-acute course of the first 6 weeks (M=12.8; SD=12.74; Cohen's *d*=1.036), and in the post-maintenance course of 12 weeks (M=10; SD=11.29; Cohen's *d*=1.37), with a slight increase toward the 6-month mark (M=13.25; SD=13.27; Cohen's *d*=0.97), as compared to baseline pre-treatment (M=24.66; SD=9.97). In addition to this, these findings demonstrate a decrease in anxiety as measured by self-reports administered by the BAI scale (see Figure 5) following an acute course of 6 weeks (M=11.83; SD=10.31; Cohen's d=0.4) and post-trial after 12 weeks (M=7; SD=2.73; Cohen's *d*=1.68). These gains were sustained over the next 6

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Table 1 Baseline, 6-week, 12-week, and 6-month scores for the ED-related measures

Clinical scale	Baseline mean (SD)	6 weeks (post-acute)	*p*-Value	Cohen's d (baseline/6 weeks)	12 weeks (post-trial)	*p*-Value	Cohen's d (baseline/ 12 weeks)	6 months (f/u)	*p*-Value	Cohen's d (baseline/f-u)
YBC-EDS	23.4 (3.4)	22.8 (2.3)	0.5399	0.21	18.8 (5.9)	0.1427	0.96	19.76 (3.76)	0.1343	1.02
HDRS	12.22 (5.05)	6.83 (5.36)	0.1199	1.99	5.5 (4.7)	0.1199	1.31	10.25 (5.1)	0.1199	0.37
MADRS	17.88 (5.25)	11.6 (8.93)	0.1199	0.85	11 (7.9)	0.1199	1.31	15 (5)	0.5315	0.56
BDI	24.66 (9.97)	12.8 (12.7)	0.036	1.37	10 (11.3)	0.036	1.37	13.25 (13.3)	0.1622	0.97
BAI	15.44 (7)	11.83 (10.3)	0.2358	0.4	7 (2.73)	0.0699	1.68	6.25 (3.76)	0.042	1.63
BMI	16.7	17.0625	17.0625	16.88333333	16.325	16.65	16.8	16.975	17.725	16.7

Abbreviations: YBC-EDS, Yale-Brown-Cornell Eating Disorder Scale; HDRS, Hamilton Depression Rating Scale; MADRS, Montgomery–Asberg Depression Rating Scale; BDI, Beck Depression Inventory; BAI, Beck Anxiety Inventory.

months, demonstrating a decrease in scores (M=6.25; SD=3.76; Cohen's *d*=1.63) as compared to pre-treatment (M=15.44; SD=7).

We are unable to conclude that differences in AN-related symptoms of obsessions, compulsions, depression, and anxiety are due to dTMS due to the limited statistical power. However, a potentially moderate-to-large effect size (Cohen's *d*=0.5–1.65) suggests that the difference between these indicators may be large enough to be considered as clinically significant and grants further investigation.

Strengths and limitations

This study failed to demonstrate statistically significant results for clear clinical benefits due to limited statistical power. However, the study demonstrated some encouraging results, such as a clinical improvement in AN-related psychopathology, specifically in the decrease of the severity of obsessions and compulsions as measured by YBC-EDS change in total scores, and concerns around shape, weight, and calorie intake as measured by EDE. These findings are consistent with others reported in the use of TMS in AN,[30] suggesting that the use of neuromodulation treatment modalities in those with SE-AN may be a promising direction to pursue, as it can help patients with a severe and enduring AN to make some changes and has the potential to improve their overall quality of life. The effect on more complex behaviors, such as self-perceptions, urge to restrict, and urge to engage in compensatory behaviors is less clear. Overall, dTMS was safe and well tolerated, providing preliminary evidence toward its potential use in this severe treatment-resistant population.

Limitations of the research study

We planned on enrolling 12 subjects. However, recruitment proved to be difficult due to a low number of referrals, constrained resources to advertise widely, and a high attrition rate due to an extensive time commitment, considering the treatment protocol was 12 weeks, with multiple assessments on a bi-weekly basis, which included clinical assessments, physical, and laboratory testing. Even though all participants were able to complete daily treatments for the first 6 weeks, only 4 participants continued with the remaining 6 weeks of the maintenance course and follow-up sessions. Given that all subjects were able to complete the acute phase, which included treatments 5 days per week for 6 weeks, we believe that tolerability was less of an issue in this trial. Participants consistently reported the time commitment, along with

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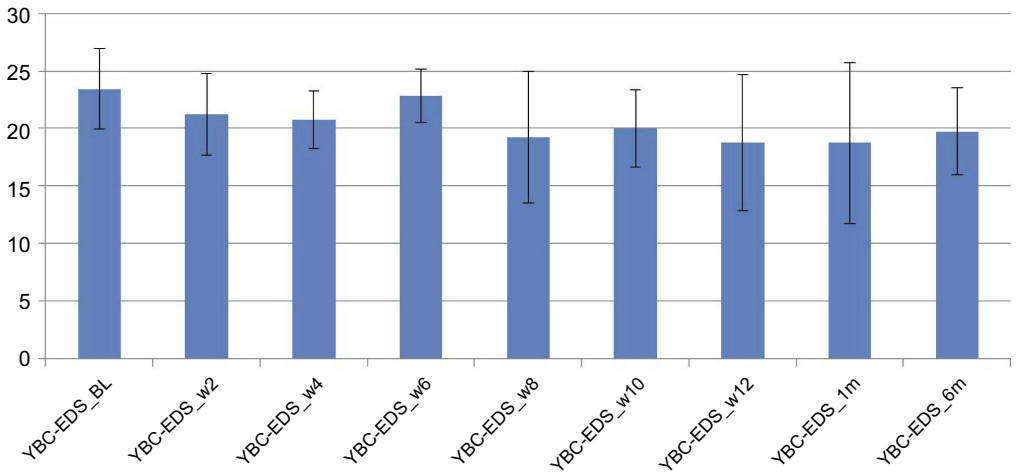

Figure 1 Yale-Brown-Cornell Eating Disorder Scale (YBC-EDS).

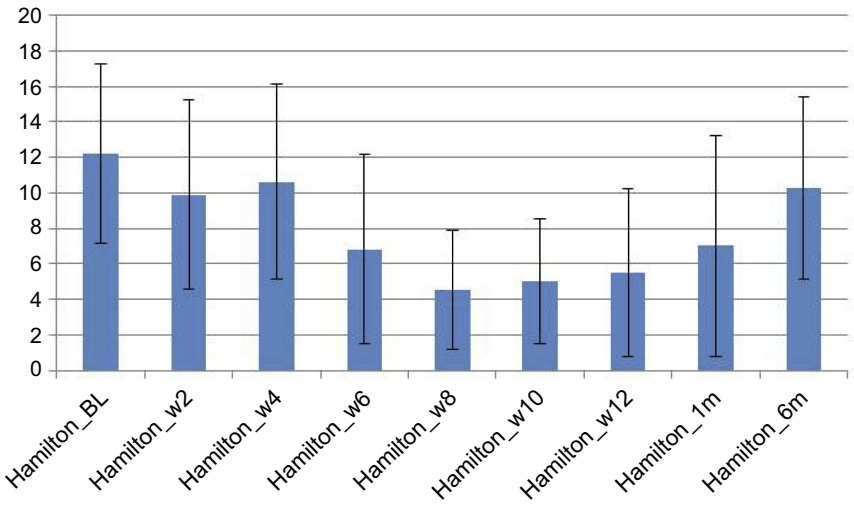

Figure 2 Hamilton Rating Scale for Depression Scores.

extensive assessments, including psychological scales and blood work every 2 weeks, as major limitations in continuing this trial. These limitations should definitely be considered in further trials.

Next, while promising, our findings were not statistically significant and that was largely due to the small number of subjects (ie, eight) that were included in this trial. Future clinical trials in this population should aim to be multicenter given the recruitment challenges seen in the early stages and development of this trial and should be randomized controlled trial (RCT) comparing sham versus real dTMS. Also, given the high attrition rate, future protocols should be limited to 4–6 weeks and assessments performed pre- and post-treatment to avoid burdening patients.

The findings of this study contribute to a field of neurotherapeutics and treatment of severe and hard-to-treat AN. There are few recent studies on the therapeutics of brain stimulation modalities in AN,[26,27] with none exploring dTMS targeting the insula, as was done in this study. This study provided preliminary evidence for the therapeutic potential of dTMS targeting the insula in TrAN. In line with other literature on the effects of rTMS on affective symptoms,[19,21] the results also indicate a reduction in affective symptoms as measured by HDRS, MADRS, BDI, and BAI.

Strengths of the research study

The findings are of clinical interest given the severity the participants' illness and treatment history, even though the

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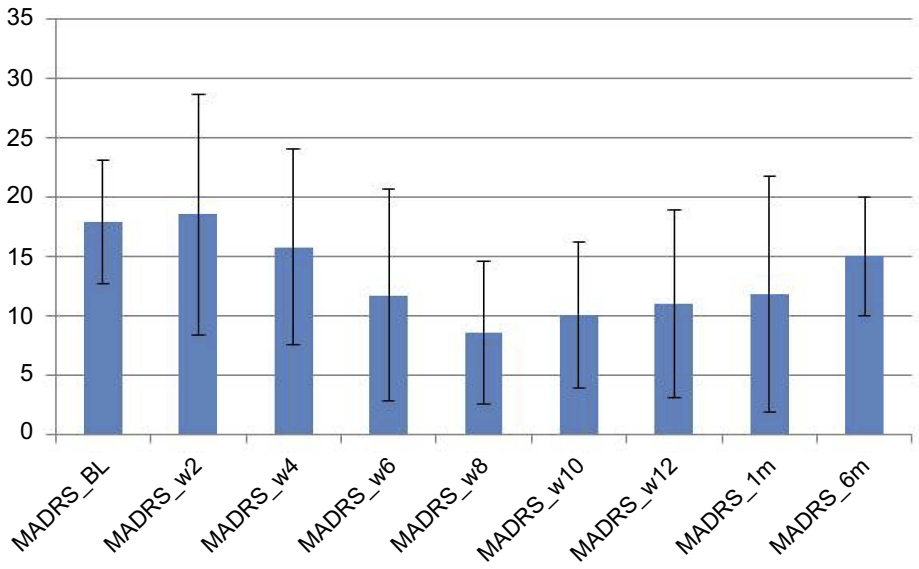

Figure 3 Montgomery-Asberg Depression Rating Scale Scores (MADRS).

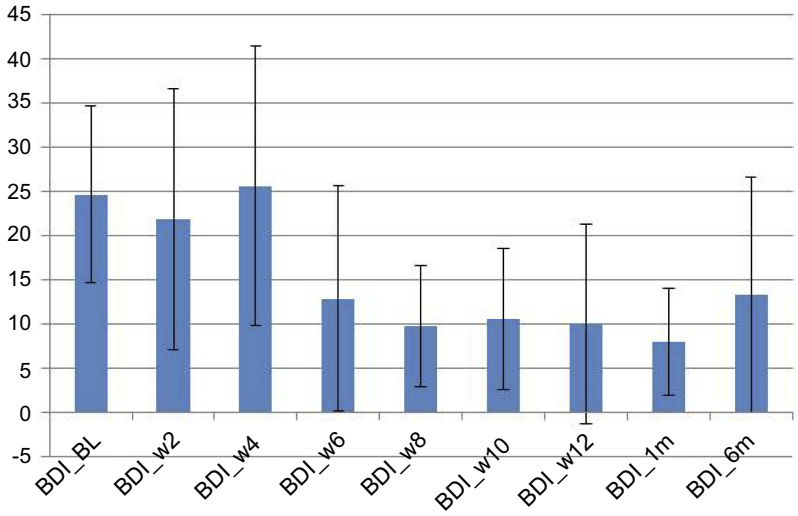

Figure 4 Beck DepressionInventory (BDI).

small sample size does not allow us to make any statistical comparisons. All eight participants in this study were middle-aged women first diagnosed with anorexia in their early or mid-teens, with an average duration of anorexia for 10–15 years and with a history of many treatments, including intensive re-feeding, with little long-term impact. Thus, we would posit that given the severity of their AN and their history of treatment resistance, any reported improvement in symptoms following an experimental treatment such as dTMS merits a properly conducted RCT in a larger group of subjects comparing active treatment with sham TMS.

Conclusion

This study was exploratory in nature and primarily conducted to test safety and feasibility, which it successfully demonstrated in small number of subjects. The findings of this study have potential clinical value in this difficult to treat, very ill group of patients and merit follow-up with a larger sample in a RCT that also measures biological target engagement.

Summary

Strengths and limitations of this study include next:

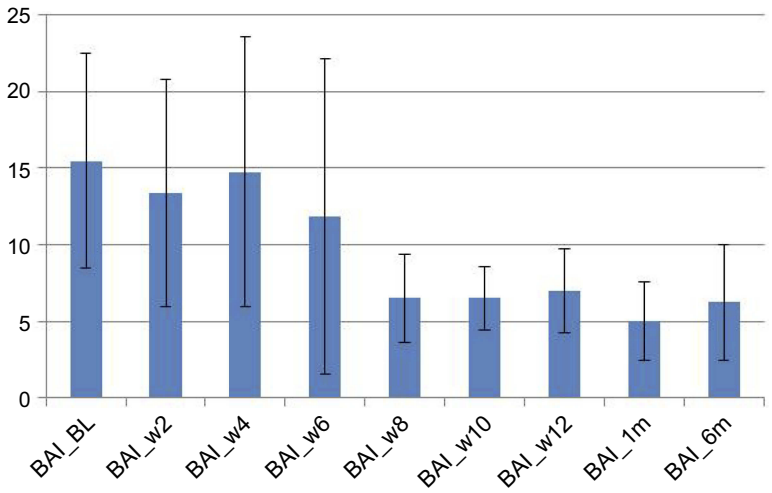

Figure 5 Beck AnxietyInventory (BAI).

- This is a first study testing safety and tolerability of deep H-coil TMS in people with severe and enduring anorexia nervosa.
- We demonstrated deep TMS is safe and well tolerated and may be beneficial to improve symptoms in those with SE-AN.
- Small sample size does not allow to generalize findings to a larger population.
- More research, specifically a RCT comparing real versus sham dTMS, is needed to be able to demonstrate the potential clinical utility of this treatment modality in this population.

Data statement

Dataset is stored at the Centre for Addiction and Mental Health, Toronto repository.

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Author contributions

Dr Allan S Kaplan is the principle investigator on this study. Dr Yuliya O Knyahnytska is the study MD, study coordinator, and first author on this manuscript. Dr Zafiris J Daskalakis is the brain stimulation supervisor and the main developer of the research protocol. Dr Daniel M Blumberger is the Medical Head of Brainstimulation Services with clinical responsibilities and provided overseeing on H-coil functioning. Dr Reza Zomorrodi is the Project Scientist who provided supervision with statistical analysis, and manuscript preparation. All authors contributed to data analysis, drafting and revising the article, gave final approaval, for the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

Dr Kaplan is the chairman of Shire Binge Eating Disorder Advisory Board for Canada for which he receives support. Dr Daniel M Blumberger reports in-kind equipment support as an investigator of initiated trials from Magventure, and as a site principle investigator of three sponsored trials from Brainsway, and attending one advisory board meeting from Janssen, during the conduct of the study. Dr Zafiris J Daskalakis reports industry sponsored clinical trial from Brainsway Inc, and equipment support from Magventure Inc, during the conduct of the study. The authors report no other conflicts of interest in this work.

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