Journal of Affective Disorders 321 (2023) 182–190

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Cognitive-affective processes and suicidality in response to repetitive transcranial magnetic stimulation for treatment resistant depression

Alex R. Terpstra [a,*], Fidel Vila-Rodriguez [b,c], Joelle LeMoult [a], Trisha Chakrabarty [d], Medha Nair [a], Afifa Humaira [b], Elizabeth C. Gregory [b], Rebecca M. Todd [a,c]

[a] Department of Psychology, The University of British Columbia, Vancouver, BC, Canada
[b] Non-Invasive Neurostimulation Therapies (NINET) Laboratory, Department of Psychiatry, The University of British Columbia, Vancouver, BC, Canada
[c] Djavad Mowafaghian Centre for Brain Health, The University of British Columbia, Vancouver, BC, Canada
[d] Department of Psychiatry, The University of British Columbia, Vancouver, BC, Canada

ARTICLE INFO

Keywords:
Treatment resistant depression
Repetitive transcranial magnetic stimulation
Suicidality
Reward sensitivity
Self-referential processing

ABSTRACT

Background: Repetitive transcranial magnetic stimulation (rTMS) can elicit 45–55 % response rates and may alleviate suicidality symptoms in treatment resistant depression (TRD). Blunted anticipatory reward sensitivity and negatively biased self-referential processing may predict trajectories of depressive and suicidality symptoms in rTMS for TRD and be modulated during treatment.

Methods: Fifty-five individuals with TRD received four weeks of low-frequency rTMS applied to the right dorsolateral prefrontal cortex (LFR-rTMS) and were followed until 17 weeks post-baseline. Participants completed behavioral measures of anticipatory reward sensitivity and self-referential processing at baseline and five weeks post-baseline (approximately one-week post-treatment). We examined whether baseline anticipatory reward sensitivity and self-referential processing predicted trajectories of depressive and suicidality symptoms from baseline to follow-up and whether these cognitive-affective variables showed change from baseline to week five.

Results: Anticipatory reward sensitivity and negative self-referential encoding at baseline were associated with higher overall depressive symptoms and suicidality from baseline to 17 weeks post-baseline. At week five, participants self-attributed a higher number of positive traits and a lower number of negative traits and had a lesser tendency to remember negative relative to positive traits they had self-attributed, compared to baseline.

Limitations: The specificity of these results to LFR-rTMS is unknown in the absence of a comparison group, and our relatively small sample size precluded the interpretation of null results.

Conclusions: Baseline blunted anticipatory reward sensitivity and negative biases in self-referential processing may be risk factors for higher depressive symptoms and suicidality during and after LFR-rTMS, and LFR-rTMS may modulate self-referential processing.

1. Introduction

Fewer than half of individuals diagnosed with Major Depressive Disorder (MDD) will recover after their first treatment (Connolly and Thase, 2011; Holtzheimer and Mayberg, 2011). Furthermore, 20–30 % of individuals with MDD suffer from treatment-resistant depression (TRD), defined as failure to respond to one or more adequate trials of antidepressant medication treatment (Rizvi et al., 2014; Trevino et al., 2014; Zhdanava et al., 2021). Repetitive transcranial magnetic stimulation (rTMS), which involves repeated stimulation of the cortex using a magnetic coil, typically targeting dorsolateral prefrontal cortex (DLPFC; Brunoni et al., 2017), is a safe and non-invasive first-line treatment for TRD that demonstrates 45–55 % response rates (Chen et al., 2013; Milev et al., 2016). Stimulation with rTMS not only activates DLPFC neurons locally but also propagates through functional pathways to influence more distant regions and can alleviate mood and anxiety symptoms (Eshel et al., 2020; Ge et al., 2020; Ge et al., 2022; Li et al., 2004). Importantly, suicidality is highly prevalent among individuals with TRD (Bergfeld et al., 2018), and there is preliminary evidence suggesting that rTMS may alleviate suicidality symptoms, although findings are mixed

* Corresponding author at: Department of Psychology, University of British Columbia, 2136 West Mall, Vancouver, BC V6T 1Z4, Canada.
E-mail address: alexander.terpstra@psych.ubc.ca (A.R. Terpstra).

https://doi.org/10.1016/j.jad.2022.10.041
Received 4 September 2022; Received in revised form 19 October 2022; Accepted 22 October 2022
Available online 28 October 2022

(Bozzay et al., 2020; Chen et al., 2022; Cui et al., 2021; Mehta et al., 2022a; Mehta et al., 2022b; Weissman et al., 2018).

Challenges assigning appropriate treatments for individuals with MDD has prompted research examining cognitive-affective processes altered by various depression treatments as well as clinical, behavioral, and neuroimaging predictors of response. Relevant research to date has focused primarily on pharmacological and psychological interventions (Clark et al., 2009; Harmer et al., 2017; Holmes et al., 2018; Roiser et al., 2012), but there is a growing need for predictors of response to rTMS and a greater understanding of the specific cognitive-affective processes it may modulate.

MDD is associated with important differences in cognitive-affective processes, such as blunted anticipatory reward sensitivity, referring to the tendency to experience approach motivation in response to potentially rewarding stimuli, situations, and events (Husain and Roiser, 2018). In addition, there is aberrance in self-referential processing, a broad construct capturing cognitive processes involving evaluations of the self and predominantly studied in terms of self-referential encoding (the tendency to attribute positive or negative characteristics to oneself) and self-referential memory bias (the tendency to recall characteristics about oneself that are either positive or negative), both found to be negatively biased in MDD (Dainer-Best et al., 2018; Northoff et al., 2006). These cognitive-affective processes are also associated with suicidality (Bulteau et al., 2021; Hutchinson et al., 2021; Stewart et al., 2019; Tsypes et al., 2019, 2021). Both blunted anticipatory reward sensitivity and negatively biased self-referential processing not only change in response to pharmacological and psychological interventions, but have also been useful in predicting changes in depressive symptoms (Allen et al., 2019; Burkhouse et al., 2016; Dichter et al., 2009; Dunlop et al., 2020; Fisher et al., 2022; Whitton et al., 2020). However, little is known about cognitive-affective changes associated with rTMS or whether individual differences in cognitive-affective processing prior to LFR-rTMS may be associated with changes in depressive and suicidality symptoms in response to treatment.

Limited research to date suggests that low-frequency rTMS, which is thought to have an inhibitory effect on cortical excitability (Riedel et al., 2019; Watanabe et al., 2014), may alter reward sensitivity and self-referential processing in healthy individuals. Non-clinical studies have shown changes in reward-related valuations and decision making following a single session of low-frequency rTMS applied to the right DLPFC (LFR-rTMS; Camus et al., 2009; Tulviste and Bachmann, 2019). There is also evidence suggesting low-frequency rTMS applied to the medial prefrontal cortex may alter processing of negative personality attributes (De Pisapia et al., 2019). However, no previous studies have examined how low-frequency rTMS may influence reward sensitivity and self-referential processing in MDD, despite the fact that LFR-rTMS has good evidence of treatment efficacy for TRD (Miron et al., 2020).

To address these gaps, the objectives of this study were to examine in a sample of participants with TRD who received a course of LFR-rTMS whether (1) baseline anticipatory reward sensitivity and self-referential processing was associated with trajectories of depressive and suicidality symptom change over the course of treatment and up to 17 weeks post-baseline and (2) anticipatory reward sensitivity and self-referential processing changed from baseline to five weeks post baseline (approximately one week post-treatment). While we consider the research questions addressed in this study exploratory given the limited related research to date, we formulated tentative hypotheses based on existing literature. Informed by previous findings that blunted reward sensitivity and negatively biased self-referential processing may be associated with trajectories of depressive and suicidality symptoms, we hypothesized that these cognitive-affective processes at baseline would also be associated with changes in depressive and suicidality symptoms in response to LFR-rTMS. We also predicted that anticipatory reward sensitivity would increase and negative biases in self-referential processing would decrease from baseline to week five, particularly for treatment responders (defined as a $\geq$ 50 % decrease in depressive symptoms at five weeks compared to baseline), consistent with research showing changes in these cognitive-affective processes in response to psychological and pharmacological treatments for depression.

2. Methods

2.1. Participants and procedures

This study was part of an open-label clinical trial of LFR-rTMS in TRD (NCT03642522) approved by the University of British Columbia and Vancouver Coastal Health Research Institute Clinical Research Ethics Boards. Participants were adult psychiatric outpatients recruited from November 1, 2018, to March 30, 2020, in British Columbia, Canada. Eligible participants had a Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 1998) confirmed diagnosis of MDD and were in an acute depressive episode at study enrollment (defined as a score of 22 or greater on the Inventory of Depressive Symptomatology; Rush et al., 1986), were between 18 and 80 years old, and had a history of treatment-resistance to antidepressant medication (i.e., had failed to achieve a clinical response to at least one adequate dose of an antidepressant based on an Antidepressant Treatment History Form [ATHF; Oquendo et al., 2003] score of $\geq$3 in the current episode or had been unable to tolerate at least two separate trials of antidepressants of inadequate dose and duration [ATHF 1 or 2]). Exclusion criteria were major medical comorbidities, a psychiatric diagnosis causing greater impairment than MDD, alcohol and substance dependence or abuse within the three months prior to recruitment, active suicidal intent, and prescribed anticonvulsants or high-dose benzodiazepines. Written informed consent was obtained from all participants. The Supplementary Material includes additional details regarding inclusion and exclusion criteria.

Computer-based behavioral tasks were administered at baseline and five weeks post-baseline to measure anticipatory reward sensitivity and self-referential processing. Of 73 patients screened, 55 were eligible and enrolled in the study. All participants completed the behavioral tasks at baseline and 48 at baseline and week five. Of the seven participants who did not complete the tasks at week five, three participants withdrew from the study, three missed their week five assessment, and one completed the week five assessment online due to in-person visit restrictions associated with the COVID-19 pandemic.

2.2. Repetitive transcranial magnetic stimulation treatment

Participants underwent low-frequency (1 Hz) rTMS applied to the right DLPFC for 30 min five days per week for four weeks. The right DLPFC was localized using an MRI-guided Neuronavigation system (Visor 2.0, ANT Neuro, Enschede, Netherlands) based on Montreal Neurological Institute coordinates (x = 36; y = 44; z = 26). rTMS was delivered at 120 % RMT for a total of 1800 pulses per 30-min session.

2.3. Measures

2.3.1. Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998)

The MINI is a clinician-administered structured diagnostic interview that assesses for current and past neuropsychiatric disorders based on DSM-IV criteria. In this study, the MINI was used to determine eligibility. We also report frequencies of recurrent MDD diagnoses and any co-morbid anxiety disorder (i.e., Panic Disorder, Social Anxiety Disorder, Agoraphobia, or Generalized Anxiety Disorder). The MINI was designed as a brief and highly sensitive measure of common neuropsychiatric disorders compatible with both the DSM-IV and International Classification of Diseases (ICD-10) suitable for use in clinical and research settings (Sheehan et al., 1998). The validity and reliability of the MINI as a diagnostic screening tool have been established (Sheehan et al., 1998; Sheehan et al., 1997).

2.3.2. Montgomery-Åsberg Depression Rating Scale (MADRS; Montgomery and Åsberg, 1977)

The MADRS is a 10-item clinician-rated scale measuring depressive symptoms. Symptoms assessed include 'apparent sadness', 'reported sadness', 'inner tension', 'reduced sleep', 'reduced appetite', 'concentration difficulties', 'lassitude', 'inability to feel', 'pessimistic thoughts', and 'suicidal thoughts.' Items are rated as 0, 2, 4, or 6 based on severity. The MADRS has demonstrated excellent internal consistency, construct validity, and convergent validity (Carmody et al., 2006; Müller et al., 2003). Treatment response was defined as ≥50 % reduction in MADRS score, and non-response as a < 50 % reduction in MADRS score, from baseline to week five. In the current study, the MADRS was administered at baseline and weeks 2, 4, 5, 9, and 17.

2.3.3. Concise Health Risk Tracking (CHRT; Trivedi et al., 2011)

The CHRT scale is a 14-item measure of suicidality with three subscales: suicide propensity (e.g., "I feel that there is no reason to live"), impulsivity (e.g., "I find myself saying or doing things without thinking"), and suicide risk (e.g., "I have a plan to kill myself"). The internal consistency of the total and subscale scores have been found to be good to excellent and its construct validity and sensitivity to change have also been established (Mayes et al., 2018). In this study, the CHRT was administered at baseline as well as weeks 2, 4, 5, and 17.

2.3.4. Behavioral tasks

2.3.4.1. Monetary incentive delay (MID) task. We administered a behavioral MID task to measure anticipatory reward sensitivity. This measure was chosen because anticipation of potential financial reward can invoke incentive reward motivation, i.e., reward 'wanting' (Novak and Foti, 2015), shown to be blunted in MDD (Whitton et al., 2015). The task included eight rounds (i.e., trials) during which participants were presented with a cue and instructed to respond as quickly as possible to win between 1 and 4 tickets towards a $100 prize draw. Outcomes were fixed, such that all participants won every time when playing for one or two tickets, half the time when playing for three tickets, and not at all when playing for four tickets. At the beginning of each round, participants were presented with the number of tickets they were playing for and were subsequently prompted to rate on a scale from 0 to 100, "How excited do you feel?". After each round, they were asked to rate how excited, disappointed, and frustrated they felt, also on a scale from 0 to 100.[1] For the current study, only anticipatory reward sensitivity, measured as the average of participants' excitement ratings made before each round, was used in our analyses, based on the well-established association between blunted anticipatory reward sensitivity and depressive symptoms (Rizvi et al., 2016; Sherdell et al., 2012). We previously examined the construct validity and test-retest reliability of a nearly identical task. In a non-clinical sample of 438 undergraduate students, average anticipatory excitement ratings were significantly associated with self-reported approach motivation ($r = 0.22$) on the Behavioral Activation Scale (Carver and White, 1994), anhedonia symptoms ($r = 0.18$) on the Dimensional Anhedonia Rating Scale (Rizvi et al., 2015), and hypomania symptoms ($r = 0.15$) on the Hypomania Symptoms Checklist-32 (Angst et al., 2005). In a separate non-clinical sample of undergraduate participants who completed the task at baseline, 24 h, and one week, the measure was found to have good test-retest reliability after 24 h ($n = 30$, $ICC_{2,1} = 0.87$) and one week ($n = 25$, $ICC_{2,1} = 0.86$). A detailed description and schematic of the MID task are included in the Supplementary Material (Supplementary Fig. S1).

2.3.4.2. Self-referential encoding and memory task (SRET). The SRET is a computer-based task in which participants were presented with a series of personal attributes (e.g., 'attractive', 'lazy') and asked to indicate whether each of the words described them (yes or no response to, 'Describes me?'). After the task, participants were spontaneously asked to recall as many words as they could remember from the task. The SRET has been used in numerous studies to capture emotional biases in the encoding and memory of information attributed to the self in depression (Dainer-Best et al., 2018; Dainer-Best et al., 2017). Three variables were derived from the task: positive self-referential encoding, negative self-referential encoding, and negative self-referential memory bias. Positive and negative self-referential encoding were operationalized as the total number of positive or negative words that participants indicated as describing them, respectively. Negative self-referential memory bias was calculated as the number of negative traits endorsed and recalled divided by the total number of traits endorsed and recalled, resulting in a proportion ranging from 0 (none of the negative traits the participant endorsed were recalled) to 1 (only negative traits that the participant endorsed were recalled). A schematic of the SRET is presented in the Supplementary Material (Supplementary Fig. S2).

2.4. Data analysis

Data analyses were performed using IBM SPSS Version 28 and R 4.2.1 (Bates et al., 2014; Makowski, 2018; R Core Team, 2022) through RStudio (RStudio Team, 2022). For all analyses, an alpha of 0.05 (two-tailed) was employed. We did not control for multiple comparisons with the implication that the results of our study are hypothesis-generating and will require further investigation and replication.

We calculated descriptive statistics for baseline demographic and clinical characteristics of the total sample and treatment response status subgroups. We also compared the treatment response subgroups' demographic and clinical characteristics using independent-samples *t*-tests and chi-square analyses and examined the correlation between age and CHRT scores to assess for age-related differences in suicidality levels. Our first research question explored whether baseline anticipatory reward sensitivity and self-referential processing scores were associated with trajectories of depressive and suicidality symptoms from baseline to week 17. Here we used repeated-measures linear mixed models (LMMs) to examine whether baseline reward sensitivity and self-referential processing scores were significant predictors of overall MADRS and CHRT scores as well as their change trajectories from baseline to follow-up. LMMs were used to allow for modeling the random effects of subject-baseline scores, correlations between time points, unevenly spaced measurement periods, potential non-linear change in symptoms across time, and sporadically missing data. Measurement periods included baseline and weeks 2, 4, 5, 9, and 17 for the MADRS, and baseline plus weeks 2, 4, 5, and 17 for the CHRT scale. To assess for systematic differences between participants with complete vs. incomplete MADRS and CHRT data, we compared their baseline demographic and clinical characteristics. Maximum likelihood estimation was used to handle sporadically missing MADRS and CHRT data and to allow for model comparisons.

We tested unconditional mean models to examine whether there were inter-individual differences in grand mean MADRS, CHRT total, and CHRT subscale scores, unconditional linear and quadratic growth models incorporating only subject intercepts as a random effect, unconditional linear or quadratic growth models incorporating intercepts and slopes as random effects, and models incorporating cognitive-affective predictors and their interactions with time as fixed effects. These included separate models for baseline anticipatory reward sensitivity, positive self-referential encoding, negative self-referential encoding, and negative self-referential memory bias. Cognitive-

[1] Note that for the majority of task administrations, the anticipatory excitement rating scale was labelled 0 'Neutral' to 100 'Very excited'. However, for some administrations, the scale was labelled 0 'Not at all excited' to 100 'Very excited'. We compared ratings depending on the anchor label used ('Neutral' or 'Not at all excited') and there were no significant differences (Supplementary Table S1).

affective predictors were converted to z-scores for these analyses to aid in the interpretation of results and facilitate model convergence (Meteyard and Davies, 2020). A first-order autoregressive covariance structure with heterogeneous variances was specified for all models as correlations in symptom scores between time points were expected to be higher for adjacent time points than for those further apart. In cases of non-convergence or if the final Hessian matrix was not positive definite, a first-order autoregressive covariance structure without heterogeneous variances was used to reduce the number of parameters being estimated. A scaled identity covariance structure was specified for the estimation of random effects when only subjects were included as a random effect. For models with additional random effects, an unstructured covariance was specified. Model comparisons were carried out using Likelihood Ratio Tests. Marginal and conditional R^2 were computed for the final models. Marginal R^2 provides an estimate of the variance in the outcome variable accounted for by the fixed effects alone, whereas conditional R^2 provides an estimate of the variance accounted for by fixed and random effects included in the model (Nakagawa et al., 2017; Nakagawa and Schielzeth, 2013). Therefore, marginal R^2 can be used to estimate differences in the proportion of variance explained depending on the predictors included in a model as fixed effects.

To address our second research question, we examined whether anticipatory reward sensitivity and self-referential processing changed from baseline to week five. We ran repeated measures analyses of variance (ANOVAs) examining the main effect of time (baseline vs. week five) and a time × treatment response status (responders vs. non-responders) interaction effect in separate models including average anticipatory excitement ratings during the MID task, numbers of positive and negative traits endorsed, and negative self-referential memory bias as dependent variables. We included treatment response status as a factor to assess whether changes in cognitive-affective variable scores corresponded to whether participants responded to treatment.

3. Results

Demographic and clinical characteristics for the total sample and treatment response status subgroups are presented in Table 1. Results of independent samples *t*-tests and Chi-square analyses showed that treatment responders did not differ significantly from non-responders in age, education, or MADRS scores at baseline compared to non-responders (all *p* values >.05). The non-responder subgroup had a significantly greater proportion of females ($X^2[1, N = 47] = 5.23$, $p = .022$), participants with recurrent MDD ($X^2[1, N = 47] = 3.94$, $p = .047$), and benzodiazepine use ($X^2[1, N = 47] = 6.52$, $p = .011$), as well as higher baseline CHRT total scores ($t[45] = 2.28$, $p = .028$) compared to the responder subgroup. (See Supplementary Tables S2 and S3 in for results of the subgroup comparisons.) Age and CHRT scores at baseline were not significantly correlated, $r(53) = 0.01$, $p = .950$. Cognitive-affective variable scores for the total sample and treatment response status subgroups are presented in Table 2.

3.1. Cognitive-affective predictors of depressive symptom score trajectories

We conducted repeated-measures LMMs to examine baseline predictors of MADRS score trajectories from baseline to weeks 2, 4, 5, 9, and 17. All 55 participants were included in the LMMs except those used to examine self-referential memory bias as a potential significant predictor, which included only the 51 participants with a self-referential memory bias score at baseline. Of the 55 participants, 39 had MADRS scores at all six time points. Baseline demographic and clinical characteristics did not differ between participants with complete vs. incomplete MADRS data (Supplementary Table S4).

We first tested an unconditional mean model to determine whether there was significant variability in overall MADRS scores between participants, followed by models examining linear and quadratic growth trajectories from baseline to weeks 2, 4, 5, 9, and 17, and finally models that included the predictor variables of interest (main effects and interactions with linear and/or quadratic time variables; see Supplementary Tables S6 and S7). In an unconditional growth curve model including linear and quadratic time variables as fixed effects, the mean estimated initial MADRS score for the sample was 29.00 (95 % CI = 26.57, 31.43) and decreased significantly from baseline to week 17 ($\beta = -2.18$, SE = 0.28, $p < .001$). The quadratic time variable was statistically significant ($\beta = 0.09$, SE = 0.01, $p < .001$), suggesting that decreases in MADRS scores became less rapid with time. The model including linear and quadratic time variables as fixed effects and participant intercepts as a random effect had a marginal R^2 value of 0.15.

Subsequent models included baseline anticipatory reward sensitivity, number of positive and negative words endorsed, and negative self-referential memory bias as fixed effects, followed by models incorporating interactions between time and the predictors of interest as fixed effects. Results of the final models revealed that lower average anticipatory excitement ratings ($\beta = -1.96$, SE = 0.94, $p = .042$; marginal $R^2 = 0.19$), and a higher number of negative traits endorsed ($\beta = 2.24$, SE = 0.95, $p = .021$; marginal $R^2 = 0.19$), at baseline were associated with

Table 1
Sample characteristics.

	N	Total Sample	n	Responders[a]	n	Non-Responders
Age *M* (SD), Range	55	42.4 (15.5), 19–78	20	43.7 (14.1), 22–71	27	41.7 (17.5), 19–78
Years of Education *M* (SD), Range	55	15.4 (2.2), 10–20	20	15.5 (2.4), 10–20	27	15.3 (2.0), 12–20
n Female (%)	55	39 (71 %)	20	11 (55 %)	27	23 (85 %)
Baseline Body Mass Index *M* (SD), Range	53	27.0 (7.3), 18.4–53.6	20	28.2 (8.1), 19.4–48.0	25	26.7 (7.4), 18.4–53.6
n Taking Antidepressant Medication (%)	55	47 (86 %)	20	16 (80 %)	27	24 (89 %)
Escitalopram-Equivalent Dose (mg) *M* (SD), Range	55	23.3 (20.3), 0–80	20	20.9 (17.0), 0–50	27	26.2 (23.0), 0–80
n Recurrent Major Depressive Disorder (%)	55	35 (64 %)	20	16 (80 %)	27	14 (52 %)
n Comorbid Anxiety Disorder (%)	55	22 (40 %)	20	5 (25 %)	27	14 (52 %)
MADRS[b]						
Baseline *M* (SD), Range	54	29.9 (6.3), 18–45	20	29.9 (5.7), 18–39	27	29.4 (7.1), 19–45
Week 5 *M* (SD), Range	48	19.7 (10.9), 2–40	20	9.8 (3.9), 2–17	27	26.5 (8.4), 12–40
CHRT						
Baseline *M* (SD), Range	55	28.8 (8.5), 9–48	20	25.4 (7.2), 9–40	27	30.8 (8.6), 14–48
Week 5 *M* (SD), Range	48	19.8 (10.6), 0–42	15	14.2 (9.4), 0–40	27	22.5 (9.9), 6–42

Note. M, mean; SD, standard deviation; MADRS, Montgomery Äsberg Depression Rating Scale; CHRT, Concise Health Risk Tracking Scale.

[a] Treatment response was defined as a ≥ 50 % reduction in MADRS score from baseline to week five.

[b] Forty-seven participants had MADRS data at both baseline and week five (of eight participants without treatment response status data, seven had MADRS scores at baseline only and one had a MADRS score at week five only).

Table 2
Cognitive-affective variable scores at baseline and week five for the total sample and treatment response status subgroups.

	N	Total Sample	n	Responders[a]	n	Non-Responders
Average Anticipatory Excitement Rating						
Baseline *M* (SD), Range	55	22.6 (20.9), 0–65	20	25.6 (18.5), 1–63	27	19.2 (21.3), 0–65
Week 5 *M* (SD), Range	48	23.3 (23.7), 0–100	19	27.7 (20.4), 1–71	27	19.7 (25.4), 0–100
Number of Positive Traits Endorsed						
Baseline *M* (SD), Range	55	7.7 (4.6), 1–20	20	6.6 (4.7), 1–20	27	8.1 (4.5), 2–18
Week 5 *M* (SD), Range	48	9.1 (5.1), 0–20	19	9.8 (4.8), 1–20	27	8.2 (5.2), 0–18
Number of Negative Traits Endorsed						
Baseline *M* (SD), Range	55	10.3 (4.5), 2–20	20	8.9 (4.6), 2–19	27	11.5 (4.2), 4–20
Week 5 *M* (SD), Range	48	9.2 (5), 0–20	19	6.6 (4.1), 0–17	27	11 (4.9), 2–20
Negative Self-Referential Memory Bias						
Baseline M (SD), Range	51	0.5 (0.3), 0–1	18	0.6 (0.3), 0–1	25	0.6 (0.2), 0–1
Week 5 *M* (SD), Range	46	0.4 (0.3), 0–1	19	0.3 (0.3), 0–1	25	0.5 (0.3), 0–1

Note. M, mean; SD, standard deviation.
[a] Treatment response was defined as a ≥ 50 % reduction in Montgomery Äsberg Depression Rating Scale score from baseline to week five.

higher grand mean MADRS scores. Based on the marginal R^2 values for the final models, average anticipatory excitement ratings and number of negative traits endorsed each explained an additional 4 % of the variance in MADRS scores. No other significant main effects or interactions were observed (Supplementary Table S16).

3.2. Cognitive-affective predictors of suicidality score trajectories

We tested a series of LMMs to examine whether average anticipatory excitement ratings during the MID, number of positive and negative traits endorsed, and negative self-referential memory bias at baseline were associated with CHRT total and subscale scores from baseline to week 17. As above, 55 participants were included in all models except those used for testing baseline self-referential memory bias as a potential significant predictor, which included only the 51 participants who had self-referential memory bias scores at baseline. Thirty-seven of the 55 participants had CHRT scores at all five time points. Baseline demographic and clinical characteristics did not differ between participants with complete vs. incomplete CHRT data (Supplementary Table S5).

We first tested unconditional mean models to determine whether there was significant variability in overall CHRT Total, Propensity, Impulsivity, and Risk scores between participants. We next tested models examining growth trajectories from baseline to weeks 2, 4, 5, and 17, and finally models that included the baseline cognitive-affective variables of interest alone and in interaction with the linear and quadratic time variables, where applicable (Supplementary Tables S8-S15).

Our results revealed that CHRT Total, Propensity, and Risk scores decreased significantly from baseline to week 17, and these decreases became less rapid with time. In contrast, CHRT Impulsivity scores did not change significantly with time. The mean estimated initial scores for the total sample were 28.16 (95 % CI = 25.44, 30.87) for CHRT Total, 21.25 (95 % CI = 19.22, 23.28) for Propensity, 3.72 (95 % CI = 3.34, 4.11) for Impulsivity, and 3.10 (95 % CI = 2.30, 3.89) for Risk scores. There were also significant associations between the linear and quadratic time variables and CHRT Total (time: $\beta = -1.95$, SE = 0.32, $p < .001$; time^2: $\beta = 0.09$, SE = 0.02, $p < .001$; marginal $R^2 = 0.09$), Propensity (time: $\beta = -1.63$, SE = 0.26, $p < .001$; time^2: $\beta = 0.08$, SE = 0.01, $p < .001$; marginal $R^2 = 0.10$), and Risk (time: $\beta = -0.30$, SE = 0.10, $p = .004$; time^2: $\beta = 0.02$, SE = 0.01, $p = .003$; marginal $R^2 = 0.03$).

Subsequent models included fixed effects of baseline anticipatory reward sensitivity, number of positive and negative words endorsed, and negative self-referential memory bias scores and their interactions with the linear and quadratic time variables. In the final models, baseline average anticipatory excitement ratings during the MID task were negatively associated with grand mean CHRT Total ($\beta = -2.61$, SE = 1.12, $p = .024$; marginal $R^2 = 0.14$), Propensity ($\beta = -1.80$, SE = 0.83, $p = .035$; marginal $R^2 = 0.14$), and Risk ($\beta = -0.65$, SE = 0.31, $p = .039$; marginal $R^2 = 0.08$) scores. In addition, a greater number of negative traits endorsed at baseline was associated with grand mean CHRT Total ($\beta = 4.16$, SE = 1.05, $p < 0.001$; marginal $R^2 = 0.23$), Propensity ($\beta = 2.94$, SE = 0.78, $p < .001$; marginal $R^2 = 0.21$) and Risk ($\beta = 0.77$, SE = 0.31, $p = .016$; marginal $R^2 = 0.11$) scores (see Supplementary Tables S17-S20). No other significant main effects or interactions were observed. Marginal R^2 values for the final models suggested that average anticipatory excitement ratings explained an additional 4–8 % of the variance in CHRT Total, Propensity, and Risk scores and number of negative traits endorsed explained an additional 8–14 %. A visualization of these results is presented in Fig. 1.

3.3. Changes in anticipatory reward sensitivity and self-referential processing from baseline to week five by treatment response status

Table 3 shows the results of the repeated measures ANOVAs examining the within-subjects main effect of time (baseline vs. week five) and within-between interaction of time × treatment response status for each cognitive-affective variable of interest. We found significant main effects of time on the number of positive and negative traits participants endorsed as well as participants' negative self-referential memory bias. There was also a significant interaction of time × treatment response status for the number of positive traits endorsed. There were no significant main effects or interactions observed for participants' average anticipatory excitement ratings during the MID task. Plots showing baseline and week five scores for the cognitive-affective variables of interest are presented in Fig. 2.

4. Discussion

This is the first study to explore potential cognitive-affective processes associated with response to, and modulated by, LFR-rTMS for TRD. We found that lower anticipatory reward sensitivity and higher negative self-referential encoding scores at baseline were associated with greater depressive symptoms, total suicidality, suicide propensity, and suicide risk from baseline to 17 weeks post-baseline. From baseline to week five, positive self-referential encoding increased, and negative self-referential encoding and memory bias decreased. These findings highlight the potential roles of blunted anticipatory reward sensitivity and negatively biased self-referential processing in risk for depressive symptoms and suicidality, as well as specific cognitive-affective processes that may be modulated by LFR-rTMS for TRD.

Our reported changes in self-referential processing may be explained in part by evidence suggesting that LFR-rTMS may alleviate treatment-resistant depressive symptoms by modulating activity in several brain regions comprising the default mode network (Kito et al., 2008; Kito

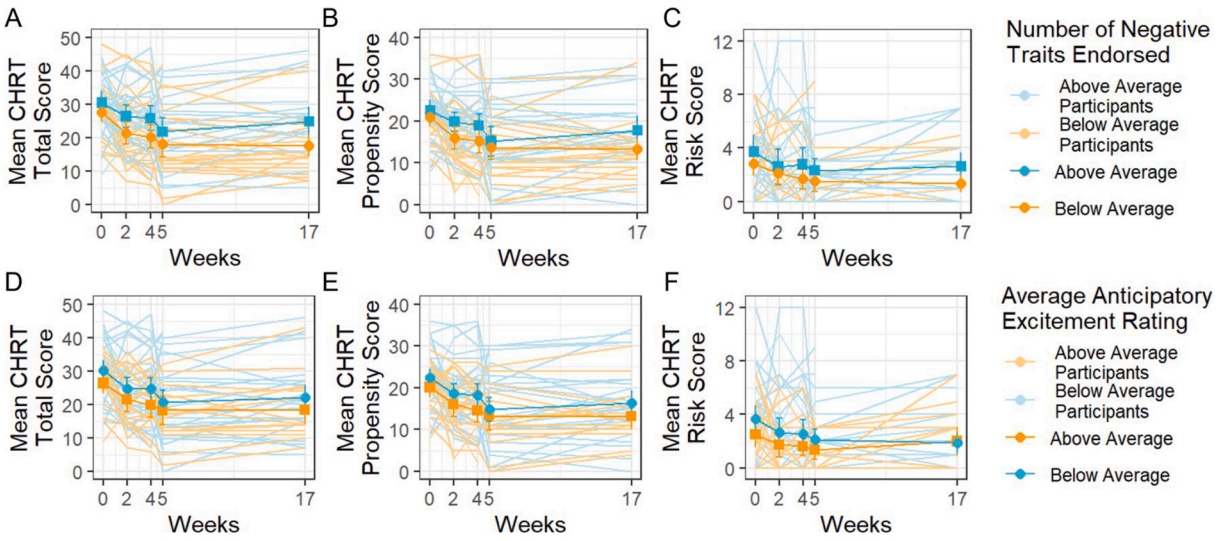

Fig. 1. Suicidality Symptom Trajectories from Baseline to 17 Weeks for Participants with Above versus Below Average Negative Self-Referential Encoding and Anticipatory Reward Sensitivity Scores at Baseline

Note. CHRT, Concise Health Risk Tracking Scale. For visualization only, participants were categorized as 'Above Average' or 'Below Average' in anticipatory reward sensitivity/negative self-referential encoding bias relative in the overall sample. Plots depict statistically significant results only. Participants who endorsed a higher-than-average number of negative traits at baseline had higher CHRT Total (A), Propensity (B), and Risk (C) scores from baseline to week 17. Participants with higher-than-average anticipatory excitement ratings during the monetary incentive delay task at baseline had higher CHRT Total (D), Propensity (E), and Risk (F) scores from baseline to week 17.

Table 3

Results of repeated measures analyses of variance examining changes in anticipatory reward sensitivity and self-referential processing from baseline to week five by treatment response status.

	Average Anticipatory Excitement Rating ($N = 46$)				Number of Positive Traits Endorsed ($N = 46$)				Number of Negative Traits Endorsed ($N = 46$)				Negative Self-Referent Memory Bias ($N = 41$)			
	SS	df	*F*	*p*	SS	df	*F*	*p*	SS	df	*F*	*p*	SS	df	*F*	*p*
Time	69.97	1	0.36	0.550	56.92	1	13.86	**<0.001**	31.49	1	5.00	**0.031**	0.53	1	15.76	**<0.001**
Time×Response	32.96	1	0.171	0.681	54.31	1	13.22	**<0.001**	11.14	1	1.77	0.191	0.12	1	3.65	0.063
Error	8495.36	44			180.75	44			277.27	44			1.31	39		

Note. P values <.05 are presented in bold.

et al., 2011), which has also been associated with self-referential processing in MDD (Sheline et al., 2009). Modulating default mode network connectivity using LFR-rTMS may therefore also reduce negatively biased self-referential processing. Whether changes in self-referential biases with treatment may simply reflect lower levels of depression arising from treatment rather than a mechanistic process is a question that our study cannot resolve but it merits further research. In contrast to the observed changes in self-referential processing scores, we did not find a significant change in anticipatory reward sensitivity from baseline to five weeks post baseline, despite some evidence suggesting that LFR-rTMS may influence reward valuations (Camus et al., 2009).

Greater negative self-referential encoding was associated with higher total and subscale (except Impulsivity) suicidality scores. Baseline positive self-referential encoding and negative self-referential memory bias were however not found to be significantly related to any aspect of suicidality. The association between negative self-referential encoding and suicidality algins with previous research demonstrating a relationship between these features of MDD (Bulteau et al., 2021; Burke et al., 2016). An interesting research question following from these findings is whether higher suicidality may be associated with a greater tendency to self-attribute negative traits, but not a lesser tendency to self-attribute positive traits.

Our finding that blunted subjective anticipatory reward sensitivity during a MID task was associated with higher suicidality over the course of rTMS treatment represents a novel contribution to the literature. Consistent with our results, previous studies have demonstrated associations between neural responsiveness to monetary reward and suicidal ideation (Tsypes et al., 2019) and a history of suicide attempts (Dombrovski et al., 2013). Discounting of delayed rewards may explain why individuals with higher suicidal ideation in our study showed lower baseline excitement ratings for tickets towards a *future* reward (Dombrovski et al., 2012; Dombrovski et al., 2011). However, the influence of anticipatory reward sensitivity on suicidality should also be considered. For example, blunted anticipatory reward sensitivity may increase suicide risk by impairing an individual's ability to generate positive future events (van Heeringen et al., 2011).

Although LFR-rTMS did not appear to influence anticipatory reward sensitivity in this study, it is noteworthy that a diminished response of the *left* DLPFC to reward value differences has been associated with greater suicidality (Vanyukov et al., 2016). It may follow that excitation of the left DLPFC could increase its responsiveness to rewards and in turn reduce suicidality. By altering functional connectivity between the DLPFC and orbitofrontal cortex (OFC), high frequency rTMS applied to the left DLPFC (HFL-rTMS) for TRD could enhance inputs to the OFC, alter the computed values of anticipated rewards, and in turn reduce suicidality – questions that may be worth exploring in future studies of HFL-rTMS.

There are limitations of this study that should be noted. First, there were no comparison groups included in this study, which precluded an examination of how anticipatory reward sensitivity and self-referential processing may have changed over the five-week period for individuals with TRD who were undergoing a different rTMS treatment

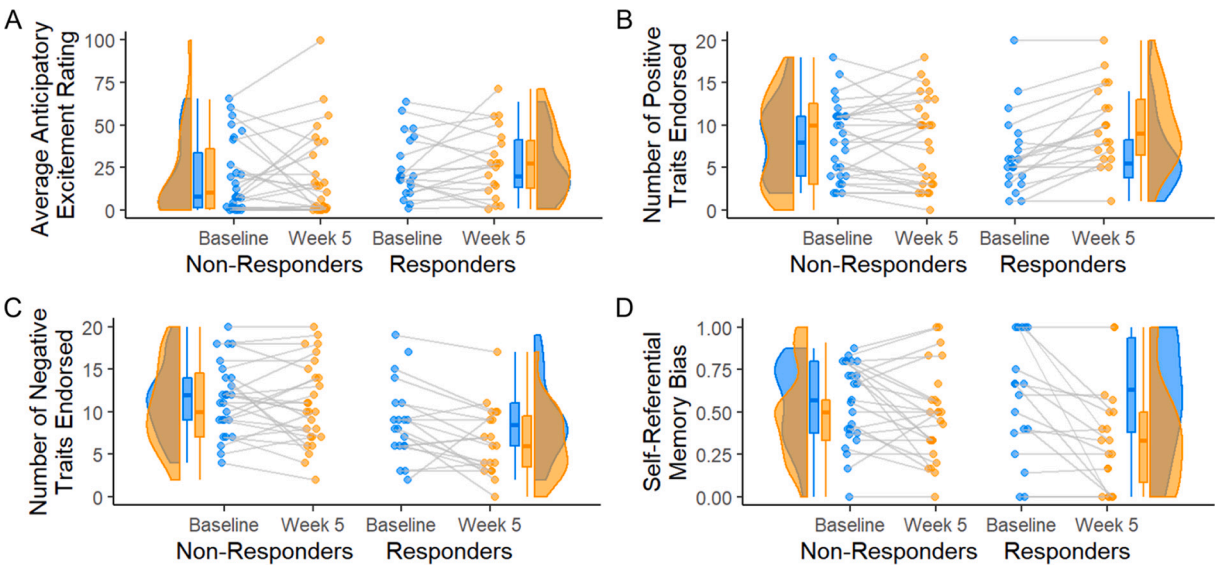

Fig. 2. Anticipatory Reward Sensitivity and Self-Referential Processing Variable Scores at Baseline and Week Five by Treatment Response Status
Note. This figure shows data for participants who completed the behavioral tasks at baseline and week five. From baseline to week five, there was a significant increase in the number of positive traits participants endorsed (B) and significant decreases in the number of negative traits endorsed (C) and negative self-referential memory bias (D). There was a significant interaction of time × treatment response status for the number of positive traits endorsed, where treatment responders showed a greater increase. We did not observe significant main effects or interactions for participants' average anticipatory excitement ratings during the monetary incentive delay task (A).

protocol or depression treatment, or individuals without a mental health diagnosis. The specificity of these effects to LFR-rTMS also remains unknown. Another limitation of this study was our sample size, which may not have provided sufficient power for establishing the validity of our null results. As such, the null findings in this study should not be interpreted as establishing the lack of an association between the relevant variables. Finally, since potential participants with active suicidal intent were excluded from this study, the results of our analyses examining suicidality symptoms may not be generalizable to TRD patients experiencing the highest levels of suicidality.

In sum, this is the first study to examine the roles of anticipatory reward sensitivity and self-referential processing in response to rTMS treatment for TRD. The results of this study suggest that blunted anticipatory reward sensitivity and negatively biased self-referential encoding may be associated with higher depressive and suicidality symptoms over the course of LFR-rTMS for TRD and up to 17 weeks post-baseline. Moreover, LFR-rTMS may increase positive self-referential encoding and reduce negative self-referential encoding and biases in self-referential memory in TRD. Further research is needed to establish whether LFR-rTMS influences unique aspects of self-referential processing relative to other rTMS treatment protocols (e.g., HFL-rTMS) and other antidepressant treatments. This study provides a starting point for research examining specific cognitive-affective features of TRD that may be associated with response to, and altered by, LFR-rTMS.

CRediT authorship contribution statement

ART prepared the first draft of the manuscript. ART, RMT, JL, and TC contributed to the formulation of research questions and the selection of behavioral tasks for this study. FVR was responsible for conceiving and conducting the trial. FVR, ART, RMT, JL, and TC contributed to the study design. FVR, ART, MN, AH, and ECG contributed to data collection. ART analyzed the data and MN assisted with data analysis. All authors contributed to the interpretation of the findings and revisions to the manuscript. All authors reviewed and approved the manuscript for submission.

Funding sources

The trial was conducted with support from Brain Canada, the Michael Smith Foundation for Health Research, and the Vancouver Coastal Health Research Institute. ART was supported by the Canadian Institutes of Health Research (CIHR) Vanier Canada Graduate Scholarship. FVR receives research support from CIHR, Brain Canada, Michael Smith Foundation for Health Research, Vancouver Coastal Health Research Institute, and Weston Brain Institute for investigator-initiated research, as well as philanthropic support from Seedlings Foundation. JL has received research grants from CIHR, Social Sciences and Humanities Research Council (SSHRC), Natural Sciences and Engineering Research Council (NSERC), and the Michael Smith Foundation for Health Research. TC has received grant funding from the Michael Smith Foundation for Health Research and the National Research Council Canada Collaborative Science, Technology and Innovation Program. RMT is supported by a Michael Smith Foundation for Health Research Scholar Award (16897), and an NSERC Discovery Grant (RGPIN-2020-05354).

Conflict of Interest

FVR receives in-kind equipment supports for this investigator-initiated trial from MagVenture and has received honoraria for participation in advisory board for Janssen. The rest of the authors declare no competing interests.

Acknowledgements

We thank Patrick Klaiber for assisting with the statistical analyses for this manuscript.

Appendix A. Supplementary data

Supplementary material to this article can be found online at https://doi.org/10.1016/j.jad.2022.10.041.

References

Allen, T.A., Lam, R.W., Milev, R., Rizvi, S.J., Frey, B.N., MacQueen, G.M., Müller, D.J., Uher, R., Kennedy, S.H., Quilty, L.C., 2019. Early change in reward and punishment sensitivity as a predictor of response to antidepressant treatment for major depressive disorder: a CAN-BIND-1 report. Psychol. Med. 49, 1629–1638.

Angst, J., Adolfsson, R., Benazzi, F., Gamma, A., Hantouche, E., Meyer, T.D., Skeppar, P., Vieta, E., Scott, J., 2005. The HCL-32: towards a self-assessment tool for hypomanic symptoms in outpatients. J. Affect. Disord. 88, 217–233.

Bates, D., Mächler, M., Bolker, B., Walker, S., 2014. Fitting linear mixed-effects models using lme4. In: arXiv Preprint arXiv:1406.5823.

Bergfeld, I.O., Mantione, M., Figee, M., Schuurman, P.R., Lok, A., Denys, D., 2018. Treatment-resistant depression and suicidality. J. Affect. Disord. 235, 362–367.

Bozzay, M.L., Primack, J., Barredo, J., Philip, N.S., 2020. Transcranial magnetic stimulation to reduce suicidality–a review and naturalistic outcomes. J. Psychiatr. Res. 125, 106–112.

Brunoni, A.R., Chaimani, A., Moffa, A.H., Razza, L.B., Gattaz, W.F., Daskalakis, Z.J., Carvalho, A.F., 2017. Repetitive transcranial magnetic stimulation for the acute treatment of major depressive episodes: a systematic review with network meta-analysis. JAMA Psychiatry 74, 143–152.

Bulteau, S., Péré, M., Blanchin, M., Poulet, E., Brunelin, J., Sauvaget, A., Sébille, V., 2021. Higher negative self-reference level in patients with personality disorders and suicide attempt(s) history during biological treatment for major depressive disorder: clinical implications. Front. Psychol. 12, 631614.

Burke, T.A., Connolly, S.L., Hamilton, J.L., Stange, J.P., Abramson, L.Y., Alloy, L.B., 2016. Cognitive risk and protective factors for suicidal ideation: a two year longitudinal study in adolescence. J. Abnorm. Child Psychol. 44, 1145–1160.

Burkhouse, K.L., Kujawa, A., Kennedy, A.E., Shankman, S.A., Langenecker, S.A., Phan, K. L., Klumpp, H., 2016. Neural reactivity to reward as a predictor of cognitive behavioral therapy response in anxiety and depression. Depress Anxiety 33, 281–288.

Camus, M., Halelamien, N., Plassmann, H., Shimojo, S., O'Doherty, J., Camerer, C., Rangel, A., 2009. Repetitive transcranial magnetic stimulation over the right dorsolateral prefrontal cortex decreases valuations during food choices. Eur. J. Neurosci. 30, 1980–1988.

Carmody, T.J., Rush, A.J., Bernstein, I., Warden, D., Brannan, S., Burnham, D., Woo, A., Trivedi, M.H., 2006. The Montgomery Åsberg and the Hamilton ratings of depression: a comparison of measures. Eur. Neuropsychopharmacol. 16, 601–611.

Carver, C.S., White, T.L., 1994. Behavioral inhibition, behavioral activation, and affective responses to impending reward and punishment: the BIS/BAS scales. J. Pers. Soc. Psychol. 67, 319.

Chen, J., Zhou, C., Wu, B., Wang, Y., Li, Q., Wei, Y., Yang, D., Mu, J., Zhu, D., Zou, D., Xie, P., 2013. Left versus right repetitive transcranial magnetic stimulation in treating major depression: a meta-analysis of randomised controlled trials. Psychiatry Res. 210, 1260–1264.

Chen, G.-W., Hsu, T.-W., Ching, P.-Y., Pan, C.-C., Chou, P.-H., Chu, C.-S., 2022. Efficacy and tolerability of repetitive transcranial magnetic stimulation on suicidal ideation: a systemic review and meta-analysis. FrontiersPsychiatry 13.

Clark, L., Chamberlain, S.R., Sahakian, B.J., 2009. Neurocognitive mechanisms in depression: implications for treatment. Annu. Rev. Neurosci. 32, 57–74.

Connolly, K.R., Thase, M.E., 2011. If at first you don't succeed. Drugs 71, 43–64.

Cui, Y., Fang, H., Bao, C., Geng, W., Yu, F., Li, X., 2021. Efficacy of transcranial magnetic stimulation for reducing suicidal ideation in depression: a meta-analysis. Front. Psychiatry 12.

Dainer-Best, J., Trujillo, L.T., Schnyer, D.M., Beevers, C.G., 2017. Sustained engagement of attention is associated with increased negative self-referent processing in major depressive disorder. Biol. Psychol. 129, 231–241.

Dainer-Best, J., Lee, H.Y., Shumake, J.D., Yeager, D.S., Beevers, C.G., 2018. Determining optimal parameters of the self-referent encoding task: A large-scale examination of self-referent cognition and depression. Psychological assessment 30 (11), 1527–1540.

De Pisapia, N., Barchiesi, G., Jovicich, J., Cattaneo, L., 2019. The role of medial prefrontal cortex in processing emotional self-referential information: a combined TMS/fMRI study. Brain Imaging Behav. 13, 603–614.

Dichter, G.S., Felder, J.N., Petty, C., Bizzell, J., Ernst, M., Smoski, M.J., 2009. The effects of psychotherapy on neural responses to rewards in major depression. Biol. Psychiatry 66, 886–897.

Dombrovski, A.Y., Szanto, K., Siegle, G.J., Wallace, M.L., Forman, S.D., Sahakian, B., Reynolds III, C.F., Clark, L., 2011. Lethal forethought: delayed reward discounting differentiates high-and low-lethality suicide attempts in old age. Biol. Psychiatry 70, 138–144.

Dombrovski, A.Y., Siegle, G.J., Szanto, K., Clark, L., Reynolds, C., Aizenstein, H., 2012. The temptation of suicide: striatal gray matter, discounting of delayed rewards, and suicide attempts in late-life depression. Psychol. Med. 42, 1203–1215.

Dombrovski, A.Y., Szanto, K., Clark, L., Reynolds, C.F., Siegle, G.J., 2013. Reward signals, attempted suicide, and impulsivity in late-life depression. JAMA Psychiatry 70, 1020–1030.

Dunlop, K., Rizvi, S.J., Kennedy, S.H., Hassel, S., Strother, S.C., Harris, J.K., Zamyadi, M., Arnott, S.R., Davis, A.D., Mansouri, F., 2020. Clinical, behavioral, and neural measures of reward processing correlate with escitalopram response in depression: a Canadian biomarker integration network in depression (CAN-BIND-1) report. Neuropsychopharmacology 45, 1390–1397.

Eshel, N., Keller, C.J., Wu, W., Jiang, J., Mills-Finnerty, C., Huemer, J., Wright, R., Fonzo, G.A., Ichikawa, N., Carreon, D., 2020. Global connectivity and local excitability changes underlie antidepressant effects of repetitive transcranial magnetic stimulation. Neuropsychopharmacology 45, 1018–1025.

Fisher, P.M., Ozenne, B., Ganz, M., Frokjaer, V.G., Dam, V.N., Penninx, B.W., Sankar, A., Miskowiak, K., Jensen, P.S., Knudsen, G.M., 2022. Emotional faces processing in major depressive disorder and prediction of antidepressant treatment response: a NeuroPharm study. J. Psychopharmacol. 02698811221089035.

Ge, R., Downar, J., Blumberger, D.M., Daskalakis, Z.J., Vila-Rodriguez, F., 2020. Functional connectivity of the anterior cingulate cortex predicts treatment outcome for rTMS in treatment-resistant depression at 3-month follow-up. Brain Stimul. 13, 206–214.

Ge, R., Humaira, A., Gregory, E., Alamian, G., MacMillan, E.L., Barlow, L., Todd, R., Nestor, S., Frangou, S., Vila-Rodriguez, F., 2022. Predictive value of acute neuroplastic response to rTMS in treatment outcome in depression: a concurrent TMS-fMRI trial. American Journal of Psychiatry 179, 500–508.

Harmer, C.J., Duman, R.S., Cowen, P.J., 2017. How do antidepressants work? New perspectives for refining future treatment approaches. Lancet Psychiatry 4, 409–418.

van Heeringen, C., Bijttebier, S., Godfrin, K., 2011. Suicidal brains: a review of functional and structural brain studies in association with suicidal behaviour. Neurosci. Biobehav. Rev. 35, 688–698.

Holmes, E., Ghaderi, A., Harmer, C., Ramchandani, P., Cuijpers, P., Morrison, A., Rosier, J., Bockting, C., O'Connor, R., Shafran, R., 2018. Psychological treatments research in tomorrow's science: seeing further. Lancet Psychiatry 5.

Holtzheimer, P.E., Mayberg, H.S., 2011. Stuck in a rut: rethinking depression and its treatment. Trends Neurosci. 34, 1–9.

Husain, M., Roiser, J.P., 2018. Neuroscience of apathy and anhedonia: a transdiagnostic approach. Nat. Rev. Neurosci. 1.

Hutchinson, E.A., Sequeira, S.L., Silk, J.S., Jones, N.P., Oppenheimer, C., Scott, L., Ladouceur, C.D., 2021. Peer connectedness and pre-existing social reward processing predicts U.S. adolescent girls' suicidal ideation during COVID-19. J. Res. Adolesc. 31, 703–716.

Kito, S., Fujita, K., Koga, Y., 2008. Regional cerebral blood flow changes after low-frequency transcranial magnetic stimulation of the right dorsolateral prefrontal cortex in treatment-resistant depression. Neuropsychobiology 58, 29–36.

Kito, S., Hasegawa, T., Koga, Y., 2011. Neuroanatomical correlates of therapeutic efficacy of low-frequency right prefrontal transcranial magnetic stimulation in treatment-resistant depression. Psychiatry Clin. Neurosci. 65, 175–182.

Li, X., Nahas, Z., Kozel, F.A., Anderson, B., Bohning, D.E., George, M.S., 2004. Acute left prefrontal transcranial magnetic stimulation in depressed patients is associated with immediately increased activity in prefrontal cortical as well as subcortical regions. Biol. Psychiatry 55, 882–890.

Makowski, D., 2018. The psycho package: an efficient and publishing-oriented workflow for psychological science. J. Open Source Softw. 3, 470.

Mayes, T.L., Kennard, B.D., Killian, M., Carmody, T., Grannemann, B.D., Rush, A.J., Jha, M.K., Hughes, J., Emslie, G.J., Trivedi, M.H., 2018. Psychometric properties of the concise health risk tracking (CHRT) in adolescents with suicidality. J. Affect. Disord. 235, 45–51.

Mehta, S., Downar, J., Mulsant, B.H., Voineskos, D., Daskalakis, Z.J., Weissman, C.R., Vila-Rodriguez, F., Blumberger, D.M., 2022a. Effect of high frequency versus theta-burst repetitive transcranial magnetic stimulation on suicidality in patients with treatment-resistant depression. Acta Psychiatr. Scand. 145, 529–538.

Mehta, S., Konstantinou, G., Weissman, C.R., Daskalakis, Z.J., Voineskos, D., Downar, J., Mulsant, B.H., Blumberger, D.M., 2022b. The effect of repetitive transcranial magnetic stimulation on suicidal ideation in treatment-resistant depression: a meta-analysis. J. Clin. Psychiatry 83, 39202.

Meteyard, L., Davies, R.A., 2020. Best practice guidance for linear mixed-effects models in psychological science. J. Mem. Lang. 112, 104092.

Milev, R.V., Giacobbe, P., Kennedy, S.H., Blumberger, D.M., Daskalakis, Z.J., Downar, J., Modirrousta, M., Patry, S., Vila-Rodriguez, F., Lam, R.W., 2016. Canadian network for mood and anxiety treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: section 4. Neurostimulation treatments. Can. J. Psychiatry 61, 561–575.

Miron, J.-P., Sheen, J., Mansouri, F., Blumberger, D.M., Daskalakis, Z.J., Vila-Rodriguez, F., Downar, J., 2020. The role of low-frequency repetitive transcranial magnetic stimulation in major depression: a call to increase the evidence base. Brain Stimul 13, 1296–1297.

Montgomery, S., Åsberg, M., 1977. A NewDepression Scale Designed to be Sensitive to Change. Acad. Department of Psychiatry, Guy's Hospital.

Müller, M.J., Himmerich, H., Kienzle, B., Szegedi, A., 2003. Differentiating moderate and severe depression using the Montgomery-Åsberg depression rating scale (MADRS). J. Affect. Disord. 77, 255–260.

Nakagawa, S., Schielzeth, H., 2013. A general and simple method for obtaining R2 from generalized linear mixed-effects models. Methods Ecol. Evol. 4, 133–142.

Nakagawa, S., Johnson, P.C., Schielzeth, H., 2017. The coefficient of determination R 2 and intra-class correlation coefficient from generalized linear mixed-effects models revisited and expanded. J. R. Soc. Interface 14, 20170213.

Northoff, G., Heinzel, A., De Greck, M., Bermpohl, F., Dobrowolny, H., Panksepp, J., 2006. Self-referential processing in our brain—a meta-analysis of imaging studies on the self. NeuroImage 31, 440–457.

Novak, K.D., Foti, D., 2015. Teasing apart the anticipatory and consummatory processing of monetary incentives: an event-related potential study of reward dynamics. Psychophysiology 52, 1470–1482.

Oquendo, M.A., Baca-Garcia, E., Kartachov, A., Khait, V., Campbell, C.E., Richards, M., Sackeim, H.A., Mann, J.J., 2003. A computer algorithm for calculating the adequacy of antidepressant treatment in unipolar and bipolar depression. The Journal of clinical psychiatry 64, 3571.

R Core Team, 2022. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria.

Riedel, P., Heil, M., Bender, S., Dippel, G., Korb, F.M., Smolka, M.N., Marxen, M., 2019. Modulating functional connectivity between medial frontopolar cortex and amygdala by inhibitory and excitatory transcranial magnetic stimulation. Hum. Brain Mapp. 40, 4301–4315.

Rizvi, S.J., Grima, E., Tan, M., Rotzinger, S., Lin, P., McIntyre, R.S., Kennedy, S.H., 2014. Treatment-resistant depression in primary care across Canada. Can. J. Psychiatry 59, 349–357.

Rizvi, S.J., Quilty, L.C., Sproule, B.A., Cyriac, A., Bagby, R.M., Kennedy, S.H., 2015. Development and validation of the dimensional anhedonia rating scale (DARS) in a community sample and individuals with major depression. Psychiatry Res. 229, 109–119.

Rizvi, S.J., Pizzagalli, D.A., Sproule, B.A., Kennedy, S.H., 2016. Assessing anhedonia in depression: potentials and pitfalls. Neurosci. Biobehav. Rev. 65, 21–35.

Roiser, J.P., Elliott, R., Sahakian, B.J., 2012. Cognitive mechanisms of treatment in depression. Neuropsychopharmacology 37, 117.

RStudio Team, 2022. In: RStudio: Integrated Development Environment for R, 42. RStudio, PBC, Boston, MA, p. 84.

Rush, A.J., Giles, D.E., Schlesser, M.A., Fulton, C.L., Weissenburger, J., Burns, C., 1986. The inventory for depressive symptomatology (IDS): preliminary findings. Psychiatry Res. 18, 65–87.

Sheehan, D.V., Lecrubier, Y., Sheehan, K.H., Janavs, J., Weiller, E., Keskiner, A., Schinka, J., Knapp, E., Sheehan, M., Dunbar, G., 1997. The validity of the Mini international neuropsychiatric interview (MINI) according to the SCID-P and its reliability. Eur. Psychiatry 12, 232–241.

Sheehan, D.V., Lecrubier, Y., Sheehan, K.H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., Dunbar, G.C., 1998. The Mini-International Neuropsychiatric Interview (MINI): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. Journal of clinical psychiatry 59 (Suppl. 20), 22–33 quiz 34-57.

Sheline, Y.I., Barch, D.M., Price, J.L., Rundle, M.M., Vaishnavi, S.N., Snyder, A.Z., Mintun, M.A., Wang, S., Coalson, R.S., Raichle, M.E., 2009. The default mode network and self-referential processes in depression. Proceedings of the National Academy of Sciences 106, 1942–1947.

Sherdell, L., Waugh, C.E., Gotlib, I.H., 2012. Anticipatory pleasure predicts motivation for reward in major depression. J. Abnorm. Psychol. 121, 51–60.

Stewart, J.G., Polanco-Roman, L., Duarte, C.S., Auerbach, R.P., 2019. Neurocognitive processes implicated in adolescent suicidal thoughts and behaviors: applying an RDoC framework for conceptualizing risk. Curr. Behav. Neurosci. Rep. 6, 188–196.

Trevino, K., McClintock, S.M., Fischer, N.M., Vora, A., Husain, M.M., 2014. Defining treatment-resistant depression: a comprehensive review of the literature, 26 (3 26), 222–232.

Trivedi, M.H., Wisniewski, S.R., Morris, D.W., Fava, M., Gollan, J.K., Warden, D., Nierenberg, A.A., Gaynes, B.N., Husain, M.M., Luther, J.F., 2011. Concise health risk tracking scale: a brief self-report and clinician rating of suicidal risk. J. Clin. Psychiatry 72, 757–764.

Tsypes, A., Owens, M., Gibb, B.E., 2019. Blunted neural reward responsiveness in children with recent suicidal ideation. Clin. Psychol. Sci. 7, 958–968.

Tsypes, A., Owens, M., Gibb, B.E., 2021. Reward responsiveness in suicide attempters: an electroencephalography/event-related potential study. Biol. Psychiatry: Cogn. Neurosci. Neuroimaging 6, 99–106.

Tulviste, J., Bachmann, T., 2019. Diminished risk-aversion after right DLPFC stimulation: effects of rTMS on a risky ball throwing task. J. Int. Neuropsychol. Soc. 25, 72–78.

Vanyukov, P.M., Szanto, K., Hallquist, M.N., Siegle, G.J., Reynolds 3rd, C.F., Forman, S. D., Aizenstein, H.J., Dombrovski, A.Y., 2016. Paralimbic and lateral prefrontal encoding of reward value during intertemporal choice in attempted suicide. Psychol. Med. 46, 381–391.

Watanabe, T., Hanajima, R., Shirota, Y., Ohminami, S., Tsutsumi, R., Terao, Y., Ugawa, Y., Hirose, S., Miyashita, Y., Konishi, S., 2014. Bidirectional effects on interhemispheric resting-state functional connectivity induced by excitatory and inhibitory repetitive transcranial magnetic stimulation. Hum. Brain Mapp. 35, 1896–1905.

Weissman, C.R., Blumberger, D.M., Brown, P.E., Isserles, M., Rajji, T.K., Downar, J., Mulsant, B.H., Fitzgerald, P.B., Daskalakis, Z.J., 2018. Bilateral repetitive transcranial magnetic stimulation decreases suicidal ideation in depression. J. Clin. Psychol. 79, 5831.

Whitton, A.E., Treadway, M.T., Pizzagalli, D.A., 2015. Reward processing dysfunction in major depression, bipolar disorder and schizophrenia. Curr. Opin. Psychiatry 28, 7–12.

Whitton, A.E., Reinen, J.M., Slifstein, M., Ang, Y.-S., McGrath, P.J., Iosifescu, D.V., Abi-Dargham, A., Pizzagalli, D.A., Schneier, F.R., 2020. Baseline reward processing and ventrostriatal dopamine function are associated with pramipexole response in depression. Brain 143, 701–710.

Zhdanava, M., Pilon, D., Ghelerter, I., Chow, W., Joshi, K., Lefebvre, P., Sheehan, J.J., 2021. The prevalence and national burden of treatment-resistant depression and major depressive disorder in the United States. J. Clin. Psychol. 82, 29169.