A Randomised Controlled Trial of Neuronavigated Repetitive Transcranial Magnetic Stimulation (rTMS) in Anorexia Nervosa

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Abstract

Background

Anorexia nervosa (AN) is associated with morbid fear of fatness, extreme food restriction and altered self-regulation. Neuroimaging data implicate fronto-striatal circuitry, including the dorsolateral prefrontal cortex (DLPFC).

Methods

In this double-blind parallel group study, we investigated the effects of one session of sham-controlled high-frequency repetitive transcranial magnetic stimulation (rTMS) to the left DLPFC (l-DLPFC) in 60 individuals with AN. A food exposure task was administered before and after the procedure to elicit AN-related symptoms.

Outcomes

The primary outcome measure was ‘core AN symptoms’, a variable which combined several subjective AN-related experiences. The effects of rTMS on other measures of psychopathology (e.g. mood), temporal discounting (TD; intertemporal choice behaviour) and on salivary cortisol concentrations were also investigated. Safety, tolerability and acceptability were assessed.

Results

Forty-nine participants completed the study. Whilst there were no interaction effects of rTMS on core AN symptoms, there was a trend for group differences ($p = 0.056$): after controlling for pre-rTMS scores, individuals who received real rTMS had reduced symptoms post-rTMS and at 24-hour follow-up, relative to those who received sham stimulation. Other
psychopathology was not altered differentially following real/sham rTMS. In relation to TD, there was an interaction trend ($p = 0.060$): real versus sham rTMS resulted in reduced rates of TD (more reflective choice behaviour). Salivary cortisol concentrations were unchanged by stimulation. rTMS was safe, well–tolerated and was considered an acceptable intervention.

Conclusions
This study provides modest evidence that rTMS to the l-DLPFC transiently reduces core symptoms of AN and encourages prudent decision making. Importantly, individuals with AN considered rTMS to be a viable treatment option. These findings require replication in multiple-session studies to evaluate therapeutic efficacy.

Trial Registration
www.Controlled-Trials.com ISRCTN22851337

Introduction
Anorexia Nervosa (AN) is a disorder with a high mortality rate and is characterised by a pathological fear of food, eating and gaining weight [1]. In adults with AN, only 10–30% recover with the best available psychotherapies [2–4]. Pharmacological interventions are largely ineffective and have low acceptability [5, 6]. Thus, there is a need to improve treatments [7, 8]. Emerging neuroscience-based technologies that target neural substrates of AN could offer more effective treatment options and may help elucidate disease mechanisms [9–11].

AN is associated with brain changes such as reduced grey matter in fronto-limbic-striatal areas [12, 13]. Functional neuroimaging studies suggest over-representation of limbic drives, e.g. from the insula and amygdala, together with altered prefrontal activity [14]. Alterations in dopamine, 5-hydroxytryptamine (5-HT) and brain-derived neurotrophic factor (BDNF) have also been found i.e. in systems which have been implicated in reward processing, mood and symptom plasticity [15, 16]. Such neuroimaging data have been incorporated into disease models of AN, which suggest altered interactions between ‘bottom-up’ limbic drives (e.g. reward and emotional processing) and ‘top-down’ frontal lobe-mediated cognitive control [17–24].

More specifically, hypoactivity of prefrontal cortex (PFC) regions during response inhibition [25, 26] and set-shifting tasks [27] has been reported in AN. Since set-shifting is assumed to involve the inhibition of a pre-potent rule or behavioural response [28], poor inhibitory control may play a key role in set-shifting difficulties in AN—a well-examined phenomenon that seems to contribute to the maintenance of the disorder. Reduced activity in the PFC may therefore contribute to AN symptoms related to both impaired inhibitory control (i.e. binge eating and purging) and poor cognitive flexibility (e.g. compulsions such as body checking, exercising, and the obsessive pre-occupation with eating, weight and shape).

The dorsolateral prefrontal cortex (DLPFC) has a key role in such self-regulatory control mechanisms and is a common target for neuromodulatory interventions in disorders of fronto-limbic dysregulation. Repetitive transcranial magnetic stimulation (rTMS) applied to the DLPFC is a recognized second-line treatment for depression in the USA [29] and has demonstrated potential in reducing addictive behaviours and craving for nicotine, alcohol and cocaine [30–33]. Similarly, in two sham-controlled trials, our group found that a single session
of high-frequency (i.e. excitatory) rTMS over the left DLPFC (l-DLPFC) suppressed food craving in 28 healthy individuals [34] and in 38 patients with bulimia nervosa (BN) [35]. The BN patients also reported fewer binge-eating episodes. Another study did not replicate the effects of rTMS on food craving [36] but was limited by its sample size (N = 10) and crossover design. It is important to note that these single-session studies aimed to assess the short-term effects of rTMS and its feasibility as a therapeutic intervention. They are an important first step in informing treatment trials (involving multiple-sessions) that aim to explore long-term clinical efficacy. In a small therapeutic trial (i.e. 15 sessions) of rTMS in 14 individuals with BN, no differences between real and sham rTMS on eating disorder (ED) symptoms or mood were found [37]. Case studies have however, found lasting improvements in symptoms of BN following rTMS treatment [38, 39].

Given its demonstrated efficacy and acceptability in other psychiatric disorders (i.e. BN, addictions and depression), rTMS may be a viable treatment option for AN [40]. Indeed, an uncontrolled case series (N = 10) of a single session of high-frequency rTMS to the l-DLPFC demonstrated short-term reductions in levels of anxiety, feeling full and feeling fat in people with AN [41]. Moreover, case studies/series have found lasting (i.e. up to 12 months) improvements in AN psychopathology and mood following 20 rTMS sessions [42–44].

The physiological and psychological processes underlying the effects of rTMS in AN (and other disorders) are unclear. The DLPFC is implicated in models of emotion regulation [45] and thus rTMS could improve maladaptive emotion regulation strategies in AN (i.e. dietary restraint) [46]. Equally, changes in synaptic plasticity may be involved [47–49], which is in accordance with reported increases in BDNF [47, 50], modulation of extrastriatal dopamine [51] and bilateral DLPFC levels of 5-HT following rTMS [52]. These neural substrates have all been implicated in the aetiopathogenesis of AN [16, 46]. Furthermore, high-frequency rTMS to the DLPFC may remediate hypoactivity within prefrontal brain regions that has been associated with poor inhibitory control [25, 26] and impaired cognitive flexibility [27] in AN.

In psychiatric disorders, including AN, difficulties in inhibitory control have been examined using temporal discounting (TD) tasks, which measure the degree to which a reward is subjectively discounted in relation to its temporal delay. TD tasks provide a measure of choice impulsivity (increased TD i.e. preference for smaller-sooner [SS] rewards) and temporal foresight (reduced TD i.e. a preference for larger-later [LL] rewards) [53]. In a study relevant to AN, healthy participants given a glucose drink demonstrated a preference for LL rewards whilst those given an artificial sweetener drink favoured SS rewards [54]. Given that blood glucose is typically low in AN, these individuals might also demonstrate choice impulsivity. However in AN, TD data are mixed—patients have shown both ‘normal’ [55] and reduced TD behaviour [56, 57]. Interestingly, despite recovered AN patients demonstrating ‘normal’ TD behaviour, task-related functional alterations in the neural substrates of reward and cognitive control (e.g. the DLPFC) are reported to persist [57, 58]. The DLPFC has been implicated in TD [59] and modulation of the PFC by rTMS has been reported to both increase [60] and decrease TD in healthy participants [61, 62]. Given that people with AN may demonstrate aberrant TD behaviour and that rTMS to the PFC has been shown to modulate rates of TD, the present study has explored the effects of rTMS to the l-DLPFC on TD in people with AN.

Lastly, hyperactivity in the hypothalamic-pituitary-adrenal (HPA) axis has been reported in AN [63, 64] and, whilst there were no rTMS-induced changes in our pilot study of AN [41], rTMS has been shown to reduce cortisol concentrations in experimentally-stressed healthy people [65], in depression [66] and in BN [67]. Thus, we have examined the effects of rTMS on cortisol levels in AN.

As discussed previously, single-session rTMS studies a) have demonstrated transient improvements in ED related symptoms [34, 35], b) can be used to elucidate the mechanisms of
rTMS and c) are useful in informing future therapeutic trials (re: study design, outcomes, acceptability etc). Therefore, this proof-of-concept study assessed the short-term (i.e. up to 24 hours) effects of a single session of sham-controlled rTMS applied to the l-DLPFC on a) core AN symptomatology, b) TD behaviour and c) stress responses (salivary cortisol). Cardiac safety, tolerability and acceptability of the intervention were also investigated. The primary hypothesis was that real versus sham rTMS would reduce core AN symptoms. Secondary hypotheses were that, compared to sham, real rTMS would improve other psychopathology (anxiety, stress and mood), alter TD (this was exploratory due to conflicting data), reduce salivary cortisol, be safe and tolerable, and be viewed as an acceptable form of treatment to people with AN.

Materials and Methods

The protocol for this trial and supporting CONSORT checklist are available as supporting information (see S1 Protocol and S1 CONSORT Checklist). Ethical approval was given on 2nd November 2012 by the London City & East National Research Ethics Service Committee (reference number: 12/LO/1525) and all participants gave written informed consent. The trial was registered prior to commencement (8th February 2013 at www.controlled-trials.com, registration number: ISRCTN22851337). The raw data are available upon request to the authors.

Participants

Using G’ Power 3.1.9.2, a mixed 2 x 3 ANCOVA sample size calculation (i.e. incorporating a baseline covariate and accounting for interaction effects) was conducted based on our previous rTMS studies [34, 35]. This indicated that a total of 51 participants were required for an effect size of $d = 0.90$ with 80% power at two-sided $p = 0.05$. Accounting for a 5% dropout rate, a total of 27 people per group (i.e. total N = 54) were needed to obtain desired power.

Male and female participants >18 years of age were recruited from a specialist Eating Disorders Service and via the national eating disorder charity website www.b-eat.co.uk from 22nd April 2013 until 28th May 2014 (which was the planned length of time for study recruitment). Inclusion criteria were a current DSM-5 diagnosis of AN, established via referring clinicians and/or the Eating Disorder Diagnostic Scale (EDDS) [68] and a body mass index (BMI) between 14.5–18.5 kg/m². Contra-indications to rTMS were checked with the TMS Adult Safety Screen (TASS) [69]. Further exclusion criteria were left-handedness, being on a dose of psychotropic medication that had not been stable for at least 14 days, pregnancy, and alcohol consumption (>3 units/day) and/or nicotine use (>15 cigarettes/day) [70].

Procedures

This study followed recommendations for non-invasive brain stimulation trials [71]. As shown in the CONSORT diagram (Fig 1), participants’ eligibility was established using a pre-randomisation assessment which included; i) collection of demographic information (background, physical and psychiatric health, ED history, medications, alcohol/smoking behaviours), ii) administration of the TASS [69], iii) confirmation of diagnosis (via EDDS) and iv) assessment of psychiatric co-morbidity via the screening module of the Structured Clinical Interview for DSM-IV Axis I Disorders [72]. An independent researcher randomised eligible participants ($n = 60$) with STATA in a parallel design stratifying by AN-subtype using a random block design (block sizes of 2, 4, 6, and 8). The researcher administering rTMS was unblinded. To ensure allocation concealment, the independent researcher (randomiser) provided allocation details (stimulation type) via a participant ID-coded email to the rTMS administrator.
immediately before the rTMS session. Participants remained blind to stimulation type until the end of procedures, as did the researcher conducting assessments.

Nine participants withdrew post-randomization, e.g. due to feeling unwell. The remaining 51 completed procedures over one or two days and all study procedures took place at the Institute of Psychiatry, Psychology and Neuroscience, King’s College London. Participants underwent a structural magnetic resonance imaging scan [43]. This was used with Brainsight to neuronavigate the TMS coil to the l-DLPFC using Talaraich co-ordinates, x = -45, y = 45, z = 35 [73]. Participants were instructed to refrain from eating for at least one hour prior to the testing session.

Fig 2 shows the testing protocol. All procedures were identical between groups, except for the rTMS. At the start (TP0), information on ED symptoms and general psychopathology was collected using the Eating Disorder Examination Questionnaire (EDE-Q version 6) [74] and the Depression Anxiety and Stress scales (DASS-21) [75]. Visual analogue scales (VAS; 10cm) assessing levels of urge to restrict, feeling full, feeling fat, stress and anxiety were administered immediately after the rTMS session. Participants remained blind to stimulation type until the end of procedures, as did the researcher conducting assessments.

Fig 2. Testing protocol timeline. FCTpre & FCTpost: food challenge task before and after rTMS. TDpre & TDpost: temporal discounting task before and after rTMS. Collection of main visual analogue scales (VAS) at TP0 (pre-FCT); main VAS & additional VAS at TP1 (post-FCT/pre-rTMS) & TP2 (post-rTMS & FCT); main VAS only at TP3 (end of session) & TP4 (24 hours following). Saliva samples collected at S0 (pre-FCT), S1 (post-FCT/pre-rTMS), S2 (immediately after rTMS), S3 (post-rTMS/post-FCT) and S4 (end of session).
A saliva sample (S0) was obtained using Salivettes® along with measures of blood pressure (BP) and heart rate (pulse).

This was followed by the first administration of the food challenge task (FCTpre) [41]. The FCT required participants to watch a 2-minute film of people eating highly palatable foods (chocolate, nuts, crisps, biscuits) while the same foods were in the room, and then rate their perceived smell, taste, appearance and urge to eat these foods. This task serves as symptom provocation—it seeks to elicit AN-related experiences. At this point (TP1), the main VAS and ‘additional’ VAS regarding mood, calmness, hunger, general urge to eat, urge to binge, and urge to purge were completed. A saliva sample (S1) was collected and a computerised monetary TD task (TDpre) was administered [53].

The Brainsight® neuronavigation and Magstim® Rapid device (Magstim®, UK) were then used to establish participants’ motor threshold (MT) using peripheral electromyography; MT was defined as the minimum stimulation required to evoke 5 out of 10 motor evoked potentials greater than 50μV [76, 77]. Following MT measurement, BP and pulse were recorded. A real/sham coil was then used to administer neuronavigated rTMS; 5 second trains/25 second inter-train intervals, 1Hz, 110% MT, delivering 1000 pulses over 20 minutes to the l-DLPFC. Real and sham rTMS are identical to one another in terms of their set-up, duration and sound. Real rTMS emits a magnetic field that induces an electrical current in the brain (i.e. alters neural activity). Sham rTMS however, does not emit the magnetic field that can induce these changes in neural activity. Immediately after the 20th train, BP and pulse were recorded, a saliva sample was collected (S2) and a 10cm VAS measuring discomfort experienced during the rTMS was completed.

The TD task was then re-administered (TDpost), followed by the FCT (FCTpost). Main and additional VAS were collected (TP2), followed by a saliva sample (S3). At the end of the session, the main VAS were repeated (TP3), a final saliva sample (S4) was collected and BP/pulse were recorded. Participants were phoned the next day for a 24-hour follow up (TP4) during which the main VAS were repeated, adverse events were discussed, and blinding was assessed and then revealed. Finally, participants were asked whether, if rTMS proved to be efficacious in AN, they would consider it as a treatment (i.e. 20 daily sessions).

**Temporal discounting task.** The TD task requires participants to choose between a smaller, variable amount of money (£0-£100) available immediately and a larger, fixed amount (£100) available after four different time delays (1 week, 1 month, 1 year and 2 years). The task is individually adjusted by an algorithm that changes the value of the immediate reward depending on the subject’s previous choices. This allows the calculation of each individual’s ‘indifference point’ i.e. the point at which the immediate reward is deemed equal to the fixed delayed amount [78, 79]. Using the indifference point values for each delay period, a hyperbolic decay function is calculated that describes the relationship between an individual’s subjective value of a reward as a function of its delay [53]: it involves a constant (k) that characterises an individual’s overall rate of discounting. Whilst the k value can be used as the main dependent variable, area under the curve (AUC) analysis provides a theoretically neutral account of TD. AUC is more appropriate for investigations with quantitative, inferential statistics, when k values are skewed and when relatively few time delays are used [80]. AUC values are between 0 and 1; smaller values reflect higher TD (choice impulsivity; higher sensitivity to delay) while larger values represent lower TD (less sensitivity to delay; temporal foresight).

**Analyses**

The primary outcome variable was ‘core AN symptoms’ (computed by summation of VAS scores on urge to restrict, levels of feeling full and levels of feeling fat; maximum score of 30). All
other outcomes were secondary. The effects of real versus sham rTMS on core AN symptoms and the five individual main VAS scores over time were evaluated using mixed ANCOVAs, i.e. both between and within group comparisons (group: real/sham rTMS x time: TP2, TP3 and TP4) controlling for scores at TP1 (TP1 scores were deemed our baseline as this was the time point immediately before the intervention). The effects of real versus sham rTMS on additional VAS (mood, calmness, hunger and urge to eat/binge/purge) were evaluated using mixed ANOVAs (group: real/sham rTMS x time: TP1, TP2).

In the analysis of the TD task, agreement between k and AUC were checked via correlation and then AUC was used as the outcome variable. The effect of real versus sham rTMS on AUC was evaluated using a mixed ANOVA (group: real/sham rTMS x time: TDpre, TDpost). Paired-sample t-tests were also used to look at the effects of real/sham rTMS within each AN subtype.

Salivary cortisol concentrations were analysed as previously described [67]. Correlation analyses between initial cortisol concentrations (S0) and psychopathology indices (EDEQ, DASS-21) were conducted. The effects of real versus sham rTMS on cortisol concentrations over time were evaluated using a mixed ANCOVA (group: real/sham rTMS x time: S2, S3 and S4) controlling for cortisol levels at S1. The effects of real versus sham rTMS on BP and pulse were evaluated using mixed ANCOVAs (group: real/sham rTMS x time: post-MT, post-rTMS, TP4) controlling for BP/pulse at TP0.

In this proof-of-concept study we were interested in the effects of rTMS in those who actually received their allocated intervention (real or sham rTMS) and completed all outcome assessments. Therefore, per-protocol statistical analyses were performed using IBM® SPSS® software (Version 22). When normality or other ANOVA assumptions were violated, non-parametric alternatives, log transformations or post-hoc bootstrapping methods with Bonferroni corrections were employed. All tests were two-tailed and the level of significance was set at $\alpha = 0.05$. Partial eta squared ($\eta^2$) and Cohen’s $d$ effect sizes are reported for mixed ANOVAs/ANCOVAs and independent sample $t$-tests, respectively.

### Results

#### Participant Flow and Baseline Characteristics

Two participants (both binge/purge AN) randomised to real rTMS withdrew following the first few trains of rTMS due to discomfort. Therefore, data from 49 females, randomised to real ($n = 21$) or sham rTMS ($n = 28$), were analysed. Table 1 shows demographic and clinical data. Of note, the median illness duration in the real rTMS group was 3 years shorter than the sham group but this was not statistically significant. There were no other significant between-group differences, except for the EDE-Q weight [$t(47) = -2.05, p = 0.046, d = 0.60$] and shape [$t(47) = -2.06, p = 0.045, d = 0.60$] subscale scores, which were higher in the sham group.

#### Salience of the Food Challenge Task

This was assessed via the main VAS before (TP0) and after (TP1) the first administration of the FCT. In the sample as a whole, the FCT significantly increased VAS anxiety scores [$t(48) = -2.19, p = 0.034, d = 0.60$] and there was a trend towards an increased urge to restrict [$t(48) = -1.70, p = 0.095, d = 0.49$]. By chance, at TP0 the sham group scored significantly higher on core AN symptoms [$t(31.97) = -2.22, p = 0.034, d = 0.78$] (real: $M = 16.50, SD = 7.11$; sham: $M = 20.44, SD = 4.56$) and feeling fat [$t(36.21) = -2.62, p = 0.013, d = 0.87$] (real: $M = 5.37, SD = 2.96$; sham: $M = 7.40, SD = 2.26$); however, these differences were not significant following the FCT, i.e. at TP1 (the rTMS intervention baseline).
Primary outcome: core AN symptoms

Mixed ANCOVA analyses controlling for pre-rTMS scores (TP1) showed no significant stimulation type x time interaction \([F(1.35) = 0.14, p = 0.780, \eta^2 = 0.00]\); however, there was a main effect of time \([F(1.35) = 13.58, p < 0.001, \eta^2 = 0.23]\) and a trend towards group differences \([F(1) = 3.86, p = 0.056, \eta^2 = 0.08]\) (Fig 3). Those who received real rTMS reported lower levels of core AN symptoms after stimulation. Post hoc, bootstrapped comparisons suggested these group differences were significant at each of the three time points; TP2 (post-FCT2) \([t(47) = -2.31, p = 0.030, d = 0.67]\), TP3 \([t(47) = -2.24, p = 0.035, d = 0.65]\) and TP4 \([t(47) = -2.51, p = 0.021, d = 0.73]\). However, these differences were not significant following Bonferroni corrections for multiple comparisons.

Secondary outcomes

Across the individual main VAS, mixed ANCOVA analyses controlling for pre-rTMS (TP1) scores demonstrated no interaction effects (Table 2). There was an effect of time on stress \([F(1.55) = 8.40, p = 0.001, \eta^2 = 0.15]\), anxiety \([F(1.72) = 4.93, p = 0.013, \eta^2 = 0.10]\), feeling full \([F(1.28) = 21.89, p < 0.001, \eta^2 = 0.32]\) and feeling fat \([F(1.44) = 11.40, p < 0.001, \eta^2 = 0.20]\). There was also a trend for between group differences in levels of feeling fat \([F(1) = 3.01, p = 0.089, \eta^2 = 0.06]\); reduced levels of feeling fat were reported following real rTMS. Post hoc, bootstrapped comparisons suggested that these group differences were significant at each of the three time points; TP2 \([t(47) = -2.50, p = 0.030, d = 0.73]\), TP3 \([t(47) = -2.82, p = 0.015, d = 0.73]\) and TP4 \([t(47) = -2.51, p = 0.021, d = 0.73]\).

Table 1. Baseline characteristics (mean ± SD).

| Participants (n = 49) | Real rTMS (n = 21) | Sham rTMS (n = 28) |
|----------------------|-------------------|-------------------|
| **Demographic information** | | |
| AN subtype (R/BP) | 13/8 | 15/13 |
| Age | 25.29 ± 6.88 | 27.68 ± 9.89 |
| Illness duration; yrs | 9.05 ± 7.02\(^\dagger\) | 11.27 ± 8.01\(^\dagger\) |
| Meals/day | 2.05 ± 0.92 | 2.29 ± 0.97 |
| BMI | 16.73 ± 1.59 | 16.38 ± 1.76 |
| Smokers (yes/no) | 6/21 | 9/28 |
| On medication (yes/no) | 12/21 | 22/28 |
| **Eating disorder psychopathology** | | |
| EDE-Q global | 3.90 ± 1.26 | 4.43 ± 1.07 |
| EDE-Q restraint | 4.17 ± 1.68 | 4.41 ± 1.23 |
| EDE-Q eating | 3.63 ± 1.17 | 4.01 ± 1.32 |
| EDE-Q weight\(^*\) | 3.48 ± 1.66 | 4.33 ± 1.28 |
| EDE-Q shape\(^*\) | 4.32 ± 1.22 | 4.96 ± 0.98 |
| **General psychopathology** | | |
| DASS-21 total | 29.67±13.65 | 33.93±12.32 |
| DASS-21 depression | 10.14 ± 5.98 | 12.00 ± 5.92 |
| DASS-21 anxiety | 7.05 ± 4.29 | 8.50 ± 4.37 |
| DASS-21 stress | 12.47 ± 4.99 | 13.43 ± 4.36 |

\(^*\) sig \(p < .05\). R: restrictive; BP: binge/purge; \(^\dagger\) large variation/SD in illness duration, Real rTMS Mdn = 7 years, range = 3–35 years, Sham rTMS Mdn = 10 years, range = 1–38 years; EDE-Q scores: ≥ 2.8 indicate clinical severity; DASS-21 scores: 10+ depression, 6+ anxiety and 10+ stress indicate moderate/severe psychopathology.

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$d = 0.82$] and TP4 $t(47) = -2.27, p = 0.036, d = 0.66]$. However, following Bonferroni corrections for multiple comparisons only differences at TP3 remained significant.

### Additional VAS

There were no significant interactions across any of the additional VAS administered during the two FCT (Table 2). There was a significant effect of time $[F(1) = 26.75, p < 0.001, \eta^2 = 0.36]$ and

![Fig 3. Mean ± SD of core AN symptoms pre-rTMS, post-rTMS, at the end of the session and after 24 hours. * $p < .05$ (prior to Bonferroni corrections). This composite core AN symptom outcome was composed of the urge to restrict (0–10), levels of feeling full (0–10) and levels of feeling fat (0–10) VAS and therefore scores can range from 0–30.](https://doi.org/10.1371/journal.pone.0148606.g003)

| Table 2. Secondary outcomes; mean ± SD within each group across time points. AN-R: restrictive subtype; AN-BP: binge/purge subtype. Note: the values above are based on 10cm visual analogue scales (VAS). Scales were scored from ‘no urge to restrict/eat/binge eat/be sick or purge’ or ‘not feeling full/ fat/hungry at all’ (0) to ‘extremely strong urge to restrict/eat/binge eat/be sick or purge’ or ‘feeling extremely full/fat/calm/hungry’ (10). The mood VAS was scored from ‘feeling extremely low’ (0) to ‘feeling extremely high’ (10) and the calmness VAS was scores from ‘feeling extremely calm’ (0) to ‘feeling extremely tense’ (10). |
|---|---|
| **Real rTMS (n = 21)** | **Sham rTMS (n = 28)** |
| **AN-R (n = 13), AN-BP (n = 8)** | **AN-R (n = 15), AN-BP (n = 13)** |
| **‘Main’ VAS** | **‘Main’ VAS** |
| TP1 (pre) | TP1 (pre) |
| TP2 (post) | TP2 (post) |
| TP3 (end) | TP3 (end) |
| TP4 (24hrs) | TP4 (24hrs) |
| **Restrict** | 7.05 ±2.91 | 6.17 ±2.39 | 5.76 ±2.52 | 6.79 ±2.11 |
| 5.62 ±3.00 | 5.18 ±3.04 | 5.57 ±2.48 | 7.38 ±2.94 |
| 3.33 ±2.73 | 5.14 ±2.90 | 6.08 ±3.38 | 4.91 ±3.18 |
| 4.07 ±3.41 | 5.19 ±2.56 | 4.44 ±3.22 | 6.00 ±2.70 |
| **Feeling full** | 5.03 ±3.39 | 4.25 ±3.18 | 6.61 ±3.02 | 4.45 ±2.94 |
| 3.53 ±2.80 | 3.60 ±3.27 | 5.00 ±3.10 | 5.46 ±2.63 |
| 3.33 ±2.73 | 4.38 ±2.33 | 4.43 ±2.90 | 5.21 ±2.38 |
| **Feeling fat** | 5.55 ±3.23 | 4.01 ±2.93 | 6.79 ±2.14 | 5.21 ±2.41 |
| 4.55 ±3.19 | 3.65 ±3.26 | 4.24 ±2.90 | 4.32 ±3.54 |
| 4.07 ±3.41 | 4.27 ±3.06 | 4.32 ±3.54 | 5.02 ±3.07 |
| **Anxiety** | 5.87 ±3.32 | 2.88 ±2.68 | 2.39 ±2.84 | 2.97 ±3.37 | 4.43 ±3.10 |
| 4.25 ±3.18 | 4.27 ±3.06 | 4.27 ±3.06 | 4.27 ±3.06 |
| 3.60 ±3.27 | 4.38 ±2.33 | 4.32 ±3.54 | 5.02 ±3.07 |
| **Stress** | 4.61 ±3.21 | 0.99 ±1.95 | 2.27 ±3.14 | 2.27 ±3.14 |
| 3.87 ±3.15 | 1.12 ±2.13 | 1.10 ±2.03 | 1.10 ±2.03 |
| 3.65 ±3.26 | 2.38 ±2.60 | 3.26 ±3.68 | 3.26 ±3.68 |
| 4.24 ±2.90 | 2.38 ±2.60 | 3.26 ±3.68 | 3.26 ±3.68 |
| **Mood** | 4.12 ±1.88 | 4.48 ±2.13 | 3.79 ±1.58 | 4.56 ±1.68 |
| 4.01 ±2.93 | 4.67 ±2.14 | 6.79 ±2.14 | 5.21 ±2.41 |
| 3.65 ±3.26 | 4.24 ±2.90 | 4.32 ±3.54 | 5.02 ±3.07 |
| **Calmness** | 5.87 ±3.32 | 2.88 ±2.68 | 2.39 ±2.84 | 2.97 ±3.37 | 4.43 ±3.10 |
| 4.25 ±3.18 | 4.27 ±3.06 | 4.27 ±3.06 | 4.27 ±3.06 |
| 3.60 ±3.27 | 4.38 ±2.33 | 4.32 ±3.54 | 5.02 ±3.07 |
| **Urge to eat** | 2.38 ±2.60 | 0.99 ±1.95 | 2.27 ±3.14 | 2.27 ±3.14 |
| 3.93 ±2.84 | 1.12 ±2.13 | 1.10 ±2.03 | 1.10 ±2.03 |
| 2.97 ±3.37 | 2.22 ±3.24 | 3.26 ±3.68 | 3.26 ±3.68 |
| **Urge to binge eat** | 2.38 ±2.60 | 0.99 ±1.95 | 2.27 ±3.14 | 2.27 ±3.14 |
| 3.93 ±2.84 | 1.12 ±2.13 | 1.10 ±2.03 | 1.10 ±2.03 |
| 2.97 ±3.37 | 2.22 ±3.24 | 3.26 ±3.68 | 3.26 ±3.68 |
| **Urge to be sick/purge** | 2.38 ±2.60 | 0.99 ±1.95 | 2.27 ±3.14 | 2.27 ±3.14 |
| 3.93 ±2.84 | 1.12 ±2.13 | 1.10 ±2.03 | 1.10 ±2.03 |
| 2.97 ±3.37 | 2.22 ±3.24 | 3.26 ±3.68 | 3.26 ±3.68 |

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a trend for group differences \[ F(1) = 2.91, p = 0.095, \eta^2 = 0.06 \] on reported levels of calmness/tension. In addition, an effect of time on reported mood \[ F(1) = 13.32, p = 0.001, \eta^2 = 0.22 \], hunger \[ F(1) = 15.29, p < 0.001, \eta^2 = 0.25 \], urge to eat \[ F(1) = 13.11, p < 0.001, \eta^2 = 0.22 \], and urge to be sick or purge \[ F(1) = 7.65, p = 0.008, \eta^2 = 0.14 \] was found. There was no effect of time or group on participants’ urge to binge eat.

**Temporal discounting**

Data from the TD task administered pre-rTMS were used for preliminary analyses. Data for the TD outcome variable, \( k \), were highly skewed. Since Spearman’s correlation indicated agreement between \( k \) and AUC in measuring TD \( [r_s = -0.78, p < .001] \) AUC values were used in analyses. A mixed ANOVA indicated a trend towards a significant stimulation type x time interaction effect on AUC \( [F(1) = 3.71, p = 0.060, \eta^2 = 0.07] \) (Fig 4). Paired sample \( t \)-tests suggested that real rTMS significantly increased AUC (i.e. reduced the rate of TD) \( [t(20) = -3.16, p = 0.005, d = 0.54] \), whilst sham rTMS had no effect on TD. Paired sample \( t \)-tests revealed that the effects of real rTMS on TD were significant within the restrictive AN subtype \( [t(12) = -2.91, p = 0.013, d = 0.54] \) but not within the binge/purge subtype.

**Cortisol**

Salivary cortisol levels vary with time of day [81], therefore, all participants were tested in the afternoon. Forty-five complete data sets were available for analysis (19 real, 26 sham). As data were skewed, non-parametric correlation analyses were employed and log transformations were used in the mixed ANCOVA. Median baseline cortisol concentrations did not indicate hypercortisolaemia (6.63±5.09nmol/L). There were no significant associations between initial cortisol concentrations and psychopathology. There were also no initial (S0) differences in cortisol concentrations between real/sham groups, nor did the first FCT significantly alter cortisol levels. Controlling for pre-rTMS (S1) values, no significant interaction effects or effects of time or stimulation type were observed.

**Blinding**

Although participants guessed stimulation type at a rate better than chance \( [\chi^2(1) = 4.59, p = 0.032] \), there were no significant differences between real/sham groups in the ability to correctly guess stimulation type; 43% who had real rTMS thought they had sham, while 29% who had sham rTMS thought they received real. Both groups had similar levels of certainty regarding how sure they were of which intervention they had received; real \( (M = 4.67, SD = 2.32) \), sham \( (M = 4.79, SD = 2.78) \). Researchers were not able to guess stimulation type at a rate better than chance. Levels of certainty in researchers were similar across groups; real \( (M = 2.24, SD = 2.32) \), sham \( (M = 2.43, SD = 2.30) \).

**Safety, tolerability and acceptability**

Controlling for BP and pulse at TP0, there were no significant interaction, time or group effects. Real rTMS was experienced as more uncomfortable by participants than sham \( [t(46) = 6.33, p < 0.001, d = 1.87] \); real \( (M = 5.51, SD = 2.48) \), sham \( (M = 1.38, SD = 2.04) \). However, there were no significant differences between real/sham groups in the number of physical complaints (typically feeling dizzy/dazed or having a headache) 24 hours after the session (5/21 real; 4/28 sham) or whether participants had to take painkillers (2/21 real, 1/28 sham). 90% of people who had real rTMS said that if rTMS proved to be efficacious in treating AN, they would consider having it as a treatment (i.e. 20 daily sessions).
Discussion

In this proof-of-concept randomised controlled trial of rTMS in AN, individuals who received real rTMS (versus sham) tended to report reduced AN symptoms (statistical trend). However, given some improvements across this and other measures over time following both real and sham rTMS, there is also an indication of a placebo effect. The rate of TD was reduced following real (but not sham) rTMS (again, only at trend level), suggesting that rTMS may encourage more prudent decision making. Cortisol concentrations were not altered and rTMS was a safe, tolerable and acceptable procedure for people with AN.

Our findings, albeit only at trend level, are in line with existing evidence that neuromodulation may be able to alter AN symptomatology and intertemporal choice behaviour [40, 44, 60, 82, 83]. Our uncontrolled pilot study reported that a single rTMS session temporarily reduced anxiety, levels of feeling full and feeling fat in participants with AN [41] and our case series also reported reductions within sessions across these symptoms [44]. Although existing data regarding TD in AN are not consistent, our modest findings regarding the effects of rTMS on TD are consistent with other research showing that the l-DLPFC is a key mediator of TD [59] and inhibitory/excitatory rTMS to the prefrontal cortex can increase/reduce TD, respectively [60, 62]. The lack of change in cortisol following rTMS replicates our previous findings in AN [41], but is not consistent with studies in healthy controls and other psychiatric groups, including BN [65–67].

We examined the effects of rTMS in AN across a range of psychological, neurocognitive and biological measures. We also used improved methodologies—the motor evoked potential method of estimating MT is more accurate and safer than other methods [84] and neuronavigated rTMS provides a more individualised, precise and effective method of targeting the DLPFC than older methods [73, 84, 85]. In addition, whilst participants were able to guess
stimulation type better than chance, there was no difference between groups and thus blinding was partially successful.

This study is somewhat underpowered because of dropout. Our per-protocol analysis is also a limitation and may have led to statistical bias. The inclusion of a healthy comparison group would have been informative, particularly in terms of the TD findings. Furthermore, in relation to TD in AN, we did not measure or control for blood glucose levels. Whilst our choice of rTMS target, the l-DLPFC, is theoretically based, the optimal brain areas to target with neuro-modulation in AN are unknown. The illness duration of the group who received real rTMS was, by chance but not significantly, shorter than those who received sham. On a neural level, illness duration may influence an individual’s responsivity to the effects of rTMS and thus it should be considered in future. By chance, initial ED and mood symptoms were higher in the sham group. Whilst this should be considered in the interpretation of results, there were no group differences immediately prior to real/sham rTMS and we are confident that our results are independent of this.

In terms of the mechanisms underlying therapeutic effects of rTMS in AN, our data suggest that real and sham rTMS do not differentially alter mood-related outcomes. Therefore, the trend for effects of rTMS on AN symptoms reported here may be independent of modulating emotion regulation abilities. Taken together, our findings of a tendency for real rTMS to reduce AN symptoms and improve intertemporal choice behaviour (i.e. cognitive control) suggest that transiently increasing PFC activity may temporarily improve AN symptoms relating to impaired inhibitory control [25, 26] and cognitive inflexibility [27]. More generally, this could imply that excitatory rTMS to the DLPFC in AN may (in the short-term) improve cognitive control mechanisms over symptoms that are described as rewarding, habitual, compulsive and ‘out-of-control’ (e.g. starvation, weight loss, exercise etc.) [21, 24, 86].

Given previous and current findings regarding rTMS in AN, together with the success of rTMS in treating other psychiatric disorders, further research is warranted. Proof-of-concept studies (such as this) are an important first step for non-invasive neuromodulation research in psychiatric conditions, although some have not demonstrated short-term psychological effects in other disorders [66]. Such single-session rTMS studies are limited in their validity and generalisability with regards to long-term therapeutic benefits and mechanisms of response. Preliminary evidence for the clinical utility of therapeutic rTMS in AN is encouraging [42–44]. Future research should include controlled therapeutic trials to establish/confirm the therapeutic efficacy of rTMS in AN. Neuroimaging modalities should also be used in order to probe disease mechanisms and identify biomarkers of response [87].

Supporting Information

S1 Protocol. Trial protocol.

(DOCX)

S1 CONSORT Checklist. CONSORT Checklist.

(DOC)

S1 Dataset.

(SAV)

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Author Contributions
Conceived and designed the experiments: JM FVE ICC US. Performed the experiments: JM MK NB SN TD. Analyzed the data: JM MK. Contributed reagents/materials/analysis tools: JM TD FVE ASD KR. Wrote the paper: JM MK ICC US.

References

1. Arcelus J, Mitchell AJ, Wales J, Nielsen S. Mortality rates in patients with anorexia nervosa and other eating disorders: A meta-analysis of 36 studies. Arch Gen Psychiatry. 2011; 68(7):724–31. Epub 2011/07/06. doi: 10.1001/archgenpsychiatry.2011.74 PMID: 21727255.

2. Steinhausen HC. The outcome of anorexia nervosa in the 20th century. American Journal of Psychiatry. 2002; 159(6):1284–93. PMID: 12153817

3. Schmidt U, Oldershaw A, Jichi F, Sternheim L, Startup H, McIntosh V, et al. Out-patient psychological therapies for adults with anorexia nervosa: randomised controlled trial. Br J Psychiatry. 2012; 201(5):392–9. Epub 2012/09/22. doi: 10.1192/bjp.bp.112.112078 PMID: 22995832.

4. Zipfel S, Löwe B, Reas DL, Deter H-C, Herzog W. Long-term prognosis in anorexia nervosa: lessons from a 21-year follow-up study. The Lancet. 2000; 355(9205):721–2. doi: 10.1016/s0140-6736(99)05363-5

5. Mitchell JE, Roerig J, Steffen K. Biological therapies for eating disorders. International Journal of Eating Disorders. 2013; 46(5):470–7. Epub 2013/05/10. doi: 10.1002/eat.22104 PMID: 23658094.

6. Tortorella A, Fabrazzo M, Monteleone A, Steardo L, Monteleone P. The role of drug therapies in the treatment of anorexia and bulimia nervosa: a review of the literature. Journal of Psychopathology. 2014; 20:50–65.

7. NICE. National Institute for Health and Care Excellence, Eating Disorders CG9. In: NICE, editor. London 2004.

8. Watson HJ, Bulik CM. Update on the treatment of anorexia nervosa: review of clinical trials, practice guidelines and emerging interventions. Psychological Medicine. 2012; 42(6):740–7. Epub 2012/12/12. doi: 10.1017/s0033291712002620 PMID: 23217606.

9. Insel TR, Gogtay N. National Institute of Mental Health clinical trials: new opportunities, new expectations. JAMA psychiatry. 2014; 71(7):745–6. Epub 2014/05/09. doi: 10.1001/jamapsychiatry.2014.426 PMID: 24806613.

10. Schmidt U, Campbell IC. Treatment of eating disorders can not remain ‘brainless’: the case for brain-directed treatments. European Eating Disorders Review. 2013; 21(6):425–7. Epub 2013/10/15. doi: 10.1002/erv.2257 PMID: 24123463.

11. Val-Laillet D, Aarts E, Weber B, Ferrari M, Quaresima V, Stoeckel L, et al. Neuroimaging and neuromodulation approaches to study eating behavior and prevent and treat eating disorders and obesity. Neurimage: Clinical. 2015; 8:1–31.

12. Van den Eynde F, Suda M, Broadbent H, Guillaume S, Van den Eynede M, Steiger H, et al. Structural magnetic resonance imaging in eating disorders: a systematic review of voxel-based morphometry studies. European Eating Disorders Review. 2012; 20(2):94–105. Epub 2011/11/05. doi: 10.1002/erv.1163 PMID: 22052722.

13. Titova OE, Hjorth OC, Schlöth HB, Brooks SJ. Anorexia nervosa is linked to reduced brain structure in reward and somatosensory regions: a meta-analysis of VBM studies. BMC psychiatry. 2013; 13(1):110.

14. Zhu Y, Hu X, Wang J, Chen J, Guo Q, Li C, et al. Processing of food, body and emotional stimuli in anorexia nervosa: a systematic review and meta-analysis of functional magnetic resonance imaging studies. European Eating Disorders Review. 2012; 20(6):439–50. Epub 2012/09/05. doi: 10.1002/erv.2197 PMID: 22945872.

15. Phillipou A, Rossell SL, Castle DJ. The neurobiology of anorexia nervosa: a systematic review. Aust N Z J Psychiatry. 2014; 48(2):128–52. Epub 2013/11/07. doi: 10.1177/0004864413509693 PMID: 24194589.

16. Brandys MK, Kas MJ, van Elburg AA, Campbell IC, Adan RA. A meta-analysis of circulating BDNF concentrations in anorexia nervosa. World J Biol Psychiatry. 2011; 12(6):444–54. Epub 2011/04/14. doi: 10.3109/15622975.2011.562244 PMID: 21486106.
17. Kaye W, Fudge J, Paulus M. New insights into symptoms and neurocircuit function of anorexia nervosa. Nature Reviews Neuroscience. 2009; 10(8):573–84. doi: 10.1038/nnr2682 PMID: 19603056

18. Friederich HC, Wu M, Simon JJ, Herzog W. Neurocircuit function in eating disorders. International Journal of Eating Disorders. 2013; 46(5):425–32. Epub 2013/05/10. doi: 10.1002/eat.22099 PMID: 23658085.

19. Lipsman N, Woodside DB, Lozano AM. Neurocircuity of limbic dysfunction in anorexia nervosa. Cortex, 2014; Epub ahead of print. doi: 10.1016/j.cortex.2014.02.020 PMID: 24703713.

20. Marsh R, Maia TV, Peterson BS. Functional disturbances within frontostriatal circuits across multiple childhood psychopathologies. American Journal Psychiatry. 2009; 166(6):664–74. Epub 2009/05/19. doi: 10.1176/appi.ajp.2009.08091354 PMID: 19448188; PubMed Central PMCID: PMC2734479.

21. Park RJ, Godier LR, Cowdrey FA. Hungry for reward: How can neuroscience inform the development of treatment for Anorexia Nervosa? Behav Res Ther. 2014. Epub 2014/08/26. doi: 10.1016/j.brat.2014.07.007 PMID: 25151600.

22. Sanders N, Smeets PA, van Elburg AA, Danner UN, van Meer F, Hoek HW, et al. Altered food-cue processing in chronically ill and recovered women with anorexia nervosa. Front Behav Neurosci. 2015; 9:46. Epub 2015/03/17. doi: 10.3389/fnbeh.2015.00046 PMID: 25774128.

23. Brooks SJ, Rask-Andersen M, Benedict C, Schiøth HB. A debate on current eating disorder diagnoses in light of neurobiological findings: is it time for a spectrum model? BMC psychiatry. 2012; 12:76. Epub 2012/07/10. doi: 10.1186/1714-1244-12-76 PMID: 22770364; PubMed Central PMCID: PMC3475111.

24. O’Hara CB, Campbell IC, Schmitz U. A reward-centred model of anorexia nervosa: A focussed narrative review of the neurological and psychophysiological literature. Neurosci Biobehav Rev. 2015; 52:131–62. Epub 2015/03/05. doi: 10.1016/j.neubiorev.2015.02.012 PMID: 25735957.

25. Oberndorfer TA, Kaye WH, Simmons AN, Strigo IA, Matthews SC. Demand-specific alteration of medial prefrontal cortex response during an inhibition task in recovered anorexic women. International Journal of Eating Disorders. 2011; 44(1):1–8. Epub 2010/02/04. doi: 10.1002/eat.20750 PMID: 21272942.

26. Wierenga C, Bischoff-Grethe A, Grenesko-Stevens E, Wagner A, et al. Altered BOLD response during inhibitory and error processing in adolescents with anorexia nervosa. PloS one. 2014; 9(3):e92017. Epub 2014/03/22. doi: 10.1371/journal.pone.0092017 PMID: 24651705; PubMed Central PMCID: PMC3961291.

27. Sato Y, Saito N, Utsumi A, Aizawa E, Izumiyama M, et al. Neural basis of impaired cognitive flexibility in patients with anorexia nervosa. PloS one. 2013; 8(5):e61108. Epub 2013/05/16. doi: 10.1371/journal.pone.0061108 PMID: 23675408; PubMed Central PMCID: PMC3651087.

28. Monsell S. Task switching. Trends in cognitive sciences. 2003; 7(3):134–7. doi: 10.1016/S1364-6613(03)00028-7 PMID: 12639695.

29. Gaynes BN, Lloyd SW, Lux L, Gartlehner G, Hansen RA, Brode S, et al. Repetitive transcranial magnetic stimulation for treatment-resistant depression: a systematic review and meta-analysis. J Clin Psychiatry. 2014; 75(5):477–89. Epub 2014/06/13. doi: 10.4088/JCP.13r08815 PMID: 24922485.

30. Barr MS, Farzan F, Wing VC, George TP, Fitzgerald PB, Daskalakis ZJ. Repetitive transcranial magnetic stimulation and drug addiction. International Review of Psychiatry. 2011; 23(5):454–66. Epub 2011/12/28. doi: 10.3109/09540261.2011.618827 PMID: 22200135.

31. Grall-Bronnec M, Sauvaget A. The use of repetitive transcranial magnetic stimulation for modulating craving and addictive behaviours: a critical literature review of efficacy, technical and methodological considerations. Neurosci Biobehav Rev. 2014; 47:592–613. Epub 2014/12/03. doi: 10.1016/j.neubiorev.2014.10.013 PMID: 25454360.

32. Gorenlick DA, Zangen A, George MS. Transcranial magnetic stimulation in the treatment of substance addiction. Ann N Y Acad Sci. 2014; 1327:79–93. Epub 2014/07/30. doi: 10.1111/nyas.12479 PMID: 25069523; PubMed Central PMCID: PMC4206564.

33. Jansen JM, Daams JG, Koeter MW, Veltman DJ, van den Brink W, Goudriaan AE. Effects of non-invasive neurostimulation on craving: a meta-analysis. Neurosci Biobehav Rev. 2013; 37(10 Pt 2):2472–80. Epub 2013/08/07. doi: 10.1016/j.neubiorev.2013.07.009 PMID: 23916527.

34. Uher R, Yoganathan D, Mogg A, Eranti SV, Treasure J, Campbell IC, et al. Effect of left prefrontal repetitive transcranial magnetic stimulation on food craving. Biol Psychiatry. 2005; 58(10):840–2. doi: 10.1016/j.biopsych.2005.05.043 PMID: 16084855.

35. Van den Eynde F, Claudino AM, Mogg A, Horrell L, Stahl D, Ribeiro W, et al. Repetitive transcranial magnetic stimulation reduces cue-induced food craving in bulimic disorders. Biol Psychiatry. 2010; 67(8):793–5. doi: 10.1016/j.biopsych.2009.11.023 PMID: 20060105.

36. Barth KS, Rydin-Gray S, Kose S, Borckardt JJ, O'Neil PM, Shaw D, et al. Food cravings and the effects of left prefrontal repetitive transcranial magnetic stimulation using an improved sham condition.
Kekic M, McClelland J, Campbell I, Nestler S, Rubia K, David AS, et al. The effects of prefrontal cortex
Cho SS, Strafella AP. rTMS of the left dorsolateral prefrontal cortex modulates dopamine release in the
Ridding MC, Rothwell JC. Is there a future for therapeutic use of transcranial magnetic stimulation?
Zanardini R, Gazzoli A, Ventriglia M, Perez J, Bignotti S, Rossini PM, et al. Effect of repetitive transcra-
Baeken C, De Raedt R, Bossuyt A, Van Hove C, Mertens J, Dobbeleir A, et al. The impact of HF-rTMS
treatment on serotonin(2A) receptors in unipolar melancholic depression. Brain Stimulation. 2011; 4
Kamolz S, Richter MM, Schmidtkle A, Fallgatter AJ. Transcranial magnetic stimulation for comorbid
depression in anorexia. Nervenarzt. 2008; 79(9):1071–3. doi: 10.1007/s00115-008-2537-8
WOS:000259157700009. PMID: 18661116
McClelland J, Bozhilova N, Nestler S, Campbell IC, Jacob S, Johnson-Sabine E, et al. Improvements in
McClelland J, Kekic M, Campbell IC, Schmidt U. Repetitive Transcranial Magnetic Stimulation (rTMS)
Ochsner KN, Gross JJ. The neural architecture of emotion regulation. Handbook of emotion regulation.
Kaye W. Neurobiology of anorexia and bulimia nervosa. Physiology and Behaviour. 2008; 94(1):121–35,
Epub 2008/01/01. doi: 10.1016/j.physbeh.2007.11.037 PMID: 18164737; PubMed Central PMCID:
PMCID: PMC2601682.
Gersner R, Kravetz E, Feil J, Pell G, Zangen A. Long-term effects of repetitive transcranial magnetic
Journal of Neuroscience. 2011; 31(20):7521–6. Epub 2011/05/20. doi: 10.1523/jneurosci.6751-10.
2011 PMID: 21593336.
Medina FJ, Tunez I. Mechanisms and pathways underlying the therapeutic effect of transcranial
magnetic stimulation. Rev Neurosci. 2013; 24(5):507–25. doi: 10.1515/revenuro-2013-0024 PMID:
24077617.
Ridding MC, Rothwell JC. Is there a future for therapeutic use of transcranial magnetic stimulation?
Nature Reviews Neuroscience. 2007; 8(7):559–67. PMID: 17565358.
Zanardini R, Gazzoli A, Ventriglia M, Perez J, Bignotti S, Rossini PM, et al. Effect of repetitive transcranial
magnetic stimulation on serum brain derived neurotrophic factor in drug resistant depressed
patients. Journal of Affective Disorders. 2006; 91(1):83–6. Epub 2006/02/02. doi: 10.1016/j.jad.2005.12.028. PMID: 16448701.
Cho SS, Strafella AP. rTMS of the left dorsolateral prefrontal cortex modulates dopamine release in the
ipsilateral anterior cingulate cortex and orbitofrontal cortex. PLoS one. 2008; 3(6):e6725. doi: 10.1371/journal.pone.0006725 PMID: 19696930.
Baeken C, De Raedt R, Bossuyt A, Van Hove C, Mertens J, Dobbeleir A, et al. The impact of HF-rTMS
treatment on serotonin(2A) receptors in unipolar melancholic depression. Brain Stimulation. 2011; 4
(2):104–11. Epub 2011/04/23. doi: 10.1016/j.brs.2010.09.002 PMID: 21511211.
Kecic M, McClelland J, Campbell I, Nestler S, Rubia K, David AS, et al. The effects of prefrontal cortex
transcranial direct current stimulation (tDCS) on food craving and temporal discounting in women with
frequent food cravings. Appetite. 2014; 78:55–62. doi: 10.1016/j.appet.2014.03.010 PMID: 24656950.
Wang XT, Dvorak RD. Sweet future: fluctuating blood glucose levels affect future discounting. Psychol Sci. 2010; 21(2):183–8. Epub 2010/04/29. doi: 10.1177/0956797609358096 PMID: 20420442.
63. Lawson EA, Holsen LM, Desanti R, Santin M, Meenaghan E, Herzog DB, et al. Increased hypothalamic-pituitary-adrenal drive is associated with decreased appetite and hypoactivation of food-motivation neurocircuitry in anorexia nervosa. Eur J Endocrinol. 2013; 169(5):639–47. Epub 2013/08/16. doi: 10.1530/eje-13-0433 PMID: 23946275; PubMed Central PMCID: PMCPmc3807591.

64. Connan F, Lightman SL, Landau S, Wheeler M, Treasure J, Campbell IC. An investigation of hypothalamic-pituitary-adrenal axis hyperactivity in anorexia nervosa: the role of CRH and AVP. Journal of Psychosomatic Research. 2007; 41(6):1329–34. Epub 2007/06/14. doi: 10.1016/j.jpsychores.2007.01.009 PMID: 17513082; PubMed Central PMCID: PMCPmc1857133.

65. Sheffer CE, Mennemeier M, Landes RD, Bickel WK, Brackman S, Dornhoffer J, et al. Neuromodulation of delay discounting, the reflection effect, and cigarette consumption. J Subst Abuse Treat. 2013; 45(2):206–14. Epub 2013/03/23. doi: 10.1016/j.jsat.2013.01.012 PMID: 23518286; PubMed Central PMCID: PMCPmc3690153.

66. Cho SS, Koshimori Y, Aminian K, Obeso I, Rusjan P, Lang AE, et al. Investing in the Future: Stimulation of the Medial Prefrontal Cortex Reduces Discounting of Delayed Rewards. Neuropsychopharmacology. 2014; 2014. Epub ahead of print. Epub 2014/08/08. doi: 10.1038/npp.2014.211 PMID: 25168685.

67. Decker JH, Figner B, Knoch D, Johnson EJ, Krosch AR, Lisanby SH, Fehr E, et al. Lateral prefrontal cortex and delay discounting. Biological psychiatry. 2014; 75(6):435–40. Epub 2014/06/04. doi: 10.1016/j.biopsych.2013.10.007 PMID: 25216073; PubMed Central PMCID: PMCPmc4359668.

68. Wesley MJ, Bickel WK. Remember the future II: meta-analyses and functional overlap of working memory and delay discounting. Biological psychiatry. 2014; 75(6):435–48. Epub 2013/09/18. doi: 10.1016/j.biopsych.2013.08.008 PMID: 24041504; PubMed Central PMCID: PMCPmc3943930.

69. Figner B, Knoch D, Johnson EJ, Krosch AR, Lisanby SH, Fehr E, et al. Lateral prefrontal cortex and self-control in intertemporal choice. Nat Neurosci. 2010; 13(5):538–9. doi: 10.1038/nn.2516 PMID: 20346919.

70. Steinglass JE, Berkowitz S, Simpson HB, Weber EU, Walsh BT. Increased capacity to delay reward in women remitted from anorexia nervosa. Biological psychiatry. 2015; 77(7):642–52. Epub 2014/12/08. doi: 10.1016/j.biopsych.2014.09.024 PMID: 25481622; PubMed Central PMCID: PMCPmc4359668.

71. Wesemann CE, Bischoff-Grethe A, Melrose AJ, Irvine Z, Torres L, Bailer UF, et al. Hunger does not motivate reward in women remitted from anorexia nervosa. Biological psychiatry. 2015; 77(7):642–52. Epub 2014/12/08. doi: 10.1016/j.biopsych.2014.09.024 PMID: 25481622; PubMed Central PMCID: PMCPmc4359668.
73. Fitzgerald, Hoy K, McQueen S, Maller JJ, Herring S, Segrave R, et al. A randomized trial of rTMS targeted with MRI based neuro-navigation in treatment-resistant depression. Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology. 2009; 34(5):1255–62. doi:10.1038/npp.2008.233 PMID: 19145228.

74. Fairburn CG. Eating Disorder Examination (Edition 16.0D) and Eating Disorder Examination Questionnaire (EDE-Q 6.0). Cognitive therapy and eating disorders. New York, USA: Guilford Press; 2009. p. 265.

75. Lovibond PF, Lovibond SH. Manual for the Depression Anxiety and Stress Scale (2nd. Ed.). Sydney: Psychology Foundation; 1995.

76. Rossini PM, Barker AT, Berardelli A, Caramia MD, Caruso G, Cracco RQ, et al. Non-invasive electrical and magnetic stimulation of the brain, spinal cord and roots: basic principles and procedures for routine clinical application. Report of an IFCN committee. Electroencephalogr Clin Neurophysiol. 1994; 91(2):79–92. Epub 1994/08/01. PMID: 7519144.

77. Rothwell JC, Hallett M, Berardelli A, Eisen A, Rossini P, Paulus W. Magnetic stimulation: motor evoked potentials. The International Federation of Clinical Neurophysiology. Electroencephalogr Clin Neurophysiol Suppl. 1999; 52:97–103. Epub 1999/12/11. PMID: 10590980.

78. Rubia K, Halari R, Christakou A, Taylor E. Impulsiveness as a timing disturbance: neurocognitive abnormalities in attention-deficit hyperactivity disorder during temporal processes and normalization with methylphenidate. Philosophical transactions of the Royal Society of London Series B, Biological sciences. 2009; 364(1525):1919–31. doi:10.1098/rstb.2009.0014 PMID: 19487194; PubMed Central PMCID: PMC2685816.

79. Christakou A, Brammer M, Rubia K. Maturation of limbic corticostriatal activation and connectivity associated with developmental changes in temporal discounting. NeuroImage. 2011; 54(2):1344–54. doi:10.1016/j.neuroimage.2010.08.067 PMID: 20816974.

80. Myerson J, Green L, Warusawitharana M. Area under the curve as a measure of discounting. J Exp Anal Behav. 2001; 76(2):235–43. Epub 2001/10/16. doi:10.1901/jeab.2001.76-235 PMID: 11599641; PubMed Central PMCID: PMCPmc1284836.

81. Kudielka BM, Hellhammer DH, Wust S. Why do we respond so differently? Reviewing determinants of human salivary cortisol responses to challenge. Psychoneuroendocrinology. 2011; 36(2):18–26. doi:10.1016/j.psyneuen.2010.11.004 PMID: 21187194; PubMed Central PMCID: PMC2685816.

82. Godier LR, Park RJ. Compulsivity in anorexia nervosa: a transdiagnostic concept. Front Psychol. 2014; 5:777. Epub 2014/08/08. doi: 10.3389/fpsyg.2014.00778 PMID: 25101036; PubMed Central PMCID: PMCPmc4101893.

83. Bartholdy S, McClelland J, Kekic M, O’Daly OG, Campbell IC, Werthmann J, et al. Clinical outcomes and neural correlates of 20 sessions of repetitive transcranial magnetic stimulation in severe and enduring anorexia nervosa (the TIARA study): study protocol for a randomised controlled feasibility trial. Trials. 2015; 16(1):1–13.