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Volume 12 • Issue 2 • February 2025

ISSN 2050-4373

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DOI 10.3310/WVNY5029

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Extended Research Article

Connectivity guided intermittent theta burst stimulation versus repetitive transcranial magnetic stimulation in moderately severe treatment resistant depression: the BRIGhTMIND RCT

Richard Morriss,[1,2,3,4*] Lucy Webster,[2,5] Luke Ingram,[6] Mohamed Abdelghani,[7] Adriana Anton,[8] Shaun Barber,[6] Peter Bates,[5] Paul Briley,[1,2,5] Clement Boutry,[1,4] Cassandra Brookes,[6] Edward Cox,[8] Beth Hall,[9,10] Marilyn James,[8] Matthew Keane,[8] Micheal Kurkar,[11] Sudheer Lankappa,[2] Peter Liddle,[1,2] Hamish McAllister-Williams,[9,10] Hyerin Oh,[1,5] Alexander O'Neill-Kerr,[12] Jehill Parikh,[13] Stefan Pszczolkowski,[1,2] Ana Suazo Di Paola,[6] Louise Thomson,[1,5] Yvette Walters[6] and Dorothee Auer[1,2]

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Published February 2025
DOI: 10.3310/WVNY5029

This report should be referenced as follows:

Morriss R, Webster L, Ingram L, Abdelghani M, Anton A, Barber S, *et al.* Connectivity guided intermittent theta burst stimulation versus repetitive transcranial magnetic stimulation in moderately severe treatment resistant depression: the BRIGhTMIND RCT. *Efficacy Mech Eval* 2025;**12**(2). https://doi.org/10.3310/WVNY5029

Efficacy and Mechanism Evaluation

ISSN 2050-4373 (Online)

A list of Journals Library editors can be found on the NIHR Journals Library website

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This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: journals.library@nihr.ac.uk

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The EME programme is funded by the Medical Research Council (MRC) and the National Institute for Health and Care Research (NIHR), with contributions from the Chief Scientist Office (CSO) in Scotland and National Institute for Social Care and Health Research (NISCHR) in Wales and the Health and Social Care Research and Development (HSC R&D), Public Health Agency in Northern Ireland.

This article

The research reported in this issue of the journal was funded by the EME programme as award number 16/44/22. The contractual start date was in February 2018. The draft manuscript began editorial review in March 2023 and was accepted for publication in August 2024. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The EME editors and production house have tried to ensure the accuracy of the authors' manuscript and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this article.

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Abstract

Background: Transcranial magnetic stimulation may lead to short-term improvement in depression symptoms. Pilot work suggested that personalised magnetic resonance imaging connectivity-guided intermittent theta burst stimulation might lead to sustained improvement in depression symptoms in treatment-resistant depression.

Objectives: To determine the efficacy, acceptability, and cost-effectiveness of connectivity-guided intermittent theta burst stimulation over 8, 16 and 26 weeks on depression symptoms (Hamilton Rating Scale for Depression-17) compared with repetitive transcranial magnetic stimulation. To explore the mechanism of action of transcranial magnetic stimulation through effective and functional connectivity, and gamma-aminobutyric acid and glutamate+glutamine in the prefrontal cortex, subgenual anterior cingulate cortex and right anterior insula.

Design: A multicentre parallel group, double-blind, randomised controlled trial, to test the efficacy of connectivity-guided intermittent theta burst stimulation versus repetitive transcranial magnetic stimulation without connectivity guidance, in patients with moderate to severe treatment-resistant major depressive disorder (treatment-resistant depression).

Setting: Secondary care mental health services across five study sites.

Participants: Aged 18 years or over with major depressive disorder, Massachusetts General Hospital Treatment Resistant Depression staging score ≥ 2, and Hamilton Rating Scale for Depression-17 score ≥ 16. Exclusions: bipolar disorder, secondary depression, suicidality, current substance abuse or dependence, neurological conditions, prior brain surgery, major unstable medical illness, standard contraindications to magnetic resonance imaging, change in prescribed medication or benzodiazepines or hypnotics ≥ 5 mg diazepam equivalents daily in 2 weeks before baseline.

Trial interventions: In total 3000 pulses were delivered in each 37.5-minute repetitive transcranial magnetic stimulation or connectivity-guided intermittent theta burst stimulation session for 20 sessions over 4–6 weeks. Personalised transcranial magnetic stimulation stimulation targets were identified from magnetic resonance imaging (F3 site for repetitive transcranial magnetic stimulation, maximum effective connectivity from right anterior insula to left dorsolateral prefrontal cortex for connectivity-guided intermittent theta burst stimulation) using neuronavigation to deliver transcranial magnetic stimulation.

Main outcome measures: The primary outcome measure was mean change in depression symptoms from baseline and at 8, 16 and 26 weeks using the Grid version of the Hamilton Rating Scale for Depression-17. Secondary outcomes were response, remission, sustained response, self-rated depression (Patient Health Questionnaire-9, Beck Depression Inventory-II), generalised anxiety-7, function (Work and Social Adjustment Scale), quality of life (Euroqol five-dimension five line), overall improvement (Euroqol five-dimension five-line scale), acceptability, with cognition (THINC-it battery), resting state functional magnetic resonance imaging and magnetic resonance spectroscopy (baseline and 16 weeks) and costs from health and society perspectives.

Results: A total of 255 participants were randomised (128 connectivity-guided intermittent theta burst stimulation, 127 repetitive transcranial magnetic stimulation). There were no significant differences between repetitive transcranial magnetic stimulation and connectivity-guided intermittent theta burst stimulation in the Hamilton Rating Scale for Depression-17 score [intention-to-treat adjusted mean −0.31 (95% confidence interval −1.87 to 1.24)] nor on any secondary outcome. Sustained response rates at 26 weeks were 22/127 (17.3%) repetitive transcranial magnetic stimulation, and 29/128 (22.7%) connectivity-guided intermittent theta burst stimulation. Connectivity-guided intermittent theta burst stimulation was dominant over repetitive transcranial magnetic stimulation in cost-effectiveness (0.009 greater quality-adjusted life-year gain and £180 greater cost saving to health services per individual), albeit overlapping 95% confidence interval between treatment groups demonstrates uncertainties. One serious adverse event in each group (mania, psychosis) was attributable to transcranial magnetic stimulation. Both treatments were equally acceptable. Clinical improvement was associated with measures of effective or functional connectivity between left dorsolateral prefrontal cortex and right anterior insula, subgenual anterior cingulate cortex and left dorsomedial prefrontal cortex, and spectroscopy baseline gamma-aminobutyric acid.

Limitations: Participants may have benefited from > 20 transcranial magnetic stimulation sessions. There was no sham control group.

Conclusion: Connectivity-guided intermittent TBS was not superior in efficacy to standard repetitive transcranial magnetic stimulation. Magnetic resonance imaging neuronavigation personalised repetitive transcranial magnetic stimulation or intermittent theta burst stimulation are acceptable methods to reduce depression symptoms over 26 weeks in treatment-resistant depression alongside other reasons for improvement.

Study registration: Current Controlled Trials ISRCTN19674644.

Funding: This award was funded by the National Institute for Health and Care Research (NIHR) Efficacy and Mechanism Evaluation (EME) programme (NIHR award ref: 16/44/22) and is published in full in *Efficacy and Mechanism Evaluation*; Vol. 12, No. 2. See the NIHR Funding and Awards website for further award information.

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List of abbreviations

AEs	adverse events
A&E	accident and emergency
AI	anterior insula
BDI-II	Beck Depression Inventory, version 2
BOLD	blood oxygenation level dependent
BRC	Biomedical Research Centre
CRF	case report form
CEN	central executive network
CI	confidence interval
cgiTBS	connectivity-guided intermittent theta burst stimulation
COVID-19	coronavirus disease discovered in 2019
Cr	creatine
CRLB	Craemer-Rao Lower Bound
CRT	choice reaction time
CTQ	Childhood Trauma Questionnaire
dACC	dorsal anterior cingulate cortex
DBS	deep brain stimulation
DLPFC	dorsolateral prefrontal cortex
DMEC	Data Monitoring and Ethics Committee
DMN	default mode network
DMPFC	dorsomedial prefrontal cortex
DSM-5	Diagnostic and Statistical Manual of Mental Disorder version 5
DSST	Digit Symbol Substitution Test
ECT	electroconvulsive therapy
eFC	effective functional connectivity
EQ-5D-5L	EuroQol-5 Dimensions, five-level version
EVPI	Expected Value of Perfect Information
FC	functional connectivity
fMRI	functional magnetic resonance imaging
FSL	functional and structural MRI software library
GABA	gamma-aminobutyric acid
GABA+	gamma-aminobutyric acid and macromolecules
GABA/Glx	gamma-aminobutyric acid ratio to glutamate and glutamine
GAD-7	General Anxiety Disorder-7
Glx	glutamate and glutamine
GlxCr	glutamate, glutamine, and creatine
Glx/tCr	Glutamate and glutamine ratio to creatine and phosphocreatine
GP	general practitioner
GRID-HDRS-17	Grid version of the Hamilton Rating Scale for Depression, 17 item
HDRS-17	Hamilton Rating Scale for Depression-17
HEAP	Health economics analysis protocol
ICER	incremental cost-effectiveness ratio
ID	identification number
INBID	incremental net monetary benefits
iTBS	intermittent theta burst stimulation
ITT	intention to treat
lDMPFC	left dorsomedial prefrontal cortex
LEAP	Lived Experience Advisory Panel
MATLAB	multi-paradigm computer programming language
MCFLIRT	Motion Correction using FMRIB's Linear Image Registration Tool
MDD	major depressive disorder
mg	milligrams
MGH-S	Massachusetts General Hospital Staging Score
MNI	Montreal Neurological Institute
MPFC	medial prefrontal cortex
MRI	magnetic resonance imaging
MRS	magnetic resonance spectroscopy
NVIDIA CUDA	NVIDIA produced accelerated computing toolkit
XNAT	eXtensible Neuroimaging Archive Toolkit
PCC	posterior cingulate cortex
PDQ	Perceived Deficits Questionnaire

PFC	prefrontal cortex
PHQ-9	Patient Health Questionnaire, 9-item
PI	principal investigator
PPI	patient and public involvement
PSS	personal social services
PSSRU	Personal Social Service Research Unit
PTSD	post-traumatic stress disorder
QALYs	quality-adjusted life-years gained
QC	quality control
RA	research assistants
rAI	right anterior insula
RCTs	randomised controlled trials
rMT	resting motor threshold
rsfMRI	resting state (task-free) functional MRI
RT	response time
rTMS	repetitive transcranial magnetic stimulation
REST	RESting-state fMRI data analysis Toolkit
SAE	serious adverse event
SCID	Standardised Clinical Interview for DSM-V
SD	standard deviation
SE	standard error
sgACC	subgenual anterior cingulate cortex
SOP	standard operating procedure
SN	salience network
SNT	Stanford neuromodulation therapy protocol
SPMIC	Sir Peter Mansfield Imaging Centre
SPM12	Statistical Parametric Mapping toolkit version 12
TBS	theta burst stimulation
THINC-it	THINC-integrated tool for cognitive assessment
TMS	transcranial magnetic stimulation
TRD	treatment-resistant depression
TSC	Trial Steering Committee
VAS	visual analogue scale
VMPFC	ventromedial prefrontal cortex
VNS	vagus nerve stimulation
WSAS	Work and Social Adjustment Scale

Plain language summary

Transcranial magnetic stimulation delivers magnetic bursts of energy to the skull. It is recommended for use in the National Health Service in the United Kingdom by the National Institute for Health and Care Excellence as a treatment for treatment-resistant depression. Treatment-resistant depression is depression that has not improved with at least two different courses of treatment.

In this trial, we randomly allocated (like a toss of a coin) 255 individuals with treatment-resistant depression to either the usual repetitive transcranial magnetic stimulation delivered to a standard brain region, or to an alternative patterned form of transcranial magnetic stimulation delivered to an individually personalised site called connectivity-guided intermittent theta burst stimulation. We used the participants' magnetic resonance brain imaging scans to choose the site. All participants in the trial received 20 transcranial magnetic stimulation sessions over 4–6 weeks.

We measured depression, anxiety, functioning, thinking, memory, acceptability, side effects, quality of life, and costs of both treatments at baseline and at 8, 16 and 26 weeks after they were randomised. We used brain imaging techniques before and 16 weeks after they were randomised to measure brain connectivity (how parts of the brain interact with each other) and chemical changes in the brain that may change with depression symptoms.

Contrary to what we predicted, connectivity-guided intermittent theta burst stimulation was not more effective than repetitive transcranial magnetic stimulation on any of the outcomes except it might have cost a little less and slightly improved quality of life. About 20% of both groups showed a response lasting 26 weeks. Both treatment protocols were safe but often produced mild temporary side effects. Both treatments were acceptable. There were some associations between chemicals in the brain and improvement with treatments. There were similar changes in the way some parts of the brain interacted with each other when depression symptoms improved with transcranial magnetic stimulation.

We concluded that both transcranial magnetic stimulation treatments produce lasting improvements for some people with treatment-resistant depression. However, there were reasons other than transcranial magnetic stimulation why some of these people might have improved.

Scientific summary

Background

Major depressive disorder (MDD) is estimated by the World Health Organization in 2017 to be the leading cause of disability and suicide. About a third of MDD managed in specialist mental health services and 22% in primary care is treatment-resistant depression (TRD) that does not respond to two or more attempts to treat it. Alternative treatment approaches are required in addition to antidepressants and psychological treatments. Transcranial magnetic stimulation (TMS) was approved by the National Institute for Care Excellence for the management of depression and TRD because there is robust evidence of the effectiveness of active repetitive transcranial magnetic stimulation (rTMS) over sham rTMS. A recent large randomised controlled trial found that intermittent theta burst stimulation (iTBS) was non-inferior to rTMS in TRD but more cost-effective. However, there are concerns that rTMS and iTBS may be short-lived in effectiveness. Pilot work suggested that precise personalised iTBS stimulation using MRI measurement of effective connectivity between the right anterior insula (rAI) and left dorsolateral prefrontal cortex (lDLPFC) and neuronavigation might lead to longer duration of improvement in depression symptoms in TRD. Moreover, improvements in depression symptoms over 12 weeks were correlated with reductions in functional connectivity (FC) between the lDLPFC and the left dorsomedial prefrontal cortex (lDMPFC) and increases in gamma-aminobutyric acid (GABA) levels in the lDLPFC with connectivity-guided intermittent theta burst stimulation (cgiTBS) and MRI-neuronavigated rTMS. We propose that personalising iTBS through measuring effective connectivity between the rAI and lDLPFC may increase the duration of improvement in depression symptoms compared to standard rTMS.

Objectives

1. To determine the efficacy, that is the superiority, of personalised neuronavigated connectivity-guided intermittent theta burst stimulation (cgiTBS) over 8, 16 and 26 weeks on objective depression symptoms measured by the Hamilton Rating Scale for Depression-17 (HDRS-17) compared with personalised neuronavigated rTMS.
2. To explore secondary clinical outcomes namely subjective depression, anxiety, cognition, social function, quality of life and overall clinical improvement over 8, 16 and 26 weeks.
3. To examine cost-effectiveness of cgiTBS versus rTMS in a UK NHS population.
4. To examine the patient's acceptability and experience of cgiTBS and rTMS.
5. To explore baseline effective connectivity (EC) from rAI to lDLPFC and changes in EC between baseline and 16 weeks from rAI to lDLPFC, and clinical improvement in depression symptoms.
6. To explore change in FC between the lDLPFC-DMPFC, and clinical improvement in depression symptoms.
7. To explore the relationship of baseline FC between lDLPFC and subgenual anterior cingulate cortex (sgACC), and changes in FC between the lDLPFC and sgACC with clinical improvement in depression symptoms.
8. To explore baseline GABA, change in GABA from baseline to 16 weeks, and clinical improvement in depression symptoms.
9. To explore change in Glx (glutamate + glutamine) and GABA/Glx ratio from baseline to 16 weeks and clinical improvement in depression symptoms.

Methods

Design

This study was a multicentre parallel group, double-blind, randomised controlled trial, to test the efficacy of cgiTBS versus neuronavigated rTMS without connectivity guidance, in patients with a primary diagnosis of moderate to severe MDD, which was treatment resistant in their current episode.

Setting

This study was carried out at five sites across the UK NHS: Nottingham, Camden and Islington, Newcastle, Northampton and Oldham. Participants were recruited through secondary care services across the five study sites,

self-referrals, and patient identification centres compromising primary care services and secondary care services at neighbouring NHS trusts near the main study sites.

Inclusion criteria

- Adults ≥ 18 years.
- Diagnosis of current MDD (defined according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition), that is treatment resistant defined as scoring 2 or more on the Massachusetts General Hospital Treatment Resistant Depression Staging Score (MGH-S).
- Have an HDRS-17 score of 16 or more (moderate to severe depression).
- Capacity to provide informed consent before any trial-related activities.

Exclusion criteria

- History of bipolar disorder (due to risk of mania) or depression secondary to other mental disorder.
- Neurological conditions, for example brain neoplasm, cerebrovascular events, epilepsy, neurodegenerative disorders and prior brain surgery.
- Standard contraindications to MRI, that is irremovable metal objects in and around the body (e.g. a cardiac pacemaker or implanted medication pump) and pregnancy (any doubt was resolved by a pregnancy test, with women of childbearing age taking precautions against pregnancy) This included other potential complicated factors such as red tattoos, which consist of iron on the head, neck, and back, and claustrophobia.
- Major unstable medical illness requiring further investigation or treatment.
- Change in prescribed medication 2 weeks before baseline assessment.
- Prescription of lamotrigine, gabapentin, or pregabalin in the 2 weeks prior to baseline assessment.
- Daily prescription of benzodiazepine above 5 mg diazepam equivalents, zopiclone above 7.5 mg, zolpidem above 10 mg or zaleplon above 10 mg. These drugs should not be used intermittently in the 2 weeks before baseline assessment.
- Current substance abuse or dependence [defined by Diagnostic and Statistical Manual of Mental Disorder version 5 (DSM-5) criteria).
- At risk of suicidality.
- Potential complicated factors relating to the TMS treatment, such as hairstyles that would impair magnetic transmission and piercings. Participants would be excluded only if they chose to not make the changes required to ensure effective treatment.
- Involved with any other clinical trial at the time of consent or 6 months prior.
- Unable to read or understand English.

Randomisation

Participants were randomly assigned in a 1 : 1 ratio into the rTMS and cgiTBS arms. Randomisation was stratified by study site and minimised on severity of depression (HDRS-17 score 16–23 moderate or ≥ 24 severe) and degree of treatment resistance [low 2–3.5, medium 4–6, high (≥ 6.5) as assessed at baseline].

Blinding to trial arm

Participants, referring clinical teams, and the outcomes assessors were kept blinded with respect to the assigned treatment until after the participants' final follow-up assessment. Any unintended unblinding of outcome assessors were recorded, with other assessors completing all further assessments for that participant. At each follow-up assessment, the outcomes assessor was asked to guess the participants' treatment allocation.

Trial interventions

A total of 3000 pulses were delivered in each rTMS or cgiTBS session, with 20 TMS sessions delivered over a 4–6-week period. Each session for both cgiTBS (80% motor threshold) and rTMS (120% motor threshold) lasted approximately 37.5 minutes in total for the purposes of blinding participants and assessors of outcome. Multimodal magnetic resonance imaging (MRI) was acquired for each participant at baseline (before TMS treatment) with T1-weighted (structural MRI) and resting state (task-free) functional MRI (rsfMRI). Personalised TMS stimulation targets were identified from MRI (F3 site for rTMS, maximum EC from rAI to lDLPFC for cgiTBS) and the site was delivered via neuronavigation.

Primary outcome

The primary outcome measure was mean change in depression symptoms from baseline over 26 weeks using the 17-item Grid version of the HDRS-17 assessed at baseline and at 8, 16 and 26 weeks.

Secondary outcomes

Secondary outcomes were response (50% drop from baseline HDRS-17 score) and remission (< 8 on HDRS-17) at 8, 16 and 26 weeks, and sustained response at 16 and 26 weeks. HDRS-17 score measured separately at 8, 16 and 26 weeks. Self-rated measures of depression (PHQ-9, BDI-II), Generalised Anxiety Disorder-7, function (WSAS), quality of life [EuroQol-5 Dimensions, five-level version (EQ-5D-5L)], and overall improvement (EQ-5D-5L VAS) were collected at 8, 16 and 26 weeks. Service use was recorded at baseline, 16 and 26 weeks. Cognition (THINC-it battery) was tested at baseline and 16 weeks. Patient-rated overall health and acceptability were rated after each TMS session and at 8, 16 and 26 weeks with the adverse events (AEs) checklist recorded after each TMS session.

Sample size calculation

A sample size of 266 participants provides 89.3% power to detect a mean difference of 3 points in the HDRS-17 over 26 weeks between the groups at a 5% two-sided significance level assuming a standard deviation (SD) of 8, with a correlation between follow-up measures of 0.7 and 20% data loss/drop-out.

Statistical analysis

Primary analysis of the primary outcome used the intention-to-treat (ITT) population with the multiple imputation technique being implemented to deal with missing data in instances where participants were missing any of the HDRS-17 scores.

Qualitative methods and analysis

A purposive sample was collected of participants and non-participants to explore facilitators and barriers to participation in the trial, and the acceptability of the trial treatments. Analysis was inductive using thematic analysis of transcribed interview data.

Neuroimaging

Participants' baseline and 16-week MRI scans (the London site underwent scanning at the baseline time point only), were carried out at the same site and using the same scanner platform (all 3T), using a core protocol across the

treatment sites (scanner sites Nottingham for Nottingham and Northampton; Newcastle, London, and Manchester for Oldham). rsfMRI and structural MRI was conducted at all sites and Mesher-Garwood Point Resolved Spectroscopy (MEGA-PRESS) magnetic resonance spectroscopy (MRS) scans in the DlPFC at Nottingham and Newcastle only. Using rsfMRI, FC and EC were calculated to address the mechanism-of-action hypotheses. Neurochemical changes were assessed as ratios of GABA+ (including macromolecules) and glutamate and glutamine (Glx) to total creatine (tCr).

Health economics analysis

The primary costing perspective was of the NHS and personal social services, in line with NICE guidance. A secondary broader societal perspective was also considered. Health-related quality of life (HRQoL), health service resource use and broader societal costs were collected at baseline and 16 and 26 weeks for assessing the cost-effectiveness of cgiTBS and rTMS to the NHS. Planned analyses included a within-trial descriptive assessment of costs and outcomes, and a fully incremental cost-effectiveness analysis with uncertainty explored using deterministic and probabilistic sensitivity analyses.

Results

Baseline characteristics and flow into the study

Completion of initial telephone screening was undertaken with 685 individuals: 317 consented to the trial, 39 were excluded and 23 withdrew from baseline to first randomisation. A total of 255 participants were randomised, 128 to cgiTBS and 127 to rTMS. There were no significant differences in treatment completion between the groups, with 235 (92.8%) completing all 20 TMS sessions or follow-up in rTMS or cgiTBS, respectively, at 8 weeks (112/127, 88.2% vs. 111/128, 86.7%), 16 weeks (112/127, 88.2% vs. 112/128, 87.3%) or 26 weeks (102/127, 80.3% vs. 104/128, 81.3%).

At baseline, participants had a mean (SD) age of 43.7 (14.0) years, 132 (51.8%) were female, 232 (91%) were of white ethnicity and 23 (9%) were from ethnic minority backgrounds. A total of 138 (54.1%) were in full-time or other employment, 87(34.1%) were unemployed, and 30 (11.8%) were retired. The mean duration of the current depression episode was 113.9 months. A total of 95 participants (37.3%) were categorised as high treatment resistance, 73 (28.6%) medium treatment resistance and 87 (34.1%) low treatment resistance. A total of 198 participants (77.6%) were taking antidepressants.

Primary outcome

The mean (SD) HDRS-17 scores in the rTMS and cgiTBS groups at baseline were 23.9 (4.7) and 22.9 (4.7), at 8 weeks 15.8 (7.3) and 14.6 (6.2), at 16 weeks 16.1 (7.5) and 15.2 (7.3), and at 26 weeks 16.5 (7.9) and 14.9 (6.9). There were no significant differences between rTMS and cgiTBS in the primary outcome in the ITT {adjusted mean −0.31 [95% confidence interval (CI) −1.87 to 1.24]}, completers or per-protocol analyses.

Secondary outcome

There were no significant differences between rTMS and cgiTBS on any of the secondary outcome measures. Response rates in the rTMS group were 35/112 (31.3%) at 8 weeks, 38/112 (33.9%) at 16 weeks and 31/102 (30.4%) at 26 weeks; in the cgiTBS group they were 39/111 (35.1%) at 8 weeks, 39/112 (34.8%) at 16 weeks, and 36/104 (34.6%) at 26 weeks. Remission at 8 and 16 weeks was 23/127 (18.1%) in the rTMS group and 28/128 (21.9%) in the cgiTBS group. Sustained response rates at 16 and 26 weeks were 22/127 (17.3%) in the rTMS and 29/128 (22.7%) in the cgiTBS groups. There were improvements in subjective cognition, attention and sustained attention as a result of improved depression on the THINC-it cognitive battery. Subjective overall improvement accumulated over the whole 20 sessions in both rTMS and cgiTBS. Health service and societal costs were lowest for cgiTBS; differences between arms were predominantly driven by outpatient hospitalisation attendances, productivity losses and private service utilisation.

Moderators

Baseline severity of depression, treatment resistance, number of treatment sessions, baseline anxiety, age and childhood trauma did not interact with treatment arn to predict treatment response. However, baseline severity of depression and anxiety, number of treatment sessions delivered per protocol and treatment resistance alone predicted severity of depression.

Adverse events

There were two deaths, both in the cgiTBS group, that were judged to be unrelated to TMS. There was one serious adverse event (SAE) in each group (mania and psychosis with depression and anxiety) that might be attributable to TMS, but in both instances there were other contributory factors. A total of 204 (80.3%) participants reported at least one AE. There were more mild or moderate AEs possibly related to TMS in the cgiTBS group than the rTMS group, with the vast majority resolving the same day and without any treatment or sequelae.

Patient acceptability

There were no differences in patient acceptability between the treatments. A total of 180 (75.2%) reported TMS treatments to be acceptable at the 20th TMS session, 52 (21.9%) were neutral and 5 (2.1%) report treatments to be unacceptable.

Functional connectivity

The balance of influence between IDLPFC and right AI at baseline predicted clinical improvement on the observer-rated HDRS-17. However, contrary to the hypothesis, greater influence from IDLPFC to right AI at baseline was associated with greater improvement. Baseline FC between sgACC and the intended treatment target within IDLPFC predicted self-reported reduced depression symptoms at 8 weeks but worse depression symptoms at 16 and 26 weeks. Greater reduction in FC between left DMPFC and a posterior IDLPFC site from baseline to 16 weeks was associated with reductions in self-reported depression symptoms at 16 and 26 weeks.

Magnetic spectroscopy

Higher baseline prefrontal GABA+/tCr moderated greater clinical improvement in observer-rated depression symptoms when depression change was averaged over 8, 16 and 26 weeks, with a trend for self-reported depression over 16 and 26 weeks. Decrease in glutamate and glutamine ratio to creatine and phosphocreatine from baseline to follow-up was associated with trends towards greater clinical improvement on HDRS-6 at 16 and 26 weeks and HDRS-17 at 26 weeks.

Health economics

From a health service perspective, cgiTBS dominated rTMS by producing moderately greater improvements in HRQoL and related quality-adjusted life-years gained (QALYs) [cgiTBS 0.275 (95% CI 0.26 to 0.29) QALYs; rTMS 0.265 (95% CI 0.25 to 0.28) QALYS] at a marginally cheaper cost [cgiTBS £3256.79 (95% CI £2994.69 to £3522.75); rTMS £3436.98 (95% CI £3148.63 to £3719.60)]. Findings were consistent between adjusted and unadjusted analyses. This finding was consistent when a broader societal viewpoint was considered. In some scenarios, cgiTBS remained dominant, for example the use of EuroQol-5 Dimensions, five-level version (EQ-5D-5L) preference values, when assuming MRI was not required for rTMS but theta burst stimulation (TBS) would take 30 minutes less time to deliver relative to rTMS; but not in others, for example when assuming MRI was not required for rTMS.

Conclusion

Connectivity-guided intermittent theta burst stimulation was not superior in efficacy to standard rTMS although it was dominant in terms of cost-effectiveness, but with uncertainties. Using MRI to personalise rTMS or iTBS together with neuronavigation alongside usual care is a safe, acceptable, and clinically efficacious method of substantially reducing depression symptoms for at least 26 weeks in people with moderately severe TRD of long duration, albeit with frequent minor self-limiting AEs and non-specific reasons for such improvement.

Study registration

Current Controlled Trials ISRCTN19674644.

Funding

This award was funded by the National Institute for Health and Care Research (NIHR) Efficacy and Mechanism Evaluation (EME) programme (NIHR award ref: 16/44/22) and is published in full in *Efficacy and Mechanism Evaluation*; Vol. 12, No. 2. See the NIHR Funding and Awards website for further award information.

Chapter 1 Introduction

Clinical efficacy

Worldwide, major depressive disorder (MDD) affects 13% of the general population,[2] making it the leading cause of disability and suicide.[3] Antidepressants and psychotherapies, such as low-intensity psychological interventions and cognitive–behavioural therapy, are found to be effective for MDD. However, a proportion of individuals with MDD will be 'treatment resistant', with 33% patients in specialist care[4] and 22% in primary care failing to adequately respond to two trials of antidepressants.[5] Compared with MDD that is not treatment resistant, treatment-resistant depression (TRD) is associated with higher rates of suicide,[6] hospitalisation, poor physical health, and increased costs.[7] Therefore, it is essential to find alternative treatments for such TRD.

Therapeutic interventions that can directly modulate the function of targeted brain regions such as electroconvulsive therapy (ECT)[8] and repetitive transcranial magnetic stimulation (rTMS)[9] can have a significant impact on reducing the burden of TRD symptoms. rTMS employs strong magnetic pulses to alter activity in neural circuits in the brain implicated in the pathophysiology of depression. Compared to ECT, rTMS does not require anaesthesia. While ECT can be associated with a negative impact on cognitive functioning,[10] rTMS has shown modest cognitive enhancing effects when compared to sham treatments.[11,12] However, it is difficult to ascertain whether these potential modest cognitive enhancing benefits are separate or secondary to overall depression improvement as well as the influence of practice effects.[13] Repetitive transcranial magnetic stimulation is also reported to be a more cost-effective first-line treatment than ECT due to better health outcomes and being less expensive.[14]

Repetitive transcranial magnetic stimulation is either high frequency to generally increase excitability or low frequency to generally induce inhibition, with the left dorsolateral prefrontal cortex (lDLPFC) most targeted for MDD. Meta-analyses of randomised controlled trials (RCTs) have shown that when compared to sham treatments, high-frequency rTMS[15] and low-frequency rTMS[16] were significantly associated with improvement in clinical symptoms in MDD. These findings also extend to TRD, showing reductions in depression symptoms and increases in response and remission rates after rTMS treatment.[9] Hence in 2015, the National Institute for Health and Care Excellence (NICE) recommended the use of rTMS, including theta burst stimulation (TBS), for use of depression and TRD in the NHS.[17] Stratified data have also demonstrated that the effectiveness of rTMS may be higher when used as an add-on to antidepressant medication.[18] The majority of RCTs have focused on the immediate efficacy of rTMS, with only a few RCTs reporting long-term follow-up efficacy. However, the beneficial effects of rTMS on mood in TRD may be relatively short, lasting only 1–3 months.[9,17] Therefore, while rTMS appears to be effective for MDD and TRD in the short term, there is uncertainty about patient selection for TMS, the best TMS treatment regime for use, its use as a maintenance treatment (given the relatively short-lived duration of response after each course of treatment), and long-term outcomes of patients undergoing the treatment. Hence NICE encourages studies addressing these issues.[17]

Theta burst stimulation is an alternative patterned form of rTMS, which employs high-frequency stimulation, with each treatment administration requiring less time. Unlike standard rTMS, TBS uses bursts of magnetic pulses that mimic endogenous theta rhythms, and it is associated with cortical long-term potentiation that may induce plasticity in more distal brain areas, such as the hippocampus, potentially leading to a higher proportion of responders and a longer duration of effect in TRD.[19] This includes intermittent TBS (iTBS), which is expected to enhance cortical excitability, and continuous TBS, which is expected to supress cortical excitability. In addition, rTMS is sometimes used as a generic term for all forms of TMS, including iTBS, but in this report we use it to refer to repetitive transcranial magnetic stimulation only and not as a generic term.

Recent meta-analyses including RCTs, and uncontrolled clinical trials have shown that TBS is superior to sham treatments in MDD.[20–22] One meta-analysis also reported that TBS is non-inferior versus left DPLFC high-frequency rTMS,[22] albeit this finding was due to one large high-quality non-inferiority RCT of 414 TRD patients.[23] Furthermore, a recent meta-analysis reported that TBS applied to the DLPFC has high tolerability, and the optimal parameters of TBS protocols may include ≥ 1800 pulses per session, subthreshold stimulation intensities, and protocols including iTBS.[21]

It is proposed that more precise identification of DLPFC targets may improve the efficacy of TMS treatments. Neuronavigation technology can co-register a patient's head with their structural magnetic resonance imaging (MRI) scans, which can enable real-time and on-line feedback for how to adjust the TMS coil to be on target.[24] A recent study found that compared to neuronavigated targeting, traditional elastic cap scalp targeting was significantly more off-target in relation to distance, roll/pitch angle and yaw angle deviation, with greater coil drift over time.[24] One prospective MDD clinical trial found MRI-guided neuronavigation TMS had significantly greater clinical efficacy compared to scalp-based targeting methods,[25] whereas other small studies have found no difference in clinical efficacy when comparing these targeting methods.[26,27] However, theoretically, off-target stimulation and coil drift during TMS sessions may suboptimally stimulate neural circuits of interest, which may affect clinical response.[24]

To our knowledge there are two RCTs that have compared 600 pulse iTBS versus high-frequency rTMS, using structural MRI-guided neuronavigation to target the DLPFC. As previously mentioned, the large high-quality Three-D trial found that iTBS was non-inferior to higher-frequency rTMS at 4 and 12 weeks after treatments.[23] There is also the THETA-DEP trial that found similar response and remission rates, between MRI-guided neuronavigated iTBS and rTMS, with both groups having a similar sustained decrease in depression scores up to 6 months after baseline.[28] It should be noted that this latter trial was published after recruitment to the BRIGhTMIND trial had completed. In addition, while it is limited by a small sample size of 60 participants and a single centre study with modest treatment resistance and duration of depression episode, it does demonstrate that MRI-neuronavigated treatments may provide longer-lasting durations of depression response.

In addition, non-invasive neuromodulation may affect brain networks rather than just the local stimulation site targeted, and it has further been proposed that modulation of targeted brain networks may yield therapeutic potential.[29] Thus, there is increasing recognition of the value of using brain connectivity changes as detected by non-invasive resting state (task-free) functional MRI (rsfMRI) to individualise neurostimulation therapy of MDD.[30] Towards these aims, two complementary characteristics of brain network function can be derived from rsfMRI: metrics that quantify the degree of synchronisation of neural activity between regions or networks known as functional connectivity (FC),[31] or the influence one brain region's activity exerts on another known as effective functional connectivity (eFC).[32,33] Importantly, FC-guided personalised TMS targets have been found to be reliably and robustly pinpointed, remaining stable over 1 year, with target locations varying widely across individuals.[34] This demonstrates that connectivity-guided personalised TMS targets can be reproduced with excellent precision which do not trivially converge to a group-average site.[34]

A triple network model comprising inter-region brain connectivity between the default mode network (DMN), salience network (SN), and central executive network (CEN) may represent a major abnormality across psychiatric disorders.[35] The DMN is involved in internally directed/self-referential mental activity and comprises the ventromedial prefrontal cortex (VMPFC), the posterior cingulate cortex (PCC), bilateral inferior parietal cortex, and the middle temporal lobe.[36] The SN is involved in detecting and filtering relevant salient external and internal stimuli and comprises the anterior insula (AI) and the dorsal anterior cingulate cortex.[37] The CEN is crucial for maintaining and manipulating decision-making and working memory and primarily comprises the dorsolateral prefrontal cortex (DLPFC) and posterior parietal cortex.[38] It is proposed that TMS stimulation of the DLPFC (key node of the CEN) may directly modulate key nodes within the SN and DMN, which in turn rebalances abnormal FC between and within networks.[39] A disruption of the reciprocal loop between the DLPFC and insula has been found in depression,[33] and given these are key nodes of the CEN and SN respectively, dysfunction of such a loop would have greater effects on these major brain networks. Therefore, the insula is suggested to be a target for neuromodulation.[40]

One biotype of MDD, characterised by strong FC between the insula and other regions of the brain, has been related to at least 25% improvement in depression symptoms in 82.5% of participants following rTMS delivered to the

dorsomedial prefrontal cortex (DMPFC).[41] However, these findings were not replicated in a more recent methodological extension of this study when utilising a more heterogeneous sample of individuals with depression and anxiety.[42] In addition, in a small pilot study of 27 TRD patients, individualised connectivity-guided IDLPFC targets were determined using Granger causality analysis to provide a measure of eFC seeded from the right anterior insula (rAI).[43] They found in the 18 participants who completed all follow-ups that there were a higher proportion of participants with at least 50% reduction in depression symptoms at the 3-month follow-up favouring connectivity-guided iTBS (cgiTBS; 89% of participants) over connectivity-guided rTMS (44% of participants). These findings did not reach statistical significance, but they suggest that iTBS delivered according to connectivity with the insula could lead to longer-lasting efficacy.

It should also be highlighted that alongside the right AI, there is also a significant amount of work to suggest that the subgenual anterior cingulate cortex (sgACC) might be a potential target for TMS treatment. A number of studies have shown that stronger baseline anti-correlations between DLPFC treatment sites and the sgACC are predictive of response to TMS.[44–46] Additionally, clinical response to TMS was significantly greater for participants whose actual targets (beam F3) were serendipitously closer to personalised connectivity-guided targets (based on strongest anti-correlation between DLPFC and sgACC).[47] It also needs to be acknowledged that since the conceptualisation of the BRIGhTMIND study, the Stanford neuromodulation therapy (SNT) protocol has been developed.[48,49] The SNT protocol includes 10 sessions of iTBS per day over 5 consecutive days at an adjusted 90% resting motor threshold (rMT) (1800 pulses per session with 50-minute inter-session intervals) and a personalised individual IDLPFC treatment target based on the strongest FC anti-correlation between the IDLPFC and sgACC. Following the SNT protocol, an open-label study and an RCT with placebo control demonstrated 90.5% and 46.2% reached response and remission, respectively at least once in the 4 weeks after treatment.[48,49] The remission rates identified in these studies are commendable; however, they are currently limited by small sample sizes, were not necessarily sustained even at the end of 4 weeks, and equally it is difficult to disentangle whether the efficacy of this protocol may be a consequence of a combination or singular components of its parameters (for example DLPFC targeting method, or greater dose of treatments). Nevertheless, they further emphasise the importance of the continued refinement of TMS protocols and parameters to improve the clinical efficacy of iTBS.

Overall, the research suggests that iTBS may induce widespread and longer-term network change, but that precise anatomical localisation of the target circuitry may be required for maximal efficacy of iTBS to normalise dysfunctional fronto-limbic circuitry. In our view, the clinical importance of cgiTBS is in its potential for a longer duration of response to 16 or even 26 weeks, permitting people with TRD to remain well with 1 or 2 courses of TMS per year. Thus, the study of choice in terms of maximising clinical effectiveness would be a comparison of cgiTBS versus neuronavigated rTMS. Such changes may increase the proportion of people with TRD who reduce their depression symptoms over 26 weeks or obtain a sustained response compared with neuronavigated rTMS.

Primary and secondary clinical efficacy objectives

Therefore, the primary aim of BRIGhTMIND was to examine the efficacy of cgiTBS versus neuronavigated standard rTMS, in treatment-resistant moderate to severe MDD (TRD), originally before the coronavirus disease discovered in 2019 (COVID-19) pandemic by response at 16 weeks, and then by their mean change in depression symptoms over 8, 16 and 26 weeks. We reported on a multicentre RCT in patients with TRD who had a Massachusetts General Hospital Staging Score (MGH-S) of 2 or more, who had not responded to two different antidepressant regimes, antidepressant augmentation strategies, high prolonged dosages of antidepressants, or ECT in their current episode. Study hypotheses are reported in *Table 1*.

We also reported on other secondary clinical outcomes of importance to patients and clinicians, namely cognition, anxiety symptoms, social function, quality of life and overall clinical improvement. Clinically important change would be supported by improvements across all these outcomes.

Safety, acceptability, facilitators and barriers of transcranial magnetic stimulation

Evidence suggests that TMS in depression is generally well tolerated, and a recent meta-analysis showed common side effects such as headaches, discomfort and pain at the stimulation site are mostly mild and transient after TMS treatment,

TABLE 1 Clinical efficacy and mechanism-of-action hypotheses

Clinical efficacy primary hpothesis
'cgiTBS is more efficacious in reducing the mean HDRS-17 score over 26 weeks compared to standard rTMS in patients with TRD'
Clinical efficacy secondary hypotheses
'cgiTBS is more efficacious for secondary clinical outcomes compared to standard rTMS in patients with TRD' 'Treatment with rTMS and cgiTBS will lead to an improvement in cognition and reduction in inter individual variability between baseline and week 16 that correlates with improvement in mood'
Mechanism of action – baseline connectivity primary hypothesis
'Greater clinical improvement on 17-item HDRS, averaged across all post-treatment time points (8, 16 and 26 weeks), will be associated with more positive baseline EC from rAI to lDLPFC, and this relationship will be stronger in the cgiTBS group'
Mechanism of action – baseline connectivity secondary hypotheses
'Greater clinical improvement on 17-item HDRS (averaged across all post-treatment time points), will be associated with more positive baseline net outflow from rAI to lDLPFC, and this relationship will be stronger in the cgiTBS group' 'Greater clinical improvement on 17-item HDRS (averaged across all post-treatment time points), will be associated with more negative baseline FC between subgenual anterior cingulate cortex (sgACC) and lDLPFC across both treatment groups'
Mechanism of action – connectivity change primary hypothesis
'Reduction in lDLPFC–lDMPFC FC from baseline to 16 weeks will be associated with greater clinical improvement (averaged across all post-treatment time points), across both treatment groups'
Mechanism of action – connectivity change secondary hypotheses
'Reduction in lDLPFC – lDMPFC FC from baseline to 16-week follow-up will be greater in HDRS-17 responders than non-responders (averaged across all post-treatment time points), across both treatment groups' 'Reduction in rAI-to-lDLPFC EC from baseline to 16-week follow-up will be associated with greater clinical improvement (averaged across all post-treatment time points), and this relationship will be stronger in the cgiTBS group' 'Reduction in net outflow from rAI to lDLPFC from baseline to 16-week follow-up will be associated with greater clinical improvement, and this relationship will be stronger in the cgiTBS group' 'Increase in sgACC–lDLPFC FC (reduction in anti-correlation) from baseline to 16-week follow-up will be associated with greater clinical improvement, across both treatment groups'
Mechanism of action – baseline and change in GABA primary hypotheses
'Greater clinical improvement on 17-item HDRS (16 weeks versus baseline) will be associated with increase in GABA between baseline and 16 weeks (post minus pre-treatment) in both treatment groups' 'Greater clinical improvement on 17-item HDRS (26 weeks versus baseline) will be associated with increase in GABA between baseline and 16 weeks (post minus pre-treatment) in both treatment groups' 'Greater clinical improvement on 17-item HDRS (16 and 26-week vs baseline) will be associated with lower GABA at baseline across both treatment groups'
Mechanism of action – spectroscopy secondary hypotheses
'GABA+/Cr increase will be higher in cgiTBS compared to rTMS group (all patients)' 'Greater averaged and sustained clinical improvement on 17-item HDRS (averaged over 8-,16-, and 26-week follow-up) will be associated with more GABA+/Cr change across both treatment groups' 'Greater averaged and sustained clinical improvement on 17-item HDRS (averaged over 8-, 16-, and 26-week follow-up) will be associated with lower GABA+/Cr at baseline across both treatment groups' 'Glx/Cr increase will be higher in cgiTBS compared to rTMS group (all patients)' 'Changes in depression symptoms on 17-item HDRS (16 weeks versus baseline, and 26 weeks versus baseline) will be associated with change in Glx/Cr between baseline and 16 weeks (post minus pre-treatment) in both treatment groups' Exploratory hypotheses: 'GABA+/Glx changes will be associated with clinical outcomes (17-item HDRS at 16 and 26 weeks)'

with the risk of more serious adverse events (SAEs) such as seizure, syncope and mood switches considered rare.[50] A further meta-analysis showed no significant difference in combined serious and non-SAEs between TBS and either rTMS or sham treatments.[22] However, self-rated intensity of pain was significantly greater for TBS treatment than rTMS, and the comparison of adverse events between TBS and rTMS was limited to two RCTs and combined both SAEs and

non-SAEs.[22] Therefore, further work is required that provides greater descriptive details of the comparison of side effect profiles for both TBS and rTMS as well as the influence of connectivity-guided personalised targets.

Patient experience is also an important aspect of treatment, and this insight alongside evidence of side effects may help identify important topics for patients both willing and not willing to undergo TMS treatment, which could improve both future research and clinical service implementation.[51] Acceptability of TMS for depression has been widely reported in relation to treatment adherence, with no differences in drop-out rates when comparing either rTMS or TBS protocols with sham protocols.[20,52] A small number of qualitative and quantitative studies have investigated other facets of acceptability and experience of TMS treatments for depression. A telephone survey study reported that the vast majority of individuals undertaking TMS found it helpful and more acceptable than the prospect of having ECT, and would have TMS again, as well as recommending it to others.[53] However, surveys alone provide a small amount of information which limits the exploration of the patients' experience. A study using open-ended interviews has also explored the acceptability of rTMS for TRD, which highlighted the frustration and helplessness linked to pharmacological treatments, the experience of TMS (including physical response to treatments), mindfulness and awareness experienced during sessions, and the importance of the rapport with the clinician.[54] Clinician rapport has further recently been established as a key non-clinical factor of TMS treatments suggested to influence participants response and experience. Notably, clinicians have an important role from delivering TMS treatment, to engaging in constructive therapeutic conversations, providing a relaxing and friendly environment, as well as supportive long-term management.[55]

This prior research provides significant implications for practice guidance. However, while it focuses predominantly on the patients' experience of rTMS, patients' experience of TBS treatment has not been explored, as well as factors impacting decisions to undergo TMS treatment or not, and any concerns individuals may have.

One recent study, which was related to the original pilot study, has examined emails using thematic analysis to explore the reasons why individuals with depression self-referred for TMS treatment. Six themes were identified, namely: treatment resistance; side effects of other treatments; desperation for relief; proactively seeking information; long-term illness; and illness getting worse.[56] The authors of this study recommend that future research should include interviews with participants to further explore reasons for seeking TMS treatment, to see whether similar reasons are identified.[56] In addition, this study did not identify barriers to participants unwilling to undergo TMS treatment and this too requires further exploration.

Safety, acceptability, facilitators and barriers of transcranial magnetic stimulaton objectives

Therefore, objectives of the BRIGhTMIND study were to: (1) compare AEs and side effect profiles of rTMS versus cgiTBS; (2) explore patients views on the acceptability and experience of rTMS and cgiTBS, as determined by adjustments made to TMS protocols for tolerability, qualitative interviews assessing patient experiences and quantitative measures of patient acceptability; and (3) understand the initial barriers and facilitators to recruitment of participants to the trial.

Economic evaluation objective

To examine whether cgiTBS represents a cost-effective use of resources compared to rTMS in treating moderate to severe TRD in the UK NHS setting.

Economic evaluation

In addition to examining the clinical efficacy of cgiTBS, the BRIGhTMIND study will also examine the cost-effectiveness of cgiTBS relative to rTMS.

Treat resistant depression was estimated to cost the UK economy £3.8M in 2018 with direct health and social costs of £4383 per patient and indirect costs of £22,124.[57] High indirect costs were largely driven by absenteeism and costs to

families. The direct costs are in line with previous research in specialist mental health services that we have conducted. In direct NHS and social care costs, TRD costs about £4–5000 per patient per year often for many years, while patients seen in a specialist depression service offering both NICE-recommended psychotherapy and pharmacotherapy, the costs are typically £7–8000.[58]

Treatment-resistant depression is a heterogeneous condition with many different patterns of progression and outcome. This complexity, combined with individual patient circumstances, has led to diverse range of treatment pathways for TRD. In addition to ECT, other invasive neuromodulation approaches such as deep brain stimulation (DBS) or vagus nerve stimulation (VNS) may be employed. These all carry high degrees of risk by their nvasive nature or through serious and sometimes permanent cognitive side effects. They require the expertise of other specialist services such as anaesthetists and neurosurgeons. A major problem is that most patients with TRD are managed within secondary care mental health services that do not have expertise in high-level psychotherapy or pharmacotherapy or around the use of DBS and VNS. An easy to deliver, effective, well tolerated and relatively cheap intervention for TRD, such as TMS, is therefore required. Improvements in therapeutic treatment options for TRD stands to address a variety of unmet needs, alleviate substantial decrements to health, and may achieve health service and societal savings.

Prior studies have shown rTMS to be a dominant/cost-effective alternative when compared with pharmacotherapy and sham treatments with higher quality-adjusted life-years gained (QALYs) for individuals with TRD.[59–61] Cost savings from rTMS accrued via reductions in medication courses psychotherapy and ECT sessions compared with usual care. In addition, the shorter session durations and increased treatment capacity associated with iTBS led to significant cost savings per patient and per remission when compared to standard rTMS.[62] However, it remains unknown about the cost-effectiveness of iTBS when utilising personalised connectivity-guided targets (known as connectivity-guided iTBS or cgiTBS).

While the current proposed cgiTBS requires structural and functional magnetic resonance imaging (fMRI) to maximise efficacy, such scans are readily available in current NHS facilities and have the additional potential of individual response prediction. Furthermore, given that personalised connectivity-guided targets are suggested to be reliable and stable over time,[34] MRI scans may be required only once for a patient even if multiple courses of treatment are needed to maintain their health over the longer term, demonstrating the potential practical utility of the technique. It is likely that if cgiTBS had efficacy over 3–6 months with high patient acceptability and tolerability, there would be widespread benefits to health services and society. These arise not only from reduced use of other types of treatment for depression, reduced self-harm, suicide, and hospitalisation but also from return to work, improved physical health, and improved parental and other family care. Given how highly recurrent MDD can be, especially for patients with TRD, long-term maintenance of health is also critically important. Patients who remain well with cgiTBS over 6 months may only require two courses per year, again further decreasing costs of repeated treatment that is often necessary in practice with rTMS, hence potential long-term saving with cgiTBS.

Mechanism of action

A further objective of the BRIGhTMIND RCT was to analyse the mechanism of action of TMS by studying underlying neurochemical changes using magnetic resonance spectroscopy (MRS) and brain connectivity using rsfMRI.

As previously mentioned, stimulation of the CEN may directly modulate key nodes within the SN and DMN.[39] TMS studies in depression have shown baseline FC strength between the lDLPFC and bilateral insula,[63] and between the PCC and right AI,[64] are positively correlated with treatment response. Importantly the former finding only demonstrated predictive effect when the seed of the lDLPFC was selected as a node in the CEN rather than the traditional BA9 or BA46.[63] Following connectivity-guided rTMS or iTBS, baseline eFC of net rAI outflow to lDLPFC was associated with treatment response at participants' 1 month follow-ups, but not 3-month follow-ups.[43] More specifically early response to treatment was superior in those that had greater positive rAI to lDLPFC influence (outflow) than lDLPFC to rAI influence (inflow) at baseline, suggesting more normal inflow/outflow balance between these brain regions could better facilitate fronto-insular modulation, in turn alleviating depressive symptoms.[43] Further modulatory evidence of fronto-insular connectivity comes from studies comparing FC before and after TMS treatments. Following iTBS treatments, reduced FC from lDLPFC to the rAI has been found in depressed individuals[65] and healthy controls,[40] with dampening

of DMPFC-bilateral insula connectivity also associated with better treatment response.[66] Overall, the findings suggest an important role of the SN CEN/DMN interaction, with stronger baseline connectivity of the lDLPFC-insula and dampening of this connectivity following TMS treatments to be particularly predictive of clinical efficacy.

Preliminary mechanistic evidence further suggests that lDLPFC-targeted TMS may modulate connectivity between the CEN and DMN in depression. While baseline connectivity between the lDLPFC and nodes of the CEN or DMN were not associated with treatment response, there were TMS induced anti-correlated connectivity between the lDLPFC and left medial prefrontal DMN nodes.[67] This is further supported by the pilot work, which showed a reduction in FC between the DLPFC and lDMPFC following TMS and change in lDLPFC-lDMPFC FC significantly associated with change in depression symptoms.[68] A more recent study also reported a significant relationship between symptom changes and altered bilateral DMPFC-right DLPFC FC following ECT.[69]

Alongside the rAI, there is also a significant amount of work to suggest that the sgACC should be a potential target for TMS treatment. Several studies have shown that stronger baseline anti-correlations between lDLPFC treatment sites and the sgACC are predictive of response to TMS.[44–47] Additionally, reduction in connectivity between the sgACC and nodes in the DMN,[64,70] ECN[64] and SN[70] have been associated with treatment response following TMS. A more recent study also demonstrated a decrease in FC between sgACC and the right DLPFC, fusiform gyrus and middle occipital cortex, both in responders and in non-responders.[71] The results overall suggesting that TMS may result in a reduction in connectivity (reduced anti-correlations) between the sgACC and the CEN, which may correlate with treatment response.

In regard to neurochemical changes, brain gamma-aminobutyric acid (GABA) and/or glutamate systems play a key role in inhibitory and excitatory neural processes associated with both changes in long-term potentiation and depression of synaptic transmission.[72] It is proposed that the mechanism of action of TMS and other antidepressant treatment modalities involve GABA and or/glutamate systems.[73,74]

A recent systematic review demonstrated that following lDLPFC rTMS, frontal-lobe increases of GABA, glutamatergic compounds and *N*-acetylated compounds were commonly associated with clinical improvement in MDD.[75] For example, following rTMS an increase in GABA in the MPFC[76] and lDLPFC[77] has been observed, with changes in lDLPFC GABA found in responders[74] and correlating with symptom change.[77] A more recent study found no changes in lDLPFC GABA following rTMS, however there was an increase in lDLPFC Glx (glutamate + glutamine) post rTMS, with baseline Glx levels correlating with symptom change.[78] Furthermore, Dubin *et al.*[76] found GABA/W and Glx/W were highly correlated in severely depressed patients at baseline but less so after TMS.

In comparison to rTMS, the exploration of GABA and glutamate systems in response to iTBS in MDD is currently sparse. However, it is suggested that iTBS may also affect brain cortical systems through altering inhibitory GABA-related and excitatory glutamate-mediated activity both at the site of stimulation and more distally.[79–82] In bipolar depression, MPFC GABA levels, but not Glx levels, have been found to increase significantly following lDLPFC iTBS,[82] with a reduction in the lDLPFC and ACC GABA/Glx ratios found following connectivity-guided iTBS in a non-clinical sample.[40] Additionally, the pilot work showed a strong significant correlation between baseline prefrontal GABA levels and depression symptoms at 3 months post connectivity-guided iTBS.[68] Based on the prior literature, the exact underpinnings of intermittent TBS-induced neurochemical changes and the physiological differences between rTMS and cgiTBS is unclear and requires further exploration.

Mechanism-of-action objectives

Therefore, the overarching objectives of the mechanism-of-action analysis were to explore: (1) baseline EC from rAI to lDLPFC and changes in EC from rAI to lDLPFC with clinical improvement; (2) change in FC between the DLPFC-DMPFC with clinical improvement; (3) baseline FC between lDLPFC and sgACC and changes in FC between the lDLPFC and sgACC with clinical improvement; (4) baseline GABA, change in GABA with clinical improvement; and (5) change in Glx and change in GABA/Glx ratio with clinical improvement.

Chapter 2 Methods

Study design

This study was a multicentre parallel group, double-blind, randomised controlled trial, to test the efficacy of cgiTBS versus neuronavigated rTMS without connectivity guidance, in patients with a primary diagnosis of moderate to severe MDD, which was treatment resistant in their current episode (TRD). This study was carried out at five sites across the UK National Health Service: Nottinghamshire Healthcare Foundation NHS Trust (Nottingham site), Northamptonshire Healthcare NHS Foundation Trust (Northampton site), Cumbria, Northumberland, Tyne, and Wear NHS Foundation Trust (Newcastle site), Camden and Islington NHS Foundation Trust (London site) and Pennine Care NHS Foundation Trust (Oldham site). MRI scans were performed at Nottingham (for Nottingham and Northampton), Newcastle, London (baseline only) and Manchester (for Oldham). Participants were recruited through secondary care services across the five study sites, self-referrals, and patient identification centres compromising primary care services and secondary care services at neighbouring NHS trusts near the main study sites.

Ethical approval was granted by East Midlands Leicester Central Research Ethics Committee (ref: 18/EM/0232) on 30 August 2018. The study was registered on 2 October 2018 (ISRCTN19674644) under the public title 'BRIGhTMIND: brain imaging guided transcranial magnetic stimulation in depression'. The trial protocol and Magnetic Resonance Imaging Protocol were published.[18,83] Of note, the latter protocol provided details of changes to main study design because of COVID-19 (see *Appendix 1* for more details). The trial was sponsored by the Research and Evidence Team, Nottinghamshire Healthcare NHS Foundation Trust.

Trial management

Study meetings with the research team occurred monthly for the duration of the BRIGhTMIND trial and was attended by the chief investigator, trial statistician, trial manager, patient and public involvement (PPI) lead, principal investigator (PI) from each centre and the site-specific research assistants (RA).

Data Monitoring and Ethics Committee

The Data Monitoring and Ethics Committee (DMEC) reviewed unblinded accumulating data on trial conduct and participant safety and reported their recommendations with regard to the trial continuing to the Trial Steering Committee (TSC). The DMEC had entirely independent membership. The trial statistician presented the study data unblinded in closed sessions, and the blinded progress and demographic data was reviewed in open sessions attended by the chief investigator, trial manager and imaging lead. In total there were eight DMEC meetings between (3 October 2018 and 25 January 2023).

Trial Steering Committee

The TSC would meet following the production of the DMEC reports. Although the majority of the TSC had independent membership, the meetings were attended by the chief investigator, trial statistician, PPI lead, trial manager, imaging lead and PI from each centre. In addition, the TSC and DMEC also reserved the right to meet independently to draw

conclusions about the progress of the trial and deliberate their recommendations. In total there were eight TSC meetings between (2 May 2018 to 22 March 2022).

Internal pilot

The reporting of the internal pilot consisted of providing DMEC and TSC with the recruitment rates. Stopping guidelines were based on recruitment rate, with sites expected to recruit 3 participants per month within the last 3 months of the internal pilot (1 April 2019 to 30 June 2019) for a total of 36 participants. The study succeeded in meeting the recruitment target of 36 participants. The DMEC reviewed progress with recruitment and safety in July 2019 and recommended continuation of the trial, with the committee looking for an increase in recruitment with each site aiming for four participants per month.

Data management and quality assurance

All source data collected on participants case report forms (CRFs) was entered onto a MACRO system trials database (Elsevier UK, London, UK), set up and managed by the Leicester Clinical Trials Unit (LCTU). The MACRO data could be accessed by the LCTU statisticians, trial manager, site research staff, and TMS staff. Of note, unblinded information could be accessed only by the TMS staff and LCTU statisticians. For MRI scans, the subject digital imaging and communications in medicine (DICOM) session files were uploaded onto an XNAT (Washington University School of Medicine; https://www.xnat.org/) database infrastructure using anonymised subject numbers. The MRI scanning data were then downloaded to a University of Nottingham research drive that could be accessed only by the MRI imaging team. Qualitative interview transcripts were stored on a Nottinghamshire Healthcare NHS Foundation Trust research drive, with the research drive accessible only to the researchers at the Nottingham site.

The trial manager carried out monthly quality checks, alongside queries produced by the LCTU statistician regarding the data entered onto MACRO. Furthermore, quality assurance checks were completed for each of the research sites by the trial manager to ensure compliance with good clinical practice and scientific integrity. This included 4 checks for the London site, 7 checks for the Nottingham site, 6 checks for the Newcastle site, 4 checks for the Northampton site and 2 checks for the Oldham site. This included both physical and remote monitoring checks.

Protocol amendments

The substantial amendments made to the BRIGhTMIND protocol are provided in *Appendix 1*, *Table 27*. Amendments made that are important to note here firstly include substantial amendment 1, which occurred prior to project start. Due to a technological breakthrough by the TMS Company, neuronavigation was implemented rather than the manual BEAM methods that were proposed in the funded grant application. This neuronavigation system allowed for more reproducible accuracy of TMS stimulation and without this change the trial might have been criticised for not being as precise in terms of target stimulation as it was possible to be.

After recruitment to the trial commenced, there was a second substantial amendment for a change to the exclusion criteria. Initially, any benzodiazepine use was an exclusion and only the occasional use of other hypnotic drugs zopiclone, zolpidem, zaleplon and promethazine was allowed. This changed to the following exclusion criteria: 'Daily prescription of benzodiazepine above 5 mg diazepam equivalents, zopiclone above 7.5 mg, zolpidem above 10 mg or zaleplon above 10 mg. These drugs should not be used intermittently in the 2 weeks before baseline assessment'. There was growing clinical opinion that intermittent hypnotic drug use rather than continuous hypnotic drug use might be associated with seizures or syncope following TMS.

In the third substantial amendment, the definition of treatment resistance was amended to reflect the scoring of the MGH-S. This changed from 'who have not responded to treatment with at least two antidepressants in their current episode' to 'patients with TRD who have a MGH score of 2 or more, who are not responding to 2 different

antidepressant regimes, antidepressant augmentation strategies, high prolonged dosages of antidepressants or ECT in their current episode'.

In the fourth substantial amendment, baseline imaging and associations with baseline clinical characteristics and changes in cognition, and a qualitative substudy to explore the reasons and meanings why participants request a copy of their MRI images, were added but are not reported on here.

In the fifth substantial amendment, the original sample size was reduced, primary clinical outcome was changed, and the study end date extended by 16 months. The sample size was reduced to 266 participants (133 per arm). This was due to site set-up and recruitment being delayed by 8 months to implement the neuronavigation technology. In addition, because recruitment to the study was paused for 5 months (March–August 2020), due to the COVID-19 pandemic and the funds and time available, it would not have been possible to recruit the original sample size of 368. Therefore, the primary outcome was also changed to ensure sufficient power (89.3%) with the new sample size stated. The primary outcome changed from 'cgiTBS is more efficacious at 16 weeks than standard rTMS in patients with TRD as assessed by the proportion of patients who show a response [50% reduction in depression symptoms from baseline on the Hamilton Rating Scale for Depression-17 (HDRS-17)]' to 'cgiTBS is more efficacious in reducing the mean HDRS-17 score over 26 weeks compared to standard rTMS in patients with TRD'.

The Northampton site was closed as it was not possible to open the site after the COVID-19 pandemic and in the sixth non-substantial amendment, a fifth site – Oldham, Greater Manchester – was added instead, and commenced recruitment in August 2021. Study timelines are reported in *Appendix 1*, *Table 28*. The report from this point on refers to the final approved protocol.

Participant inclusion/exclusion criteria

Inclusion criteria

- Adults ≥ 18 years.
- Diagnosis of current MDD (defined according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition), that is treatment resistant defined as scoring 2 or more on the MGH-S.
- Have a HDRS-17 score of 16 or more (moderate to severe depression).
- Capacity to provide informed consent before any trial-related activities.

Exclusion criteria

- History of bipolar disorder (due to risk of mania) or depression secondary to other mental disorder.
- Neurological conditions for example, brain neoplasm, cerebrovascular events, epilepsy, neurodegenerative disorders, and prior brain surgery.
- Standard contraindications to MRI, that is irremovable metal objects in and around the body (e.g. cardiac pacemaker or implanted medication pump) and pregnancy (any doubt was resolved by a pregnancy test, with women of childbearing age taking precautions against pregnancy). This includes other potential complicated factors such as red tattoos, which consist of iron on the head, neck and back, and claustrophobia.
- Major unstable medical illness requiring further investigation or treatment.
- Change in prescribed medication 2 weeks before baseline assessment.
- Prescription of lamotrigine, gabapentin or pregabalin in the 2 weeks prior to baseline assessment.
- Daily prescription of benzodiazepine above 5 mg diazepam equivalents, zopiclone above 7.5 mg, zolpidem above 10 mg or zaleplon above 10 mg. These drugs should not be used intermittently in the 2 weeks before baseline assessment.
- Current substance abuse or dependence (defined by DSM-5 criteria).
- Prior TMS treatment.
- At risk of suicidality.

- Potential complicated factors relating to the TMS treatment, such as hairstyles that would impair magnetic transmission and piercings. Participants would be excluded only if they chose to not make the changes required to ensure effective treatment.
- Involved with any other clinical trial at the time of consent or 6 months prior.
- Unable to read or understand English.

A pre-screening questionnaire was used to telephone screen interested participants first, with potentially eligible participants invited to attend a baseline assessment. At the baseline assessment, all participants gave written informed consent and study eligibility was determined. Diagnosis was assessed by the Structured Clinical Interview[84] for the Diagnostic and Statistical Manual of Mental Disorders (SCID), Fifth Edition.[85] Treatment resistance was measured by the MGH-S[86] (adapted for new treatment options – see *Appendix 1*, *Table 29*). Depression severity and the primary outcome measure were assessed using the Grid version of the Hamilton Rating Scale for Depression-17 (GRID-HDRS-17[87]). The Childhood Trauma Questionnaire (CTQ[88]) was used in place of the post-traumatic stress disorder on the SCID. Information on sociodemographic was also collected at baseline assessment. Furthermore, to assist with determining study eligibility, medical and psychiatric history including a detailed assessment of treatment resistance were be obtained from secondary care mental health service case files where available and primary care notes.

Randomisation and blinding

Randomisation was conducted via a web-based randomisation system (Sealed Envelope, www.sealedevelope.com) and conveyed by the trial manager to the unblinded TMS nurse practitioners and healthcare assistant delivering TMS at each study site, immediately prior to the start of the participant's first intervention session. Baseline eligibility was assessed by blinded outcome assessors who conveyed the information to the trial manager for randomisation and determination of treatment allocation. Participants were randomly assigned in a 1 : 1 ratio into the rTMS and cgiTBS arms. Randomisation was stratified by study site and minimised on severity of depression (HDRS-17 score 16-23 moderate or ≥ 24 severe) and degree of treatment resistance [low 2–3.5, medium 4–6, high (≥ 6.5) as assessed at baseline].

Participants, referring clinical teams and the outcomes assessors were kept blinded with respect to the treatment protocol assigned and administered, until after the participant's final follow-up assessment. Any unintended unblinding of outcome assessors were recorded, with other assessors completing all further assessments for that participant. At each follow-up assessment, the outcomes assessor was asked to guess the participants' treatment allocation.

Participants were to be randomised within 4 weeks of the baseline assessment and within 2 weeks of the baseline MRI scan. If the time window between baseline assessment and randomisation exceeded 4 weeks, then the HDRS-17 interview and MGH-S were reassessed prior to randomisation taking place. If the reassessed HDRS measure showed a total score < 16, treatment was still to be administered with intention-to-treat (ITT) analysis.

Interventions

A 70 mm figure-of-eight coil (E-z Cool coil) and a Magstim Horizon Performance Stimulator with StimGuide Navigated TMS Package (Magstim Company, Whitland, UK) was used for all treatments. A total of 3000 pulses were delivered in each rTMS or cgiTBS session, with 20 TMS sessions delivered over a 4- to 6-week period. Each session for both cgiTBS and rTMS lasted approximately 37.5 minutes in total for the purposes of blinding participants and assessors of outcome. MultimodalMRI was acquired for each participant at baseline (before TMS treatment) with T1-weighted (structural MRI) and task-free functional MRI (rsfMRI). The protocol paper outlines the brain imaging acquisition and analysis used to create personalised TMS targets for the BRIGhTMIND study.[83] Interventions were delivered by a nurse and HCA at each session. They were trained to deliver the intervention and use the neuronavigation by study PIs and staff from Magstim plc. Treatment was delivered in specially adapted intervention rooms with a separate waiting area at each site. During the pandemic, no waiting was allowed, and additional hygiene and COVID-19 protection measures were employed.

Connectivity-guided intermittent theta burst stimulation treatment arm

Participants assigned to cgiTBS received bursts of three pulses (80% motor threshold) at 50 Hz applied at a frequency of 5 Hz (i.e. every 200 ms). Each 10-second cycle consisted of 10 bursts (consisting of 2 seconds of stimulation and 8 seconds' rest) with a total of 20 cycles performed per run. The pulses were repeated for a total of 5 runs with 5-minute rest intervals between runs, with a total of 3000 pulses per session. The cgiTBS brain target was defined based on the Granger causality analysis of maximal strength of EC between the rAI and the lDLPFC from the participant's rsfMRI and T1-weighted structural MRI scans. The StimGuide Navigated TMS Package computed the nearest location for TBS stimulus on the scalp from an individualised head model based on the structural MRI and three fiducial points – the nasion, left preauricular and right preauricular sites.

Neuronavigated repetitive transcranial magnetic stimulation treatment arm

Participants assigned to rTMS followed the standard protocol approved by the US Food and Drug Administration. Stimulation was at 120% motor threshold with 75 × 4-second trains of 10 Hz interspersed by 26-second intertrain intervals, with a total of 3000 pulses per session. The rTMS site brain target was determined by the participant's structural and rsfMRI scans by computing the voxel in the brain parenchyma that is closest to it [i.e. Montreal Neurological Institute (MNI) co-ordinates: x = −41.0, y = 43.0 mm, z = 32.0 mm] to target the F3 site over the lDLPFC. As with the cgiTBS treatment arm, the StimGuide Navigated TMS Package was used to compute the F3 site over the lDLPFC for TMS from the same individualised head model and three fiducial points mentioned above.

Percentage rMT was determined at the first treatment session and tested again on the sixth treatment session for both treatment arms.

Standardised steps (below) were developed for participants who were unable to tolerate the cgiTBS or rTMS protocols as per the MRI data: (1) StimGuide reset to 1 cm upwards or backwards from the site (within 2 cm diameter the original site); (2) StimGuide reset to 1 cm forwards of the site (within 2 cm diameter of the original site); (3) rMT reduced with StimGuide reset at the original site (as per MRI data.) including details of the new percentage rMT; (4) rMT reduced with StimGuide reset at 1 cm upwards or backwards from the site (within 2 cm diameter of the original site) including details of the new percentage rMT; (5) rMT reduced with StimGuide reset to 1 cm forwards of the site (within 2 cm diameter of the original site) including details of the new percentage rMT; and (6) revert StimGuide to standard F3 site (ensure allocated TBS or TMS is delivered). If treatment protocols were not administered as per the MRI data, then protocol deviations were recorded.

Further deviations were recorded if participants completed the 20 treatment sessions after 6 weeks and if there were gaps of more than 4 days between treatments in the course of 20. If MDD pharmacotherapy or psychotherapy changed prior to the 16-week follow-up being completed, these were also recorded as protocol deviations.

Follow-up intervals and assessments at each visit

The assessment of outcome measures was completed at 0 weeks (baseline) and 8-, 16- and 26-week follow-ups (± 1 week from randomisation). Researchers at each site collected the local data listed in the schedule of study assessments below. The primary outcome was observer-rated with all secondary outcomes self-rated. The baseline MRI scan was completed within 2 weeks of the baseline assessment, and the follow-up MRI scan was to be completed within 14 days of 16-week follow-up assessment, except at the London site where the 16-week scan was not completed because of the cost of the scan at that site (see *Figure 1*). Travel expenses were covered for participation in the study along with a £10 shopping voucher at 16- and 26-week follow-up assessments as a mark of respect and gratitude for the time and input of the participants to the follow-up aspects of the trial. Protocol deviations were recorded for any assessments completed out of the correct time frame or if components of assessments were not completed.

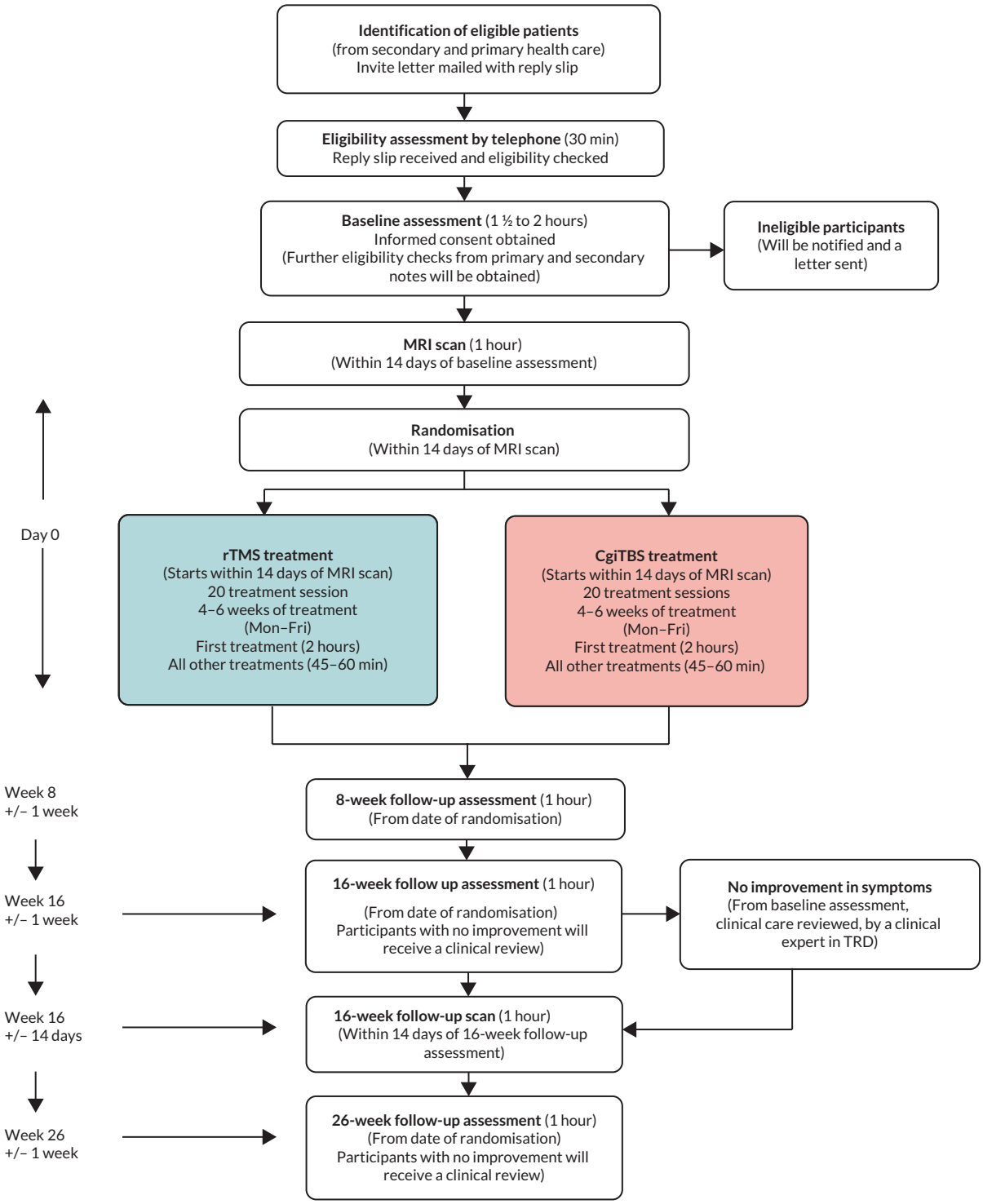


FIGURE 1 Study flow chart.

Clinical efficacy outcomes

Hamilton Rating Scale for Depression-17

The primary outcome measure was assessed using the GRID-HDRS-17 over 26 weeks at 8-, 16- and 26-week assessments. The HDRS-17 is a widely used interview measure of depression symptoms and the GRID form was utilised given evidence of improved inter-rater reliability.[87]

The total score for the HDRS-17 was also utilised for secondary outcomes, assessed separately at each assessment at 8, 16 and 26 weeks. In addition, secondary outcomes also included the exploration of HDRS-17 response rate and remission rates. Remission rates at 8, 16 and 26 weeks were defined as a score of 8 or less on the HDRS-17. Responder rates at 8, 16 and 26 weeks were defined as a 50% or greater reduction in HDRS-17 score at each of the specified time points from baseline. Sustained response at 16 and 26 weeks was defined as a continuing response as defined above following a response at the previous time point.

Other clinical secondary outcome measures

To answer all further secondary outcome clinical efficacy objectives, we collected the following self-report measures at baseline and all three follow-up time points (8-, 16- and 26-week follow-ups), unless specifically stated otherwise below (see *Table 2*).

Depression measures included the Beck Depression Inventory, version 2 (BDI-II[89]), Patient Health Questionnaire-9 (PHQ-9[90]), and Quick Inventory of Depressive Symptomology (QIDS-SR16[91]). Of note, the QIDS-SR16 was collected at all time points except for the 26-week follow-up and only from March 2020, as this measure was included specifically for a mechanistic substudy (substantial amendment 3). Results for QIDS-SR will therefore not be included in this report, which does not cover the substudy. The Generalised Anxiety Disorder Assessment (GAD-7[92]) was used to measure anxiety symptoms, the Work and Social Adjustment Scale (WSAS[93]), was used to assess impairment and functioning, and the EuroQol-5 Dimensions, five-level version (EQ-5D-5L) visual analogue scale (EQ VAS[94]) was used as a measure of health outcome. Additionally, we adapted the patient global impression of change measure after review by the Lived Experience Advisory Panel (LEAP), which recommended from a 7-point scale with 2 ratings for being worse, 1 unchanged and 4 for improvement, to a shortened 5-point Likert scale (1 = much worse to 5 = much better with as many rating points for worse and improved mental state) to assess participants belief about the efficacy of treatment. This was assessed after each TMS session and at each follow-up time point.[95]

TABLE 2 Study schedule and assessments

	Time points						
Trial procedures	**Baseline assessment**	**Baseline MRI scan (within 14 days of baseline assessment)**	**Treatment Mon–Fri for 4 weeks (+ 14 days of MRI scan)**	**8-week follow-up assessment (± 1 week from rando-misation)**	**16-week follow-up assessment (± 1 week from rando-misation)**	**16-week MRI scan (within 14 days of 16-week follow-up assessment)**	**26-week follow-up assessment (± 1 week from rando-misation)**
Informed consent	✓						
Randomisation			✓				
Eligibility assessments							
SCID research interviews	✓						
MGH-S	✓		✓ Only if baseline assessment exceeds 4 weeks				
Assessments: primary outcome							
HDRS-17	✓		✓ Only if baseline assessment exceeds 4 weeks	✓	✓		✓

TABLE 2 Study schedule and assessments (*continued*)

Trial procedures	Time points						
	Baseline assessment	Baseline MRI scan (within 14 days of baseline assessment)	Treatment Mon–Fri for 4 weeks (+ 14 days of MRI scan)	8-week follow-up assessment (± 1 week from randomisation)	16-week follow-up assessment (± 1 week from randomisation)	16-week MRI scan (within 14 days of 16-week follow-up assessment)	26-week follow-up assessment (± 1 week from randomisation)
Assessments: secondary outcomes							
CTQ (replaces PSTD section in SCID questionnaire)	✓						
BDI-II	✓			✓	✓		✓
PHQ-9	✓			✓	✓		✓
WSAS	✓			✓	✓		✓
GAD7	✓			✓	✓		✓
EQ-5D-5L	✓			✓	✓		✓
THINC-it	✓	✓ (When completed at a separate visit while COVID-19 mitigation restrictions in place)		✓ (Not completed while COVID-19 mitigation restrictions in place)	✓	✓ (When completed at a separate visit while COVID-19 mitigation restrictions in place)	✓ (Not completed while COVID-19 mitigation restrictions in place)
QIDS-SR16	✓			✓	✓		
Client resource Questionnaire	✓				✓		✓
Patient acceptability			✓	✓	✓		✓
Side effects checklist (AEs)			✓	✓			
MRI scans							
MRI		✓				✓ (Not in London)	
rsfMRI		✓				✓ (Not in London)	
Diffusion weighted imaging		✓				✓ (Not in London)	
MRS (not in London and Oldham)		✓				✓ (Not in London)	
Arterial spin labelling (not in London and Newcastle)		✓				✓ (Not in London)	

The THINC-Integrated Tool (THINC-iT) assessed subjective and objective cognitive functioning (THINC-it Task Force, http://thinc.progress.im/en). The THINC-it tasks were presented to participants on an iPad, with responses to be made by touching the screen. All tasks were defined as continuous outcomes. 'Spotter' is based on a choice reaction task (CRT[96]) viewed as a measure of sustained attention, with the primary outcome being mean response time (RT). 'Trials' is based on part B Trails Making Task (TMT[97]) viewed as a measure of executive function with a primary outcome of the total time to complete the task. CRT was recorded in milliseconds and TMT recorded in seconds, with better performances indicated by lower scores. The 'codebreaker' is based on the Digit Symbol Substitution Test (DSST[98]) whereby performance is considered dependent on the functional integrity of various cognitive skills, including working memory, attention, and executive function. 'Symbol check' is based on the one-back paradigm (*N*-back[99]) viewed as a measure of working memory. The primary outcome of interest for these two tasks was the total number of correct responses in 2 minutes, with better performances indicated by higher scores. Finally, the subjective Perceived Deficits Questionnaire, 5 domains (PDQ-5-D[100]) is a measure of subjective cognitive function, and the outcome of interest was the sum of scores from the 5 questions, with each question scored 1–5, with 1 being no concerns of any problem, to 5 being very significant problems. As a result, better performance is indicated by lower scores. From this point on, the more conventional cognitive task name or abbreviation will be used.

Each of these tasks were ran once at each of the participant's assessments, except for the CRT, which was completed twice. The purposes of this were to facilitate ex-Gaussian analysis, in order to assess intra-individual variability (IIV) of sustained attention. Intra-individual variability was assessed only for the CRT task, with this considered a secondary outcome. Three parameters of an ex-Gaussian distribution (a combination of a Gaussian and an exponential function) are fitted to the distribution of RTs for a given individual.[101] The three ex-gaussian parameters of IIV allow for a better separation of mean RT (mu), variability in RT (sigma) and abnormally slow responses (tau).[102] In terms of interpretation, generalised slowing of RTs is reflected by higher values for all three parameters. We also analysed individual participant standard deviations (iSD) and coefficient of variation (CoV) – iSD normalised by mean RT, for comparability with other studies.

Adherence

The following variables were used to measure adherence with treatments:

1. Number of TMS sessions delivered as per protocol or as per changes allowed in the TMS standard operating procedure (SOP) within 6 weeks after randomisation.
2. The number of breaks between TMS sessions of more than 4 days as well as the average break length between TMS sessions of more than 4 days (measured in days).
3. Number of participants whose existing psychotropic medications or psychological interventions were not kept stable for 16 weeks for the duration of the trial, except for those at risk to themselves or others.
4. Number of participants whose daily prescription of benzodiazepine was above 5 mg diazepam, zopiclone was above 7.5 mg, zolpidem or zaleplon was above 10 mg from baseline assessment to the end of TMS treatment.

Power calculation for primary hypothesis for the clinical efficacy analysis

As agreed with the funders, TSC, and DMEC, we planned to enrol 266 participants, with 133 participants per treatment arm. A sample size of 266 participants would provide 89.3% power to detect a mean difference of 3 points in the HDRS-17 over 26 weeks between the groups at the 5% two-sided significance level assuming a SD of 8 informed from both the pilot study and a multicentre RCT in chronic persistent depressive disorder led by the chief investigator,[58] a correlation between follow-up measures of 0.7 (1 baseline measure with correlation of 0.27 to the follow-up measures) and 20% data loss/drop-out. NICE defined 3 points as a clinically important difference in outcome on the HDRS-17 in its NICE Clinical Guideline for Depression in 2004.[103] Given the uncertainties of recruitment to the study due to the COVID 19 pandemic, we note that under the same assumptions, a sample size of 253 would have yield 87.8% power and 232 participants 85.1% power.

Clinical efficacy analysis

The statistical analysis plan for the clinical efficacy is published (https://doi.org/10.6084/m9.figshare.21271140.v1) and we summarise the plan here rather than providing the detailed plan in its entirety. Statisticians at the LCTU conducted

the analysis for all clinical outcomes detailed above, except for cognitive functioning as assessed by the THINC-iT. These data were analysed by the lead PI and researchers at the Newcastle site.

Primary analysis of the primary outcome

The primary analysis of the primary outcome was conducted on the ITT population with the multiple imputation technique being implemented to deal with missing data in instances where participants were missing any of the HDRS-17 scores. To ensure the population remained truly ITT, variables such as gender, ethnicity, age, centre, baseline HDRS-17 score and degree of TRD were used as predictors of the primary outcome to substitute the missing data with the predicted values from a multivariate normal regression equation. A total of 20 imputations were estimated.

Secondary and sensitivity analysis of the primary outcome

A completer's population analysis and a per-protocol analysis of the primary outcome were completed using an available data approach. Sensitivity analysis included a Missing Not at Random (MNAR) assumption analysis was implemented using a control-based imputation approach, a pre-/post-COVID-19 period analysis, and a centre as random effect analysis, both of which were conducted on the ITT population using the imputed datasets from the primary analysis of the primary outcome. Furthermore, moderator analyses were conducted on the ITT population using an available data approach, with age, baseline CTQ, baseline HDRS-17, baseline GAD-7 and degree of treatment resistance as continuous moderator variables, and the number of TMS sessions completed (20 sessions or < 20 sessions) as a categorical moderator variable. Further details on these analyses can be found at https://doi.org/10.6084/m9.figshare.21271140.v1.

Mixed linear regression models were used for all the aforementioned analyses. All models were adjusted for centre (stratification variable), baseline HDRS-17 score, and baseline MGH-S for TRD (minimisation variables), visit number and a categorical variable for treatment arm (rTMS arm as reference).The pre-/post-COVID analysis also included a categorical variable for the pre-/post-COVID-19 period and an interaction term between the pre-/post-COVID-19 period and treatment arm and the moderator analyses also included two interaction terms: one between moderator of the primary outcome and treatment arm; and another between each of the follow-up time points and treatment arm. Participant identification number (ID) was included as random effect for all analyses, except for the centre as random effect analyses, whereby the centre was included as the random effect and not as a predictor variable. The variance-covariance matrix for the random effects was assumed to be unstructured and the models were estimated using restricted maximum likelihood. Treatment comparison estimates are presented for all models as adjusted mean differences between the treatment arms, with two-sided 95% CIs and *p*-values, with statistical significance considered at ≤ 5%.

Analysis of secondary outcomes

1. Analyses were conducted on HDRS-17 measured separately at 8, 16 and 26 weeks, conducted on the ITT population using an available data approach.
2. Analyses were conducted on the proportion of responders at 8, 16 and 26 weeks, proportion of remitters at 8, 16 and 26 weeks, and proportion of sustained responders at 16 and 26 weeks, on the ITT population using an available data approach.
3. Analyses were conducted on the total scores of the BDI-II, PHQ-9, GAD-7, WSAS and EuroQol-5D-5L (VAS score) across 26 weeks for the ITT population using an available data approach.

Binary logistic models were used for the responders, remitters and sustained responders' analyses, and linear regression models used to assess HDRS-17 at the separate 8-, 16- and 26-week time points. All models were adjusted for centre (stratification variable), baseline HDRS-17 score and baseline MGH-S (minimisation variables) and a categorical variable for treatment arm (rTMS arm as reference). Mixed linear regression models were used for the other secondary continuous outcome variables, with each model adjusted for their respective baseline measure. Treatment arm, treatment centre (stratification variable), baseline HDRS-17 score, and degree of treatment resistance (minimisation variables) were fitted as fixed effects in the models, while the participant ID was fitted as a random effect. Treatment comparison estimates are the same as reported for the primary analyses of the primary outcome, except for the binary logistic models reporting adjusted odds ratios.

As reported in *Table 2*, prior to the suspension of recruitment to the study due to the COVID-19 pandemic, the THINC-iT was measured at the baseline assessment and all three follow-up time points. Between this suspension date and the reopening of sites to recruitment (30 April 2020 to 1 August 2020) no face-to-face assessments were completed, with the THINC-iT not collected at any follow-up time points during this time period. From 1 August 2020 onwards, the THINC-iT was collected at the baseline MRI scan and 16-week follow-up MRI scan, due to the COVID-19 mitigation restrictions in place. Therefore, the analyses conducted and reported in *Chapter 3* only includes the THINC-iT outcomes at baseline and 16 weeks.

Linear mixed models (LMMs) were used for the cognition analyses. The cognition outcomes were the dependent variables, and the independent variables of interest were the THINC-it time point (baseline and 16 weeks), treatment group (rTMS and cgiTBS), baseline GAD-7, baseline HDRS-17, and change in HDRS-17 score between baseline and week 16. These models also included three interaction terms: treatment group*time point, time point*change in HDRS-17 and change in HDRS-17*treatment group*time point. Confounder variables included age, gender, site, and MGH group. Any confounder variable not found to be significant on initial testing were removed from the models and the analysis re-run, with the results from these re-run analyses presented in *Chapter 3*.

The analyses were conducted on the ITT population (all participants randomised to treatments) using an available data approach. However, important to note from a quality control (QC) perspective, outliers were removed for any scores on the CRT, DSST or *N*-back (primary outcomes) that were four times the SD for the whole cohort at that time point on that task.[104] Similarly total time to complete the TMT of over 5 minutes was removed. Additionally, if any individual did not have at least 3 of the 4 objective tasks scores meeting quality control (QC) (or not completed), then they were completely removed from that time point in the analysis.

Finally, if a participant only completed the CRT task once, the data from the completed task was used with the following provisos:

1. The RT results are reported as described above based on the one running of the task. The participant was not included in analysis comparing the first and second running of the task.
2. The number of correct responses obtained was doubled prior to inclusion in the group analysis.
3. The participant's data at this time point were not included in the IIV analysis due to the limited number of responses available.

If the ex-Gaussian curve fitting routine was unable to fit a participant's data at a specific time point, then values for mu, sigma and tau were set as missing data for that time point, with a record that these missing data were as a result of an inability to fit the data rather than missing or excluded CRT data.

Finally, regarding participants' global impression of change, these were defined as categorical outcomes, reported descriptively, and listed by treatment arm and overall.

Safety, acceptability, facilitators and barriers

Safety outcomes

1. Internationally agreed definitions were adopted for AEs (i.e. any untoward medical occurrence in a clinical trial subject administered TMS whether or not it has a causal relationship with TMS) and SAEs (any AE or adverse reaction that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect).
2. Common TMS side effects (i.e. headaches, neck pain, scalp discomfort, tinnitus, dizziness, jaw ache, nausea, and watering eyes) as well as reports of any uncommon side effects were recorded on an adverse checklist after every TMS session and at the 8-week follow-up assessment.
3. Syncope was recorded as an AE, unless participants were admitted to hospital, in which case it was defined as an SAE.

4. In the event of a seizure, treatment was stopped, and no further treatment was administered. Seizures were reported as SAE.
5. Any participant found to be at risk to themselves (suicide, neglect) or others, or developing a SAE were referred to relevant clinical services. A review by a clinical expert in TRD was offered to any participant whose depression has become more severe at 16- and 26-week follow-ups for safety reasons.
6. The DMEC reviewed all unblinded accumulating data on trial conduct and participant safety and reported their recommendations with regard to the trial continuing to the TSC.

Facilitators, barriers, and acceptability outcomes

Patient acceptability was assessed with a purposively designed 5-point Likert measure rated from 1 = unacceptable (negative effects outweigh benefits) to 5 = acceptable (beneficial effects outweigh the negative effects). This was assessed at every TMS session and for all follow-up assessments. Participants were also given the option after each TMS session and each of the follow-ups to provide any additional open-ended comments about their experience of the TMS or the study so far, which were utilised for the qualitative analysis.

Semistructured topic guides were developed to qualitatively assess facilitators, barriers, and acceptability of TMS. For participants who were randomised to treatment and either completed all follow-ups or withdrew during or after treatments, topic guides included five broad questions: (1) how they found out about the trial; (2) their initial reaction on hearing about the trial and treatment involved; (3) the factors that motivated their decision about participation; (4) whether they had any concern about taking part in the trial; and (5) the acceptability of the treatment. Those who were not randomised to treatment and declined to participate in the trial had a topic guide which included the first three questions above, and whether they thought there would have been any potential positive outcomes from taking part in the study (see *Appendix 1*, *Table 30*).

Sample size for qualitative facilitator, barriers and acceptability analysis

We aimed to achieve a purposive sample of 25–30 participants or interviewing until saturation of data was achieved (i.e. no more themes were emerging in subsequent interviews). We aimed to include a variety of participants, reflecting a mix of demographic characteristics, consent, or non-consent to participate, adherence and non-adherence to treatment and follow-up.

Safety and acceptability analysis

Statisticians at LCTU conducted analysis of the safety outcomes and quantitative acceptability. Qualitative analysis was conducted by the qualitative PI and researchers at the Nottingham site.

Common and uncommon side effects were summarised by treatment arm and overall using data collected at 8, 16 and 26 weeks as well as at each TMS treatment session. The overall proportion of participants with any side effects in addition to the frequency and duration (in days) of all side effects were also reported by treatment arm and overall. All safety data were presented according to the safety population. All AEs were listed by treatment arm and overall based on the following characteristics: seriousness; duration (measured in days); relatedness; severity; action taken and outcome.

Quantitative measures of patient acceptability were defined as categorical outcomes reported descriptively and listed by treatment arm and overall.

All qualitative interviews were completed by BRIGhTMIND RAs or members of the clinical research network. Interviews were anonymously recorded on an encrypted digital voice recorder then transcribed using the professional transcription service DICT8 (https://www.dict8.com/). Qualitative interviews were combined across the two treatment groups and an inductive thematic analysis using a grounded approach was adopted.[105] The first 8 transcripts were read and coded by two researchers to ensure they were immersed in the data.[106] One researcher read and coded all further transcripts. The two researchers agreed consensus that data had reached saturation as no new or meaningful codes emerged after 12 transcripts.[107] However, some further interviews were conducted to see if any new data was identified due to the COVID-19 pandemic. Initial codes were then summarised into broader categories. Consultations with the qualitative PI took place, whereby the overarching framework of themes and naming of themes were produced and refined. The

framework of themes and supporting quotations were also presented to the BRIGhTMIND PPI team across the sites, with PPI contributors aiding the interpretation of said themes. This allowed us to check the credibility of the analysis and results, further improving the trustworthiness of the results.[108] Coding and themes were input into a framework matrix using NVivo 12 (QSR International, Warrington, UK).

Inductive thematic analysis was also used to analyse the optional comments that were recorded on the quantitative acceptability measures mentioned above, in order to determine if any further subthemes/themes could be identified outside of the qualitative interviews. These comments were read repeatedly and coded by one researcher, with a second researcher reviewing these codes for reliability. Following this, the framework and naming of themes was further refined and approved by the qualitative analysis team.

Economics evaluation

The economic evaluation was designed and analysed by health economists at the University of Nottingham. The health economics analysis plan can be found at https://figshare.com/articles/online_resource/BRIGhTMIND_Health_Economics_Analysis_Plan/22093148 and in *Appendix 1*, *Table 31*. The CHEERS checklist is also found in *Appendix 1*, *Table 32*.

Resource use and costs

The viewpoint for the study is broad as such data were collected on health care and social care at baseline and during the treatment and intervention regime, but in addition sought to collect societal costs such as productivity (days off work where appropriate) and the direct patient cost of illness. Resource use data were collected at baseline, 16- and 26-week follow-up time points using a purposely designed patient-informed resource use questionnaire with PPI input. Baseline forms recorded resource use from 3 months prior to trial entry. The resource use questionnaire is collected directly in clinic and has the advantage that research nurses can assist patients should any confusion arise. Follow-up forms collected resource use between assessment periods (e.g. collection at week 16 represents resource use utilised between baseline and week 16). Costs reflected Great British pounds at 2020–1 prices and were divided between NHS and personal social services (PSS) (health service) perspective costs (in accordance with NICE guidance[109]) and broader societal costs. Health service costs include intervention-related costs; inpatient hospital service costs; outpatient service costs; primary care costs; community service costs, and mental-health-related medication costs. Broader societal costs include participant out-of-pocket expenses from travel, over-the-counter medication, and private services, together with societal productivity costs.

Intervention costs were calculated on an ITT using a micro-costing framework comprising three elements: imaging costs; staff costs, and equipment costs. Imaging costs included all structural and resting-state functional MRI scans provided to participants before randomisation.[1] MRI scans were pooled between arms given their a priori nature (i.e. by definition unrelated to allocation). MRS scans were deemed unrelated to treatment (done for research purposes only), hence not considered in the costing. Since rTMS does not necessitate MRI scans, a scenario analysis considers removing all imaging costs from rTMS. Staffing costs equated to the number, band, and time of healthcare professionals dedicated to treatment appointments, as recorded from site reports. Staff costs for each participant were calculated by multiplying the number of treatment sessions attended (protocol: 20 sessions) by the treatment-specific average staff appointment cost. COVID-19-related expenses (i.e. advanced personal protective equipment, cleaning, etc.) were omitted due to their exceptional nature and general equality between arms. The staff and equipment logs of delivering treatment were checked using a study log completed by a purposive sample of nurses and healthcare assistants. Since trial protocols insisted on consistent contact times, a second intervention-related scenario considered a 30-minute time saving for cgiTBS relative to rTMS informed via published expert opinion.[62] A third scenario jointly considered removing all imaging costs from rTMS and the 30-minute time saving between cgiTBS and rTMS appointments. Treatment equipment costs were informed via financial records from the trial and were distributed across all participants on an ITT basis using the average site throughput (n = 51). Participants randomised to cgiTBS and rTMS received treatment from the same machines, incurring the same equipment cost. Base-case intervention costs only differed between arms via differences in treatment attendance and staff requirements observed. All intervention-related unit costs are provided in *Appendix 1*, *Table 33*.

Inpatient, outpatient, primary care, and community services were costed according to the number of recorded attendances, multiplied by relevant unit costs from NHS Reference costs and Personal Social Service Research Unit (PSSRU).[110,111] Unit costs were inflated to 2020–21 prices using the PSSRU pay and prices index where necessary. All 'other' recorded cases in each healthcare setting were costed on a case-by-case basis. All procedures were assumed to be provided by the NHS unless stated otherwise. Medication costs considered all 'current' mental-health-related medications participants recorded at baseline, and at 8-, 16- and 26-week follow-ups. Since it was unknown when changes in participants' medication schedules occurred between assessment periods, medication costs were interpolated between follow-up periods using drug costs from eMIT and BNF databases.[112,113] The analysis assumed no drug wastage and that medications taken 'as required' were applied fortnightly.

Broader societal out-of-pocket travel costs, over-the-counter medication costs, and private service expenses were taken from the costs directly reported by participants during the trial. Participants driving to and from healthcare settings were assumed to incur a £0.45 cost per mile.[114] Productivity costs were calculated using the human capital approach, specifically combining self-reported depression-related absenteeism with salary costs from the Office for National Statistics.[115] In the absence of occupation or earnings data for informal carers; informal care was not costed but instead considered as a secondary outcome (see *Chapter 2, Economic outcomes*).

Table 3 provides an overview of all the resource use and costs considered in the economic evaluation. All specific health service and broader societal unit costs can be found in *Appendix 1*, *Table 34*.

Economic outcomes

The primary outcome used in the cost-effectiveness analysis was QALYs, a generic health measure in which the benefits, in terms of length of life, are adjusted to reflect quality of life.[116] One QALY is equal to 1 year of life in perfect health. The health-related quality of life (HRQoL) of trial participants was assessed using the EQ-5D-5L, a questionnaire asking individuals to rate their health according to five broad health dimensions (mobility, self-care, usual activity, pain/discomfort and anxiety/depression) at five levels of severity (no problems, some problems, moderate problems, severe problems or extreme problems).[117] The EQ-5D-5L has 3125 possible health states, each defined according to a unique combination of severity ratings.[118] The HRQoL associated with each health state is calculated through a preference-based weighting derived from a representative sample of the UK population.[117] Study outcomes were assessed at baseline and at week-8, week-16 and week-26 follow-ups.

Consistent with UK guidance for economic evaluations, HRQoL weights were estimated from a published mapping of EQ-5D-5L responses onto HRQoL values based on a UK population survey for the EQ-5D-3L instrument.[109] Mapping was conducted using the Stata® (StataCorp LP, College Station, TX, USA) package eq5dmap.[119] To evaluate differentials and dynamics in HRQoL during the trial, EQ-5D responses were descriptively assessed at every assessment period by domain and severity strata. Average observed and imputed HRQoL preference values were also compared between arms. QALYs for each participant were calculated using an area under the curve approach using linear interpolation in HRQoL between time points. Base-case cost-effectiveness analyses considered QALYs using mapped EQ-5D-3L preference values.[109] Cost-effectiveness findings using EQ-5D-5L preference values will be considered in a scenario analysis.

Informal care requirements were considered as a secondary outcome and were assessed via descriptive comparisons of informal care needs during the trial. Informal care was defined as care support received via friends or family only and was assumed constant between follow-ups.

Economic evaluation

The economic evaluation compared health service and societal costs both within resource categories and those aggregated into total costs, alongside EQ-5D responses, QALYs, and informal care. In line with UK guidelines on assessing cost-effectiveness, health outcomes were expressed as QALYs and costs measured in Great British pounds (2020–1) from health sector and broader societal perspectives (i.e. considering factors beyond the health service). Cost, QALY and cost-effectiveness comparisons are presented using unadjusted (using observed data only) and adjusted analyses (considering imputed data with econometric modelling controlling for patient co-variables). Cost-effectiveness was assessed using incremental cost-effectiveness ratios (ICERs) and incremental net monetary benefits

TABLE 3 Resource use and costing summary

	Resource use	Costing sources and technical notes
Health service		
Intervention costs	The equipment, staffing, and imaging costs required for the delivery of cgiTBS and rTMS in BRIGhTMIND	Equipment costs taken directly from trial sources using an ITT analysis with average trial throughput. Staff costs calculated according to PSSRU healthcare professional time costs combined with the personnel required and time spent managing participants as reported in site diaries. Imaging costs were taken from NHS Reference costs (2020–1) (10, 11)
Inpatient hospital services	Acute psychiatric ward stays and general medical ward stays	PSSRU (2021) (cost per day calculated by dividing average cost per stay by average length of stay) (10)
Outpatient hospital services	Psychiatric outpatient visits; psychologist visits; A&E attendances; day hospital attendances; non-psychiatric outpatient visits; other	NHS Reference costs (2020–1) (11)
Primary care	GP surgery visits; GP home visits; practice nurse surgery visits; district nurse visits; community psychiatric nurse visits; social worker visits; occupational therapist visits; advocates; home help/care worker visits; community matron visits; other	PSSRU (2021) and NHS Reference costs (2020–1) (10, 11)
Community services	Day care centre visits; drop-in centre visits; specialist education facility visits; sheltered workshop visits	PSSRU (2021) (10)
Medication	All prescribed depression-related medicines	BNF and eMIT (12, 13), medication costs interpolated between recorded follow-ups
Societal		
Travel	Self-reported out-of-pocket payments for transport and miles driven to appointments	Travel costs calculated as the direct out-of-pocket payments made by participants combined with a £0.45 cost per mile (14)
Productivity	Time taken off work as a result of depression	Human capital approach with days off work multiplied by ONS average day salary data (linked to individuals' employment status and occupation) (15)
Over-the-counter medications	Self-reported depression-related out-of-pocket payments for over-the-counter medications (including homeopathic remedies and supplements)	Costs as given
Private services	Self-reported depression-related out-of-pocket payments for private services	Costs as given

A&E, accident and emergency; BNF, British National Formulary; cgiTBS, short bursts of high-frequency theta burst transcranial magnetic stimulation; eMIT, drugs and pharmaceutical electronic market information tool; ONS, Office for National Statistics; rTMS, repetitive transcranial magnetic stimulation.

(INMB).[120] Uncertainty was evaluated using probabilistic sensitivity analysis and explored further via scenario and threshold analyses.

Incremental cost-effectiveness ratios are a measure of the additional cost per additional unit of health gain (QALY) generated by one intervention compared with another. INMB represent the monetary value from the health gains of a strategy less that which would have otherwise been generated elsewhere, had the same resources been allocated for alternative purposes. This opportunity cost is defined by the cost-effectiveness threshold (k) and represents the cost per unit of health gain (QALY) at which a technology represents an efficient use of limited NHS resources, otherwise described as the marginal productivity of the healthcare system. Interventions with positive INMBs and those with ICERs below the threshold are deemed cost-effective when compared to the next best relevant comparator.[120]

To increase efficiency and reduce the risk of bias, missing cost and outcome data were imputed.[121] To best estimate predicted values, and to keep imputed values within their natural bounds, missing values were populated using multiple imputation by chained equations with predicted mean matching.[122] The imputation model included variables that are associated with both the missing data and CEA outcomes (cost-level and EQ-5D-level variables), and includes all covariates used in the adjusted cost-effectiveness analysis (see below).[121] The number of datasets (n = 20) was informed via the proportion of missing data. All subsequent analyses of multiple data sets followed Rubin's rules.[123] Both observed and imputed outcomes and costs were evaluated. Observable total costs and QALYs were presented on a complete case basis (i.e. data required across all follow-up periods). The time horizon of the analysis was 26 weeks, the length of the BRIGhTMIND study. Costs and QALYs were not discounted as they accrue within a 12-month period.

Cost-effectiveness was assessed using two perspectives, the first from a health service perspective in line with the NICE guidelines (NHS and PSS), and the second from a broader societal perspective incorporating productivity costs and all travel, private service, and over-the-counter medication costs borne by participants. Cost-effectiveness analyses were also conducted using two separate analytical approaches: an unadjusted analysis using observed trial data; and an adjusted analysis using multiply imputed data and regression methods to estimate costs and QALYs while controlling for a set of relevant participant co-variables. From these approaches, the adjusted health service perspective analysis was considered the primary analysis, from which scenario and sensitivity analyses was extended. *Table 4* summarises the four analytical approaches taken for assessing the cost-effectiveness of cgiTBS and rTMS.

Unadjusted cost-effectiveness analysis

Unadjusted cost-effectiveness findings compared mean total costs and QALYs observed in BRIGhTMIND over the trial horizon. To represent the uncertainty about observed mean values, 5000 bootstrap replications were produced reflecting the variability in mean estimates.[124] The sampling distribution for total costs and QALYs consisted only of observed complete cases.

Adjusted cost-effectiveness analysis

For the adjusted cost-effectiveness analysis, costs and outcomes were estimated using multiply imputed data and regression methods. Regression analyses controlled for treatment allocation, participant age, gender, ethnicity, site, and baseline depression status (HDRS-17 severe vs. moderate). To control for broader imbalances in baseline HRQoL between arms (i.e. beyond that measured by the HDRS-17), QALY regression analyses also controlled for baseline EQ-5D preference values.[125] Ordinary least square regressions were applied for the QALY analysis while generalised linear models were used for the cost analysis, accounting for the non-normality and typically skewed nature of the cost data (gamma family distribution selected on the basis of superior model fit). Total broader societal costs were modelled separately on the log scale. Uncertainty in the estimated regression coefficients was estimated using Monte Carlo simulation with 5000 simulations, assuming multivariate normality of the regression coefficients and applying a Cholesky transformation to the variance-covariance matrix to account for correlation.[126] Considering the statistical analysis identified no moderator variables (factors identified as interacting with treatment effectiveness), no subgroup analyses were considered.

TABLE 4 Analytical approaches used to assess cost-effectiveness

	Unadjusted analysis: Assessment of bootstrapped costs and QALYs, resampling those observed during trial	Adjusted analysis: Assessment of estimated costs and QALYs using regression methods with multiply imputed data
Health service perspective: Health service utilisation applicable to the NHS & PSS	✓	✓[a]
Broader societal perspective: The inclusion of productivity, travel, and out-of-pocket service and medication costs	✓	✓

a Primary analysis.

Cost-effectiveness

For each analytical approach cost-effectiveness was assessed according to ICERs and INMB. The probability that an intervention is cost-effective was calculated via the proportion of simulated costs and QALYs that would be judged as cost-effective. The probability of being cost-effective and INMBs are calculated at cost-effectiveness thresholds of £20,000 and £30,000 per QALY, the range used by NICE.[109] The probability that cgiTBS would be considered cost-effective was plotted in a cost-effectiveness acceptability curve with threshold values up to £50,000 per QALY considered.[127] The expected value of perfect information was also evaluated (i.e. the expected net monetary value from attaining perfect information to inform decision-making).[120]

In the absence of a placebo/sham arm in BRIGhTMIND, a hypothetical scenario analysis considered pairwise comparisons of cgiTBS and rTMS with an artificial placebo. The artificial placebo was assumed to maintain average baseline HRQoL (mapped baseline EQ-5D-3L) and incur the same health service costs as its comparator, thereby contrasting intervention costs with the improvements in HRQoL observed in the trial (compared to what could be considered broadly representative HRQoL in the absence of intervention). Conclusions from this scenario must be interpreted with caution given the largely hypothetical nature of the artificial placebo.

All costs, outcomes and exploratory analyses considered in this analysis were reviewed and informed by the LEAP, comprising members with personal experiences of depression and treatment.

Mechanism-of-action outcomes

Magnetic resonance imaging acquisition

Six MRI scanners operating at 3T were used during the BRIGhTMIND study: Newcastle – Achieva dStream (Philips); London – Prisma (Siemens); Oldham – Achieva (Philips); Nottingham and Northampton used the following three scanners at Nottingham (sequentially) over the course of the trial owing to a scanner upgrade carried out midtrial: (1) Discovery MR750 (GE Healthcare); (2) Ingenia (Philips); and (3) Premier (GE Healthcare). Participants' baseline and 16-week MRI scans (London site underwent scanning at baseline time point only) were carried out at the same site and using the same scanner platform, using a core protocol across the treatment sites. Details of the multimodal scanning sequences can be found in the BRIGhTMIND Magnetic Resonance Imaging Protocol.[83]

All participants underwent high-resolution structural T1-weighted scans using sagittal fast-spoiled gradient echo BRAVO (or equivalent) sequences with 1 mm^3 isotropic voxels covering the whole head from the vertex to the neck. All participants also underwent eyes open rsfMRI scans using a gradient echo EPI sequence aligned with the anterior commissure-posterior commissure line, with acquisition covering from the vertex downward (repetition time [TR]/echo time [TE] = 2000/32 ms; flip angle = 77°; 35 slices; voxel size = 3 mm^3; slice gap = 0.5 mm; field of view = 192 × 192 mm; interleaved bottom/up; 240 volumes; phase encoding direction = posterior > anterior). Directly before the rsfMRI, forward- and reverse-phase-encoded blood oxygenation level dependent (BOLD) sequences were also acquired with the same image dimensions as the rsfMRI, to facilitate distortion correction. Additionally, participants at Nottingham, Newcastle and Northampton also underwent a Mesher-Garwood Point Resolved Spectroscopy (MEGA-PRESS) MRS scan acquired using the same schema described by Mikelsen *et al.* (voxel dimensions are 45 × 30 × 20 mm for anterior/posterior [A/P], left/right [L/R], inferior/superior [I/S] directions, respectively; TR/TE = 2000/68 ms; 320 averages).[128]

Magnetic resonance imaging analysis

The mechanism-of-action analysis was completed by researchers at the Nottingham site. Statistical analysis plans for the functional and effective outcomes are available online at http://doi.org/10.17639/nott.7251 and the MRS outcomes available at http://doi.org/10.17639/nott.7275.

Functional and effective connectivity processing

For QC of the structural and functional MRI scans, we used the MRIQC v0.11.0 QC XNAT container. Exclusion criteria included: average and maximum framewise displacement of BOLD images > 1 mm and 3 mm, respectively; BOLD

images showing long-lasting intensity changes or image artefacts; and T1w images that did not contain whole head coverage and contained incidental findings or image artefacts.

Pre-processing of the structural and functional MRI scans was carried out using the Sir Peter Mansfield Imaging Biomedical Research Centre (SPMIC-BRC) pipeline, version 1.5.5, 23 August 2021 (github.com/SPMIC-UoN/BRC_Pipeline). Pre-processing steps were the same as those used during the trial for computing cgiTBS target co-ordinates, as detailed in the trial MRI protocol.[83] This is except for the use of advanced Eddy current and movement correction tool (EDDY) slice-to-volume and volume-to-volume motion correction,[129] which was used in place of the Motion Correction using FMRIB's Linear Image Registration Tool (MCFLIRT) six degrees-of-freedom volume-to-volume correction used in the trial. The SPMIC-BRC pipeline is based on tools from Statistical Parametric Mapping toolkit version 12 (SPM12), the functional and structural MRI software library (FSL), and Freesurfer. EDDY motion correction uses the NVIDIA produced accelerated computing toolkit (NVIDIA CUDA). Further details on the structural and functional pre-processing steps can be found in the resting-state fMRI analysis plan (http://doi.org/10.17639/nott.7251).

Functional connectivity analyses were conducted using the FSL and Granger causality analysis was computed using REST (resting state fMRI data processing toolkit) software.[130] Correlations of interest were Fisher's *r*-to-*z* transformed with the converted Z-scores serving as measures of FC. Effective connectivity values were also converted to z-scores using Fisher's *r*-to-*z* conversion, with the mean z-score output across all voxels in *y* (when considering the influence of *x* on *y*) or *x* (when considering the influence of *y* on *x*) serving as the measure of EC. The rAI-to-lDLPFC EC (rAI 'outflow') minus the lDLPFC-to-rAI effective connectivity (rAI 'inflow') was used to calculate net out flow from right AI to lDLPFC, as used in Iwabuchi *et al.*[43]

For all connectivity analyses regions of interests (ROIs) were 6 mm spheres with MNI co-ordinates reported. For the EC analysis, the seed regions for the rAI was (x = 30, y = 24, z = −14[131]) and the individual DLPFC cgiTBS co-ordinates for each participant (regardless of treatment group). For the DLPFC-DMPFC FC analysis, the seed regions were the anterior DLPFC (x = −44, y = 40, z = 29[67]), posterior DLPFC (x = −44, y = 22, z = 36[132]) and DMPFC (x = −7, y = 49, z = 18[133]). For the DLPFC-sgACC FC analysis, the seed regions were the sgACC (x = 6, y = 16, z = −10[134]), and the target co-ordinates used based on the treatment participants received. For participants who received rTMS, their rTMS co-ordinates were projected 6-mm deeper into the brain,[135] giving MNI-co-ordinates x = −38, y = 40, z = 29.

Magnetic resonance spectroscopy processing

We originally planned to perform the entire MRS analysis for GABA and Glx estimation using linear combination model (LCM) as per the published protocol.[83] However, during pre-processing it was noted that data from only one scanning vendor was compatible for the in-house analysis pipeline. Therefore, due to resource and time constraints, we instead used GANNET MATLAB (multi-paradigm computer programming language) package (V3.3.0) for GABA estimates with the default setting.[136] For Glx estimates for best-practice estimation from off spectra, instead of using GANNET MATLAB we ultimately implemented LCM for all vendor spectra as the preferred approach for reliable Glx metrics derived from MEGA-PRESS.[137]

In brief for estimation of GABA+ (without macromolecule suppression), as per published protocol all spectra were visually inspected by an experienced researcher blinded to any clinical or treatment arm information, followed by GANNET processing that uses time domain signals that were frequency and phase corrected by spectral registration. A 3-Hz exponential line broadening and zero-filling with a factor of 16 was applied for filtration. Each pair of spectra (edited − non edited) were aligned, and edited spectra was subtracted from non-edited spectra to detect a GABA peak. The processed spectra were averaged and fit to Gaussian function to the GABA and Glx peak at 3.0 and 3.8 ppm, respectively. GABA peak was modelled using a five-parameter Gaussian model (2.19–3.55 ppm) and water peak was modelled using a Gaussian-Lorentzian function. Creatine (Cr) and *N*-acetylaspartate were modelled as two Lorentzians in the non-edited spectra. The integral Cr area in non-edited spectra were used to calculate GABA+ ratio relative to total (t)Cr. For GABA QC measurements with > 10% water referenced GABA+ fit error[138] were excluded, and negative measurements were also excluded.

For Glx estimation, LCM was used limiting the analysis to off spectra. Different from edited MRS approach for GABA, Glx fit results at 3T are highly dependent on the MRS quality, especially shim and baseline results, and expected to vary

between scanner platforms. We hence applied a more stringent QC by visual inspection for Glx spectra (assessing issues with line width, peak separation, water suppression, baseline model and bias in fit residuals based on LCM outputs) undertaken by an MRS experienced researcher fully blinded to the clinical details and treatment assignment of subjects but aware of the pre- versus post-status of the spectra. This in-depth QC process was limited to available spectra pairs pre- and post-completed intervention for Glx only and also included a qualitative and quantitative review of the anatomical position versus target, and achieved anatomical overlap of the spectrum position before and after treatment after co-registration of MRS with anatomical MRI in native and template space.

Further details on the MRS processing and analysis can be found in the MRS analysis plan (http://doi.org/10.17639/nott.7275).

Power calculations for the primary hypotheses for the mechanistic imaging analysis

> *Hypothesis: Reduction in IDLPFC – left DMPFC FC from baseline to 16 weeks will be associated with greater clinical improvement (averaged across all post-treatment time points), across both treatment groups.*

A sample size of 120 achieves 96.3% power to detect a difference of −0.3 between the null hypothesis of a correlation between clinical improvement and change in FC of 0.2 and the alternative hypothesis correlation of 0.5 using a two-sided hypothesis test with $\alpha = 0.05$. The null hypothesis of 0.2 represents a very weak or weak correlation, whereas the alternative of 0.5 represents a moderate correlation.[139] The correlation between DLPFC-DMPFC FC change at 12 weeks and HDRS-17 change at 12 weeks in the pilot data was 0.58.

> *Hypothesis: Greater clinical improvement on 17-item HDRS, averaged across all post-treatment time points (8, 16, and 26 weeks), will be associated with more positive baseline EC from right AI to IDLPFC, and this relationship will be stronger in the cgiTBS group.*

Sensitivity analyses are presented to evidence that the revised sample size for BRIGhTMIND will still allow for testing of these hypotheses. Sensitivity analysis based on a one-tailed test with $\alpha = 0.05$, 90% power, and a sample size of 232, suggests a required effect size of $|\rho| = 0.19$. This correlation of EC from the insula-DLPFC with changes in HDRS-17 at 12 weeks in the pilot data was −0.26.

> *Hypothesis: Changes in depression symptoms on 17-item HDRS (averaged over all three-post treatment-time points at 8, 16, and 26 weeks) will be associated with change in GABA between baseline and 16 weeks (post minus pre-treatment) in both treatment groups.*

Sensitivity analysis following the same formula but with a lower expected sample size of 111 (as outlined for DMPFC-DLPFC FC hypothesis), suggests a required effect size of $|\rho| = 0.27$. The correlation between GABA and HDRS-17 changes at 12 weeks in the pilot data was 0.68.

Functional and effective connectivity analysis

Linear mixed models were used for the functional and effective connectivity analyses. Analyses was conducted on the ITT population (all participants randomised to treatments), with participants excluded if TMS was delivered to unintended targets (primarily cases where TMS co-ordinates were uploaded incorrectly to neuronavigation software), or participants received fewer than 15 TMS sessions, or if the 20 TMS sessions were completed in > 6 weeks. All analyses included HDRS-17 time point as an independent variable and HDRS-17 treatment response as the dependent variable, with participant as a random effect. All analyses also included independent variables of baseline effective connectivity or FC, specific to the hypothesis being explored (e.g. baseline effectivity from right AI to IDLPFC). Change in connectivity analyses also included an independent variable of change in FC or EC again specific to the hypothesis being explored. For baseline connectivity analyses, models included three interaction terms: baseline EC or FC * HDRS-17 time point, baseline EC or FC * treatment group, and baseline EC or FC* HDRS-17 time point * treatment group, with the change in connectivity analyses including interaction terms based on change in EC or FC, rather than baseline connectivity. Confounder variables included age, gender, site and MGH group. Any confounder variable not found to be significant on initial testing were removed from the models and the analysis re-run, with the results from these re-run analyses presented in *Chapter 3*. All hypotheses were also tested with other measures of depression to test the

robustness of the findings, with the HDRS-17 time point and HDRS-17 treatment response replaced by the HDRS-6 (6 of the 17-item HDRS which measures the core symptoms of depression[140]), BDI-II, or PHQ-9 measures.

Magnetic resonance spectroscopy analysis

Linear regression models were largely used for the MRS analyses. Analyses was conducted on the ITT population, with participants excluded if they had a major protocol deviation for receiving the incorrect treatment. The dependent variable was change in depression score (baseline minus follow-up at 16 or 26 weeks, or averaged over 8, 16 and 26 weeks), with the predictor variable of interest being baseline GABA+/Cr, change in GABA+/Cr (follow-up minus baseline), Glutamate and glutamine ratio to creatine and phosphocreatine (Glx/tCr) change (follow-up minus baseline) or GABA/Glx ratio (follow-up minus baseline). This is with the exception of the hypotheses comparing change in GABA+/Cr and change in Glx/Cr between treatment groups, in which instance the spectra variable was the dependent variable and the treatment groups (rTMS and cgiTBS) the predictor variable of interest. The primary baseline GABA hypothesis baseline GABA as a predictor of clinical improvement (16 and 26 weeks vs. baseline), was analysed using an LMM. Participant was included as a random effect, and post-treatment time points (16 and 26 weeks) were included as an independent variable. For analyses, covariates of no interest included baseline depression score, MGH treatment resistance category, gender, age, treatment group, study centre, MRS platform, and spectra fit errors (GABA+ fitting errors at baseline and follow-up where appropriate and baseline and follow-up CRLB values where appropriate). For the two primary hypotheses related to GABA change, $p < 0.025$ was the level considered for statistical significance ($p < 0.05/2$, i.e. 5% significance level with Bonferonni correction), for all other hypotheses $p < 0.05$ was the level considered for statistical significance. The HDRS-17 was the primary depression measure of interest, and the HDRS-6, BDI-II, and PHQ-9 exploratory depression measures. All analyses were re-ran removing non-significant covariates with these final models reported.

For missing data (e.g. due to poor spectra quality, participants' absence for the scanning, or incompleteness of whole MRS sessions) we took an available data approach, meaning individuals with enough data for a model were included in that model's analysis.

Chapter 3 Results

Clinical efficacy

Participant flow

The Consolidated Standards of Reporting Trials (CONSORT) diagram illustrates the recruitment process (see *Figure 2*). During trial recruitment, 685 individuals completed the initial telephone eligibility screening, and at this stage, *N* = 261 were excluded for not meeting inclusion criteria, and *N* = 107 declined to take part in the trial. This resulted in 317 participants who consented to the BRIGhTMIND trial and attended the baseline assessment, with 39 participants not meeting inclusion criteria. The most common reasons for exclusion at this stage were that they were not diagnosed as MDD with HDRS-17 ≥16, or not diagnosed as TRD. Other exclusion reasons at the baseline assessment stage included: history of bipolar disorder (due to risk of mania) or depression secondary to other mental disorder; risk of suicidality; and change in prescribed medication within 2 weeks of baseline assessment.

Between baseline assessment and randomisation (post-consent), there were 23 withdrawals, with the reasons including: time commitments; concerns of treatment exacerbating physical illness; no capacity to deliver TMS treatment due to staffing and the COVID-19 pandemic; personal reasons, anxiety relating to TMS and unknown side effects; and unable to tolerate scan or not attending MRI scan visit. This left 255 participants who were randomised to cgiTBS (*N* = 128) or rTMS (*N* = 127). The first randomisation was on 22 January 2019, with the final randomisation on 31 January 2022. The last follow-up assessment was 3 August 2022.

The Nottingham, Newcastle, Northampton, and London sites were given permission to commence recruitment between November 2018 and March 2019. Recruitment to the entire study was suspended on 30 April 2020 because of the COVID-19 pandemic, with sites permitted to recommence recruitment on 1 August 2020. This was with the exception of the Northampton site, which did not reopen to recruitment in August 2020 and was informed of the decision to close the site in December 2020, owing to low recruitment numbers and lack of staff to deliver either the TMS or research assessments. To increase recruitment, Oldham (Pennine Care NHS Foundation Trust) was opened as a study site and commenced recruitment in August 2021. The total number of participants randomised to treatments per site included 113 participants for Nottingham, 59 for London, 47 for Newcastle, 29 for Northampton and 7 for Oldham (see *Appendix 2*, *Figure 18*).

Post-randomisation discontinuation to trial

Of the 255 participants randomised, only 3.2% (*N* = 4) of participants discontinued their involvement in the trial altogether, during the treatments. This included one participant who had a flare up of a pre-existing physical health condition, one participant who found the commitment to the treatments and study too great, one participant who had to reduce their percentage rMT in order to tolerate treatments but felt this would not be effective, and one participant who experienced a suspected seizure at the motor threshold testing at their first treatment and was lost to follow-up. At the 8-week follow-up, completion rates were 88.2%, *N* = 112 of 127 versus 86.7%, *N* = 111 of 128, 16-week follow-up 88.2%, *N* = 112 of 127 versus 87.5%, *N* = 112 of 128 and at the 26-week follow-up 80.3%, *N* = 102 of 127 versus 81.3%, *N* = 104 of 128, for the rTMS and cgiTBS groups, respectively. The most frequent reason for discontinuation was loss to follow-up. Reasons for discontinuation are presented in *Table 5*.

Adherence to treatment and protocol

A total of 235 major protocol deviations were recorded for 144 participants (56.5%). In the rTMS group there were 117 major protocol deviations for 68 participants and in the cgiTBS group 118 major protocol deviations for 76 participants (see *Table 6*). These numbers are high because: (1) participants accumulated a protocol deviation for every different break they had of 4 days or more missed consecutive dates for treatment; and (2) participants accumulated a protocol deviation for every different psychotropic medication or psychological intervention that was not kept stable for 16 weeks.

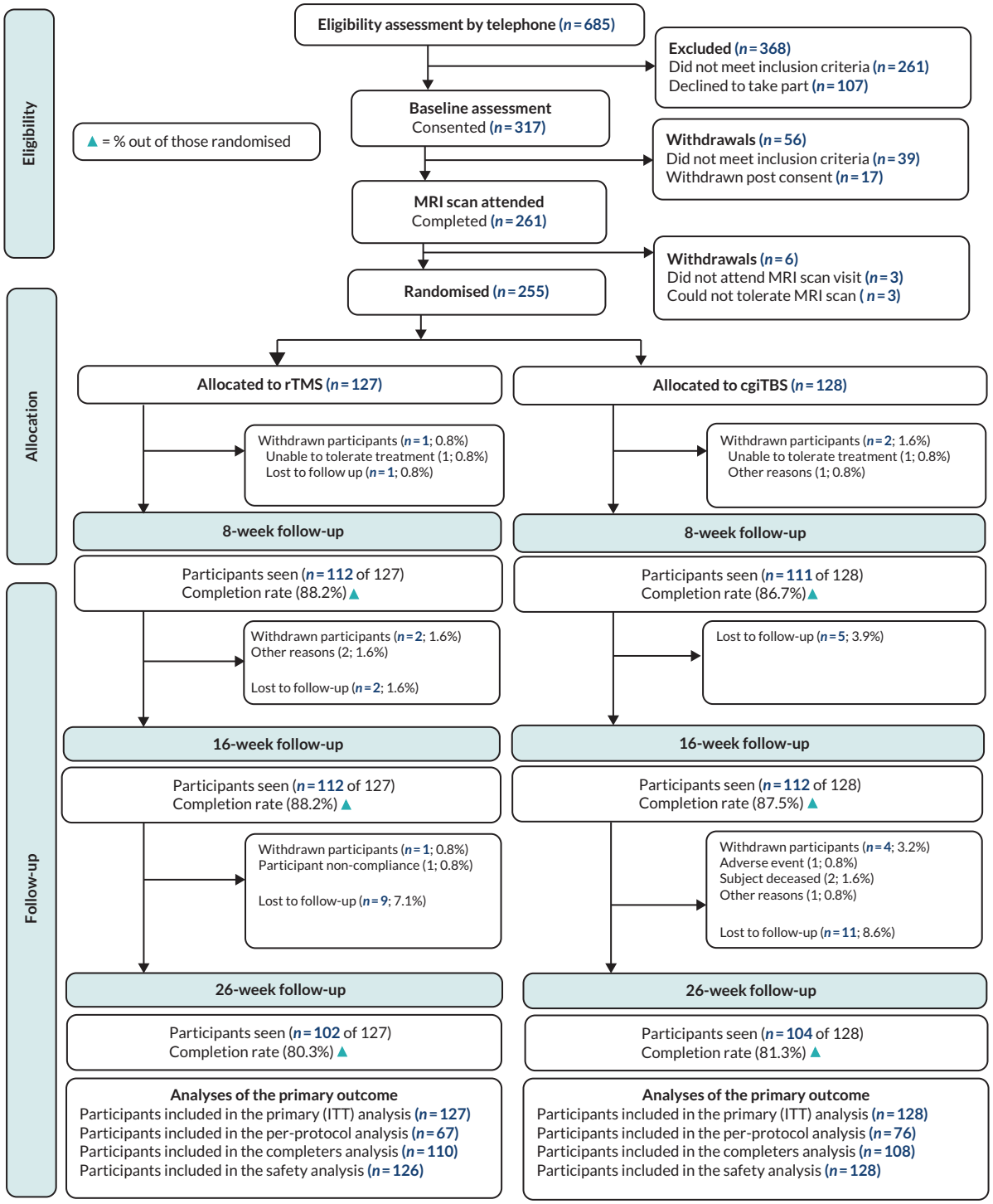


FIGURE 2 CONSORT diagram.

In terms of treatment adherence, 70 participants (27.5%) had a gap of more than 4 days of missed consecutive treatments with an average break length of 5.8 days. Most of these participants had 1 or 2 breaks (see *Table 7*). In addition, 48 participants' (18.8%) psychotropic medications or psychological interventions were changed between the baseline assessment and 16-week follow-up assessment (not including participants classed as at risk to themselves or others), and 5 participants (1.9%) commenced a daily prescription of benzodiazepines or 'Z' drugs (i.e. zopiclone, zolpidem, or zaleplon) that exceeded the criteria of maximum dose allowed for the trial, between baseline and the end of TMS treatments.

TABLE 5 Disposition of participants and reasons for discontinuation

		rTMS *n* = 127	cgiTBS *n* = 128	Overall *n* = 255
At baseline	Provided consent, *n* (%)	127 (100%)	128 (100%)	255 (100%)
	MRI scan performed, *n* (%)	127 (100%)	128 (100%)	255 (100%)
	Entered trial and provided data, *n* (%)	127 (100%)	128 (100%)	255 (100%)
At 8-week follow-up	Attended and provided data, *n* (%)	112 (88.2%)	111 (86.7%)	223 (87.5%)
At 16-week follow-up	Attended and provided data, *n* (%)	112 (88.2%)	112 (87.5%)	224 (87.8%)
	MRI scan performed[a], *n* (%)	67 (52.8%)	65 (50.8%)	132 (51.8%)
At 26-week follow-up	Completed trial, *n* (%)	102 (80.3%)	104 (81.3%)	206 (80.8%)
Discontinued, *n*	16	22	38	
Reason for discontinuation	AE, *n* (%)	0 (0.0%)	1 (4.6%)	1 (2.6%)
	Unable to tolerate treatment, *n* (%)	1 (6.3%)	1 (4.6%)	2 (5.3%)
	Participant non-compliance, *n* (%)	1 (6.3%)	0 (0.0%)	1 (2.6%)
	Subject deceased, *n* (%)	0 (0.0%)	2 (9.1%)	2 (5.3%)
	Other[b], *n* (%)	2 (12.5%)	2 (9.1%)	4 (10.5%)
	Lost to follow-up, *n* (%)	12 (75%)	16 (72.7%)	28 (73.7%)

a MRI, rsfMRI, MRS and Diffusion Weighted Imaging were not performed at London site at 16 weeks. Additionally, MRS was not performed at Oldham site at this time point.
b Other reasons were:
- Commitment too great, causing significant distress.
- Participant feels too unwell (mentally) to complete 26-week follow-up.
- Unwell and busy with family duties.
- Participant decision.

Note
Only data corresponding to participants who were randomised into the trial were entered into the MACRO database. Figures for provision of data account for participants who completed and provided any data at each individual time point.

TABLE 6 Breakdown of major protocol deviation reasons by deviation type and number of participants affected by deviation type

	rTMS		cgiTBS		Overall	
Major protocol deviation reason	***p***	***N***	***p***	***N***	***p***	***N***
Ineligibility post randomisation, *n* (%)	1 (0.9%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	1 (0.4%)	1 (0.4%)
Non-compliance with randomised treatment						
Participant received < 20 sessions over a period of 4–6 weeks, *n* (%)	11 (9.4%)	11 (8.7%)	9 (7.6%)	9 (7.0%)	20 (8.5%)	20 (7.8%)
Receiving wrong treatment as per randomised allocation,[a] *n* (%)	9 (7.7%)	9 (7.1%)	13 (11.0%)	13 (10.2%)	22 (9.4%)	22 (8.6%)
Session stopped part way through treatment, *n* (%)	5 (4.3%)	5 (3.9%)	3 (2.5%)	3 (2.3%)	8 (3.4%)	8 (3.1%)
Time between the first and last session exceeds 6 weeks, *n* (%)	0 (0.0%)	0 (0.0%)	2 (1.7%)	2 (1.6%)	2 (0.9%)	2 (0.8%)
Break between treatment sessions of more than 4 days,[b] *n* (%)	46 (39.3%)	38 (29.9%)	43 (36.4%)	32 (25.0%)	89 (37.9%)	70 (27.5%)

TABLE 6 Breakdown of major protocol deviation reasons by deviation type and number of participants affected by deviation type (*continued*)

	rTMS		cgiTBS		Overall	
Major protocol deviation reason	***p***	***N***	***p***	***N***	***p***	***N***
Missing primary outcome data (including loss to follow-up),[c] *n* (%)	9 (7.7%)	9 (7.1%)	13 (11.0%)	13 (10.2%)	22 (9.4%)	22 (8.6%)
Receiving concomitant medications that should not be taken while receiving treatment (i.e. lamotrigine, pregabalin or gabapentin), *n* (%)	2 (1.7%)	2 (1.6%)	3 (2.5%)	3 (2.3%)	5 (2.1%)	5 (1.9%)
Psychotropic medications or psychological interventions not kept stable for 16 weeks for the duration of the trial (except for those at risk to themselves or others),[d] *n* (%)	31 (26.5%)	22 (17.3%)	30 (25.4%)	26 (20.3%)	61 (25.9%)	48 (18.8%)
Daily prescription of benzodiazepine above 5 mg, diazepam equivalents, zopiclone above 7.5 mg, zolpidem above 10 mg or zaleplon above 10 mg from baseline assessment to the end of TMS treatment, *n* (%)	3 (2.6%)	3 (2.4%)	2 (1.7%)	2 (1.6%)	5 (2.1%)	5 (1.9%)
Overall, *n* (%)	117 (100%)	68 (53.5%)	118 (100%)	76 (59.4%)	235 (100%)	144 (56.5%)

a This includes instances where TMS treatment was delivered to the incorrect co-ordinates as opposed to as per MRI data or the TMS SOP.
b A deviation of this type was added to the summary table above for participants that had a break of more than four days between TMS sessions and did not have a protocol deviation recorded for this on the protocol deviations CRF.
c Defined as the failure to provide the HDRS-17 score at all of the follow-up assessment time points: 8, 16 and 26 weeks.
d Changes in psychotropic medications were captured under the category of 'Other deviation' and they were adjudicated by the chief investigator as to determine whether or not they were classed as this type of medication.

Note
There are three participants who completed 20 TMS sessions in < 4 weeks and who have not been excluded from the per-protocol analysis. Major deviations related to missing primary outcome data and psychotropic medications not kept stable for 16 weeks were not captured in the protocol deviations CRF. Therefore, they were derived using other parts of the data extracted from MA.
p, number of protocol deviations by deviation type, *N*, number participants affected per deviation type. The percentage corresponding to the proportion of participants affected per major deviation type (including the total for each treatment arm and overall) was calculated out of the total number of participants randomised.

TABLE 7 Measures of compliance with treatment

Measure of compliance with treatment		**rTMS**	**cgiTBS**	**Overall**
Number of TMS sessions delivered (as per protocol or as per changes allowed in the TMS SOP) within 6 weeks after randomisation	*N*	126[a]/127	127[b]/128	253/255
	Mean (SD)	18.4 (4.1)	19.1 (3.2)	18.9 (3.7)
Number of breaks between TMS sessions of more than 4 days per participant	1	32 (84.2%)	22 (68.8%)	54 (77.1%)
	2	5 (13.2%)	9 (28.1%)	14 (20%)
	3	0 (0.0%)	1 (3.1%)	1 (1.4%)
	4	1 (2.6%)	0 (0.0%)	1 (1.4%)

continued

TABLE 7 Measures of compliance with treatment (*continued*)

Measure of compliance with treatment		rTMS	cgiTBS	Overall
Break length between TMS sessions of more than 4 days (measured in days)	*N*	46/127	43/128	89/255
	Mean (SD)	5.9 (2.6)	5.7 (1.5)	5.8 (2.2)
Number of participants whose existing psychotropic medications or psychological interventions were not kept stable for 16 weeks, except for those at risk to themselves or others[c]	*N* (%)	22/127 (17.3%)	26/128 (20.3%)	48/255 (18.8%)
Number of participants whose daily prescription of benzodiazepine was above 5 mg, diazepam equivalents, zopiclone was above 7.5 mg, zolpidem was above 10 mg or zaleplon was above 10 mg from baseline assessment to the end of TMS treatment[c]	*N* (%)	3/127 (2.4%)	2/128 (1.6%)	5/255 (1.9%)

a One participant at the Oldham site did not have any TMS treatment delivered due to experiencing an SAE.
b One participant at the Newcastle site only had one TMS session delivered. This was due to flare up of arthritis, which began before TMS treatment. Participant was unable to commit to daily journeys and withdrew from treatment.
c These figures were calculated out of the number of participants randomised into the trial.

Further major protocol deviations related to non-adherence with randomised treatment, included 20 participants (7.8%) who received < 20 TMS sessions, 8 participants (3.1%) stopping one TMS session part way through treatment, and 2 participants (0.8%) whose course of treatments exceeded 6 weeks. There were also 22 participants (8.6%) who received the wrong treatment as per randomised allocation. Of these participants, 12 had treatments delivered at the incorrect site due to their TMS co-ordinates being uploaded incorrectly (*N* = 3 for 1 session, *N* = 1 for 3 sessions, *N* = 1 for 4 sessions, *N* = 1 for 6 sessions, *N* = 1 for 7 sessions, *N* = 1 for 11 sessions, *N* = 2 for 14 sessions and *N* = 2 for all 20 sessions). Furthermore, there were four participants whose treatment dose was set incorrectly for a portion of one treatment session and one participant whose treatment dose was set incorrectly for an entire session. One participant also had a train of treatment delivered of the incorrect treatment, one participant had six trains of treatment delivered with a shorter gap than expected, and one participant whose treatment co-ordinates were not correct. All of these occurred at one session only. Finally, there were two participants for whom no additional details were provided (see *Appendix 2*, *Table 35*).

Additional trial-related major protocol deviations included one eligibility violation of a person who was judged to be at risk of suicidality at baseline assessment. This became evident after the participant completed the study, that their baseline HDRS-17 suicidality score was recorded as 4, and while at the time it was indicated that the participant had strong protective factors in place, the PI was unable to be sure that the patient was not suicidal, due to lack of information on duration of suicidal ideation. Additionally, 5 participants (1.9%) commenced lamotrigine, pregabalin or gabapentin, after their TMS treatments had commenced but prior to their 16-week follow-up, and 22 participants (8.6%) were missing primary outcome data. Minor protocol deviations are not reported in detail here and can be found in *Appendix 2*, *Table 36*.

Participant characteristics

Table 8 summarises the demographic and baseline characteristics of the sample (post-randomisation). Participants had a mean age of 43.7, *SD* = 14.0 years, with *N* = 132 (51.8%) female gender, and a total of *N* = 232 (91%) of white ethnicity and *N* = 23 (9%) from ethnic minority backgrounds. In addition, *N* = 138 (54.1%) were in full-time or other employment, *N* = 87 (34.1%) were unemployed, and *N* = 30 (11.8%) were retired.

In regard to depression characteristics, the mean duration of current episode was 113.9, *SD* = 119 months [median 6.1 (IQR 2.1–12.1) years], and mean number of depressive episodes was 3.2, *SD* = 5.2 [median 2 (IQR 1–4.2) years]. In

terms of medication use at baseline, 198 participants (77.6%) were taking antidepressants, with 41 participants (16.1%) having a combination of two or more antidepressants. Augmentation medications at baseline included antipsychotics, buspirone, lithium, methylphenidate, modafinil, pramipexole, and triiodothyronine. In addition, 16 participants (6.3%%) were taking hypnotics/sleeping tablets and 14 participants (5.5%) taking anxiolytics. Regarding treatment resistance,

TABLE 8 Baseline characteristics

		rTMS	cgiTBS	Overall
		N = 127	*N* = 128	*N* = 255
Age (years)	Mean (SD)	43.8 (13.1)	43.7 (15.0)	43.7 (14.0)
Gender	Male, *n* (%)	65 (51.2%)	58 (45.3%)	123 (48.2%)
	Female, *n* (%)	62 (48.8%)	70 (54.7%)	132 (51.8%)
Ethnicity	White British, *n* (%)	106 (83.5%)	108 (84.4%)	214 (83.9%)
	White Irish, *n* (%)	4 (3.1%)	1 (0.8%)	5 (2.0%)
	Other white, *n* (%)	6 (4.7%)	7 (5.5%)	13 (5.1%)
	White/Black African, *n* (%)	1 (0.8%)	2 (1.6%)	3 (1.2%)
	White/Asian, *n* (%)	1 (0.8%)	0 (0.0%)	1 (0.4%)
	Other mixed, *n* (%)	1 (0.8%)	2 (1.6%)	3 (1.2%)
	Indian, *n* (%)	4 (3.1%)	2 (1.6%)	6 (2.4%)
	Pakistani, *n* (%)	2 (1.6%)	2 (1.6%)	4 (1.6%)
	Bangladeshi, *n* (%)	0 (0.0%)	1 (0.8%)	1 (0.4%)
	Other Asian, *n* (%)	0 (0.0%)	1 (0.8%)	1 (0.4%)
	Black Caribbean, *n* (%)	1 (0.8%)	0 (0.0%)	1 (0.4%)
	Chinese, *n* (%)	0 (0.0%)	1 (0.8%)	1 (0.4%)
	Other ethnicity, *n* (%)	1 (0.8%)	1 (0.8%)	2 (0.8%)
Marital status: *Married/cohabiting*	Yes, *n* (%)	76 (59.8%)	55 (43.0%)	131 (51.4%)
Dependants (children/other)	Yes, *n* (%)	42 (33.1%)	36 (28.1%)	78 (30.6%)
Employment/education	Full-time, *n* (%)	39 (30.7%)	37 (28.9%)	76 (29.8%)
	Other employment, *n* (%)	36 (28.3%)	26 (20.3%)	62 (24.3%)
	Retired, *n* (%)	13 (10.2%)	17 (13.3%)	30 (11.8%)
	Unemployed, *n* (%)	39 (30.7%)	48 (37.5%)	87 (34.1%)
Receipt of benefits	Yes, *n* (%)	52 (40.9%)	45 (35.2%)	97 (38.0%)
Duration of current major depressive episode (months)	*N*	117	122	239
	Mean (SD)	106.7 (108.2)	120.9 (128.6)	113.9 (119.0)
Number of depressive episodes	*N*	84	91	175
	Mean (SD)	2.8 (2.8)	3.5 (6.8)	3.2 (5.2)
Baseline CTQ	*N*	120	120	240
	Mean (SD)	47.1 (17.4)	45.1 (16.2)	46.1 (16.8)

continued

TABLE 8 Baseline characteristics (*continued*)

		rTMS	cgiTBS	Overall
		N = 127	*N* = 128	*N* = 255
	N	127	128	255
Category of baseline MGH-S	Low: 2–3.5, *n* (%)	42 (33.1%)	45 (35.2%)	87 (34.1%)
	Medium: 4–6, *n* (%)	36 (28.3%)	37 (28.9%)	73 (28.6%)
	High: ≥ 6.5, *n* (%)	49 (38.6%)	46 (35.9%)	95 (37.3%)
Baseline medication use				
Antidepressants	Yes, *n* (%)	94 (74.0%)	104 (81.3%)	198 (77.6%)
Tricyclic antidepressants	Yes, *n* (%)	10 (7.9%)	11 (8.6%)	21 (8.2%)
MAOIs	Yes, *n* (%)	1 (0.8%)	0 (0.0%)	1 (0.4%)
SSRIs	Yes, *n* (%)	41 (32.3%)	46 (35.9%)	87 (34.1%)
SNRI	Yes, *n* (%)	31 (24.4%)	39 (30.5%)	70 (27.5%)
Other	Yes, *n* (%)	34 (26.8%)	36 (28.1%)	70 (27.5%)
Antidepressant combination	Yes, *n* (%)	22 (17.3%)	19 (14.8%)	41 (16.1%)
Antipsychotic augmentation	Yes, *n* (%)	19 (15.0%)	23 (18.0%)	42 (16.5%)
Lithium augmentation	Yes, *n* (%)	3 (2.4%)	11 (8.6%)	14 (5.5%)
Methylphenidate augmentation	Yes, *n* (%)	0 (0.0%)	1 (0.8%)	1 (0.4%)
Modafinil augmentation	Yes, *n* (%)	0 (0.0%)	1 (0.8%)	1 (0.4%)
Triiodothyronine augmentation	Yes, *n* (%)	0 (0.0%)	3 (2.3%)	3 (1.2%)
Hypnotics/sleeping tablets	Yes, *n* (%)	7 (5.5%)	9 (7.0%)	16 (6.3%)
Anxiolytics	Yes, *n* (%)	7 (5.5%)	7 (5.5%)	14 (5.5%)
Electroconvulsive therapy during current episode of depression	Yes, *n* (%)	6 (4.7%)	4 (3.1%)	10 (3.9%)

Note
Other baseline medication refers to the following antidepressants: trazadone, bupropion, mirtazapine, reboxetine, agomelatine or vortioxetine. The number of current major depressive episodes has been set to missing for participants whose number was entered as 99. The duration of current major depressive episodes was calculated using the date of randomisation and start date of the episode.

95 participants (37.3%) were categorised as high treatment resistance (non-response to more than approximately 6 treatments), 73 participants (28.6%) as medium treatment resistance (non-response to about 4–5 treatments), and 87 participants (34.1%) categorised as low treatment resistance (non-response to about 2–3 treatments), with 10 participants (3.9%) receiving ECT in their current episode of depression.

Primary outcome analysis

Primary hypothesis 'cgiTBS is more efficacious in reducing the mean HDRS-17 score over 26 weeks compared to standard rTMS in patients with TRD'

Table 9 summarises the HDRS-17 descriptive statistics for the primary and secondary analyses. In the ITT analysis, the participants were analysed in the groups they were allocated to (rTMS *n* = 127, cgiTBS *n* = 128). *Table 10* summarises the descriptive statistics for the cognition outcome variable. The breakdown of baseline and follow-up HDRS-17 by research site, and also for the sensitivity and moderator analyses is reported in *Appendix 2*, *Table 37*.

As shown in *Table 11*, the primary analysis of the primary outcome (HDRS-17 over 26 weeks) indicated the adjusted mean difference between the rTMS and cgiTBS treatment arms was non-significant [−0.31 points (95% CI −1.87 to

1.24)]. This is contrary to the clinical efficacy hypothesis, demonstrating that cgiTBS does not show superior clinical efficacy compared to MRI-neuronavigated rTMS. The primary analysis demonstrated a clinically substantial change in HDRS-17 scores[141] at 26 weeks, with a 7.8-point and 8-point reduction from baseline, for rTMS and cgiTBS, respectively. *Figure 3*. also shows that depression symptom improvement was maintained between 8 and 26 weeks following rTMS or cgiTBS.

TABLE 9 Hamilton Rating Scale for Depression-17 descriptive statistics for the primary and secondary analyses and secondary clinical outcome measure descriptive statistics

		Baseline		8 weeks		16 weeks		26 weeks	
		rTMS	cgiTBS	rTMS	cgiTBS	rTMS	cgiTBS	rTMS	cgiTBS
Primary analysis[a] HDRS-17	*N*	127	128	127	128	127	128	127	128
ITT (multiple imputation)	Mean (SD)	23.9 (4.7)	22.9 (4.7)	15.6	14.5	15.9	15.3	16.1	14.9
	SE			0.7	0.6	0.6	0.8	0.8	0.7
Secondary analyses									
Per-protocol HDRS-17	*N*	67	76	58	61	55	63	52	58
	Mean (SD)	24.1 (4.8)	23.2 (4.8)	17.2 (8.4)	15.0 (6.4)	17.4 (8.3)	15.3 (8.1)	17.6 (9.2)	14.2 (7.9)
Completers HDRS-17	*N*	110	108	104	105	110	108	98	98
	Mean (SD)	24.0 (4.9)	22.6 (4.6)	15.5 (7.5)	14.4 (6.6)	15.8 (7.9)	15.0 (7.7)	16.2 (8.6)	14.4 (7.6)
Secondary clinical outcome measures									
BDI-II	*N*	127	128	111	109	109	110	99	102
	Mean (SD)	34.4 (8.9)	32.3 (8.8)	23.5 (12.6)	21.3 (10.7)	24.7 (12.2)	22.3 (12.4)	23.6 (12.6)	21.6 (12.0)
PHQ-9	*N*	127	128	111	109	109	109	99	102
	Mean (SD)	20.2 (4.6)	19.4 (4.4)	13.4 (7.5)	12.3 (6.3)	13.8 (7.2)	13.5 (7.3)	13.7 (7.6)	13.1 (7.5)
GAD-7	*N*	127	128	111	109	109	108	99	102
	Mean (SD)	13.3 (4.7)	13.1 (4.6)	9.3 (6.3)	8.9 (4.9)	9.3 (5.5)	9.1 (5.3)	9.9 (6.1)	8.9 (5.6)
WSAS	*N*	127	128	111	109	109	109	99	102
	Mean (SD)	29.0 (6.8)	27.6 (7.8)	22.1 (10.9)	21.2 (9.5)	22.2 (10.7)	22.4 (10.2)	22.2 (10.7)	21.5 (10.8)
EQ-5D-5L VAS	*N*	127	128	111	109	109	109	98	102
	Mean (SD)	43.0 (19.3)	43.4 (17.1)	52.8 (21.0)	54.7 (18.8)	53.2 (20.2)	56.7 (19.4)	53.8 (21.2)	55.8 (20.5)

a It was not possible to calculate descriptive statistics such as SD, Median, IQR, Min and Max for the HDRS-17 follow-up measures because multiple imputations were used to perform the primary analysis.

TABLE 10 Cognition variables descriptive statistics

		Baseline				16 Weeks			
		rTMS		cgiTBS		rTMS		cgiTBS	
CRT response time (ms)	*N*	123		127		76		72	
	Mean (SD)	717.67	(238.55)	708.05	(249.25)	606.28	(183.02)	614.12	(210.71)
DSST total correct	*N*	122		127		76		72	
	Mean (SD)	51.17	(18.26)	49.15	(21.18)	55.76	(16.93)	52.36	(19.59)
N-back total correct	*N*	122		126		76		72	
	Mean (SD)	22.82	(10.81)	21.56	(9.66)	25.28	(9.25)	24.56	(9.63)
TMT response time (s)	*N*	123		126		76		72	
	Mean (SD)	30.08	(15.99)	34.70	(25.26)	27.11	(16.34)	31.07	(25.10)
PDQ-5-D score	*N*	123		127		75		71	
	Mean (SD)	12.89	(4.47)	13.29	(4.46)	10.55	(5.07)	10.83	(94.79)
CRT– mu	*N*	116		120		76		71	
	Mean (SD)	541.74	(208.44)	521.99	(183.89)	486.41	(167.62)	474.25	(187.54)
CRT– sigma	*N*	116		120		76		71	
	Mean (SD)	84.12	(58.54)	78.61	(48.51)	71.91	(48.59)	66.35	(44.89)
CRT–tau	*N*	116		120		76		71	
	Mean (SD)	152.55	(71.07)	151.64	(75.82)	119.87	(48.27)	136.99	(69.50)
CRT– iSD	*N*	122		126		76		72	
	Mean (SD)	187.13	(74.79)	181.85	(66.50)	149.09	(53.42)	155.72	(64.56)
CRT– CoV	*N*	122		126		76		72	
	Mean (SD)	0.26	(0.06)	0.26	(0.07)	0.24	(0.05)	0.25	(0.06)

Secondary and sensitivity analyses of primary outcome

The per-protocol analysis included *n* = 59 (46.5%) and *n* = 63 (49.3%) participants for rTMS and cgiTBS treatment arms respectively, and the completers analysis included *N* = 110 (86.6%) and *N* = 108 (84.4%) participants. The pre-/post-COVID-19 analysis showed that 72% of the entire sample (*N* = 184) were classed as 'Post-COVID'. Participants whose 26-week HDRS-17 assessment was due before or up to 18 March 2020 (pause to recruitment due to COVID-19) were classified as 'Pre-COVID' and those whose assessment was due after this date were classed as 'Post-COVID'. Across all secondary and sensitivity analyses there were no statistically significant differences between the cgiTBS and rTMS treatment groups. The results of these analyses demonstrated that the reductions in HDRS-17 scores at 26 weeks for both treatment arms were comparable to what was observed in the primary outcome analysis.

Analyses of moderators

The moderator analyses demonstrated that the following moderator variables alone significantly predicted the primary outcome: baseline HDRS-17 score [adjusted mean = 0.69 (95% CIs 0.45 to 0.93); $p < 0.001$], baseline GAD-7 [adjusted mean = 0.36 (95% CIs 0.11 to 0.61); $p = 0.004$] and number of TMS sessions delivered as per protocol (i.e. completing 20 sessions as planned vs. completing < 20 sessions as planned with completing < 20 sessions as reference) [adjusted mean = −5.64 (95% CIs −9.48 to −1.80); $p = 0.004$]. The results demonstrating that higher baseline HDRS-17, higher baseline GAD-7, and completion of < 20 sessions as planned, predicted greater depression symptoms over 26-week follow-up. The following moderator variables alone did not significantly predict the primary outcome: age at baseline

TABLE 11 Summary of primary outcome results: HDRS-17 score measured over 26 weeks at 8, 16 and 26 weeks

	Number of participants		Baseline HDRS-17 score Mean (SD)		cgiTBS vs. rTMS over 26 weeks	
	rTMS	cgiTBS	rTMS	cgiTBS	Adjusted mean difference (95% CI)[a]	*p*-value
Primary analysis						
ITT(m ultiple imputation)	127	128	23.9 (4.7)	22.9 (4.7)	−0.31 (−1.87 to 1.24)	0.689
Secondary analyses						
Per protocol[b]	59	63	24.1 (4.8)	23.2 (4.8)	−1.39 (−3.63 to 0.86)	0.225
Completers[c]	110	108	24.0 (4.9)	22.6 (4.6)	−0.25 (−1.80 to 1.30)	0.753
Sensitivity analyses						
Primary analysis under MNAR assumption	127	128	23.9 (4.7)	22.9 (4.7)	−0.57 (−1.94 to 0.81)	0.420
Pre-/post-COVID-19 period[d]	127	128	24.7 (5.3)	23.2 (5.3)	1.71 (−1.85 to 5.28)	0.346
			23.5 (4.4)	22.9 (4.5)		
Centre as random effect	*N*/A	*N*/A	23.9 (4.7)	22.9 (4.7)	−0.36 (−1.49 to 0.78)	0.536
Subgroup analyses[e]						
Moderator: baseline HDRS-17 score	118	115	23.9 (4.8)	22.6 (4.6)	−0.09 (−0.43 to 0.24)	0.593
Moderator: baseline MGH-S	118	115	23.9 (4.8)	22.6 (4.6)	0.05 (−0.38 to 0.48)	0.830
Moderator: age at baseline	118	115	23.9 (4.8)	22.6 (4.6)	−0.02 (−0.13 to 0.09)	0.723
Moderator: number of TMS sessions[f]	118	115	23.9 (4.8)	22.6 (4.6)	3.48 (−2.20 to 9.17)	0.230
Moderator: baseline CTQ score	111	108	23.7 (4.7)	22.5 (4.6)	0.01 (−0.08 to 0.11)	0.788
Moderator: baseline GAD-7 score	118	115	23.9 (4.8)	22.6 (4.6)	−0.10 (−0.42 to 0.23)	0.569

a Adjusted for: treatment centre (stratification variable), baseline HDRS-17 score and degree of TRD (minimisation variables) and treatment arm with participant ID as the random effect (with the exception of one of the sensitivity analyses in which Centre was treated as the random effect).
b Reasons for exclusion from per-protocol analysis: did not complete at least one TMS session of their allocated intervention, had at least 1 major protocol deviation recorded.
c Reasons for exclusion from completers analysis: had < 10 rTMS or cgiTBS sessions delivered at the correct co-ordinates as per MRI data, were not assessed at baseline and/or 16-week follow-up.
d The model for this analysis was also adjusted for a variable of pre-/post-COVID-19 period as well as an interaction term for pre-/post-COVID-19 period and treatment arm. The estimates shown for this analysis correspond to the interaction term between the variable of pre-/post-COVID-19 period and treatment arm.
e The adjusted mean and 95% CI shown for each subgroup analysis correspond to the estimates calculated for the interaction term between the moderator and the treatment arm.
f This includes number of rTMS or cgiTBS treatment sessions that were delivered as per MRI data or as per changes allowed in the TMS SOP. This moderator was included in the model as a dichotomous variable.

[adjusted mean = −0.04 (95% CIs −0.12 to 0.05); p = 0.391], baseline CTQ [adjusted mean = 0.004 (95% CIs −0.06 to 0.07); p = 0.915], and with baseline MGH-S reaching marginal significance [adjusted mean = 0.30 (95% CIs −0.01 to 0.61); p = 0.058]. The interactions between treatment arm and all moderator variables were not statistically significant. This indicates that the moderator variables did not influence the relationship between treatment arms and the primary outcome. Gender was also examined as an exploratory moderator variable (i.e. female vs. male, with male as reference), which did not predict the primary outcome alone [adjusted mean = 0.61 (95% CIs −1.57 to 2.80); p = 0.581] or by interaction [adjusted mean = −2.19 (95% CIs −5.32 to 0.94); p = 0.171].

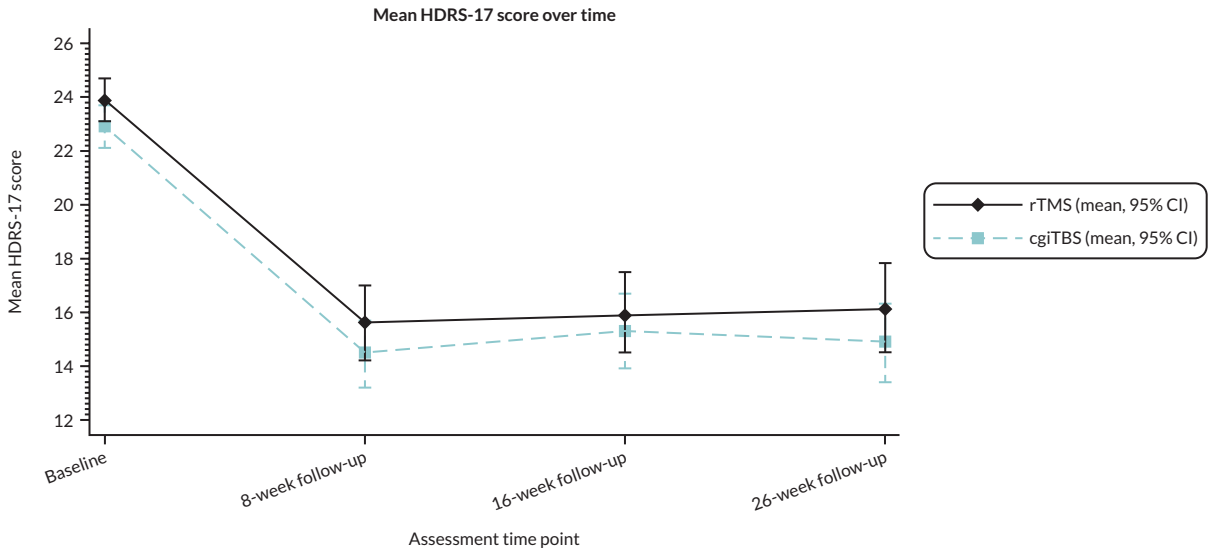


FIGURE 3 The HDRS-17 mean scores for the primary analysis – ITT (multiple imputation).

Secondary outcome analyses

Secondary hypothesis 'cgiTBS is more efficacious for secondary clinical outcomes compared to standard rTMS in patients with TRD'

Table 12 reports the results of the binary outcome results comparing rTMS versus cgiTBS for responders and remitters at 8, 16 and 26 weeks, and sustained responders at 16 and 26 weeks. Consistent with the primary outcome analysis, there were no significant differences found between the treatment arms, for any of the responder, remitters, or sustained responder time points. Descriptively the overall proportion of responders was *N* = 74 of 223 (33.2%), *N* = 77 of 224 (34.4%) and *N* = 67 of 206 (32.5%) for the 8-, 16- and 26-week follow-up time points, respectively. The overall proportion of remitters was *N* = 42 of 223 (18.8%), *N* = 46 of 224 (20.5%) and *N* = 47 of 206 (22.8%) for the 8-, 16- and 26-week follow-up time points, respectively. Finally, the overall proportion of sustained responders at both 16 weeks and 26 weeks was *N* = 51 of 255 (20%).

In addition, given that degree of treatment resistance reached marginal significance as a predictor of the primary outcome, we were interested in descriptively exploring the breakdown of the number of responders by category of treatment resistance at the 8-, 16- and 26-week follow-ups (see *Appendix 2*, *Table 38*). In the cgiTBS group, there were 14 out of 34 classed as responders for low treatment resistance, 13 out of 30 for medium treatment resistance and 9 out of 31 for high treatment resistance at the 26-week follow-up. For the rTMS group, there were 16 out of 34 classed as responders for low treatment resistance, 9 out of 26 for medium treatment resistance and 6 out of 42 for high treatment resistance at the 26-week follow-up. This suggests that there were a slightly higher proportion of responders in the medium and high treatment resistance categories for the cgiTBS group at the 26-week follow-up, compared to the rTMS group, and overall more responders with low and medium resistance compared to those with high treatment resistance.

The same picture was found for the continuous secondary outcome analyses, with none of these variables demonstrating significant differences between rTMS and cgiTBS (see *Table 13*). At 26 weeks there was an overall decrease in self-report depression and anxiety scores, including a 6.4-point reduction on the PHQ-9, 10.7-point reduction on the BDI-II, and a 3.8-point reduction on the GAD-7. There was also a 6.5-point decrease in impairment of functioning as measured by the WSAS total score, and an 11.6-point increase in perceived health as measured by the EQ-5D-5L VAS score. Prior research has indicated that minimum clinically important differences for the PHQ-9 is ≥ 3.7 points,[142] BDI-II is ≥ 6.0 points,[143] GAD-7 is ≥ 3.3 points,[142] WSAS is ≥ 3.7 points[144] and EQ-5D-5L VAS is ≥ 8.0 points.[145] Therefore, the findings demonstrate minimum clinical important differences for all these outcomes. Overall, alongside improvements in depression, there are improvements in anxiety symptoms, quality of life and functioning, which also appear to be maintained over 6 months in line with the primary outcome analysis.

TABLE 12 Summary of secondary binary outcome results

	Number of participants		Rate in each treatment arm		cgiTBS vs. rTMS	
	rTMS	cgiTBS	rTMS	cgiTBS	Adjusted odds ratio (95% CI)	*p*-value
Proportion of responders at						
8-week follow-up	112	111	35/112 (31.3%)	39/111 (35.1%)	1.13 (0.63 to 2.03)	0.682
16-week follow-up	112	112	38/112 (33.9%)	39/112 (34.8%)	1.03 (0.57 to 1.87)	0.916
26-week follow-up	102	104	31/102 (30.4%)	36/104 (34.6%)	1.18 (0.63 to 2.20)	0.615
Proportion of remitters at						
8-week follow-up	112	111	19/112 (16.9%)	23/111 (20.7%)	1.09 (0.53 to 2.26)	0.818
16-week follow-up	112	112	23/112 (20.5%)	23/112 (20.5%)	0.84 (0.42 to 1.69)	0.631
26-week follow-up	102	104	21/102 (20.6%)	26/104 (25.0%)	1.21 (0.61 to 2.41)	0.590
Proportion of sustained responders at						
16-week follow-up	127	128	23/127 (18.1%)	28/128 (21.9%)	1.21 (0.64 to 2.29)	0.557
26-week follow-up	127	128	22/127 (17.3%)	29/128 (22.7%)	1.40 (0.74 to 2.66)	0.307

Cognition hypothesis 1: 'Treatment with rTMS and cgiTBS will lead to an improvement in cognition between baseline and week 16 that correlates with improvement in mood'

As per the QC checks detailed in the methods chapter, outliers were removed for any scores on the CRT, DSST, or *N*-back (primary outcomes) that were four times the SD of the overall sample (baseline CRT = 32, 16-week CRT 25, baseline DSST = 14, 16-week DSST = 19 and 16-week *N*-back = 7). In addition, 1 participant's TMT score was removed from baseline for taking longer than 5 minutes to complete, with five participants' baseline data not having at least three of the four objective tasks scores meet QC or not completed.

In regard to hypothesis 1, there were significant main effects of time point on CRT [$F(1, 155.486) = 11.275$, $p = 0.001$], TMT [$F(1, 152.446) = 5.499$, $p = 0.020$] and *N*-back [$F(1, 151.091) = 7.748$, $p = 0.006$], indicating improvements over time for sustained attention, executive functioning and working memory (see *Figure 4*). Significant interactions of time point*HDRS-17 change were found on CRT [$F(1, 151.349) = 6.321$, $p = 0.013$], and PDQ-5-D [$F(1, 161.111) = 55.602$, $p = 0.001$]. This arose because improvement on the HDRS-17 was a predictor of sustained attention (CRT) and subjective cognitive performance (PDQ-5-D) at the 16-week time point only (see *Figure 5*). The only significant main effect of the treatment group was on the DSST [$F(1, 211.880) = 4.080$, $p = 0.045$]. Interaction terms: treatment group*time point and time point*change in HDRS-17 score*treatment group were non-significant for all cognitive variable outcomes (p's > 0.05), indicating no differential effect of treatment (rTMS vs. cgiTBS) on cognition outcomes, with the main effect of the treatment group observed on the DSST related only to a between-group baseline difference (better baseline performance for cgiTBS participants compared to rTMS participants). Of note, age was retained as a confounder for all cognitive outcomes, gender retained as a confounder for the DSST analysis, site retained as a confounder for the *N*-back analysis, and baseline GAD-7 retained as a confounder for the PDQ-5-D analysis.

Hypothesis 2: 'Treatment with rTMS and cgiTBS will lead to a reduction in IIV in CRT performance that correlates with improvement in mood'

The results of these mixed linear regression models demonstrated significant main effects of time point on tau [$F(1, 182.523) 6.784$, $p = 0.001$] and iSD [$F(1, 176.622) = 13.033$, $p = 0.001$], suggestive of a reduction in the number and/or length of abnormally slow responses and less variability in RT. Additionally, there were significant interactions of time point* HDRS-17 change on sigma [$F(1, 158.255) = 12.909$, $p = 0.001$], and mu [$F(1, 149.396) = 11.645$, $p = 0.001$], demonstrating improved speed (consistent with the finding seen for the mean CRT RT), and less variability in RT with

TABLE 13 Summary of secondary continuous outcome results

	Number of participants		Baseline score mean (SD)		cgiTBS vs. rTMS	
	rTMS	cgiTBS	rTMS	cgiTBS	Adjusted mean difference (95% CI)[a]	*p*-value
HDRS-17 score at						
8-week follow-up	112	111	23.8 (4.8)	22.6 (4.6)	−0.42 (−2.18 to 1.28)	0.626
16-week follow-up	112	112	24.0 (4.9)	22.6 (4.7)	0.11 (−1.82 to 2.04)	0.912
26-week follow-up	102	104	23.8 (4.9)	22.8 (4.6)	−0.89 (−3.04 to 1.25)	0.412
PHQ-9 score at						
8-, 16-, and 26-week follow-up	118	114	20.2 (4.6)	19.4 (4.4)	−0.12 (−1.54 to 1.30)	0.871
GAD-7 score at						
8-, 16- and 26-week follow-up	118	114	13.3 (4.7)	13.1 (4.6)	−0.19 (−1.24 to 0.86)	0.726
WSAS score at						
8-, 16- and 26-week follow-up	118	114	29.0 (6.8)	27.6 (7.8)	0.60 (−1.39 to 2.59)	0.554
BDI-II score at:						
8-, 16- and 26-week follow-up	118	114	34.4 (8.9)	32.3 (8.8)	−0.54 (−2.90 to 1.82)	0.653
EuroQol-5D-5L (VAS score) at:						
8-, 16- and 26-week follow-up	118	114	43.0 (19.3)	43.4 (17.1)	1.98 (−1.96 to 5.91)	0.325

a Adjusted for: treatment centre (stratification variable), baseline HDRS-17 score and degree of TRD (minimisation variables) and treatment arm.

improvement in HDRS-17 scores. No significant effects were observed on CoV. Furthermore, there were no significant main effects of treatment group, or group*time point interaction for any of the IIV variables (*p*'s > 0.05), consistent with the findings related to hypothesis 1, indicating no differential effect of treatment (rTMS vs. cgiTBS) on cognition outcomes. Of note, age was retained as a confounder for all IVV outcomes, and site retained as a confounder for the mu analysis.

Based on these results, an additional exploratory secondary analysis (see *Appendix 2*, *Table 39*) was conducted to examine the relationship between participants change in HDRS-17 score and change in the cognition and IVV variables (i.e. baseline to week 16). Significant moderate correlations were found between HDRS-17 change and change in PDQ-5-D (r = 0.48, N = 145, p = 0.001), change in mu (r = 0.31, N = 140, p < 0.001) and change in sigma (r = 0.30, N = 140, p < 0.001). Significant weak correlations were also found between HDRS-17 change and change in CRT (r = 0.21, N = 147, p < 0.008) and change in DSST (r = −0.180, N = 147, p < 0.029). The overall results were consistent with improvement in cognition with reduction in depression severity.

Patients' global impression of change

Descriptive statistics regarding participants' impression of change at each treatment session and follow-up time point are reported in *Appendix 2*, *Tables 40–41*, with *Figure 6* showing the percentage of participants reporting feeling somewhat, or much, better after each session for illustrative purposes. Overall, at the end of the final 20th TMS treatment, N = 1 (0.4%) of participants rated themselves as much worse, N = 7 (3%) as somewhat worse, N = 74 (31.2%) as just the same, N = 111 (46.8%) as somewhat better, and N = 44 (18.6%) as much better. By session 10, 45 participants (37.2%) and 60 participants (48.3%) reported feeling somewhat, or much, better for rTMS and cgiTBS, respectively. By session 20, this was reported for 76 participants (65%) and 79 participants (65.8%). The relationship between session number and perceived improvement appeared linear across the 20 sessions for the rTMS group. The relationship for cgiTBS was generally similar but appeared to rise somewhat faster over sessions 7 to 10, before

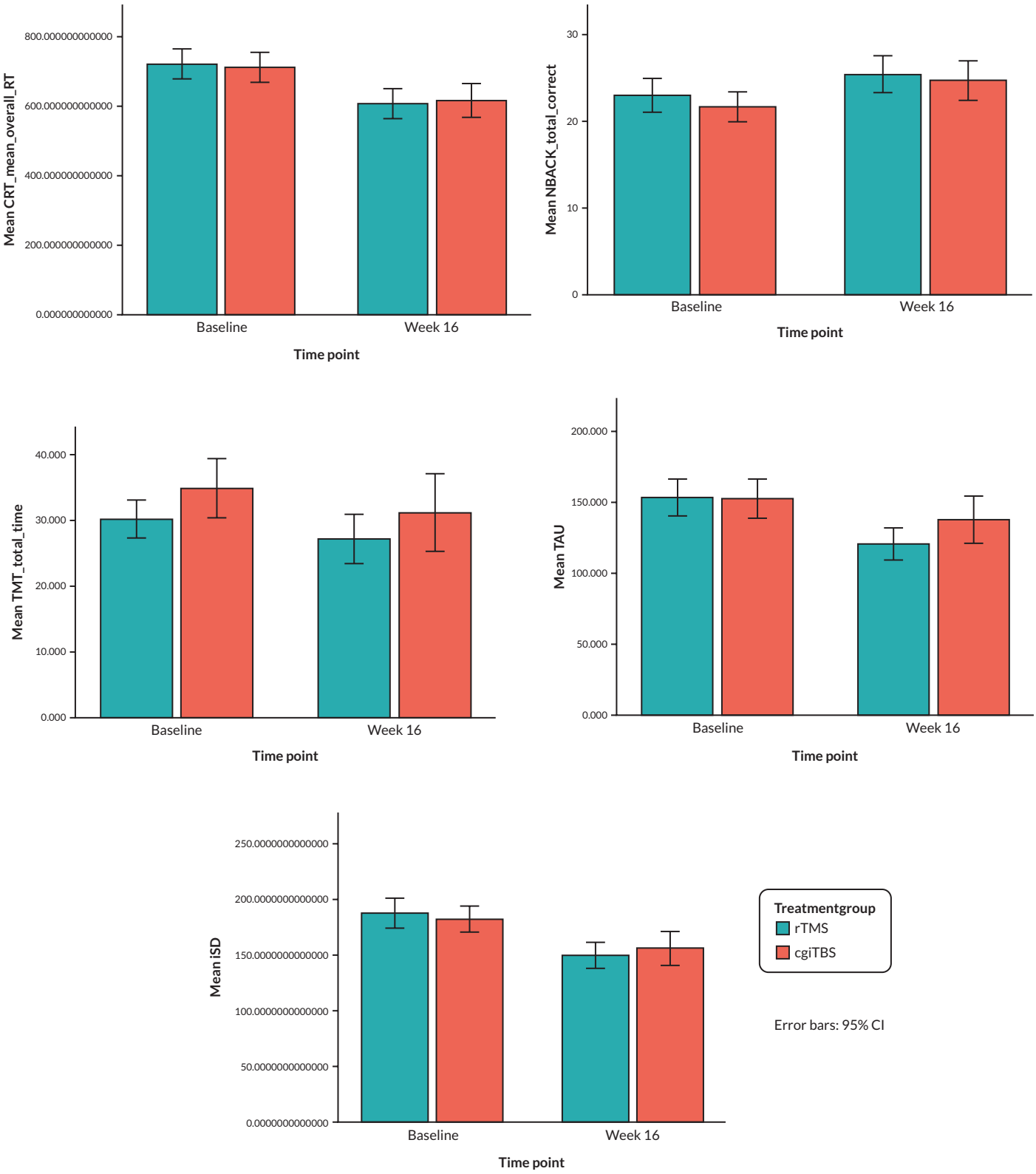


FIGURE 4 Clustered bar mean of cognition and IIV variables at baseline and 16-week time points for rTMS and cgiTBS group.

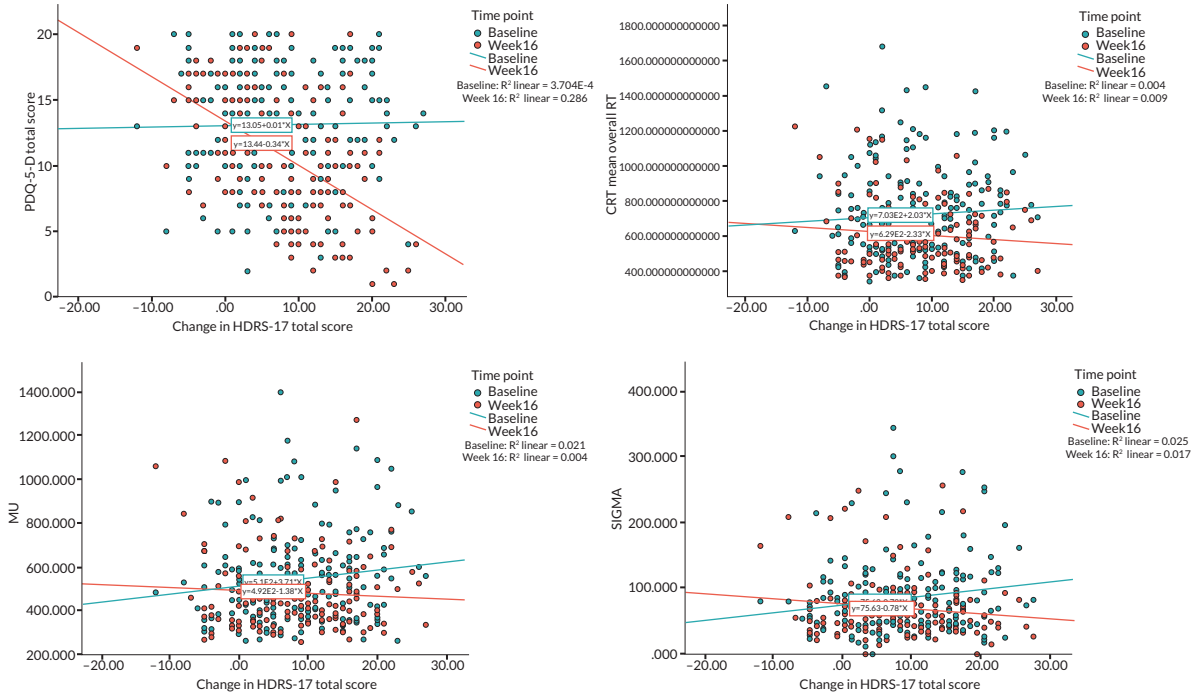


FIGURE 5 Grouped scatter plots of relationship between HDRS-17 score and change in cognition and IIV variables.

plateauing then returning to a similar linear trend as for rTMS. In both groups, the proportion experiencing a benefit continued to increase even at the 19th and 20th sessions.

Across the 8-, 16- and 26-week time points, respectively, the number of participants rating themselves as much worse was *N* = 3 (1.4%), *N* = 6 (2.7%) and *N* = 4 (2%), and the number of participants rating themselves as somewhat worse was *N* = 17 (7.7%), *N* = 17 (7.7%) and *N* = 23 (11.3%). In addition, the proportion of participants that rated themselves as just the same was *N* = 73 (32.9%), *N* = 90 (40.7%) and *N* = 70 (34.5%). Finally, the number of participants reporting feeling somewhat better was *N* = 86 (38.7%), *N* = 63 (28.5%) and *N* = 63 (31%), and those reporting feeling much better was *N* = 43 (19.4%), *N* = 45 (20.4%) and *N* = 42 (21.2%). Further analysis will explore in more detail the trajectory of illness and its relationship to a range of clinical, sociodemographic, cognitive and imaging variables.

Study blinding and treatment arm prediction

In total there were three unintentional unblinding for two participants. One participant's treatment was unblinded to both the site-specific PI and the site-specific RA, and another participant's treatment unblinded to the site-specific RA only. In these instances, another blinded RA completed both of these participants' follow-up assessments. In terms of researchers' treatment allocation prediction, correct guesses for the cgiTBS group were at 5.4%, 9.8% and 16.3% across the 8-, 16- and 26-week follow-ups, respectively. For the rTMS group correct guesses were at 8%, 13.4% and 16.7% across the follow-up time points respectively. Most predictions were that of 'don't know', with overall rates of 84.8%, 79.5% and 74.3% across the time points (see *Appendix 2*, *Table 42*).

Inter-rater reliability of primary outcome measure

To ensure high inter-rater reliability on the HDRS-17, specific training was provided by the chief investigator for all RAs. In addition, an inter-rater reliability assessment was performed by seven RAs from the Nottingham, Newcastle, Northampton and London sites, who conducted the HDRS-17 for the BRIGhTMIND study, and three LEAP members, who volunteered to be assessed by the researchers, drawing on their lived experience of depression, at a meeting in November 2019.The intra-class coefficient for the total HDRS-17 score was 0.94, with a 95% reference interval for the difference (between any pair of raters) in total HDRS-17 score of 0.66 to 0.99. Inter-rater reliability was not assessed towards to the end of recruitment as originally expected due to the COVID-19 pandemic.

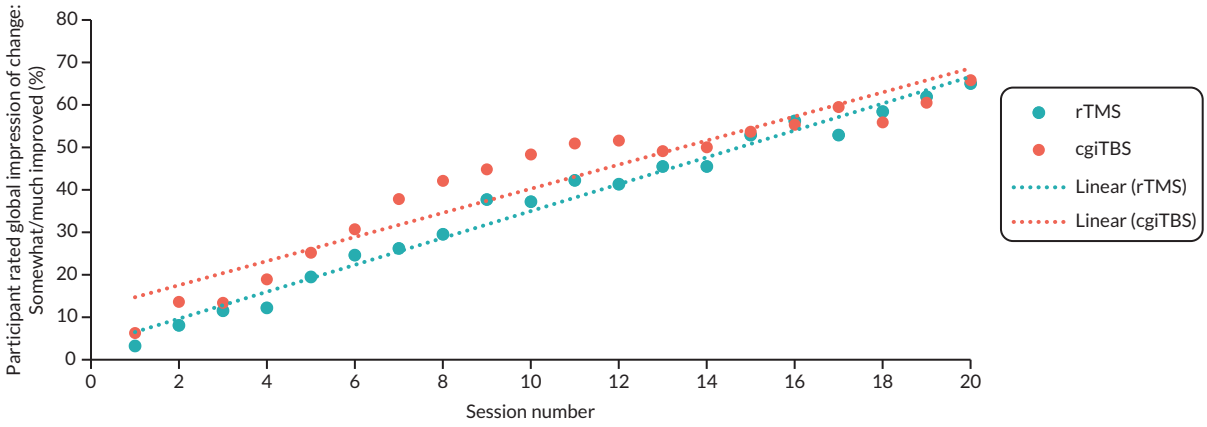


FIGURE 6 Percentage of participants who felt somewhat or much better over the 20 TMS sessions.

Accuracy of transcranial magnetic stimulation targets

An exploratory analysis was conducted to test how close the TMS stimulus was delivered on the first session to the MRI treatment co-ordinates provided, and how close TMS stimulus was delivered at the rest of the sessions compared to the first session. This was done by computing the Euclidean/angular distance measured from the given target position/orientation to the mean position/orientation that was delivered on the first session, and by computing the Euclidean/angular distance measured from the mean position/orientation that was delivered on the first session to the mean position/orientation that was delivered on each subsequent session and averaged over the number of subsequent sessions. The angular distance is a geodesic measure that quantifies how far away on a sphere one orientation is from another, so the range is between 0 and 180 degrees. As shown in *Table 14*, the median distance between treatment targets to where treatment was delivered on the first session, and between the first session and subsequent sessions was under or about half a centimetre difference and with a median angle difference under or about seven degrees. *Appendix 2*, *Figures 19–22* show some outliers. However, overall adherence to target stimulation sites at the first session and across all treatment sessions were acceptable and similar across both treatment groups.

Summary of findings

1. Connectivity-guided intermittent theta burst stimulation (iTBS) was not superior to rTMS on any of the primary or secondary outcome measures.
2. Nevertheless, in this treatment-resistant moderately severe depression population, MRI and neuronavigation personalised TMS (cgiTBS or rTMS) was associated with one in three participants achieving a clinical response and in a fifth this was sustained at 26 weeks. About 20% of TRD patients might be kept well with MRI-neuronavigated TMS delivered twice per year.
3. There were no clinical or demographic moderators of clinical response in terms of depression or cognition to cgiTBS or rTMS.
4. Clinical improvement with cgiTBS or rTMS was gradual and required at least 20 TMS sessions. After 20 TMS sessions some participants reported a slight improvement and might have benefited for further TMS sessions irrespective of receiving cgiTBS or rTMS.

Safety, acceptability, facilitators and barriers

All adverse events and serious adverse events

A total of 1850 AEs were reported in 204 (80.3%) participants who were both randomised into the BRIGhTMIND trial and included in the safety population (*N* = 254) (see *Table 15*). There were 153 participants (60.3%) with 1 to 10 AEs, 42 participants (16.7%) with 11–30 AEs, and 9 participants (3.6%) with 31 or more AEs (see *Appendix 3*, *Table 43*). The overall number of AEs was greater in the cgiTBS group (1008 AEs) compared to the rTMS group (842 AEs), but this was largely accounted for by three participants in the cgiTBS group with an exceptionally high number of AEs. Regarding relatedness of AEs to the study, 4.9% were classed as not related, 9.3% were unlikely, 33.8% were possible, 49.6% were probable and 2.4% were classed as definitely related, with the expectedness of AEs at 66.4%. Furthermore, the majority

TABLE 14 Target session and inter-session distance and angle

	Median (25th, 75th percentiles)	
	rTMS	cgiTBS
Target session distance (mm)	4.20 (2.99, 8.66)	4.66 (2.62, 8.10)
Target session angle (degrees)	7.09 (5.02, 9.69)	6.82 (3.89, 9.54)
Inter-session distance (mm)	5.17 (3.88, 8.25)	4.63 (3.73, 7.48)
Inter-session angle (degrees)	7.51 (5.47, 10.07)	6.73 (5.31, 10.22)

Note
Target session – difference between MRI derived co-ordinates for TMS stimulation and site of delivery of TMS as recorded by neuronavigation in terms of maximum distance and angle.
Inter-session – variability in the maximum distance and angle of stimulation across the course of TMS (up to 20 sessions).

of AEs were classed as mild (91.8%), with most AEs requiring no treatment (91.7%). Listing of adverse events in the rTMS and cgiTBS arm are reported in *Appendix 3*, *Tables 44* and *45*.

A total of 18 SAEs events were reported in 13 (5.2%) participants who were randomised into the BRIGhTMIND trial (see *Table 16*). There were two deaths in the cgiTBS group. One participant had underlying cardiovascular health conditions and passed away from a heart attack. Additionally, one participant passed away from opiate poisoning, with coroner's inquest concluding accidental death. Both participants had completed their course of TMS treatments and died close to the 26-week assessment, with both reported as unlikely to be related to TMS treatments.

All further SAEs events reported required hospital admission, except for the suspected seizure. Two SAEs were reported as being possibly related to TMS treatment. In the cgiTBS group, one participant was hospitalised due to a manic episode which occurred after their 14th TMS treatment session. In the rTMS group, one participant was hospitalised for a psychotic episode with severe anxiety/depression 1 month after their TMS treatments were completed. There were, however, situational factors and a life event to take into consideration for these two participants, and while TMS may have contributed to these events, they were unlikely to be the only contributing factor. One further participant in the rTMS group was also admitted to hospital for nausea and vomiting following their baseline MRI scan, with this event reported as probably related.

In addition, there was one further SAE of a suspected 2-second seizure that occurred during the participant's motor threshold testing at their first TMS session. A consultant psychiatrist and nurse both witnessed the event and determined that this appeared to be a seizure, so the TMS session did not precede. The participant reported remembering prior to the event happening that they suddenly felt dizzy and in a dream-like state. The participant also reported that they had a history of previous collapsing events and reporting that their sibling developed epilepsy as an adolescent. The participant's general practitioner (GP) was made aware of the event, and the participant was also told to report it themself to arrange a review by their GP. The participant's treatment was discontinued, and the Research Ethics Committee (REC) deemed the outcome satisfactory with no further action required. All further SAEs were reported as unrelated to the study.

Finally, in the rTMS group, one participant also experienced a vasovagal episode during their first treatment, and one participant experienced syncope during motor threshold testing at the first treatment. Both were reported as AEs rather than SAEs as no treatment or hospital admission was required. Both participants treatment was suspended for that given day, with both participants approved to continue with the rest of their sessions with no further incidents reported. In addition, there was one participant in the cgiTBS group who was suspected of having multiple seizures with focal onset. These events occurred outside of the TMS sessions, and were confirmed by neurology as being dissociative seizures, rather than epileptic seizures, and so while this was initially classed as an SAE it was then downgraded to an AE. It was decided by the PI and participant to discontinue treatments due to these health issues, and no further TMS sessions took place.

TABLE 15 Characteristics of all AEs

	rTMS	cgiTBS	Total
Overall number of AEs, *n* (%)	842 (100%)	1008 (100%)	1850 (100%)
Severity			
Mild, *n* (%)	781 (92.8%)	918 (91.1%)	1699 (91.8%)
Moderate,[a] *n* (%)	46 (5.5%)	78 (7.7%)	124 (6.7%)
Severe,[b] *n* (%)	15 (1.8%)	10 (1.0%)	25 (1.4%)
Fatal,[c] *n* (%)	0 (0.0%)	2 (0.2%)	2 (0.1%)
Outcome			
Resolved, *n* (%)	822 (97.6%)	982 (97.4%)	1804 (97.5%)
Resolved with sequelae, *n* (%)	7 (0.8%)	6 (0.6%)	13 (0.7%)
Continuing, *n* (%)	2 (0.2%)	3 (0.3%)	5 (0.3%)
Fatal, *n* (%)	0 (0.0%)	2 (0.2%)	2 (0.1%)
Unknown, *n* (%)	11 (1.3%)	13 (1.3%)	24 (1.3%)
Unobtainable, *n* (%)	0 (0.0%)	2 (0.2%)	2 (0.1%)
Treatment			
None, *n* (%)	785 (93.2%)	912 (90.5%)	1697 (91.7%)
Concomitant medication, *n* (%)	40 (4.8%)	85 (8.4%)	125 (6.8%)
Non-drug therapy, *n* (%)	17 (2.0%)	8 (0.8%)	25 (1.4%)
Concomitant medication and non-drug therapy, *n* (%)	0 (0.0%)	3 (0.3%)	3 (0.2%)
Action taken			
None, *n* (%)	834 (99.0%)	994 (98.6%)	1828 (98.8%)
Study interrupted, *n* (%)	4 (0.5%)	9 (0.9%)	13 (0.7%)
Study discontinued, *n* (%)	4 (0.5%)	5 (0.5%)	9 (0.5%)
Relatedness			
Not related, *n* (%)	52 (6.2%)	39 (3.9%)	91 (4.9%)
Unlikely, *n* (%)	70 (8.3%)	102 (10.1%)	172 (9.3%)
Possible, *n* (%)	294 (34.9%)	332 (32.9%)	626 (33.8%)
Probable, *n* (%)	403 (47.9%)	514 (51.0%)	917 (49.6%)
Definite, *n* (%)	23 (2.7%)	21 (2.1%)	44 (2.4%)
Serious			
Yes, *n* (%)	10 (1.2%)	7 (0.7%)	17 (0.9%)
No, *n* (%)	832 (98.8%)	1001 (99.3%)	1833 (99.1%)
Expectedness			
Yes, *n* (%)	540 (64.1%)	688 (68.3%)	1228 (66.4%)
No, *n* (%)	302 (35.9%)	320 (31.7%)	622 (33.6%)

a Five of the moderate AEs were classed as SAEs: rTMS = 3, cgiTBS = 2.
b 10 of the severe AEs were classes as SAEs: rTMS = 7, cgiTBS = 3.
c Both fatal AEs were classed as SAEs.

TABLE 16 Frequency of SAEs by type and number of participants affected by SAE type

	rTMS		cgiTBS		Overall	
SAE type	SAE	*N*	SAE	*N*	SAE	*N*
Hospitalisation for nausea and vomiting	1 (9.1%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	1 (0.4%)
Hospitalisation for pulmonary embolism	1 (9.1%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	1 (0.4%)
Hospitalisation for COVID-19	0 (0.0%)	0 (0.0%)	1 (14.3%)	1 (0.8%)	1 (5.6%)	1 (0.4%)
Death from accidental opiate poisoning	0 (0.0%)	0 (0.0%)	1 (14.3%)	1 (0.8%)	1 (5.6%)	1 (0.4%)
Hospitalisation from investigation of fatigue	0 (0.0%)	0 (0.0%)	1 (14.3%)	1 (0.8%)	1 (5.6%)	1 (0.4%)
Hospitalisation for head injury	1 (9.1%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	1 (0.4%)
Hospitalisation for headache	1 (9.1%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	1 (0.4%)
Death from myocardial infarction	0 (0.0%)	0 (0.0%)	1 (14.3%)	1 (0.8%)	1 (5.6%)	1 (0.4%)
Hospitalisation for high temperature	0 (0.0%)	0 (0.0%)	1 (14.3%)	1 (0.8%)	1 (5.6%)	1 (0.4%)
Hospital admission for anaphylaxis due to insect bites	1 (9.1%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	1 (0.4%)
Hospital admission for chest pains and breathlessness	1 (9.1%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	1 (0.4%)
Hospital admission for low blood pressure	1 (9.1%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	1 (0.4%)
Hospital admission related to pre-existing Hidradenitis Suppurativa	1 (9.1%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	1 (0.4%)
Hospital admission-psychotic episode with severe anxiety/depression	1 (9.1%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	1 (0.4%)
Hospitalisation due to mania episode	0 (0.0%)	0 (0.0%)	1 (14.3%)	1 (0.8%)	1 (5.6%)	1 (0.4%)
Hospitalisation for shortness of breath	0 (0.0%)	0 (0.0%)	1 (14.3%)	1 (0.8%)	1 (5.6%)	1 (0.4%)
Voluntary hospital admission for ECT	1 (9.1%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	1 (0.4%)
Suspected seizure before first TMS session[a]	1 (9.1%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	1 (0.4%)
Total, *n* (%)	11 (100%)	9 (7.2%)	7 (100%)	4 (3.1%)	18 (100%)	13 (5.2%)

SAE, number of SAEs by SAE type; *N*, number participants affected per SAE type.
a Not included in the safety population as the participant did not have any TMS treatment delivered due to experiencing a seizure.

Note
The percentage corresponding to the number of participants affected per SAE type (including the total for each treatment arm and overall) was calculated out of the total number of participants randomised.

Adverse events reported as possible, probable, or definitely related to the study

Regarding AEs that were classed as possible, probable, or definitely related to the study (see *Table 17*); there was a greater proportion of mild (809 AEs) and moderate (53 AEs) in the cgiTBS group compared to the rTMS group (mild AEs = 697; moderate AEs = 20). Severe AEs were comparable across rTMS (three severe AEs) and cgiTBS (five severe AEs). Of note of these 8 severe AEs, 5 were classed as severe but not an SAE, and 3 reported as severe and an SAE. All SAEs have been reported in the previous section. In terms of duration of possible, probable, or definitely related AEs, 1038 AEs were resolved the same day, 313 resolved within 1–6 days, 125 resolved within 1–4 weeks, 56 resolved within 4–8 weeks, 24 resolved in 8–16 weeks, 10 resolved within 16–26 weeks, 6 resolved in 26–52 weeks and 15 classed as unknown, continuing, or unobtainable.

Table 18 also provides a breakdown of outcome, treatment and expectedness by mild, moderate, and severe AEs for those that were classed as possible, probable, or definitely related to the study. Overall, mild AEs required more concomitant medication, non-drug therapy or a combination of both (93 AEs) when compared to moderate (16 AEs)

TABLE 17 Breakdown of AE duration for mild, moderate and severe AEs recorded as being possible, probable or definitely related to study

	Mild AEs		Moderate AEs		Severe AEs		Total	
	rTMS	cgiTBS	rTMS	cgiTBS	rTMS	cgiTBS	rTMS	cgiTBS
Resolved same day	460 (63.9%)	541 (62.4%)	10 (1.4%)	25 (2.9%)	1 (0.1%)	1 (0.1%)	471 (65.4%)	567 (65.4%)
Resolved within 1–6 days	125 (17.4%)	168 (19.4%)	3 (0.4%)	16 (1.8%)	1 (0.1%)	0 (0.0%)	129 (17.9%)	184 (21.2%)
Resolved within 7 to 27 days (1–4 weeks)	61 (8.5%)	52 (6.0%)	2 (0.3%)	8 (0.9%)	0 (0.0%)	2 (0.2%)	63 (8.8%)	62 (7.2%)
Resolved within 28–55 days (4–8 weeks)	34 (4.7%)	19 (2.2%)	1 (0.1%)	0 (0.0%)	1 (0.1%)	1 (0.1%)	36 (5.0%)	20 (2.3%)
Resolved within 56 days – 111 days (8–16 weeks)	6 (0.8%)	16 (1.8%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	7 (1.0%)	17 (2.0%)
Resolved within 112–181 days (16–26 weeks)	5 (0.7%)	3 (0.3%)	0 (0.0%)	2 (0.2%)	0 (0.0%)	0 (0%)	5 (0.7%)	5 (0.6%)
Resolved within 182–364 days (26–52 weeks)	2 (0.3%)	2 (0.2%)	2 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (0.6%)	2 (0.2%)
Unknown/ continuing/ unobtainable	4 (0.6%)	8 (0.9%)	1 (0.1%)	2 (0.2%)	0 (0.0%)	0 (0.0%)	5 (0.7%)	10 (1.2%)
Overall	697 (96.8%)	809 (93.3%)	20 (2.8%)	53 (6.1%)	3 (0.4%)	5 (0.6%)	720 (100.0%)	867 (100.0%)

Note
Percentages for rTMS are out of the total number of possible, probable, and definitely related AEs in that treatment arm (n = 720).
Percentages for cgiTBS are out of the total number of possible, probable and definitely related AEs in that treatment arm (n = 867).

TABLE 18 Breakdown of AE outcome, treatment, and expectedness for mild, moderate, and severe AEs recorded as being possible, probable or definitely related to study

	Mild AEs		Moderate AEs		Severe AEs		Total	
	rTMS	cgiTBS	rTMS	cgiTBS	rTMS	cgiTBS	rTMS	cgiTBS
Outcome								
Resolved, *n* (%)	693 (96.3%)	799 (92.2%)	18 (2.5%)	51 (5.9%)	2 (0.3%)	5 (0.6%)	713 (99.0%)	855 (98.6%)
Resolved with sequelae, *n* (%)	1 (0.1%)	2 (0.2%)	1 (0.1%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	3 (0.4%)	2 (0.2%)
Continuing, *n* (%)	2 (0.3%)	2 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.3%)	2 (0.2%)
Unknown, *n* (%)	1 (0.1%)	4 (0.5%)	1 (0.1%)	2 (0.2%)	0 (0.0%)	0 (0.0%)	2 (0.3%)	6 (0.7%)
Unobtainable, *n* (%)	0 (0.0%)	2 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.2%)
Treatment								
None, *n* (%)	666 (92.5%)	747 (86.2%)	19 (2.6%)	38 (4.4%)	1 (0.1%)	2 (0.2%)	686 (95.3%)	787 (90.8%)
Concomitant medication, *n* (%)	19 (2.6%)	59 (6.8%)	1 (0.1%)	11 (1.3%)	2 (0.3%)	2 (0.2%)	22 (3.1%)	72 (8.3%)

continued

TABLE 18 Breakdown of AE outcome, treatment, and expectedness for mild, moderate, and severe AEs recorded as being possible, probable or definitely related to study (*continued*)

	Mild AEs		Moderate AEs		Severe AEs		Total	
	rTMS	cgiTBS	rTMS	cgiTBS	rTMS	cgiTBS	rTMS	cgiTBS
Non-drug therapy, *n* (%)	12 (1.7%)	2 (0.2%)	0 (0.0%)	3 (0.3%)	0 (0.0%)	0 (0.0%)	12 (1.7%)	5 (0.6%)
Concomitant medication and non-drug therapy, *n* (%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	3 (0.3%)
Expectedness								
Yes, *n* (%)	518 (71.9%)	633 (73.0%)	9 (1.3%)	28 (3.2%)	1 (0.1%)	3 (0.3%)	528 (73.3%)	664 (76.6%)
No, *n* (%)	179 (24.9%)	176 (20.3%)	11 (1.5%)	25 (2.9%)	2 (0.3%)	2 (0.2%)	192 (26.7%)	203 (23.4%)

Note
Percentages for rTMS are out of the total number of possible, probable, and definitely related AEs in that treatment arm (*n* = 720).
Percentages for cgiTBS are out of the total number of possible, probable, and definitely related AEs in that treatment arm (*n* = 867).

and severe (5 AEs). In addition, there was a greater proportion of mild (62 AEs) and moderate (15 AEs) in the cgiTBS that required concomitant medication, non-drug therapy or a combination of both when compared to the rTMS group (mild AEs = 31; moderate AEs = 1). Overall, 73.3% of AEs in the rTMS group and 76.6% of AEs in the cgiTBS group were expected. In addition, 1568 AEs were resolved, 5 resolved with sequalae, and 14 reported as continuing, unknown or unobtainable. Of those that were resolved with sequalae, 3 were mild AEs (tinnitus, tongue discomfort, and neck pain), 1 was a moderate AE (migraine) and 1 reported as a severe AE (the hospital admission for psychotic episode with severe anxiety/depression), with resolved with sequalae meaning episodically recurring but not continuously and/or needing medication to prevent it happening again. Of those that were reported as continuing, unknown or unobtainable, 3 were headaches, 3 were tinnitus, 2 were cognitive difficulties, 1 was tiredness, 1 was disturbed sleep, 1 was anxiety, 1 was jaw ache, 1 was short periods of elevated mood, and 1 was neck pain.

Summary of common and uncommon side effects data collected after TMS sessions

The summary of common and uncommon side effects collected at each individual TMS session is reported in (see *Appendix 3*, *Tables 46–67*). Of the 254 participants included in the safety population, on average at an individual session: *N* = 38 (15.0%) reported headaches, *N* = 23 (9.1%) reported neck pain, *N* = 21 (8.3%) reported scalp discomfort, *N* = 13 (5.1%) reported tinnitus, *N* = 16 (6.3%) reported dizziness, *N* = *14* (5.6%) reported jaw ache, *N* = *11* (4.4%) reported nausea, *N* = 7 (2.8%) reported watering eyes, and *N* = 26 (10.2%) reporting uncommon side effects (see *Table 19*). These were all considered to be probably, possible or definitely related.

The most frequently reported common side effect at the TMS sessions and the least reported was watering eyes. The side effect profiles across the two treatment arms were comparable except for higher rates of tinnitus in the cgiTBS group (*N* = 9 of 128; 7.0%) versus rTMS group (*N* = 4 of 126; 3.2%). Uncommon side effects at each TMS session were recorded as verbatim comments, therefore exact numbers cannot be provided. However, during treatments there were reports of but not limited to: increased agitation/irritability; anxiety; fatigue; insomnia/nightmares; potential cognitive difficulties (such as brain fog, difficulty finding words, slight memory loss); facial tingling; pain in eyes; and toothache.

Tolerability

As reported in the minor protocol deviations (see *Appendix 2*, *Table 36*) there were a higher proportion of participants in the rTMS group (*N* = 29, 22.8%) compared to the cgiTBS group (*N* = 10, 7.8%) whose treatment was adjusted due to not being able to tolerate the TMS protocols. *Table 20* provides a breakdown of these adjustments and shows there were a greater proportion of participants in the rTMS group (*N* = 11; 8.7%) who had to reduce their rMT when compared to the cgiTBS group (*N* = 4; 3.1%). The number of participants whose targets were moved or who had a combination of moving the target and reducing motor threshold was largely comparable across both TMS treatment groups. There was also a greater proportion of participants in the rTMS group (*N* = 11; 8.7%) that required more than

TABLE 19 Average number of participants with common and uncommon side effects at an individual TMS session

		rTMS *n* = 126	cgiTBS *n* = 128	Overall *n* = 254
Average number of participants with common side effects at an individual TMS session				
Headaches	*n* (%)	18 (14.3%)	20(15.6%)	38 (15.0%)
Neck pain	*n* (%)	12 (9.5%)	11 (8.6%)	23 (9.1%)
Scalp discomfort	*n* (%)	11 (8.7%)	10 (7.8%)	21 (8.3%)
Tinnitus	*n* (%)	4 (3.2%)	9 (7.0%)	13 (5.1%)
Dizziness	*n* (%)	7 (5.6%)	9 (7.0%)	16 (6.3%)
Jaw ache	*n* (%)	7 (5.6%)	7 (5.5%)	14 (5.6%)
Nausea	*n* (%)	5 (4.0%)	6 (4.7%)	11 (4.4%)
Watering eyes	*n* (%)	4 (3.2%)	3 (2.3%)	7 (2.8%)
Average number of participants with uncommon side effects at an individual TMS session	*n* (%)	13 (10.3%)	13(10.2%)	26 (10.2%)

TABLE 20 Breakdown of minor protocol deviations related to treatment adjusted as participant could not tolerate

	rTMS		cgiTBS		Overall	
Treatment adjusted as participant could not tolerate	***p***	***N* 127**	***p***	***N* 128**	***p***	***N* 255**
Threshold reduced once between session 1 and 20	11 (18.6%)	11 (8.7%)	4 (26.7%)	4 (3.13%)	15 (20.3%)	15 (5.9%)
Target moved away from treatment co-ordinates once between session 1 and 20	5 (8.5%)	5 (3.9%)	3 (20%)	3 (2.34%)	8 (10.8%)	8 (3.1%)
Combination of reducing threshold and moving away from treatment co-ordinates once between session 1 and 20	1 (1.7%)	1 (0.8%)	0 (0%)	0 (0%)	1 (1.4%)	1 (0.4%)
Participants with more than one adjustment made between session 1 and 20	41 (69.5%)	11 (8.7%)	7 (46%)	2 (1.6%)	48 (64.9%)	13 (5.1%)
EEG cap used	0 (0%)	0 (0%)	1 (6.7%)	1 (0.8%)	1 (1.4%)	1 (0.4%)
No reason available	1 (1.7%)	1 (0.8%)	0 (0%)	0 (0%)	1 (1.4%)	1 (0.4%)
Overall, *n* (%)	59 (100%)	29 (22.8%)	15 (100%)	10 (7.8%)	74 (100%)	39 (15.3%)

p, number of protocol deviations; *n*, number of participants.

Note
Threshold reduced also included participants whose threshold was attempted to be increased over a session or multiple sessions but was still below the expected treatment motor threshold.

one adjustment across the TMS sessions in order to tolerate the treatments, when compared to the cgiTBS group (*N* = 2; 1.6%). Participants would have accumulated a protocol deviation for every TMS session where an additional adjustment had to be made, hence the greater proportion of protocol deviations per participant for this deviation. Additional details can be found in *Appendix 3*, *Table 68*. Furthermore, motor threshold was tested at the first session and retested at the sixth session. Regarding the first session, there were 16 participants for the rTMS group and 4 participants for the cgiTBS group that reduced percentage rMT in order to tolerate treatments. For these participants,

the TMS intensity at the first session was delivered on average at 87.8% rMT rather than the expected 120% rMT for the rTMS participants, and at 68.2% rMT rather than the expected 80% rMT for the cgiTBS participants.

Quantitative acceptability

Patient acceptability for each of the 20 TMS sessions and three follow-up time points are reported descriptively in *Appendix 3*, *Tables 69* and *70*. At the final 20th TMS session, 75.9% of participants (*N* = 180) found the treatments acceptable, 21.9% (*N* = 52) were neutral, unsure or waiting to find out, and 2.1% (*N* = 5) found the treatments unacceptable. Similar rates were also observed at the final 26-week follow-up, with 71.5% of participants (*N* = 145) rating the treatments as acceptable, 22.7% (*N* = 46) neutral, unsure or waiting to find out, and 5.9% (*N* = 12) finding treatments unacceptable. For illustrative purposes, *Figure 7* shows that the percentage of participants who found TMS treatments to be acceptable increased over the course of TMS sessions, which appeared to be maintained until the final 26-week follow-up. There were a slightly higher percentage of participants in the rTMS group who found treatments unacceptable at the three follow-up time points (8.1%, 4.5% and 7%) compared to the cgiTBS group (3.6%, 1.8% and 4.8%). Equally, there was a slightly higher percentage of participants in the cgiTBS group who found treatments acceptable at the 8- and 16-week follow-up (68.4% and 71.5%) compared to the rTMS group (64.8% and 68.4%). The findings overall demonstrate that TMS is an acceptable treatment for this population in both the short term and longer term.

Qualitative facilitators, barriers and acceptability

Nineteen participants completed qualitative interviews. This included 15 participants who completed all treatments and follow-ups, and four participants who declined to participate in the trial prior to being randomised into treatments. No participants who withdrew from the trial during or after treatments expressed an interest in the interviews. Demographic characteristics were consistent with the demographics of the main BRIGhTMIND trial. The participants were aged 29–67 years (*M* = 49.7, *SD* = 12.6 years), 53% male, 90% White British or other and 10% participants of Asian or Asian British ethnicity. A total of 42% of participants were in full-time or other employment, 37% were unemployed, and 21% were retired. Of those that completed treatments, seven participants received rTMS treatment and eight received cgiTBS treatment. A total of 582 verbatim comments were also recorded across TMS treatments end of session feedback sheet and the three follow-up time points.

Four main facilitators to treatment were identified: (1) hope; (2) influence of staff; (3) interest in new treatments; and (4) altruism. Two main barriers were identified: (1) commitment concerns; and (2) treatment-related concerns. Additionally, three main themes arose for the acceptability research question: (1) the TMS experience; (2) variation in symptom changes; and (3) lay theories of effectiveness (see *Table 21*). These themes are illustrated with example quotes below and further detailed quotes can be found in *Appendix 3*, *Table 71*.

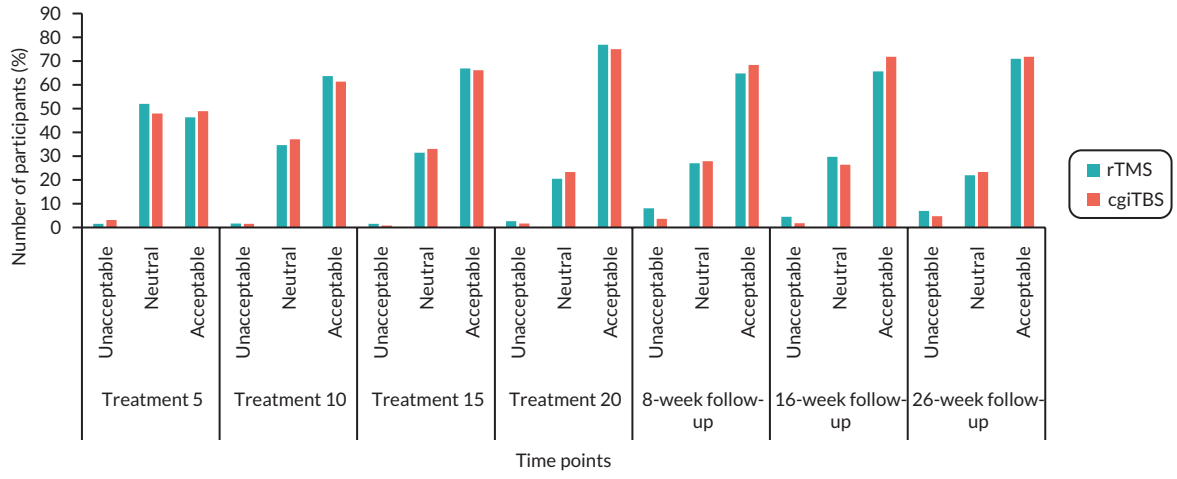


FIGURE 7 Acceptability of TMS treatments over the course of TMS sessions and three follow-up time points.

TABLE 21 Qualitative facilitator, barriers and acceptability themes and subthemes

Research question	Themes	Subthemes
Facilitators	Hope	• Keen to try alternatives • Grateful for opportunity
	Influence of staff	• Positive interactions – positive experience • Reassurance about treatment
	Interest in new treatments	• Need for new treatments for depression • Treatment with lesser side effects
	Altruism	
Barriers	Commitment concerns	• Having to attend daily sessions • Concerns about not being able to attend sessions due to ill-health
	Treatment concerns	• Fear of side effects and links to ECT • Not knowing what to expect, sensations and invasiveness
Acceptability	The TMS experience	• Overall experience of TMS • Staff support • Tolerability of TMS • Side effects
	Variation in symptom changes	• No, subtle, and significant responses • Short-lived and sustained responses • Specific symptom responses
	Lay theories of effectiveness	• Perceived reasons for mood improvement • Explanation for lack of change in depression symptoms • A desire for access to extended TMS treatments

Facilitators

Hope

Participants had long durations of depression and resistance to various treatments. As previous medication and psychotherapies had not been beneficial, they were keen to try an alternative hoping to improve depressive symptoms. When participants considered TMS treatments prior to their study involvement, receiving TMS privately was deemed unaffordable and the waiting times too long within NHS TMS clinics. As a result, they were grateful for the opportunity to access the treatments for free through the trial, particularly given that all participants received active treatments.

> *To give me a sense of hope, the way my psychiatrist described the treatment study, it can be quite effective in some cases and in some cases, it could even offer a cure for resistant depression, obviously if there was a chance that that could help me then I was very keen to give it a go.*
>
> *Participant 9 qualitative interview*

Influence of staff

Participants felt that staff involved in the BRIGhTMIND study were fully informed, professional, compassionate, and sensitive, with all these characteristics contributing to participants feeling comfortable and knowing what to expect from the treatment. Additionally, participants felt they were able to freely discuss their concerns and fears with staff members, who listened and provided appropriate reassurance which helped alleviate their concerns.

> *They were very careful to check in how I was when I arrived and when we'd finished the treatment, so there was an opportunity if I needed it to talk about any concerns.*
>
> *Participant 3 qualitative interview*

Interest in new treatments

The treatment-resistant nature of participants' depression caused frustration but also a sense of desperation. This meant they were willing to try any new treatment that might help relieve their symptoms. Some participants reported

that following the trial of several medications with notable side effects and no response, they were particularly open to try alternative non-pharmaceutical treatments. Despite expecting some side effects related to TMS, they felt these would be minimal in comparison to medication-related side effects. Therefore, participants were particularly keen to try TMS, due to its reported safeness and non-invasiveness. Furthermore, the location of the treatment site within the NHS sites and the clinical members of staff delivering the TMS treatment, further reassured participants of the closeness of medical contact in the event of an AE.

> *I was just looking at options for treatment of depression. non-antidepressants, this is one of the things that came up. it seemed pretty safe. and different to taking pills and I was very keen to try it.*
>
> *Participant 10 qualitative interview*

Altruism

There was a good understanding of the need for research in order to introduce new treatments and advance knowledge about depression. As participants were keen for new treatments to be introduced, they felt motivated to take part in the trial beyond consideration of their own benefits and they expressed an interest in wanting to help others in a similar situation.

> *My participation in the research could well help other people in the future. […] I might possibly benefit and something that I would not normally be able to benefit from, so the direct potential benefits for me was also a sense putting something back into society about being part of the pool of research subjects.*
>
> *Participant 6 qualitative interview*

Barriers

Barriers to participating in the BRIGhTMIND trial were experienced by those who were randomised and completed treatments, as well as those who declined to participate in the trial. For those that declined, the barriers and concerns outweighed the positives and potential benefits of taking part in the trial.

Commitment concerns

Transcranial magnetic stimulation was provided during office hours. It was reported that having to attend 20 TMS sessions over a 4- to 6-week period was a challenging commitment. Some participants had to build their daily routines around the treatments. It may be suggested that treatments were more accessible for those who are self-employed or not working, with several employed participants using annual or sick leave to attend appointments. Additionally, as there could only be a maximum of four consecutive missed treatment days, participants were worried about becoming too unwell due to their health to attend the daily sessions. Once out of the house, anxiety related to the prospect of commuting and finding parking was also highlighted as a barrier, particularly in participants who were not comfortable with crowds or relying on public transport.

> *The scheduling was quite intense, and it was every day, well five days a week.*
>
> *Participant 4 qualitative interview*

> *Sometimes my depression does make me kind of anxious about travelling anyway, and I just thought it was unfair to take part in the study and then maybe not to fully attend.*
>
> *Participant 14 qualitative interview*

Treatment-related concerns

Other concerns that acted as a barrier to participating in the trial were directly linked to the nature of the treatment. Participants initially drew comparisons between TMS and ECT, with fears of memory loss and seizures. However, information provided to participants, including the rate of TMS-associated seizures and that they would be able to drive home immediately after treatments. This reassured them of the differences between these types of treatments and the safety of TMS. Additionally, the location of the treatment room at one of the TMS research sites was next to an ECT suite evoking negative feelings, due to the negative preconceptions surrounding ECT treatments and negative memories for those who received or know of people who received ECT.

> *I've always been very wary of ECT, so you know, learning more about [TMS], that it wasn't like ECT, was an important part of helping me to feel comfortable.*
>
> *Participant 3 qualitative interview*

There were also concerns about not knowing what to expect from the treatment in terms of sensation and potential pain. These fears seemed to be linked to the neuromodulation treatment making direct changes to the brain, and some participants were concerned that the treatment could make their depression worse.

> *The idea of something directly going to your brain is quite a weird one.*
>
> *Participant 3 qualitative interview*

Acceptability

The TMS experience

Participants who reported perceived improvements found TMS treatments acceptable, positive, would recommend to others, with TMS outweighing other treatments tried regarding improvements and side effects. Some participants who did not see improvement also found TMS acceptable and were glad to have taken part, whereas others found the TMS less acceptable due to the side effects and lack of response to treatments. Several individuals also suggested long sessions and significant treatment commitment would be acceptable if there were sustained improvements.

> *TMS has been the best treatment for anxiety and depression I have received from the NHS in the last 20 years. It has none of the side effects and negative response of talk therapy e.g. CBT.*
>
> *Participant 87 verbatim comment*

The supportive, caring, and considerate nature of the TMS staff and the continuity of dealing with the same staff members also helped participants feel comfortable and at ease during the TMS sessions. They enjoyed the conversations and options of listening to music, reading books or doing quizzes.

> *Staff always been cheerful, shown compassion and understanding. Felt at ease and easy to go through the sessions.*
>
> *Participant 45 verbatim comment*

Tolerability of TMS varied between individuals, with some describing the sensation the coil triggered as: (1) painful; (2) an unusual sensation; or (3) comfortable and relaxing with none or minimal discomfort. This experience appeared to improve over the course of the treatment sessions, with adjustments to the positioning of the coil and motor threshold also contributing to better tolerability. Some participants also expressed that the feeling of the TMS treatments were not as expected, whilst also articulating the sensations they felt during the treatment sessions, such as 'tingling' or 'tapping'.

> *I mean the discomfort it is a weird, very strange sensation like a static electric shock going into your head. So, it gives you sort of pain, where it is not too bad once you process that it is going to be coming every 30 seconds. It was … not really nice, but not really painful.*
>
> *Participant 4 qualitative interview*

Furthermore, the MRI scan was mostly well received as participants were keen to get the treatment and understood its necessity for the study. Some participants reported that while it was not a pleasant experience due to the feelings of claustrophobia; having the MRI scan was worth it to take part in the trial.

> *Thought that perhaps it might not be very nice being in a claustrophobic sort of situation during the period, but there was no great concern to me because I thought that you know the benefits of this would far outweigh just having to lie in a scanner. It did not really bother me.*
>
> *Participant 5 qualitative interview*

Regarding side effects: a number of individuals reported none or minimal side effects during TMS treatments. Others reported common side effects including headaches, dizziness, nausea, and scalp tingling, which were largely transient and less frequent over the course of the TMS sessions. Feelings of tiredness and fatigue were also mentioned during the course of treatments, and several participants also mentioned that their anxiety was still prominent or worse, together with vivid nightmares, more agitation and poorer sleep.

> *Have had some dizziness but it hasn't lasted too long.*
>
> *Participant 90 verbatim comment*

Variation in symptom changes

Those who reported perceived treatment benefits experienced them in varied ways, with some noticing improvements during the course of treatments, others only after the course of treatment were complete. The perceived benefits ranging from subtle to significant. Regarding response duration, some participants reported sustained improvement at the final follow-up assessment, and others witnessed treatment effects wearing off. This wearing off ranged from immediately after treatments, to across the 8-, 16- and 26-week follow-up time points. Improvement in different depression symptoms was also reported, which included improvements in mood, sleep, concentration, cognition, anxiety, motivation, relaxation, suicidal thoughts, and physical symptoms such as migraines and headaches. Some participants who reported no therapeutic benefit commented that it was disappointing but understood that not all individuals would have a response to TMS.

> *I think during the treatment […]I wasn't sure whether it was just like a placebo effect that I was having or whether it was really happening, and the week after I had finished, I noticed that the symptoms that I had had were subsiding.*
>
> *Participant 7 qualitative interview*

Lay theories of effectiveness

This theme reflects the participants' own explanations and interpretations of the perceived effectiveness of the treatment received. Some participants related the improvements in depressive symptoms especially to the TMS treatments, while others felt improvements could be attributed to a combination of TMS treatments and other factors including psychological therapy, medications, and environmental changes. Additionally, some individuals felt that the routine of having to leave the house, attend the appointments, or the interactions with the TMS staff may also have had therapeutic benefit.

> *It is hard to say what contributed to my recovery and what was like, the percentage of that, meaning, how much the medication helped, how much therapy helped, how much RTMS helped but even the fact of having a treatment and doing it made me feel better because I felt like I am actually doing something about my health issues.*
>
> *Participant 8 qualitative interview*

Furthermore, those who reported experiencing environmental stressors during or after the TMS treatment suggested that without these, the TMS treatments may have been more beneficial. Some participants also reported a lack of confidence in the effectiveness of TMS due to variability across treatment sessions (despite a lack of objective evidence for this observation by the neuronavigation machine or staff account). This included the perception of inconsistent coil placement dependent on the TMS staff member delivering treatment, and concerns that the coil movement away from the scalp and target location during treatments may have impacted the level of treatment received.

> *As soon as my head touched [the coil], or there was a bit of pressure, it would kind of ping off it wasn't very a lot, but you need obviously contact, and there was not contact, so I did wonder whether I was actually getting any treatment at all.*
>
> *Participant 1 qualitative interview*

There was also the perception that receiving a longer course of treatment sessions may have led to more substantial improvements for a number of individuals. Participants with perceived short-lived benefits expressed the need for further top-up treatments.

> *I felt like something was happening with it on the last week so I felt like personally for me it like I could probably done another week or two […] so whether there was a way doing may be four weeks then a week's rest and then another two weeks or something like that for people where it wasn't really working until towards the end.*
>
> *Participant 12 qualitative interview*

Summary of findings

1. Both cgiTBS and rTMS were safe with only 1 probable (mania) and 1 possible (psychosis with depression and anxiety) SAE that might be attributed to TMS.
2. Connectivity-guided ITBS may have been associated with more frequent AEs than rTMS but the vast majority of these were mild and lasted less than a day. Tinnitus was experienced twice as often with cgiTBS than rTMS.
3. Repetitive transcranial magnetic stimulation was associated with more reduction in motor threshold and changes in the site of stimulation than cgiTBS because of lack of tolerability within the TMS session.
4. Both cgiTBS and rTMS were regarded as equally highly acceptable in this population with similarly high rates of completion of all 20 TMS sessions.

Economic evaluation

Economic data

The characteristics of the BRIGhTMIND participants who informed the economic analysis can be found in *Table 8*. Missingness was generally modest and broadly consistent across variables of interest. Resource use data was available for approximately 84–88% of participants at week 16 and 79–81% at week 26. EQ-5D and informal care data was available for 85% and 87% of participants at week 16, and 79% and 80% of cases at week 26, respectively. All variables considered had complete information at baseline with only one exception (productivity). The degree of missing data for each variable incorporated into the economic analysis is presented in *Appendix 4*, *Table 72*.

Costs

Intervention costs

The average intervention costs observed for cgiTBS and rTMS are presented in *Table 22*. Participants underwent 1.08 structural MRI and rsfMRI scans on average, at a mean cost of £479.10. Those randomised to cgiTBS attended an average of 19.35 treatment sessions lasting 52 minutes each, totalling £770.97 in staff-related costs. Those randomised to rTMS attended 19.13 separate 56-minute sessions on average, equating to £816.11 in staff-related costs. Mean equipment costs were £1058.82 per trial participant. Total intervention costs in the trial amounted to £2308.90 and £2354.04 for cgiTBS and rTMS, respectively.

Resource use and costs

Table 23 reports average imputed health service and broader societal costs for rTMS and cgiTBS in total, and for each individual resource category assessed in the trial. The primary cost drivers in the trial were from the intervention costs, outpatient hospital attendances, primary care, and productivity costs. Inpatient hospitalisations were relatively rare (approximately only 2% experiencing any inpatient admission), while community service costs, travel costs, and over-the-counter medication costs were generally modest. From both a health service and a broader societal perspective (excluding health service costs), average total costs were found to be lower for cgiTBS relative to rTMS with cost savings of approximately £165 and £100, respectively. Individuals randomised to cgiTBS incurred higher medication and private service costs but incurred markedly lower outpatient and productivity costs relative to rTMS. Overall, cost differentials were in favour of cgiTBS and predominately driven by outpatient hospitalisation attendances, productivity losses, and private service utilisation. The analysis of complete cases found similar results, albeit with larger cost differences. *Appendix 4*, *Tables 73* and *74* show service use for rTMS and cgiTBS groups. *Appendix 4*, *Tables 75* and *76* provide a complete case analysis breakdown of all costs recorded in the trial for each arm by follow-up period. Imputed costs by follow-up period are also displayed in *Appendix 4*, *Tables 77* and *78*.

TABLE 22 Intervention costs per participant

	cgiTBS *n* = 128	rTMS *n* = 127
Staffing costs		
Mean attendances	19.35	19.13
Staff costs per attendance	£39.84	£42.67
Staff costs	£770.97	£816.11
Equipment costs		
Machine costs	£1058.82	
Imaging costs		
Mean MRI and rsfMRI scans[a]	1.08	
Average structural MRI cost	£263.83	
Average rsfMRI	£215.28	
Total imaging costs	£479.10	
Total costs	£2308.90	£2354.04

a All participants received a structural MRI and a resting-state functional MRI scan prior to randomisation (a requirement for all trial participants), 16 participants required to repeat the initial MRI tests due to failed quality assurance and two participants were required to repeat the MRI scan again due to failed quality assurance checks.

TABLE 23 Imputed total costs by resource category (£, 2020/21)

	rTMS (*n* = 127)		cgiTBS (*n* = 128)		Difference
	Mean	SD	Mean	SD	Mean
Health service perspective					
Intervention cost	2354.04	159	2308.90	109	45.14
Inpatient hospital services	34.69	264	38.21	384	−3.52
Outpatient hospital services	752.40	1368	605.67	1604	146.73
Primary care	210.15	360	192.82	319	17.32
Community services	24.09	165	38.08	263	−13.99
Medication	55.28	127	81.96	184	−26.68
Societal perspective					
Travel	19.88	53	16.79	69	3.08
Productivity	1085.05	3746	903.38	3444	181.67
Over-the-counter medications	4.65	26	6.74	26	−2.09
Private services	50.34	278	133.93	584	−83.59
Total costs					
Health service perspective costs	3430.63	1620	3265.64	1766	165.00
Societal perspectives costs	1159.91	3749	1060.85	3534	99.07
Total costs	4590.55	4576	4326.48	4602	264.06

Outcomes

Figure 8 presents the proportion of participants observed as having a problem in each domain of the EQ-5D by treatment arm and assessment period. Over the course of the trial the proportion of participants experiencing problems, and the severity of those problems, were generally reduced. Improvements appeared largest in the self-care and usual activities domains; however, severe problems with anxiety and depression did develop in both arms compared to baseline. A further descriptive assessment found moderate improvements in the usual activities, pain/discomfort, and anxiety/depression severity scales with cgiTBS relative to rTMS (see *Appendix 4*, *Figure 23*).

Figure 9 presents average imputed EQ-5D-3L preference scores for cgiTBS and rTMS. Baseline scores were higher for cgiTBS relative to rTMS (+ 0.027). Scores markedly increased in both arms following treatment. cgiTBS extended and maintained higher scores relative to rTMS over the course of the trial. Differences in imputed EQ-5D-3L (mapped) and EQ-5D-5L scores translated into average QALY gains of approximately 0.013 and 0.017 for cgiTBS relative to rTMS, respectively. *Appendix 4*, *Figure 24* presents the same analysis using imputed EQ-5D-5L preference scores. Full details of average imputed health-related quality of life and QALY outcomes are reported *in Appendix 4*, *Table 79*.

Baseline informal care requirements were highest for the cgiTBS group (those up to 3 months prior to baseline assessment), with an average of 107.5 hours of care versus 68.6 hours for rTMS, suggesting an imbalance in baseline care needs. The additional informal care hours associated with cgiTBS relative to rTMS were reduced to 6.3 hours (cgiTBS: 80.0; rTMS: 73.7) at week-16 follow-up and −2.4 hours (cgiTBS: 51.83; rTMS: 54.23) at week-26 follow-up. Informal carers taking time off work was relatively rare, predominantly due to participant depression and followed a comparable trajectory to total hours. Full details of the informal care requirements observed in the trial are displayed in *Appendix 4*, *Table 80*.

Cost-effectiveness analysis

Table 24 reports the unadjusted and adjusted base-case mean cost, QALY and cost-effectiveness results from health service and broader societal costing perspectives. *Appendix 4*, *Tables 81* and *82* present the regression analyses used to estimate the QALYs and costs evaluated in the adjusted cost-effectiveness analyses.

Connectivity-guided iTBS was found to have marginally lower costs and to be modestly more effective compared to rTMS across all perspectives and approaches considered (i.e. cgiTBS dominated rTMS). The unadjusted analysis found cgiTBS was associated with an additional 0.0157 QALYs and £341.74 in health service cost savings. These cost savings were extended to £788.63 when including broader societal costs. The adjusted analysis found cgiTBS was associated with an additional 0.0091 QALYs, £180.19 in health service cost savings [QALYS gained cgiTBS 0.275 (95% CI 0.26 to 0.29); iTBS 0.265 (95% CI 0.25 to 0.28); total costs cgiTBS £3256.79 (95% CI £2994.69 to £3522.75); iTBS £3436.98 (95% CI £3148.63 to 3719.60)], and £336.00 when including broader societal savings. For the adjusted (unadjusted) analysis, the INMB associated with cgiTBS at a £20,000/QALY threshold equalled £362 (£656) from a health service perspective, and £451 (£1103) from a broader societal perspective. INMB values increased with the cost-effectiveness threshold. A graphical display of INMB for each approach is provided in *Appendix 4*, *Figure 25*.

Figure 10 displays the cost-effectiveness planes for the unadjusted and adjusted health service perspective cost-effectiveness analyses. Predicted incremental costs and QALYs in all analyses had considerable overlap between positive and negative values, suggesting a significant level of decision uncertainty. The probability of being cost-effective remained > 80% across a wide range of thresholds (see *Figure 11*). Expected value of perfect information (EVPI) was highest in the adjusted analysis, generally increased with the cost-effectiveness threshold and reached £17.11 per participant from a health service costing perspective at a £30,000/QALY threshold. EVPI is presented graphically in *Appendix 4*, *Figure 26*.

Sensitivity analysis

Table 25 presents cost-effectiveness findings from each scenario analysis using a health service costing perspective. Compared to base-case findings, EQ-5D-5L preference weights had minimal impact on incremental QALYs or cost-effectiveness findings but did increase average QALYs in each arm. Removing imaging costs for rTMS (£479) made cgiTBS the most expensive alternative in both unadjusted and adjusted analyses. In this scenario, cost-effectiveness was highly sensitive to the analytic method, with ICERs of £8750 and £32,920 for cgiTBS relative to rTMS in unadjusted and adjusted analyses, respectively. Applying a 30-minute time saving for cgiTBS appointments relative

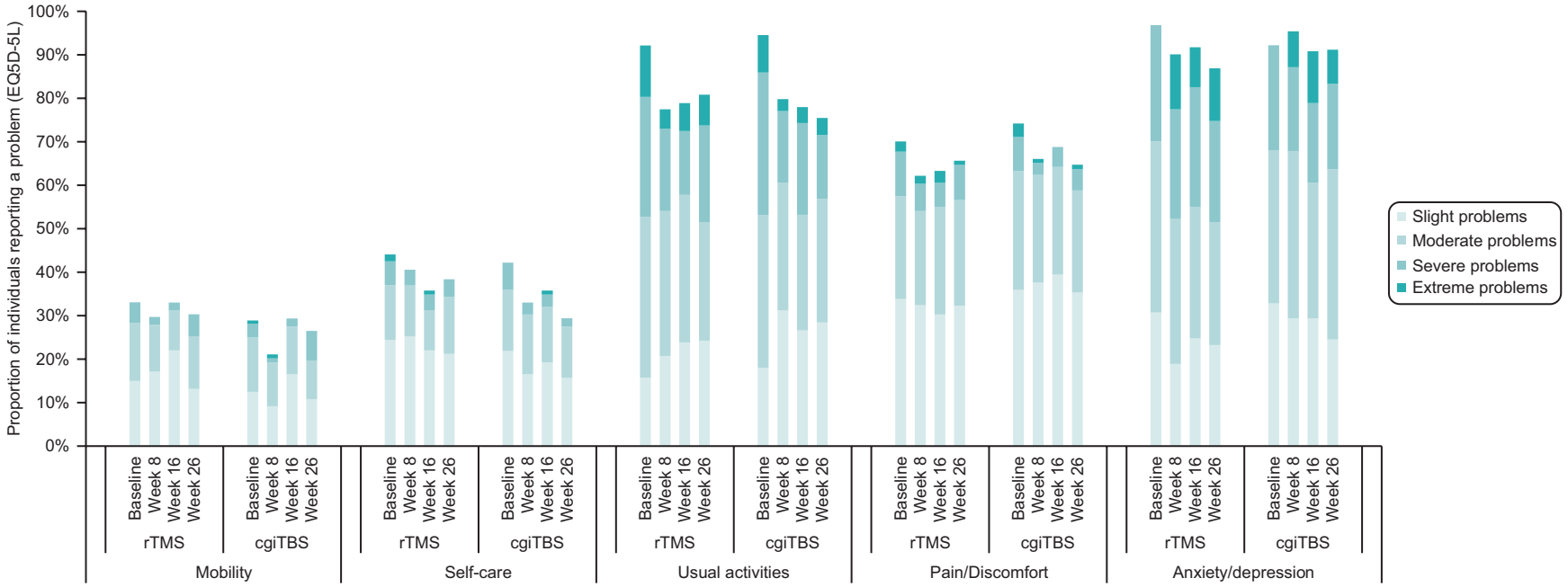
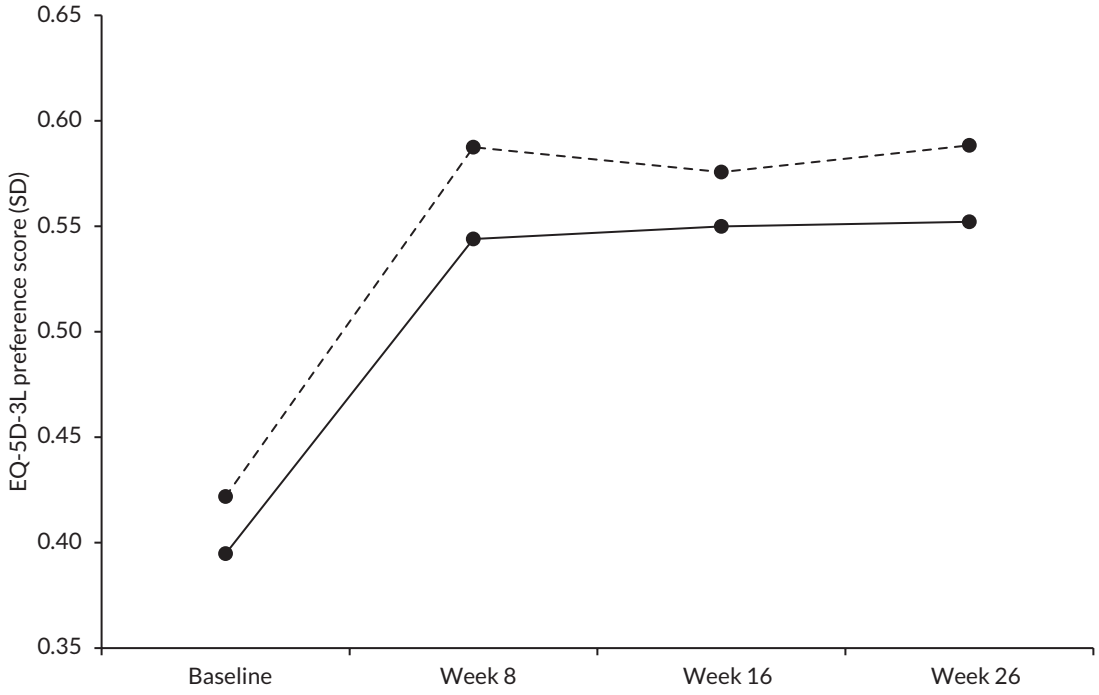


FIGURE 8 The proportion of observed problems reported by treatment arm and follow-up assessment.



cgiTBS, mean (SD)	0.42 (0.25)	0.59 (0.25)	0.58 (0.28)	0.59 (0.27)
rTMS, mean (SD)	0.39 (0.24)	0.54 (0.27)	0.55 (0.27)	0.55(0.28)

FIGURE 9 Average imputed EQ-5D-3L score by treatment arm.

TABLE 24 Base-case cost-effectiveness results

	Costs (95% CI)	QALYs (95% CI)	Inc. costs (95% CI)	Inc. QALYs (95% CI)	ICER
Unadjusted analyses					
Health service perspective					
cgiTBS	£3079.67 (£2887 to £3299)	0.27982 (0.25 to 0.31)			
rTMS	£3421.41 (£3202 to £3657)	0.26412 (0.23 to 0.29)	£341.74 (£30.10 to £653.70)	−0.01570 (−0.05 to 0.02)	Dominated
Inclusion of broader societal costs					
cgiTBS	£3861.59 (£3351 to £4436)	0.27982 (0.25 to 0.31)			
rTMS	£4650.22 (£3877 to £5583)	0.26412 (0.23 to 0.29)	£788.63 (−£191.00 to £1829.33)	−0.01570 (−0.05 to 0.02)	Dominated
Adjusted analyses					
Health service perspective					
cgiTBS	£3256.79 (£2995 to £3523)	0.27454 (0.26 to 0.29)			
rTMS	£3436.98 (£3149 to £3720)	0.26534 (0.25 to 0.28)	£180.19 (−£197.92 to £555.93)	−0.00921 (−0.03 to 0.01)	Dominated
Inclusion of broader societal costs					
cgiTBS	£4243.44 (£3553 to £5007)	0.27454 (0.26 to 0.29)			
rTMS	£4579.44 (£3831 to £5393)	0.26534 (0.25 to 0.28)	£336.00 (−£689 to £1357)	−0.00921 (−0.03 to 0.01)	Dominated

CI, confidence interval; Inc, incremental; QALY, quality-adjusted life-year.

to those for rTMS, improved the cost-effectiveness of cgiTBS via extending its cost savings by approximately £385. The joint scenario considering both the removal of imaging costs for rTMS and 30-minute time savings for cgiTBS appointments resulted in a moderate reduction (£94) in cost savings associated with cgiTBS in both the unadjusted (from £342 to £248) and adjusted analyses (from £180 to £94 savings). In this joint scenario, cgiTBS remained the dominant strategy. When separately comparing cgiTBS and rTMS to artificial placebos, ICERs were above £30,000/QALY for both analytic methods. ICERs fell below £30,000/QALY in all cases when equipment costs were distributed across 98 people over the lifetime of the machine (base-case analysis: 51 people). At base-case settings, ICERs for cgiTBS relative to rTMS were within the £20,000-£30,000/QALY threshold range at incremental costs of £313–£470 (unadjusted) and £184–£276 (adjusted).

Summary of findings

1. Both cgiTBS and rTMS recorded significant improvements in HRQoL from baseline values. Connectivity-guided iTBS was associated with further improvements in HRQoL and lower health service and broader societal costs compared to rTMS.
2. Connectivity-guided iTBS was considered a cost-effective alternative to rTMS treatment in the base-case analysis of the BRIGhTMIND study (more effective, less costly), albeit with considerable uncertainty.
3. Cost-effectiveness findings were sensitive to the imaging and staffing costs associated with each treatment, examples of which include non-routine use of pre-screen imaging in rTMS.
4. Connectivity-guided iTBS was considered cost-effective relative to rTMS in all economic analyses, provided it could be delivered at a cost of £184 or less than rTMS treatment (cgiTBS was associated with cost savings in all base-case analyses).

Mechanism of action

Functional connectivity and effective connectivity

A total of 255 participants completed baseline structural and rsfMRI scans for the study. Of these participants, 18 had to repeat the baseline scans with 2 having to have a second repeat, due to scans failing the QC criteria in order to generate the TMS target co-ordinates (see *Table 26*).

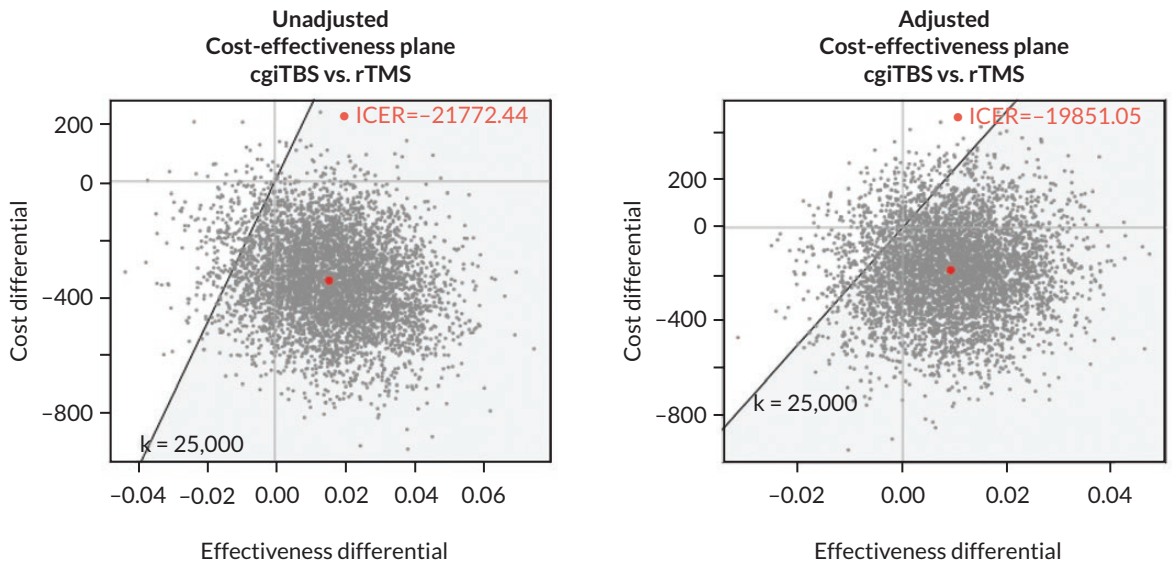


FIGURE 10 Cost-effectiveness planes for unadjusted and adjusted health service perspective cost-effectiveness analyses.

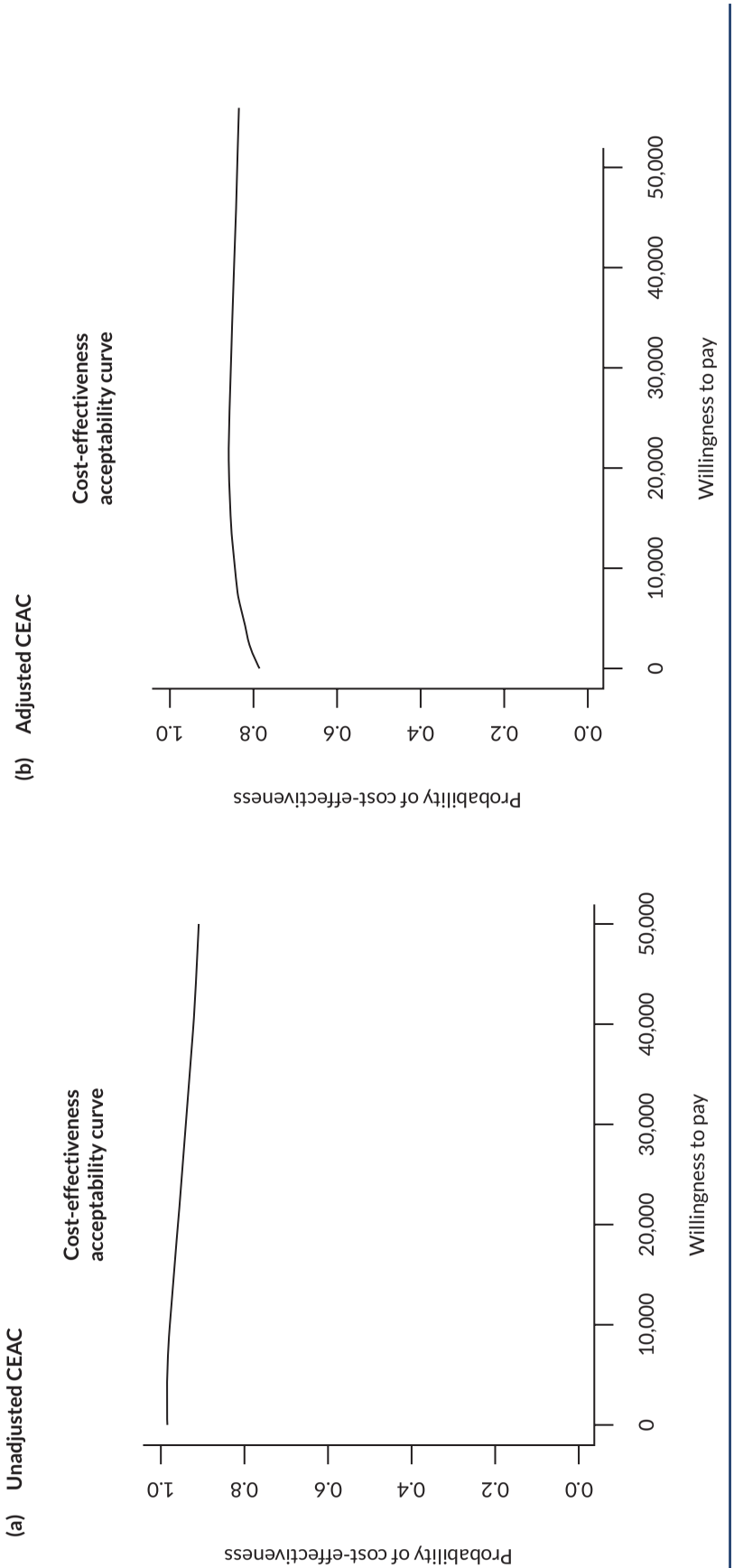


FIGURE 11 Base-case health service perspective cost-effectiveness acceptability curves (CEACs).

TABLE 25 Scenario analyses from a health service costing perspective

	Unadjusted analysis			Adjusted analysis		
	Costs	QALYs	ICER	Costs	QALYs	ICER
Base case						
cgiTBS	£3080	0.27982		£3257	0.27458	
rTMS	£3422	0.26412	Dominated	£3437	0.26550	Dominated
EQ-5D-5L preference values						
cgiTBS	£3080	0.33267		£3257	0.32963	
rTMS	£3422	0.32041	Dominated	£3437	0.32040	Dominated
Removing imaging costs for rTMS						
rTMS	£2943	0.26412		£2958	0.26550	
cgiTBS	£3080	0.27982	£8750	£3257	0.27458	£32,920
cgiTBS appointments 30-minute time saving relative to rTMS						
cgiTBS	£2695	0.27982		£2872	0.27982	
rTMS	£3422	0.26412	Dominated	£3437	0.26412	Dominated
Removing imaging costs for rTMS + cgiTBS 30-minute time saving relative to rTMS						
cgiTBS	£2695	0.27982		£2872	0.27982	
rTMS	£2943	0.26412	Dominated	£2958	0.26412	Dominated
Artificial placebo (AP) comparator (vs. cgiTBS)						
AP	£771	0.20417		£771	0.20417	
cgiTBS	£3080	0.27982	£30,520	£3257	0.27458	£35,306
Artificial placebo (AP) comparator (vs. rTMS)						
AP	£1067	0.20417		£1067	0.20417	
rTMS	£3422	0.26412	£39,281	£3437	0.26550	£38,641

TABLE 26 Structural and rsfMRI scans completed at baseline and 16-week follow-up

MRI scan performed		rTMS	cgiTBS	Overall
Baseline T1w and rsfMRI scans-	*n* (%)	127 (100%)	128 (100%)	255 (100%)
Passed quality image control	Yes, *n* (%)	116 (91.3%)	112 (87.5%)	228 (89.4%)
	No, *n* (%)	5 (3.9%)	13 (10.2%)	18 (7.1%)
	Unobtainable,*n*(%)	6 (4.7%)	3 (2.3%)	9 (3.5%)
Repeat baseline T1w and rsfMRI scans × 1	*n* (%)	5 (100%)	13 (100%)	18 (100%)
Passed quality image control	Yes, *n* (%)	3 (60.0%)	13 (100%)	16 (88.9%)
	No, *n* (%)	2 (40.0%)	0 (0.0%)	2 (11.1%)
Repeat baseline T1w and rsfMRI scans × 2	*n* (%)	2 (100%)	0 (0.0%)	2 (100%)
Passed quality image control	Yes, *n* (%)	2 (100%)	0 (0.0%)	2 (100%)
16-week T1w and rsfMRI scans (not completed in London)	Yes, *n* (%)	65 (97.0%)	62 (95.4%)	127 (96.2%)

Note
Passed quality image control in the table refers to whether baseline scans met the inclusion requirements for TMS co-ordinates to be generated.

In terms of the mechanism-of-action functional and effective connectivity analyses, 46 were excluded due to having no clinical follow-up time points (*N* = 24), receiving treatment to an unintended target (*N* = 9), incorrect scanning parameters (*N* = 5), completing fewer than 15 treatment sessions (*N* = 4), failing QC (*N* = 3) or there being more than 6 weeks between the first and final treatment (*N* = 1). A total of 127 participants completed follow-up scans. A total of 26 were excluded due to baseline scans not being usable (*N* = 13), incorrect scanning parameters (*N* = 10) or failing QC (*N* = 3). Statistical analyses were with LMMs, unless otherwise specified. The dependent variable of the LMM was change in depression scores (baseline depression minus depression scores at follow-up at 8, 16 or 26 weeks), with higher positive scores indicating better clinical improvement. The HDRS-17 was the primary depression outcome measure, and the HDRS-6, BDI-II and PHQ-9 were exploratory depression outcome measures.

Baseline brain connectivity as a predictor of clinical response

The primary hypothesis was that greater clinical improvement would be associated with more positive baseline EC from the rAI (a region of the brain's 'salience' network[37]) to left dorsolateral prefrontal cortex (lDLPFC, a region of the 'central executive network'[38]), and that this relationship would be stronger in the cgiTBS group.

As reported in the introduction, EC refers to the directed influence of one region on another, calculated using Granger causality (greater EC is thought to reflect greater influence of one region's activity on another's). *Figure 12* illustrates the location of the right rAI region of interest (purple), as well as the lDLPFC regions of interest for individual participants (blue). In this analysis, the cgiTBS target was used as the location of lDLPFC for each participant, regardless of their treatment group. This was because the cgiTBS site was itself chosen as the site that maximised baseline EC from rAI.

The primary hypothesis was not supported (LMM: dependent variable of reduction in depression measure from baseline to follow-up; random effect of participant; fixed factors of treatment group, follow-up time point, baseline EC from right AI to cgiTBS site as covariate, confounders – site, age, gender, MGH treatment resistance category; and 200/201/185 participants included at follow-up time points 8, 16, and 26 weeks). Baseline EC from the rAI site to the cgiTBS target did not predict clinical improvement on any of the measures of depression ($p > 0.1$; HDRS-17; HDRS-6, BDI-II, and PHQ-9).

The rAI site (purple), individual cgiTBS sites (blue), mean cgiTBS site across participants (green), rTMS site (red), and sgACC site (yellow) are shown on a standard brain template.[146]

We pre-specified two secondary hypotheses concerning baseline connectivity as a predictor of response. One hypothesised that greater clinical improvement would be associated with more positive baseline net outflow from rAI to lDLPFC, and this relationship will be stronger in the cgiTBS group.

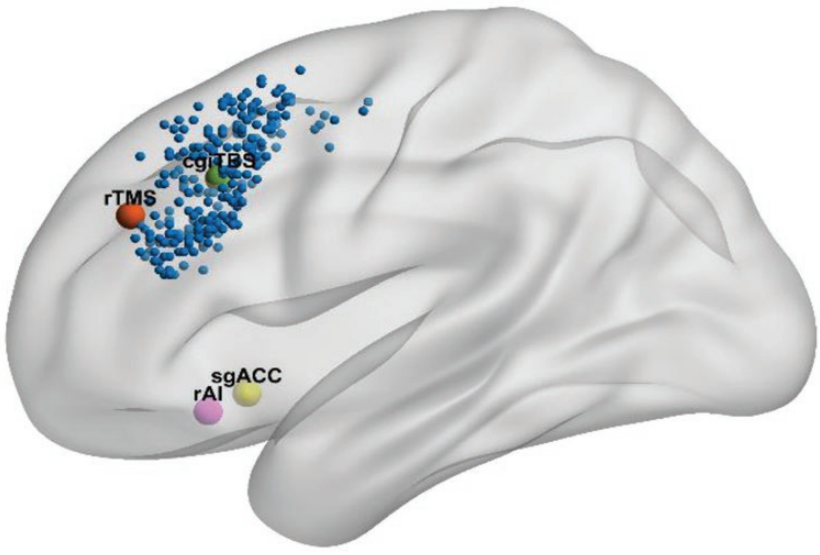


FIGURE 12 Sites of TMS stimulation on the brain.

Net outflow from rAI to lDLPFC was calculated as: EC from rAI to lDLPFC minus EC from lDLPFC to rAI. This analysis did find that net outflow was a significant predictor of clinical improvement on the HDRS-17 [*Figure 13*; $F(1195.992) = 4.035$, $p = 0.046$; significant confounders retained in model: site, MGH treatment resistance group]. However, inconsistent with the pre-specified hypothesis, it was lower net outflow from rAI to lDLPFC which predicted greater improvement (i.e. improvement was greater if there was greater influence of lDLPFC on rAI, than of rAI influence on lDLPFC). This effect did not differ by treatment group or by post-treatment time point ($p > 0.1$). In terms of the exploratory depression outcome measures, the relationship approached significance for the HDRS-6 ($p = 0.102$) but was not significant for the BDI-II or PHQ-9 self-report depression measures.

Given the above findings, we also conducted an exploratory analysis with baseline EC from lDLPFC to rAI as a predictor (as opposed to EC from rAI to lDLPFC as in the primary analysis). There was no significant relationship with improvement on HDRS-17 ($p > 0.1$), however there was a significant relationship with clinical improvement on the HDRS-6 [$F(1196.855) = 4.209$, $p = 0.042$; confounders retained: site, MGH]. Greater baseline EC from lDLPFC to rAI was associated with greater clinical improvement (this effect did not differ by treatment group or by post-treatment time point, $p > 0.1$). The relationship also showed marginal significance for the BDI-II ($p = 0.098$) but was not significant for the PHQ-9.

The final secondary analysis in this section used FC (correlation between the fMRI time courses from two regions, with greater FC thought to reflect greater co-operation between regions), between the sgACC (yellow sphere in *Figure 12*) and the lDLPFC. It was hypothesised that greater clinical improvement would be associated with more negative baseline FC between the sgACC and lDLPFC across both treatment groups. This analysis used the intended stimulation target for each individual as the locus of lDLPFC (i.e. the personalised cgiTBS target for the cgiTBS group, and the rTMS target for the rTMS group; significant confounders retained: site, MGH).

While baseline FC between sgACC and lDLPFC did not predict improvement in observer-rated depression (17-/6-item HDRS), it did predict improvement on self-rated depression (BDI-II, with borderline significance for PHQ-9). Specifically, there was a significant interaction of the effects of baseline FC and post-treatment time point [BDI-II: $F(2362.262) = 4.130$, $p = 0.017$; PHQ-9: $F(2378.800) = 2.944$, $p = 0.054$]. Effects did not differ by treatment group ($p > 0.1$). The interaction arose because baseline FC initially showed a negative relationship with depression improvement at 8 weeks but showed a positive relationship at 16 and 26 weeks (see *Figure 14*).

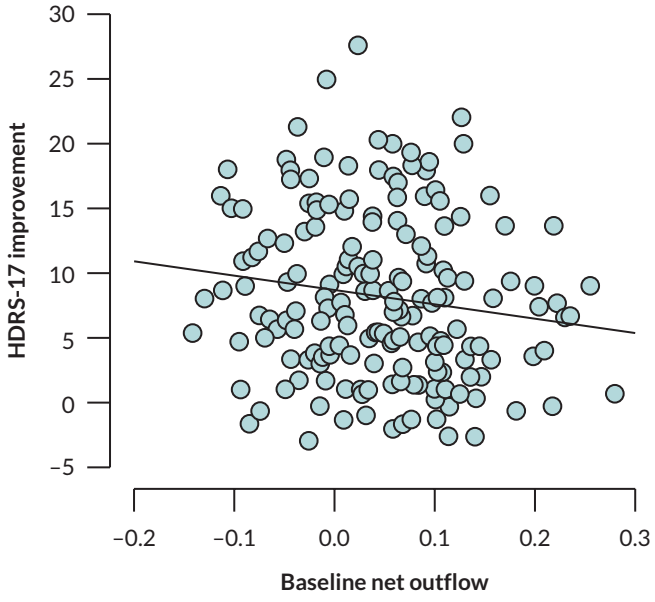


FIGURE 13 Hamilton Rating Scale for Depression-17 improvement from baseline to follow-up (collapsed across follow-up time points) vs. baseline net outflow from rAI to lDLPFC. Each circle is a participant.

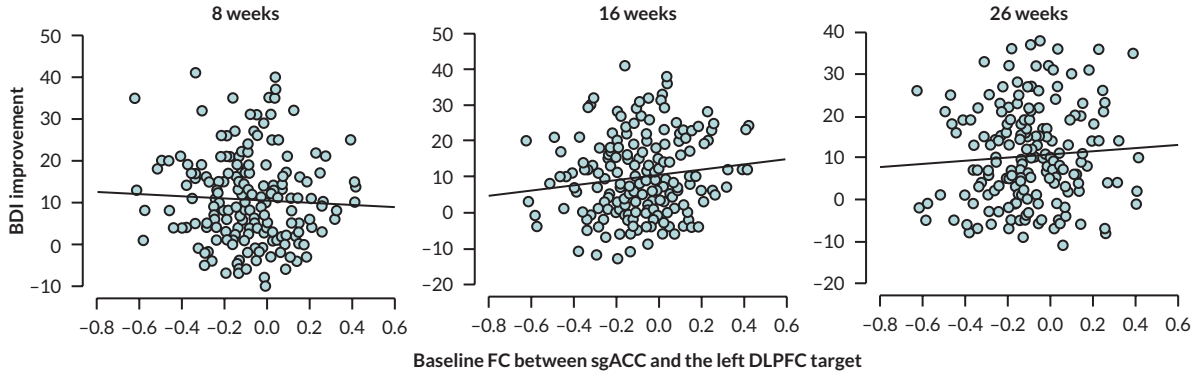


FIGURE 14 Beck Depression Inventory-II improvement from baseline to each follow-up time point vs. baseline FC between sgACC and the lDLPFC target. Each circle is a participant.

In exploratory analysis, while there were no significant group effects, it is notable that mean baseline FC with the sgACC was significantly more negative for the rTMS site than the personalised cgiTBS site [−0.124 vs. 0.033, paired-sample *t*-test, $t(229) = 5.363$, $p < 0.001$]. In addition, baseline FC between the rAI and sgACC was significantly positive [0.066, $t(229) = 5.343$, $p < 0.001$].

Clinical response and change in brain connectivity

The primary hypothesis was that reduction in FC between the lDLPFC and the lDMPFC, a region of the 'default mode network',[36]) from baseline to follow-up would be associated with greater clinical improvement. For this analysis, we pre-specified 1 lDMPFC site, and 2 lDLPFC sites (1 more posterior site, which lay closer to the rTMS target, and 1 more anterior site, which lay closer to the average cgiTBS target), from previous literature.

No significant effects were observed using the more anterior lDLPFC site ($p > 0.1$; 98/101/93 participants included at follow-up time points 8, 16, and 26 weeks; no confounders retained), on any of the depression measures.

Using the more posterior site, reduction in FC between lDLPFC and lDMPFC from baseline to follow-up was associated with significantly greater improvement on the self-reported depression measures [PHQ-9: $F(1107.685) = 6.959$, $p = 0.010$; BDI-II: $F(1106.408) = 4.555$, $p = 0.035$]. These effects were not significant for the 17- or 6-item HDRS ($p > 0.1$). The effects did not differ by treatment group or post-treatment time point ($p > 0.1$). The correlation between improvement on the PHQ-9 (collapsed across post-treatment time points) and reduction in FC between lDLPFC and lDMPFC was 0.252 (see *Figure 15*; $df = 96$, $p = 0.013$).

Pre-specified secondary analyses examined relationships between clinical improvement and change in: rAI to lDLPFC EC, rAI to lDLPFC net outflow, and FC between sgACC and lDLPFC. There were no significant effects on these analyses for any of the depression measures ($p > 0.1$).

Magnetic resonance spectroscopy analysis

A total of 190 baseline MRS scans, and 98 follow-up MRS scans were available for data analysis. All spectra GABA and Glx were reviewed by an MRI physicist with spectroscopy experience. Following this QC, 131 scans were included for the baseline GABA+/Cr analysis, and 64 paired scans (both baseline and follow-up) for the GABA+/Cr change analysis. The paired scans underwent further review by an MRI expert with > 20 years of MRS experience, whereby off spectra used for the Glx fitting were reviewed for issues with line width, SNR, water suppression, baseline, fit quality and voxel position, dimensions, and repositioning (aided by individual and MNI space voxel reconstruction and derived overlap score). Following this, 45 paired scans were available for both Glx/Cr change and GABA/Glx ratio change analysis (QC exclusion flowchart, *Appendix 5*, *Figure 27*).

Descriptive statistics for the baseline GABA+/Cr, GABA+/Cr change, Glx+/Cr change and GABA/Glx ratio change analyses, broken down by MRS scanner platform and treatment group can be found in *Appendix 5*, *Table 83*. Of note only one pair of Newcastle data was available for the GABA+/Cr and Glx/Cr change, therefore this was

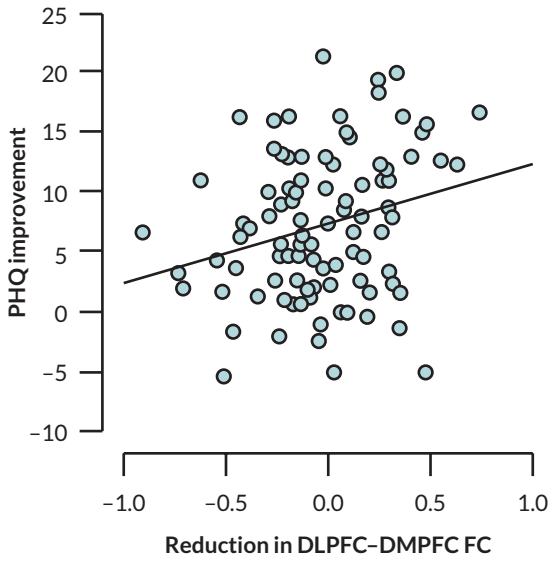


FIGURE 15 Patient Health Questionnaire-9 improvement from baseline to follow-up (collapsed across post-treatment type points) vs. reduction in FC between the lDLPFC (posterior site) and lDMPFC. Each circle is a participant.

omitted from final statistical analysis. Sensitivity analysis indicated results remained unchanged when including this Newcastle dataset.

Baseline GABA+/Cr as a predictor of clinical improvement

The primary hypothesis was that 'greater clinical improvement on 17-item HDRS (16 and 26-week vs. baseline) will be associated with lower GABA+/Cr at baseline across both treatment groups'. The LMM revealed that baseline GABA+/Cr did not predict clinical improvement over 16- and 26-week follow-up for the primary outcome measure – HDRS-17, nor the exploratory HDRS-6 measure ($p > 0.1$). However, there was a trend for greater *b*aseline GABA predicting better clinical improvement on the self-report PHQ-9 [F (1, 118.651) = 2.945, $p = 0.089$; significant confounders retained in model: MGH treatment resistance category] that is, in the opposite direction to what we hypothesised (see *Figure 16*).

Linear regression models for secondary hypotheses also showed that higher baseline GABA significantly predicted improvement when depression change was averaged over 8, 16 and 26 weeks for the HDRS-17 ($\beta = 0.247$, $t = 2.556$, $p = 0.012$, significant covariates retained in model: study centre, MRS platform, treatment resistance category and baseline HDRS-17) and HDRS-6 ($\beta = 0.219$, $t = 2.136$, $p = 0.035$, significant covariates retained in model: study centre, MRS platform, treatment resistance category and baseline HDRS-17), again opposite to the direction hypothesised. Exploratory correlation analysis comparing associations between baseline GABA+/Cr and clinical improvement by MRS scanner platform, suggest findings were driven by the GE scanners (see *Appendix 5*, *Table 84*).

GABA+/Cr change and clinical improvement

Primary hypotheses were:

> *Changes in depression symptoms on 17-item HDRS (baseline minus 16 weeks, and baseline minus 26 weeks) will be associated with change in GABA+/Cr between baseline and 16 weeks (post minus pre-treatment) in both treatment groups, with increase in GABA+/Cr expected to be associated with better clinical improvement.*

Linear regression models revealed these hypotheses were not supported at either 16- or 26-week follow-up for the primary outcome (HDRS-17) or the exploratory depression measures (HDRS-6, BDI-II, PHQ-9), all p, s > 0.1. Furthermore, change in GABA+/Cr did not predict clinical improvement (baseline minus follow-up averaged over 8, 16 and 26 weeks) for any depression measure, as per secondary hypotheses, nor were there differences in GABA+/Cr between treatment groups.

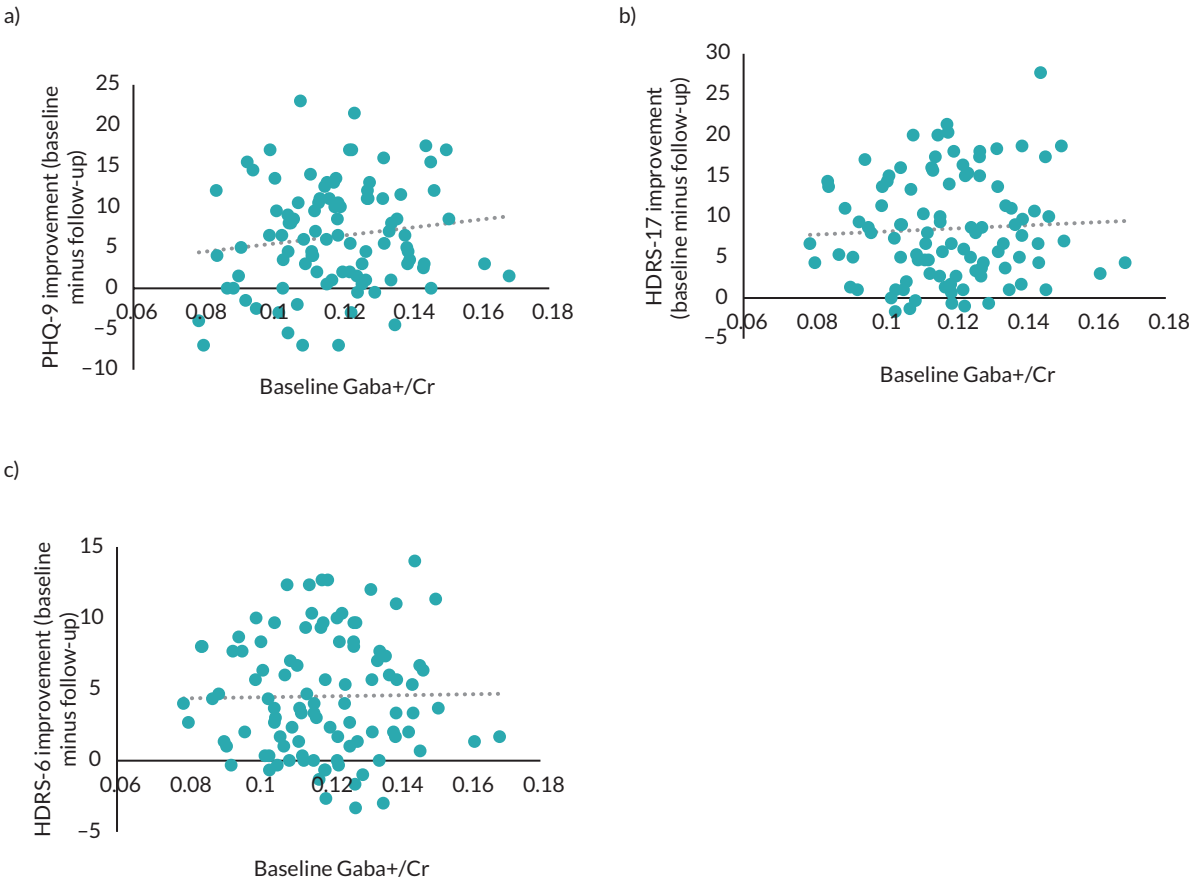


FIGURE 16 Depression improvement from baseline to follow-up vs. baseline GABA+/Cr. Each circle is a participant. Note: PHQ-9 (follow-up averaged over 16 and 26 weeks), HDRS-6 and HDRS-17 (follow-up averaged over 8, 16 and 26 weeks).

Glx/tCr change, GABA/Glx ratio change and clinical improvement

For Glx/Cr change, secondary hypotheses were 'change in depression symptoms on HDRS-17 (baseline minus 16 weeks minus baseline and baseline minus 26 weeks) will be associated with change in Glx/Cr (follow-up minus baseline)', and the 'increase in Glx/Cr will be higher in cgiTBS compared to rTMS group'.

Linear regression models revealed a trend for a decrease in Glx/Cr predicting better clinical improvement on the HDRS-6 at 16 weeks (β = −0.247, t = −1.793, p = 0.083, significant covariate retained: study centre) and at 26 weeks the HDRS-17 (β = −0.211, t = −1.697, p = 0.097 significant covariates retained: study centre), and a significant relationship with 26-week HDRS-6 change (β = −0.260, t = −2.036, p = 0.048, significant covariate study centre retained). These findings were in the opposite direction to what was hypothesised, and the scatterplot between Glx/Cr change and HDRS improvement indicated one relatively extreme value of Glx/Cr (see *Figure 17*). Analysis was re-ran excluding this outlier, which revealed the relationship between Glx/Cr change and HDRS-6 improvement at 26 weeks went from significant to trend-level significance (β = −0.223, t = −1.714, p = 0.094; study centre retained). Additionally, the p-values for the two trends, HDRS-6 at 16 weeks and HDRS-17 at 26 weeks increased to p = 0.111 and p = 0.108, respectively.

No differences between treatment groups for Glx/tCr change were observed. Finally, an exploratory hypothesis was to examine whether GABA/Glx ratio change would predict improvement on the HDRS-17 at 16 weeks and 26 weeks. No significant results were identified for any depression measure at either follow-up time point.

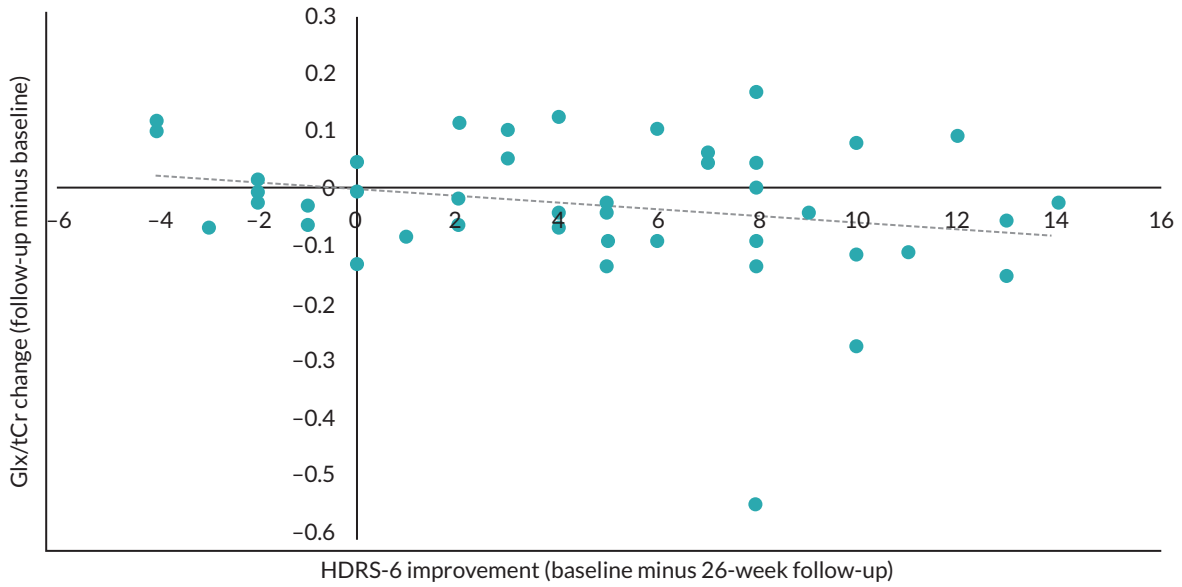


FIGURE 17 Hamilton Rating Scale for Depression-6 improvement (baseline minus 26-week follow-up) vs. change in Glx+/Cr. Each circle is a participant.

Summary of findings

1. The balance of influence between lDLPFC and rAI at baseline predicted clinical improvement on the observer-rated HDRS-17. Specially, greater influence from lDLPFC to rAI at baseline was associated with greater improvement.
2. Baseline FC between sgACC and the intended treatment target within lDLPFC predicted self-reported clinical improvement. The relationship appeared to change across follow-up time points, with more negative baseline FC being associated with greater response when measured at the first time point, but poorer response when measured at subsequent time points.
3. Greater self-reported clinical improvement was associated with greater reduction in FC between lDMPFC and a posterior lDLPFC site from baseline to follow-up.
4. Higher baseline GABA+/Cr predicted greater clinical improvement on observer-rated depression measures, when averaged over 8, 16 and 26 weeks, with a trend for self-reported depression over 16 and 26 weeks. These findings may be MRS platform specific.
5. Decrease in Glx/Cr from baseline to follow-up predicted greater clinical improvement on HDRS-6 at 26 weeks, with trends for HDRS-17 at 26 weeks and HDRS-6 at 16 weeks, when 1 extreme Glx/tCr value was retained in the analysis. Once the outlier was removed the relationship between Glx/Cr change and HDRS-6 at 26 weeks was of trend-level significance.

Chapter 4 Discussion

The BRIGhTMIND study is the UK's largest ever randomised controlled trial of TMS for TRD and the first adequately powered trial of TBS with outcomes at 26 weeks.

Clinical efficacy

Contrary to the hypotheses, there were no statistically significant differences between cgiTBS and rTMS on the primary and secondary clinical outcomes across 26 weeks, demonstrating that cgiTBS does not show superior clinical efficacy compared to MRI-neuronavigated rTMS. The primary outcome analysis of the HDRS-17 demonstrated clinically substantial improvements for both treatment arms at the final 26-week follow-up.[141] There were substantial improvements in self-rated depression measures and clinically important improvements in anxiety, cognition, function, and quality of life over 26 weeks. The results also indicated that both rTMS and cgiTBS are efficacious in terms of achieving a response (50% drop in HDRS-17 score) in 30–35% participants with TRD at 26 weeks; about 65–70% obtained much less benefit or no benefit. About a fifth to a quarter of participants with TRD might achieve a remission after treatment that is still sustained for 6 months. Severity of depression, severity of anxiety, and treatment resistance were predictors of depression score after TMS, but none of them distinguished whether participants would respond to cgiTBS or rTMS. Age, gender, comorbidity, or previous experience of childhood trauma neither predicted depression score after TMS or treatment group. From a clinical perspective, a group of otherwise unresponsive patients with TRD could obtain a sustained remission, with a proportion of patients potentially remaining well with 1–2 courses of rTMS or iTBS per year.

Two trials that are in closest comparison to ours are the THREE-D[23] and THETA-DEP,[28] both of which compared iTBS versus rTMS, with both their treatment arms using structural MRI neuronavigation. This study's response and remission rates were largely consistent with those observed in the THETA-DEP study, which at the end of treatments showed response rates of about 33–37% and remission rates a little lower than the present study's of 15–19%, with depression symptom improvement maintained over 6 months.[28] Thus, while prior evidence suggests that the beneficial effects of rTMS on mood in TRD may be relatively short, lasting only 1–3 months, both TMS protocols actually appear to maintain improvement for over 6 months post treatment.[9,17] Additionally, the THREE-D study reported rates of 40–50% for response and 20–30% for remission, which are slightly higher rates than what we found.[23] However that trial provided up to 30 TMS sessions for a number of their participants, rather than the set 20 sessions in the present study.

The patient global impression of change showed that the proportion of participants experiencing a benefit continued to increase even at the 19th and 20th sessions, and the qualitative work also indicated variability in symptom improvement. These findings taken together with the THREE-D study suggest that for a number of participants, additional sessions in those who started to make a response may have resulted in better response, which could have been observed had the present study allowed for a longer course of treatment. In support of this suggestion, a recent study indicated different response trajectories following TMS, whereby there was a rapid response group who showed dramatic improvement after 2 weeks of treatment, and two intermediate groups which showed a slower, linear improvement over 6 weeks of treatment. Importantly the two intermediate groups showed no apparent plateau of improvement.[147] Therefore, from a clinical perspective the duration of a TMS treatment course for TRD might be decided on a case-by-case basis, but would normally last at least 20 sessions, possibly extended to 30 sessions if there is some response for example, 25% drop in HDRS-17 from baseline by the end of the TMS course. A further RCT to inform clinical practice for TMS in people with TRD would be a RCT offering 20 iTBS or rTMS sessions and an additional 10 sessions if there is a 25–49% drop in HDRS-17 or MADRS score at the end of treatment versus offering everyone either 20 or 30 sessions of TMS with outcomes at 16 and 26 weeks.

We provided 3000 pulses per session for both rTMS and cgiTBS, with the iTBS protocol including five runs of 600 pulses with 5-minute intervals to ensure that the duration of sessions were the same for both treatment arms for the purposes of blinding, as per the pilot work.[43] An advantage to this was that the duration of therapeutic contact, the number of pulses per session, and the number of sessions were matched. Thus, non-specific effects of TMS were

matched between the treatment arms. The results were largely comparable with THETA-DEP and THREE-D, both of which used 600 pulses of iTBS per session, which indicates that increasing pulses up to 3000 per session does not lead to better response rates but might be associated with higher remission and sustained response and remission rates, compared to 600 pulses per session.[23,28] From a clinical perspective, the standard 600 pulse iTBS is advantageous in the respect that it requires a shorter duration of administration, meaning more patients can be treated per day, and it can do so without compromising clinical efficacy. However, we also should acknowledge that giving more pulses per session may have been superior, but the 5-minute intervals between runs might have diluted clinical efficacy.

Research suggests that dosage and time intervals between TBS protocols may affect meta-plasticity either by reducing or reversing the effect of synaptic plasticity or by increasing the effect of synaptic plasticity. Studies of healthy controls have shown that the delivery of two iTBS sessions to the motor cortex (with 5-minute intervals between sessions), led to a reduction in excitability[148] or no change in excitability,[149] whereas 15-minute intervals increased excitability.[147] Additionally, a study of 3 runs of standard iTBS with 15-minute intervals have been found to significantly increase cortical excitability compared to 2 runs or 1 run,[150] although no studies have explored clinical or adverse effects following 5 runs of iTBS until now. It is difficult to ascertain how translatable these findings are to depression and TMS delivery to the lDLPFC. However, a recent study did find that motor cortex rTMS induced modulation of corticospinal excitability predicted antidepressant response to lDLPFC 10 Hz rTMS in MDD.[151] Therefore, it is plausible that the 5-minute gaps between the present study's iTBS runs could have impeded a potential cumulative effect of cortical excitability, limiting the therapeutic efficacy of the cgiTBS to the first 600 pulses. Since the pilot intervention of cgiTBS with five runs of 600 pulses with 5-minute intervals seemed more effective than rTMS, we did not alter the iTBS intervention in the light of the emerging data.[148]

In addition, the moderator analyses demonstrated that higher baseline HDRS-17, higher baseline GAD-7, higher treatment resistance and completion of < 20 sessions as planned, predicted greater depression symptoms over 26-week follow-up, which is consistent with prior research.[152,153] It is suggested some patients could respond to iTBS but not rTMS or vice versa,[22] a view supported by members of the LEAP group. However, the findings indicate that the moderators of choice did not influence the relationship between treatment arms and depression response. It may be the case that the relationship between clinical predictors and response to different TMS protocols could be more nuanced than what can be observed at a group or population level, and instead we could explore clinical predictors based on distinct trajectories of response, as well as investigating other potential predictors such as benzodiazepine and other psychotropic medication use, number of depression episodes, depression durations, fMRI connectivity, site of stimulation, and THINC-it response. Although an association between the different rTMS and iTBS protocols and response trajectory was not found, characteristics of membership in a rapid response group included older age, lower baseline depression scores, and absence of benzodiazepine use, whereas characteristics of membership to a non-response group included higher baseline depression scores.[147] Therefore, further research on the exploration of response trajectories is warranted.

The present study also found that alongside improvements in depression, there were also clinically important improvements in anxiety symptoms and quality of life, which also appear to be maintained over 6 months, in line with the findings of the THETA-DEP study.[28] A further strength of the present study was identifying that there were cognitive improvements over time for sustained attention, executive functioning, working memory, and a reduction in inter-individual variability for sustained attention. The findings are consistent with a recent meta-analysis which found rTMS led to modest cognitive enhancing effects specific to psychomotor speed, visual scanning, and set-shifting ability in MDD patients.[11] The absence of a placebo arm means that at least part of the improvement in cognition over time may be a practice effect. However, given that improvement in depression was a predictor of improved sustained attention, subjective cognitive performance, and a reduction in individual variability for sustained attention, this would imply that some of these improvements were a consequence of the TMS treatments, and that as depression symptoms improved so did cognitive performance.

It is also important to note that we did not match the percentage rMT (80% baseline rMT for cgiTBS and 120% baseline rMT for rTMS, as per the pilot work).[43] However, 120% baseline rMT is part of the extensively used rTMS protocol,[154] and TBS protocols with subthreshold rMTs may have better clinical efficacy.[21] In some further preparatory work at one of the sites leading to the trial, we found that iTBS at > 80% rMT led to more participants wanting to withdraw from

treatment before the course of iTBS was completed. In addition, while the study found that more participants needed to reduce motor threshold in the rTMS group, we do not believe the chosen motor thresholds would have impacted the clinical efficacy of either of the treatment groups.

As noted in *Chapter 2*, prior to the revision of the primary outcome analysis and sample size, the original primary outcome was to determine efficacy of cgiTBS at 16 weeks (primary clinical outcome, 50% drop in HDRS-17 score from baseline to 16 weeks). However, the responders' results at 16 weeks show a difference of < 1% between the two treatment arms, and it would be very unlikely for this finding to be different even if we had recruited the whole of the original sample. There was good inter-rater reliability among research assessors, blinding was excellent with few unblindings, in the vast majority of cases the site of stimulation of TMS varied by < 1 cm and the angle of stimulation < 10 degrees from the target site and over the course of 20 sessions, and over 90% of the sample received 20 TMS sessions close to the site of stimulation in under 6 weeks. Therefore, the findings are unlikely to be due to the quality of the trial.

Given the lack of a sham control, we cannot rule out that some of the responses may have been due to non-specific factors such as regression to the mean, expectancy effects and hope (as demonstrated in the qualitative data), change in routine (as shown in the qualitative data) or other treatment for depression, particularly between 16 and 26 weeks, but it was not ethical to withhold such treatment in participants with moderate to severe depression. A meta-analysis of placebo responses in RCTs of rTMS in TRD reported response and remission rates of 20% and 11% at the end of treatment, versus 33% and 19%, respectively, in BRIGhTMIND.[155] The long duration of illness and degree of treatment resistance of the participants in BRIGhTMIND also suggest that the magnitude of effects seen are unlikely to be placebo-related. In BRIGhTMIND, the mean duration was over 9 years. In terms of treatment resistance, while the magnitude of the effect of sham TMS in patients with depression can be large (g = 0.8), this drops in studies of those whose depression has failed to respond to 1 or more treatments (g = 0.67) and even further for 2 or more treatments (g = 0.5).[156] In BRIGhTMIND, all had failed at least 2 and the majority at least 4.

Therefore, it is likely that the sustained improvements over 26 weeks in both treatment groups is likely to reflect a significant treatment effect. The response and remission rates in this study are striking, especially comparing them with those seen in similar patients with chronic persistent depression in specialist mental health care across three sites in England, receiving usual mental health care over 6 months (15% and 9% for response and remission respectively – less than half the response rates with TMS in this trial).[58] Overall, we conclude that the clinically substantial improvements in depression over 26 weeks including sustained remission seem to be largely due to rTMS or cgiTBS alongside usual care for moderately severe depression, but some of the improvement was also likely to be due to regression to the mean and non-specific effects other than TMS.

Equality, diversity and inclusion

National and international studies report that the gender ratio (women: men) of depressive disorders is over 1.7 for lifetime prevalence, indicating that women are about twice as likely as are men to develop depression during their lifetime.[157] The study population, on the other hand, had roughly equal rates of males and females, which is contrary to other French and Canadian TMS trials, which included higher rates of women than men.[23,28] Therefore, it is possible that TMS may be an acceptable treatment to males in the UK. This is important given that in the UK about three quarters of deaths from suicide each year are men.[158] The mean age of the present study's participants was also 43.7 years (range: 18.0 to 83.0 years), indicating a wide spread of age, and in keeping with the rates of moderate and severe depression symptoms by age group.[159]

In addition, we noted that only 9% of the sample were of ethnic minority backgrounds. This is lower than expected given that prevalence of depression is reported to be higher in these groups in the UK than in the majority white ethnic group.[160,161] We expected that recruitment would be challenging, given that ethnic minority groups are reported to be less likely to seek professional help for mood disorders,[162] which is why we selected sites to reflect geographical diversity (London, North and Midlands), adding Oldham deliberately to improve ethnic diversity (particularly South Asian population). However, we were limited by the need to include NHS sites with experience and expertise with TMS

(Nottingham, Newcastle, Camden and Islington) or other invasive treatments for TRD (Newcastle). We also ensured that the LEAP included members from different ethnic backgrounds (3 South Asian and 1 Chinese ethnicity) and included a range of age, different experience of TMS and other treatments for severe or chronic depression, included a carer and representatives with neurodiversity. They commented on all materials and procedures used in the study to ensure that they would be understandable to people from different ethnic, demographic, and neurodiverse backgrounds. Further LEAP member involvement in the BRIGhTMIND study is reported in the PPI *Chapter 5*.

A final limitation of the study is that the ethical requirement for capacity to consent precluded the inclusion of the most severely ill patients with depression who were unable to give consent.

Safety, acceptability, facilitators and barriers

The study demonstrates that cgiTBS and rTMS treatments are safe, but with a lot of minor side effects, which were largely resolved either the same day or within 1–6 days. There were two SAEs reported as being possibly related, including a manic episode and a psychotic episode with severe anxiety/depression. However, there were situational factors and a life event to take into consideration for these two participants, and while TMS may have contributed to these events they were unlikely to be the only contributing factor. Overall, cgiTBS was associated with more minor and moderate AEs than rTMS, including these requiring more drug treatment. The most frequently reported side effects overall were headaches, which is comparable with prior TMS trials.[23] Furthermore, whilst the side effect profiles between rTMS and cgiTBS were largely comparable, there did appear to be a slightly higher proportion of participants experiencing tinnitus for the cgiTBS group, which is contrary to the THREE-D trial findings.[23] All the participants were advised to wear earplugs. However, factors that can affect the amount of sound reaching patients' ears following TMS include, but are not limited to, the duration, pattern and intensity of TMS pulses; the closeness of the coil to ear; hearing protection; and coil contact with the head.[163–165] Perception of loudness also integrates over time,[166] so as iTBS pulses were closer together than rTMS pulses, this may have likely lead to greater perceived loudness. The mean cgiTBS target locataion was also closer to the ears than the rTMS location, which too may have led to higher rates of tinnitus. This further emphasises the significant importance of using well-fitted, approved hearing protection to reduce the chances of temporary or permanent hearing changes, and that there needs to be greater research into side effect profiles of longer durations of TBS, multiple TBS sessions in a day (accelerated protocols) and personalised target sites. In addition, while a small proportion of participants reported cognitive difficulties such as brain fog and difficulty findings words, as well as increased anxiety, these events were largely transient, not detectable on the THINC-it battery at follow-up, with the clinical outcome data demonstrating improvements in cognition and anxiety as previously discussed.

Furthermore, while there were more mild and moderate adverse events in the cgiTBS group, there were more participants in the rTMS group that needed to reduce their percentage rMT with changes of position both temporarily and throughout the course of treatment to ensure that the TMS course was tolerable. The qualitative work also indicated tolerability of treatment improved over the course of sessions, which is in line with quantitative results reported in prior rTMS trials.[167] We tested motor threshold at the first session and tested again at the sixth session. However, recent evidence suggests that percentage rMT can vary significantly across days, and weekly motor threshold testing can increase the accuracy of treatment dose determination.[168] Therefore, it could be suggested that testing motor threshold weekly may help participants to achieve accurate treatment doses.

The qualitative and quantitative work also indicated that both TMS protocols are an acceptable treatment for this population in both the short term and longer term, with 92% of participants completing all 20 TMS sessions within the 4- to 6-week treatment period. The study also demonstrated that patients with TRD are particularly open to trying non-pharmaceutical treatments, with a clear understanding of the need for research in order to introduce new treatments and advance knowledge about the disorder.

Staff reassurance and communications was also an important facilitator, which improved the acceptability of treatments, with staff interactions perceived to have had therapeutic benefit, in line with prior research.[55] The findings of the study clearly set the clinician as facilitators of TMS for those with TRD, requiring staff to be approachable and show empathy, as well as preparing to explain the treatment to patients and reassure them about the side effects and clarify

the differences with ECT. Clinicians need to also be able to describe the TMS sensation to patients and illustrate the treatment journey while monitoring patients' expectation of the treatment.

From a clinical perspective, there should be attempts to have flexibility around the treatment schedule. Given that the treatment commitment is intense and work commitments might be an issue for patients with more rigid work schedules, offering treatment in the evening as an alternative will prove useful for patients. Alternatively, the effects of condensed TMS treatment sessions delivered over 1 or 2 weeks might also be more feasible for the working population wanting to access TMS treatments.[48,49]

Finally, while some participants did report concerns that treatment felt varied dependent on the TMS staff delivering the sessions, the neuronavigation data indicated that there were only very small median differences in distance and angle between the first session and subsequent sessions. In line with prior research that shows there are still some variabilities in terms of target positioning and coil drift (coil moving during a session) for neuronavigated TMS over sessions.[24] Nevertheless, these reports indicate that patients can feel even the smallest of adjustments.

Economic evaluation

The cost-effectiveness analysis of the BRIGhTMIND RCT suggests cgiTBS is a cost-effective alternative to rTMS over the 6-month trial time horizon. The analysis finds cgiTBS is associated with a 0.009 QALY gain and a £180 cost saving to the health service per individual. Cost savings and QALY gains were largest when using unadjusted (observed complete case) analyses and when considering broader societal costs. The cost-effectiveness of cgiTBS was predominantly driven by intervention-, outpatient- and productivity-related cost savings and from improvements in HRQoL relative to rTMS (primarily in usual activity, pain/discomfort and anxiety/depression health domains). Informal care hours also reduced fastest in the cgiTBS arm during the trial. Results suggested considerable decision uncertainty with the 95% CI for costs and QALYs overlapping between rTMS and cgiTBS, although the probability cgiTBS being cost-effective remained above 80% across a wide range of thresholds at base-case settings. Findings were highly sensitive to the exclusion of rTMS imaging costs, with cgiTBS having an ICER (£32,920) above NICE's maximum threshold (£30,000/QALY) when making this cost adjustment. These findings were offset however when considering 30-minute time savings for cgiTBS treatment appointments relative to those for rTMS. The marked improvements in HRQoL observed following both treatments translated into health gains considered borderline cost-effective when assuming in the absence of treatment non-intervention healthcare costs are unchanged, HRQoL remains constant at baseline values and equipment costs are distributed across 98 or more individuals.

This is the first study to estimate the cost-effectiveness of cgiTBS relative to rTMS in the UK context. Study findings were broadly consistent with related works and other findings from the BRIGhTMIND study. Mendlowitz *et al.*'s cost-analysis demonstrated iTBS as a cost-saving intervention relative to rTMS within the Canadian healthcare setting.[62] McCrone *et al.*'s UK cost analysis of TRD patients found outpatient visits and primary care contacts also constitute the highest mean health service costs.[57] McCrone *et al.* did, however, report markedly higher inpatient costs than BRIGhTMIND.[57] In line with the primary outcome analysis in this report, the economic evaluation also found (non-statistically significant) improvements in outcomes for cgiTBS that were maintained over the trial period relative to rTMS. Study findings also align with the global analysis of patients' impressions of change during treatment, showing participants typically felt 'somewhat' or 'much better' on cgiTBS compared to rTMS.

This economic evaluation was largely confined to the scope of the BRIGhTMIND study. Future economic evaluations of electromagnetic therapies in TRD can go further by considering a broader range of comparators than those considered in BRIGhTMIND (e.g. pharmacological augmentation strategies, psychotherapeutic strategies, DBS, etc.); assessing cost-effectiveness over longer time horizons, incorporating broader forms of evidence (e.g. observational data, meta-analytic findings, expert opinion, etc.) using decision analytic modelling approaches,[169] and accounting for the broader impacts TRD alleviation may have on individuals, families and wider society.

Strengths of this study include a relatively large and diverse sample of TRD patients from which costs were compiled using relevant UK costing sources and HRQoL measured using a validated instrument; study methodology was

consistent with NICE methodological guidance and reviewed by a LEAP; there was a high completion rate of all economic measures at all time points; findings considered alternative analytical methods (unadjusted and adjusted approaches); cost-effectiveness was assessed using multiple costing perspectives, and the robustness in base-case findings were explored via scenario and threshold analyses. Limitations include highly uncertain predictions resulting from treatment effects estimated from a trial not powered to detect for such differences in costs and QALYs; no extrapolation of treatment benefits beyond the trial's 6-month time horizon, and the generalisability of the findings limited by the trial's exclusion criteria, treatment protocol (imaging for rTMS and comparable appointment times between arms), and smaller-scale equipment throughput. Furthermore, in the absence of a placebo/sham arm in the trial, assessments for the cost-effectiveness of cgiTBS and rTMS relative to no electromagnetic therapy could not be directly established. The artificial placebo scenario explored in this economic evaluation is largely hypothetical and must be interpreted with caution.

The cost-effectiveness for cgiTBS could have been underestimated for a number of reasons. First, expert opinion suggests cgiTBS sessions can provide significant time savings for healthcare professionals compared to TMS appointments.[28,62] Mendlowitz *et al.* reports the 30-minute time saving per appointment the single-largest cost-saving factor in their analysis (US$394, 2018).[62] While these direct savings were explored in scenario analyses, this economic evaluation may neglect potentially broader benefits from improvements in treatment capacity within an already highly constrained setting. Second, the removal of imaging costs considered for rTMS may also be applicable to cgiTBS given the Beam method allows neuronavigation without the need for an MRI scan. Third, HRQoL benefits associated with cgiTBS were present at final follow-up. This benefit combined with the potential for a longer duration of effect compared with rTMS, as evidenced by cgiTBS having a higher proportion of sustained responders,[43] suggests a longer-term follow-up would likely capture additional benefits not accounted for within this evaluation.

Overall, evidence from the BRIGhTMIND trial suggests cgiTBS could be considered a cost-effective alternative to rTMS for patients with moderate to severe TRD. In all economic analyses, cgiTBS was considered cost-effective from a health service perspective provided it cost £184 or less than rTMS treatment (cgiTBS was a cost-saving intervention in all base-case analyses). The cost-effectiveness of cgiTBS is particularly dependent on imaging costs and the potential for larger staff cost savings than those observed in BRIGhTMIND. The overall cost-effectiveness of cgiTBS and rTMS treatments compared to non-electromagnetic treatment options is likely to be contingent on the longevity in treatment benefit, health service, societal cost savings and equipment throughput.

Future research recommendations might focus on delivering a pragmatic clinical trial to establish the clinical and cost-effectiveness of delivering accelerated brief sessions of iTBS up to five times per day versus rTMS without MRI scans within a usual care setting to reflect growing TMS practice. While the current research makes the case for both being cost-effective it required the use of applying assumptions about the care pathway that were untested because of the research nature of the project under EME guidelines for example matching of number of pulses and duration of TMS sessions. Such a trial could include the important null hypothesis or third arm of testing the effectiveness and cost-effectiveness of delivering transcranial stimulation methods (i.e. rTMS and cgiTBS) compared to routine NHS or standard care for individuals with treatment-resistant moderate to severe depression without any transcranial stimulation treatment. Further studies and models could consider the longer-term efficacy of transcranial stimulations on this patient population beyond the 6-month trial period. BRIGhTMIND showed promising results for both cgiTBS and rTMS up to 6 months but there might be further gains over routine care over 2 years or not of more.

Mechanism of action

Based on the findings and these prior MRI-neuronavigated RCTs, it could be that the method for targeting the DLPFC is perhaps less relevant, and if the DLPFC site of choice is accurately and consistently targeted during and at each session, then the stimulation of neural circuits of interest may be optimised, which may lead to more sustained depression responses. Neuronavigation is advantageous in this respect, as it has less coil drift and has significantly less off-target placement, when compared to traditional elastic cap scalp targeting.[24] While one previous MDD study reported greater clinical efficacy for MRI-guided neuronavigated TMS versus scalp-based targeting methods,[25] others have found no difference in clinical efficacy.[26,27] Importantly, these studies focused on immediate efficacy rather than longer-term

efficacy; however, future research may want to compare clinical efficacy for MRI-neuronavigated TMS versus non-neuronavigated TMS over longer-term follow-ups. This may be particularly important given the costs of additional neuronavigation systems, MRI scans, and staff to process scans and identify target co-ordinates.

On the other hand, while we cannot at present make any confident conclusions about image guidance, one of the findings in BRIGhTMIND is consistent with the hypothesis of that therapeutic effect is greater for a target site with greater effective connectivity from target to rAI, which provides modest evidence in favour of the image guidance. Specifically, the hypothesis that the baseline influence of the rAI on the lDLPFC would predict clinical response to TMS was not confirmed. However, there was evidence that the reverse (the influence of lDLPFC on rAI), and the balance of influence between the two regions, could predict improvement on the observer-rated HDRS-17. Greater influence from lDLPFC to rAI at baseline was associated with greater improvement. The rAI locus was used in pilot work based on previous observations that glucose metabolism within this region was able to distinguish responders from non-responders to antidepressant treatments.[131] It is conceivable that a stronger baseline influence of lDLPFC on rAI would allow the effects of TMS to lDLPFC to spread more readily to rAI, thereby exerting greater clinical benefit. In post hoc analyses, we will therefore explore the extent to which clinical response can be predicted from proximity of the actual used target to the point within lDLPFC with maximal influence on the rAI in each participant. This may yield an alternative treatment targeting approach that could be explored in future work.

More negative baseline FC (anti-correlation) between the sgACC and the targeted region within the lDLPFC has previously been shown to predict short-term clinical improvement.[134] This finding built on work showing abnormally elevated sgACC activity in depression, and reduction of sgACC activity in successful treatment response.[170,171] Examining several potential lDLPFC targets, Fox *et al.* found that the 'F3' 10 : 20 scalp location, as used for the rTMS group in the current study, had the weakest anti-correlation with the sgACC.[44] Nevertheless, the rTMS seed showed stronger anti-correlation with sgACC than did the cgiTBS seeds. It may be that the algorithm for identifying the cgiTBS seed inherently selects seeds with weaker anti-correlation with the sgACC, since the algorithm selects the DLPFC target with greatest (positive) effective connectivity from the rAI, and the activities of rAI and sgACC are themselves positively correlated.

In the study, FC between the sgACC and the lDLPFC target at baseline did show the expected (albeit weak) negative relationship with self-reported clinical improvement, when measured shortly after the end of the treatment course. It may be, since lDLPFC exhibits negative FC with sgACC at baseline, that 'excitatory' stimulation to lDLPFC gives rise to suppression of sgACC activity (and thus therapeutic effect). This suppression may be more effective when negative FC between the lDLPFC and sgACC is stronger. It is interesting then, that the relationship between baseline DLPFC-sgACC connectivity and clinical response is reversed when considering the later follow-up time points in the data (16 and 26 weeks). The effect at later time points was also shown by Hopman *et al.* who found that baseline FC with sgACC did not predict response immediately after the end of a treatment course, but greater (more positive) FC between sgACC and a frontal region within the executive control network did predict response at 2 months post treatment.[172] Despite the promise of baseline DLPFC-sgACC FC as a predictor of TMS outcome shown in other studies, it will be important in future work to examine TMS outcomes not only in the short term but also in the longer term. In post hoc analyses, we will explore the pattern of clinical response across follow-up time points in people with more, and less, negative baseline FC between DLPFC and sgACC, to clarify this relationship further, as well as the effective connectivity from the TMS targets to sgACC to examine if this is also predictive of therapeutic effect.

One of the most consistent findings in a meta-analysis of brain connectivity in MDD was greater (positive) FC between the executive control network (e.g. DLPFC) and the DMN (e.g. DMPFC).[173] These networks are typically uncorrelated, or anti-correlated, in health. Greater positive correlation could represent interference between default mode brain areas involved in internally directed mental activity and rumination and areas involved in attention and executive function. Indeed, in non-clinical populations, poorer performance, and greater performance variability, on attentional tasks is related to more positive FC between the default mode and executive control networks.[174,175]

We found that improvement on self-report depression measures was associated with greater reduction, from baseline to follow-up, in FC between the DLPFC and DMPFC (consistent with findings from a small sample by Liston *et al.*).[67] This relationship was not seen on the observer reported HDRS-17 and HDRS-6 measures, suggesting that it most

strongly reflects a reduction in the subjectively experienced intrusion of internally directed mental activity (e.g. rumination) during attempts to attend to the external world. Of note, the self-report measures include items on concentration or decision-making, whereas the HDRS-17 does not have such items.

From the pre-specified hypotheses, the decrease in FC between lDLPFC and lDMPFC from baseline to follow-up was the only relationship of connectivity change associated with clinical response. Separately, we plan to explore relationships between change in lDLPFC and lDMPFC connectivity (or, more broadly, change in connectivity between the default mode – DMN, and executive control – ECN, brain networks) and change in performance on the THINC-it cognitive tasks. This is under the hypothesis that abnormally elevated DMN-ECN connectivity in MDD may reflect intrusion of internal-world processing (e.g. rumination) on external world processing. MDD can be associated with marked cognitive difficulties,[176,177] and such difficulties may be primary mediators of occupational and psychosocial dysfunction.[178] This connectivity relationship could represent a treatment target for cognitive difficulties in MDD. Taken together the three findings of associations between clinical outcome and effective or FC could be seen as different facets of a more homogenous improvement from TMS or they could represent different biotypes of response, possibly related to the course of improvement of TMS. However, there is no evidence in any of the findings that cgiTBS or rTMS are inherently associated with different patterns of improvement or clinical response.

Additionally, the spectroscopy findings add to the plethora of inconsistent pre-trial literature evidence on GABA and Glx. In line with the pilot study results,[68] we did find significant associations between baseline GABA and clinical improvement, albeit in the opposite direction to what we hypothesised with the significant findings driven by the GE scanners. The findings suggest that participants with higher inhibitory tone had better response to TMS treatments, which is in line with a recent study that found greater baseline cortical inhibition was associated with better response to TMS in youth depression.[179] While caution has to be applied due to the large voxel size, variability induced by different scanners and substantial quality-related attrition, this finding together with the eFC prediction may suggest that greater inhibitory influence of the dlPFC over RAI as mechanism of TMS response. Furthermore, while some studies have found increases in glutamatergic compounds are associated with better symptom improvement following TMS,[75] we found decreases in Glx predicted better response on the HDRS-6 at 26 weeks (changing to trend-level significance when removing the relatively extreme value of Glx change). The findings are in line with a prior study which found decreased Glx was associated with better treatment response following CBT,[180] and may reflect a regional normalisation in the prefrontal cortex (reduced hyperactivity). However, we interpret this finding with caution considering the smaller sample size within the analysis and the one relatively extreme value of Glx change.

Overall the MRS findings within the study are not robust. A major limitation includes losing a considerable number of MRS data due to QC issues, so findings are based on relatively small sample sizes. Thus, we suggest the findings are exploratory requiring the need for further replication and study. A further limitation was the use of several MRS platforms. Descriptive statistics revealed variability in signal to noise ratio across scanners, better GABA fitting error for GE scanners, but better Glx fitting error for Phillips scanners. In addition, a number of MRS scans were excluded due to miss-matched voxel locations between baseline and follow-up scans. In future studies, higher field strength (i.e. 7 tesla) scanning platforms may improve quantification of GABA and glutamatergic compounds.[181]

Finally, the mechanism-of-action findings refers to pre-specified analyses of the BRIGhTMIND data, selected to address the mechanistic hypotheses that motivated the trial itself. Multivariate machine-learning algorithms that draw on a large array of imaging features show promise for predicting outcomes in MDD.[182] The well-characterised BRIGhTMIND dataset, with outcomes at multiple time points, variability in targeted location for cgiTBS, and imaging data from multiple modalities (including MRS), provides an ongoing resource for identifying and evaluating cutting-edge approaches for predicting treatment outcomes and for identifying potential novel treatment targets.

Summary of limitations of the trial

There was no sham or treatment as usual control group. We therefore cannot be sure that the changes in the trial were not due to non-specific effects or regression to the mean. Treatments such as TMS that are not usually available to participants may carry a high degree of hope and expectancy effects as illustrated by the qualitative data. Getting up

each day for 4 to 6 weeks may have created order and routine which might have had a therapeutic effect as described in the qualitative data. Ideally, additional treatments would not be altered throughout the course of the follow-up period as well as the TMS treatment itself, but this was not ethically or clinically indicated in such a severe clinically vulnerable effect. It is therefore important to consider that this trial is of two different courses of TMS in addition to usual care. It is possible that some of the changes in outcome in both groups, especially at 16 and 26 weeks, were due to these additional treatments. Of note the qualitative data reported that they experienced an increase in anxiety after both forms of TMS but there was no evidence of a rise in GAD-7 scores at 8, 16 or 26 weeks.

Nevertheless, these are participants with a very long duration of their current depression episode, with a median duration of over 6 years and a history of treatment resistance to multiple treatment attempts. Two thirds of the sample had four or more adequate levels of treatment of sufficient duration and dosage of antidepressants, augmentation, or ECT. Moreover, this is likely to be an underestimate of their treatment resistance since psychological treatments and social interventions were not recorded. Given the duration, severity, and history of treatment resistance, regression to the mean and non-specific effects of treatment may have been quite low. Furthermore, there were substantial mean changes of clinical importance on all measures of depression, anxiety, function, and quality of life, indicating that both groups did show considerable improvement in the trial. The findings of response in a third and sustained response or remission in a fifth of these participants is therefore clinically important, even if some of these results were due to changes in usual care, changes in routine or other non-specific effects of treatment.

In terms of the sample, there were slightly more men, married/cohabiting and employed participants than might be anticipated in community samples of people with depression with few participants of retirement age. This may reflect the novelty and appeal of TMS in terms of men and participants of working age, the need to find alternative treatments to remain in employment, and the wish for someone to support the participant during a TMS course. Analysis of demographic and clinical moderators of outcome such as age, gender, and comorbidity suggest that the results are likely to be generalisable despite some of these demographic differences.

In terms of delivery of TMS, there were some errors in the correct location of the site for the TMS treatment as none of the sites had previous experience with MRI-neuronavigated TMS. However, the data on the closeness of the site of TMS stimulation and how little this varied across 20 TMS sessions suggests that this factor had little bearing on the main findings of the study. More importantly, some participants in both groups started to improve only towards the end of the course of TMS, so greater improvements in outcome might have been achieved with longer courses of TMS. In the cgiTBS group, iTBS was delivered with only 5-minute intervals between bursts of 600 pulses; optimal delivery might have been achieved with 15-minute intervals between bursts of 600 pulses.

The trial was conducted during the COVID-19 pandemic, but analysis suggested that this had little overall effect on the results, except possibly in relation to THINC-it and imaging, where there was some loss of follow-up scans and THINC-it assessments during the period of COVID-19 closedown and restrictions. Participants who completed the trial before the pandemic closedown completed THINC-it assessments at baseline, 8, 16 and 26 weeks and on restart at baseline and 16 weeks. Performance may have improved with greater practice. We also changed the primary outcome from response at 16 weeks to mean change in HDRS-17 at 8, 16 and 26 weeks. Inspection of response data shows that if recruitment to the original sample size and primary outcome had been possible, the overall results and conclusions of the study would not have been different.

In terms of bias, there were few unblindings and on few occasions did outcome assessors or participants identified their treatment allocation. Inter-rater reliability was high in terms of assessment of the primary outcome, suggesting that the results were not due to a lack of imprecision in the assessment of outcome. There were lots of major deviations of the study, but these were largely because the majority of participants undertook a break in TMS treatment of 4 days or more. Analysis of the primary outcome using various forms of sensitivity analysis showed very little difference to the ITT analysis with a consistent pattern of results across all outcomes. Therefore, the results of the study are likely to be sound.

Conclusion

Connectivity-guided intermittent theta burst stimulation was not superior in clinical efficacy to rTMS, although it was dominant in terms of cost-effectiveness but not under all assumptions. About one fifth of participants with moderate to severe TRD achieved remission or a sustained response, which raises the possibility that some patients unresponsive to their treatments could be kept well with 1 or 2 MRI navigated courses of 20 or sometimes 30 iTBS or rTMS sessions. Not all the improvement is likely to be due to the direct physiological effects of TMS but due to non-specific factors and usual care for depression. Adverse events are common but minor and time-limited, and few that can be related to TMS are serious. There are a number of changes in FC and cognition that were found, largely consistent with other emerging literature, but worthy of further exploration in this large, well-characterised sample.

Chapter 5 Patient and public involvement

Introduction

Within the UK, funders such as the National Institute of Health and Care Research (NIHR) have developed a strong policy approach, whereby there is an expectation for active PPI in research that they fund.[183] Additionally, there is increasing awareness of the benefits of PPI contributors and their involvement in health research in order to deliver health services that meet patients' needs.[184] The impact of PPI on processes and outcomes of mental health research have shown that health interventions which included patient or lay involvement in design or delivery of patient information lead to greater recruitment rates[185] and greater relevance of dissemination.[186,187]

In addition, it should be acknowledged that PPI contributions can vary from study to study and there is a useful pragmatic framework to measure this.[186] They refer to low-level involvement as PPI contributors providing views to inform research decision-making, medium-level involvement as shared ongoing decision-making between PPI contributors and researchers, and high-level involvement as individuals with experience of the health issue having the dominant voice, delivering, and managing the research.[79]

It is important to note that we worked with the Involvement Centre at Nottinghamshire Healthcare NHS Foundation Trust to create a Magnetic Stimulation Advisory Group who co-produced the treatment pathway for prior pilot work,[43] that was then extended to an LEAP. This chapter will focus on the LEAP's involvement during the set up and delivery of the BRIGhTMIND study and throughout the chapter we will use the terms LEAP and PPI contributors interchangeably, but it refers to the same individuals.

The aims of PPI in the BRIGhTMIND study were to advise on: (1) study design and ethical issues; (2) take an active role in recruitment and selection of research and TMS operating staff appointed to the study; (3) co-designing participant information sheets and other study materials for example patient and public targeted study website; (4) provide recommendations for study and site-specific barriers; (5) assist with the inter-rater reliability and training of research assessors for the primary outcome measure of the study; (6) assist in the interpretation of findings, in particular the emerging qualitative analysis on barriers to recruitment and patient acceptability of TMS; and (7) assisting in the future dissemination of findings, whereby the voice of experts by experience will be heard in all dissemination activities. Additionally, over time, and with the challenge of the pandemic, the LEAP members also took on additional roles that are outlined below.

As we will report throughout this chapter, the LEAP members' experiences and knowledge ensured that the study participants' voices would be heard. This helped the trial consistently maintain strong patient focus.

Methods

Participants

Each research site was invited to nominate two PPI representatives to form an LEAP. We aimed to achieve a blend of experience with the previous work and new voices, as well as diversity, geography, and relevant experience (of TRD, TMS, and research methods).

The LEAP process was overseen by an experienced PPI lead who had trained supported and mentored several PPI groups over recent years, and who had previously worked with the chief investigator in a similar role.

As of 11 April 2022, the LEAP panel compromised of 4 females and 6 males, aged between 36 and 68 years, with three members Asian or Asian British and all others White British. The LEAP panel consisted of carers, individuals with lived experience of TRD and some members who had received TMS treatments themselves. Over the course of the study, there were five withdrawals from the LEAP, and when there were withdrawals the PPI lead advertised for new members by liaising with the research sites to find suitable replacements.

PPI recruitment for the TSC and DMEC were appointed through invitation from the funding body. This was on the suggestion of the PPI lead, as this needed to include people with no significant links to the LEAP.

Methods through which patient and public involvement members were involved

National LEAP panel meetings were conducted quarterly, to include all LEAP members, the PPI lead, chief investigator, and trial manager, which were originally face to face, before moving to remote video conferences due to the COVID-19 pandemic. The LEAP members felt the regular attendance of the chief investigator and trial manager at these meetings were helpful and very much appreciated. Researchers and site PIs were also invited to a number of these meetings to discuss the MRI imaging and qualitative elements of the study. On average there were seven LEAP representatives in attendance for the national LEAP meetings.

Participation payments and reimbursement of travel expenses were in place to cover national LEAP meetings and for the separate PPI contributors who attended TSC and DMEC meetings. The core commitment for the LEAP was the attendance to the quarterly national LEAP meetings. Members could freely choose whether or not to engage in other opportunities around the study. There was also financial support for these voluntary additional duties. The payment rates were in line with payment guidance provided by the NIHR Centre for Engagement and Dissemination (CED) and previously INVOLVE (national advisory group which promotes and supports greater public involvement in NHS, public health, and social care research), before its function was taken over by CED. For example, one of the meetings lasting 2–3 hours would attract a participant payment of £60 plus expenses.

Measurement of the impact of patient and public involvement

The impact of PPI on the BRIGhTMIND study was assessed through documented minutes of the national LEAP meetings and feedback from the individual research sites. Initially, these meeting notes and feedback were scrutinised by a member of the research team to assess impact of PPI. This narrative was then discussed with the PPI group to ensure there were no omissions.

In preparing this chapter, the Guidance for Reporting Patient and Public Involvement (GRIPP2) checklist short form was used as a framework. This aims to improve quality, transparency, and consistency of PPI evidence to ensure best practice.[188] We also refer to low-level, medium-level, and high-level involvement when discussing PPI contributions.[188]

Results

The results section broadly summarises the PPI contributors' involvement in trial design and development, trial considerations, recruitment of staff and participants, trial results and dissemination and COVID-19 practicalities.

Trial design and development

Low-level involvement

1. Provided feedback on strengths, weaknesses, opportunities, and threats (SWOT analysis), which informed decision-making on elements of the trial.
2. Recommended travel buddies and filming routes to facilities to help participants to appointments. We were unable to action this due to time constraints and funding. However, based on the PPI's suggestions, RAs tried to ensure they were available to meet participants for MRI scans, with directions and maps provided to all participants and contact numbers for the research team and TMS staff.

Medium-level involvement

3. Patient information sheets and advertisement documentation were co-designed by PPI contributors and the research team.
4. Contributed to the monthly BRIGhTMIND newsletters, which were circulated to the study team to provide updates on study progress.
5. Qualitative acceptability study topic guides were amended based on suggestions provided by PPI contributors.

6. LEAP provided unanimous recommendations for preferred secondary outcome self-report measures which were adopted by the research team.
7. Voluntarily completed mock interviews of the primary outcome measure, for RAs to assess for inter-rater reliability and to provide feedback on how RAs could improve their performance.

High-level involvement

8. Had a significant dominant voice for including an adapted version of the Patient Global Impression of Change scale.[95] Based on their advice, this measure alongside the patient acceptability measure were adopted. Without this, we would have had no measurement of change in outcome while the patients was receiving TMS.
9. Recommended a qualitative substudy to explore the reasons why BRIGhTMIND participants were requesting copies of their MRI scans. This substudy was co-designed and co-produced between PPI contributors and the research team.
10. PPI contributors provided, at first from their own initiative and then subsequently invited to submit reports to DMEC and TSC. The report detailed the work of the LEAP group and its impact, and a portion of both the DMEC and TSC meetings were set aside for such reports.

Trial considerations

Low-level involvement

11. During study design, it was initially proposed that 20 TMS sessions would need to be completed Monday to Friday for a 4-week period. However, based on the PPI contributors' advice this treatment programme was adapted to a 6-week programme, with participants only able to have a maximum of 4 consecutive missed treatment days.
12. PPI contributors suggested we should offer a degree of flexibility in terms of the TMS clinic hours to take into consideration those that were employed and preferences for morning or afternoon slots. TMS was only provided within usual working hours Monday to Friday, however all sites however tried to ensure that the participants' timeslot worked for them.

Medium-level involvement

13. The PPI contributors raised an important topic regarding participants not having access to further 'top up' treatments after the 20 sessions had been completed. They suggested this could be an ethical issue, and that variation in response to treatment and the duration of response should be clearer in documentation and conversations. The study was not able to provide 'top up' treatments. However, based on their advice, an amendment was made to the general practice enrolment letter and patient information sheets to state this.

Recruitment of research and transcranial magnetic stimulation staff

Medium-level involvement

14. A large proportion of staff members were employed to the study via redeployment or secondment. However, for those that recruited via formal, open, competitive interview, 71% of panels included a PPI representative. The PPI representatives had a significant impact on the outcome of interviews, with positive feedback provided from PPI representatives, other panellists, and job applicants.

Recruitment of participants

Low-level involvement

15. The PPI members suggested advertising the study on radio or TV. The BRIGhTMIND study was therefore featured on BBC East Midlands TV news. This helped the local site maintain consistent recruitment rates from June 2021 until the end of study recruitment. While this feature was focused within the East Midlands, it reached individuals outside of this location, with a number of referrals received by other research sites.

16. Recommended promoting the study at General Practitioner Continuing Professional Development events, Improving Access to Psychological Therapies (IAPT) services, primary care Clinical Research Network services and secondary care mental health services. These recommendations were utilised to varying degrees across the study sites. In particular a number of primary care and IAPT presentations were done in London and Newcastle.
17. The PPI members provided a number of suggestions for how to promote the study to increase diversity at sites in in East Midlands and North East England. This included targeting local areas with greater ethnic minority representation and advertising at places of worship. Posters were not put within places of worship due to the COVID-19 pandemic, however Newcastle promoted the study to the Community Treatment Team in the West End of Newcastle, which includes an area where a larger population of Asian people live and Nottingham targeted GP practices with greater percentages of BAME patients.

High-level involvement

18. The PPI contributors unanimously felt that the initial material on the BRIGhTMIND webpage (created on the Nottingham Institute of Mental Health website in December 2018) included too much scientific language. This feedback was actioned, with one LEAP member taking a lead in rewriting significant portions of the webpage content, and reviewing other sections written by researchers. Following an amendment approved by the REC, the webpage was recreated April 2020. Prior to these changes, the website averaged 139 views per month, which increased to 238 views per month following their input. The Northern Centre for Mood Disorders website also contained information on the BRIGhTMIND study, which was reviewed by PPI contributors, with recommendations for amendments including more accessible information on TMS actioned.

Trial results and dissemination

Low-level involvement

19. The PPI contributors asked us to consider wider dissemination beyond academic papers. This includes disseminating clinical and cost-effectiveness of the study to NHS Trusts, and sharing the standard operating procedures with NHS TMS clinics, to assist with good, standardised practice.

Medium-level involvement

20. The PPI contributors have aided the interpretation and naming themes for the qualitative acceptability study and with the research team, co-analysed the qualitative substudy exploring participants' requests for MRI scans.
21. PPI contributors are being given the opportunity to co-author upcoming manuscripts and will be involved in the early stages of manuscript developments up until publication.

COVID-19 practicalities

Low-level involvement

22. The PPI members recommended a COVID-19 patient information sheet, which was adopted, to detail changes made to previous BRIGhTMIND study procedures. This was to help alleviate anxiety about face-to-face contact and detail measures put in place to ensure infection control and safety.
23. Most contact between researchers and participants changed to remote methods, with face-to-face contact requiring staff and participants to wear face masks. PPI recommended a document, which was adopted, with staff's photographs and profiles, to help alleviate participants' anxiety and break communication barriers and worries.
24. The PPI contributors reminded the researchers of the importance of family support and the impact of relatives no longer being able to join participants at face-to-face meetings. As such, sites gave participants the option for family to be present during the remote appointments. Family members were also able to attend MRI scans and TMS treatments in exceptional circumstances – once it was safe and permitted to do so.
25. The PPI contributors were also concerned that travelling and transportation to and from the treatments could be an issue during the pandemic. Family members providing transport would also have nowhere to wait due to lockdown/safety issues. While these concerns were acknowledged by the research team, no further changes for travel could be actioned due to both funding and COVID-19 legally binding restrictions.

26. The PPI members recommended that the BRIGhTMIND study webpage should be updated to notify the general public of when the study would resume recruitment. This recommendation was actioned, and the webpage was updated when each site was permitted to restart recruitment.

Discussion, reflections and critical perspectives

The BRIGhTMIND study demonstrated that a combination of low, medium, and high levels of PPI contribution can have a successful impact on the development and implementation of a complex health intervention. This is the first multicentre trial of MRI-neuronavigated TMS in the UK, and it was essential for both the research team and the LEAP group to co-produce important elements of the project to ensure its successful completion. This chapter demonstrates that involvement is not a fixed role, but of one that can grow over time as an organic process dependent on context and the need to adapt to challenges. The PPI contributors' conduct, invaluable knowledge, and input into the trial led only to improvements and there were no negative factors identified.

The LEAP provided significant input into the design, development and running of the study, including the co-production of patient-facing documentation (e.g. patient information sheets, posters, and websites) and qualitative topic guides. They had a dominant voice in improving website advertisement information, initiating the set up of a substudy and the selection of certain secondary outcome measures. The LEAP continuously ensured that the trial maintained a strong patient focus, providing recommendations for study design, treatment considerations and COVID-19 practicalities, in order to improve the research participant's experience. They provided several different recommendations for promotion of the BRIGhTMIND study, which helped to enhance recruitment, and had significant input into the recruitment of research and TMS staff. Finally PPI was crucial for the analysis of the qualitative work, dissemination of publications and further recommendations for dissemination beyond that of academic papers.

A further strength of the LEAP was its heterogeneity (diversity of demographic characteristics, geography, and relevant experience). First, the PPI contributors ensured there was a strong service user focus, by viewing and providing feedback on issues or topics through the lens of their own experience. This also enabled the research team to deal with practicalities that may not have been highlighted without the PPI's feedback. Second, the PPI contributors had various experience in the medical, mental health field and prior PPI involvement, and it was felt this led to more efficient outcomes and the ability to deal with a wide range of topics.

One suggestion for improvement could be the communications between each of the site's research teams and their local LEAP representatives. While there was funding available for local PPI contributors to meet with their site RAs, and PPI contributors were eager to meet site RAs, this did not occur until midpoint through the BRIGhTMIND trial. The nurture of good interpersonal relationships is crucial for effective PPI involvement,[189] and the PPI contributors recommended that introducing the site-specific researchers to the LEAP group at an earlier meeting could have been beneficial. As a result, future research should ensure that extra time, training, and funding is provided for both researchers and PPI members to maximise involvement and impact.[190] In addition, expectations for communication, involvement, and responsibilities between study sites and PPI contributors should be clearly outlined during the set up of studies.

Conclusion

This chapter demonstrates that the PPI approach is suitable for the context of setting up complex multisite trials. The COVID-19 pandemic was a unique challenge, but it shows the robustness of such an approach in being able to adapt to the most extreme and unexpected challenges. Future complex trials may benefit from a comprehensive PPI plan at the grant application stage which would, for example, take into consideration how PPI members may have a blend in low, medium, and high involvement, the need for an experienced PPI lead, and the need for heterogeneity of PPI members.

Additional information

Contributions of authors

Richard Morriss (https://orcid.org/0000-0003-2910-4121) (Professor of Psychiatry, University of Nottingham) was the chief investigator of the study, obtained funding for the study and study permissions, designed the study, led its conduct, and wrote the first draft of the report with Lucy Webster and Luke Ingram. He is the guarantor of the study.

Lucy Webster (https://orcid.org/0000-0003-0424-2587) (lead research assistant, Nottinghamshire Healthcare NHS Foundation Trust) designed the qualitative analysis of the study, collected the clinical and qualitative data for the Nottingham site, analysed the imaging and qualitative data, and wrote the first draft of the EME report with Richard Morriss and Luke Ingram.

Luke Ingram (https://orcid.org/0000-0001-5711-7400) (trial manager, Clinical Trials Unit, University of Leicester) was the trial co-ordinator from 2021, obtained permissions for the study, and wrote the first draft of the EME report with Richard Morriss and Lucy Webster.

Mohamed Abdelghani (https://orcid.org/0000-0002-9888-6588) (consultant psychiatrist, Camden and Islington NHS Foundation Trust) was the principal investigator for the London site, including the clinical lead for TMS at the site, and obtained funding for the study as a grant applicant. He helped to design the TMS treatment delivery and interpret the TMS analysis. He commented on the first draft of the report.

Adriana Anton (https://orcid.org/0000-0002-1356-4513) (magnetic resonance physicist, University of Nottingham) carried out the second MRS analysis of GABA and the first of glutamate Cr.

Shaun Barber (https://orcid.org/0000-0002-8073-2687) (medical statistician, Clinical Trials Unit, University of Leicester) helped to the design the clinical trial, carried out power calculations for the study, helped to design the statistical analysis plan for the clinical trial and advised on the anaalysis of the MRS data. He produced a first draft of the clinical trial results.

Peter Bates (https://orcid.org/0000-0002-0558-6907) (patient and public involvement co-ordinator, Nottinghamshire Healthcare NHS Foundation Trust) helped to design and led the PPI in the study throughout. He commented on drafts of the report and helped to design the analysis of the PPI contribution to the report.

Paul Briley (https://orcid.org/0000-0002-5372-6505) (Clinical Lecturer in Psychiatry, University of Nottingham) helped to design and carried out the MRI analysis of the study and the first draft of the functional MRI analysis and interpretation. He advised on the statistical analysis of the THINC-it data.

Clement Boutry (https://orcid.org/0000-0002-6781-2201) (research assistant, University of Nottingham) carried out analysis of the qualitative data along with Lucy Webster and Louise Thompson.

Cassandra Brookes (https://orcid.org/0000-0002-0084-0400) (Senior Statistician, Clinical Trials Unit, University of Leicester) was the lead statistician for the clinical trial and grant holder. She supervised the statistical analysis and the first draft of the clinical trial results.

Edward Cox (https://orcid.org/0000-0001-8981-0699) (Senior Health Economist, University of Nottingham) carried out the economic analysis of the trial data and wrote the first draft of the health economics report.

Beth Hall (https://orcid.org/0000-0002-5812-3121) (research fellow, Cumbria, Northumberland, Tyne and Wear NHS Foundation Trust) carried out the THINC-it analysis with Hamish McAllister-Williams and drafted the THINC-it analysis report.

Marilyn James (https://orcid.org/0000-0003-0408-7898) (Professor of Health Economics, University of Nottingham) was the health economics lead for the study, designed the health economics analysis, and was the grant holder. She co-wrote the health economics part of the report.

Matthew Keane (https://orcid.org/0000-0002-8428-9870) (health economist, University of Nottingham) carried out the economic analysis of the trial data and wrote the first draft of the health economics report.

Micheal Kurkar (https://orcid.org/0000-0002-9424-0747) (consultant psychiatrist, Pennine Care NHS Foundation Trust) was the principal investigator at the Oldham site in the study and was the clinical lead for TMS at the site.

Sudheer Lankappa (https://orcid.org/0000-0002-2804-7877) (consultant psychiatrist, Nottinghamshire Healthcare NHS Foundation Trust) was the principal investigator at the Nottingham site and the TMS clinical lead at Nottingham. He helped to devise the TMS intervention for the study and was a grant holder.

Peter Liddle (https://orcid.org/0000-0001-6473-7640) (Professor of Psychiatry, University of Nottingham) helped to devise the neuroimaging for the study including the method of computation of the TMS stimulation sites from MRI data. He was a grant holder.

Hamish McAllister-Williams (https://orcid.org/0000-0001-9966-1834) (Professor of Psychiatry, University of Newcastle) was the principal investigator at the Newcastle site including being the clinical lead for the Newcastle site. He devised the THINC-it analysis and adapted the MGHS measure of treatment resistance for the study.

Hyerin Oh (https://orcid.org/0000-0001-5179-2480) (research fellow, University of Nottingham) carried out the MRS for the study.

Alexander O'Neill-Kerr (https://orcid.org/0009-0001-0023-4152) (consultant psychiatrist, Northamptonshire Healthcare NHS Foundation Trust) was the principal investigator at the Northampton site and supervised the TMS delivery at Northampton. He helped to devise the TMSS treatment in the study and was a grant holder.

Jehill Parikh (https://orcid.org/0000-0002-6504-9239) (research fellow, Magnetic Resonance Imaging Centre, University of Newcastle) helped to design the MRS and analysis.

Stefan Pszczolkowski (https://orcid.org/0000-0002-5859-3190) (research fellow, Precision Imaging Beacon, University of Nottingham) wrote the computer programme and automated method for calculating the site of TMS stimulation from MRI data, and calculated the precision of TMS stimulation delivered by the neuronavigation from the MRI calculated target site.

Ana Suazo Di Paola (https://orcid.org/0000-0002-8523-8557) (medical statistician, Clinical Trials Unit, University of Leicester) provided statistical support throughout the study and carried out the statistical analysis under the supervision of Shaun Barber and Cassandra Brookes. She wrote the first draft of the statistical analysis plan and the first draft of the statistical results with them.

Louise Thomson (https://orcid.org/0000-0003-1736-7506) (associate professor of occupational psychology, University of Nottingham) was the qualitative methods lead for the study and supervised all the qualitative analysis. She was also a grant holder.

Yvette Walters (https://orcid.org/0000-0001-8691-0440) (trial manager, Clinical Trials Unit, University of Leicester) was the study manager from the inception of the trial until September 2021. She then supervised Luke Ingram took over the role.

Dorothee Auer (https://orcid.org/0000-0002-4745-3635) (Professor of Neuroimaging, University of Nottingham) was the neuroimaging lead for the study and obtained funding for the study as a grant applicant. She designed the MRI

design with Peter Liddle, and the MRS design as well as the MRI analysis with Paul Briley and Peter Liddle, and the MRS analysis with Hyerin Oh and Jehil Parikh.

Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review.

Ethics statement

The project received NHS ethics approval from the East Midlands-Leicester Central Research Ethics Committee (REC reference 18/EM/0232, IRAS project ID 245025) on 30 August 2018.

Information governance statement

Nottinghamshire Healthcare NHS Foundation Trust is committed to handling all personal information in line with the UK Data Protection Act (2018) and the General Data Protection Regulation (EU GDPR) 2016/679. Under the Data Protection legislation, Mark Howells is the Data Controller, and you can find out more about how we handle personal data, including how to exercise your individual rights and the contact details for our Data Protection Officer here: https://www.nottinghamshirehealthcare.nhs.uk/privacy-policy#:~:text=The%20nominated%20Data%20Protection%20Officer,%40nottshc.nhs.uk.

Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/WVNY5029.

Primary conflicts of interest: Richard Morriss has received funding from Novartis for sitting on a Data Monitoring Ethics Committee. Mohamed Abdelghani has received funding for advising manufacturers of equipment for transcranial magnetic stimulation. Hamish McAllister-Williams has received funding from Liva Nova for consultancy and P1Vital for chairing a Data Monitoring Ethics Committee.

Publication

Morriss R, Briley PM, Webster L, Abdelghani M, Barber S, Bates P, *et al.* Connectivity-guided intermittent theta burst versus repetitive transcranial magnetic stimulation for treatment-resistant depression: a randomized controlled trial. *Nat Med* 2024;**30**:403–13. https://doi.org/10.1038/s41591-023-02764-z

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Appendix 1 Methods chapter supplemental information

TABLE 27 Summary of substantial amendments

Version and date	Substantial amendments	Approved date	Reason for change
Version 2.0, 03 October 2018	Substantial amendment 1 (prior to project start)	REC: 22 October 2018 HRA: 23 October 2018 Sponsor R&D: 31 October 2018	First approved version. Ethics approval from the NHS REC was originally received on 30 August 2018, but the HRA required additional changes resulting in substantial amendment 1 passed on 23 October 2018.
Version 3.0, 22 March 2019	Substantial amendment 2 (SA02)	REC: 4 June 2019 HRA: 4 June 2019 Sponsor R&D: 20 June 2019	Section 4.2 Secondary Objectives Changed the rating of acceptability scale from 0 to 5 to 1–5 to correspond with the rating acceptability scale form used for the study. Section 5.1.2 Anticipated Project Timeline Changed months of project timelines. Section 5.3 Participant Recruitment Details changed to recruitment to take into account the recruitment times reduced by 3 months. Added details of medication requirements from baseline to the end of TMS treatment and end of study. Section 6.2 Exclusion Criteria Exclusion criteria regarding medication has been changed for patient safety reasons to minimise the risk of seizures and syncope during TMS treatment. Section 7.6 Qualitative Analysis Name of transcription service to be used to transcribe the qualitative interviews
Version 4.0, 22 January 2020	Substantial amendment 3 (SA03)	REC: 27 February 2020 HRA: 28 February 2020 Sponsor R&D: 9 March 2020	Treatment Resistance Definition Amended to reflect the scoring of the MGH-S. Study Design 4.1 Main objective 5.1 Study Outline 15 Appendices *Appendix 1*: QIDS secondary outcome measure. 5.2.1 Baseline Characteristics and outcome measures. Secondary outcome measures. 5.2.3 Outcome measures table Secondary Outcome 4.2 Secondary objective added – To examine the independence of changes in brain activity associated with improvements in cognition from changes associated with improvement in mood. 7.1 Data Analysis. Exploratory analysis relating to self-reported mood to brain scanning changes and changes in cognition with depression. 7.7 Cognitive Analysis 7.7.1 Brain Scanning changes 7.7.2 Cognition changes. 14 Reference References 56 and 57 added. 15 Appendices *Appendix 2*: Inserted Cognitive Scanning Changes

continued

TABLE 27 Summary of substantial amendments (*continued*)

Version and date	Substantial amendments	Approved date	Reason for change
Version 5.0, 14 December 2020	Substantial amendment 4 (SA04)	REC: 21 December 2020 HRA: 21 December 2020 Sponsor R&D: 4 January 2021.	Protocol change to include an qualitative optional substudy to explore the reasons and meanings behind why participants request a copy of the images taken during their MRI scan. About 25–30 participants in the main BRIGhTMIND study have asked for a copy of the images that were taken during their MRI scan. The LEAP suggested this warranted further investigated. This was agreed, as there has been little research that has provided an in-depth exploration of the reasons behind why people want copies of their MRI scans or reports, particularly in individuals with mental health conditions. Study documents include optional consent form. Information sheet and letters. This will be funded from a separate award and delivered at one site.
Version 6.0, 06 September 2021	Substantial amendment 5 (SA05)	REC: 21 September 2021 HRA: 21 September 2021 Sponsor R&D: 24 September 2021	**Summary of changes:** • Reduce sample size and extend study end date by 16 months. Participant numbers had been decreased to 266 (133 per arm). This was due to the funds and time available it would not be possible to recruit to the original sample size of 368. Due to a technological breakthrough by TMS company, site set-up and recruitment was delayed by 8 months to implement the new technology. The technology, a simple-to-use neuronavigation system allowed more reproducible accuracy of TMS stimulation over 20 sessions than the manual BEAM methods that we proposed in the funded grant application. The trial would have been obsolete on completion without the change. In addition, recruitment to the study was paused for 5 months, March–August 2020, due to the COVID-19 pandemic and was unable to reopen Northampton site due to staffing issues and previous low recruitment. This in addition to the uncertainty to future recruitment, meant sample size of 368 could not be achieved. There had been a change to the primary outcome to ensure there was sufficient power (89.3%) with the sample size stated. • Change to the main objective Primary outcome has been changed from response at 16 weeks (primary clinical outcome, 50% drop in HDRS-17 score from baseline to 16 weeks) to mean change in the HDRS-17 score over 26-week follow-up. There were 3 follow-up time points at 8, 16, and 26 weeks. Such an analysis would achieve the primary clinical objective of the study, which was to explore whether connectivity guide iTBS is superior in reducing depression symptoms over a longer duration of time. • Description of Intervention in more detail The description of iTBS required more detail on the protocol to ensure it was not confused with continuous TBS and currently did not accurately describe the ITBS process that has been followed in the SOP and continuously in the trial by the TMS machine that delivers the ITBS treatment. • Details of scan amended The details of scan type, which was included in MRI umbrella changes made, and the fMRI row removed from the outcome measures table as this was inserted in error. Only an rsfMRI was conducted, also stated which scans were not being performed in Oldham. In addition, Arterial spin labelling details were added as they were not previously included. • Wording on protocol regarding existing psychotropic medication changes. 'Existing psychotropic medications or psychological interventions will be kept stable for 16 weeks for the duration of the trial except for those at risk to themselves or others', so that it read: 'Existing psychotropic medications or psychological interventions will be kept stable for 16 weeks after randomisation except for those at risk to themselves or others' as to add clarity in terms of the period during which the medications or interventions should be kept stable for

HRA, Health Research Authority; R&D, Research and Development; SOP, standard operating procedure.

TABLE 28 Study timelines

Study timeline		
Date (YYYY/MM/DD)	**Event/meeting**	**Action**
2018		
2018/05/02	TSC	Committee established, first meeting
2018/08/23	DMEC	Committee established, first meeting, reviewed letter of recommendations from TSC
2018/August/30-31	Opening of study HRA + REC approvals granted	
2018/11/27	TSC	
2019		
January 2019	Nottingham (Notts)	Site open to recruitment
March 2019	Camden & Islington (C&I)	Site open to recruitment
March 2019	Newcastle (NTW)	Site open to recruitment
2019-07-24	DMEC	
2019-08-21	TSC	
2019-11	Northampton (NHFT)	Site open to recruitment
2020		
2020-02-04	DMEC	
2020-02	COVID-19 pandemic	Recruitment paused at all sites
2020-03-25	TSC	
2020-06-23	DMEC	
2020-07-29	TSC	
2020-08	COVID-19 pandemic	Recruitment at sites resumed – Northampton closedown
2021		
2021-01-19	DMEC	
2021-02-17	TSC	
2021-07-27	DMEC	
2021-08-24	TSC	
2021-08/09	Pennine Care Trust (NHSFT)	Site open to recruitment
2021-09	Substantial Amendment 5 (SA05)	No cost study extension – recruitment period extended to 31 January 2022
2022		
2022-01-31	Recruitment period end	
2022-02-08	DMEC	
2022-03-22	TSC	
2023		
2023-01	Site closedown performed at all sites	

continued

TABLE 28 Study timelines (*continued*)

Study timeline		
Date (YYYY/MM/DD)	**Event/meeting**	**Action**
2023-01-25	Joint TSC/DMEC final meeting	
2023-02-08	Final trial management group meeting	
Monthly Trial Management Group Meetings occurred from 2017 to 2023		

Assessment of degree of treatment resistance

The definition and assessment of the degree of TRD in the BRIGhTMIND study is operationalised using the MGH-S system (Fava *et al.*, 2003)[86]. This assesses the number of previous biological treatments for depression, given as an adequate treatment trial, in the current episode of depression. The use of psychological treatments is not assessed by this tool because it can be challenging to obtain reliable accounts of structured psychotherapy from participant's accounts (Lobban *et al.*, 2017)[191]. To date, the relationship between non-response to psychotherapy and response to TMS has not been investigated. This is in contrast to evidence that the degree of treatment resistance to biological treatments may moderate treatment outcome to TMS (Lee *et al.*, 2012)[192]. The use of, and response to, psychological therapy is recorded separately to the MGH-S in the BRIGhTMIND study for use as an exploratory variable in relation to predictors of response.

The MGH-S is based on one point being scored for every different antidepressant prescribed at the minimum effective dose for a minimum of 6 weeks, without response. An extra 0.5 points is scored if the trial has been at least 10 weeks and if the dose of the antidepressant has been optimised to a defined level. A further 0.5 can be scored if the antidepressant has been augmented by a second drug. Any course of electroconvulsive therapy lasting a minimum of four treatment sessions is given a score of 3 points.

The MGH-S tool used in BRIGhTMIND is an updated version of that published by Fava *et al.* in 2003[86], with medications not available at that time added and ones that are no longer, or where never, available in the UK removed . Specifically, the tricyclic antidepressants amoxapine, desipramine, maprotiline and protriptyline, and the 'other' antidepressant nefazadone, that were included in the scoring table in Fava *et al.* (2003),[86] were removed. The tricyclic antidepressants dosulepin (75 and 150 mg) lofepramine (140 and 210 mg), monoamine oxidase inhibitor moclobemide (300 and 600 mg), and 'other' antidepressants such as reboxetine (8 and 12 mg), agomelatine (25 and 50 mg) and vortioxetine (10 and 20 mg) were added with minimum and optimised doses indicated in brackets. These doses were based on the various drugs' Summary of Product Characteristics and consensus of the clinicians involved in the setup of BRIGhTMIND.

In the scoring table published by Fava *et al.* (2003),[86] the definition of which drugs could be counted towards augmenting an antidepressant is vague, simply presenting examples: for example, buspirone (Buspar), lithium, psychostimulants such as methylphenidate (Ritalin), atypical antipsychotics such as olanzapine (Zyprexa). It was decided that more precise guidance should be provided. The drugs included are based on consensus of BRIGhTMIND clinicians and British Association for Psychopharmacology (BAP) Guidelines (Cleare *et al.*, 2015).[193] All first- and second-line BAP options were included [lithium, aripiprazole, quetiapine, risperidone, olanzapine, and tri-iodothyronine (T3)]. BAP guidelines also include mirtazapine augmentation of another antidepressant. Because of the diverse range of antidepressant combinations sometimes used in clinical practice, 'mirtazapine' was broadened to 'any second antidepressant'. The two remaining drugs specifically mentioned by Fava *et al.* (2003),[86] buspirone and methylphenidate,

were retained (i.e. all drugs specifically mentioned by Fava *et al.* are included). Two extra drugs were then added by consensus on the basis of awareness of their use in the centres involved in the BRIGhTMIND study: modafinil and pramipexole. These both have some RCT evidence supporting their use as augmentation agents (Goss *et al.*, 2013; Tundo *et al.*, 2019).[194,195]

In BRIGhTMIND each participant was scored on the adapted MGH TRD scoring system. The inclusion criterion for the RCT is a score of 2 points or more. This is broadly in line with the conventional definition of TRD as being failure to respond to 2 adequate courses of different antidepressants (Brown *et al.*, 2019)[196]: failure to respond to 2 different antidepressants prescribed at the minimum dose for 6 weeks each would score 2 × 1 point. However, it should be noted that dose optimisation and a treatment trial of a single antidepressant could lead to the same score (1 + 0.5 + 0.5 points).

Scoring the MGH-S is dependent on having information regarding the patient's past treatments during this current episode. In BRIGhTMIND, this is established through a combination of interview with the patient and examination of primary and secondary care case notes. Patients are interviewed using timeline follow-back techniques to identify when the current episode of depression started. However, the MGH TRD scores are very susceptible to error due to mis-remembered details and inadequate, inaccurate or inaccessible case notes. Rather than focusing on the specific MGH TRD score, patients in BRIGhTMIND are allocated to three categories of degree of treatment resistance: low, medium, and high. These are defined on the basis of data collected in a previous RCT in patients with TRD, the ADD study (McAllister-Williams *et al.*, 2016)[197], by scores of 2–3.5, 4–6 and ≥ 6.5, respectively. If there is any concern that there is incomplete data on past treatments, then a patient is allocated to the high resistance group.

The specific guidance on using the MGH TRD scoring system in BRIGhTMIND is as follows:

1. The scale assesses the degree of treatment resistance in the current episode. For some patients with long histories of depression, it can be difficult to determine the beginning of an episode. Count a new episode of depression from the end of any period of substantially better mood for a minimum of 2 months.

2. Confirm if any antidepressants have been taken (not just prescribed) in the current episode. If not, then the patient is excluded.
3. If the participant has taken any antidepressants in the current episode then collect information regarding what has been taken (all psychotropics), at what dose and for how long at the minimum dose or greater. Then, using supplementary *Table 1*:

    a. In column A, tick an antidepressant the patient has taken at the minimum dose for at least 6 weeks during this episode of depression.
    b. For antidepressants ticked in column A, put another tick in column B if the treatment continued for at least 10 weeks.
    c. Tick column C if the patient has taken the drug at a dose equal to or greater than the maximum dosage listed for that medication. (There is no extra score for doses higher than the maximum.)
    d. If the patient has been prescribed any of the drugs listed here (taken for at least 4 weeks) during the same time period to boost the antidepressant effect, write the name in column D.

        i. NB – if an antidepressant combination is used, then only score for one of these with the second antidepressant being the augmentation agent. For example if a patient on venlafaxine has mirtazapine added, put a tick in the venlafaxine row and write 'mirtazapine' in column D. Do not tick the mirtazapine row (unless this was also used in monotherapy).
        ii. NB – augmentation agents should in theory be used at minimum effective doses. However, there is a lack of consensus as to what these should be. If in any doubt seek a view of the local PIs or chief investigator.

4. Add the scores:

    a. For each antidepressant, add a score to column E. This is + 1 for the antidepressant, + 0.5 if used for at least 10 weeks (at minimum dose or above), + 0.5 if the maximum dose or greater was used and + 0.5 for each augmentation agent used.
    b. If the patient has received ECT in this episode, then add 3 into column E on the ECT row at the bottom.
    c. Calculate the total MGH TRD score adding up all scores in column E.

TABLE 29 Adapted Massachusetts General Hospital Staging Method to classify treatment-resistant depression for the BRIGhTMIND Study

Has the patient received any treatment with antidepressant medications since the beginning of this current episode or period of depression? 1 = Yes 2 = No □If No – Exclude from study

If Yes
1) On the grid below in column A, tick an antidepressants the patient has taken at the minimum dose for at least 6 weeks during this episode of depression.

2) For antidepressants ticked in column A, put another tick in column B if the treatment continued for at least 10 weeks.

3) Tick column C if the patient has taken the drug at a dose equal to or greater than the maximum dosage listed for that medication. *(There is no extra score for doses higher than the maximum.)*

4) If the patient has been prescribed any of the drugs listed here during the same time period to boost the antidepressant effect, write the name in column D, *amisulpride, aripiprazole, buspirone, lithium, methylphenidate, modafinil, olanzapine, pramipexole, quetiapine, risperidone, triiodothyronine (T3), and any second antidepressant.*

If ticked score			1	0.5		0.5	0.5	
			A	B		C	D	
	Generic name	**Min dose (mg/day)**	**At least 6 weeks**	**At least 10 weeks**	**Max dose (mg/day)**	**Equal or greater**	**Name of drug added to augment this antidepressant**	**Score**
Tricyclic antidepressants	Doxepin	150			250			
	Clomipramine	150			250			
	Amitriptyline	150			250			
	Nortriptyline	75			125			
	Trimipramine	150			250			
	Imipramine	150			250			
	Dosulepin	75			150			
	Lofepramine	140			210			
MAOIs	Isocarboxazid	30			60			
	Phenelzine	45			90			
	Tranylcypromine	30			60			
	Moclobemide	300			600			
SSRIs	Fluvoxamine	50			150			
	Paroxetine	20			60			
	Fluoxetine	20			60			

TABLE 29 Adapted Massachusetts General Hospital Staging Method to classify treatment-resistant depression for the BRIGhTMIND Study (*continued*)

	Generic name	Min dose (mg/day)	At least 6 weeks	At least 10 weeks	Max dose (mg/day)	Equal or greater	Name of drug added to augment this antidepressant	Score
	Sertraline	50			150			
	Citalopram	20			60			
	Escitalopram	10			30			
SNRI	Venlafaxine	125			250			
	Duloxetine	60			100			
Other	Trazodone	300			600			
	Bupropion	300			450			
	Mirtazapine	15			45			
	Reboxetine	8			12			
	Agomelatin	25			50			
	Vortioxetine	10			20			
Did the patient receive ECT during the current episode (score 3)?								
							Total MGH score	

TABLE 30 Qualitative interview topic guides

Interview Topics for Service User who agreed to take part

- How did you hear about the research study?
  - Who first mentioned the research study to you?
- What was your initial reaction to the invitation to participate?
  - How did you feel about taking part?
- What factors impacted on your decision to take part in the study?
  - Why did you decide to join the research study?
  - Was there anything in particular that persuaded you to join the study?
  - Prompts: health (current symptoms)
  - Prompts: attitudes to research (opportunity to access new services, altruism)
  - Prompts: engaging the patient (active promotion and marketing, trust, clarity of trial process)
- Were there also concerns that you had about taking part?
  - Were there any factors that put you off?
  - Prompts: health (expression of depression symptoms, fear of symptom exacerbation/risk of trial to mental health, concern over side effects of TMS, vulnerability)
  - Prompts: attitudes to research (randomisation, negative views about one of the treatment options)
  - Prompts: engaging the patient (perceived stigma, challenges of understanding the trial, burden)
  - Prompts: practical issues (travel to the treatment centre, required time off work or from other commitments, availability of carers)
  - Did you complete the full cycle of treatment?
- Having received treatment through the study, can you tell me about your views on the treatment you received?
  - Are there any benefits that you have experienced?
  - Have there been any disadvantages/anything you disliked about the treatment?
  - How acceptable did you find the treatment?
  - PROMPT: on a 1 to 5 scale, where 1 is very unacceptable and 5 is very acceptable, how would you rate this treatment? [visual prompt to be provided]

continued

TABLE 30 Qualitative interview topic guides (*continued*)

Interview topics for service user who declined to take part

- How did you hear about the research study?
  - Who first mentioned the research study to you?
- What was your initial reaction to the invitation to participate?
  - How did you feel about taking part?
- What factors impacted on your decision to not take part in the study?
  - Why did you decide not to join the research study?
  - Prompts: health (expression of depression symptoms, fear of symptom exacerbation/risk of trial to mental health, concern over side effects of TMS, vulnerability)
  - Prompts: attitudes to research (randomisation, negative views about one of the treatment options)
  - Prompts: engaging the patient (perceived stigma, challenges of understanding the trial, burden)
  - Prompts: practical issues (travel to the treatment centre, required time off work or from other commitments, availability of carers)
- Were there any positives to taking part in the study for you?
  - Was there anything that could have persuaded you to take part in the study?
  - Prompts: health (current symptoms)
  - Prompts: attitudes to research (opportunity to access new services, altruism)
  - Prompts: engaging the patient (active promotion and marketing, trust, clarity of trial process)

Interview topics for service users who consented to take part in the trial, but withdrew during or after treatment

- How did you hear about the research study?
  - Who first mentioned the research study to you?
- What was your initial reaction to the invitation to participate?
  - How did you feel about taking part?
- What factors impacted on your initial decision to take part in the study?
  - Why did you decide to join the research study?
  - Was there anything in particular that persuaded you to join the study?
  - Prompts: health (current symptoms)
  - Prompts: attitudes to research (opportunity to access new services, altruism)
  - Prompts: engaging the patient (active promotion and marketing, trust, clarity of trial process)
- What factors led you to withdraw from the study?
  - Why did you stop your involvement in the TMS study?
  - Prompts: health (expression of depression symptoms, fear of symptom exacerbation/risk of trial to mental health, concern over side effects of TMS, vulnerability)
  - Prompts: attitudes to research (randomisation, negative views about one of the treatment options)
  - Prompts: engaging the patient (perceived stigma, challenges of understanding the trial, burden)
  - Prompts: practical issues (travel to the treatment centre, required time off work or from other commitments, availability of carers)
  - How many treatment sessions did you complete?
- Was there anything that could have helped you to continue in the study?
  - What would have persuaded you to continue with the treatment?
  - Prompts: practical assistance?
  - Prompts: explanation of research study?
  - Prompts: explanation of the TMS treatment?
- Having received some treatment through the study, do you have any views on the treatment you received?
  - Are there any benefits that you have experienced?
  - Have there been any disadvantages/anything you disliked about the treatment?
  - How acceptable did you find the treatment?
  - PROMPT: on a 1 to 5 scale, where 1 is very unacceptable and 5 is very acceptable, how would you rate this treatment? [visual prompt to be provided]

TABLE 31 Health economics analysis plan V3 23 August 2021

Authors: Prof Marilyn James Matthew Keane,
Purpose of HEAP
The aim of this HEAP is to lay out the design and analytical methods which will be used to evaluate the cost-effectiveness of Connectivity-Guided intermittent Theta-burst Stimulation (cgiTBS) at 16 weeks and 26 weeks compared with standard Repetitive Transcranial Magnetic Stimulation (rTMS), in people with Treatment Resistant Depression (TRD). The methods specified in this document are prospective and are subject to change in line with recommendations of official bodies and/or guidelines of best practice, external factors, and evolving data analysis boundaries

TABLE 31 Health economics analysis plan V3 23 August 2021 (*continued*)

Economic perspective

In accordance with NICE guidance, the primary analysis will take an NHS and personal social services cost perspective.[198] Parallel analysis will take a broader perspective to include a societal approach

Economic data and management

Software

All data will be imported from Microsoft Excel and analysed in StataSE (Release 16; StataCorp, USA)

Data cleaning

Plausibility checks will be performed on data fields relevant to the economic evaluation of the trial. For example, a participant reporting double digit inpatient hospital admissions within a 3-month period may be considered implausible. More extreme examples, such as triple digit service use, are likely impossible and may be a result of transcription error or participant confusion. Where problems are identified, the health economic analyst will contact the data manager and/or other relevant members of staff for clarification and/or further investigation

Outcomes

Primary outcomes	Measurement	Technical notes
Health-related quality of life for participant	EuroQoL-5D five level (5L) version.[199] Completed by the participant at baseline, 6 weeks, 3 months, 6 months, and 12 months	A multi-attribute utility instrument, recommended by the National Institute for Health and Care Excellence (NICE), for estimating health-related quality of life. In addition to a descriptive profile, the EQ-5D may produce a single index value for health status. The EQ-5D health state utility score is derived from five individual items (domains) with five response levels, which when combined with a suitable valuation set (representing societal preferences), produces a cardinal index value ranging from −0.59 to 1, with 0 representing death, 1 of perfect health, and < 0 of health states worse than death. The EQ-5D instrument includes the EuroQol Visual Analogue Scale (EQ-VAS), where recipients self-assess their health state 'today' and is rated on a scale from 0 (worst imaginable health) to 100 (best imaginable health). Following an official statement of position there is no recommended population tariff available for the EQ-5D.[198] The EQ-5D-L may be mapped to the EQ-5D-3L while a new tariff is under development

Derivation of indices of HRQoL and calculation of quality-adjusted life-years

Indices of HRQoL for the EQ-5D will be derived using relevant population tariffs. If a suitable tariff is not available for the EQ-5D five level (5L) version by trial data-lock then the 5L responses will be mapped to the 3L variant so that an established UK valuation set may be used

EQ-VAS scores represent individual rather than societal preferences, and as such do not require a valuation set. These scores will be divided by 100 before QALY construction to ease comparison with other administered HRQol instruments

Area under the curve (AUC) will be used to adjust participant HRQoL for the time spent in their respective health states, constructing quality-adjusted life-years (QALYs)

Health care and other resource use

The viewpoint for the study is broad as such data will be collected on health care and social care at baseline and during the treatment and intervention regime, but in addition seek to collect societal costs such as productivity (days off work where appropriate) and the direct patient cost of illness. A purposely designed resource use collection to collect health and social care resources has been designed and will be administered at baseline 16- and 26-week collection points. A purposely designed health resource questionnaire has been developed (MJ) and important with patient input collaboratively with patient and public involvement (comments from the study's lived experience advisory panel. Resource use collected includes medication, inpatient and outpatient hospital visits and primary and community care use, societal costs and patient-related costs of treatment. BRIGhTMIND is well placed to maximise data collection of resource use, as the resource use questionnaire is collected directly in clinic and has the advantage that research nurses can assist patient should any confusion arise. To fully understand the costs of the treatment options themselves, equipment to deliver treatment will be fully costed and apportioned across the patient pathway. A further study log has been developed that will be completed by a purposive sample of nurses and healthcare assistant at each centre will complete a diary of time spent managing each participant in the trial to derive treatment costs for rTMS and cgiTBS and to record the consumable required to deliver care. It is important to note this may be different pre and post COVID (the period incorporated within this study).

continued

TABLE 31 Health economics analysis plan V3 23 August 2021 (*continued*)

Costing of resource use	
Resource use	**Costing sources and technical notes**
Direct intervention costs	
• Mental health nurse • Healthcare assistant • Higher research assistant • Time with patient pre and post pandemic.	Unit Costs of Health and Social Care[200]
NHS Cost	
	All related healthcare cost will be collected by purposely designed Health Resource Use Questionnaires directly administered at treatment visits with a research nurse
NHS inpatient admissions	The National Cost Collection (NHS England, 2020)[201]
NHS outpatient visits and primary/community services	Unit Costs of Health and Social Care[200]
Cost of equipment	• cgiTBS • rTMS • Handling equipment • Cleaning equipment pre and post pandemic for example hand sanitiser, alcohol wipes etc
Societal costs	
Productivity losses	The costs of absenteeism will be estimated through the lost wages approach including a suitable team multiplier[202] (Nicholson *et al.*, 2006)[203]; where reports of health-realted time taken off work will be combined with population-level gross weekly salaries from the Annual Survey of Hours and Earnings,[204] stratified by full/part-time employment status, age, and gender
Out-of-pocket expenses	Participant self-reports of costs will be used for travel, parking, private healthcare visits, private prescriptions
Procedures for missing data	
Handling of missing data will follow guidelines for intention to treat analysis with incomplete observations.[205] tests of missingness mechanisms will be conducted to determine the feasibility of the missing at random (MAR) assumption. If missingness can be predicted through observed data, such as demographics or clinical measurements, then methods of multiple imputation will be applied using available case data, such as Multiple Imputation of Chained Equations (MICE), which build into their models the inherent uncertainty associated with the missing data; specifying a separate conditional distribution for each imputed variable.[206,207] Otherwise, methodologies which do not presume MAR will be employed	
Within-trial analysis	
Population and time horizon	
The economic evaluation will take an incremental approach between the two groups using an intention-to-treat (ITT) population (irrespective of treatment received) and a 12-month time horizon	
Discount rates	
No discounting will be applied to derived QALYs or costs due to their being incurred within a 12-month period	
Analysis of outcomes and resource use	
Viewpoint	
Analyses will be presented from both a health and societal care perspective and a broader societal perspective	
HRQoL outcomes and QALYs, alongside healthcare service use and derived costs, will be summarily presented for each arm of the trial. 95% confidence intervals will be estimated through the non-parametric method of bootstrapping in lieu of standard deviations due to the heavy-tailed distributions of count data, and the frequent multimodal distributions (in addition to ceiling and floor effects) of HRQoL indices and their subsequently derived QALYs	

TABLE 31 Health economics analysis plan V3 23 August 2021 (*continued*)

The outcome for the primary cost–utility analysis will be a participants QALYs using the EQ-5D. outcomes will then be jointly analysed as paired units with their direct-to-NHS costs, and more broadly societal costs
Owing to the different methods used to elicit intervention resource data (e.g. at different sites there will be different staff members, waiting times, etc.) we will conduct further costing scenarios to examine their impact on the decision recommendations. Furthermore, due to the COVID-19 pandemic there will be differences in cost from patients recruited before the pandemic and during/post pandemic largely in cleaning costs this will further contribute to the elicit resource use data. These are reported under the sensitivity analysis section of the HEAP and include costs difference due to COVID-19
QoL Ananalsysi will use Area Under the Curve AUC approach. Between-arm differences will be estimated through methods such as seemingly unrelated regressions (SUR)
Sampling uncertainty
The regression-based estimates of mean differences will be bootstrapped to derive 95% confidence intervals, and resultant point estimates used to construct incremental cost-effectiveness ratios (ICERS), where: $= \frac{\Delta Cost}{\Delta QALY} = \frac{Cost_{Intervention}}{QALY}$
These will be scattered on the cost-effectiveness plane to visually represent sampling uncertainty.
Cost-effectiveness acceptability curves (CEACs) will then be constructed using the net monetary benefit framework, which represents the monetary value to the NHS when the willingness-to-pay thresholds (λ) for a specified outcome is known (Hoch *et al.*, 2002),[208] where: $(\lambda * \Delta Outcome) - (Cost_{Intervention} -$
By rearranging the decision rule, where a treatment is cost-effective if the incremental cost-effectiveness ratio (ICER) is less than the threshold, a therapy should be adopted if the incremental net monetary benefit > 0. Accordingly, we will derive an INMB across a range of thresholds for each bootstrapped iteration of the multivariate distributions of incremental outcomes and costs. The resulting plot will present the non-parametric proportion (probability) cost-effective (0–100%) of cgiTBS compared to rTMS treatment by willingness-to-pay thresholds for one QALY
Sensitivity analyses
• Complete case data may be reported alongside data derived by multiple imputation. Data missingness will be reported. Other strategies may involve worst/best case assumptions for HRQoL • Costing centre observations (such as multicentre effects in the case of costs) and potential variations in treatment costs and their technologies will be reported if such effects are observed • We will seek to address cost discrepancies pre and post COVID in a sensitivity analysis
Modelling
Life course
Treatment resistant depression (TRD) has a major impact on quality of life (QoL), however due to the heterogeneity of TRD this renders CUA modelling infeasible and noted that this study is not funding the development of an economic model
Future research
While not a designed outcome, the BRIGhTMIND trial has wealth of data on the use of HRQoL measurements on those with TRD. This could inform the national picture of costs and treatment for those suffering with TRD within the NHS
Reporting
Reporting standards
The final report of the trial will be submitted by peer review alongside a Cheers checklist dependent on submission requirements.[209]
Reporting deviations from HEAP
Any deviations from the HEAP will be reported in the first instance to the study team and disclosed alongside publication submissions as a supplementary note where deemed informative

CEAC, cost-effectiveness acceptability curve; HEAP, health economics analysis protocol.

TABLE 32 CHEERS 2022 checklist

	Item	Guidance for reporting	Reported in section
Title			
Title	1	Identify the study as an economic evaluation and specify the interventions being compared	Pages 1
Abstract			
Abstract	2	Provide a structured summary that highlights context, key methods, results and alternative analyses	Pages 3, 11
Introduction			
Background and objectives	3	Give the context for the study, the study question and its practical relevance for decision-making in policy or practice	Pages 20–21
Methods			
Health economic analysis plan	4	Indicate whether a health economic analysis plan was developed and where available	Page 41
Study population	5	Describe characteristics of the study population (such as age range, demographics, socioeconomic, or clinical characteristics)	Page 54–55, 73–75
Setting and location	6	Provide relevant contextual information that may influence findings	Pages 20–21
Comparators	7	Describe the interventions or strategies being compared and why chosen	Page 21, 30–32 Rationale: Pages 14–18
Perspective	8	State the perspective(s) adopted by the study and why chosen	Page 41
Time horizon	9	State the time horizon for the study and why appropriate	Page 44–45
Discount rate	10	Report the discount rate(s) and reason chosen.	Page 45
Selection of outcomes	11	Describe what outcomes were used as the measure(s) of benefit(s) and harm(s)	Pages 44–46
Measurement of outcomes	12	Describe how outcomes used to capture benefit(s) and harm(s) were measured	Pages 44–45
Valuation of outcomes	13	Describe the population and methods used to measure and value outcomes	Pages 44–45
Measurement and valuation of resources and costs	14	Describe how costs were valued	Pages 40–43
Currency, price date, and conversion	15	Report the dates of the estimated resource quantities and unit costs, plus the currency and year of conversion	Page 41
Rationale and description of model	16	If modelling is used, describe in detail and why used. Report if the model is publicly available and where it can be accessed	*N*/A
Analytics and assumptions	17	Describe any methods for analysing or statistically transforming data, any extrapolation methods, and approaches for validating any model used	Pages 44–46
Characterising heterogeneity	18	Describe any methods used for estimating how the results of the study vary for subgroups	Page 46
Characterising distributional effects	19	Describe how impacts are distributed across different individuals or adjustments made to reflect priority populations	*N*/A
Characterising uncertainty	20	Describe methods to characterise any sources of uncertainty in the analysis	Pages 44–46

TABLE 32 CHEERS 2022 checklist (*continued*)

	Item	Guidance for reporting	Reported in section
Approach to engagement with patients and others affected by the study	21	Describe any approaches to engage patients or service recipients, the general public, communities, or stakeholders (e.g. clinicians or payers) in the design of the study	Page 46
Results			
Study parameters	22	Report all analytic inputs (e.g. values, ranges, references) including uncertainty or distributional assumptions	Appendix
Summary of main results	23	Report the mean values for the main categories of costs and outcomes of interest and summarise them in the most appropriate overall measure	Pages 73–76
Effect of uncertainty	24	Describe how uncertainty about analytic judgments, inputs, or projections affect findings. Report the effect of choice of discount rate and time horizon, if applicable	Pages 74–77
Effect of engagement with patients and others affected by the study	25	Report on any difference patient/service recipient, general public, community, or stakeholder involvement made to the approach or findings of the study	Page 46
Discussion			
Study findings, limitations, generalisability, and current knowledge	26	Report key findings, limitations, ethical or equity considerations not captured, and how these could impact patients, policy, or practice	Pages 91–93
Other relevant information			
Source of funding	27	Describe how the study was funded and any role of the funder in the identification, design, conduct, and reporting of the analysis	Pages 10, 12
Conflicts of interest	28	Report authors conflicts of interest according to journal or International Committee of Medical Journal Editors requirements	Complete

TABLE 33 Intervention unit costs

Resource use	Unit cost	Unit	Source
Imaging unit costs			
Structural MRI	£246.43	Per scan	NHS reference costs (2020–21)[a]
rsfMRI	£201.08	Per scan	NHS reference costs (2020–21)[b]
Staff costs			
Nurse (band 6)	£55	Per hour	PSSRU, 2021
Healthcare assistant (band 4)	£35	Per hour	PSSRU, 2021
Healthcare assistant (band 5)	£41	Per hour	PSSRU, 2021
Higher research assistant (band 5)	£41	Per hour	PSSRU, 2021
Device costs			
Electromagnetic device	£54,000	Per device	Trial costing

a Imaging outpatient: Magnetic resonance imaging scan of one area, without contrast, 19 years and over.
b Imaging outpatient: Magnetic resonance imaging scan of two or three areas, without contrast.

TABLE 34 Unit costs

Resource category	Cost	Unit	Source
Inpatient hospital services[a]			
Acute psychiatric ward	£296.27[a]	Per day	PSSRU 2021[a] (10)
General medical ward	£195.34[a]	Per day	PSSRU 2021[a] (10)
Outpatient hospital services			
Psychiatric outpatient visit	£324.00	Per attendance	NHS costs 2021 (11)
Psychologist visit	£222.00	Per attendance	NHS costs 2021 (11)
A&E attendance	£296.46	Per attendance	NHS costs 2021 (11)
Day hospital attendance	£333.60	Per attendance	NHS costs 2021 (11)
Non-psychiatric outpatient visit	£229.43	Per attendance	NHS costs 2021 (11)
Community-based day services			
Day care centre	£39.00	Per day	PSSRU 2021 (10)
Drop-in centre	£39.00	Per day	PSSRU 2021 (10)
Specialist education facility	£267.63	Per day	PSSRU 2021 (10)
Sheltered workshop	£39.00	Per day	PSSRU 2021 (10)
Primary care contacts			
GP (at surgery)	£39.23	Per contact	PSSRU 2021 (10)
GP (at home)	£108.50	Per contact	PSSRU 2021 (10)
Practice nurse	£42.00	Per contact	PSSRU 2021 (10)
District nurse	£51.84	Per contact	NHS costs 2021 (11)
Community psychiatric nurse	£51.84	Per contact	NHS costs 2021 (11)
Social worker	£52.00	Per contact	PSSRU 2021 (10)
Occupational therapist	£50.00	Per contact	PSSRU 2021 (10)
Advocate	£30.70	Per contact	PSSRU 2021 (10)
Home help/care worker	£33.00	Per contact	PSSRU 2021 (10)
Community matron	£51.84	Per contact	PSSRU 2021 (10)
Productivity costs			
Manager/administrator full-time	£171.40	Daily salary	ONS (15)
Manager/administrator part-time	£48.20	Daily salary	ONS (15)
Professional (health, teaching, legal) full-time	£159.40	Daily salary	ONS (15)
Professional (health, teaching, legal) part-time	£81.40	Daily salary	ONS (15)
Associate professional (technical, nursing) full-time	£121.60	Daily salary	ONS (15)
Associate professional (technical, nursing) part-time	£50.00	Daily salary	ONS (15)
Clerical worker/ secretary full-time	£95.80	Daily salary	ONS (15)
Clerical worker/ secretary part-time	£44.60	Daily salary	ONS (15)
Services/sales full-time	£83.20	Daily salary	ONS (15)
Services/sales part-time	£36.80	Daily salary	ONS (15)

TABLE 34 Unit costs (*continued*)

Resource category	Cost	Unit	Source
Skilled labourer (building, electrical) full-time	£110.20	Daily salary	ONS (15)
Skilled labourer (building, electrical) part-time	£42.00	Daily salary	ONS (15)
Factory worker full-time	£85.60	Daily salary	ONS (15)
Factory worker part-time	£27.80	Daily salary	ONS (15)
Other full-time	£128.00	Daily salary	ONS (15)
Other part-time	£45.60	Daily salary	ONS (15)
Medication costs			
Agomelatine 25 mg	£0.33	Per pill	eMIT (12)
Amisulpride 200 mg	£0.08	Per pill	eMIT (12)
Amitriptyline 50 mg	£0.02	Per pill	eMIT (12)
Aripiprazole 15 mg	£0.14	Per pill	eMIT (12)
Atomexatine 40 mg	£0.19	Per pill	eMIT (12)
Bisacodyl 5 mg	£0.04	Per pill	eMIT (12)
Bisoprolol 5 mg	£0.03	Per pill	BNF (13)
Bupropion 150 mg	£0.10	Per pill	BNF (13)
Buspirone 10 mg	£0.20	Per pill	eMIT (12)
Calcichew calcium 500 mg	£0.06	Per pill	BNF (13)
Chlorpromazine 100 mg	£0.61	Per pill	eMIT (12)
Circadian 2 mg	£0.51	Per pill	BNF (13)
Citalopram 20 mg	£0.02	Per pill	eMIT (12)
Citalopram (liquid form) 40 mg	£6.83	Per bottle	eMIT (12)
Clomipramine 25 mg	£0.05	Per pill	eMIT (12)
Clonazepam 2 mg	£0.12	Per pill	eMIT (12)
Concerta 18 mg	£1.04	Per pill	BNF (13)
Dexamphetamine 5 mg	£0.53	Per pill	eMIT (12)
Diazepam 10 mg	£0.02	Per pill	eMIT (12)
Dosulepin 75 mg	£0.32	Per pill	eMIT (12)
Doxepin 50 mg	£5.50	Per pill	BNF (13)
Doxycycline 100 m	£0.10	Per pill	eMIT (12)
Duloxetine 20 mg	£0.06	Per pill	eMIT (12)
Escitalopram 10 mg	£0.02	Per pill	eMIT (12)
Fluoxetine 20 mg	£0.01	Per pill	eMIT (12)
Folic acid 5 mg	£0.01	Per pill	eMIT (12)
Haloperidol 5 mg	£2.86	Per pill	eMIT (12)
Hydrochloroquin 200 mg	£0.05	Per pill	eMIT (12)

continued

TABLE 34 Unit costs (*continued*)

Resource category	Cost	Unit	Source
Imipramine 25 mg	£0.07	Per pill	eMIT (12)
Isocarboxazid 10 mg	£4.45	Per pill	BNF (13)
Lamotrigine 50 mg	£0.07	Per pill	BNF (13)
Lansoprazole 15 mg	£0.13	Per pill	BNF (13)
Levothyroxine 25 mcg	£0.02	Per pill	eMIT (12)
Liothyronine 20 mcg	£1.70	Per pill	eMIT (12)
Lisdexamfetamine 70 mg	£2.97	Per pill	BNF (13)
Lithium carbonate (Priadel) 400 mg	£0.09	Per pill	BNF (13)
Lithium citrate 520 mg	£0.04	Per pill	BNF (13)
Lofepramine 70 mg	£0.15	Per pill	eMIT (12)
Lorazepam 1 mg	£0.06	Per pill	eMIT (12)
L-Tryptophan 500 mg	£0.00	Per pill	BNF (13)
Melatonin 3 mg	£0.20	Per pill	BNF (13)
Mirtazapine 30 mg	£0.03	Per pill	eMIT (12)
Moclobemide 150 mg	£0.41	Per pill	eMIT (12)
Modafanil 100 mg	£0.07	Per pill	eMIT (12)
Nortriptyline 10 mg	£0.01	Per pill	BNF (13)
Olanzapine 10 mg	£0.04	Per pill	eMIT (12)
Paroxetine 20 mg	£0.02	Per pill	eMIT (12)
Phenelzine 15 mg	£1.20	Per pill	BNF (13)
Pregabalin 25 mg	£0.04	Per pill	eMIT (12)
Promethazine hydrochloride 25 mg	£0.12	Per pill	eMIT (12)
Propranolol 40 mg	£0.01	Per pill	eMIT (12)
Quetiapine 300 mg	£0.07	Per pill	eMIT (12)
Reboxetine 4 mg	£0.32	Per pill	BNF (13)
Risperidone 1 mg	£0.01	Per pill	eMIT (12)
Sertraline 50 mg	£0.02	Per pill	eMIT (12)
Thiamine 100 mg	£0.03	Per pill	eMIT (12)
Tolterodine 2 mg	£0.03	Per pill	eMIT (12)
Tranylcypromine 10 mg	£10.30	Per pill	BNF (13)
Trazodone 50 mg	£0.04	Per pill	eMIT (12)
Valproic Acid 500 mg	£0.42	Per pill	eMIT (12)
Vencarm XL 225 mg	£0.35	Per pill	BNF (13)
Venlafaxine 75 mg	£0.04	Per pill	BNF (13)
Venlafaxine (quick release) 150 mg	£0.13	Per pill	BNF (13)
Venlafaxine (sustained release) 75 mg	£0.10	Per pill	BNF (13)

TABLE 34 Unit costs (*continued*)

Resource category	Cost	Unit	Source
vitamin d 25 mg	£0.10	Per pill	BNF (13)
Vortioxetine 20 mg	£0.99	Per pill	BNF (13)
Zopiclone 3.75 mg	£0.01	Per pill	eMIT (12)
Other costs: outpatient attendances			
ACP by phone	£88.00	Per attendance	PSSRU (10)
CBT tTherapist	£39.00	Per attendance	PSSRU (10)
CPN – telephone consultation	£5.67	Per attendance	NHS reference costs (11)
Care co-ordinator	£41.00	Per attendance	PSSRU (10)
Counsellor	£54.00	Per attendance	PSSRU (10)
Counsellor phone calls	£54.00	Per attendance	PSSRU (10)
Crisis team	£66.00	Per attendance	PSSRU (10)
Diabetes clinic	£180.76	Per attendance	NHS reference costs (11)
Doctor secondary care phone call	£8.67	Per attendance	PSSRU (10)
G.I. clinic	£165.00	Per attendance	NHS reference costs (11)
Group therapy	£117.41	Per attendance	NHS reference costs (11)
Gynaecologist	£204.78	Per attendance	NHS reference costs (11)
Hospital spinal physiotherapy	£52.00	Per attendance	PSSRU (10)
Non-medical prescriber	£35.00	Per attendance	PSSRU (10)
Nurse consultant	£88.00	Per attendance	PSSRU (10)
Ophthalmology	£166.24	Per attendance	NHS reference costs (11)
Physiotherapist	£39.00	Per attendance	PSSRU (10)
Therapist telephone call	£113.78	Per attendance	NHS reference costs (11)
Rheumatology	£175.11	Per attendance	NHS reference costs (11)
SDS psychiatrist – video consultation	£65.00	Per attendance	PSSRU (10)
Scan (physical health)	£132.90	Per attendance	NHS reference costs (11)
Specialist CPN, QMC	£51.84	Per attendance	NHS reference costs (11)
Step 4 CBT by phone	£39.00	Per attendance	PSSRU (10)
Thrombosis clinic	£193.24	Per attendance	NHS reference costs (11)
X-ray	£203.73	Per attendance	NHS reference costs (11)
Physiotherapist and pain consultant	£64.67	Per attendance	PSSRU (10)
Clinical pharmacist phone call	£54.00	Per attendance	PSSRU (10)
Diabetes clinic – telephone	£180.76	Per attendance	NHS reference costs (11)
ECT	£132.71	Per attendance	NHS reference costs (11)
BUPA mental health consultant telephone call	£50.00	Per attendance	PSSRU (10)
Cardiology	£191.12	Per attendance	NHS reference costs (11)

continued

TABLE 34 Unit costs (*continued*)

Resource category	Cost	Unit	Source
Charity therapist	£47.00	Per attendance	PSSRU (10)
Colorectal	£151.35	Per attendance	NHS reference costs (11)
Crisis team home visits	£66.00	Per attendance	PSSRU (10)
Dermatology o/patients	£168.29	Per attendance	NHS reference costs (11)
Employment support	£47.00	Per attendance	PSSRU (10)
Place of safety	£97.31	Per attendance	NHS reference costs (11)
Psychiatrist – video consultation	£75.00	Per attendance	PSSRU (10)
Psychotherapist	£88.00	Per attendance	PSSRU (10)
Telephone appointment with urology	£144.25	Per attendance	PSSRU (10)
Work counsellor telephone call	£54.00	Per attendance	PSSRU (10)
Bariatric psychologist	£113.78	Per attendance	NHS reference costs (11)
ADHD referral psychiatrist	£266.77	Per attendance	NHS reference costs (11)
Group therapy – video consultation	£97.31	Per attendance	NHS reference costs (11)
IAPT telephone call	£54.00	Per attendance	PSSRU (10)
Mindfulness refresher session online	£65.00	Per attendance	PSSRU (10)
Nurse prescriber at local CMHT	£65.33	Per attendance	PSSRU (10)
Psychiatry nurse practitioner – nurse consultation	£7.14	Per attendance	PSSRU (10)
Follow-up call about endoscopy	£15.47	Per attendance	PSSRU (10)
Clinical pharmacist phone call	£54.00	Per attendance	PSSRU (10)
Crisis community psychiatric nurse call	£55.00	Per attendance	PSSRU (10)
Mindfulness-based cognitive therapy	£75.00	Per attendance	PSSRU (10)
Radiology	£203.72	Per attendance	NHS reference costs (11)
Mindfulness group	£97.31	Per attendance	NHS reference costs (11)
Pain clinic	£238.26	Per attendance	NHS reference costs (11)
Psychiatrist	£266.77	Per attendance	NHS reference costs (11)
Rheumatology nurse telephone call	£6.01	Per attendance	PSSRU (10)
Other costs: Community-based services			
Crisis team	£66.00	Per attendance	PSSRU (10)
Mind group	£25.00	Per attendance	PSSRU (10)
Young women's outreach service	£25.00	Per attendance	PSSRU (10)
Community mental health team	£25.00	Per attendance	PSSRU (10)
Halfday course at the 'workshop' in Bulwell	£100.00	Per attendance	PSSRU (10)
Chronic fatigue clinic	£325.92	Per attendance	NHS reference costs (11)
Listening place	£25.00	Per attendance	PSSRU (10)
Psychology group work	£97.31	Per attendance	NHS reference costs (11)
Touchpoint Barnett	£155.00	Per attendance	PSSRU (10)

TABLE 34 Unit costs (*continued*)

Resource category	Cost	Unit	Source
Anger management and Anxiety management	£115.22	Per attendance	NHS reference costs (11)
Children's first worker	£25.00	Per attendance	PSSRU (10)
Other costs: primary care			
Care co-ordinator	£33.00	Per attendance	PSSRU (10)
Community psychiatric nurse call	£5.67	Per attendance	PSSRU (10)
Community mental health team	£66.00	Per attendance	PSSRU (10)
Crisis team	£66.00	Per attendance	PSSRU (10)
Family worker	£46.00	Per attendance	PSSRU (10)
GP – phone consultation	£8.67	Per attendance	PSSRU (10)
Link worker – social prescribing	£33.58	Per attendance	PSSRU (10)
Mental health support worker (home visit)	£51.84	Per attendance	PSSRU (10)
Peer support worker	£25.00	Per attendance	PSSRU (10)
Phlebotomist	£39.23	Per attendance	PSSRU (10)
Physio	£39.00	Per attendance	PSSRU (10)
Practice nurse phone calls	£4.59	Per attendance	PSSRU (10)
Specialist diabetic nurse	£82.49	Per attendance	NHS reference costs (11)
Support worker	£25.00	Per attendance	PSSRU (10)
Day care centre occupational therapist phone call	£115.22	Per attendance	NHS reference costs (11)
Mindfulness-based CBT group	£20.83	Per attendance	PSSRU (10)
Occupational health doctor	£120.00	Per attendance	PSSRU (10)
Advanced nurse practitioner	£55.00	Per attendance	PSSRU (10)
Counsellor phone call	£54.00	Per attendance	PSSRU (10)
Diabetes clinic	£180.76	Per attendance	NHS reference costs (11)
Framework weekly home visits	£11.25	Per attendance	PSSRU (10)
IAPT therapist	£113.78	Per attendance	NHS reference costs (11)
Mindfulness group	£97.31	Per attendance	NHS reference costs (11)
Occupational health QMC	£117.66	Per attendance	NHS reference costs (11)
Online DBT group therapy	£97.31	Per attendance	PSSRU (10)
Out-of-hour services	£39.23	Per attendance	PSSRU (10)
Phlebotomist/HCA	£39.23	Per attendance	PSSRU (10)
Psychiatrist	£266.77	Per attendance	PSSRU (10)
Support worker –telephone	£25.00	Per attendance	PSSRU (10)
Therapist	£115.23	Per attendance	NHS reference costs (11)
Victim support service	£66.00	Per attendance	NHS reference costs (11)
Counsellor	£54.00	Per attendance	PSSRU (10)

continued

TABLE 34 Unit costs (*continued*)

Resource category	Cost	Unit	Source
Counsellor (sexual violence)	£129.82	Per attendance	NHS reference costs (11)
Pain management clinic	£238.26	Per attendance	NHS reference costs (11)
Walk-in centre	£52.58	Per attendance	NHS reference costs (11)
Advanced clinical practitioner telephone appointment	£88.00	Per attendance	PSSRU (10)
Community care worker	£25.00	Per attendance	PSSRU (10)
Dietician	£97.33	Per attendance	NHS reference costs (11)
Domestic violence support worker (telephone)	£19.60	Per attendance	NHS reference costs (11)
Pharmacist	£54.00	Per attendance	PSSRU (10)
Sexual health clinic	£76.00	Per attendance	NHS reference costs (11)
Support worker home visits	£33.00	Per attendance	PSSRU (10)
Work occupational health phone call	£19.60	Per attendance	NHS reference costs (11)
Phlebotomist at GP	£39.23	Per attendance	PSSRU (10)
Travel costs			
Car mile	£0.45	Per mile	Royal college of nursing(14)

A&E, accident and emergency.
a Cost per day derived by dividing NHS cost of stay by average number of bed days reported by the King's fund (29).

Appendix 2 Clinical efficacy results supplemental information

FIGURE 18 Overall recruitment per month.

TABLE 35 Listings of major protocol deviations that fall under the category of 'Receiving wrong treatment as per randomised allocation'

Trial ID	Treatment	Deviation date	Deviation reason	Additional details
BRI1031	cgiTBS	7 October 2019	Participant received incorrect study treatment	When commencing treatment, the nurse had not altered the settings on the magstim so a train of the incorrect treatment was administered. The machine was stopped and altered accordingly and the correct treatment was carried out. The participant was fine with this and did not notice anything untoward
BRI1033	rTMS	23 October 2019	Participant received incorrect study treatment	Magstim horizon set to 40% of MT for first treatment (as per SOP), however the machine delivered at a higher level. The machine was paused and recalibrated. The treatment was delivered without any issues after this. The 'power' box on the screen of the magstim was yellow when the machine seemed to deliver at a higher level than indicated. It went back to being light grey/blue after the machine was paused and recalibrated. The machine had been set up the same was as usual; the box normally changes from yellow to light grey/blue when the lower dose is selected. However, on this occasion it did not
BRI1067	cgiTBS	7 January 2021	Participant received incorrect study treatment	Treatment was mistakenly delivered incorrectly. The settings on the magstim horizon were incorrect, and a little under 6 trains of theta burst stimulations were delivered with a shorter gap than is specified in the treatment CRF. Staff spotted this issue and stopped the treatment to rectify this problem; participant was informed. A total of 170 pulses were delivered in this way before staff spotted this. The machine was then set correctly, and the full treatment was delivered in accordance with treatment CRF. The participant reported no side effects after treatment or the following day. The PI was informed; no concerns were raised and no further action advised

continued

TABLE 35 Listings of major protocol deviations that fall under the category of 'Receiving wrong treatment as per randomised allocation' (*continued*)

Trial ID	Treatment	Deviation date	Deviation reason	Additional details
BRI3015	rTMS	25 September 2019	Participant received incorrect study treatment	The participant's target was incorrect, so treatment was restarted at correct target
BRI3018	cgiTBS	22 October 2019	Participant received incorrect study treatment	Treatment was delivered to incorrect co-ordinates for 1 session. The participant was offered 1 extra session
BRI3028	cgiTBS	10 January 2020	Participant received incorrect study treatment	Treatment power was set at 1% lower than required by mistake. The MT went down at session 6, so treatment power was correct from session 6 onwards
BRI3037	cgiTBS	14 October 2020	Participant received incorrect study treatment	The treatment was started at incorrect power (lower). Extra stimulations was added at the end to compensate for this
BRI3045	cgiTBS	14 June 2021	Participant received incorrect study treatment	
BRI4001	rTMS	1 April 2019	Participant received incorrect study treatment	The treatment delivered was not in the correct place as co-ordinates were not uploaded correctly. Received 20 sessions in the wrong place
BRI4002	cgiTBS	30 April 2019	Participant received incorrect study treatment	The treatment delivered was not in the correct place as the co-ordinates were not uploaded correctly
BRI4003	cgiTBS	7 May 2019	Participant received incorrect study treatment	The treatment delivered was not in the correct place as the coiordinates were not uploaded correctly. A total of 11 sessions were delivered in the wrong place
BRI4004	rTMS	13 May 2019	Participant received incorrect study treatment	The treatment delivered was not in the correct place as the co-ordinates were not uploaded correctly. A total of 7 sessions were delivered in the wrong place
BRI4020	rTMS	13 December 2019	Participant received incorrect study treatment	
BRI4024	cgiTBS	31 January 2020	Participant received incorrect study treatment	The MRI co-ordinates were not uploaded properly – the treatment was not delivered at correct co-ordinates (wrong data in file) on 31 January 20 only. The error on treatment day 1 was identified and subsequent treatments delivered correctly

TABLE 35 Listings of major protocol deviations that fall under the category of 'Receiving wrong treatment as per randomised allocation' (*continued*)

Trial ID	Treatment	Deviation date	Deviation reason	Additional details
BRI4034	rTMS	14 December 2020	Participant received incorrect study treatment	An incorrect initial treatment dose was administered for 20 trains at 79%. Subsequent trains were administered at the correct dose at 66%
BRI4035	cgiTBS	3 February 2021	Participant received incorrect study treatment	The first two trains were delivered at 52% instead of 53%. The last three trains delivered at correct 53% power
BRI4036	cgiTBS	19 April 2021	Participant received incorrect study treatment	The co-ordinates were not uploaded correctly to Stimguide. Therefore the patient received TMS treatment in the wrong location from 19 April 2021 to 18 May 2021 (20 sessions in total)
BRI4037	rTMS	29 April 2021	Participant received incorrect study treatment	The co-ordinates were not uploaded correctly to Stimguide. Therefore the patient received TMS treatment in an incorrect location from 29 April 2021 to 24 May 2021 (14 sessions in total)
BRI4038	rTMS	17 May 2021	Participant received incorrect study treatment	The co-ordinates were not uploaded correctly to Stimguide. Therefore the patient received TMS treatment in incorrect location from 17 May 2021 to 24 May 2021 (4 sessions in total)
BRI4039	cgiTBS	17 May 2021	Participant received incorrect study treatment	The co-ordinates were not correctly uploaded to Stimguide. Therefore the patient received TMS in an incorrect location from 17 May 2021 to 24 May 2021 (6 sessions in total)
BRI4040	cgiTBS	24 May 2021	Participant received incorrect study treatment	The co-ordinates were not uploaded correctly to Stimguide. Therefore the patient received TMS treatment in an incorrect location on 24 May 2021 (1 session)
BRI4047	rTMS	20 October 2021	Participant received incorrect study treatment	The co-ordinates were not uploaded to Stimguide correctly. The patient therefore received treatment in the wrong location on 3 sessions dated: 20 October 2021, 25 October 2021 and 26 October 2021

TABLE 36 Breakdown of minor protocol deviation: reasons by deviation type and number of participants affected by deviation type

	rTMS		cgiTBS		Overall	
Minor protocol deviation reason	***p***	***N***	***p***	***N***	***p***	***N***
Time window deviations at any of the visits listed below[a]:						
8-week follow-up, *n* (%)	12 (5.1%)	12 (9.4%)	11 (6.3%)	11 (8.6%)	23 (5.6%)	23 (9.0%)
16-week follow-up, *n* (%)	15 (6.4%)	15 (11.8%)	12 (6.9%)	12 (9.4%)	27 (6.6%)	27 (10.6%)

continued

TABLE 36 Breakdown of minor protocol deviation: reasons by deviation type and number of participants affected by deviation type (*continued*)

	rTMS		cgiTBS		Overall	
Minor protocol deviation reason	***p***	***N***	***p***	***N***	***p***	***N***
26-week follow-up, *n* (%)	16 (6.8%)	16 (12.6%)	16 (9.2%)	16 (12.5%)	32 (7.8%)	32 (12.5%)
Non-compliance with treatment						
Treatment adjusted as participant could not tolerate[b], *n* (%)	59 (25.1%)	29 (22.8%)	15 (8.6%)	10 (7.8%)	74 (18.1%)	39 (15.3%)
Visit/assessment not performed as per protocol						
Did not attend/unsuccessful contact, *n* (%)	33 (14.0%)	25 (19.7%)	21 (12.1%)	16 (12.5%)	54 (13.2%)	41 (16.1%)
Attended/contacted out of time frame[c], *n* (%)	63 (26.8%)	46 (36.2%)	56 (32.2%)	39 (30.5%)	119 (29.1%)	85 (33.3%)
Component of assessment/procedure not done[d], *n* (%)	37 (15.7%)	26 (20.5%)	43 (24.7%)	29 (22.7%)	80 (19.6%)	55 (21.6%)
Overall, *n* (%)	235 (100%)	85 (66.9%)	174 (100%)	74 (57.8%)	409 (100%)	159 (62.4%)

p, number of protocol deviations by deviation type, *N*, number participants affected per deviation type.
a Each of the follow-up visits had a ± 7 day time window. The number of deviations corresponding to each follow-up time point was calculated out of participants who attended their visit.
b This includes instances where the TMS site of stimulation was moved away from the co-ordinates to improve comfort in accordance with the TMS SOP.
c These protocol deviations were reported by sites to the LCTU.
d This does not include the HDRS-17 assessments (primary outcome data).

Note
- While missing secondary outcome assessments is classed as a minor protocol deviation in the SAP, this was not captured in the protocol deviations CRF. However, this may have been recorded as a protocol deviation related to a component of assessment/procedure not done.
- Minor deviations related to time window deviations were not captured in the protocol deviations CRF. They were therefore derived using other parts of the data extracted from MACRO.
- Please note the percentage corresponding to the number of participants affected per minor deviation type (including the total for each treatment arm and overall) was calculated out of the total number of participants randomised.

TABLE 37 HDRS-17 descriptive statistics for the sensitivity and moderator analyses

		Baseline		8 weeks		16 weeks		26 weeks	
HDRS-17 score		**rTMS**	**cgiTBS**	**rTMS**	**cgiTBS**	**rTMS**	**cgiTBS**	**rTMS**	**cgiTBS**
Sensitivity analyses									
Primary analysis under MNAR assumption	*N*	127	128	127	128	127	128	127	128
	Mean (SD)	23.9 (4.7)	22.9 (4.7)	15.8 (7.3)	14.6 (6.2)	16.1 (7.5)	15.2 (7.3)	16.5 (7.9)	14.9 (6.9)
Pre-/post-COVID-19 period									
Pre-COVID 19	*N*	35	36						
	Mean (SD)	24.7 (5.3)	23.2 (5.3)						
Post-COVID 19	*N*	92	92						
	Mean (SD)	23.5 (4.4)	22.9 (4.5)						

TABLE 37 HDRS-17 descriptive statistics for the sensitivity and moderator analyses (*continued*)

		Baseline		8 weeks		16 weeks		26 weeks	
HDRS-17 score		**rTMS**	**cgiTBS**	**rTMS**	**cgiTBS**	**rTMS**	**cgiTBS**	**rTMS**	**cgiTBS**
Centre as random effect[a]									
Nottingham	*N*	56	57	56	57	56	57	56	57
	Mean (SD)	23.9 (4.9)	22.3 (4.7)	16.5 (0.9)	16.0 (0.9)	15.9 (1.2)	17.1 (1.0)	16.0 (1.2)	15.9 (0.9)
Northampton	*N*	14	15	14	15	14	15	14	15
	Mean (SD)	25.9 (4.7)	25.9 (3.1)	11.2 (2.4)	11.5 (2.0)	12.3 (2.1)	11.1 (2.1)	13.5 (2.7)	8.9 (1.8)
London	*N*	30	29	30	29	30	29	30	29
	Mean (SD)	21.9 (3.6)	21.2 (4.0)	15.5 (1.3)	13.3 (1.2)	17.3 (1.4)	13.6 (1.5)	17.4 (1.6)	16.1 (1.8)
Newcastle	*N*	23	24	23	24	23	24	23	24
	Mean (SD)	23.7 (4.0)	24.5 (5.4)	14.9 (1.9)	13.6 (1.7)	15.5 (1.8)	16.3 (1.8)	14.5 (1.9)	15.6 (1.9)
Oldham	*N*	4	3	4	3	4	3	4	3
	Mean (SD)	30 (6.1)	25.3 (3.2)	24.6 (5.0)	20 (6.8)	24.8 (5.1)	9.7 (2.7)	29.9 (4.8)	12.4 (5.8)
Moderator analyses									
Baseline HDRS-17, baseline MGHS score, Age, number of TMS sessions and GAD-7	*N*	118	115	112	111	112	112	102	104
	Mean (SD)	23.9 (4.8)	22.6 (4.6)	15.8 (7.8)	14.4 (6.6)	16.1 (8.0)	15.1 (7.8)	16.5 (8.8)	14.6 (7.7)
Baseline CTQ	*N*	111	108	106	105	105	105	96	98
	Mean (SD)	23.7 (4.7)	22.5 (4.6)	15.9 (7.9)	14.3 (6.6)	15.7 (8.0)	14.9 (7.7)	16.2 (8.7)	14.5 (7.7)

a This summary statistics were calculated using the ITT population and multiple imputation.

TABLE 38 Breakdown of responder rates by treatment group and category of treatment resistance

	rTMS	cgiTBS	Total
Category of treatment resistance: Low			
Responder at 8 weeks	13 (36.1%)	13 (37.1%)	26 (36.6%)
Non-responder at 8 weeks	23 (63.9%)	22 (62.9%)	45 (63.4%)
Category of treatment resistance: Medium			
Responder at 8 weeks	11 (36.7%)	15 (44.1%)	26 (40.6%)
Non-responder at 8 weeks	19 (63.3%)	19 (55.9%)	38 (59.4%)
Category of treatment resistance: High			
Responder at 8 weeks	11 (23.9%)	11 (26.2%)	22 (25.0%)
Non-responder at 8 weeks	35 (76.1%)	31 (73.8%)	66 (75.0%)

continued

TABLE 38 Breakdown of responder rates by treatment group and category of treatment resistance (*continued*)

	rTMS	cgiTBS	Total
Category of treatment resistance: Low			
Responder at 16 weeks	16 (44.4%)	18 (48.6%)	34 (46.6%)
Non-responder at 16 weeks	20 (55.6%)	19 (51.4%)	39 (53.4%)
Category of treatment resistance: Medium			
Responder 16 weeks	11 (35.5%)	11 (33.3%)	22 (34.4%)
Non-responder 16 weeks	20 (64.5%)	22 (66.7%)	42 (65.6%)
Category of treatment resistance: High			
Responder at 16 weeks	11 (24.4%)	10 (23.8%)	21 (24.1%)
Non-responder at 16 weeks	34 (75.6%)	32 (76.2%)	66 (75.9%)
Category of treatment resistance: Low			
Responder at 26 weeks	16 (47.1%)	14 (41.2%)	30 (44.1%)
Non-responder at 26 weeks	18 (52.9%)	20 (58.8%)	38 (55.9%)
Category of treatment resistance: Medium			
Responder at 26 weeks	9 (33.3%)	13 (43.3%)	22 (38.6%)
Non-responder at 26 weeks	18 (66.7%)	17 (56.7%)	35 (61.4%)
Category of treatment resistance: High			
Responder at 26 weeks	6 (14.6%)	9 (22.5%)	15 (18.5%)
Non-responder at 26 weeks	35 (85.4%)	31 (77.5%)	66 (81.5%)

TABLE 39 Pearson correlation coefficients for the relation between change in HDRS score vs. the change in each cognition and IIV variable from baseline to week 16

Variables	1
1. HDRS-17 change	–
2. CRT change	0.218[a]
3. *N*-back change	−0.024
4. DSST change	−0.180[b]
5. TMT change	−0.033
6. PDQ-5-D change	0.484[a]
7. iSD change	0.120
8. CoV change	0.005
9. Mu change	0.310[a]
10. Tau change	−0.021
11. Sigma change	0.309[a]

a Correlation is significant at the 0.01 level (two-tailed).
b Correlation is significant at the 0.05 level (two-tailed).

TABLE 40 Patient impression of change after TMS sessions

Patient impression of change after each TMS session		rTMS	cgiTBS	Total
TMS session 1				
Experience with the TMS treatment received so far	Somewhat worse, *n* (%)	2 (1.6%)	0 (0.0%)	2 (0.8%)
	Just the same, *n* (%)	119 (94.4%)	120 (93.8%)	239 (94.1%)
	Somewhat better, *n* (%)	4 (3.2%)	8 (6.3%)	12 (4.7%)
	Response not available, *n* (%)	1 (0.8%)	0 (0.0%)	1 (0.4%)
TMS session 2				
Experience with the TMS treatment received so far	Much worse, *n* (%)	1 (0.8%)	0 (0.0%)	1 (0.4%)
	Somewhat worse, *n* (%)	0 (0.0%)	3 (2.4%)	3 (1.2%)
	Just the same, *n* (%)	112 (91.1%)	105 (84.0%)	217 (87.5%)
	Somewhat better, *n* (%)	10 (8.1%)	17 (13.6%)	27 (10.9%)
TMS session 3				
Experience with the TMS treatment received so far	Much worse, *n* (%)	1 (0.8%)	1 (0.8%)	2 (0.8%)
	Somewhat worse, *n* (%)	2 (1.6%)	2 (1.6%)	4 (1.6%)
	Just the same, *n* (%)	105 (86.1%)	106 (83.5%)	211 (84.7%)
	Somewhat better, *n* (%)	14 (11.5%)	15 (11.8%)	29 (11.6%)
	Much better, *n* (%)	0 (0.0%)	2 (1.6%)	2 (0.8%)
	Response not available, *n* (%)	0 (0.0%)	1 (0.8%)	1 (0.4%)
TMS session 4				
Experience with the TMS treatment received so far	Much worse, *n* (%)	1 (0.8%)	0 (0.0%)	1 (0.4%)
	Somewhat worse, *n* (%)	5 (4.1%)	6 (4.7%)	11 (4.4%)
	Just the same, *n* (%)	102 (82.9%)	97 (76.4%)	199 (79.6%)
	Somewhat better, *n* (%)	15 (12.2%)	22 (17.3%)	37 (14.8%)
	Much better, *n* (%)	0 (0.0%)	2 (1.6%)	2 (0.8%)
TMS session 5				
Experience with the TMS treatment received so far	Much worse, *n* (%)	1 (0.8%)	1 (0.8%)	2 (0.8%)
	Somewhat worse, *n* (%)	5 (4.1%)	9 (7.1%)	14 (5.6%)
	Just the same, *n* (%)	93 (75.6%)	85 (66.9%)	178 (71.2%)
	Somewhat better, *n* (%)	24 (19.5%)	30 (23.6%)	54 (21.6%)
	Much better, *n* (%)	0 (0.0%)	2 (1.6%)	2 (0.8%)
TMS session 6				
Experience with the TMS treatment received so far	Much worse, *n* (%)	1 (0.8%)	0 (0.0%)	1 (0.4%)
	Somewhat worse, *n* (%)	4 (3.3%)	8 (6.3%)	12 (4.8%)

continued

TABLE 40 Patient impression of change after TMS sessions (*continued*)

Patient impression of change after each TMS session		rTMS	cgiTBS	Total
	Just the same, *n* (%)	87 (71.3%)	80 (63.0%)	167 (67.1%)
	Somewhat better, *n* (%)	30 (24.6%)	37 (29.1%)	67 (26.9%)
	Much better, *n* (%)	0 (0.0%)	2 (1.6%)	2 (0.8%)
TMS session 7				
Experience with the TMS treatment received so far	Much worse, *n* (%)	1 (0.8%)	0 (0.0%)	1 (0.4%)
	Somewhat worse, *n* (%)	3 (2.5%)	6 (4.7%)	9 (3.6%)
	Just the same, *n* (%)	86 (70.5%)	73 (57.5%)	159 (63.9%)
	Somewhat better, *n* (%)	31 (25.4%)	45 (35.4%)	76 (30.5%)
	Much better, *n* (%)	1 (0.8%)	3 (2.4%)	4 (1.6%)
TMS session 8				
Experience with the TMS treatment received so far	Much worse, *n* (%)	1 (0.8%)	0 (0.0%)	1 (0.4%)
	Somewhat worse, *n* (%)	4 (3.3%)	4 (3.2%)	8 (3.2%)
	Just the same, *n* (%)	81 (66.4%)	69 (54.8%)	150 (60.5%)
	Somewhat better, *n* (%)	35 (28.7%)	48 (38.1%)	83 (33.5%)
	Much better, *n* (%)	1 (0.8%)	5 (4.0%)	6 (2.4%)
TMS session 9				
Experience with the TMS treatment received so far	Much worse, *n* (%)	1 (0.8%)	0 (0.0%)	1 (0.4%)
	Somewhat worse, *n* (%)	5 (4.1%)	2 (1.6%)	7 (2.8%)
	Just the same, *n* (%)	69 (56.6%)	67 (53.6%)	136 (55.1%)
	Somewhat better, *n* (%)	44 (36.1%)	51 (40.8%)	95 (38.5%)
	Much better, *n* (%)	2 (1.6%)	5 (4.0%)	7 (2.8%)
	Response not available, *n* (%)	1 (0.8%)	0 (0.0%)	1 (0.4%)
TMS session 10				
Experience with the TMS treatment received so far	Much worse, *n*(%)	1 (0.8%)	1 (0.8%)	2 (0.8%)
	Somewhat worse, *n*(%)	2 (1.7%)	4 (3.2%)	6 (2.4%)
	Just the same, *n* (%)	73 (60.3%)	59 (47.6%)	132 (53.9%)
	Somewhat better, *n* (%)	40 (33.1%)	53 (42.7%)	93 (38.0%)
	Much better, *n* (%)	5 (4.1%)	7 (5.6%)	12 (4.9%)
TMS session 11				
Experience with the TMS treatment received so far	Much worse, *n* (%)	1 (0.8%)	1 (0.8%)	2 (0.8%)
	Somewhat worse, *n* (%)	3 (2.5%)	5 (4.0%)	8 (3.3%)
	Just the same, *n* (%)	66 (54.5%)	55 (44.4%)	121 (49.4%)
	Somewhat better, *n* (%)	45 (37.2%)	55 (44.4%)	100 (40.8%)
	Much better, *n* (%)	6 (5.0%)	8 (6.5%)	14 (5.7%)

TABLE 40 Patient impression of change after TMS sessions (*continued*)

Patient impression of change after each TMS session		rTMS	cgiTBS	Total
TMS session 12				
Experience with the TMS treatment received so far	Somewhat worse, *n* (%)	7 (5.8%)	4 (3.3%)	11 (4.5%)
	Just the same, *n* (%)	64 (52.9%)	55 (45.1%)	119 (49.0%)
	Somewhat better, *n* (%)	43 (35.5%)	53 (43.4%)	96 (39.5%)
	Much better, *n* (%)	7 (5.8%)	10 (8.2%)	17 (7.0%)
TMS session 13				
Experience with the TMS treatment received so far	Much worse, *n* (%)	1 (0.8%)	0 (0.0%)	1 (0.4%)
	Somewhat worse, *n* (%)	6 (5.0%)	6 (4.9%)	12 (4.9%)
	Just the same, *n* (%)	59 (48.8%)	56 (45.9%)	115 (47.3%)
	Somewhat better, *n* (%)	48 (39.7%)	48 (39.3%)	96 (39.5%)
	Much better, *n* (%)	7 (5.8%)	12 (9.8%)	19 (7.8%)
TMS session 14				
Experience with the TMS treatment received so far	Much worse, *n* (%)	2 (1.7%)	0 (0.0%)	2 (0.8%)
	Somewhat worse, *n* (%)	5 (4.1%)	5 (4.1%)	10 (4.1%)
	Just the same, *n* (%)	59 (48.8%)	56 (45.9%)	115 (47.3%)
	Somewhat better, *n* (%)	48 (39.7%)	49 (40.2%)	97 (39.9%)
	Much better, *n* (%)	7 (5.8%)	12 (9.8%)	19 (7.8%)
TMS session 15				
Experience with the TMS treatment received so far	Much worse, *n* (%)	2 (1.7%)	0 (0.0%)	2 (0.8%)
	Somewhat worse, *n* (%)	5 (4.1%)	5 (4.1%)	10 (4.1%)
	Just the same, *n* (%)	50 (41.3%)	51 (42.1%)	101 (41.7%)
	Somewhat better, *n* (%)	52 (43.0%)	56 (46.3%)	108 (44.6%)
	Much better, *n* (%)	12 (9.9%)	9 (7.4%)	21 (8.7%)
TMS session 16				
Experience with the TMS treatment received so far	Much worse, *n* (%)	1 (0.8%)	0 (0.0%)	1 (0.4%)
	Somewhat worse, *n* (%)	4 (3.3%)	4 (3.3%)	8 (3.3%)
	Just the same, *n* (%)	48 (39.7%)	50 (41.3%)	98 (40.5%)
	Somewhat better, *n* (%)	53 (43.8%)	58 (47.9%)	111 (45.9%)
	Much better, *n* (%)	15 (12.4%)	9 (7.4%)	24 (9.9%)
TMS session 17				
Experience with the TMS treatment received so far	Much worse, *n* (%)	1 (0.8%)	0 (0.0%)	1 (0.4%)
	Somewhat worse, *n* (%)	4 (3.3%)	4 (3.3%)	8 (3.3%)

continued

TABLE 40 Patient impression of change after TMS sessions (*continued*)

Patient impression of change after each TMS session		rTMS	cgiTBS	Total
	Just the same, *n* (%)	52 (43.0%)	45 (37.2%)	97 (40.1%)
	Somewhat better, *n* (%)	49 (40.5%)	60 (49.6%)	109 (45.0%)
	Much better, *n* (%)	15 (12.4%)	12 (9.9%)	27 (11.2%)
TMS session 18				
Experience with the TMS treatment received so far	Much worse, *n* (%)	1 (0.8%)	0 (0.0%)	1 (0.4%)
	Somewhat worse, *n* (%)	2 (1.7%)	5 (4.2%)	7 (2.9%)
	Just the same, *n* (%)	47 (39.2%)	48 (40.0%)	95 (39.6%)
	Somewhat better, *n* (%)	53 (44.2%)	50 (41.7%)	103 (42.9%)
	Much better, *n* (%)	17 (14.2%)	17 (14.2%)	34 (14.2%)
TMS session 19				
Experience with the TMS treatment received so far	Somewhat worse, *n* (%)	4 (3.4%)	4 (3.4%)	8 (3.4%)
	Just the same, *n* (%)	41 (34.7%)	43 (36.1%)	84 (35.4%)
	Somewhat better, *n* (%)	52 (44.1%)	51 (42.9%)	103 (43.5%)
	Much better, *n* (%)	21 (17.8%)	21 (17.6%)	42 (17.7%)
TMS session 20				
Experience with the TMS treatment received so far	Much worse, *n* (%)	1 (0.9%)	0 (0.0%)	1 (0.4%)
	Somewhat worse, *n* (%)	2 (1.7%)	5 (4.2%)	7 (3.0%)
	Just the same, *n* (%)	38 (32.5%)	36 (30.0%)	74 (31.2%)
	Somewhat better, *n* (%)	53 (45.3%)	58 (48.3%)	111 (46.8%)
	Much better, *n* (%)	23 (19.7%)	21 (17.5%)	44 (18.6%)

TABLE 41 Patient-rated acceptability measure at follow-up

Patient-rated acceptability at 8-, 16- and 26-week follow-up		rTMS	cgiTBS	Total
8-week follow-up				
Overall, how acceptable was the TMS treatment?	Unacceptable. Negative effects outweigh benefits, *n* (%)	3 (2.7%)	2 (1.8%)	5 (2.3%)
	Unacceptable. Negative effects and benefits are about equal, *n* (%)	6 (5.4%)	2 (1.8%)	8 (3.6%)
	Neutral, unsure or waiting to find out, *n* (%)	30 (27.0%)	31 (27.9%)	61 (27.5%)
	Acceptable. Negative effects and benefits are about equal, *n* (%)	26 (23.4%)	22 (19.8%)	48 (21.6%)
	Acceptable. Benefit effects outweigh the negative effects, *n* (%)	46 (41.4%)	54 (48.6%)	100 (45.0%)

TABLE 41 Patient-rated acceptability measure at follow-up (*continued*)

Patient-rated acceptability at 8-, 16- and 26-week follow-up		rTMS	cgiTBS	Total
16-week follow-up				
Overall, how acceptable was the TMS treatment?	Unacceptable. Negative effects outweigh benefits, *n* (%)	3 (2.7%)	1 (0.9%)	4 (1.8%)
	Unacceptable. Negative effects and benefits are about equal, *n* (%)	2 (1.8%)	1 (0.9%)	3 (1.4%)
	Neutral, unsure or waiting to find out, *n* (%)	33 (29.7%)	29 (26.4%)	62 (28.1%)
	Acceptable. Negative effects and benefits are about equal, *n* (%)	25 (22.5%)	31 (28.2%)	56 (25.3%)
	Acceptable. Benefit effects outweigh the negative effects, *n* (%)	48 (43.2%)	48 (43.6%)	96 (43.4%)
26-week follow-up				
Overall, how acceptable was the TMS treatment?	Unacceptable. Negative effects outweigh benefits, *n* (%)	4 (4.0%)	3 (2.9%)	7 (3.4%)
	Unacceptable. Negative effects and benefits are about equal, *n* (%)	3 (3.0%)	2 (1.9%)	5 (2.5%)
	Neutral, unsure or waiting to find out, *n* (%)	22 (22.0%)	24 (23.3%)	46 (22.7%)
	Acceptable. Negative effects and benefits are about equal, *n* (%)	22 (22.0%)	24 (23.3%)	46 (22.7%)
	Acceptable. Benefit effects outweigh the negative effects, *n* (%)	49 (49.0%)	50 (48.5%)	99 (48.8%)

TABLE 42 Outcome assessor predictions of treatment allocation

	8 weeks		16 weeks		26 weeks	
	rTMS	cgiTBS	rTMS	cgiTBS	rTMS	cgiTBS
Don't know	94 (83.9%)	95 (85.6%)	90 (80.4%)	88 (78.6%)	77 (75.5%)	76 (73.1%)
Correct guess	9 (8.0%)	6 (5.4%)	15 (13.4%)	11 (9.8%)	17 (16.7%)	17 (16.3%)
Incorrect guess	9 (8.0%)	10 (9.0%)	7 (6.3%)	12 (10.7%)	8 (7.8%)	11 (10.6%)
Unobtainable	–	–	0 (0%)	1 (0.9%)	–	–

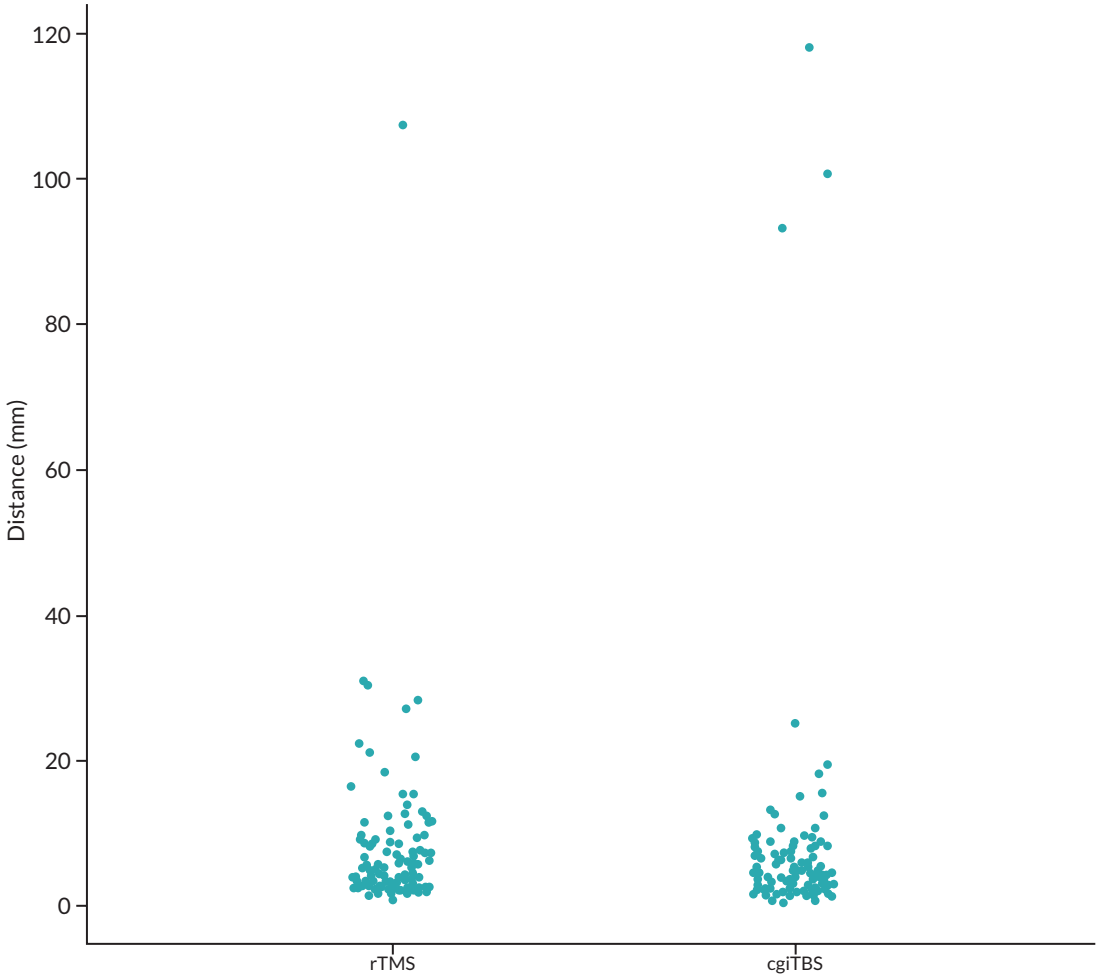

FIGURE 19 Euclidean distance between target and first session data.

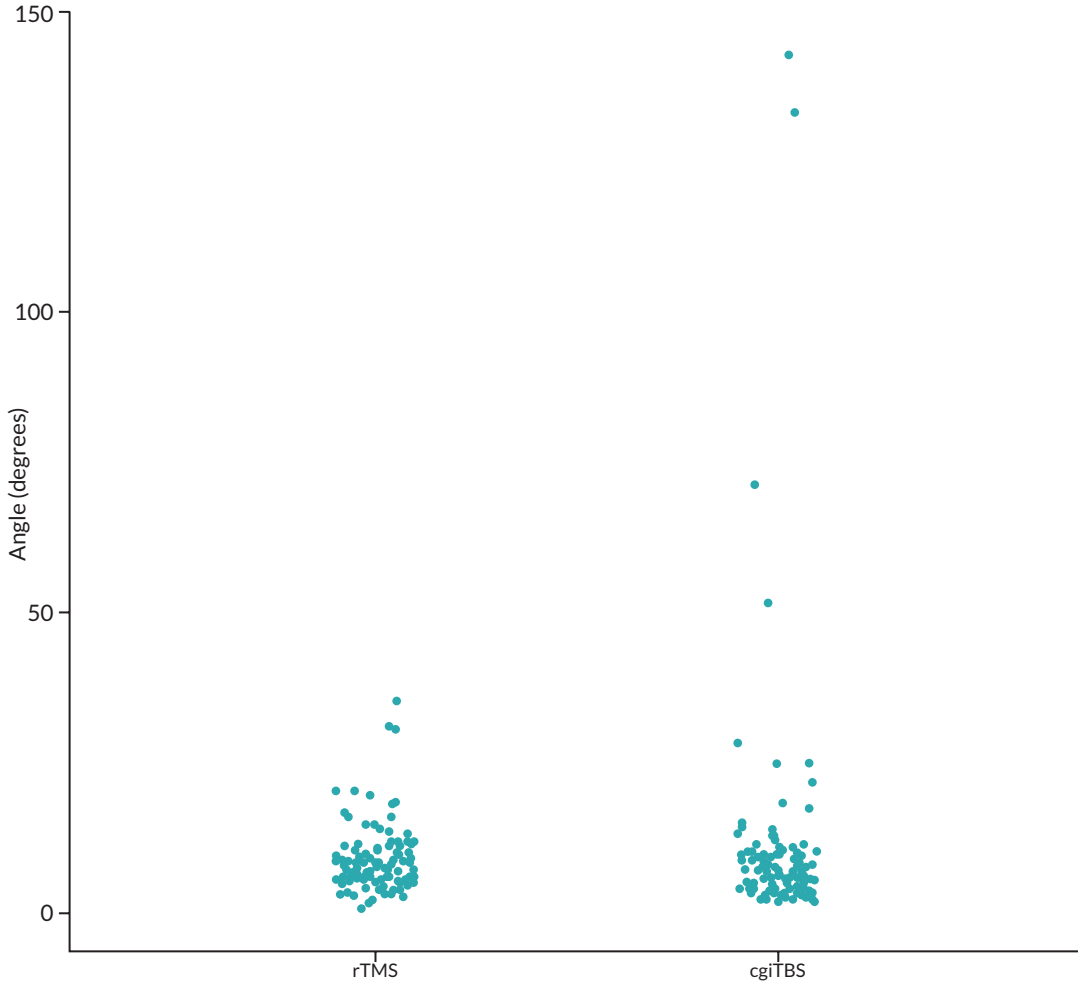

FIGURE 20 Angular coil orientation distance between target and first session data.

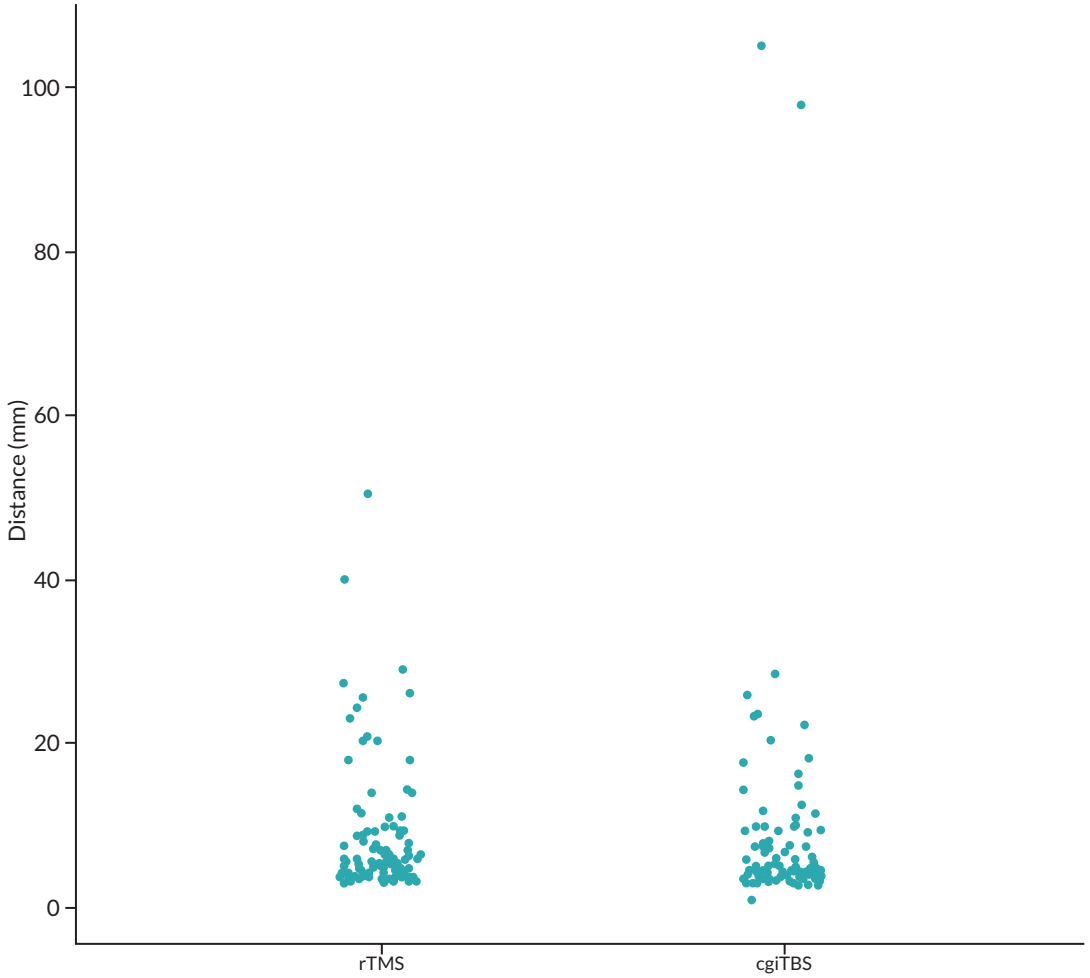

FIGURE 21 Mean Euclidean distance between first session data and each subsequent session data.

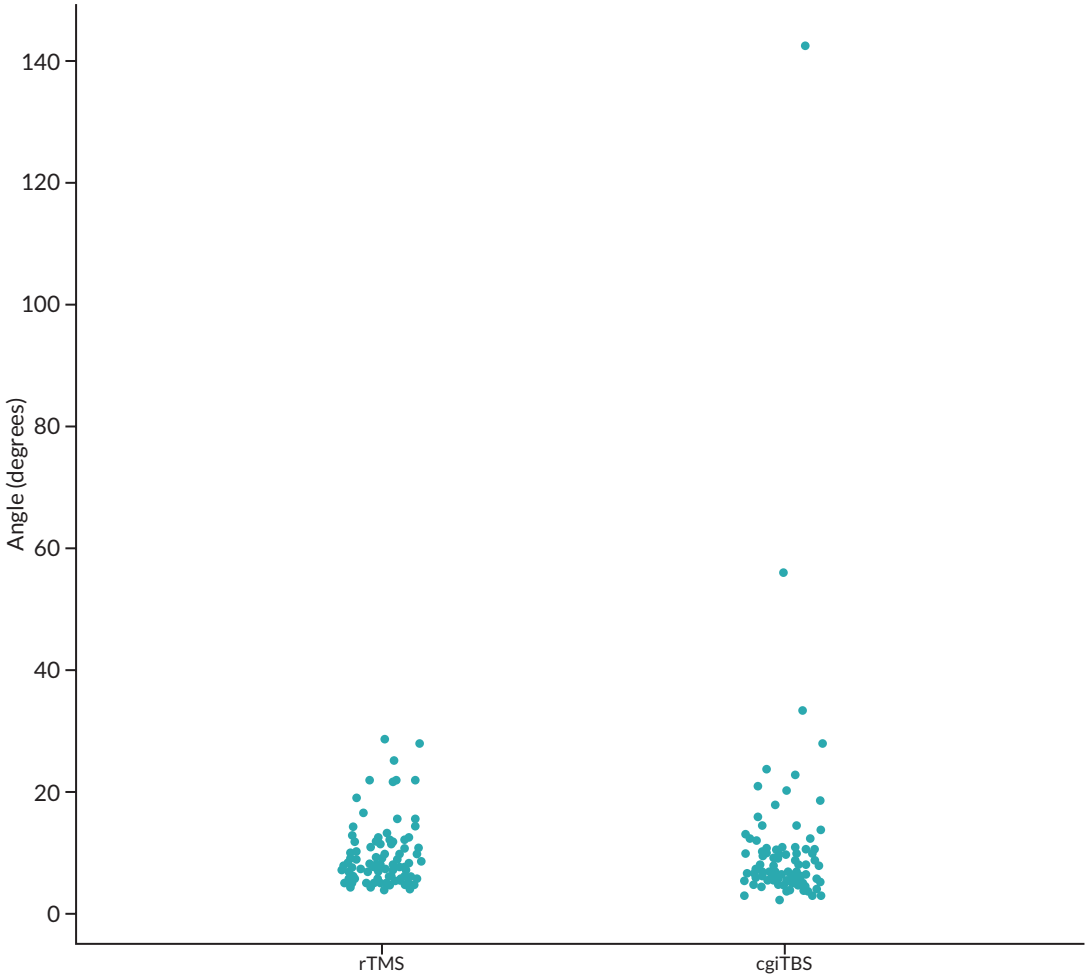

FIGURE 22 Mean angular coil orientation distance between first session data and each subsequent session data.

Appendix 3 Safety, acceptability, facilitator and barriers results supplemental information

TABLE 43 Number of participants with adverse events

	rTMS	cgiTBS	Overall
Randomised participants, *n* (%)	127 (100%)	128 (100%)	255 (100%)
Participants with AEs, *n* (%)	105 (83.3%)	99 (77.3%)	204 (80.3%)
Participants with no AEs, *n* (%)	21 (16.7%)	29 (22.7%)	50 (19.7%)
Participants with 1 AE, *n* (%)	11 (8.7%)	12 (9.4%)	23 (9.1%)
Participants with 2 AEs, *n* (%)	14 (11.1%)	12 (9.4%)	26 (10.2%)
Participants with 3 AEs, *n* (%)	11 (8.7%)	11 (8.6%)	22 (8.7%)
Participants with 4 AEs, *n* (%)	7 (5.6%)	4 (3.1%)	11 (4.3%)
Participants with 5 AEs, *n* (%)	9 (7.1%)	11 (8.6%)	20 (7.9%)
Participants with 6 AEs, *n* (%)	7 (5.6%)	6 (4.7%)	13 (5.1%)
Participants with 7 AEs, *n* (%)	8 (6.3%)	6 (4.7%)	14 (5.5%)
Participants with 8 AEs, *n* (%)	6 (4.8%)	5 (3.9%)	11 (4.3%)
Participants with 9 AEs, *n* (%)	3 (2.4%)	3 (2.3%)	6 (2.4%)
Participants with 10 AEs, *n* (%)	3 (2.4%)	4 (3.1%)	7 (2.8%)
Participants with 11 AEs, *n* (%)	5 (4.0%)	2 (1.6%)	7 (2.8%)
Participants with 12 AEs, *n* (%)	5 (4.0%)	4 (3.1%)	9 (3.5%)
Participants with 13 AEs, *n* (%)	1 (0.8%)	0 (0.0%)	1 (0.4%)
Participants with 14 AEs, *n* (%)	5 (4.0%)	2 (1.6%)	7 (2.8%)
Participants with 15 AE, *n* (%)	2 (1.6%)	1 (0.8%)	3 (1.2%)
Participants with 16 AEs, *n* (%)	0 (0.0%)	2 (1.6%)	2 (0.8%)
Participants with 17 AEs, *n* (%)	1 (0.8%)	0 (0.0%)	1 (0.4%)
Participants with 18 AEs, *n* (%)	0 (0.0%)	1 (0.8%)	1 (0.4%)
Participants with 19 AEs, *n* (%)	0 (0.0%)	1 (0.8%)	1 (0.4%)
Participants with 20 AEs, *n* (%)	1 (0.8%)	2 (1.6%)	3 (1.2%)
Participants with 21 AEs, *n* (%)	0 (0.0%)	3 (2.3%)	3 (1.2%)
Participants with 23 AEs, *n* (%)	0 (0.0%)	1 (0.8%)	1 (0.4%)
Participants with 26 AEs, *n* (%)	0 (0.0%)	1 (0.8%)	1 (0.4%)
Participants with 29 AEs, *n* (%)	0 (0.0%)	1 (0.8%)	1 (0.4%)
Participants with 30 AEs, *n* (%)	0 (0.0%)	1 (0.8%)	1 (0.4%)
Participants with 31 AEs, *n* (%)	1 (0.8%)	0 (0.0%)	1 (0.4%)
Participants with 32 AEs, *n* (%)	1 (0.8%)	0 (0.0%)	1 (0.4%)
Participants with 33 AEs, *n* (%)	1 (0.8%)	0 (0.0%)	1 (0.4%)

TABLE 43 Number of participants with adverse events (*continued*)

	rTMS	cgiTBS	Overall
Participants with 37 AEs, *n* (%)	1 (0.8%)	0 (0.0%)	1 (0.4%)
Participants with 45 AEs, *n* (%)	1 (0.8%)	0 (0.0%)	1 (0.4%)
Participants with 51 AEs, *n* (%)	1 (0.8%)	0 (0.0%)	1 (0.4%)
Participants with 75 AEs, *n* (%)	0 (0.0%)	1 (0.8%)	1 (0.4%)
Participants with 94 AEs, *n* (%)	0 (0.0%)	1 (0.8%)	1 (0.4%)
Participants with 121 AEs, *n* (%)	0 (0.0%)	1 (0.8%)	1 (0.4%)

TABLE 44 Listing of adverse events reported in rTMS arm

Trial ID	Adverse event	Duration (days)	Severity	Outcome	Treatment	Related	Serious	Expected
BRI1001	Headache	10	Moderate	Resolved	None	Not related	No	No
BRI1001	Tiredness (more severe/ excessive)	0	Mild	Resolved	Non-drug therapy	Possible	No	No
BRI1001	Breast pain and discomfort	45	Mild	Resolved	None	Not related	No	No
BRI1001	Headache	0	Mild	Resolved	Non-drug therapy	Possible	No	No
BRI1001	Sore eyes (dry eyes)	2	Mild	Resolved	None	Not related	No	No
BRI1004	Scalp discomfort	0	Mild	Resolved	Non-drug therapy	Possible	No	Yes
BRI1004	Scalp discomfort	0	Mild	Resolved	Non-drug therapy	Possible	No	Yes
BRI1004	Scalp discomfort	0	Mild	Resolved	Non-drug therapy	Possible	No	Yes
BRI1004	Neck pain	0	Mild	Resolved	Non-drug therapy	Possible	No	Yes
BRI1004	Scalp discomfort	0	Mild	Resolved	Non-drug therapy	Possible	No	Yes
BRI1004	Scalp discomfort	0	Mild	Resolved	Non-drug therapy	Possible	No	Yes
BRI1004	Scalp discomfort	0	Mild	Resolved	Non-drug therapy	Possible	No	Yes
BRI1004	Headache	0	Mild	Resolved	Non-drug therapy	Possible	No	Yes
BRI1004	Jaw ache	0	Mild	Resolved	Non-drug therapy	Possible	No	Yes
BRI1006	Anxiety	.	Moderate	Unknown	None	Not related	No	No
BRI1006	Scalp discomfort	33	Mild	Resolved	None	Possible	No	No
BRI1006	Headache	2	Mild	Resolved	None	Possible	No	Yes
BRI1006	Shingles	39	Mild	Resolved	None	Not related	No	No
BRI1006	Insomnia	5	Moderate	Resolved	None	Unlikely	No	No

continued

TABLE 44 Listing of adverse events reported in rTMS arm (*continued*)

Trial ID	Adverse event	Duration (days)	Severity	Outcome	Treatment	Related	Serious	Expected
BRI1006	Disturbed sleep	92	Moderate	Resolved	None	Not related	No	No
BRI1006	Paranoia	12	Mild	Resolved	None	Unlikely	No	No
BRI1006	Nightmares	5	Moderate	Resolved	None	Possible	No	No
BRI1006	Nightmares	92	Moderate	Resolved	None	Not related	No	No
BRI1007	Scalp discomfort	0	Mild	Resolved	None	Possible	No	Yes
BRI1007	Headache	1	Mild	Resolved	None	Possible	No	Yes
BRI1010	Jaw movement	0	Mild	Resolved	Non-drug therapy	Definite	No	No
BRI1010	Headache	1	Severe	Resolved	Non-drug therapy	Not related	Yes	No
BRI1011	Hospital admission for chest pains and breathlessness	2	Severe	Resolved	Non-drug therapy	Not related	Yes	No
BRI1011	Worsened breathlessness	109	Severe	Resolved	Concomitant medication	Not related	No	No
BRI1011	Headache	0	Mild	Resolved	Concomitant medication	Possible	No	Yes
BRI1011	Blood clots on lungs	8	Severe	Resolved	Concomitant medication	Not related	Yes	No
BRI1011	Headache	0	Mild	Resolved	Concomitant medication	Possible	No	Yes
BRI1011	Headache	0	Mild	Resolved	Concomitant medication	Possible	No	Yes
BRI1011	Headache	0	Mild	Resolved	Concomitant medication	Possible	No	Yes
BRI1011	Headache	0	Mild	Resolved	Concomitant medication	Possible	No	Yes
BRI1014	Disturbed sleep	128	Moderate	Resolved	None	Unlikely	No	No
BRI1014	Pain in hand	155	Mild	Resolved	None	Not related	No	No
BRI1014	Nightmares	2	Moderate	Resolved	None	Unlikely	No	No
BRI1015	Scalp discomfort	1	Mild	Resolved	None	Probable	No	No
BRI1015	Nausea	1	Mild	Resolved	None	Probable	No	No
BRI1015	A&E admission for nausea and vomiting	1	Severe	Resolved	Concomitant medication	Probable	Yes	No
BRI1015	Vomiting	1	Mild	Resolved	None	Probable	No	No
BRI1015	Tonsilitis	5	Mild	Resolved	Concomitant medication	Not related	No	No
BRI1015	Tingling in right forearm	0	Mild	Resolved	None	Possible	No	No
BRI1015	Hospital admission for anaphylaxis due to insect bites	1	Severe	Resolved	Concomitant medication	Not related	Yes	No

TABLE 44 Listing of adverse events reported in rTMS arm (*continued*)

Trial ID	Adverse event	Duration (days)	Severity	Outcome	Treatment	Related	Serious	Expected
BRI1015	Urinary Tract Infection	21	Moderate	Resolved	Concomitant medication	Not related	No	No
BRI1015	Nausea and anxiety	0	Mild	Resolved	None	Unlikely	No	No
BRI1020	Excessive fatigue	.	Moderate	Unknown	None	Not related	No	No
BRI1020	Nosebleed	0	Mild	Resolved	None	Unlikely	No	No
BRI1020	Nosebleed	0	Mild	Resolved	None	Unlikely	No	No
BRI1021	Tonsilitis	2	Mild	Resolved	None	Not related	No	No
BRI1027	Vasovagal episode during treatment	0	Moderate	Resolved	None	Possible	No	No
BRI1028	Twitching sensation in both eyes	5	Mild	Resolved	None	Possible	No	No
BRI1028	Nausea	0	Mild	Resolved	None	Possible	No	No
BRI1028	Anxiety	42	Mild	Resolved	None	Possible	No	No
BRI1028	Hospital admission related to pre-existing Hidradenitis Suppurativa	2	Severe	Resolved	Concomitant medication	Not related	Yes	No
BRI1028	Nausea and flickering of eye	36	Mild	Resolved	None	Possible	No	No
BRI1028	Dizziness	0	Mild	Resolved	None	Possible	No	No
BRI1028	Headache	2	Moderate	Resolved	Concomitant medication	Not related	No	No
BRI1028	Pin and needles in the back of the head	0	Mild	Resolved	None	Possible	No	No
BRI1029	Flu-like symptoms	35	Mild	Resolved	Concomitant medication	Not related	No	No
BRI1029	Dizziness	0	Mild	Resolved	None	Possible	No	No
BRI1029	Tingling sensation in left eye, left cheek and nose	4	Mild	Resolved	None	Possible	No	No
BRI1029	Mole on chest wall. Biopsy taken	71	Mild	Resolved	None	Not related	No	No
BRI1029	Watering eyes	1	Mild	Resolved	None	Possible	No	No
BRI1029	Headache	1	Mild	Resolved	None	Possible	No	No
BRI1029	Lump on anus (not haemorrhoid). For colonoscopy	108	Mild	Resolved	None	Not related	No	No
BRI1029	Tinnitus	0	Mild	Resolved	None	Possible	No	No
BRI1029	Headache	1	Mild	Resolved	None	Possible	No	No
BRI1029	Headache	0	Mild	Resolved	None	Possible	No	Yes
BRI1032	Headache	93	Mild	Resolved	None	Not related	No	No
BRI1032	Headache	4	Mild	Resolved	None	Possible	No	No

continued

TABLE 44 Listing of adverse events reported in rTMS arm (*continued*)

Trial ID	Adverse event	Duration (days)	Severity	Outcome	Treatment	Related	Serious	Expected
BRI1032	Headache	5	Mild	Resolved	None	Possible	No	Yes
BRI1032	Dizziness	1	Mild	Resolved	None	Possible	No	Yes
BRI1032	Headache	0	Mild	Resolved	None	Possible	No	Yes
BRI1032	Headache	3	Mild	Resolved	None	Possible	No	Yes
BRI1032	Dizziness	14	Mild	Resolved	None	Not related	No	No
BRI1032	Headache	14	Mild	Resolved	None	Not related	No	No
BRI1032	Headache	0	Mild	Resolved	None	Possible	No	Yes
BRI1032	Headache	0	Mild	Resolved	None	Possible	No	Yes
BRI1032	Neck pain	3	Mild	Resolved	None	Possible	No	Yes
BRI1032	Dry mouth	0	Mild	Resolved	None	Unlikely	No	No
BRI1032	Jaw ache	0	Mild	Resolved	None	Possible	No	Yes
BRI1033	Nausea	0	Mild	Resolved	None	Possible	No	No
BRI1033	Stiff neck	0	Mild	Resolved	None	Possible	No	No
BRI1033	Jaw movement	6	Mild	Resolved	None	Probable	No	Yes
BRI1033	Neck pain	0	Mild	Resolved	None	Possible	No	Yes
BRI1033	Jaw ache	0	Mild	Resolved	None	Not related	No	Yes
BRI1033	Nausea	0	Mild	Resolved	None	Not related	No	No
BRI1033	Lightheadedness	3	Mild	Resolved	None	Possible	No	Yes
BRI1033	Jaw ache	3	Mild	Resolved	None	Possible	No	No
BRI1033	Headache	0	Mild	Resolved	None	Possible	No	No
BRI1033	Stiff neck	0	Mild	Resolved	None	Possible	No	No
BRI1033	Headache	3	Mild	Resolved	None	Possible	No	No
BRI1033	Body ache	0	Mild	Resolved	None	Not related	No	No
BRI1035	Ears ringing sensation	0	Mild	Resolved	None	Possible	No	No
BRI1035	Headache	26	Mild	Resolved	Concomitant medication	Unlikely	No	No
BRI1035	Self-harm	13	Moderate	Resolved	None	Unlikely	No	No
BRI1035	Headache	1	Mild	Resolved	None	Possible	No	No
BRI1035	Headache	0	Mild	Resolved	None	Possible	No	No
BRI1035	Headache	0	Mild	Resolved	None	Possible	No	No
BRI1035	Dizziness	0	Mild	Resolved	None	Possible	No	No
BRI1039	Voluntary hospital admission	30	Moderate	Resolved	Concomitant medication	Not related	No	No
BRI1039	Tinnitus	25	Mild	Resolved	None	Not related	No	Yes
BRI1039	Neck pain	1	Mild	Resolved	None	Possible	No	No
BRI1040	Jaw ache	5	Mild	Resolved	None	Possible	No	No
BRI1040	Headache	5	Mild	Resolved	None	Possible	No	No

TABLE 44 Listing of adverse events reported in rTMS arm (*continued*)

Trial ID	Adverse event	Duration (days)	Severity	Outcome	Treatment	Related	Serious	Expected
BRI1040	Headache	1	Mild	Resolved	None	Possible	No	No
BRI1040	Headache	0	Mild	Resolved	None	Possible	No	No
BRI1040	Tiredness	5	Mild	Resolved	None	Possible	No	No
BRI1042	Headache	3	Mild	Resolved	None	Possible	No	No
BRI1042	Headache	0	Mild	Resolved	None	Possible	No	No
BRI1042	Stiff neck	1	Mild	Resolved	None	Possible	No	No
BRI1042	Headache	0	Mild	Resolved	None	Possible	No	No
BRI1042	Headache	0	Mild	Resolved	None	Possible	No	No
BRI1042	Headache	1	Mild	Resolved	None	Possible	No	No
BRI1042	Headache	0	Mild	Resolved	None	Possible	No	No
BRI1045	Knee injury	31	Mild	Resolved	None	Not related	No	No
BRI1045	Tooth pain	0	Mild	Resolved	None	Possible	No	No
BRI1045	Pulled back	.	Moderate	Unknown	Concomitant medication	Not related	No	No
BRI1046	Jaw ache	1	Mild	Resolved	None	Probable	No	Yes
BRI1046	Strained neck and back pain from historical injury	10	Moderate	Resolved	None	Not related	No	No
BRI1046	Headache	2	Moderate	Resolved	None	Probable	No	Yes
BRI1047	Watering eyes	1	Mild	Resolved	None	Possible	No	Yes
BRI1047	Watering eyes	0	Mild	Resolved	None	Possible	No	No
BRI1047	Watering eyes	0	Mild	Resolved	None	Possible	No	Yes
BRI1047	Watering eyes	0	Mild	Resolved	None	Probable	No	Yes
BRI1047	Watering eyes	0	Mild	Resolved	None	Possible	No	Yes
BRI1047	Watering eyes	0	Mild	Resolved	None	Probable	No	Yes
BRI1047	Watering eyes	1	Mild	Resolved	None	Possible	No	No
BRI1051	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI1051	Ears burning	1	Mild	Resolved	None	Unlikely	No	Yes
BRI1051	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI1051	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI1051	Neck pain	0	Mild	Resolved	None	Possible	No	Yes
BRI1051	Headache	0	Mild	Resolved	None	Possible	No	Yes
BRI1051	Visual disturbance	0	Mild	Resolved	None	Possible	No	Yes
BRI1051	Sleepiness	0	Mild	Resolved	None	Possible	No	No
BRI1051	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI1051	Dizziness	0	Mild	Resolved	None	Probable	No	Yes

continued

TABLE 44 Listing of adverse events reported in rTMS arm (*continued*)

Trial ID	Adverse event	Duration (days)	Severity	Outcome	Treatment	Related	Serious	Expected
BRI1051	Neck pain	0	Mild	Resolved	None	Possible	No	Yes
BRI1051	Headache	0	Mild	Resolved	None	Possible	No	Yes
BRI1051	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI1051	Jaw ache	0	Mild	Resolved	None	Possible	No	Yes
BRI1051	Headache	1	Mild	Resolved	None	Possible	No	Yes
BRI1051	Headache	0	Mild	Resolved	None	Possible	No	Yes
BRI1051	Jaw ache	0	Mild	Resolved	None	Probable	No	Yes
BRI1051	Sleepiness	5	Mild	Resolved	None	Possible	No	No
BRI1051	Dizziness	137	Mild	Resolved	None	Possible	No	Yes
BRI1051	Scalp discomfort	0	Mild	Resolved	None	Possible	No	No
BRI1051	Neck pain	0	Mild	Resolved	None	Possible	No	Yes
BRI1051	Scalp discomfort	0	Mild	Resolved	None	Possible	No	Yes
BRI1051	Nausea	0	Mild	Resolved	None	Probable	No	Yes
BRI1051	Sleepiness	24	Mild	Resolved	None	Possible	No	No
BRI1051	Pain behind left ear	0	Mild	Resolved	None	Possible	No	No
BRI1051	Dizziness	0	Moderate	Resolved	None	Probable	No	Yes
BRI1051	Dizziness	0	Mild	Resolved	None	Possible	No	Yes
BRI1051	Headache	0	Mild	Resolved	None	Possible	No	Yes
BRI1051	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI1051	Scalp discomfort	1	Mild	Resolved	None	Probable	No	Yes
BRI1051	Jaw ache	0	Mild	Resolved	None	Possible	No	Yes
BRI1051	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI1051	Neck pain	0	Mild	Resolved	None	Possible	No	Yes
BRI1051	Dizziness	164	Mild	Resolved	None	Possible	No	Yes
BRI1051	Jaw ache	28	Mild	Resolved	None	Possible	No	Yes
BRI1051	Back pain	0	Mild	Resolved	None	Unlikely	No	No
BRI1051	Neck pain	0	Mild	Resolved	None	Possible	No	Yes
BRI1051	Neck pain	0	Mild	Resolved	None	Possible	No	Yes
BRI1051	Dizziness	0	Mild	Resolved	None	Possible	No	Yes
BRI1051	Headache	.	Mild	Unknown	None	Possible	No	Yes
BRI1051	Watering eyes	0	Mild	Resolved	None	Probable	No	Yes
BRI1051	Tinnitus	0	Mild	Resolved	None	Possible	No	Yes
BRI1051	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI1051	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI1051	Headache	1	Mild	Resolved	None	Possible	No	Yes
BRI1051	Headache	1	Mild	Resolved	None	Possible	No	Yes

TABLE 44 Listing of adverse events reported in rTMS arm (*continued*)

Trial ID	Adverse event	Duration (days)	Severity	Outcome	Treatment	Related	Serious	Expected
BRI1051	Nausea	0	Mild	Resolved	None	Possible	No	Yes
BRI1051	Neck pain	20	Mild	Resolved	None	Possible	No	Yes
BRI1051	Migraine	1	Mild	Resolved	None	Probable	No	No
BRI1051	Neck pain	0	Mild	Resolved	None	Possible	No	Yes
BRI1051	Tinnitus	158	Mild	Resolved	None	Possible	No	Yes
BRI1055	Scalp discomfort	0	Mild	Resolved	None	Possible	No	No
BRI1057	Worsened neck discomfort	45	Mild	Resolved	None	Unlikely	No	No
BRI1057	Headache	0	Mild	Resolved	None	Possible	No	Yes
BRI1057	Right side nasal discomfort during stimulation	0	Mild	Resolved	None	Possible	No	No
BRI1057	Headache	2	Mild	Resolved	None	Probable	No	Yes
BRI1057	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI1057	Right-side nasal discomfort during stimulation	0	Mild	Resolved	None	Possible	No	No
BRI1057	Headache	21	Mild	Resolved	None	Possible	No	Yes
BRI1057	Scalp pain during stimulation	0	Mild	Resolved	None	Definite	No	No
BRI1058	Fatigue	42	Mild	Resolved	None	Unlikely	No	No
BRI1058	Dizziness	0	Mild	Resolved	None	Possible	No	Yes
BRI1058	Nightmares	0	Moderate	Resolved	None	Unlikely	No	No
BRI1058	Dizziness	71	Mild	Resolved	None	Possible	No	Yes
BRI1058	Nausea	11	Mild	Resolved	None	Possible	No	Yes
BRI1058	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI1058	Headache	1	Mild	Resolved	None	Possible	No	Yes
BRI1058	Tiredness	38	Mild	Resolved	None	Possible	No	No
BRI1058	Small non-existent rotting matter intermittently	138	Mild	Resolved	None	Unlikely	No	No
BRI1058	Hot flashes	20	Mild	Resolved	None	Unlikely	No	No
BRI1058	Tension/headache during treatment	0	Mild	Resolved	None	Probable	No	Yes
BRI1058	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI1058	Nausea	0	Mild	Resolved	None	Possible	No	Yes
BRI1058	Dizziness	0	Mild	Resolved	None	Possible	No	Yes
BRI1058	Nausea	0	Mild	Resolved	None	Possible	No	Yes
BRI1061	Tiredness	578	Moderate	Unknown	None	Possible	No	No

continued

TABLE 44 Listing of adverse events reported in rTMS arm (*continued*)

Trial ID	Adverse event	Duration (days)	Severity	Outcome	Treatment	Related	Serious	Expected
BRI1061	Nausea	30	Mild	Resolved	None	Possible	No	Yes
BRI1061	Shoulder pain	1	Mild	Resolved	None	Possible	No	No
BRI1061	Cognitive issue	1	Moderate	Resolved	None	Possible	No	Yes
BRI1061	Scalp discomfort	4	Mild	Resolved	None	Possible	No	Yes
BRI1061	Vivid dreams	319	Moderate	Resolved	None	Possible	No	No
BRI1061	Headache	15	Mild	Resolved	None	Possible	No	Yes
BRI1061	Dizziness	0	Moderate	Resolved	None	Possible	No	Yes
BRI1061	Discomfort in left eyebrow	9	Mild	Resolved	None	Probable	No	No
BRI1061	Headache	53	Mild	Resolved	None	Probable	No	Yes
BRI1061	Cramps in both hands	119	Moderate	Resolved with sequelae	None	Not related	No	No
BRI1062	Headache	0	Mild	Resolved	None	Possible	No	Yes
BRI1062	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI1062	Tinnitus	0	Mild	Resolved	None	Possible	No	Yes
BRI1062	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI1062	Tinnitus	0	Mild	Resolved	None	Possible	No	Yes
BRI1062	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI1062	Tinnitus	0	Mild	Resolved	None	Possible	No	Yes
BRI1062	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI1062	Headache	0	Mild	Resolved	None	Possible	No	Yes
BRI1062	Headache	0	Mild	Resolved	None	Possible	No	Yes
BRI1062	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI1064	Shoulder/back tension	0	Mild	Resolved	None	Probable	No	No
BRI1064	Eye pain	0	Mild	Resolved	None	Probable	No	No
BRI1066	Headache	0	Mild	Resolved	None	Possible	No	Yes
BRI1066	Headache	0	Mild	Resolved	None	Possible	No	Yes
BRI1066	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI1066	Headache	0	Mild	Resolved	None	Unlikely	No	Yes
BRI1066	Headache	0	Mild	Resolved	None	Possible	No	Yes
BRI1066	Headache	0	Mild	Resolved	None	Possible	No	Yes
BRI1070	Tooth pain	0	Mild	Resolved	None	Probable	No	No
BRI1070	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI1070	Tooth pain	0	Mild	Resolved	None	Probable	No	No
BRI1070	Tooth pain	0	Mild	Resolved	None	Probable	No	No
BRI1070	Headache	0	Mild	Resolved	None	Probable	No	Yes

TABLE 44 Listing of adverse events reported in rTMS arm (*continued*)

Trial ID	Adverse event	Duration (days)	Severity	Outcome	Treatment	Related	Serious	Expected
BRI1070	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI1070	Neck discomfort	0	Mild	Resolved	None	Possible	No	Yes
BRI1070	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI1072	Watering eyes	0	Mild	Resolved	None	Probable	No	Yes
BRI1072	Headache	0	Moderate	Resolved	None	Probable	No	Yes
BRI1072	Dizziness	0	Mild	Resolved	None	Possible	No	Yes
BRI1072	Dizzy spells	370	Moderate	Unknown	None	Unlikely	No	No
BRI1072	Fractured wrist from fall (during dizzy spell)	336	Moderate	Unknown	Non-drug therapy	Unlikely	No	No
BRI1074	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI1076	Jaw ache	0	Moderate	Resolved	None	Probable	No	Yes
BRI1076	Jaw ache	0	Mild	Resolved	None	Probable	No	Yes
BRI1076	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI1079	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI1079	Tiredness	34	Mild	Resolved	None	Possible	No	No
BRI1083	Headache	1	Mild	Resolved	None	Not related	No	Yes
BRI1084	Jaw ache	0	Mild	Resolved	None	Probable	No	Yes
BRI1084	Jaw ache	0	Mild	Resolved	None	Probable	No	Yes
BRI1084	Nausea	0	Mild	Resolved	None	Probable	No	Yes
BRI1084	Watering eyes	0	Mild	Resolved	None	Probable	No	Yes
BRI1084	Nausea	0	Mild	Resolved	None	Definite	No	Yes
BRI1084	Jaw ache	0	Mild	Resolved	None	Probable	No	Yes
BRI1084	Nausea	0	Mild	Resolved	None	Probable	No	Yes
BRI1084	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI1084	Nausea	0	Mild	Resolved	None	Probable	No	Yes
BRI1084	Back pain	46	Moderate	Resolved	None	Unlikely	No	No
BRI1084	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI1084	Sensation down right leg	0	Mild	Resolved	None	Unlikely	No	No
BRI1084	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI1084	Nausea	0	Mild	Resolved	None	Definite	No	Yes
BRI1084	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI1084	Acid reflux	16	Mild	Resolved	Concomitant Medication	Not related	No	No
BRI1084	Headache	0	Mild	Resolved	None	Definite	No	Yes
BRI1084	Headache	0	Mild	Resolved	None	Definite	No	Yes

continued

TABLE 44 Listing of adverse events reported in rTMS arm (*continued*)

Trial ID	Adverse event	Duration (days)	Severity	Outcome	Treatment	Related	Serious	Expected
BRI1084	Headache	0	Mild	Resolved	None	Definite	No	Yes
BRI1084	Neck discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI1084	Sensation down right leg	0	Mild	Resolved	None	Unlikely	No	No
BRI1084	Nausea	3	Mild	Resolved	None	Probable	No	Yes
BRI1084	Nausea	1	Mild	Resolved	None	Probable	No	Yes
BRI1084	Jaw ache	237	Moderate	Unknown	Concomitant medication	Unlikely	No	No
BRI1084	Jaw ache	0	Mild	Resolved	None	Probable	No	Yes
BRI1084	Headache	0	Mild	Resolved	None	Definite	No	Yes
BRI1084	Watering eyes	0	Mild	Resolved	None	Probable	No	Yes
BRI1084	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI1084	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI1084	Nausea	0	Mild	Resolved	None	Probable	No	Yes
BRI1084	Jaw ache	0	Mild	Resolved	None	Probable	No	Yes
BRI1084	Dizziness	0	Mild	Resolved	None	Probable	No	Yes
BRI1084	Nausea	0	Mild	Resolved	None	Definite	No	Yes
BRI1085	Filling came out at home after treatment	0	Moderate	Resolved	None	Possible	No	No
BRI1085	Slight pressure/scalp discomfort near site of treatment	128	Mild	Resolved	None	Probable	No	Yes
BRI1090	Headache	0	Mild	Resolved	None	Possible	No	Yes
BRI1090	Watering eyes	0	Mild	Resolved	None	Possible	No	Yes
BRI1090	High blood pressure	3	Mild	Resolved	None	Not related	No	No
BRI1090	Viral infection (sore throat, etc.)	19	Mild	Resolved	None	Not related	No	No
BRI1090	Dry mouth	0	Mild	Resolved	None	Possible	No	No
BRI1092	COVID-19	6	Mild	Resolved	None	Not related	No	No
BRI1093	Neck pain	0	Mild	Resolved	None	Possible	No	Yes
BRI1093	Scalp discomfort	0	Mild	Resolved	None	Possible	No	Yes
BRI1093	Neck pain	0	Mild	Resolved	None	Possible	No	Yes
BRI1096	Pin and needles in the back of the head	0	Mild	Resolved	None	Possible	No	No
BRI1096	Nausea	0	Mild	Resolved	None	Possible	No	Yes
BRI1097	Upper-left-side molars discomfort during stimulation	0	Mild	Resolved	None	Probable	No	No
BRI1097	Upper-left-side molars discomfort during stimulation	0	Mild	Resolved	None	Probable	No	No

TABLE 44 Listing of adverse events reported in rTMS arm (*continued*)

Trial ID	Adverse event	Duration (days)	Severity	Outcome	Treatment	Related	Serious	Expected
BRI1097	Upper-left side molars discomfort during stimulation	0	Mild	Resolved	None	Probable	No	No
BRI1097	Nightmares	1	Mild	Resolved	None	Unlikely	No	No
BRI1097	Disturbed sleep	2	Mild	Resolved	None	Unlikely	No	No
BRI1097	Tingling in the left nostril during stimulations and stayed all weekend	3	Mild	Resolved	None	Possible	No	No
BRI1097	Upper-left-side molars discomfort during stimulation	0	Mild	Resolved	None	Probable	No	No
BRI1099	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI1099	Scalp discomfort	0	Mild	Resolved	None	Possible	No	Yes
BRI1099	COVID-19	3	Mild	Resolved	None	Not related	No	No
BRI1101	Tinnitus (pre-existing condition)	30	Mild	Resolved	None	Possible	No	Yes
BRI1101	Scalp discomfort	0	Mild	Resolved	None	Possible	No	Yes
BRI1101	Neck pain	1	Mild	Resolved	None	Probable	No	Yes
BRI1101	Anxiety/difficulty sleeping	8	Mild	Resolved	None	Probable	No	No
BRI1101	Tension in the shoulders	0	Mild	Resolved	None	Possible	No	No
BRI1102	Tinnitus (daily), started 1 week after treatments completed	132	Mild	Resolved	None	Possible	No	No
BRI1102	Feeling of something still touching head at site of stimulations	5	Mild	Resolved	None	Probable	No	No
BRI1102	Epididymitis (right testicle)	30	Mild	Resolved	Non-drug therapy	Not related	No	No
BRI1102	Headache	1	Mild	Resolved	Concomitant medication	Probable	No	Yes
BRI1102	COVID-19	8	Mild	Resolved	None	Not related	No	No
BRI1102	Noise in the right ear during stimulations	0	Mild	Resolved	None	Possible	No	No
BRI1102	Headache	1	Mild	Resolved	Concomitant medication	Possible	No	Yes
BRI1102	Syncope	0	Moderate	Resolved	None	Possible	No	No
BRI1103	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI1103	Small scab at the site of stimulations	0	Mild	Resolved	None	Probable	No	No

continued

TABLE 44 Listing of adverse events reported in rTMS arm (*continued*)

Trial ID	Adverse event	Duration (days)	Severity	Outcome	Treatment	Related	Serious	Expected
BRI1103	COVID-19	5	Mild	Resolved	None	Not related	No	No
BRI1108	Dizziness	1	Mild	Resolved	None	Possible	No	Yes
BRI1108	Headache	1	Mild	Resolved	None	Possible	No	Yes
BRI1108	Dry throat during treatment	0	Mild	Resolved	None	Possible	No	No
BRI1108	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI1108	Numbness in back of head	0	Mild	Resolved	None	Possible	No	No
BRI1108	Scalp discomfort	4	Mild	Resolved	None	Probable	No	Yes
BRI1108	Tingling nose	4	Mild	Resolved	None	Possible	No	No
BRI1108	Scalp discomfort	3	Mild	Resolved	None	Possible	No	Yes
BRI1108	Tightness at back of scalp	5	Mild	Resolved	None	Possible	No	No
BRI1108	Scalp discomfort	11	Mild	Resolved	None	Probable	No	Yes
BRI1108	Dizziness	0	Mild	Resolved	None	Probable	No	Yes
BRI1108	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI1110	Tinnitus (pre-existing condition)	0	Mild	Resolved	None	Probable	No	Yes
BRI1110	Tinnitus (pre-existing condition)	0	Mild	Resolved	None	Probable	No	Yes
BRI1110	Tinnitus (pre-existing condition)	0	Mild	Resolved	None	Probable	No	Yes
BRI1110	Tinnitus (pre-existing condition)	0	Mild	Resolved	None	Probable	No	Yes
BRI1110	Tinnitus (pre-existing condition)	2	Mild	Resolved	None	Possible	No	Yes
BRI1110	Tinnitus (pre-existing condition)	0	Mild	Resolved	None	Probable	No	Yes
BRI1110	Hospital admission for low blood pressure	1	Moderate	Resolved with sequelae	None	Not related	Yes	No
BRI1110	Tinnitus (pre-existing condition)	0	Mild	Resolved	None	Probable	No	Yes
BRI1110	Tinnitus (pre-existing condition)	0	Mild	Resolved	None	Probable	No	Yes
BRI1110	Tinnitus (pre-existing condition)	0	Mild	Resolved	None	Probable	No	Yes
BRI1111	Headache	0	Mild	Resolved	None	Possible	No	Yes
BRI1111	Feeling of trapped wind on left side	1	Mild	Resolved	None	Unlikely	No	No
BRI1111	Period delayed	4	Mild	Resolved	None	Unlikely	No	No
BRI1111	Headache	0	Mild	Resolved	None	Possible	No	Yes

TABLE 44 Listing of adverse events reported in rTMS arm (*continued*)

Trial ID	Adverse event	Duration (days)	Severity	Outcome	Treatment	Related	Serious	Expected
BRI1111	Headache	0	Mild	Resolved	None	Unlikely	No	No
BRI1111	Tiredness	11	Mild	Resolved	None	Possible	No	No
BRI1111	Headache	0	Mild	Resolved	None	Possible	No	Yes
BRI1111	Nausea	0	Mild	Resolved	None	Unlikely	No	No
BRI1111	Headache	0	Mild	Resolved	None	Possible	No	Yes
BRI1111	Discomfort in back of head	0	Mild	Resolved	None	Possible	No	No
BRI1111	Sleepiness	4	Mild	Resolved	None	Possible	No	No
BRI1111	Headache	0	Mild	Resolved	None	Possible	No	Yes
BRI1111	Struggle to fall asleep	11	Mild	Resolved	Concomitant medication	Possible	No	No
BRI1111	Nausea	0	Mild	Resolved	None	Unlikely	No	Yes
BRI2002	obsessive compulsive disorder being more prominent	0	Mild	Resolved	None	Possible	No	No
BRI2002	Headache	9	Mild	Resolved	None	Probable	No	Yes
BRI2002	Nausea	0	Mild	Resolved	None	Probable	No	Yes
BRI2002	Jaw ache	9	Mild	Resolved	None	Probable	No	Yes
BRI2002	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI2002	Jaw ache	0	Mild	Resolved	None	Probable	No	Yes
BRI2002	Tinnitus	0	Mild	Resolved	None	Probable	No	Yes
BRI2002	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI2002	Feeling out of sorts probably due to combination of side effects (all of which are mild)	0	Mild	Resolved	None	Possible	No	No
BRI2002	Nausea	0	Mild	Resolved	None	Probable	No	Yes
BRI2002	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI2002	Tiredness (more severe/ excessive)	0	Mild	Resolved	None	Possible	No	No
BRI2002	Watering eyes	0	Mild	Resolved	None	Probable	No	Yes
BRI2002	Watering eyes	0	Mild	Resolved	None	Probable	No	Yes
BRI2004	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI2004	Bleeding gums and aching teeth mainly around root filling area	0	Mild	Resolved	None	Possible	No	No
BRI2004	Headache	5	Mild	Resolved	None	Probable	No	Yes
BRI2004	Jaw ache	7	Mild	Resolved	None	Probable	No	Yes

continued

TABLE 44 Listing of adverse events reported in rTMS arm (*continued*)

Trial ID	Adverse event	Duration (days)	Severity	Outcome	Treatment	Related	Serious	Expected
BRI2004	Tooth pain	0	Mild	Resolved	None	Possible	No	No
BRI2004	Pronounced pressure of speech at times	0	Mild	Resolved	None	Possible	No	No
BRI2004	Pronounced pressure of speech at times	0	Mild	Resolved	None	Possible	No	No
BRI2004	Tooth pain	0	Mild	Resolved	None	Possible	No	No
BRI2011	Patient reports saying wrong words when intending to say something else	0	Mild	Resolved	None	Possible	No	No
BRI2011	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI2011	Migraine	0	Mild	Resolved	None	Possible	No	No
BRI2011	Nausea	0	Mild	Resolved	None	Probable	No	Yes
BRI2011	Neck pain	1	Mild	Resolved	None	Probable	No	Yes
BRI2012	Jaw ache	4	Mild	Resolved	None	Probable	No	Yes
BRI2012	Neck pain	13	Mild	Resolved	None	Probable	No	Yes
BRI2012	Jaw ache	0	Mild	Resolved	None	Probable	No	Yes
BRI2012	Headache	2	Mild	Resolved	None	Probable	No	Yes
BRI2012	Jaw ache	0	Mild	Resolved	None	Probable	No	Yes
BRI2012	Pins and needles in hand	0	Mild	Resolved	None	Possible	No	No
BRI2012	'Spaced out'	0	Mild	Resolved	None	Possible	No	No
BRI2012	Jaw ache	0	Mild	Resolved	None	Probable	No	Yes
BRI2012	Jaw ache	0	Mild	Resolved	None	Probable	No	Yes
BRI2012	Pins and needles in hand	0	Mild	Resolved	None	Possible	No	No
BRI2012	Jaw ache	3	Mild	Resolved	None	Probable	No	Yes
BRI2012	Tingling lips	0	Mild	Resolved	None	Probable	No	No
BRI2012	Jaw ache	2	Mild	Resolved	None	Probable	No	Yes
BRI2012	Dizziness	7	Mild	Resolved	None	Probable	No	Yes
BRI2015	Pain across chest (tightness) lasting around 15 minutes post treatment	0	Mild	Resolved	None	Possible	No	No
BRI2015	Feeling highly anxious and tearful at present	0	Mild	Resolved	None	Possible	No	No
BRI2016	Watering eyes	0	Mild	Resolved	None	Probable	No	Yes
BRI2016	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI2016	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI2016	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes

TABLE 44 Listing of adverse events reported in rTMS arm (*continued*)

Trial ID	Adverse event	Duration (days)	Severity	Outcome	Treatment	Related	Serious	Expected
BRI2016	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI2016	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI2016	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI2017	Dizziness	7	Mild	Resolved	None	Probable	No	Yes
BRI2017	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI2017	Headache	16	Mild	Resolved	None	Probable	No	Yes
BRI2017	Dizziness	0	Mild	Resolved	None	Probable	No	Yes
BRI2017	Nausea	0	Mild	Resolved	None	Probable	No	Yes
BRI2017	Increased irritability post treatment	0	Mild	Resolved	None	Possible	No	No
BRI2022	Weight gain and disordered eating	.	Mild	Unknown	None	Unlikely	No	No
BRI2026	Dizziness	0	Mild	Resolved	None	Probable	No	Yes
BRI2026	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI2026	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI2026	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI2026	Nausea	0	Mild	Resolved	None	Probable	No	Yes
BRI2026	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI2026	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI2026	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI2026	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI2026	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI2026	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI2026	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI2027	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI2027	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI3002	Neck pain	38	Mild	Resolved with sequelae	None	Probable	No	Yes
BRI3002	Neck pain	47	Mild	Resolved	None	Probable	No	Yes
BRI3002	Nausea	0	Mild	Resolved	None	Probable	No	Yes
BRI3002	Jaw ache	47	Mild	Resolved	None	Probable	No	Yes
BRI3002	Headache	38	Mild	Resolved	None	Definite	No	Yes
BRI3002	Jaw ache	38	Mild	Resolved	None	Definite	No	Yes
BRI3002	Tinnitus	32	Mild	Resolved	None	Probable	No	Yes
BRI3002	Scalp discomfort	32	Mild	Resolved	None	Definite	No	Yes
BRI3002	Tinnitus	.	Mild	Resolved	None	Probable	No	Yes

continued

TABLE 44 Listing of adverse events reported in rTMS arm (*continued*)

Trial ID	Adverse event	Duration (days)	Severity	Outcome	Treatment	Related	Serious	Expected
BRI3002	Watering eyes	36	Mild	Resolved	None	Definite	No	Yes
BRI3002	Back pain	47	Mild	Resolved	None	Unlikely	No	No
BRI3002	Migraine	23	Moderate	Resolved with sequelae	None	Probable	No	No
BRI3003	Neck pain	10	Mild	Resolved	None	Probable	No	No
BRI3003	Tooth pain	10	Mild	Resolved	None	Probable	No	No
BRI3005	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI3006	Sinus pain	0	Mild	Resolved	None	Probable	No	No
BRI3006	Dizziness	0	Mild	Resolved	None	Probable	No	Yes
BRI3006	Jaw ache	14	Mild	Resolved	None	Unlikely	No	Yes
BRI3006	Scalp discomfort	1	Mild	Resolved	None	Probable	No	Yes
BRI3006	Scalp discomfort	14	Mild	Resolved	None	Possible	No	Yes
BRI3006	Watering eyes	35	Mild	Resolved	None	Probable	No	Yes
BRI3006	Headache	4	Mild	Resolved	None	Probable	No	Yes
BRI3006	Jabbing sensation behind eye	0	Mild	Resolved	None	Probable	No	No
BRI3006	Jaw ache	0	Mild	Resolved	None	Probable	No	Yes
BRI3006	Dizziness	0	Mild	Resolved	None	Probable	No	Yes
BRI3006	Sinus pain	0	Mild	Resolved	None	Probable	No	No
BRI3006	Headache	14	Mild	Resolved	None	Unlikely	No	Yes
BRI3006	Neck pain	14	Mild	Resolved	None	Possible	No	Yes
BRI3006	(Mild/short term) memory loss	14	Mild	Resolved	None	Unlikely	No	No
BRI3006	Dizziness	14	Mild	Resolved	None	Unlikely	No	Yes
BRI3007	Dizziness	0	Mild	Resolved	None	Probable	No	Yes
BRI3007	Headache	6	Mild	Resolved	None	Probable	No	Yes
BRI3007	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI3007	Vomiting	0	Mild	Resolved	None	Unlikely	No	No
BRI3009	Vomiting	0	Mild	Resolved	None	Possible	No	No
BRI3009	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI3009	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI3009	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI3009	Hospital admission–psychotic episode with severe anxiety/depression	31	Severe	Resolved with sequelae	Concomitant medication	Possible	Yes	No
BRI3009	Dizziness	19	Mild	Resolved	None	Probable	No	Yes
BRI3009	Jaw ache	31	Mild	Resolved	None	Probable	No	Yes

TABLE 44 Listing of adverse events reported in rTMS arm (*continued*)

Trial ID	Adverse event	Duration (days)	Severity	Outcome	Treatment	Related	Serious	Expected
BRI3012	Neck pain	13	Mild	Resolved	None	Possible	No	Yes
BRI3012	Scalp discomfort	19	Mild	Resolved	None	Definite	No	Yes
BRI3012	Watering eyes	0	Mild	Resolved	None	Possible	No	Yes
BRI3012	Headache	29	Mild	Resolved	None	Probable	No	Yes
BRI3015	Jaw ache	29	Mild	Resolved	None	Probable	No	No
BRI3015	Watering eyes	22	Mild	Resolved	None	Probable	No	No
BRI3015	Neck pain	7	Mild	Resolved	None	Probable	No	Yes
BRI3015	Scalp discomfort	29	Mild	Resolved	None	Definite	No	No
BRI3015	Jaw ache	11	Mild	Resolved	None	Probable	No	Yes
BRI3015	Hairline receding (since TMS treatment)	151	Moderate	Resolved with sequelae	None	Unlikely	No	No
BRI3015	Nausea	20	Mild	Resolved	None	Possible	No	No
BRI3015	Ache in facial nerve	11	Mild	Resolved	None	Probable	No	No
BRI3015	Dizziness	11	Mild	Resolved	None	Probable	No	Yes
BRI3015	Headache	31	Mild	Resolved	None	Probable	No	No
BRI3015	Dizziness	8	Mild	Resolved	None	Probable	No	No
BRI3015	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI3015	Neck pain	34	Mild	Resolved	None	Probable	No	No
BRI3015	Facial pain	24	Mild	Resolved	None	Definite	No	No
BRI3017	Neck pain	14	Mild	Resolved	None	Probable	No	Yes
BRI3017	Headache	24	Mild	Resolved	None	Probable	No	Yes
BRI3017	Tiredness	8	Mild	Resolved	None	Possible	No	No
BRI3017	Watering eyes	10	Mild	Resolved	None	Probable	No	Yes
BRI3017	Lack of appetite	7	Mild	Resolved	None	Unlikely	No	No
BRI3017	Jaw ache	3	Mild	Resolved	None	Probable	No	Yes
BRI3017	Self-harm	8	Mild	Resolved	None	Unlikely	No	No
BRI3017	Nausea	8	Mild	Resolved	None	Possible	No	Yes
BRI3017	Dizziness	26	Mild	Resolved	None	Probable	No	Yes
BRI3017	Eye pain	0	Mild	Resolved	None	Possible	No	No
BRI3017	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI3019	Attempt of self-harm	0	Severe	Resolved	Non-drug therapy	Unlikely	No	No
BRI3019	Attempt of self-harm	9	Severe	Resolved with sequelae	None	Unlikely	No	No
BRI3019	Scalp discomfort	1	Mild	Resolved	None	Probable	No	Yes

continued

TABLE 44 Listing of adverse events reported in rTMS arm (*continued*)

Trial ID	Adverse event	Duration (days)	Severity	Outcome	Treatment	Related	Serious	Expected
BRI3019	Nausea	1	Mild	Resolved	None	Possible	No	Yes
BRI3020	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI3020	Depersonalisation	0	Mild	Resolved	None	Possible	No	No
BRI3020	Nausea	0	Mild	Resolved	None	Probable	No	Yes
BRI3020	Dizziness	0	Mild	Resolved	None	Probable	No	Yes
BRI3020	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI3022	Neck pain	35	Mild	Resolved	None	Probable	No	Yes
BRI3022	Headache	31	Mild	Resolved	None	Probable	No	Yes
BRI3022	Tooth pain	21	Mild	Resolved	None	Probable	No	No
BRI3024	Pulsating inside head	0	Mild	Resolved	None	Probable	No	No
BRI3024	Dry eye	6	Mild	Resolved	None	Possible	No	No
BRI3024	Jaw ache	4	Mild	Resolved	None	Probable	No	Yes
BRI3024	Neck pain	25	Mild	Resolved	None	Probable	No	Yes
BRI3024	Dizziness	17	Mild	Resolved	None	Probable	No	Yes
BRI3024	Scalp discomfort	28	Mild	Resolved	None	Definite	No	Yes
BRI3024	Headache	31	Mild	Resolved	None	Probable	No	Yes
BRI3024	Tenderness on side of head	18	Mild	Resolved	None	Definite	No	Yes
BRI3024	Nausea	28	Mild	Resolved	None	Probable	No	Yes
BRI3024	Watering eyes	27	Mild	Resolved	None	Probable	No	Yes
BRI3030	Neck pain	26	Mild	Resolved	None	Probable	No	Yes
BRI3030	Back pain	3	Mild	Resolved	None	Not related	No	No
BRI3030	Scalp discomfort	27	Mild	Resolved	None	Definite	No	Yes
BRI3030	Watering eyes	23	Mild	Resolved	None	Probable	No	Yes
BRI3030	Dizziness	27	Mild	Resolved	None	Probable	No	Yes
BRI3030	Headache	27	Mild	Resolved	None	Probable	No	Yes
BRI3032	Neck pain	13	Mild	Resolved	None	Probable	No	Yes
BRI3032	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI3032	Dizziness	28	Mild	Resolved	None	Probable	No	Yes
BRI3032	Scalp discomfort	0	Mild	Resolved	None	Definite	No	Yes
BRI3033	Tooth pain	15	Mild	Resolved	None	Probable	No	No
BRI3033	Watering eyes	0	Mild	Resolved	None	Probable	No	Yes
BRI3033	Vibrating jaw	0	Mild	Resolved	None	Probable	No	No
BRI3033	Twitching sensation in both eyes	4	Mild	Resolved	None	Probable	No	No
BRI3033	Headache	2	Mild	Resolved	None	Probable	No	Yes

TABLE 44 Listing of adverse events reported in rTMS arm (*continued*)

Trial ID	Adverse event	Duration (days)	Severity	Outcome	Treatment	Related	Serious	Expected
BRI3033	Scalp discomfort	28	Mild	Resolved	None	Probable	No	Yes
BRI3033	Neck pain	2	Mild	Resolved	None	Probable	No	Yes
BRI3039	Nausea	0	Mild	Resolved	None	Possible	No	Yes
BRI3039	Jaw ache	0	Mild	Resolved	None	Probable	No	Yes
BRI3040	Neck pain	1	Mild	Resolved	None	Probable	No	Yes
BRI3040	Tooth pain	1	Mild	Resolved	None	Possible	No	No
BRI3042	Jaw ache	2	Mild	Resolved	None	Possible	No	Yes
BRI3042	Headache	2	Mild	Resolved	None	Possible	No	Yes
BRI3044	Scalp discomfort	5	Mild	Resolved	None	Probable	No	Yes
BRI3046	Headache	1	Mild	Resolved	None	Probable	No	Yes
BRI3046	Conjunctivitis	.	Mild	Unknown	Concomitant medication	Not related	No	No
BRI3046	Eczema in eye	.	Mild	Unknown	Concomitant medication	Not related	No	No
BRI3046	Watering eyes	1	Mild	Resolved	None	Probable	No	Yes
BRI3047	Neck pain	1	Mild	Resolved	None	Probable	No	Yes
BRI3047	Jaw ache	1	Mild	Resolved	None	Probable	No	Yes
BRI3047	Headache	1	Mild	Resolved	None	Probable	No	Yes
BRI3047	Neck pain	1	Mild	Resolved	None	Probable	No	Yes
BRI3047	Headache	1	Mild	Resolved	None	Probable	No	Yes
BRI3049	Dizziness	2	Mild	Resolved	None	Probable	No	Yes
BRI3049	Neck pain	6	Mild	Resolved	None	Probable	No	Yes
BRI3049	Jaw ache	2	Mild	Resolved	None	Probable	No	Yes
BRI3049	Headache	1	Mild	Resolved	None	Probable	No	Yes
BRI3049	Headache	11	Mild	Resolved	None	Probable	No	Yes
BRI3049	Neck pain	1	Mild	Resolved	None	Probable	No	Yes
BRI3049	Irritability	1	Mild	Resolved	None	Possible	No	No
BRI3049	Scalp discomfort	1	Mild	Resolved	None	Probable	No	Yes
BRI3049	Watering eyes	1	Mild	Resolved	None	Probable	No	Yes
BRI3049	Tearful	3	Mild	Resolved	None	Possible	No	No
BRI3049	Nausea	1	Mild	Resolved	None	Probable	No	Yes
BRI3052	Headache	1	Mild	Resolved	None	Not related	No	Yes
BRI3052	Scalp discomfort	1	Mild	Resolved	None	Not related	No	Yes
BRI3053	Nausea	3	Mild	Resolved	None	Probable	No	Yes
BRI3053	Headache	1	Mild	Resolved	None	Probable	No	Yes
BRI3053	Scalp discomfort	1	Mild	Resolved	None	Probable	No	Yes

continued

TABLE 44 Listing of adverse events reported in rTMS arm (*continued*)

Trial ID	Adverse event	Duration (days)	Severity	Outcome	Treatment	Related	Serious	Expected
BRI3053	Headache	7	Mild	Resolved	None	Probable	No	Yes
BRI3053	Neck pain	1	Mild	Resolved	None	Probable	No	Yes
BRI3053	Scalp discomfort	3	Mild	Resolved	None	Probable	No	Yes
BRI3055	Watering eyes	3	Mild	Resolved	None	Probable	No	Yes
BRI3055	Watering eyes	1	Mild	Resolved	None	Probable	No	Yes
BRI3055	Scalp discomfort	1	Mild	Resolved	None	Probable	No	Yes
BRI3055	Headache	1	Mild	Resolved	None	Probable	No	Yes
BRI3055	Watering eyes	1	Mild	Resolved	None	Probable	No	Yes
BRI3055	Scalp discomfort	17	Mild	Resolved	None	Probable	No	Yes
BRI3055	Tinnitus	.	Mild	Continuing	None	Probable	No	Yes
BRI3055	Tinnitus	5	Mild	Resolved	None	Probable	No	Yes
BRI3055	Neck pain	3	Mild	Resolved	None	Probable	No	Yes
BRI3055	Scalp discomfort	5	Mild	Resolved	None	Probable	No	Yes
BRI3055	Headache	12	Mild	Resolved	None	Probable	No	Yes
BRI3055	Neck pain	3	Mild	Resolved	None	Probable	No	Yes
BRI3056	Headache	.	Mild	Continuing	None	Probable	No	Yes
BRI3056	Twitching in left lip and under jaw	6	Mild	Resolved	None	Definite	No	No
BRI3056	Headache	38	Mild	Resolved	None	Probable	No	Yes
BRI3056	Nerves twitching	1	Mild	Resolved	None	Definite	No	No
BRI3059	Headache	6	Mild	Resolved	None	Probable	No	Yes
BRI3059	Headache	13	Mild	Resolved	None	Probable	No	Yes
BRI3059	Neck pain	1	Mild	Resolved	None	Probable	No	Yes
BRI3059	Memory difficulties	57	Mild	Resolved	None	Possible	No	No
BRI3059	Head feels hot on right side	1	Mild	Resolved	None	Possible	No	No
BRI3059	Throbbing behind right eye	1	Mild	Resolved	None	Possible	No	No
BRI3059	Neck pain	4	Mild	Resolved	None	Probable	No	Yes
BRI3059	Nerve above right eye/eyebrow feels uncomfortable	7	Mild	Resolved	None	Probable	No	No
BRI3059	Scalp discomfort	1	Mild	Resolved	None	Definite	No	Yes
BRI3059	Jaw ache	34	Mild	Resolved	None	Probable	No	Yes
BRI3059	Headache	6	Mild	Resolved	None	Probable	No	Yes
BRI4007	Head injury (left side)	0	Moderate	Resolved	None	Not related	Yes	No
BRI4009	Anxiety	57	Moderate	Resolved	None	Possible	No	No

TABLE 44 Listing of adverse events reported in rTMS arm (*continued*)

Trial ID	Adverse event	Duration (days)	Severity	Outcome	Treatment	Related	Serious	Expected
BRI4009	Kidney infection	31	Severe	Resolved	Concomitant Medication	Not related	No	No
BRI4012	Bit tongue	0	Mild	Resolved	None	Possible	No	No
BRI4012	Eye pain	0	Moderate	Resolved	None	Possible	No	No
BRI4012	Paresthesia	0	Moderate	Resolved	None	Possible	No	No
BRI4012	Headache	0	Mild	Resolved	None	Possible	No	Yes
BRI4020	Dizziness	0	Mild	Resolved	None	Probable	No	Yes
BRI4020	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI4020	Eye pain	0	Mild	Resolved	None	Possible	No	No
BRI4020	Tinnitus	0	Mild	Resolved	None	Probable	No	Yes
BRI4020	Watering eyes	0	Mild	Resolved	None	Possible	No	Yes
BRI4020	Dizziness	0	Mild	Resolved	None	Possible	No	Yes
BRI4022	Facial pain	0	Mild	Resolved	None	Possible	No	No
BRI4022	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI4022	Facial pain	0	Mild	Resolved	None	Probable	No	Yes
BRI4022	Face/tooth pain (left side)	0	Mild	Resolved	None	Possible	No	No
BRI4022	Face/tooth pain (left side)	0	Mild	Resolved	None	Possible	No	No
BRI4022	Tooth pain	0	Mild	Resolved	None	Possible	No	No
BRI4022	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI4022	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI4022	Nausea	0	Mild	Resolved	None	Possible	No	No
BRI4022	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI4022	Dizziness	0	Mild	Resolved	None	Possible	No	No
BRI4022	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI4022	Facial pain	0	Mild	Resolved	None	Possible	No	No
BRI4022	Dizziness	0	Mild	Resolved	None	Possible	No	No
BRI4022	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI4022	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI4022	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI4022	Face/tooth pain (left side)	0	Mild	Resolved	None	Possible	No	No
BRI4022	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI4022	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI4022	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI4022	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes

continued

TABLE 44 Listing of adverse events reported in rTMS arm (*continued*)

Trial ID	Adverse event	Duration (days)	Severity	Outcome	Treatment	Related	Serious	Expected
BRI4022	Facial pain	0	Mild	Resolved	None	Possible	No	No
BRI4022	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI4022	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI4022	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI4022	Face/tooth pain (left side)	0	Mild	Resolved	None	Possible	No	No
BRI4022	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI4022	Small amount of pain around left and right side of scalp, cheeks	0	Mild	Resolved	None	Probable	No	Yes
BRI4022	Facial pain	0	Mild	Resolved	None	Possible	No	No
BRI4022	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI4022	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI4022	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI4022	Facial pain	0	Mild	Resolved	Concomitant medication	Possible	No	No
BRI4022	Face/tooth pain (left side)	0	Mild	Resolved	None	Possible	No	No
BRI4022	Right maxilla pain (later in day)	0	Mild	Resolved	Concomitant medication	Probable	No	Yes
BRI4022	Facial pain	0	Mild	Resolved	None	Possible	No	No
BRI4026	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI4026	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI4026	Headache	0	Mild	Resolved	Concomitant medication	Probable	No	Yes
BRI4026	Watering eyes	0	Mild	Resolved	None	Unlikely	No	No
BRI4026	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI4026	Nausea	0	Mild	Resolved	None	Unlikely	No	No
BRI4026	Nausea	0	Mild	Resolved	None	Unlikely	No	No
BRI4026	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI4026	Watering eyes	0	Mild	Resolved	None	Unlikely	No	No
BRI4026	Neck pain	0	Mild	Resolved	None	Possible	No	Yes
BRI4026	Watering eyes	0	Mild	Resolved	None	Unlikely	No	No
BRI4026	Jaw ache	0	Mild	Resolved	None	Possible	No	Yes
BRI4026	Pins and needles in left arm	0	Mild	Resolved	None	Possible	No	No
BRI4026	Nausea	0	Mild	Resolved	None	Unlikely	No	No
BRI4026	Watering eyes	0	Mild	Resolved	None	Unlikely	No	No
BRI4026	Nausea	0	Mild	Resolved	None	Unlikely	No	No

TABLE 44 Listing of adverse events reported in rTMS arm (*continued*)

Trial ID	Adverse event	Duration (days)	Severity	Outcome	Treatment	Related	Serious	Expected
BRI4026	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI4026	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI4026	Jaw ache	0	Mild	Resolved	None	Possible	No	Yes
BRI4026	Watering eyes	0	Mild	Resolved	None	Unlikely	No	No
BRI4028	Paresthesia	60	Mild	Resolved	None	Possible	No	Yes
BRI4028	Neck pain	1	Mild	Resolved	None	Possible	No	Yes
BRI4028	Tinnitus	199	Moderate	Resolved	None	Possible	No	Yes
BRI4028	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI4028	Watering eyes	0	Mild	Resolved	None	Unlikely	No	Yes
BRI4028	Headache	1	Mild	Resolved	None	Probable	No	Yes
BRI4028	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI4030	Watering eyes	0	Mild	Resolved	None	Unlikely	No	No
BRI4030	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI4030	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI4030	Watering eyes	0	Mild	Resolved	None	Unlikely	No	No
BRI4030	Neck pain	7	Mild	Resolved	None	Probable	No	Yes
BRI4030	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI4030	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI4030	Watering eyes	0	Mild	Resolved	None	Unlikely	No	No
BRI4030	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI4030	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI4030	Neck pain	0	Mild	Resolved	None	Possible	No	Yes
BRI4030	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI4030	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI4030	Headache	0	Mild	Resolved	Concomitant medication	Probable	No	Yes
BRI4030	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI4030	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI4030	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI4030	Tingling/pins and needles in left hand	0	Mild	Resolved	None	Probable	No	Yes
BRI4030	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI4030	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI4030	Pins and needles in hand	0	Mild	Resolved	None	Probable	No	Yes
BRI4030	Neck pain	0	Mild	Resolved	None	Probable	No	Yes

continued

TABLE 44 Listing of adverse events reported in rTMS arm (*continued*)

Trial ID	Adverse event	Duration (days)	Severity	Outcome	Treatment	Related	Serious	Expected
BRI4030	Dizziness	0	Mild	Resolved	None	Unlikely	No	No
BRI4030	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI4030	Watering eyes	0	Mild	Resolved	None	Unlikely	No	No
BRI4030	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI4030	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI4030	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI4030	Tingling in left hand	0	Mild	Resolved	None	Probable	No	Yes
BRI4030	Jaw ache	0	Mild	Resolved	None	Probable	No	Yes
BRI4030	Tingling in left hand	0	Mild	Resolved	None	Probable	No	Yes
BRI4031	Sensitivity in capped tooth	0	Mild	Resolved	None	Possible	No	No
BRI4031	Sensitivity in capped tooth	0	Mild	Resolved	None	Possible	No	No
BRI4031	Sensitivity in capped tooth	0	Mild	Resolved	None	Possible	No	No
BRI4031	Sensitivity in capped tooth	0	Mild	Resolved	None	Possible	No	No
BRI4031	Sensitivity in capped tooth	0	Mild	Resolved	None	Possible	No	No
BRI4031	Sensitivity in capped tooth	0	Mild	Resolved	None	Possible	No	No
BRI4031	Sensitivity in capped tooth	0	Mild	Resolved	None	Possible	No	No
BRI4031	Sensitivity in capped tooth	0	Mild	Resolved	None	Possible	No	No
BRI4031	Sensitivity in capped tooth	0	Mild	Resolved	None	Possible	No	No
BRI4031	Headache	43	Moderate	Resolved	Concomitant medication	Probable	No	Yes
BRI4031	Tenderness in tooth (capped)	0	Mild	Resolved	None	Possible	No	No
BRI4031	Sensitivity in capped tooth	0	Mild	Resolved	None	Possible	No	No
BRI4031	Sensitivity in capped tooth	0	Mild	Resolved	None	Possible	No	No
BRI4031	Sensitivity in capped tooth	0	Mild	Resolved	None	Possible	No	No
BRI4031	Sensitivity in capped tooth	0	Mild	Resolved	None	Possible	No	No
BRI4031	Sensitivity in capped tooth	0	Mild	Resolved	None	Possible	No	No
BRI4031	Sensitivity in capped tooth	0	Mild	Resolved	None	Possible	No	No

TABLE 44 Listing of adverse events reported in rTMS arm (*continued*)

Trial ID	Adverse event	Duration (days)	Severity	Outcome	Treatment	Related	Serious	Expected
BRI4033	Jaw ache	0	Mild	Resolved	None	Possible	No	Yes
BRI4033	Jaw ache	0	Mild	Resolved	None	Possible	No	Yes
BRI4033	Jaw ache	0	Mild	Resolved	None	Possible	No	Yes
BRI4033	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI4033	Jaw ache	0	Mild	Resolved	None	Possible	No	Yes
BRI4033	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI4033	Jaw ache	0	Mild	Resolved	None	Possible	No	Yes
BRI4033	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI4033	Jaw ache	0	Mild	Resolved	None	Possible	No	Yes
BRI4033	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI4033	Jaw ache	0	Mild	Resolved	None	Possible	No	Yes
BRI4033	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI4033	Neck pain	0	Mild	Resolved	None	Possible	No	Yes
BRI4033	Attempt of self-harm	0	Severe	Resolved	None	Unlikely	No	No
BRI4033	Jaw ache	0	Mild	Resolved	None	Possible	No	No
BRI4033	Neck pain	0	Mild	Resolved	None	Possible	No	Yes
BRI4033	Dizziness	0	Mild	Resolved	None	Possible	No	No
BRI4033	Neck pain	0	Mild	Resolved	None	Possible	No	Yes
BRI4033	Neck pain	0	Mild	Resolved	None	Possible	No	Yes
BRI4033	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI4033	Weight loss (history of anorexia)	276	Moderate	Resolved	None	Unlikely	No	No
BRI4033	Neck pain	0	Mild	Resolved	None	Possible	No	Yes
BRI4033	Jaw ache	0	Mild	Resolved	None	Possible	No	Yes
BRI4033	Jaw ache	0	Mild	Resolved	None	Possible	No	No
BRI4033	Jaw ache	0	Mild	Resolved	None	Probable	No	Yes
BRI4033	Tiredness (more severe/ excessive)	67	Moderate	Resolved	None	Unlikely	No	No
BRI4033	Jaw ache	30	Mild	Resolved	None	Probable	No	Yes
BRI4033	Neck pain	0	Mild	Resolved	None	Possible	No	Yes
BRI4033	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI4033	Shooting pain in right leg	0	Mild	Resolved	None	Unlikely	No	No
BRI4033	Headache	0	Mild	Resolved	Concomitant medication	Probable	No	Yes
BRI4033	Headache	0	Mild	Resolved	None	Probable	No	Yes

continued

TABLE 44 Listing of adverse events reported in rTMS arm (*continued*)

Trial ID	Adverse event	Duration (days)	Severity	Outcome	Treatment	Related	Serious	Expected
BRI4034	Nausea	0	Mild	Resolved	None	Probable	No	Yes
BRI4034	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI4034	Headache	69	Mild	Resolved	None	Probable	No	Yes
BRI4034	Pain through head during stimulation	0	Mild	Resolved	None	Possible	No	Yes
BRI4034	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI4034	Jaw ache	111	Mild	Resolved	None	Possible	No	Yes
BRI4037	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI4037	Jaw ache	0	Mild	Resolved	None	Probable	No	Yes
BRI4037	Jaw ache	0	Mild	Resolved	None	Probable	No	Yes
BRI4037	Jaw ache	0	Mild	Resolved	None	Probable	No	Yes
BRI4037	Irritability	184	Mild	Resolved	None	Possible	No	No
BRI4037	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI4037	Dizziness	0	Mild	Resolved	None	Probable	No	Yes
BRI4037	Headache	0	Mild	Resolved	Concomitant medication	Probable	No	Yes
BRI4037	Jaw ache	0	Mild	Resolved	None	Probable	No	Yes
BRI4037	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI4037	Nosebleed	0	Mild	Resolved	None	Possible	No	No
BRI4037	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI4037	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI4037	Jaw ache	0	Mild	Resolved	None	Probable	No	Yes
BRI4037	Dizziness	0	Mild	Resolved	None	Probable	No	Yes
BRI4037	Jaw ache	0	Mild	Resolved	None	Probable	No	Yes
BRI4037	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI4037	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI4037	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI4037	Surly	0	Moderate	Resolved	None	Possible	No	No
BRI4037	Lightheadedness	0	Mild	Resolved	None	Probable	No	Yes
BRI4037	Neck pain	1	Mild	Resolved	None	Probable	No	Yes
BRI4037	Irritability	2	Mild	Resolved	None	Probable	No	Yes
BRI4037	'When listening to speech it was delayed from other people end'	0	Moderate	Resolved	None	Unlikely	No	No
BRI4037	Dizziness	0	Mild	Resolved	None	Probable	No	Yes
BRI4037	Dizziness	0	Mild	Resolved	None	Probable	No	Yes

TABLE 44 Listing of adverse events reported in rTMS arm (*continued*)

Trial ID	Adverse event	Duration (days)	Severity	Outcome	Treatment	Related	Serious	Expected
BRI4037	Dizziness	2	Mild	Resolved	None	Probable	No	Yes
BRI4037	Dizziness	0	Mild	Resolved	None	Probable	No	Yes
BRI4037	Dizziness	0	Mild	Resolved	None	Probable	No	Yes
BRI4037	Hot flashes	4	Mild	Resolved	None	Unlikely	No	No
BRI4037	Disturbed sleep	4	Mild	Resolved	None	Unlikely	No	No
BRI4037	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI4037	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI4037	Nosebleed	0	Mild	Resolved	None	Possible	No	No
BRI4037	Two episodes of Nose bleed	0	Mild	Resolved	None	Possible	No	No
BRI4037	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI4037	Dizziness	0	Mild	Resolved	None	Probable	No	Yes
BRI4037	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI4037	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI4037	Dizziness	0	Mild	Resolved	None	Probable	No	Yes
BRI4037	Jaw ache	0	Mild	Resolved	None	Probable	No	Yes
BRI4037	Dizziness	0	Mild	Resolved	None	Probable	No	Yes
BRI4037	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI4037	Jaw ache	0	Mild	Resolved	None	Probable	No	Yes
BRI4037	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI4038	Asthma exacerbation	1	Severe	Resolved	Concomitant medication	Unlikely	No	No
BRI4038	Dizziness	0	Mild	Resolved	None	Probable	No	Yes
BRI4038	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI4038	Headache	186	Mild	Resolved	Concomitant medication	Probable	No	Yes
BRI4038	Watering eyes	0	Mild	Resolved	None	Probable	No	Yes
BRI4038	Neck pain	4	Mild	Resolved	None	Probable	No	Yes
BRI4038	Headache	0	Mild	Resolved	Concomitant medication	Probable	No	Yes
BRI4038	Watering eyes	0	Mild	Resolved	None	Probable	No	Yes
BRI4038	Headache	0	Mild	Resolved	Concomitant medication	Probable	No	Yes
BRI4038	Urinary tract infection	9	Severe	Resolved	Concomitant medication	Unlikely	No	No
BRI4038	Nausea	0	Mild	Resolved	None	Possible	No	Yes
BRI4038	Nausea	1	Mild	Resolved	None	Possible	No	Yes
BRI4038	Common cold	6	Mild	Resolved	None	Not related	No	No

continued

TABLE 44 Listing of adverse events reported in rTMS arm (*continued*)

Trial ID	Adverse event	Duration (days)	Severity	Outcome	Treatment	Related	Serious	Expected
BRI4038	Dizziness	0	Mild	Resolved	None	Probable	No	Yes
BRI4041	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI4041	Numbness in hand (right)	0	Mild	Resolved	None	Possible	No	Yes
BRI4041	Dizziness	0	Mild	Resolved	None	Probable	No	Yes
BRI4041	Minor hand tremors	8	Mild	Resolved	None	Possible	No	Yes
BRI4041	Hand tremors in both hands	15	Mild	Resolved	None	Possible	No	Yes
BRI4043	Tiredness	37	Mild	Resolved	None	Unlikely	No	No
BRI4043	Disturbed sleep	1	Mild	Resolved	None	Unlikely	No	No
BRI4043	(Mild/short-term) memory loss	22	Mild	Resolved	None	Unlikely	No	No
BRI4044	Pain at site of stimulation	0	Severe	Resolved	None	Probable	No	Yes
BRI4044	Dizziness	17	Mild	Resolved	None	Probable	No	Yes
BRI4044	Headache	0	Mild	Resolved	Concomitant medication	Probable	No	Yes
BRI4044	Nausea	19	Moderate	Resolved	None	Possible	No	Yes
BRI4044	Headache	0	Mild	Resolved	Concomitant medication	Probable	No	Yes
BRI4044	Headache	19	Mild	Resolved	None	Probable	No	Yes
BRI4047	Headache	71	Mild	Resolved	None	Probable	No	Yes

A&E, accident and emergency.

TABLE 45 Listing of AEs events reported in cgiTBS arm

Trial ID	Adverse event	Duration (days)	Severity	Outcome	Treatment	Related	Serious	Expected
BRI1005	Scalp discomfort	0	Mild	Resolved	None	Possible	No	Yes
BRI1005	Headache	0	Mild	Resolved	None	Possible	No	Yes
BRI1008	Scalp discomfort	0	Mild	Resolved	None	Possible	No	Yes
BRI1008	Lump/cyst inside mouth (biopsy may be required)	114	Mild	Resolved	None	Not related	No	No
BRI1009	Headache	1	Mild	Resolved	None	Possible	No	Yes
BRI1009	Tinnitus	29	Mild	Resolved	None	Not related	No	No
BRI1009	Anxiety	29	Mild	Resolved	None	Not related	No	No
BRI1012	Neck pain	0	Mild	Resolved	Non-drug therapy	Not related	No	No

TABLE 45 Listing of AEs events reported in cgiTBS arm (*continued*)

Trial ID	Adverse event	Duration (days)	Severity	Outcome	Treatment	Related	Serious	Expected
BRI1012	Tension in neck and shoulders during MRI scans	0	Mild	Resolved	None	Probable	No	No
BRI1013	Jaw ache	0	Mild	Resolved	Non-drug therapy	Possible	No	Yes
BRI1013	Tingling sensation on face	86	Mild	Resolved	None	Possible	No	No
BRI1013	Tired/dazed during treatment	0	Mild	Resolved	None	Possible	No	No
BRI1013	Ear infection	17	Mild	Resolved	Concomitant medication	Not related	No	No
BRI1013	Touching sensation on cheek	0	Mild	Resolved	None	Possible	No	No
BRI1013	Jaw ache	0	Mild	Resolved	None	Possible	No	No
BRI1013	Tingling sensation on face	0	Mild	Resolved	None	Possible	No	No
BRI1017	Headache	49	Mild	Resolved	None	Unlikely	No	No
BRI1017	Tinnitus	0	Mild	Resolved	None	Possible	No	No
BRI1017	Periodic tingling at left back of head	161	Mild	Resolved	None	Unlikely	No	No
BRI1017	Headache	33	Mild	Resolved	None	Possible	No	No
BRI1017	Insomnia	56	Mild	Resolved	None	Possible	No	No
BRI1018	Suicidal thoughts prior to treatment	0	Moderate	Resolved	None	Not related	No	Yes
BRI1018	Lightheadedness	0	Mild	Resolved	None	Not related	No	No
BRI1018	Dizziness	0	Mild	Resolved	None	Possible	No	No
BRI1018	Tingling at back of tongue	0	Mild	Resolved	None	Possible	No	No
BRI1018	Physically unwell	0	Moderate	Resolved	None	Possible	No	Yes
BRI1018	Headache	0	Mild	Resolved	None	Possible	No	No
BRI1018	Tingling sensation on face	0	Mild	Resolved	None	Possible	No	No
BRI1019	Stiff neck	0	Mild	Resolved	None	Unlikely	No	No
BRI1019	Tiredness/stiff neck	0	Mild	Resolved	None	Possible	No	No
BRI1019	Sleepiness	0	Mild	Resolved	None	Unlikely	No	No
BRI1022	Tension in neck and shoulders during MRI scans	27	Mild	Resolved	None	Not related	No	No
BRI1023	Tingling in left hand (LH) shoulder	0	Mild	Resolved	None	Possible	No	No
BRI1023	Tongue discomfort	0	Mild	Resolved	None	Possible	No	No
BRI1023	Eye pain	0	Mild	Resolved	None	Possible	No	No

continued

TABLE 45 Listing of AEs events reported in cgiTBS arm (*continued*)

Trial ID	Adverse event	Duration (days)	Severity	Outcome	Treatment	Related	Serious	Expected
BRI1023	Indigestion	263	Mild	Resolved	None	Possible	No	No
BRI1023	Intermittent dizziness	.	Mild	Unknown	None	Unlikely	No	No
BRI1023	Self-harm	0	Mild	Resolved	Concomitant medication	Not related	No	No
BRI1023	Excessive fatigue	34	Mild	Resolved	None	Unlikely	No	No
BRI1023	Self-harm	0	Mild	Resolved	None	Not related	No	No
BRI1023	Tongue discomfort	0	Mild	Resolved with sequelae	None	Possible	No	No
BRI1023	(Mild/short-term) memorylLoss	.	Mild	Unknown	None	Possible	No	No
BRI1023	Speech difficulties (word finding/trouble finishing sentences/echoing in head)	.	Mild	Unknown	None	Possible	No	Yes
BRI1023	Headache	0	Mild	Resolved	None	Possible	No	No
BRI1023	Shoulder injury	0	Mild	Resolved	None	Not related	No	No
BRI1023	Tinnitus	48	Mild	Resolved	None	Possible	No	No
BRI1024	Watering eyes	0	Mild	Resolved	None	Possible	No	No
BRI1024	Jaw ache	64	Mild	Resolved	None	Possible	No	No
BRI1024	Lightheadedness	0	Mild	Resolved	None	Possible	No	No
BRI1024	Jaw ache	0	Mild	Resolved	None	Possible	No	No
BRI1024	Headache	86	Mild	Resolved	None	Possible	No	No
BRI1024	Jaw ache	86	Mild	Resolved	None	Possible	No	No
BRI1024	Back pain	163	Mild	Resolved	Concomitant medication	Unlikely	No	No
BRI1024	Facial pain	0	Mild	Resolved	None	Possible	No	No
BRI1024	Jaw ache	0	Mild	Resolved	None	Possible	No	No
BRI1024	Stomach discomfort	11	Mild	Resolved	None	Possible	No	No
BRI1025	Anxiety	58	Mild	Resolved	None	Unlikely	No	No
BRI1025	Dizziness	71	Mild	Resolved	None	Possible	No	No
BRI1025	Dizziness	0	Mild	Resolved	None	Unlikely	No	No
BRI1030	Headache	1	Mild	Resolved	None	Possible	No	No
BRI1030	Headache	4	Mild	Resolved	Concomitant medication	Possible	No	No
BRI1031	Lightheadedness	0	Mild	Resolved	None	Possible	No	No
BRI1034	Headache	0	Mild	Resolved	None	Possible	No	No
BRI1034	Headache	1	Mild	Resolved	None	Possible	No	No
BRI1034	Jaw ache	1	Mild	Resolved	None	Possible	No	No

TABLE 45 Listing of AEs events reported in cgiTBS arm (*continued*)

Trial ID	Adverse event	Duration (days)	Severity	Outcome	Treatment	Related	Serious	Expected
BRI1034	Dizziness	2	Mild	Resolved	None	Possible	No	No
BRI1034	Headache	16	Mild	Resolved	None	Possible	No	No
BRI1036	Collapse and auditory burning smell	0	Moderate	Resolved	None	Possible	No	No
BRI1036	Multiple seizures with focal onsent	11	Severe	Resolved	Concomitant medication	Definite	No	No
BRI1036	Stiff neck	0	Mild	Resolved	None	Possible	No	No
BRI1036	Nausea	0	Mild	Resolved	None	Possible	No	No
BRI1036	Headache	0	Mild	Resolved	None	Not related	No	No
BRI1036	Consciousness loss	0	Moderate	Resolved	None	Possible	No	No
BRI1036	Collapse and auditory burning smell	125	Moderate	Resolved	None	Possible	No	No
BRI1037	Insomnia	.	Moderate	Unknown	None	Unlikely	No	No
BRI1037	Overdose	0	Moderate	Resolved	None	Not related	No	No
BRI1037	Agoraphobia	.	Moderate	Unknown	None	Unlikely	No	No
BRI1037	Anxiety	.	Moderate	Unknown	None	Possible	No	No
BRI1037	Headache	0	Mild	Resolved	None	Unlikely	No	No
BRI1043	Dizziness	4	Mild	Resolved	None	Unlikely	No	No
BRI1043	Headache	1	Mild	Resolved	Concomitant medication	Possible	No	No
BRI1043	Pain in temples when eating and talking	1	Mild	Resolved	None	Possible	No	No
BRI1043	Sickness	0	Mild	Resolved	None	Unlikely	No	No
BRI1043	Foggy headed/difficulty finishing words	9	Mild	Resolved	None	Possible	No	No
BRI1044	Headache	0	Mild	Resolved	None	Probable	No	No
BRI1044	Stiff neck	4	Mild	Resolved	None	Possible	No	No
BRI1044	Scalp discomfort	0	Mild	Resolved	None	Probable	No	No
BRI1044	Jaw ache	14	Mild	Resolved	None	Possible	No	Yes
BRI1044	Stiff neck	17	Mild	Resolved	None	Possible	No	No
BRI1044	Scalp discomfort	0	Mild	Resolved	None	Possible	No	No
BRI1044	Scalp discomfort	1	Mild	Resolved	None	Possible	No	No
BRI1044	Jaw ache	12	Mild	Resolved	None	Probable	No	No
BRI1048	Watering eyes	0	Mild	Resolved	None	Probable	No	Yes
BRI1048	Watering eyes	1	Mild	Resolved	None	Possible	No	No
BRI1048	Watering eyes	0	Mild	Resolved	None	Probable	No	No
BRI1048	Watering eyes	1	Mild	Resolved	None	Possible	No	Yes

continued

TABLE 45 Listing of AEs events reported in cgiTBS arm (*continued*)

Trial ID	Adverse event	Duration (days)	Severity	Outcome	Treatment	Related	Serious	Expected
BRI1048	Watering eyes	0	Mild	Resolved	None	Possible	No	Yes
BRI1048	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI1048	Watering eyes	0	Mild	Resolved	None	Possible	No	Yes
BRI1048	Watering eyes	0	Mild	Resolved	None	Probable	No	No
BRI1048	Watering eyes	4	Mild	Resolved	None	Probable	No	Yes
BRI1048	Watering eyes	0	Mild	Resolved	None	Possible	No	No
BRI1049	Viral infection (sore throat, etc.)	.	Moderate	Unknown	None	Not related	No	No
BRI1049	Headache	1	Mild	Resolved	None	Possible	No	No
BRI1049	Sleepiness	23	Mild	Resolved	None	Possible	No	No
BRI1049	Jaw ache	0	Mild	Resolved	None	Probable	No	Yes
BRI1050	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI1050	Jaw ache	0	Mild	Resolved	None	Possible	No	Yes
BRI1050	Dizziness	0	Mild	Resolved	None	Possible	No	Yes
BRI1050	Dizziness	0	Mild	Resolved	None	Probable	No	Yes
BRI1050	Scalp discomfort	0	Mild	Resolved	None	Possible	No	Yes
BRI1050	Headache	0	Mild	Resolved	None	Possible	No	Yes
BRI1050	Jaw ache	0	Mild	Resolved	None	Probable	No	Yes
BRI1050	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI1050	Dizziness	0	Mild	Resolved	None	Possible	No	Yes
BRI1050	Dizziness	0	Mild	Resolved	None	Possible	No	Yes
BRI1050	Dizziness	0	Mild	Resolved	None	Probable	No	Yes
BRI1050	Scalp discomfort	0	Mild	Resolved	None	Possible	No	Yes
BRI1050	Sleepiness	34	Mild	Resolved	None	Possible	No	Yes
BRI1050	Dizziness	0	Mild	Resolved	None	Possible	No	Yes
BRI1050	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI1050	Dizziness	24	Mild	Resolved	None	Possible	No	Yes
BRI1050	Dizziness	0	Mild	Resolved	None	Probable	No	Yes
BRI1050	Headache	24	Mild	Resolved	None	Possible	No	Yes
BRI1050	Headache	0	Mild	Resolved	None	Possible	No	Yes
BRI1050	Dizziness	0	Mild	Resolved	None	Possible	No	Yes
BRI1050	Headache	0	Mild	Resolved	None	Possible	No	Yes
BRI1050	Jaw ache	0	Mild	Resolved	None	Possible	No	Yes
BRI1050	Sleepiness	28	Mild	Resolved	None	Possible	No	No
BRI1050	Headache	0	Mild	Resolved	None	Possible	No	Yes

TABLE 45 Listing of AEs events reported in cgiTBS arm (*continued*)

Trial ID	Adverse event	Duration (days)	Severity	Outcome	Treatment	Related	Serious	Expected
BRI1050	Jaw ache	0	Mild	Resolved	None	Possible	No	Yes
BRI1050	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI1050	Dizziness	0	Mild	Resolved	None	Possible	No	Yes
BRI1050	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI1050	Dizziness	0	Mild	Resolved	None	Possible	No	Yes
BRI1050	Sleepiness	0	Mild	Resolved	None	Possible	No	Yes
BRI1050	Dizziness	0	Mild	Resolved	None	Probable	No	Yes
BRI1050	Jaw ache	0	Mild	Resolved	None	Probable	No	Yes
BRI1050	Headache	0	Mild	Resolved	None	Possible	No	Yes
BRI1050	Dizziness	0	Mild	Resolved	None	Possible	No	Yes
BRI1050	Dizziness	0	Mild	Resolved	None	Probable	No	Yes
BRI1050	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI1050	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI1050	Headache	0	Mild	Resolved	None	Possible	No	Yes
BRI1050	Jaw ache	0	Mild	Resolved	None	Probable	No	Yes
BRI1050	Dizziness	0	Mild	Resolved	None	Possible	No	Yes
BRI1050	Scalp discomfort	0	Mild	Resolved	None	Possible	No	Yes
BRI1050	Scalp discomfort	0	Mild	Resolved	None	Possible	No	Yes
BRI1050	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI1050	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI1050	Dizziness	0	Mild	Resolved	None	Probable	No	Yes
BRI1050	Headache	0	Mild	Resolved	None	Possible	No	Yes
BRI1050	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI1050	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI1050	Sleepiness	0	Mild	Resolved	None	Possible	No	No
BRI1050	Scalp discomfort	0	Mild	Resolved	None	Possible	No	Yes
BRI1050	Jaw ache	0	Mild	Resolved	None	Probable	No	Yes
BRI1050	Dizziness	0	Mild	Resolved	None	Possible	No	Yes
BRI1050	Scalp discomfort	0	Mild	Resolved	None	Possible	No	Yes
BRI1050	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI1050	Scalp discomfort	0	Mild	Resolved	None	Possible	No	Yes
BRI1050	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI1050	Dizziness	0	Mild	Resolved	None	Possible	No	Yes
BRI1050	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI1050	Dizziness	0	Mild	Resolved	None	Probable	No	Yes

continued

TABLE 45 Listing of AEs events reported in cgiTBS arm (*continued*)

Trial ID	Adverse event	Duration (days)	Severity	Outcome	Treatment	Related	Serious	Expected
BRI1050	Headache	0	Mild	Resolved	None	Possible	No	Yes
BRI1050	Headache	0	Mild	Resolved	None	Possible	No	Yes
BRI1050	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI1050	Headache	0	Mild	Resolved	None	Possible	No	Yes
BRI1050	Jaw ache	0	Mild	Resolved	None	Possible	No	Yes
BRI1050	Jaw ache	0	Mild	Resolved	None	Probable	No	Yes
BRI1050	Dizziness	0	Mild	Resolved	None	Probable	No	Yes
BRI1050	Jaw ache	0	Mild	Resolved	None	Possible	No	Yes
BRI1050	Jaw ache	0	Mild	Resolved	None	Possible	No	Yes
BRI1050	Scalp discomfort	0	Mild	Resolved	None	Possible	No	Yes
BRI1050	Scalp discomfort	0	Mild	Resolved	None	Possible	No	Yes
BRI1050	Scalp discomfort	0	Mild	Resolved	None	Possible	No	Yes
BRI1050	Sleepiness	1	Mild	Resolved	None	Possible	No	No
BRI1050	Jaw ache	0	Mild	Resolved	None	Probable	No	Yes
BRI1050	Jaw ache	0	Mild	Resolved	None	Probable	No	Yes
BRI1050	Scalp discomfort	0	Mild	Resolved	None	Possible	No	Yes
BRI1053	Tinnitus	0	Mild	Resolved	None	Unlikely	No	No
BRI1053	Tinnitus	146	Mild	Resolved	None	Possible	No	No
BRI1053	Tinnitus	1	Moderate	Resolved	None	Possible	No	Yes
BRI1056	Nausea	0	Mild	Resolved	None	Unlikely	No	Yes
BRI1056	Headache	2	Mild	Resolved	None	Possible	No	Yes
BRI1056	Tiredness	3	Mild	Resolved	None	Possible	No	Yes
BRI1056	Sinus pain	5	Mild	Resolved	None	Possible	No	Yes
BRI1059	Manic symptoms (excessive spending and euphoric mood). Started five-and-a-half weeks post TMS	9	Moderate	Resolved	None	Possible	No	No
BRI1059	Headache	5	Mild	Resolved	None	Possible	No	Yes
BRI1059	Irritability	15	Moderate	Resolved	None	Probable	No	No
BRI1059	Headache	1	Mild	Resolved	None	Possible	No	Yes
BRI1059	Stutter/stammer	0	Moderate	Resolved	None	Probable	No	No
BRI1059	Spikes in elevated mood lasting 2–3 days at a time	501	Mild	Unknown	None	Possible	No	No
BRI1059	Neck pain	1	Mild	Resolved	None	Possible	No	Yes
BRI1059	Headache	6	Moderate	Resolved	None	Unlikely	No	Yes

TABLE 45 Listing of AEs events reported in cgiTBS arm (*continued*)

Trial ID	Adverse event	Duration (days)	Severity	Outcome	Treatment	Related	Serious	Expected
BRI1059	Neck pain	2	Mild	Resolved	None	Possible	No	Yes
BRI1059	Tinnitus	612	Mild	Unknown	None	Possible	No	Yes
BRI1059	Headache	81	Mild	Resolved	None	Possible	No	Yes
BRI1059	Headache	3	Mild	Resolved	None	Possible	No	Yes
BRI1059	Headache	0	Mild	Resolved	None	Possible	No	Yes
BRI1059	Tinnitus (louder than usual)	1	Moderate	Resolved	None	Possible	No	Yes
BRI1059	Neck pain	1	Mild	Resolved	None	Possible	No	Yes
BRI1059	Hearing loss	0	Moderate	Resolved	None	Possible	No	No
BRI1059	Headache	2	Mild	Resolved	None	Unlikely	No	Yes
BRI1059	Headache	0	Mild	Resolved	None	Unlikely	No	Yes
BRI1059	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI1060	Headache	0	Mild	Resolved	None	Possible	No	Yes
BRI1060	Headache	0	Mild	Resolved	None	Possible	No	Yes
BRI1063	Pre-existing kidney pain significantly worse	264	Moderate	Resolved	Concomitant medication	Not related	No	No
BRI1063	COVID-19	16	Moderate	Resolved	Concomitant medication	Not related	No	No
BRI1063	Neck pain	1	Mild	Resolved	None	Possible	No	Yes
BRI1065	Scalp discomfort	1	Mild	Resolved	None	Possible	No	Yes
BRI1065	Headache	1	Mild	Resolved	None	Possible	No	Yes
BRI1065	Scalp discomfort	1	Mild	Resolved	None	Possible	No	Yes
BRI1065	Tension in neck after baseline MRI scan	0	Mild	Resolved	None	Probable	No	Yes
BRI1065	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI1067	Forgetfulness	42	Mild	Resolved	None	Possible	No	No
BRI1067	Scalp discomfort	1	Mild	Resolved	None	Possible	No	Yes
BRI1067	Aching in tops of arms	15	Mild	Resolved	None	Possible	No	No
BRI1067	Lightheadedness	0	Mild	Resolved	None	Unlikely	No	Yes
BRI1067	Neck pain	1	Mild	Resolved	None	Possible	No	Yes
BRI1067	Lethargy	15	Mild	Resolved	None	Possible	No	No
BRI1067	Headache	3	Mild	Resolved	None	Possible	No	Yes
BRI1067	Nausea	1	Mild	Resolved	None	Possible	No	Yes
BRI1067	Sensation of pulsating on left-hand-side of body. Commenced during MRI scan	7	Mild	Resolved	None	Possible	No	No
BRI1067	Neck pain	15	Mild	Resolved	None	Unlikely	No	Yes

continued

TABLE 45 Listing of AEs events reported in cgiTBS arm (*continued*)

Trial ID	Adverse event	Duration (days)	Severity	Outcome	Treatment	Related	Serious	Expected
BRI1067	Watering eyes	1	Mild	Resolved	None	Unlikely	No	Yes
BRI1067	Dizziness	1	Mild	Resolved	None	Possible	No	Yes
BRI1067	Back/muscle ache	2	Mild	Resolved	None	Possible	No	Yes
BRI1067	Patient described feeling wired	6	Mild	Resolved	None	Possible	No	No
BRI1068	Jaw ache	1	Mild	Resolved	None	Possible	No	Yes
BRI1068	Jaw ache	1	Mild	Resolved	None	Possible	No	Yes
BRI1068	Jaw ache	0	Mild	Resolved	None	Probable	No	Yes
BRI1068	Headache	1	Mild	Resolved	None	Possible	No	Yes
BRI1068	Jaw ache	4	Mild	Resolved	None	Probable	No	Yes
BRI1068	Neck pain	0	Mild	Resolved	None	Possible	No	Yes
BRI1068	Jaw ache	0	Mild	Resolved	None	Probable	No	Yes
BRI1068	Jaw ache	0	Mild	Resolved	None	Probable	No	Yes
BRI1068	Dizziness	1	Mild	Resolved	None	Possible	No	Yes
BRI1068	Vivid visualisations with eyes closed	0	Mild	Resolved	None	Unlikely	No	Yes
BRI1068	Headache	1	Mild	Resolved	None	Possible	No	Yes
BRI1068	Headache	1	Moderate	Resolved	None	Possible	No	Yes
BRI1068	Neck pain	3	Mild	Resolved	None	Possible	No	Yes
BRI1068	Jaw ache	1	Mild	Resolved	None	Probable	No	Yes
BRI1068	Discomfort of the temple (left)	0	Mild	Resolved	None	Possible	No	No
BRI1068	Jaw ache	1	Mild	Resolved	None	Probable	No	Yes
BRI1068	Jaw ache	0	Mild	Resolved	None	Probable	No	Yes
BRI1068	Headache	1	Mild	Resolved	Concomitant medication	Possible	No	Yes
BRI1069	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI1069	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI1069	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI1069	Flu-like response to COVID-19 vaccination	2	Moderate	Resolved	None	Not related	No	Yes
BRI1069	Headache	5	Mild	Resolved	None	Not related	No	Yes
BRI1069	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI1069	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI1069	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI1069	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI1069	Neck pain	9	Mild	Resolved	None	Not related	No	Yes

TABLE 45 Listing of AEs events reported in cgiTBS arm (*continued*)

Trial ID	Adverse event	Duration (days)	Severity	Outcome	Treatment	Related	Serious	Expected
BRI1069	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI1069	Scalp discomfort	0	Mild	Resolved	None	Probable	No	No
BRI1069	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI1069	Vertigo	0	Moderate	Resolved	None	Possible	No	No
BRI1069	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI1069	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI1069	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI1069	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI1069	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI1069	Tinnitus	25	Mild	Resolved with sequelae	None	Not related	No	Yes
BRI1069	Headache	15	Mild	Resolved with sequelae	None	Unlikely	No	Yes
BRI1069	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI1069	Neck pain	15	Mild	Resolved with sequelae	None	Unlikely	No	Yes
BRI1069	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI1069	Headache	3	Mild	Resolved	None	Not related	No	Yes
BRI1069	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI1069	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI1069	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI1069	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI1071	Tooth pain	0	Mild	Resolved	None	Unlikely	No	No
BRI1071	Tooth pain	0	Mild	Resolved	None	Definite	No	No
BRI1071	Tooth pain	0	Mild	Resolved	None	Definite	No	No
BRI1071	Migraine	1	Moderate	Resolved	None	Unlikely	No	No
BRI1073	Headache	0	Mild	Resolved	None	Possible	No	Yes
BRI1073	Headache	0	Mild	Resolved	None	Possible	No	Yes
BRI1077	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI1077	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI1077	Neck pain	0	Mild	Resolved	None	Possible	No	Yes
BRI1077	Overdose of paracetamol and painkillers at home. Did not require hospital admission	0	Moderate	Resolved	None	Not related	No	No
BRI1077	Headache	0	Mild	Resolved	None	Probable	No	Yes

continued

TABLE 45 Listing of AEs events reported in cgiTBS arm (*continued*)

Trial ID	Adverse event	Duration (days)	Severity	Outcome	Treatment	Related	Serious	Expected
BRI1078	Increased liver enzyme	43	Severe	Resolved	None	Not related	No	No
BRI1078	Nausea	36	Mild	Resolved	None	Not related	No	No
BRI1081	Headache	0	Mild	Resolved	None	Possible	No	Yes
BRI1086	Feeling hot and clammy	2	Moderate	Resolved	None	Possible	No	No
BRI1086	Feeling faint	2	Moderate	Resolved	None	Possible	No	No
BRI1087	Neck strain (gained from exercise)	42	Mild	Resolved	None	Not related	No	No
BRI1089	Jaw ache	0	Mild	Resolved	None	Possible	No	No
BRI1094	Two episodes of nose bleed	0	Mild	Resolved	None	Unlikely	No	No
BRI1094	Mild (short term) memory loss	59	Mild	Resolved	None	Possible	No	No
BRI1094	Aspirin and paracetamol OD	0	Moderate	Resolved	None	Possible	No	No
BRI1094	Fainted at home	0	Moderate	Resolved	None	Unlikely	No	No
BRI1094	Duloxetine overdose (reported at 16-week follow-up)	0	Moderate	Resolved	None	Possible	No	No
BRI1094	Co-codamol overdose (reported at 16-week MRI)	0	Moderate	Resolved	None	Unlikely	No	No
BRI1094	ED attendance and referral to haven house following self injection of propofol	9	Moderate	Resolved	None	Unlikely	No	No
BRI1094	Mild (short term) memory loss	1	Moderate	Resolved	None	Possible	No	No
BRI1094	Emergency department attendance and referral to haven house following ketamine and cocaine overdose	9	Severe	Resolved	None	Possible	No	No
BRI1094	Feeling of brain freeze	1	Moderate	Resolved	None	Possible	No	No
BRI1095	Discomfort in left temple during three stimulations (resolved with minor change in coil position)	0	Mild	Resolved	None	Probable	No	No
BRI1095	Disturbed sleep	260	Moderate	Unknown	None	Possible	No	No
BRI1095	Nausea	0	Mild	Resolved	None	Possible	No	No
BRI1095	Feeling of pressure and discomfort in right eye	161	Moderate	Resolved	Non-drug therapy	Possible	No	No

TABLE 45 Listing of AEs events reported in cgiTBS arm (*continued*)

Trial ID	Adverse event	Duration (days)	Severity	Outcome	Treatment	Related	Serious	Expected
BRI1095	Pain above right eye during simulations	0	Moderate	Resolved	None	Probable	No	No
BRI1095	Headache	0	Moderate	Resolved	None	Possible	No	Yes
BRI1095	Confusion	0	Moderate	Resolved	None	Possible	No	No
BRI1098	Headache	13	Mild	Resolved	None	Possible	No	Yes
BRI1098	Headache	1	Mild	Resolved	None	Possible	No	Yes
BRI1098	Nausea	5	Mild	Resolved	None	Possible	No	Yes
BRI1098	Nausea (intermittent) started during treatments	36	Mild	Resolved	None	Possible	No	Yes
BRI1098	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI1098	Twitching in left cheek and behind the ear during stimulations	0	Mild	Resolved	None	Possible	No	No
BRI1098	Tiredness	6	Mild	Resolved	None	Possible	No	Yes
BRI1098	Sickness	6	Moderate	Resolved	None	Probable	No	Yes
BRI1098	Dizziness-intermittent (started during treatments)	35	Mild	Resolved	None	Possible	No	Yes
BRI1098	Brain fog	13	Moderate	Resolved	None	Possible	No	No
BRI1098	Dizziness	13	Mild	Resolved	None	Possible	No	Yes
BRI1100	Discomfort above the right eye during stimulations	0	Mild	Resolved	None	Possible	No	No
BRI1100	Discomfort above the right eye during stimulations	0	Mild	Resolved	None	Possible	No	No
BRI1100	Discomfort above the right eye during stimulations	0	Mild	Resolved	None	Possible	No	No
BRI1100	Pain above right eye during simulations	0	Mild	Resolved	None	Probable	No	Yes
BRI1100	Discomfort above the right eye during stimulations	0	Mild	Resolved	None	Probable	No	No
BRI1100	Discomfort above the right eye during stimulations	0	Mild	Resolved	None	Probable	No	No
BRI1100	Pain above right eye during simulations	0	Mild	Resolved	None	Possible	No	No
BRI1100	Pain above right eye during simulations	0	Mild	Resolved	None	Possible	No	No
BRI1100	Pain above right eye during simulations	0	Mild	Resolved	None	Possible	No	No

continued

TABLE 45 Listing of AEs events reported in cgiTBS arm (*continued*)

Trial ID	Adverse event	Duration (days)	Severity	Outcome	Treatment	Related	Serious	Expected
BRI1100	Pain above right eye during simulations	0	Mild	Resolved	None	Possible	No	No
BRI1100	Pain above right eye during simulations	0	Mild	Resolved	None	Definite	No	No
BRI1100	Pain above right eye during simulations	0	Mild	Resolved	None	Possible	No	Yes
BRI1100	Pain above right eye during simulations	0	Mild	Resolved	None	Possible	No	No
BRI1100	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI1100	Mild pain above the right eye during stimulations	0	Mild	Resolved	None	Possible	No	No
BRI1100	Pain above right eye during simulations	0	Mild	Resolved	None	Possible	No	No
BRI1100	Pain above right eye during simulations	0	Mild	Resolved	None	Possible	No	No
BRI1100	Pain above right eye during simulations	0	Mild	Resolved	None	Probable	No	Yes
BRI1100	Pain above right eye during simulations	0	Mild	Resolved	None	Possible	No	No
BRI1100	Pain above right eye during simulations	0	Mild	Resolved	None	Probable	No	No
BRI1100	Pain above right eye during simulations	0	Mild	Resolved	None	Possible	No	No
BRI1104	Watering eyes	0	Mild	Resolved	None	Possible	No	Yes
BRI1104	Lightheadedness	0	Mild	Resolved	None	Possible	No	No
BRI1104	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI1104	Twitching sensation in both eyes	0	Mild	Resolved	None	Possible	No	No
BRI1104	Headache	0	Mild	Resolved	None	Possible	No	Yes
BRI1104	COVID-19	4	Mild	Resolved	None	Not related	No	No
BRI1104	Tooth pain	0	Mild	Resolved	None	Possible	No	No
BRI1104	Headache	1	Mild	Resolved	Concomitant medication and non-drug therapy	Probable	No	Yes
BRI1105	Significant stomach pains	66	Moderate	Unknown	None	Not related	No	No
BRI1105	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI1105	Occasional cramps in legs at night	50	Mild	Resolved	None	Unlikely	No	No
BRI1105	Watering eyes	0	Mild	Resolved	None	Probable	No	Yes
BRI1105	Pain in right arm following MRI scan	2	Mild	Resolved	None	Probable	No	No

TABLE 45 Listing of AEs events reported in cgiTBS arm (*continued*)

Trial ID	Adverse event	Duration (days)	Severity	Outcome	Treatment	Related	Serious	Expected
BRI1106	Legs felt shivery during treatment	0	Mild	Resolved	None	Unlikely	No	No
BRI1106	Feeling an urge to grip ring finger and little finger on both hands	0	Mild	Resolved	None	Not related	No	No
BRI1106	Slightly numb around top of scalp	0	Mild	Resolved	None	Possible	No	No
BRI1107	Neck pain	0	Mild	Resolved	None	Possible	No	Yes
BRI1107	Worsened anxiety	30	Mild	Resolved	None	Possible	No	No
BRI1109	Worsened back pain during and after MRI scan (has chronic back condition)	1	Mild	Resolved	None	Probable	No	Yes
BRI1109	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI1109	High blood pressure	0	Moderate	Resolved	None	Possible	No	No
BRI1109	Blood pressure increase post-treatment	0	Moderate	Resolved	None	Possible	No	No
BRI1109	Right knee pain (following a fall after knocked over by a child indoors)	77	Mild	Resolved	None	Not related	No	No
BRI1112	Lightheadedness	0	Mild	Resolved	None	Probable	No	No
BRI1112	Tinnitus (pre-existing condition)	83	Mild	Unknown	None	Unlikely	No	No
BRI1112	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI1112	Sleepiness	0	Mild	Resolved	None	Probable	No	No
BRI1112	Drowsiness	1	Mild	Resolved	None	Possible	No	No
BRI1112	Lightheadedness	0	Mild	Resolved	None	Probable	No	No
BRI1112	Drowsiness	0	Mild	Resolved	None	Possible	No	No
BRI1112	Sleepiness	0	Mild	Resolved	None	Possible	No	No
BRI1112	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI1112	Lightheadedness	0	Mild	Resolved	None	Probable	No	No
BRI1112	Lightheadedness	1	Mild	Resolved	None	Possible	No	No
BRI1112	Sleepiness	0	Mild	Resolved	None	Possible	No	No
BRI1112	Sleepiness	0	Mild	Resolved	None	Possible	No	No
BRI1112	Lightheadedness	0	Mild	Resolved	None	Possible	No	No
BRI1112	Lightheadedness	0	Mild	Resolved	None	Probable	No	No
BRI1112	Lightheadedness	0	Mild	Resolved	None	Probable	No	No
BRI1112	Lightheadedness	0	Mild	Resolved	None	Probable	No	No

continued

TABLE 45 Listing of AEs events reported in cgiTBS arm (*continued*)

Trial ID	Adverse event	Duration (days)	Severity	Outcome	Treatment	Related	Serious	Expected
BRI1112	Lightheadedness	0	Mild	Resolved	None	Possible	No	No
BRI1112	Lightheadedness	0	Mild	Resolved	None	Probable	No	No
BRI1112	Headache	1	Moderate	Resolved	None	Possible	No	Yes
BRI1112	More sensitive to flashing lights	83	Mild	Unknown	None	Unlikely	No	No
BRI1113	Eyes feel sensitive to light	1	Mild	Resolved	None	Possible	No	No
BRI1113	Headache	2	Mild	Resolved	None	Possible	No	Yes
BRI1113	Eyes feel sensitive to light	0	Mild	Resolved	None	Possible	No	No
BRI2001	Bloodshot eye	0	Mild	Resolved	None	Probable	No	Yes
BRI2001	Headache	10	Mild	Resolved	None	Probable	No	Yes
BRI2003	Scalp discomfort	20	Mild	Resolved	None	Probable	No	Yes
BRI2003	Dizziness	1	Mild	Resolved	None	Probable	No	Yes
BRI2003	Nausea	0	Mild	Resolved	None	Probable	No	Yes
BRI2003	Emotional tiredness	0	Mild	Resolved	None	Possible	No	No
BRI2003	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI2003	Dizziness	0	Mild	Resolved	None	Probable	No	Yes
BRI2003	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI2003	Neck pain	7	Mild	Resolved	None	Probable	No	Yes
BRI2003	Nausea	13	Mild	Resolved	None	Probable	No	Yes
BRI2003	Scalp discomfort	5	Mild	Resolved	None	Probable	No	Yes
BRI2003	Headache	3	Mild	Resolved	None	Probable	No	Yes
BRI2003	Headache	7	Mild	Resolved	None	Probable	No	Yes
BRI2005	Tinnitus	14	Mild	Resolved	None	Probable	No	Yes
BRI2005	Blurry eyes	0	Mild	Resolved	None	Possible	No	No
BRI2005	Sensation of tight band around head. Feelings of emotional blockage	0	Mild	Resolved	None	Possible	No	No
BRI2005	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI2005	Headache	16	Mild	Resolved	None	Probable	No	Yes
BRI2006	Fatigue	1	Mild	Resolved	None	Possible	No	No
BRI2006	Dizziness	43	Mild	Resolved	None	Probable	No	Yes
BRI2006	Jaw ache	0	Mild	Resolved	None	Probable	No	Yes
BRI2006	Watering eyes	0	Mild	Resolved	None	Possible	No	No
BRI2006	Tiredness	0	Mild	Resolved	None	Possible	No	No
BRI2006	Neck pain	0	Mild	Resolved	None	Probable	No	Yes

TABLE 45 Listing of AEs events reported in cgiTBS arm (*continued*)

Trial ID	Adverse event	Duration (days)	Severity	Outcome	Treatment	Related	Serious	Expected
BRI2006	Lightheadedness	0	Mild	Resolved	None	Possible	No	No
BRI2006	Headache	36	Mild	Resolved	None	Probable	No	Yes
BRI2010	Watering eyes	0	Mild	Resolved	None	Probable	No	Yes
BRI2010	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI2010	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI2010	Pulling sensation in right-side of head following treatment	0	Mild	Resolved	None	Possible	No	No
BRI2010	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI2010	Tingling in right hand index finger	0	Mild	Resolved	None	Possible	No	No
BRI2010	Difficulty to falling asleep	0	Moderate	Resolved	None	Possible	No	No
BRI2010	Watering eyes	0	Mild	Resolved	None	Probable	No	Yes
BRI2014	Agitation and heightened emotions	0	Mild	Resolved	None	Possible	No	No
BRI2014	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI2014	Tiredness	0	Mild	Resolved	None	Possible	No	No
BRI2014	Tiredness (more severe/ excessive)	0	Mild	Resolved	None	Possible	No	No
BRI2014	Watering eyes	0	Mild	Resolved	None	Probable	No	Yes
BRI2014	Tiredness	0	Mild	Resolved	None	Possible	No	No
BRI2020	Nausea	0	Mild	Resolved	None	Possible	No	No
BRI2020	Numb feeling on the face hours afterwards	0	Mild	Resolved	None	Possible	No	No
BRI2020	Numb feeling on the face hours afterwards	0	Mild	Resolved	None	Possible	No	No
BRI2021	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI2021	Tiredness	0	Mild	Resolved	None	Possible	No	No
BRI2021	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI2021	Dry mouth	0	Mild	Resolved	None	Possible	No	No
BRI2021	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI2025	Self-harm	0	Mild	Resolved	Non-drug therapy	Not related	No	No
BRI2025	Neck pain	91	Mild	Resolved	None	Probable	No	Yes
BRI3011	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI3013	Neck pain	0	Mild	Resolved	None	Probable	No	No
BRI3013	Self-harm	1	Mild	Resolved	Non-drug therapy	Unlikely	No	No
BRI3013	Jaw ache	5	Mild	Resolved	None	Probable	No	No

continued

TABLE 45 Listing of AEs events reported in cgiTBS arm (*continued*)

Trial ID	Adverse event	Duration (days)	Severity	Outcome	Treatment	Related	Serious	Expected
BRI3013	Tinnitus	0	Mild	Resolved	None	Possible	No	No
BRI3013	Anxiety	29	Moderate	Resolved	None	Unlikely	No	No
BRI3013	Scalp discomfort	5	Mild	Resolved	None	Definite	No	No
BRI3013	Headache	0	Mild	Resolved	None	Probable	No	No
BRI3013	Dizziness	0	Mild	Resolved	None	Probable	No	No
BRI3013	Death	0	Fatal	Fatal	None	Unlikely	Yes	No
BRI3013	Drowsiness	22	Mild	Resolved	None	Possible	No	No
BRI3014	Fibroid on womb shown on scan	63	Mild	Resolved	None	Not related	No	No
BRI3014	Headache	12	Mild	Resolved	None	Probable	No	No
BRI3014	Neck pain	2	Mild	Resolved	None	Probable	No	No
BRI3016	Heart attack	0	Fatal	Fatal	None	Unlikely	Yes	No
BRI3016	Tiredness	16	Mild	Resolved	None	Possible	No	No
BRI3016	Nausea	0	Mild	Resolved	None	Possible	No	Yes
BRI3016	Headache	0	Mild	Resolved	None	Possible	No	Yes
BRI3016	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI3016	Nausea	0	Mild	Resolved	None	Possible	No	Yes
BRI3016	Nausea	0	Mild	Resolved	None	Possible	No	Yes
BRI3018	Tinnitus	24	Mild	Resolved	None	Probable	No	Yes
BRI3018	Scalp discomfort	9	Mild	Resolved	None	Definite	No	Yes
BRI3018	Headache	11	Mild	Resolved	None	Probable	No	Yes
BRI3018	Watering eyes	0	Mild	Resolved	None	Probable	No	Yes
BRI3018	Tinnitus	28	Mild	Resolved with sequelae	None	Probable	No	Yes
BRI3018	Neck pain	16	Mild	Resolved	None	Probable	No	Yes
BRI3021	Tinnitus	0	Mild	Resolved	None	Probable	No	Yes
BRI3021	Jaw ache	22	Mild	Resolved	None	Probable	No	Yes
BRI3021	Dizziness	27	Mild	Resolved	None	Probable	No	Yes
BRI3021	Scalp discomfort	2	Mild	Resolved	None	Definite	No	Yes
BRI3021	Neck pain	27	Mild	Resolved	None	Probable	No	Yes
BRI3021	Headache	8	Mild	Resolved	None	Probable	No	Yes
BRI3023	Neck pain	11	Mild	Resolved	None	Probable	No	Yes
BRI3023	Headache	11	Mild	Resolved	None	Probable	No	Yes
BRI3023	Nausea	1	Mild	Resolved	None	Probable	No	Yes
BRI3023	Scalp discomfort	5	Mild	Resolved	None	Definite	No	Yes
BRI3023	Pins and needles in hand	0	Mild	Resolved	None	Possible	No	No

TABLE 45 Listing of AEs events reported in cgiTBS arm (*continued*)

Trial ID	Adverse event	Duration (days)	Severity	Outcome	Treatment	Related	Serious	Expected
BRI3025	Tinnitus	124	Mild	Resolved	None	Possible	No	Yes
BRI3025	Attempt of self-harm	0	Moderate	Resolved	Concomitant medication and non-drug therapy	Possible	No	No
BRI3025	Nausea	0	Mild	Resolved	None	Probable	No	Yes
BRI3025	Headache	124	Moderate	Resolved	Concomitant medication	Unlikely	No	Yes
BRI3025	Neck pain	16	Mild	Resolved	None	Probable	No	Yes
BRI3025	Watering eyes	15	Mild	Resolved	None	Probable	No	Yes
BRI3025	Headache	16	Mild	Resolved	None	Probable	No	Yes
BRI3025	Irritability	0	Mild	Resolved	None	Possible	No	No
BRI3025	Neck pain	124	Mild	Resolved	None	Unlikely	No	Yes
BRI3025	Jaw ache	5	Mild	Resolved	None	Probable	No	Yes
BRI3025	Dizziness	1	Mild	Resolved	None	Probable	No	Yes
BRI3031	Headache	27	Mild	Resolved	None	Probable	No	Yes
BRI3031	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI3031	Dizziness	1	Mild	Resolved	None	Probable	No	Yes
BRI3031	Tinnitus	0	Mild	Resolved	None	Probable	No	Yes
BRI3034	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI3034	Jaw ache	0	Moderate	Resolved	Non-drug therapy	Definite	No	Yes
BRI3034	Repetitive clamping of jaw	0	Moderate	Resolved	Non-drug therapy	Definite	No	Yes
BRI3034	Neck pain	4	Mild	Resolved	None	Probable	No	Yes
BRI3034	Nausea	10	Mild	Resolved	None	Probable	No	Yes
BRI3034	Watering eyes	20	Mild	Resolved	None	Probable	No	Yes
BRI3034	Scalp discomfort	14	Mild	Resolved	None	Definite	No	Yes
BRI3034	Tooth pain	0	Mild	Resolved	None	Probable	No	No
BRI3034	Dizziness	0	Mild	Resolved	None	Probable	No	Yes
BRI3036	Tinnitus	0	Mild	Resolved	None	Probable	No	Yes
BRI3036	Fatigue	78	Moderate	Resolved	None	Not related	Yes	No
BRI3036	Dizziness	3	Mild	Resolved	None	Probable	No	Yes
BRI3036	COVID-19	11	Severe	Resolved with sequelae	Concomitant medication	Not related	Yes	No
BRI3036	Dizziness	0	Mild	Resolved	None	Probable	No	Yes
BRI3036	Watering eyes	0	Mild	Resolved	None	Probable	No	Yes

continued

TABLE 45 Listing of AEs events reported in cgiTBS arm (*continued*)

Trial ID	Adverse event	Duration (days)	Severity	Outcome	Treatment	Related	Serious	Expected
BRI3036	Shortness of breath	11	Severe	Resolved	None	Not related	Yes	No
BRI3036	Scalp discomfort	0	Mild	Resolved	None	Definite	No	Yes
BRI3036	High temperature	11	Moderate	Resolved	None	Not related	Yes	No
BRI3037	Tinnitus	0	Mild	Resolved	None	Possible	No	Yes
BRI3037	Tinnitus	0	Mild	Resolved	None	Probable	No	Yes
BRI3037	Neck pain	6	Mild	Resolved	None	Probable	No	Yes
BRI3037	Sleepiness	27	Moderate	Resolved	None	Possible	No	No
BRI3037	Scalp discomfort	28	Mild	Resolved	None	Definite	No	Yes
BRI3037	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI3037	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI3037	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI3038	Nausea	0	Mild	Resolved	None	Possible	No	Yes
BRI3038	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI3038	Disturbed sleep	0	Mild	Resolved	None	Possible	No	Yes
BRI3038	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI3038	Neck pain	0	Mild	Resolved	None	Possible	No	Yes
BRI3038	Headache	2	Mild	Resolved	None	Probable	No	Yes
BRI3038	Disturbed sleep	0	Mild	Resolved	None	Possible	No	Yes
BRI3041	Neck pain	3	Mild	Resolved	None	Probable	No	Yes
BRI3041	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI3041	Scalp discomfort	1	Mild	Resolved	None	Probable	No	Yes
BRI3041	Dizziness	3	Mild	Resolved	None	Probable	No	Yes
BRI3041	Headache	8	Mild	Resolved	None	Probable	No	Yes
BRI3041	Headache	1	Mild	Resolved	None	Probable	No	Yes
BRI3043	Neck pain	3	Mild	Resolved	None	Probable	No	Yes
BRI3045	Neck pain	1	Mild	Resolved	None	Probable	No	Yes
BRI3045	Jaw ache	1	Mild	Resolved	None	Probable	No	Yes
BRI3045	Headache	3	Mild	Resolved	None	Probable	No	Yes
BRI3048	Neck pain	1	Mild	Resolved	None	Probable	No	Yes
BRI3048	Scalp discomfort	3	Mild	Resolved	None	Probable	No	Yes
BRI3048	Watering eyes	1	Mild	Resolved	None	Probable	No	Yes
BRI3048	Scalp discomfort	2	Mild	Resolved	None	Probable	No	Yes
BRI3048	Scalp discomfort	1	Mild	Resolved	None	Probable	No	Yes
BRI3048	Scalp discomfort	1	Mild	Resolved	None	Probable	No	Yes
BRI3048	Watering eyes	2	Mild	Resolved	None	Probable	No	Yes

TABLE 45 Listing of AEs events reported in cgiTBS arm (*continued*)

Trial ID	Adverse event	Duration (days)	Severity	Outcome	Treatment	Related	Serious	Expected
BRI3048	Watering eyes	7	Mild	Resolved	None	Probable	No	Yes
BRI3048	Scalp discomfort	1	Mild	Resolved	None	Probable	No	Yes
BRI3050	Headache	2	Mild	Resolved	None	Probable	No	Yes
BRI3050	Jaw ache	4	Mild	Resolved	None	Probable	No	Yes
BRI3051	Scalp discomfort	6	Mild	Resolved	None	Probable	No	Yes
BRI3051	Nausea	1	Mild	Resolved	None	Probable	No	Yes
BRI3051	Headache	4	Mild	Resolved	None	Probable	No	Yes
BRI3051	Scalp discomfort	3	Mild	Resolved	None	Probable	No	Yes
BRI3051	Scalp discomfort	1	Mild	Resolved	None	Probable	No	Yes
BRI3051	Scalp discomfort	1	Mild	Resolved	None	Probable	No	Yes
BRI3051	Headache	1	Mild	Resolved	None	Probable	No	Yes
BRI3051	Jaw ache	2	Mild	Resolved	None	Probable	No	Yes
BRI3051	Scalp discomfort	1	Mild	Resolved	None	Probable	No	Yes
BRI3051	Tiredness/lethargy	1	Mild	Resolved	None	Possible	No	Yes
BRI3051	Teeth chattering	1	Mild	Resolved	None	Possible	No	No
BRI3051	Nausea	3	Mild	Resolved	None	Probable	No	Yes
BRI3054	Lethargy	1	Mild	Resolved	None	Possible	No	No
BRI3054	Low mood	2	Mild	Resolved	None	Possible	No	No
BRI3054	Headache	1	Mild	Resolved	None	Probable	No	Yes
BRI3054	Panic, anxiety, and flashbacks	7	Mild	Resolved	None	Possible	No	No
BRI3054	Lethargy	5	Mild	Resolved	None	Possible	No	No
BRI3054	Scalp discomfort	1	Mild	Resolved	None	Probable	No	Yes
BRI3057	Scalp discomfort	1	Mild	Resolved	None	Definite	No	Yes
BRI3057	Neck pain	2	Mild	Resolved	None	Probable	No	Yes
BRI3057	Headache	21	Mild	Resolved	None	Probable	No	Yes
BRI3057	Neck pain	22	Mild	Resolved	None	Probable	No	No
BRI3057	Fatigue	1	Mild	Resolved	None	Possible	No	No
BRI3057	Jaw ache	.	Mild	Unobtainable	None	Possible	No	Yes
BRI3057	Scalp discomfort	1	Mild	Resolved	None	Definite	No	Yes
BRI3057	Scalp discomfort	1	Mild	Resolved	None	Definite	No	Yes
BRI3057	Headache	.	Mild	Unobtainable	None	Probable	No	Yes
BRI3057	Dizziness	1	Mild	Resolved	None	Probable	No	No
BRI3057	Scalp discomfort	1	Mild	Resolved	None	Definite	No	Yes
BRI3057	Scalp discomfort	3	Mild	Resolved	None	Definite	No	Yes
BRI3058	Headache	35	Mild	Resolved	None	Probable	No	Yes

continued

TABLE 45 Listing of AEs events reported in cgiTBS arm (*continued*)

Trial ID	Adverse event	Duration (days)	Severity	Outcome	Treatment	Related	Serious	Expected
BRI3058	Neck pain	.	Mild	Continuing	None	Probable	No	Yes
BRI3058	It exacerbates my low mood	1	Mild	Resolved	None	Possible	No	No
BRI3058	Nausea	7	Mild	Resolved	None	Possible	No	Yes
BRI3058	Dizziness	2	Mild	Resolved	None	Possible	No	Yes
BRI3058	Neck pain	5	Mild	Resolved	None	Probable	No	Yes
BRI3058	Agitation/inability to relax	1	Mild	Resolved	None	Unlikely	No	No
BRI3058	Scalp discomfort	4	Mild	Resolved	None	Definite	No	Yes
BRI3058	Scalp discomfort	1	Mild	Resolved	None	Definite	No	Yes
BRI3058	Over-stimulation of brain	2	Mild	Resolved	None	Possible	No	No
BRI3058	Neck pain	2	Mild	Resolved	None	Probable	No	Yes
BRI3058	Neck pain	2	Mild	Resolved	None	Probable	No	Yes
BRI3058	Tiredness (more severe/ excessive)	1	Mild	Resolved	None	Possible	No	No
BRI3058	Dizziness	3	Mild	Resolved	None	Possible	No	Yes
BRI3058	Tinnitus	.	Mild	Continuing	None	Possible	No	Yes
BRI3058	Feeling over-stimulated	1	Mild	Resolved	None	Possible	No	No
BRI3058	Jaw ache	5	Mild	Resolved	None	Possible	No	Yes
BRI3058	Nausea	7	Mild	Resolved	None	Possible	No	Yes
BRI3058	Watering eyes	3	Mild	Resolved	None	Probable	No	Yes
BRI3058	Jaw ache	1	Mild	Resolved	None	Possible	No	Yes
BRI3058	Headache	2	Mild	Resolved	None	Possible	No	Yes
BRI3058	Difficulty concentrating	2	Mild	Resolved	None	Unlikely	No	Yes
BRI3058	Dizziness	4	Mild	Resolved	None	Possible	No	Yes
BRI3058	Scalp discomfort	4	Mild	Resolved	None	Definite	No	Yes
BRI3058	Agitation/inability to relax	3	Mild	Resolved	None	Unlikely	No	No
BRI3058	Headache	1	Mild	Resolved	None	Probable	No	Yes
BRI3058	Feeling speedy and agitated	1	Mild	Resolved	None	Unlikely	No	No
BRI3058	Spaced out and agitated	6	Mild	Resolved	None	Unlikely	No	No
BRI3058	Headache	1	Mild	Resolved	None	Probable	No	Yes
BRI3058	Nausea	4	Mild	Resolved	None	Possible	No	Yes
BRI4002	Tinnitus	207	Mild	Resolved	None	Possible	No	Yes

TABLE 45 Listing of AEs events reported in cgiTBS arm (*continued*)

Trial ID	Adverse event	Duration (days)	Severity	Outcome	Treatment	Related	Serious	Expected
BRI4005	Hospitalisation due to manic episode	47	Severe	Resolved	Concomitant medication and non-drug therapy	Possible	Yes	Yes
BRI4006	Slower hand movement	.	Mild	Continuing	None	Unlikely	No	No
BRI4006	Headache	119	Mild	Resolved	Concomitant medication	Possible	No	Yes
BRI4006	Stumbling more frequently twice a week initially then 3–4 times in a day	686	Mild	Resolved	None	Unlikely	No	No
BRI4013	Headache	20	Moderate	Resolved	None	Possible	No	Yes
BRI4017	Headache	30	Mild	Resolved	None	Probable	No	Yes
BRI4018	Jaw ache	0	Mild	Resolved	None	Probable	No	Yes
BRI4018	Nausea	0	Mild	Resolved	None	Unlikely	No	No
BRI4018	Dizziness	0	Mild	Resolved	None	Possible	No	Yes
BRI4018	Nausea	0	Mild	Resolved	None	Unlikely	No	No
BRI4018	Dizziness	0	Mild	Resolved	None	Possible	No	Yes
BRI4018	Jaw ache	0	Mild	Resolved	None	Probable	No	Yes
BRI4018	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI4018	Fatigue	2	Mild	Resolved	None	Unlikely	No	No
BRI4018	Headache	11	Mild	Resolved	Concomitant medication	Probable	No	Yes
BRI4018	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI4018	Headache	0	Mild	Resolved	None	Probable	No	No
BRI4018	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI4018	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI4018	Dizziness	0	Mild	Resolved	None	Possible	No	Yes
BRI4018	Nausea	0	Mild	Resolved	None	Unlikely	No	No
BRI4018	Jaw ache	0	Mild	Resolved	None	Probable	No	Yes
BRI4023	Tinnitus	0	Mild	Resolved	None	Probable	No	Yes
BRI4023	Tinnitus	0	Mild	Resolved	None	Probable	No	Yes
BRI4023	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI4023	Tinnitus	0	Mild	Resolved	None	Probable	No	Yes
BRI4023	Pain in hand	0	Mild	Resolved	None	Possible	No	No
BRI4023	Tinnitus	0	Mild	Resolved	None	Probable	No	Yes
BRI4023	Tinnitus	0	Mild	Resolved	None	Probable	No	Yes
BRI4023	Tinnitus	0	Mild	Resolved	None	Probable	No	Yes
BRI4023	Tinnitus	0	Mild	Resolved	None	Probable	No	Yes

continued

TABLE 45 Listing of AEs events reported in cgiTBS arm (*continued*)

Trial ID	Adverse event	Duration (days)	Severity	Outcome	Treatment	Related	Serious	Expected
BRI4023	Panic attack (not on treatment day)	0	Mild	Resolved	None	Unlikely	No	No
BRI4023	Anxiety attacks	33	Severe	Resolved	None	Not related	No	No
BRI4023	Tinnitus	0	Mild	Resolved	None	Probable	No	Yes
BRI4023	Tinnitus	0	Mild	Resolved	None	Probable	No	Yes
BRI4023	Tinnitus	0	Mild	Resolved	None	Probable	No	Yes
BRI4023	Jaw ache	0	Mild	Resolved	None	Probable	No	Yes
BRI4023	Tinnitus	0	Mild	Resolved	None	Probable	No	Yes
BRI4023	Tinnitus	0	Mild	Resolved	None	Probable	No	Yes
BRI4023	Tinnitus	0	Mild	Resolved	None	Probable	No	Yes
BRI4023	Tinnitus	0	Mild	Resolved	None	Probable	No	Yes
BRI4023	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI4023	Dizziness	0	Mild	Resolved	None	Possible	No	Yes
BRI4023	Tinnitus	0	Mild	Resolved	None	Probable	No	Yes
BRI4023	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI4023	Tinnitus	0	Mild	Resolved	None	Probable	No	Yes
BRI4023	Tinnitus	0	Mild	Resolved	None	Probable	No	Yes
BRI4023	Tinnitus	0	Mild	Resolved	None	Probable	No	Yes
BRI4024	Neck pain	0	Mild	Resolved	None	Possible	No	Yes
BRI4024	Jaw ache	0	Mild	Resolved	None	Possible	No	Yes
BRI4024	Dizziness	0	Mild	Resolved	None	Possible	No	Yes
BRI4024	Neck pain	0	Mild	Resolved	None	Possible	No	Yes
BRI4024	Jaw ache	0	Mild	Resolved	None	Possible	No	Yes
BRI4024	Neck pain	0	Mild	Resolved	None	Possible	No	Yes
BRI4024	Hot flushes	3	Mild	Resolved	None	Not related	No	No
BRI4024	Neck pain	0	Mild	Resolved	None	Possible	No	Yes
BRI4024	Back pain	0	Moderate	Resolved	Concomitant medication	Not related	No	No
BRI4024	Neck pain	0	Mild	Resolved	None	Possible	No	Yes
BRI4024	Watering eyes	0	Mild	Resolved	None	Unlikely	No	No
BRI4024	Jaw ache	0	Mild	Resolved	None	Possible	No	Yes
BRI4025	Dizziness	0	Mild	Resolved	None	Possible	No	Yes
BRI4025	Neck pain	0	Mild	Resolved	None	Possible	No	Yes
BRI4025	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI4025	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI4025	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes

TABLE 45 Listing of AEs events reported in cgiTBS arm (*continued*)

Trial ID	Adverse event	Duration (days)	Severity	Outcome	Treatment	Related	Serious	Expected
BRI4025	Dizziness	0	Mild	Resolved	None	Possible	No	Yes
BRI4025	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI4025	Nausea	0	Mild	Resolved	None	Unlikely	No	No
BRI4025	Neck pain	0	Mild	Resolved	None	Possible	No	Yes
BRI4025	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI4025	Watering eyes	0	Mild	Resolved	None	Unlikely	No	No
BRI4025	Dizziness	0	Mild	Resolved	None	Possible	No	Yes
BRI4025	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI4025	Dizziness	0	Mild	Resolved	None	Possible	No	Yes
BRI4025	Dizziness	0	Mild	Resolved	None	Possible	No	Yes
BRI4025	Dizziness	0	Mild	Resolved	None	Possible	No	Yes
BRI4025	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI4025	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI4025	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI4025	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI4027	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI4027	Migraine	0	Moderate	Resolved	Concomitant medication	Probable	No	Yes
BRI4027	Neck pain	0	Mild	Resolved	None	Possible	No	Yes
BRI4027	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI4027	Jaw ache	0	Mild	Resolved	None	Probable	No	Yes
BRI4027	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI4027	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI4027	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI4027	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI4027	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI4027	Nausea	0	Mild	Resolved	None	Possible	No	No
BRI4027	Nausea	0	Mild	Resolved	None	Possible	No	No
BRI4027	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI4027	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI4027	Nausea	0	Mild	Resolved	None	Possible	No	Yes
BRI4027	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI4027	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI4027	Nausea	0	Mild	Resolved	None	Possible	No	No
BRI4027	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI4027	Headache	0	Mild	Resolved	None	Probable	No	Yes

continued

TABLE 45 Listing of AEs events reported in cgiTBS arm (*continued*)

Trial ID	Adverse event	Duration (days)	Severity	Outcome	Treatment	Related	Serious	Expected
BRI4029	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI4029	Jaw ache	0	Mild	Resolved	None	Probable	No	Yes
BRI4029	Tinnitus	0	Mild	Resolved	None	Unlikely	No	No
BRI4029	Headache	60	Mild	Resolved	Concomitant medication	Probable	No	Yes
BRI4029	Metallic taste in mouth	0	Mild	Resolved	None	Unlikely	No	No
BRI4029	Neck pain	0	Mild	Resolved	None	Possible	No	Yes
BRI4029	Scalp discomfort	0	Moderate	Resolved	None	Probable	No	Yes
BRI4029	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI4029	Tinnitus	0	Mild	Resolved	None	Probable	No	Yes
BRI4029	Headache	60	Mild	Resolved	Concomitant medication	Probable	No	Yes
BRI4029	Tinnitus	0	Mild	Resolved	None	Probable	No	Yes
BRI4029	Nausea	0	Mild	Resolved	None	Unlikely	No	No
BRI4029	Neck pain	60	Mild	Resolved	Concomitant medication	Possible	No	Yes
BRI4029	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI4029	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI4029	Confusion	18	Mild	Resolved	None	Unlikely	No	No
BRI4029	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI4029	Nausea	0	Mild	Resolved	None	Unlikely	No	No
BRI4029	Jaw ache	0	Mild	Resolved	None	Probable	No	Yes
BRI4029	High temperature	0	Mild	Resolved	None	Unlikely	No	No
BRI4029	Paresthesia	46	Mild	Resolved	None	Possible	No	Yes
BRI4029	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI4029	Confusion	3	Mild	Resolved	None	Unlikely	No	No
BRI4029	Nausea	1	Mild	Resolved	None	Unlikely	No	No
BRI4029	Nausea	0	Moderate	Resolved	None	Unlikely	No	No
BRI4029	Neck pain	2	Moderate	Resolved	Concomitant medication	Probable	No	Yes
BRI4029	Scalp discomfort	2	Moderate	Resolved	None	Probable	No	Yes
BRI4029	Jaw ache	0	Mild	Resolved	None	Probable	No	Yes
BRI4029	Neck pain	0	Mild	Resolved	None	Possible	No	Yes
BRI4029	Jaw ache	0	Mild	Resolved	None	Probable	No	Yes
BRI4029	Tinnitus	0	Mild	Resolved	None	Probable	No	Yes
BRI4029	Jaw ache	0	Mild	Resolved	None	Probable	No	Yes
BRI4029	Lightheadedness	60	Mild	Resolved	None	Possible	No	Yes

TABLE 45 Listing of AEs events reported in cgiTBS arm (*continued*)

Trial ID	Adverse event	Duration (days)	Severity	Outcome	Treatment	Related	Serious	Expected
BRI4029	Jaw ache	21	Mild	Resolved	None	Probable	No	Yes
BRI4029	Jaw ache	0	Mild	Resolved	None	Probable	No	Yes
BRI4029	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI4029	Tinnitus	0	Mild	Resolved	None	Probable	No	Yes
BRI4029	Tinnitus	21	Mild	Resolved	None	Probable	No	Yes
BRI4029	Facial pain	0	Mild	Resolved	None	Possible	No	No
BRI4029	Tinnitus	0	Mild	Resolved	None	Probable	No	Yes
BRI4029	Eye pain	0	Mild	Resolved	None	Possible	No	No
BRI4029	Jaw ache	0	Mild	Resolved	None	Probable	No	Yes
BRI4029	Neck pain	0	Moderate	Resolved	None	Probable	No	Yes
BRI4029	Forgetfulness	19	Mild	Resolved	None	Unlikely	No	No
BRI4029	Nausea	0	Mild	Resolved	None	Unlikely	No	No
BRI4029	Tinnitus	0	Mild	Resolved	None	Probable	No	Yes
BRI4029	Jaw ache	0	Mild	Resolved	None	Probable	No	Yes
BRI4029	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI4029	High temperature	0	Mild	Resolved	None	Unlikely	No	No
BRI4029	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI4029	Confusion	3	Mild	Resolved	None	Unlikely	No	No
BRI4029	Jaw ache	0	Mild	Resolved	None	Probable	No	Yes
BRI4029	Tinnitus	0	Mild	Resolved	None	Probable	No	Yes
BRI4029	Neck pain	60	Mild	Resolved	None	Probable	No	Yes
BRI4029	Jaw ache	0	Mild	Resolved	None	Probable	No	Yes
BRI4029	Dizziness	0	Mild	Resolved	None	Unlikely	No	No
BRI4029	Scalp discomfort	21	Moderate	Resolved	None	Probable	No	Yes
BRI4029	Neck pain	0	Mild	Resolved	None	Possible	No	Yes
BRI4029	Nausea	0	Mild	Resolved	None	Unlikely	No	No
BRI4029	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI4029	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI4029	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI4029	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI4029	Headache	0	Moderate	Resolved	Concomitant medication	Probable	No	Yes
BRI4029	Scalp discomfort	1	Mild	Resolved	None	Probable	No	Yes
BRI4029	Tinnitus	1	Mild	Resolved	None	Probable	No	Yes
BRI4029	Jaw ache	0	Mild	Resolved	None	Probable	No	Yes

continued

TABLE 45 Listing of AEs events reported in cgiTBS arm (*continued*)

Trial ID	Adverse event	Duration (days)	Severity	Outcome	Treatment	Related	Serious	Expected
BRI4029	Nausea	0	Mild	Resolved	None	Unlikely	No	No
BRI4029	Paresthesia	46	Mild	Resolved	None	Possible	No	Yes
BRI4029	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI4029	High temperature	0	Mild	Resolved	None	Unlikely	No	No
BRI4029	Neck pain	0	Mild	Resolved	None	Possible	No	Yes
BRI4029	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI4029	Tinnitus	0	Mild	Resolved	None	Probable	No	Yes
BRI4029	Nausea	0	Mild	Resolved	None	Unlikely	No	No
BRI4029	Tinnitus	0	Mild	Resolved	None	Possible	No	Yes
BRI4029	Watering eyes	0	Mild	Resolved	None	Unlikely	No	No
BRI4029	Tender scalp	1	Mild	Resolved	None	Probable	No	Yes
BRI4029	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI4029	Jaw ache	0	Mild	Resolved	None	Probable	No	Yes
BRI4029	Headache	2	Moderate	Resolved	Concomitant medication	Probable	No	Yes
BRI4029	Tinnitus	0	Mild	Resolved	None	Probable	No	Yes
BRI4029	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI4029	Neck pain	0	Mild	Resolved	None	Possible	No	Yes
BRI4029	Tinnitus	0	Mild	Resolved	None	Probable	No	Yes
BRI4029	Jaw ache	0	Mild	Resolved	None	Probable	No	Yes
BRI4029	Nausea	0	Mild	Resolved	None	Unlikely	No	No
BRI4029	Tinnitus	0	Mild	Resolved	None	Probable	No	Yes
BRI4029	Headache	0	Mild	Resolved	None	Unlikely	No	No
BRI4029	Headache	0	Mild	Resolved	Concomitant medication	Probable	No	Yes
BRI4029	Tinnitus	0	Mild	Resolved	None	Probable	No	Yes
BRI4029	Dizziness	60	Mild	Resolved	None	Unlikely	No	No
BRI4029	Metallic taste in mouth	0	Mild	Resolved	None	Unlikely	No	No
BRI4029	Tinnitus	0	Mild	Resolved	None	Probable	No	Yes
BRI4029	Dizziness	0	Mild	Resolved	None	Unlikely	No	Yes
BRI4029	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI4029	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI4029	Nausea	0	Mild	Resolved	None	Unlikely	No	No
BRI4029	Tinnitus	0	Mild	Resolved	None	Probable	No	Yes
BRI4029	Nausea	0	Mild	Resolved	None	Unlikely	No	No
BRI4029	Headache	0	Mild	Resolved	None	Probable	No	Yes

TABLE 45 Listing of AEs events reported in cgiTBS arm (*continued*)

Trial ID	Adverse event	Duration (days)	Severity	Outcome	Treatment	Related	Serious	Expected
BRI4029	Jaw ache	0	Mild	Resolved	None	Probable	No	Yes
BRI4029	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI4029	Headache	0	Mild	Resolved	Concomitant medication	Probable	No	Yes
BRI4029	Nausea	0	Mild	Resolved	None	Unlikely	No	No
BRI4029	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI4029	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI4029	Headache	0	Severe	Resolved	None	Probable	No	Yes
BRI4029	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI4029	Face ache (treatment causing facial twitching)	1	Mild	Resolved	None	Possible	No	No
BRI4029	Nausea	0	Mild	Resolved	None	Unlikely	No	No
BRI4029	Jaw ache	0	Mild	Resolved	None	Probable	No	Yes
BRI4029	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI4029	Congested head/sinus	0	Mild	Resolved	None	Unlikely	No	No
BRI4029	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI4029	Neck pain	0	Mild	Resolved	None	Possible	No	Yes
BRI4029	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI4029	Dizziness	0	Mild	Resolved	None	Unlikely	No	No
BRI4029	Headache	1	Mild	Resolved	None	Probable	No	Yes
BRI4029	Jaw ache	0	Mild	Resolved	None	Probable	No	Yes
BRI4029	Headache	1	Moderate	Resolved	Concomitant medication	Probable	No	Yes
BRI4032	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI4032	Dizziness	0	Mild	Resolved	None	Unlikely	No	No
BRI4032	Dizziness	0	Mild	Resolved	None	Unlikely	No	No
BRI4032	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI4032	Dizziness	0	Mild	Resolved	None	Unlikely	No	No
BRI4032	Jaw ache	0	Mild	Resolved	None	Possible	No	No
BRI4032	Stomach pains	47	Moderate	Resolved	Concomitant medication	Unlikely	No	No
BRI4032	Dizziness	0	Mild	Resolved	None	Unlikely	No	Yes
BRI4032	Dizziness	0	Mild	Resolved	None	Unlikely	No	Yes
BRI4032	Dizziness	0	Mild	Resolved	None	Unlikely	No	Yes
BRI4032	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI4032	Dizziness	0	Mild	Resolved	None	Unlikely	No	Yes

continued

TABLE 45 Listing of AEs events reported in cgiTBS arm (*continued*)

Trial ID	Adverse event	Duration (days)	Severity	Outcome	Treatment	Related	Serious	Expected
BRI4032	Dizziness	0	Mild	Resolved	None	Unlikely	No	No
BRI4032	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI4032	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI4032	Headache	0	Moderate	Resolved	Concomitant medication	Probable	No	Yes
BRI4032	Jaw ache	0	Mild	Resolved	None	Possible	No	No
BRI4032	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI4032	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI4032	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI4032	Dizziness	0	Mild	Resolved	None	Unlikely	No	No
BRI4032	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI4032	Dizziness	0	Mild	Resolved	None	Unlikely	No	No
BRI4036	Headache	0	Mild	Resolved	Concomitant medication	Probable	No	Yes
BRI4036	Dizziness/dazed	0	Mild	Resolved	None	Probable	No	Yes
BRI4036	Tingling	0	Mild	Resolved	Concomitant medication	Probable	No	Yes
BRI4036	Headache	4	Mild	Resolved	Concomitant medication	Probable	No	Yes
BRI4036	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI4036	Tingling scalp	0	Mild	Resolved	Concomitant medication	Probable	No	Yes
BRI4036	Jaw ache	0	Mild	Resolved	None	Probable	No	Yes
BRI4036	Tinnitus	0	Mild	Resolved	Concomitant medication	Probable	No	Yes
BRI4036	Headache	1	Mild	Resolved	Concomitant medication	Probable	No	Yes
BRI4036	Headache	0	Mild	Resolved	Concomitant medication	Probable	No	Yes
BRI4036	Eye throbbing	0	Moderate	Resolved	None	Probable	No	Yes
BRI4036	Headache	0	Mild	Resolved	Concomitant medication	Probable	No	Yes
BRI4036	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI4036	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI4036	Jaw ache	0	Mild	Resolved	None	Probable	No	Yes
BRI4036	Jaw ache	0	Mild	Resolved	None	Probable	No	Yes
BRI4036	Dizziness/dazed	1	Mild	Resolved	None	Probable	No	Yes
BRI4036	Eye throbbing	0	Mild	Resolved	None	Probable	No	Yes
BRI4036	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes

TABLE 45 Listing of AEs events reported in cgiTBS arm (*continued*)

Trial ID	Adverse event	Duration (days)	Severity	Outcome	Treatment	Related	Serious	Expected
BRI4036	Dizziness/dazed	1	Mild	Resolved	Concomitant medication	Probable	No	Yes
BRI4036	Lightheadedness	0	Mild	Resolved	Concomitant medication	Probable	No	No
BRI4036	Eye throbbing	0	Mild	Resolved	Concomitant medication	Probable	No	Yes
BRI4036	Dizziness	0	Mild	Resolved	Concomitant medication	Probable	No	Yes
BRI4036	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI4036	Dizziness/dazed	0	Mild	Resolved	Concomitant medication	Probable	No	Yes
BRI4036	Headache	1	Mild	Resolved	None	Probable	No	Yes
BRI4036	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI4036	Headache	0	Mild	Resolved	Concomitant medication	Probable	No	Yes
BRI4036	Headache	0	Mild	Resolved	Concomitant medication	Probable	No	Yes
BRI4036	Neck pain	0	Mild	Resolved	Concomitant medication	Probable	No	Yes
BRI4036	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI4036	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI4036	Dizziness/dazed	1	Mild	Resolved	Concomitant medication	Probable	No	Yes
BRI4036	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI4036	Jaw ache	0	Mild	Resolved	None	Probable	No	Yes
BRI4036	Neck pain	1	Mild	Resolved	None	Probable	No	Yes
BRI4036	Tinnitus	0	Mild	Resolved	Concomitant medication	Probable	No	Yes
BRI4036	Jaw ache	0	Mild	Resolved	None	Probable	No	Yes
BRI4036	Headache	0	Mild	Resolved	Concomitant medication	Probable	No	Yes
BRI4036	Headache	0	Mild	Resolved	Concomitant medication	Probable	No	Yes
BRI4036	Eye throbbing	0	Mild	Resolved	None	Probable	No	Yes
BRI4036	Headache	0	Mild	Resolved	Concomitant medication	Probable	No	Yes
BRI4036	Jaw ache	1	Mild	Resolved	None	Probable	No	Yes
BRI4036	Jaw ache	0	Mild	Resolved	Concomitant medication	Probable	No	Yes
BRI4036	Eye throbbing	0	Mild	Resolved	Concomitant medication	Probable	No	Yes
BRI4036	Jaw ache	0	Mild	Resolved	None	Probable	No	Yes

continued

TABLE 45 Listing of AEs events reported in cgiTBS arm (*continued*)

Trial ID	Adverse event	Duration (days)	Severity	Outcome	Treatment	Related	Serious	Expected
BRI4036	Dizziness/dazed	0	Mild	Resolved	Concomitant medication	Probable	No	Yes
BRI4036	Jaw ache	0	Mild	Resolved	None	Probable	No	Yes
BRI4036	Dazed	0	Mild	Resolved	None	Probable	No	Yes
BRI4036	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI4036	Dizziness/dazed	0	Mild	Resolved	None	Probable	No	Yes
BRI4036	Jaw ache	0	Mild	Resolved	None	Probable	No	Yes
BRI4036	Jaw ache	0	Mild	Resolved	None	Probable	No	Yes
BRI4036	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI4036	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI4036	Headache	0	Mild	Resolved	Concomitant Medication	Probable	No	Yes
BRI4036	Eye throbbing	0	Mild	Resolved	Concomitant medication	Probable	No	Yes
BRI4036	Dizziness/dazed	0	Mild	Resolved	None	Probable	No	Yes
BRI4036	Neck pain	0	Mild	Resolved	Concomitant medication	Probable	No	Yes
BRI4036	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI4036	Jaw ache	0	Mild	Resolved	Concomitant medication	Probable	No	Yes
BRI4036	Headache	4	Mild	Resolved	Concomitant medication	Probable	No	Yes
BRI4036	Dizziness/dazed	0	Mild	Resolved	Concomitant medication	Probable	No	Yes
BRI4036	Dizziness/dazed	0	Mild	Resolved	Concomitant medication	Probable	No	Yes
BRI4036	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI4036	Headache	1	Mild	Resolved	Concomitant medication	Probable	No	Yes
BRI4036	Scalp tingling	0	Mild	Resolved	None	Probable	No	Yes
BRI4036	Jaw ache	1	Mild	Resolved	Concomitant medication	Probable	No	Yes
BRI4036	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI4036	Dizziness/dazed	1	Mild	Resolved	Concomitant medication	Probable	No	Yes
BRI4036	Headache	0	Mild	Resolved	Concomitant medication	Probable	No	Yes
BRI4036	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI4036	Jaw ache	0	Mild	Resolved	None	Probable	No	Yes
BRI4036	Dazed	0	Mild	Resolved	None	Probable	No	Yes
BRI4036	Jaw ache	0	Mild	Resolved	Concomitant medication	Probable	No	Yes

TABLE 45 Listing of AEs events reported in cgiTBS arm (*continued*)

Trial ID	Adverse event	Duration (days)	Severity	Outcome	Treatment	Related	Serious	Expected
BRI4036	Headache	1	Mild	Resolved	None	Probable	No	Yes
BRI4036	Neck pain	1	Mild	Resolved	Concomitant medication	Probable	No	Yes
BRI4036	Dizziness/dazed	0	Mild	Resolved	None	Probable	No	Yes
BRI4036	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI4036	Dizziness/dazed	0	Mild	Resolved	None	Probable	No	Yes
BRI4036	Neck pain	0	Mild	Resolved	Concomitant medication	Probable	No	Yes
BRI4036	Tinnitus	0	Mild	Resolved	Concomitant medication	Probable	No	Yes
BRI4036	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI4036	Eye throbbing	1	Mild	Resolved	None	Probable	No	Yes
BRI4036	Headache	1	Mild	Resolved	Concomitant medication	Probable	No	Yes
BRI4036	Neck pain	1	Mild	Resolved	None	Probable	No	Yes
BRI4036	Dizziness/dazed	0	Mild	Resolved	Concomitant medication	Probable	No	Yes
BRI4036	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI4036	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI4036	Hand twitching	0	Mild	Resolved	None	Probable	No	Yes
BRI4036	Jaw ache	0	Mild	Resolved	None	Probable	No	Yes
BRI4036	Dizziness/dazed	0	Mild	Resolved	Concomitant medication	Probable	No	Yes
BRI4036	Dizziness/dazed	0	Mild	Resolved	None	Probable	No	Yes
BRI4036	Eye throbbing	0	Mild	Resolved	Concomitant medication	Probable	No	Yes
BRI4039	Headache	0	Moderate	Resolved	None	Probable	No	Yes
BRI4039	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI4039	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI4039	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI4039	Pain behind eyes/ headache	3	Mild	Resolved	None	Probable	No	Yes
BRI4039	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI4039	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI4039	Headache	1	Mild	Resolved	None	Probable	No	Yes
BRI4039	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI4039	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI4039	Headache	0	Mild	Resolved	None	Probable	No	Yes

continued

TABLE 45 Listing of AEs events reported in cgiTBS arm (*continued*)

Trial ID	Adverse event	Duration (days)	Severity	Outcome	Treatment	Related	Serious	Expected
BRI4039	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI4039	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI4039	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI4039	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI4039	Watering eyes	3	Mild	Resolved	None	Probable	No	Yes
BRI4040	Arthritis flareup	14	Severe	Resolved	Concomitant medication	Not related	No	No
BRI4042	Watering eyes	59	Mild	Resolved	None	Probable	No	Yes
BRI4042	Diarrhoea	28	Moderate	Resolved	Concomitant medication	Unlikely	No	No
BRI4042	Watering eyes	0	Mild	Resolved	None	Probable	No	Yes
BRI4042	Watering eyes	1	Mild	Resolved	None	Probable	No	Yes
BRI4042	Back pain	47	Moderate	Resolved	Concomitant medication	Unlikely	No	No
BRI4042	Watering eyes	0	Mild	Resolved	None	Probable	No	Yes
BRI4042	Heavy legs	3	Mild	Resolved	None	Possible	No	No
BRI4042	Nausea	0	Mild	Resolved	None	Possible	No	No
BRI4042	Vertigo	0	Mild	Resolved	None	Probable	No	Yes
BRI4042	Scalp discomfort	0	Mild	Resolved	None	Probable	No	Yes
BRI4042	Headache	36	Mild	Resolved	Concomitant Medication	Probable	No	Yes
BRI4042	Fatigue	32	Mild	Resolved	None	Possible	No	No
BRI4042	Watering eyes	1	Mild	Resolved	Non-drug therapy	Probable	No	Yes
BRI4042	Vertigo	59	Severe	Resolved	Concomitant medication	Probable	No	Yes
BRI4042	Kidney infection	7	Moderate	Resolved	Concomitant medication	Unlikely	No	No
BRI4042	Jaw ache	3	Moderate	Resolved	Concomitant medication	Probable	No	Yes
BRI4042	Sensitive skin left side of face	12	Mild	Resolved	Concomitant medication	Probable	No	Yes
BRI4042	Sensitive skin left side of face	15	Moderate	Resolved	Concomitant medication	Probable	No	Yes
BRI4042	Nausea	32	Mild	Resolved	Concomitant medication	Possible	No	No
BRI4042	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI4042	Sensitive skin left side of face	1	Mild	Resolved	None	Probable	No	Yes
BRI4045	Headache	95	Mild	Resolved	Concomitant medication	Probable	No	Yes

TABLE 45 Listing of AEs events reported in cgiTBS arm (*continued*)

Trial ID	Adverse event	Duration (days)	Severity	Outcome	Treatment	Related	Serious	Expected
BRI4045	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI4045	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI4045	Tiredness	2	Mild	Resolved	None	Unlikely	No	No
BRI4045	Neck pain	0	Mild	Resolved	None	Probable	No	Yes
BRI4045	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI4045	Muscle tension in right thumb	0	Mild	Resolved	None	Probable	No	Yes
BRI4045	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI4045	Headache	2	Mild	Resolved	Concomitant medication	Probable	No	Yes
BRI4045	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI4045	Headache	0	Moderate	Resolved	Concomitant medication	Probable	No	Yes
BRI4045	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI4045	Headache	1	Mild	Resolved	None	Probable	No	Yes
BRI4045	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI4045	Headache	0	Mild	Resolved	None	Probable	No	Yes
BRI4046	Jaw ache	1	Mild	Resolved	None	Probable	No	Yes
BRI4046	Nausea	3	Mild	Resolved	None	Unlikely	No	No
BRI4046	'Spaced out'	2	Moderate	Resolved	Concomitant medication	Possible	No	Yes
BRI4046	Headache	15	Moderate	Resolved	None	Probable	No	Yes
BRI4046	Dizziness	2	Moderate	Resolved	Concomitant medication	Possible	No	Yes
BRI4046	Headache	1	Mild	Resolved	Concomitant medication	Probable	No	Yes

TABLE 46 Common side effects after TMS sessions

		rTMS	cgiTBS	Total
		n = 126	*n* = 128	*n* = 254
Common side effects after TMS session 1				
Headaches	Yes, *n* (%)	24 (19.0%)	12 (9.4%)	36 (14.2%)
	No, *n* (%)	102 (81.0%)	116 (90.6%)	218 (85.8%)
Neck pain	Yes, *n* (%)	19 (15.1%)	18 (14.1%)	37 (14.6%)
	No, *n* (%)	107 (84.9%)	110 (85.9%)	217 (85.4%)
Scalp discomfort	Yes, *n* (%)	20 (15.9%)	15 (11.7%)	35 (13.8%)
	No, *n* (%)	106 (84.1%)	113 (88.3%)	219 (86.2%)

continued

TABLE 46 Common side effects after TMS sessions (*continued*)

		rTMS	cgiTBS	Total
		n = 126	*n* = 128	*n* = 254
Tinnitus	Yes, *n* (%)	3 (2.4%)	5 (3.9%)	8 (3.1%)
	No, *n* (%)	123 (97.6%)	123 (96.1%)	246 (96.9%)
Dizziness	Yes, *n* (%)	15 (11.9%)	13 (10.2%)	28 (11.0%)
	No, *n* (%)	111 (88.1%)	115 (89.8%)	226 (89.0%)
Jaw ache	Yes, *n* (%)	12 (9.5%)	10 (7.8%)	22 (8.7%)
	No, *n* (%)	114 (90.5%)	118 (92.2%)	232 (91.3%)
Nausea	Yes, *n* (%)	6 (4.8%)	4 (3.1%)	10 (3.9%)
	No, *n* (%)	120 (95.2%)	124 (96.9%)	244 (96.1%)
Watery eyes	Yes, *n* (%)	8 (6.3%)	6 (4.7%)	14 (5.5%)
	No, *n* (%)	118 (93.7%)	122 (95.3%)	240 (94.5%)
Common side effects after TMS session 2				
Headaches	Yes, *n* (%)	32 (26.0%)	28 (22.0%)	60 (24.0%)
	No, *n* (%)	91 (74.0%)	99 (78.0%)	190 (76.0%)
Neck pain	Yes, *n* (%)	21 (17.1%)	16 (12.6%)	37 (14.8%)
	No, *n* (%)	102 (82.9%)	111 (87.4%)	213 (85.2%)
Scalp discomfort	Yes, *n* (%)	17 (13.8%)	11 (8.7%)	28 (11.2%)
	No, *n*(%)	106 (86.2%)	116 (91.3%)	222 (88.8%)
Tinnitus	Yes, *n* (%)	1 (0.8%)	6 (4.7%)	7 (2.8%)
	No, *n* (%)	122 (99.2%)	121 (95.3%)	243 (97.2%)
Dizziness	Yes, *n* (%)	11 (8.9%)	12 (9.4%)	23 (9.2%)
	No, *n* (%)	112 (91.1%)	115 (90.6%)	227 (90.8%)
Jaw ache	Yes, *n* (%)	13 (10.6%)	12 (9.4%)	25 (10.0%)
	No, *n* (%)	110 (89.4%)	115 (90.6%)	225 (90.0%)
Nausea	Yes, *n* (%)	7 (5.7%)	8 (6.3%)	15 (6.0%)
	No, *n* (%)	116 (94.3%)	119 (93.7%)	235 (94.0%)
Watery eyes	Yes, *n* (%)	5 (4.1%)	5 (3.9%)	10 (4.0%)
	No, *n* (%)	118 (95.9%)	122 (96.1%)	240 (96.0%)
Common side effects after TMS session 3				
Headaches	Yes, *n* (%)	29 (23.8%)	26 (20.5%)	55 (22.1%)
	No, *n* (%)	93 (76.2%)	101 (79.5%)	194 (77.9%)
Neck pain	Yes, *n* (%)	17 (13.9%)	10 (7.9%)	27 (10.8%)
	No, *n* (%)	105 (86.1%)	117 (92.1%)	222 (89.2%)
Scalp discomfort	Yes, *n* (%)	14 (11.5%)	14 (11.0%)	28 (11.2%)
	No, *n* (%)	108 (88.5%)	113 (89.0%)	221 (88.8%)

TABLE 46 Common side effects after TMS sessions (*continued*)

		rTMS	cgiTBS	Total
		n = 126	*n* = 128	*n* = 254
Tinnitus	Yes, *n* (%)	1 (0.8%)	8 (6.3%)	9 (3.6%)
	No, *n* (%)	121 (99.2%)	119 (93.7%)	240 (96.4%)
Dizziness	Yes, *n* (%)	7 (5.7%)	8 (6.3%)	15 (6.0%)
	No, *n* (%)	115 (94.3%)	119 (93.7%)	234 (94.0%)
Jaw ache	Yes, *n* (%)	10 (8.2%)	6 (4.7%)	16 (6.4%)
	No, *n* (%)	112 (91.8%)	121 (95.3%)	233 (93.6%)
Nausea	Yes, *n* (%)	7 (5.7%)	7 (5.5%)	14 (5.6%)
	No, *n* (%)	115 (94.3%)	120 (94.5%)	235 (94.4%)
Watery eyes	Yes, *n* (%)	8 (6.6%)	4 (3.1%)	12 (4.8%)
	No, *n* (%)	114 (93.4%)	123 (96.9%)	237 (95.2%)
TMS session 4				
Headaches	Yes, *n* (%)	20 (16.3%)	19 (15.0%)	39 (15.6%)
	No, *n* (%)	103 (83.7%)	108 (85.0%)	211 (84.4%)
Neck pain	Yes, *n* (%)	14 (11.4%)	17 (13.4%)	31 (12.4%)
	No, *n* (%)	109 (88.6%)	110 (86.6%)	219 (87.6%)
Scalp discomfort	Yes, *n* (%)	13 (10.6%)	9 (7.1%)	22 (8.8%)
	No, *n* (%)	110 (89.4%)	118 (92.9%)	228 (91.2%)
Tinnitus	Yes, *n* (%)	3 (2.4%)	8 (6.3%)	11 (4.4%)
	No, *n* (%)	120 (97.6%)	118 (92.9%)	238 (95.2%)
	Not available, *n* (%)	0 (0.0%)	1 (0.8%)	1 (0.4%)
Dizziness	Yes, *n* (%)	6 (4.9%)	12 (9.4%)	18 (7.2%)
	No, *n* (%)	117 (95.1%)	115 (90.6%)	232 (92.8%)
Jaw ache	Yes, *n* (%)	8 (6.5%)	7 (5.5%)	15 (6.0%)
	No, *n* (%)	115 (93.5%)	120 (94.5%)	235 (94.0%)
Nausea	Yes, *n* (%)	7 (5.7%)	5 (3.9%)	12 (4.8%)
	No, *n* (%)	116 (94.3%)	122 (96.1%)	238 (95.2%)
Watery eyes	Yes, *n* (%)	10 (8.1%)	3 (2.4%)	13 (5.2%)
	No, *n* (%)	113 (91.9%)	124 (97.6%)	237 (94.8%)
TMS session 5				
Headaches	Yes, *n* (%)	20 (16.3%)	16 (12.6%)	36 (14.4%)
	No, *n* (%)	103 (83.7%)	111 (87.4%)	214 (85.6%)
Neck pain	Yes, *n* (%)	15 (12.2%)	9 (7.1%)	24 (9.6%)
	No, *n* (%)	108 (87.8%)	118 (92.9%)	226 (90.4%)
Scalp discomfort	Yes, *n* (%)	13 (10.6%)	8 (6.3%)	21 (8.4%)
	No, *n* (%)	110 (89.4%)	119 (93.7%)	229 (91.6%)

continued

TABLE 46 Common side effects after TMS sessions (*continued*)

		rTMS	cgiTBS	Total
		n = 126	*n* = 128	*n* = 254
Tinnitus	Yes, *n* (%)	4 (3.3%)	7 (5.5%)	11 (4.4%)
	No, *n* (%)	119 (96.7%)	120 (94.5%)	239 (95.6%)
Dizziness	Yes, *n* (%)	8 (6.5%)	11 (8.7%)	19 (7.6%)
	No, *n* (%)	115 (93.5%)	116 (91.3%)	231 (92.4%)
Jaw ache	Yes, *n* (%)	8 (6.5%)	9 (7.1%)	17 (6.8%)
	No, *n* (%)	115 (93.5%)	118 (92.9%)	233 (93.2%)
Nausea	Yes, *n* (%)	6 (4.9%)	6 (4.7%)	12 (4.8%)
	No, *n* (%)	117 (95.1%)	121 (95.3%)	238 (95.2%)
Watery eyes	Yes, *n* (%)	6 (4.9%)	1 (0.8%)	7 (2.8%)
	No, *n* (%)	117 (95.1%)	126 (99.2%)	243 (97.2%)
TMS session 6				
Headaches	Yes, *n* (%)	21 (17.2%)	21 (16.5%)	42 (16.9%)
	No, *n* (%)	101 (82.8%)	106 (83.5%)	207 (83.1%)
Neck pain	Yes, *n* (%)	12 (9.8%)	12 (9.4%)	24 (9.6%)
	No, *n* (%)	110 (90.2%)	115 (90.6%)	225 (90.4%)
Scalp discomfort	Yes, *n* (%)	12 (9.8%)	10 (7.9%)	22 (8.8%)
	No, *n* (%)	110 (90.2%)	117 (92.1%)	227 (91.2%)
Tinnitus	Yes, *n* (%)	5 (4.1%)	10 (7.9%)	15 (6.0%)
	No, *n* (%)	117 (95.9%)	117 (92.1%)	234 (94.0%)
Dizziness	Yes, *n* (%)	8 (6.6%)	9 (7.1%)	17 (6.8%)
	No, *n* (%)	114 (93.4%)	118 (92.9%)	232 (93.2%)
Jaw ache	Yes, *n* (%)	6 (4.9%)	8 (6.3%)	14 (5.6%)
	No, *n* (%)	116 (95.1%)	119 (93.7%)	235 (94.4%)
Nausea	Yes, *n* (%)	7 (5.7%)	6 (4.7%)	13 (5.2%)
	No, *n* (%)	115 (94.3%)	121 (95.3%)	236 (94.8%)
Watery eyes	Yes, *n* (%)	4 (3.3%)	1 (0.8%)	5 (2.0%)
	No, *n* (%)	118 (96.7%)	126 (99.2%)	244 (98.0%)
Common side effects after TMS session 7				
Headaches	Yes, *n* (%)	22 (18.0%)	24 (18.9%)	46 (18.5%)
	No, *n* (%)	100 (82.0%)	103 (81.1%)	203 (81.5%)
Neck pain	Yes, *n* (%)	13 (10.7%)	12 (9.4%)	25 (10.0%)
	No, *n* (%)	109 (89.3%)	115 (90.6%)	224 (90.0%)
Scalp discomfort	Yes, *n* (%)	11 (9.0%)	10 (7.9%)	21 (8.4%)
	No, *n* (%)	111 (91.0%)	117 (92.1%)	228 (91.6%)
Tinnitus	Yes, *n* (%)	4 (3.3%)	10 (7.9%)	14 (5.6%)

TABLE 46 Common side effects after TMS sessions (*continued*)

		rTMS	cgiTBS	Total
		n = 126	*n* = 128	*n* = 254
	No, *n* (%)	118 (96.7%)	117 (92.1%)	235 (94.4%)
Dizziness	Yes, *n* (%)	6 (4.9%)	10 (7.9%)	16 (6.4%)
	No, *n* (%)	116 (95.1%)	117 (92.1%)	233 (93.6%)
Jaw ache	Yes, *n* (%)	6 (4.9%)	12 (9.4%)	18 (7.2%)
	No, *n* (%)	116 (95.1%)	115 (90.6%)	231 (92.8%)
Nausea	Yes, *n* (%)	4 (3.3%)	7 (5.5%)	11 (4.4%)
	No, *n* (%)	118 (96.7%)	120 (94.5%)	238 (95.6%)
Watery eyes	Yes, *n* (%)	4 (3.3%)	3 (2.4%)	7 (2.8%)
	No, *n* (%)	118 (96.7%)	124 (97.6%)	242 (97.2%)
TMS session 8				
Headaches	Yes, *n* (%)	19 (15.6%)	21 (16.7%)	40 (16.1%)
	No, *n* (%)	103 (84.4%)	105 (83.3%)	208 (83.9%)
Neck pain	Yes, *n* (%)	10 (8.2%)	13 (10.3%)	23 (9.3%)
	No, *n* (%)	112 (91.8%)	113 (89.7%)	225 (90.7%)
Scalp discomfort	Yes, *n* (%)	9 (7.4%)	10 (7.9%)	19 (7.7%)
	No, *n* (%)	113 (92.6%)	116 (92.1%)	229 (92.3%)
Tinnitus	Yes, *n* (%)	3 (2.5%)	11 (8.7%)	14 (5.6%)
	No, *n* (%)	119 (97.5%)	115 (91.3%)	234 (94.4%)
Dizziness	Yes, *n* (%)	7 (5.7%)	8 (6.3%)	15 (6.0%)
	No, *n* (%)	115 (94.3%)	118 (93.7%)	233 (94.0%)
Jaw ache	Yes, *n* (%)	8 (6.6%)	7 (5.6%)	15 (6.0%)
	No, *n* (%)	114 (93.4%)	119 (94.4%)	233 (94.0%)
Nausea	Yes, *n* (%)	4 (3.3%)	3 (2.4%)	7 (2.8%)
	No, *n* (%)	118 (96.7%)	123 (97.6%)	241 (97.2%)
Watery eyes	Yes, *n* (%)	3 (2.5%)	4 (3.2%)	7 (2.8%)
	No, *n* (%)	119 (97.5%)	122 (96.8%)	241 (97.2%)
TMS session 9				
Headaches	Yes, *n* (%)	19 (15.6%)	16 (12.8%)	35 (14.2%)
	No, *n* (%)	102 (83.6%)	109 (87.2%)	211 (85.4%)
	Not available, *n* (%)	1 (0.8%)	0 (0.0%)	1 (0.4%)
Neck pain	Yes, *n* (%)	8 (6.6%)	10 (8.0%)	18 (7.3%)
	No, *n* (%)	113 (92.6%)	115 (92.0%)	228 (92.3%)
	Not available, *n* (%)	1 (0.8%)	0 (0.0%)	1 (0.4%)

continued

TABLE 46 Common side effects after TMS sessions (*continued*)

		rTMS	cgiTBS	Total
		n = 126	*n* = 128	*n* = 254
Scalp discomfort	Yes, *n* (%)	8 (6.6%)	11 (8.8%)	19 (7.7%)
	No, *n* (%)	113 (92.6%)	114 (91.2%)	227 (91.9%)
	Not available, *n* (%)	1 (0.8%)	0 (0.0%)	1 (0.4%)
Tinnitus	Yes, *n* (%)	4 (3.3%)	11 (8.8%)	15 (6.1%)
	No, *n* (%)	117 (95.9%)	114 (91.2%)	231 (93.5%)
	Not available, *n* (%)	1 (0.8%)	0 (0.0%)	1 (0.4%)
Dizziness	Yes, *n* (%)	7 (5.7%)	8 (6.4%)	15 (6.1%)
	No, *n* (%)	114 (93.4%)	117 (93.6%)	231 (93.5%)
	Not available, *n* (%)	1 (0.8%)	0 (0.0%)	1 (0.4%)
Jaw ache	Yes, *n* (%)	10 (8.2%)	8 (6.4%)	18 (7.3%)
	No, *n* (%)	111 (91.0%)	117 (93.6%)	228 (92.3%)
	Not available, *n* (%)	1 (0.8%)	0 (0.0%)	1 (0.4%)
Nausea	Yes, *n* (%)	6 (4.9%)	7 (5.6%)	13 (5.3%)
	No, *n* (%)	115 (94.3%)	118 (94.4%)	233 (94.3%)
	Not available, *n* (%)	1 (0.8%)	0 (0.0%)	1 (0.4%)
Watery eyes	Yes, *n* (%)	4 (3.3%)	2 (1.6%)	6 (2.4%)
	No, *n* (%)	117 (95.9%)	123 (98.4%)	240 (97.2%)
	Not available, *n* (%)	1 (0.8%)	0 (0.0%)	1 (0.4%)
TMS session 10				
Headaches	Yes, *n* (%)	23 (19.0%)	22 (17.7%)	45 (18.4%)
	No, *n* (%)	98 (81.0%)	102 (82.3%)	200 (81.6%)
Neck pain	Yes, *n* (%)	10 (8.3%)	14 (11.3%)	24 (9.8%)
	No, *n* (%)	111 (91.7%)	110 (88.7%)	221 (90.2%)
Scalp discomfort	Yes, *n* (%)	9 (7.4%)	8 (6.5%)	17 (6.9%)
	No, *n* (%)	112 (92.6%)	116 (93.5%)	228 (93.1%)
Tinnitus	Yes, *n* (%)	3 (2.5%)	11 (8.9%)	14 (5.7%)
	No, *n* (%)	118 (97.5%)	113 (91.1%)	231 (94.3%)
Dizziness	Yes, *n* (%)	4 (3.3%)	9 (7.3%)	13 (5.3%)
	No, *n* (%)	117 (96.7%)	115 (92.7%)	232 (94.7%)
Jaw ache	Yes, *n* (%)	7 (5.8%)	8 (6.5%)	15 (6.1%)
	No, *n* (%)	114 (94.2%)	116 (93.5%)	230 (93.9%)
Nausea	Yes, *n* (%)	5 (4.1%)	8 (6.5%)	13 (5.3%)
	No, *n* (%)	116 (95.9%)	116 (93.5%)	232 (94.7%)
Watery eyes	Yes, *n* (%)	4 (3.3%)	5 (4.0%)	9 (3.7%)
	No, *n* (%)	117 (96.7%)	119 (96.0%)	236 (96.3%)

TABLE 46 Common side effects after TMS sessions (*continued*)

		rTMS	cgiTBS	Total
		n = 126	*n* = 128	*n* = 254
TMS session 11				
Headaches	Yes, *n* (%)	19 (15.7%)	21 (16.9%)	40 (16.3%)
	No, *n* (%)	102 (84.3%)	103 (83.1%)	205 (83.7%)
Neck pain	Yes, *n* (%)	10 (8.3%)	11 (8.9%)	21 (8.6%)
	No, *n* (%)	111 (91.7%)	113 (91.1%)	224 (91.4%)
Scalp discomfort	Yes, *n* (%)	13 (10.7%)	8 (6.5%)	21 (8.6%)
	No, *n* (%)	108 (89.3%)	116 (93.5%)	224 (91.4%)
Tinnitus	Yes, *n* (%)	4 (3.3%)	9 (7.3%)	13 (5.3%)
	No, *n* (%)	117 (96.7%)	115 (92.7%)	232 (94.7%)
Dizziness	Yes, *n* (%)	6 (5.0%)	6 (4.8%)	12 (4.9%)
	No, *n* (%)	115 (95.0%)	118 (95.2%)	233 (95.1%)
Jaw ache	Yes, *n* (%)	7 (5.8%)	5 (4.0%)	12 (4.9%)
	No, *n* (%)	114 (94.2%)	119 (96.0%)	233 (95.1%)
Nausea	Yes, *n* (%)	4 (3.3%)	7 (5.6%)	11 (4.5%)
	No, *n* (%)	117 (96.7%)	117 (94.4%)	234 (95.5%)
Watery eyes	Yes, *n* (%)	4 (3.3%)	2 (1.6%)	6 (2.4%)
	No, *n* (%)	117 (96.7%)	122 (98.4%)	239 (97.6%)
TMS session 12				
Headaches	Yes, *n* (%)	18 (14.9%)	18 (14.8%)	36 (14.8%)
	No, *n* (%)	103 (85.1%)	104 (85.2%)	207 (85.2%)
Neck pain	Yes, *n* (%)	12 (9.9%)	12 (9.8%)	24 (9.9%)
	No, *n* (%)	109 (90.1%)	110 (90.2%)	219 (90.1%)
Scalp discomfort	Yes, *n* (%)	10 (8.3%)	6 (4.9%)	16 (6.6%)
	No, *n* (%)	111 (91.7%)	116 (95.1%)	227 (93.4%)
Tinnitus	Yes, *n* (%)	3 (2.5%)	10 (8.2%)	13 (5.3%)
	No, *n* (%)	118 (97.5%)	112 (91.8%)	230 (94.7%)
Dizziness	Yes, *n* (%)	9 (7.4%)	8 (6.6%)	17 (7.0%)
	No, *n* (%)	112 (92.6%)	114 (93.4%)	226 (93.0%)
Jaw ache	Yes, *n* (%)	5 (4.1%)	7 (5.7%)	12 (4.9%)
	No, *n* (%)	116 (95.9%)	115 (94.3%)	231 (95.1%)
Nausea	Yes, *n* (%)	5 (4.1%)	4 (3.3%)	9 (3.7%)
	No, *n* (%)	116 (95.9%)	118 (96.7%)	234 (96.3%)
Watery eyes	Yes, *n* (%)	5 (4.1%)	1 (0.8%)	6 (2.5%)
	No, *n* (%)	116 (95.9%)	121 (99.2%)	237 (97.5%)

continued

TABLE 46 Common side effects after TMS sessions (*continued*)

		rTMS	cgiTBS	Total
		n = 126	*n* = 128	*n* = 254
TMS session 13				
Headaches	Yes, *n* (%)	19 (15.7%)	24 (19.7%)	43 (17.7%)
	No, *n* (%)	102 (84.3%)	98 (80.3%)	200 (82.3%)
Neck pain	Yes, *n* (%)	8 (6.6%)	9 (7.4%)	17 (7.0%)
	No, *n* (%)	113 (93.4%)	113 (92.6%)	226 (93.0%)
Scalp discomfort	Yes, *n* (%)	9 (7.4%)	9 (7.4%)	18 (7.4%)
	No, *n* (%)	112 (92.6%)	113 (92.6%)	225 (92.6%)
Tinnitus	Yes, *n* (%)	2 (1.7%)	11 (9.0%)	13 (5.3%)
	No, *n* (%)	119 (98.3%)	111 (91.0%)	230 (94.7%)
Dizziness	Yes, *n* (%)	5 (4.1%)	7 (5.7%)	12 (4.9%)
	No, *n* (%)	116 (95.9%)	115 (94.3%)	231 (95.1%)
Jaw ache	Yes, *n* (%)	5 (4.1%)	7 (5.7%)	12 (4.9%)
	No, *n* (%)	116 (95.9%)	115 (94.3%)	231 (95.1%)
Nausea	Yes, *n* (%)	4 (3.3%)	8 (6.6%)	12 (4.9%)
	No, *n* (%)	117 (96.7%)	114 (93.4%)	231 (95.1%)
Watery eyes	Yes, *n* (%)	2 (1.7%)	1 (0.8%)	3 (1.2%)
	No, *n* (%)	119 (98.3%)	121 (99.2%)	240 (98.8%)
TMS session 14				
Headaches	Yes, *n* (%)	13 (10.7%)	16 (13.1%)	29 (11.9%)
	No, *n* (%)	108 (89.3%)	106 (86.9%)	214 (88.1%)
Neck pain	Yes, *n* (%)	12 (9.9%)	10 (8.2%)	22 (9.1%)
	No, *n* (%)	109 (90.1%)	112 (91.8%)	221 (90.9%)
Scalp discomfort	Yes, *n* (%)	8 (6.6%)	10 (8.2%)	18 (7.4%)
	No, *n* (%)	113 (93.4%)	112 (91.8%)	225 (92.6%)
Tinnitus	Yes, *n* (%)	3 (2.5%)	11 (9.0%)	14 (5.8%)
	No, *n* (%)	118 (97.5%)	111 (91.0%)	229 (94.2%)
Dizziness	Yes, *n* (%)	6 (5.0%)	7 (5.7%)	13 (5.3%)
	No, *n* (%)	115 (95.0%)	115 (94.3%)	230 (94.7%)
Jaw ache	Yes, *n* (%)	4 (3.3%)	5 (4.1%)	9 (3.7%)
	No, *n* (%)	117 (96.7%)	117 (95.9%)	234 (96.3%)
Nausea	Yes, *n* (%)	6 (5.0%)	3 (2.5%)	9 (3.7%)
	No, *n* (%)	115 (95.0%)	119 (97.5%)	234 (96.3%)
Watery eyes	Yes, *n* (%)	4 (3.3%)	3 (2.5%)	7 (2.9%)
	No, *n* (%)	117 (96.7%)	119 (97.5%)	236 (97.1%)

TABLE 46 Common side effects after TMS sessions (*continued*)

		rTMS	cgiTBS	Total
		n = 126	*n* = 128	*n* = 254
TMS session 15				
Headaches	Yes, *n* (%)	14 (11.6%)	21 (17.4%)	35 (14.5%)
	No, *n* (%)	107 (88.4%)	100 (82.6%)	207 (85.5%)
Neck pain	Yes, *n* (%)	9 (7.4%)	9 (7.4%)	18 (7.4%)
	No, *n* (%)	112 (92.6%)	112 (92.6%)	224 (92.6%)
Scalp discomfort	Yes, *n* (%)	9 (7.4%)	10 (8.3%)	19 (7.9%)
	No, *n* (%)	112 (92.6%)	111 (91.7%)	223 (92.1%)
Tinnitus	Yes, *n* (%)	4 (3.3%)	8 (6.6%)	12 (5.0%)
	No, *n* (%)	117 (96.7%)	113 (93.4%)	230 (95.0%)
Dizziness	Yes, *n* (%)	5 (4.1%)	9 (7.4%)	14 (5.8%)
	No, *n* (%)	116 (95.9%)	112 (92.6%)	228 (94.2%)
Jaw ache	Yes, *n* (%)	7 (5.8%)	7 (5.8%)	14 (5.8%)
	No, *n* (%)	114 (94.2%)	114 (94.2%)	228 (94.2%)
Nausea	Yes, *n* (%)	3 (2.5%)	7 (5.8%)	10 (4.1%)
	No, *n* (%)	118 (97.5%)	114 (94.2%)	232 (95.9%)
Watery eyes	Yes, *n* (%)	2 (1.7%)	3 (2.5%)	5 (2.1%)
	No, *n* (%)	119 (98.3%)	118 (97.5%)	237 (97.9%)
TMS session 16				
Headaches	Yes, *n* (%)	12 (9.9%)	19 (15.7%)	31 (12.8%)
	No, *n* (%)	109 (90.1%)	102 (84.3%)	211 (87.2%)
Neck pain	Yes, *n* (%)	9 (7.4%)	7 (5.8%)	16 (6.6%)
	No, *n* (%)	112 (92.6%)	114 (94.2%)	226 (93.4%)
Scalp discomfort	Yes, *n* (%)	12 (9.9%)	5 (4.1%)	17 (7.0%)
	No, *n* (%)	109 (90.1%)	116 (95.9%)	225 (93.0%)
Tinnitus	Yes, *n* (%)	5 (4.1%)	12 (9.9%)	17 (7.0%)
	No, *n* (%)	116 (95.9%)	109 (90.1%)	225 (93.0%)
Dizziness	Yes, *n* (%)	7 (5.8%)	9 (7.4%)	16 (6.6%)
	No, *n* (%)	114 (94.2%)	112 (92.6%)	226 (93.4%)
Jaw ache	Yes, *n* (%)	5 (4.1%)	6 (5.0%)	11 (4.5%)
	No, *n* (%)	116 (95.9%)	115 (95.0%)	231 (95.5%)
Nausea	Yes, *n* (%)	3 (2.5%)	6 (5.0%)	9 (3.7%)
	No, *n* (%)	118 (97.5%)	115 (95.0%)	233 (96.3%)
Watery eyes	Yes, *n* (%)	3 (2.5%)	2 (1.7%)	5 (2.1%)
	No, *n* (%)	118 (97.5%)	119 (98.3%)	237 (97.9%)

continued

TABLE 46 Common side effects after TMS sessions (*continued*)

		rTMS	cgiTBS	Total
		n = 126	*n* = 128	*n* = 254
TMS session 17				
Headaches	Yes, *n* (%)	12 (9.9%)	18 (14.9%)	30 (12.4%)
	No, *n* (%)	109 (90.1%)	103 (85.1%)	212 (87.6%)
Neck pain	Yes, *n* (%)	11 (9.1%)	10 (8.3%)	21 (8.7%)
	No, *n* (%)	110 (90.9%)	111 (91.7%)	221 (91.3%)
Scalp discomfort	Yes, *n* (%)	11 (9.1%)	11 (9.1%)	22 (9.1%)
	No, *n* (%)	110 (90.9%)	110 (90.9%)	220 (90.9%)
Tinnitus	Yes, *n* (%)	6 (5.0%)	10 (8.3%)	16 (6.6%)
	No, *n* (%)	115 (95.0%)	111 (91.7%)	226 (93.4%)
Dizziness	Yes, *n* (%)	6 (5.0%)	7 (5.8%)	13 (5.4%)
	No, *n* (%)	115 (95.0%)	114 (94.2%)	229 (94.6%)
Jaw ache	Yes, *n* (%)	5 (4.1%)	5 (4.1%)	10 (4.1%)
	No, *n* (%)	116 (95.9%)	116 (95.9%)	232 (95.9%)
Nausea	Yes, *n* (%)	2 (1.7%)	4 (3.3%)	6 (2.5%)
	No, *n* (%)	119 (98.3%)	117 (96.7%)	236 (97.5%)
Watery eyes	Yes, *n* (%)	4 (3.3%)	1 (0.8%)	5 (2.1%)
	No, *n* (%)	117 (96.7%)	120 (99.2%)	237 (97.9%)
TMS session 18				
Headaches	Yes, *n* (%)	10 (8.3%)	17 (14.2%)	27 (11.3%)
	No, *n* (%)	110 (91.7%)	103 (85.8%)	213 (88.8%)
Neck pain	Yes, *n* (%)	8 (6.7%)	10 (8.3%)	18 (7.5%)
	No, *n* (%)	112 (93.3%)	110 (91.7%)	222 (92.5%)
Scalp discomfort	Yes, *n* (%)	10 (8.3%)	11 (9.2%)	21 (8.8%)
	No, *n* (%)	110 (91.7%)	109 (90.8%)	219 (91.3%)
Tinnitus	Yes, *n* (%)	5 (4.2%)	9 (7.5%)	14 (5.8%)
	No, *n* (%)	115 (95.8%)	111 (92.5%)	226 (94.2%)
Dizziness	Yes, *n* (%)	4 (3.3%)	7 (5.8%)	11 (4.6%)
	No, *n* (%)	116 (96.7%)	113 (94.2%)	229 (95.4%)
Jaw ache	Yes, *n* (%)	5 (4.2%)	6 (5.0%)	11 (4.6%)
	No, *n* (%)	115 (95.8%)	114 (95.0%)	229 (95.4%)
Nausea	Yes, *n* (%)	3 (2.5%)	7 (5.8%)	10 (4.2%)
	No, *n* (%)	117 (97.5%)	113 (94.2%)	230 (95.8%)
Watery eyes	Yes, *n* (%)	3 (2.5%)	4 (3.3%)	7 (2.9%)
	No, *n* (%)	117 (97.5%)	116 (96.7%)	233 (97.1%)

TABLE 46 Common side effects after TMS sessions (*continued*)

		rTMS	cgiTBS	Total
		n = 126	*n* = 128	*n* = 254
TMS session 19				
Headaches	Yes, *n* (%)	13 (11.0%)	17 (14.3%)	30 (12.7%)
	No, *n* (%)	105 (89.0%)	102 (85.7%)	207 (87.3%)
Neck pain	Yes, *n* (%)	9 (7.6%)	9 (7.6%)	18 (7.6%)
	No, *n* (%)	109 (92.4%)	110 (92.4%)	219 (92.4%)
Scalp discomfort	Yes, *n* (%)	9 (7.6%)	12 (10.1%)	21 (8.9%)
	No, *n* (%)	109 (92.4%)	107 (89.9%)	216 (91.1%)
Tinnitus	Yes, *n* (%)	5 (4.2%)	9 (7.6%)	14 (5.9%)
	No, *n* (%)	113 (95.8%)	110 (92.4%)	223 (94.1%)
Dizziness	Yes, *n* (%)	6 (5.1%)	7 (5.9%)	13 (5.5%)
	No, *n* (%)	112 (94.9%)	112 (94.1%)	224 (94.5%)
Jaw ache	Yes, *n* (%)	7 (5.9%)	3 (2.5%)	10 (4.2%)
	No, *n* (%)	111 (94.1%)	116 (97.5%)	227 (95.8%)
Nausea	Yes, *n* (%)	2 (1.7%)	3 (2.5%)	5 (2.1%)
	No, *n* (%)	116 (98.3%)	116 (97.5%)	232 (97.9%)
Watery eyes	Yes, *n* (%)	3 (2.5%)	4 (3.4%)	7 (3.0%)
	No, *n* (%)	115 (97.5%)	115 (96.6%)	230 (97.0%)
TMS session 20				
Headaches	Yes, *n* (%)	8 (6.8%)	19 (15.8%)	27 (11.4%)
	No, *n* (%)	109 (93.2%)	101 (84.2%)	210 (88.6%)
Neck pain	Yes, *n* (%)	8 (6.8%)	11 (9.2%)	19 (8.0%)
	No, *n* (%)	109 (93.2%)	109 (90.8%)	218 (92.0%)
Scalp discomfort	Yes, *n* (%)	9 (7.7%)	9 (7.5%)	18 (7.6%)
	No, *n* (%)	108 (92.3%)	111 (92.5%)	219 (92.4%)
Tinnitus	Yes, *n* (%)	5 (4.3%)	10 (8.3%)	15 (6.3%)
	No, *n* (%)	112 (95.7%)	110 (91.7%)	222 (93.7%)
Dizziness	Yes, *n* (%)	2 (1.7%)	7 (5.8%)	9 (3.8%)
	No, *n*(%)	115 (98.3%)	113 (94.2%)	228 (96.2%)
Jaw ache	Yes, *n* (%)	5 (4.3%)	7 (5.8%)	12 (5.1%)
	No, *n* (%)	112 (95.7%)	113 (94.2%)	225 (94.9%)
Nausea	Yes, *n* (%)	2 (1.7%)	4 (3.3%)	6 (2.5%)
	No, *n* (%)	115 (98.3%)	116 (96.7%)	231 (97.5%)
Watery eyes	Yes, *n* (%)	3 (2.6%)	1 (0.8%)	4 (1.7%)
	No, *n* (%)	114 (97.4%)	119 (99.2%)	233 (98.3%)

TABLE 47 Uncommon side effects after TMS sessions

		rTMS *n* = 126	cgiTBS *n* = 128	Total *n* = 254
Uncommon side effects after TMS session 1				
Participants with uncommon side effects, *n* (%)	Yes, *n* (%)	16 (12.7%)	11 (8.6%)	27 (10.6%)
	No, *n* (%)	110 (87.3%)	116 (90.6%)	226 (89.0%)
	Not available, *n* (%)	0 (0.0%)	1 (0.8%)	1 (0.4%)
Uncommon side effects after TMS session 2				
Participants with uncommon side effects, *n* (%)	Yes, *n* (%)	17 (13.8%)	18 (14.2%)	35 (14.0%)
	No, *n* (%)	106 (86.2%)	107 (84.3%)	213 (85.2%)
	Not available, *n* (%)	0 (0.0%)	2 (1.6%)	2 (0.8%)
Uncommon side effects after TMS session 3				
Participants with uncommon side effects, *n* (%)	Yes, *n* (%)	14 (11.5%)	15 (11.8%)	29 (11.6%)
	No, *n* (%)	108 (88.5%)	110 (86.6%)	218 (87.6%)
	Not available, *n* (%)	0 (0.0%)	2 (1.6%)	2 (0.8%)
Uncommon side effects after TMS session 4				
Participants with uncommon side effects, *n* (%)	Yes, *n* (%)	12 (9.8%)	14 (11.0%)	26 (10.4%)
	No, *n* (%)	111 (90.2%)	111 (87.4%)	222 (88.8%)
	Not available, *n* (%)	0 (0.0%)	2 (1.6%)	2 (0.8%)
Uncommon side effects after TMS session 5				
Participants with uncommon side effects, *n* (%)	Yes, *n* (%)	12 (9.8%)	14 (11.0%)	26 (10.4%)
	No, *n* (%)	111 (90.2%)	112 (88.2%)	223 (89.2%)
	Not available, *n* (%)	0 (0.0%)	1 (0.8%)	1 (0.4%)
Uncommon side effects after TMS session 6				
Participants with uncommon side effects, *n* (%)	Yes, *n* (%)	12 (9.8%)	11 (8.7%)	23 (9.2%)
	No, *n* (%)	110 (90.2%)	114 (89.8%)	224 (90.0%)
	Not available, *n* (%)	0 (0.0%)	2 (1.6%)	2 (0.8%)
Uncommon side effects after TMS session 7				
Participants with uncommon side effects, *n* (%)	Yes, *n* (%)	12 (9.8%)	16 (12.6%)	28 (11.2%)
	No, *n* (%)	109 (89.3%)	109 (85.8%)	218 (87.6%)
	Not available, *n* (%)	1 (0.8%)	2 (1.6%)	3 (1.2%)
Uncommon side effects after TMS session 8				
Participants with uncommon side effects, *n* (%)	Yes, *n* (%)	12 (9.8%)	13 (10.3%)	25 (10.1%)
	No, *n* (%)	109 (89.3%)	111 (88.1%)	220 (88.7%)
	Not available, *n* (%)	1 (0.8%)	2 (1.6%)	3 (1.2%)
Uncommon side effects after TMS session 9				
Participants with uncommon side effects, *n* (%)	Yes, *n* (%)	10 (8.2%)	15 (12.0%)	25 (10.1%)
	No, *n* (%)	110 (90.2%)	108 (86.4%)	218 (88.3%)
	Not available, *n* (%)	2 (1.6%)	2 (1.6%)	4 (1.6%)

TABLE 47 Uncommon side effects after TMS sessions (*continued*)

		rTMS *n* = 126	cgiTBS *n* = 128	Total *n* = 254
Uncommon side effects after TMS session 10				
Participants with uncommon side effects, *n* (%)	Yes, *n* (%)	14 (11.6%)	15 (12.1%)	29 (11.8%)
	No, *n* (%)	105 (86.8%)	106 (85.5%)	211 (86.1%)
	Not available, *n* (%)	2 (1.7%)	3 (2.4%)	5 (2.0%)
Uncommon side effects after TMS session 11				
Participants with uncommon side effects, *n* (%)	Yes, *n* (%)	14 (11.6%)	15 (12.1%)	29 (11.8%)
	No, *n* (%)	105 (86.8%)	106 (85.5%)	211 (86.1%)
	Not available, *n* (%)	2 (1.7%)	3 (2.4%)	5 (2.0%)
Uncommon side effects after TMS session 12				
Participants with uncommon side effects, *n* (%)	Yes, *n* (%)	18 (14.9%)	15 (12.3%)	33 (13.6%)
	No, *n* (%)	101 (83.5%)	104 (85.2%)	205 (84.4%)
	Not available, *n* (%)	2 (1.7%)	3 (2.5%)	5 (2.1%)
Uncommon side effects after TMS session 13				
Participants with uncommon side effects, *n* (%)	Yes, *n* (%)	13 (10.7%)	11 (9.0%)	24 (9.9%)
	No, *n* (%)	105 (86.8%)	109 (89.3%)	214 (88.1%)
	Not available, *n* (%)	3 (2.5%)	2 (1.6%)	5 (2.1%)
Uncommon side effects after TMS session 14				
Participants with uncommon side effects, *n* (%)	Yes, *n* (%)	15 (12.4%)	8 (6.6%)	23 (9.5%)
	No, *n* (%)	105 (86.8%)	111 (91.0%)	216 (88.9%)
	Not available, *n* (%)	1 (0.8%)	3 (2.5%)	4 (1.6%)
Uncommon side effects after TMS session 15				
Participants with uncommon side effects, *n* (%)	Yes, *n* (%)	13 (10.7%)	11 (9.1%)	24 (9.9%)
	No, *n* (%)	106 (87.6%)	108 (89.3%)	214 (88.4%)
	Not available, *n* (%)	2 (1.7%)	2 (1.7%)	4 (1.7%)
Uncommon side effects after TMS session 16				
Participants with uncommon side effects, *n* (%)	Yes, *n* (%)	17 (14.0%)	13 (10.7%)	30 (12.4%)
	No, *n* (%)	102 (84.3%)	106 (87.6%)	208 (86.0%)
	Not available, *n* (%)	2 (1.7%)	2 (1.7%)	4 (1.7%)
Uncommon side effects after TMS session 17				
Participants with uncommon side effects, *n* (%)	Yes, *n* (%)	15 (12.4%)	13 (10.7%)	28 (11.6%)
	No, *n* (%)	104 (86.0%)	106 (87.6%)	210 (86.8%)
	Not available, *n* (%)	2 (1.7%)	2 (1.7%)	4 (1.7%)
Uncommon side effects after TMS session 18				
Participants with uncommon side effects, *n* (%)	Yes, *n* (%)	14 (11.7%)	15 (12.5%)	29 (12.1%)
	No, *n* (%)	104 (86.7%)	103 (85.8%)	207 (86.3%)
	Not available, *n* (%)	2 (1.7%)	2 (1.7%)	4 (1.7%)

continued

TABLE 47 Uncommon side effects after TMS sessions (*continued*)

		rTMS *n* = 126	cgiTBS *n* = 128	Total *n* = 254
Uncommon side effects after TMS session 19				
Participants with uncommon side effects, *n* (%)	Yes, *n* (%)	10 (8.5%)	11 (9.2%)	21 (8.9%)
	No, *n* (%)	107 (90.7%)	107 (89.9%)	214 (90.3%)
	Not available, *n* (%)	1 (0.8%)	1 (0.8%)	2 (0.8%)
Uncommon side effects after TMS session 20				
Participants with uncommon side effects, *n* (%)	Yes, *n* (%)	10 (8.5%)	8 (6.7%)	18 (7.6%)
	No, *n* (%)	106 (90.6%)	110 (91.7%)	216 (91.1%)
	Not available, *n* (%)	1 (0.9%)	2 (1.7%)	3 (1.3%)

TABLE 48 Listing of uncommon side effects after TMS session 1

Trial ID	Uncommon side effect description	Details
Uncommon side effects after TMS session 1. Treatment group: rTMS		
BRI1027	Vasovagal attack during treatment, so treatment stopped.	
BRI1029	Tingling in nose, LH cheek and LH eye	
BRI1033	Slight twitching in jaw and neck during treatment	None
BRI1057	Pain described during stimulation which subsided immediately once stimulation stopped	
BRI1061	Discomfort left eyebrow (pressure feeling)	
BRI1064	Shoulder/back tension. Suffers with this usually, but more so today following treatment	
BRI1084	Neck discomfit mild	
BRI1090		Dry mouth
BRI2019	Fuzzy head	Fuzzy head
BRI3003	Tooth pain	
BRI3006	Sinus pain, eye jabbing (pain)	
BRI3020	Worsened depersonalisation	
BRI3024	Pulsating inside head close to scalp	
BRI3033	Slightly twitchy eye; vibrating nose; mild sharp pain in top right back teeth	
BRI3059	Nerve above right eye/eyebrow felt and feels uncomfortable. uncomfortable behind eye	
BRI4022	Left face pain. Possible vasovagal (anxious, sweaty, needed to lie flat)	
Uncommon side effects after TMS session 1. Treatment group: cgiTBS		
BRI1018	Tingling at the back of the tongue	Suffering from light headedness
BRI1023	Tingling in shoulders and arm mild on left side	

TABLE 48 Listing of uncommon side effects after TMS session 1 (*continued*)

Trial ID	Uncommon side effect description	Details
BRI1071	Low-level toothache to one tooth on the left side upper. Noticed only during treatment, but once	
BRI1100	Mild pain above the right eye during stimulations	
BRI1104	Light-headed	
BRI1106	Slightly numb around top of scalp. Mild and he does not feel concerned	Pre-existing tinnitus and nausea
BRI2005	Blurry eyes	
BRI2025	Felt spaced out after treatment	Felt spaced out after treatment
BRI3034	Repetitive clamping of jaw	
BRI4006	Slight sensation in nose	
BRI4029	Hot	

TABLE 49 Uncommon side effects after TMS session 2

Trial ID	Uncommon side effect description	Details
Uncommon side effects after TMS session 2. Treatment group: rTMS		
BRI1007	Slight pain in right shoulder, although does not feel this is related to treatment	
BRI1028	Pins and needles around the back of the head	
BRI1029	tingling nose	
BRI1032	Dry mouth during treatment. Bottle of water given	Headache – worn off by morning. Neck pain – slight stiffness during treatment
BRI1057	Right-side nasal discomfort. Very mild. Stopped after stimulation	
BRI1061	Discomfort left eyebrow remains. Cognitive issues – had difficulty focusing and more noticeable when trying to send a text as words were jumbled and spelling incorrect. Shoulder pain began today	
BRI1102	Feeling of something still touching his head on site of stimulations	
BRI1108	Slight tingling of nose. Slight tenderness at site of pulses	Scalp discomfort, which is tightness at the back of scalp – mild
BRI2015	Pain across chest lasting around 15 minutes tightness post treatment	
BRI2017	Increased irritability post yesterdays treatment (short fuse)	
BRI2019	Feeling a bit groggy post treatment	Advised to remain in clinic, given a drink until feeling better. Approx 10 minutes before feeling better

continued

TABLE 49 Uncommon side effects after TMS session 2 (*continued*)

Trial ID	Uncommon side effect description	Details
BRI3003	Toothache, shoulder and right-hand pain, stiff and numb	
BRI3040	Toothache (mild)	
BRI3049	Extreme fatigue	
BRI3059	Feels like headache/uncomfortable behind right eye. Head feels hot on right side	
BRI4022	Face pain	Better today. Still face pain around left eye/right eye. No vasovagal
BRI4041	Felt slight numbness is my left hand and arm for a period of about 10 minutes. Patient indicated this was right hand feeling numb	I found the treatment to be more intense with the being at the highest point
Uncommon side effects after TMS session 2. Treatment group: cgiTBS		
BRI1023	Described struggling finishing sentences	
BRI1067	Back and muscular pains	Mild headache began last night. Intermittent dizziness continued from yesterday. Nausea began last night. Neck pain after treatment today
BRI1071	Low-level toothache to one left-side upper, noticed during treatment	Feeling tired after treatment
BRI1100	Pain around top and side of right eye during stimulations. Stopped afterwards	Scalp discomfort – during final cycle of stimulations. Stopped after
BRI2001	Bloodshot eyes	
BRI2006	Light headache reported by participant	
BRI2010		Difficulty falling asleep which was unusual for participant
BRI2025	Swollen eye maybe due to tiredness	
BRI3028	Slight sleep disturbance after first session	
BRI3037	Feeling very sleepy	
BRI3045	Teeth chattering a bit	
BRI3051	Teeth chattering during each zap	
BRI3058	Feeling speedy and agitated	
BRI4006	Jaw twitch. Slight RHS motor sensations	
BRI4023	I had a bad headache (last night after first treatment)	I did have a pain in the left hand
BRI4029		Hot in third round – nausea – very tired a metallic taste after third round. Declining after dinner in evening. Stabbing pain in right thumb, fore, and middle fingers for a few mins. A little confusion over 24 hours and [in] train of thought
BRI4036	Eyes throb	
BRI4042	Skin sensitive on left-hand side of face	

TABLE 50 Listing of uncommon side effects after TMS session 3

Trial ID	Uncommon side effect description	Details
Uncommon side effects after TMS session 3. Treatment group: rTMS		
BRI1061	Eyebrow discomfort ongoing	Headache ongoing. Dizziness and nausea began last night
BRI1102	Feeling of something touching against site of treatment	
BRI1108	Very slight tingling at the end of nose	Headache, dull, mild fuzzy feeling. Dizziness, mild, noticed in the morning
BRI1111	Discomfort in back of head	
BRI2012	Feeling spaced out	Pins and needles in right hand
BRI2019	Slightly groggy	Slightly more relaxed, less agitated angry with issues
BRI3003	Toothache, shoulder and hand pain and tingling	
BRI3033	Twitching eye and nose, painful upper right teeth	
BRI3040	Tooth ache but went when repositioned	
BRI3049	Irritable	
BRI3059	Pain behind eye and under eye	
BRI4022	Face pain	Left face/scalp pain persists but now can tolerate a lot better
BRI4034	Pain through head when stimulating	
BRI4043	Tiredness	
Uncommon side effects after TMS session 3. Treatment group: cgiTBS		
BRI1023	Describes continued difficulty with speech and completing sentences. Reviewed by PI. Also dull ache behind left eye	
BRI1068	Described experiencing vivid moving images when eyes were closed during the evening. Specifically described visualising dancing watermelons	Jaw ache on left side last night but gone by this morning. Slight headache last night but gone by morning
BRI1071	Toothache during stimulations	
BRI1100	Pain above right eye during stimulations	
BRI1104	Toothache mild left-side upper pre-molar	
BRI1106	Legs felt shivery during treatment	Pre-existing tinnitus and nausea
BRI1112	Light-headed. Sleepy	Retrospectively reported some side effects as well
BRI2001	Bloodshot eyes	
BRI3029	Extreme dizziness yesterday. Slight electricity in left side of scalp (just for a second). Also sporadic headache lasting seconds at the front of head	
BRI3037	Feeling sleepy	
BRI3058		
BRI4006	Right nostril ‘sinus’ type discomfort during pulses	
BRI4016		Experienced crap in bed last night. Feeling cold
BRI4029		Left-side face ache – tired
BRI4036	Eye throbbing (left)	

TABLE 51 Listing of uncommon side effects after TMS session 4

Trial ID	Uncommon side effect description	Details
Uncommon side effects after TMS session 4. Treatment group: rTMS		
BRI1028	Feeling very hungry	
BRI1057	First stimulation very slight pain in right sinus then stopped after stimulation	
BRI1058	Tiredness ongoing	
BRI1061	Discomfort left eyebrow ongoing	Headache and nausea ongoing
BRI1108	Tingling in the nose and tightness at the back of the head	
BRI2012		Still pins and needles in right hand until 21:30 yesterday
BRI2019	Slightly groggy	
BRI3003	Toothache, heavy eye (left)	
BRI3059	Right temple/eye tender	
BRI4022	Face/nose pain	Pain worse today after a 3 day gap
BRI4043	Difficulty with sleeping, fatigue	
BRI5005	Tiredness	
Uncommon side effects after TMS session 4. Treatment group: cgiTBS		
BRI1023	Continuing speech difficulties completing sentences	
BRI1024	Lightheaded	BP checked – advised to drink more
BRI1050	Sleepiness	
BRI1059	Hearing loss	
BRI1100	Pain over right eye only during stimulations	
BRI1112	Ligh-headed	
BRI1113	Eyes feel sensitive to light	No
BRI2020	Numb on the face for 5 hours	
BRI3016	Slight discomfort where headrest on my head is placed	
BRI3037	Feeling very sleepy	
BRI3058	Feeling spaced out and agitated	
BRI4029		Hot
BRI4036	Eye throbs (left)	
BRI4042	Sensitive feeling on face left-hand side	

TABLE 52 Listing of uncommon side effects after TMS session 5

Trial ID	Uncommon sideeEffect description	Details
Uncommon side effects after TMS session 5. Treatment group: rTMS		
BRI1058	Tiredness ongoing	
BRI1061	Discomfort left eyebrow ongoing	Headache and nausea ongoing
BRI1079	Feeling really tired	
BRI1103	Small scab at the side of stimulations	
BRI1108	Tightness at the back of scalp	
BRI2004	Pronounced pressure of speech at times	
BRI3003	Toothache and heavy eyelids, left eye	
BRI3033	Side of head vibrating. Upper teeth sharp pain	
BRI3059	Right eye tender/temples	
BRI4031		Sensitivity to one tooth (capped) during the session but not issues after the treatment
BRI4033	Shooting pain down right leg after treatment yesterday. Lasted approx. 1.5 hours but okay after	
BRI4043	Fatigue	
Uncommon side effects after TMS session 5. Treatment group: cgiTBS		
BRI1023	Tongue feels enlarged at the tip but not dehydrated and lasts a couple of hours	Mild tinnitus
BRI1043	Feeling foggy-headed and having difficulties finding words	
BRI1067	Mentioned feeling wired – overly stimulated and cannot sleep even when body feels tired	
BRI1100	Pain above right eye only during stimulations	
BRI1104	Twitch in left eye roughly 4 hours after treatment (yesterday)	
BRI1112	Lightheaded	
BRI1113	Eyes feel sensitive to light	
BRI3013	Drowsiness	
BRI3037	Feeling very sleepy	
BRI3058	Difficulty concentrating, agitation	
BRI4006	Jaw twitch only today	
BRI4029		Face spasms – ache left side. Metallic taste in mouth. Hot
BRI4036	Eye throbs at time	
BRI4042	Sensitive skin on left-hand side of my face	

TABLE 53 Listing of uncommon side effects after TMS session 6

Trial ID	Uncommon side effect description	Details
Uncommon side effects after TMS session 6. Treatment group: rTMS		
BRI1051	Ears burning	
BRI1058	Tiredness ongoing	
BRI1061	Discomfort left eyebrow ongoing	Headache and nausea ongoing
BRI1079	Feeling very tired still	
BRI1097	Upper left-side top and bottom molars discomfort during stimulations	
BRI2004	Pronounced pressure of speech at times	
BRI2019	Slight groggyness	
BRI4022	Pain left side of face and upper left teeth	
BRI4026		Pins + needles in left arm
BRI4030		Tingling/pins/needles sensation left hand
BRI4031		Tenderness in tooth (capped) during the treatment. Only during the pulses
BRI4043	Fatigue	
Uncommon side effects after TMS session 6. Treatment group: cgiTBS		
BRI1023	States continues struggling processing words. Tongue feels dehydrated, goes same day	Tinnitus mild but has continued since 3 August 2019
BRI1056	Right sinus ache. Started Friday, very much still there as mildly tolerable	
BRI1095	Discomfort in left temple during 3 stimulations of the second cycle. resolved with minor change of the coil	
BRI1100	Pain in right eye during stimulations	
BRI1112	Lightheaded	Tingly head at site of treatment
BRI3013	Drowsiness	
BRI3037	Feeling very sleepy	
BRI3058	Agitation. Hard to concentrate	
BRI4029		Metal taste in mouth. Hot. Face twitch when treatment on left side
BRI4042	Patient verbally confirmed in session 7 that sensitive skin on face was continuing at session 6	
BRI4046	Sometimes feel dizzy and spaced out	

TABLE 54 Listing of uncommon side effects after TMS session 7

Trial ID	Uncommon side effect description	Details
Uncommon side effects after TMS session 7. Treatment group: rTMS		
BRI1051	Sleepiness	
BRI1058	Tiredness ongoing	
BRI1064	Ache behind left eye (side that was twitching throughout treatment) – lasted 1 hour	
BRI1079	Feeling really tired still	
BRI1097	Upper and lower molar left-side slight discomfort during initial stimulation but stopped halfway through	
BRI1101	Tension in the shoulders	
BRI1111	Headache after last treatment – head pre-treatment today	
BRI3022	Toothpain during treatment	
BRI4022	Face/teeth pain – same as before	
BRI4030		Pins/needles sensation in left hand
BRI4031		Sensitivity in tooth (capped) during the treatment only
BRI4043	Fatigue	
Uncommon side effects after TMS session 7. Treatment group: cgiTBS		
BRI1023	Tongue effect still occurring	Earplugs given to see if decreases yinnitus. 3 days off to restart Tuesday 13th to see if effects reduce. PI to review on next treatment
BRI1056	Tiredness more noticeable. Sinus ache continues (mild)	
BRI1059	Irritability – has noticed feeling significantly more irritable since treatment started. Unsure if related or related to external stimuli	Tinnitus has become louder now than usual. Noticeable last night watching TV
BRI1100	Pain above the right eye during stimulations	
BRI1112	Lightheaded and sleepy	Reports headache. Started yesterday and went way today
BRI3013	Drowsiness. Leg and arm twitching	
BRI3016	Maybe tiredness	More tired than normal
BRI3034	Toothache	
BRI3037	Feeling very sleepy	
BRI3038	Sleep disruption	
BRI3058	Agitated to some degree. Feeling spaced out	
BRI4006		Right nostril usual sensation less noticeable than prior
BRI4029		Hot. Left face twitch
BRI4036	Eye throbs	
BRI4042	Face sensitive and painful on left-hand side	
BRI5004	Tireness	

TABLE 55 Listing of uncommon side effects after TMS session 8

Trial ID	Uncommon side effect description	Details
Uncommon side effects after TMS session 8. Treatment group: rTMS		
BRI1051	Sleepiness	
BRI1058	Tiredness reduced but ongoing	
BRI1079	Feeling really tired still	
BRI1111	Tiredness	Fell treatment was more tolerable today. Meditated before treatment
BRI2012		Reports tingly lips for of 30 minutes last night 10.6.19
BRI3022	tooth pain in filling during treatment	
BRI3026	Unable to think things through	
BRI3059	Some twitching behind right eye	
BRI4031		Sensitivity in tooth (capped) during the treatment only
BRI4037	Broken sleep over past few nights	
BRI4041	Slight hand tremors in both hands	No other side effects experienced to date
BRI4043	Fatigue	
Uncommon side effects after TMS session 8. Treatment group: cgiTBS		
BRI1023	Tongue issue remains	Tinnitus only in right ear. Treatment felt more intense
BRI1041		
BRI1043	Following treatment on 14 January 2020, participant experienced a pain in both temples, painful to touch, painful to talk or eat. This was resolved before treatment on 15 January 20	
BRI1049		
BRI1056	Tiredness continues	
BRI1059	Irritability ongoing	Tinnitus ongoing
BRI1100	Pain above right during stimulations only	
BRI1112	Lightheaded after treatment, often goes within an hour Sleepiness after treatment, often goes within an hour	
BRI2013		Continues to experience vivid dreams since start of treatment
BRI3013	Drowsiness	
BRI4006		Right nostril sensation. Similar sensation in right supraorbital sinus
BRI4029		Hot. Congested head. Metallic taste. Left face twitch
BRI4042	Sensitivity on my face on left-hand side where I have treatment	

TABLE 56 Listing of uncommon side effects after TMS session 9

Trial ID	Uncommon side effect description	Details
Uncommon side effects after TMS session 9. Treatment group: rTMS		
BRI1051		
BRI1058	Tiredness ongoing	
BRI1079	Feeling tired still	
BRI2004	Bleeding gums and at times aching teeth, mainly around the root filling area	
BRI2019	Slightly groggy – lasting about 10 minutes. Increased appetite late at night	Slightly groggy – lasting about 10 minutes. Increased appetite late at night
BRI3015	Facial nerves affected – feels bruised	Dizziness and nausea reasonably mild
BRI4007	Unblocks my sinuses	
BRI4031		Sensitivity in tooth (capped) during the treatment
BRI4041	Hand tremors	Hand tremors were less evident than yesterday
BRI4043	Fatigue	
Uncommon side effects after TMS session 9. Treatment group: cgiTBS		
BRI1023	Tongue still feels dry, thick and swollen	Tinnitus right ear only
BRI1048		
BRI1059	Irritability ongoing	Tinnitus ongoing
BRI1067	Feeling forgetful (words during conversation)	
BRI1068		
BRI1069	Scalp discomfort sensation comes and goes, varied pattern	Scalp discomfort goes away late evening. Pre-existing headache and neckache. Pre-existing tinnitus
BRI1098	Twitching in left cheek and behind the ear during stimulations	
BRI1100	Pain above right eye during stimulations	
BRI1112	Sleepiness more noticed halfway through stimulations/ session	
BRI3013	Drowsiness	
BRI3058	Agitation. Inability to relax	
BRI4018	Itchy scalp	
BRI4029		Metallic taste. Left side face ache. Hot, Tender scalp.
BRI4036		
BRI4042	Face on left-hand side still sensitive	

TABLE 57 Listing of uncommon side effects after TMS session 10

Trial ID	Uncommon side effect description	Details
Uncommon side effects after TMS session 10. Treatment group: rTMS		
BRI1033	Body ache, difficulty staying still query withdrawal from venaflaxine	
BRI1035		
BRI1051	Sleepines	
BRI1058	Tiredness ongoing but states is slightly less	Began feeling nauseous around 5 minutes before treatment ended
BRI1079	Really tired still	
BRI1084	Back pain began morning of the 16th, moderate discomfit	Headache mild. Neck pain pre-existing
BRI1111	Still feel tiredness	Had headache before she arrived
BRI3024	Side of head feels bruised for 12–24 hours afterwards. More than just a headache	
BRI4007	Unblocked sinuses, cheers	
BRI4020		Occasional pain in left eye
BRI4030		Tingling/pins needles sensation left hand
BRI4031		Sensitivity in tooth (capped) during the treatment
BRI4041	Minor hand tremors	The hand tremors I have experienced over the last 3 days have virtually stopped
BRI4043	Tiredness	
Uncommon side effects after TMS session 10. Treatment group: cgiTBS		
BRI1023	Tingling right hand. Slight pain in chest – but going. Both hand red and itching – they look like a reaction to earplugs, as made of latex and was holding them in hands throughout treatment. Usual problem with tongue. Continued below	Will seek medical advice if required and will take Piriton when gets home. Redness very mild Tongue looked normal. Tinnitus right ear only
BRI1025		
BRI1049		
BRI1059	Irritability ongoing	Tinnitus ongoing
BRI1067	Forgetting words ongoing	
BRI1100	Pain over right eye only during stimulation. Stops at the end of treatment	
BRI1106	Feeling the urge to grip ring finger and little finger on both hands	Pre-existing tinnitus and nausea
BRI1112	Lightheaded and dowsiness	
BRI3013	Twitch in leg/arm (right). Drowsiness	
BRI3016	Maybe	Tiredness maybe side effect
BRI3038	Disrupted sleep	
BRI3058	Over-stimulation of brain	
BRI4029		Left-side face twitch/ache. Hot. Metallic taste in mouth. Tired
BRI4036	Eye throbbing, hand twitching	
BRI4042	Face sensitive on the left-hand side	

TABLE 58 Listing of uncommon side effects after TMS session 11

Trial ID	Uncommon side effect description	Details
Uncommon side effects after TMS session 11. Treatment group: rTMS		
BRI1015		
BRI1033	Jaw movement during treatment	
BRI1058	Tiredness ongoing	
BRI1079	Still feeling tired	
BRI1084	Back pain mild continued from 16th. Sensation mild down back of right leg	Headache mild and started at the very end of treatment. Neck pain is pre-existing and no worse
BRI1111	Tiredness	
BRI3005		
BRI3024	Side of head feels bruised/tender for the rest of the day	
BRI3026	Fatigue	
BRI3033	Sharp tooth pain	
BRI3049	Tearful, irritable	
BRI4031		Sensitivity in tooth (capped) during the treatment
BRI4041	Minor side effects still evident (participant verbally confirmed he was referring to his minor hand tremors)	
BRI4043	Tiredness	
Uncommon side effects after TMS session 11. Treatment group: cgiTBS		
BRI1023	Tongue still feels dehydrated	Possibly extra days off TMS he thinks may have helped
BRI1048		none
BRI1059	Irritability ongoing	Tinnitus ongoing. Reported possible improvement to pre-existing condition of anosmia as could smell faint smell of coffee this morning
BRI1067	Forgetfulness with words ongoing	
BRI1068	Discomfort in left temple	
BRI1069	Vertigo – woke up with this the day after treatment. Lasted several hours	Nausea – same day as vertigo
BRI1100	Pain during stimulations above the right eye	
BRI1112	Dizziness and drowsy	
BRI2006		Fatigue that prevents household chores to be completed
BRI2010	Pulling sensation in left side of head following treatment yesterday. Experienced nothing during treatment today	Experienced nothing during treatment today
BRI3034	Bodily lightness	
BRI3054	Increased panic/anxiety, flashbacks	
BRI3058	Very mentally over-stimulated	
BRI4029		Face twitch left. Scalp pain at site. Hot. Metallic taste. Confusion
BRI4042	Sensitivity to left-hand side of face	

TABLE 59 Listing of uncommon side effects after TMS session 12

Trial ID	Uncommon side effect description	Details
Uncommon side effects after TMS session 12. Treatment group: rTMS		
BRI1058	Tiredness ongoing	
BRI1070	Toothache during treatment only	Headache during treatment only
BRI1079	Tiredness	
BRI1084	Back pain continued from 16th mild. Sensation down right leg but mild	
BRI1085	A tooth filling has come out from a tooth on left side. Does not intend to go to the dentist until treatment completed. Has in no discomfort	
BRI1102	Noise in right ear during stimulations	
BRI1111	Ongoing tiredness	
BRI3022	The tooth pain is back!! (tooth pain during treatment)	
BRI3024	Side of the head feels bruised to the touch. Lasts about 12–24 hours	
BRI3049	Tearful	
BRI3056	Twitching in left lip and under jaw. Headache yesterday	
BRI4007	Cleared sinuses	
BRI4014		Found good relief from 9:30 to 17:30 yesterday (28 October 2019), which was best result so far
BRI4022	Face/ left teeth pain	Pain worse on left side today. Coil moved slightly which improved things
BRI4031		Sensitivity in tooth (capped) during the treatment only
BRI4037	Hot flushes during sleep	
BRI4041	Hand tremors	Minor hand tremors still evident
BRI4043	Tiredness	
Uncommon side effects after TMS session 12. Treatment group: cgiTBS		
BRI1024		Slight headache, jaw ache from yesterday, stomach off but doesn't persist – only during treatment
BRI1050	General feeling of tiredness	
BRI1059	Irritability ongoing	Tinnitus ongoing. Headache ongoing
BRI1067	Forgetfulness with words continued	
BRI1100	Pain above right eye during stimulations	
BRI2010	Experienced a tingling in right index finger intermittently. Appears to be easing now	
BRI3013	Drowsiness	
BRI3023	Pins and needles in right hand, little finger	
BRI3037	Feeling sleepy	
BRI3038	Migraine	
BRI3051	Lethargy/tiredness	
BRI3054	Panic/anxiety/flashbacks	

TABLE 59 Listing of uncommon side effects after TMS session 12 (*continued*)

Trial ID	Uncommon side effect description	Details
BRI3058	Agitation	Makes me feel weird
BRI4029		Metallic taste. Confusion. Face twitch left
BRI4042	Face sensitive on left-hand side where I receive treatment	

TABLE 60 Listing of uncommon side effects after TMS session 13

Trial ID	Uncommon side effect description	Details
Uncommon side effects after TMS session 13. Treatment group: rTMS		
BRI1058	Tiredness ongoing	
BRI1070	Toothache during stimulation and stops when treatment concludes	Headache only during stimulation and stops when treatment concludes
BRI1079	Feeling tired still	
BRI2019		Slightly groggy
BRI3022	Mild tooth pain during treatment	
BRI3024	Side of head feels bruised to the touch for about 12–24 hours	
BRI3033	Vibrating jaw	
BRI3049	Tearful, emotional	
BRI4022	During treatment no face pain	I have noticed after treatment I've had bilateral face pain around cheeks – R>L, requiring paracetamol/ibuprofen. No cold symptoms. Will keep you posted
BRI4031		Sensitivity in tooth (capped) only during the treatment
BRI4037	Hot flushes during sleep	
BRI4041	Hand tremor has almost disappeared	
BRI4043	Tiredness	
Uncommon side effects after TMS session 13. Treatment group: cgiTBS		
BRI1023	Tongue issue continues. Slight redness observed. Rubbing earplugs	Tinnitus right ear
BRI1024	Mild stomach ache – no uti lower abdomen	Slight headache around brow area
BRI1049	Sleepiness	
BRI1067	Forgetfulness with words ongoing	
BRI1100	Pain above right eye during stimulations	
BRI3037	Feeling sleepy	
BRI3054	Anxiety/panic/flashbacks	
BRI3057	Fatigue	
BRI3058	It exacerbates my low mood	
BRI4029		Tired. Confusion. Left face twitch
BRI4042	Face sensitive on left-hand side where I have my treatment	

TABLE 61 Listing of uncommon side effects after TMS session 14

Trial ID	Uncommon side effect description	Details
Uncommon side effects after TMS session 14. Treatment group: rTMS		
BRI1042		
BRI1058	Tiredness ongoing	Warm fuzzy feeling on right side of scalp occurred towards end of treatment today
BRI1070	Toothache only during stimulation. Gone immediately after treatment concludes	
BRI1079	Tiredness	
BRI1084	Back pain-mild-improving. Started from 16th	Neck pain – mild-existing-no worse
BRI1097	Nightmares/bad dreams	
BRI2004	Toothache	
BRI3017	Get very tired after the treatment and stay that way. Don't feel hungry at all. Mind feels foggy like I'm in a dream or it keeps racing and obsessing on something	
BRI3024	Feeling of bruising at side of the head for 12–24 hours afterwards	
BRI3026	Slow motor response	
BRI4022	1. Some left tooth pain during. 2. Later in day develop right maxilla pain.	Participant informed researcher he had experienced the same delayed 'cheek pain' on Saturday 18 January 2020 [same mentioned in treatment session 13 (17 January 2020)], requiring paracetamol/ibuprofen – which eases. No symptoms experienced on Sunday 19 January 2020
BRI4030		Tingling/numbness left hand
BRI4031		Sensitivity in tooth during treatment
BRI4037	Nosebleed after session 13 about 1 hour later for 10 minutes	
BRI4043	Tiredness and memory (losing words)	
Uncommon side effects after TMS session 14. Treatment group: cgiTBS		
BRI1023	Tongue remains feeling dehydrated and swollen	Tinnitus is continuous and slightly worse over last few treatments
BRI1050	Sleepiness	
BRI1067	Forgetfulness with words ongoing	
BRI1098	Brain fog 28 October 2021	Unsure if brain fog is related. However reports it started on 28 October 2021
BRI1100	Discomfort above right eye only during stimulations and mild	no
BRI3054	Anxiety/flashbacks/low mood/lethargy	
BRI4029		Hot. Tired. Face ache left
BRI4042	Face sensitivity on left-hand side	

TABLE 62 Listing of uncommon side effects after TMS session 15

Trial ID	Uncommon side effect description	Details
Uncommon side effects after TMS session 15. Treatment group: rTMS		
BRI1028	Rwitching right eye, this has been apparent for a few days	Twitching right eye, this has been apparent for a few days
BRI1051	Back pain	
BRI1058	Tiredness ongoing	
BRI1079	Tiredness	
BRI1084	Back pain – mild –improving from 16th	
BRI2004	Reports toothache	
BRI3024	Both sides of head feel bruised to the touch for about 12–24 hours after treatment	
BRI4022	Left face pain	
BRI4031		Sensitivity in tooth (capped) during the treatment
BRI4037	Hot flushes during sleep mood swings more frequent	
BRI4041	Hand tremors	Hand tremors virtually disappeared
BRI4043	Tiredness	
BRI5005	Tiredness	
Uncommon side effects after TMS session 15. Treatment group: cgiTBS		
BRI1023	Tongue feels dehydrated and swollen	Tinnitus continues, describes it as not worse. Shoulder injury swimming advised to A/E
BRI1067	Forgetfulness with words ongoing. Lightheadedness in evening last night – gone by this morning	Watery eyes in evening last night – gone by this morning
BRI1098	Brain fog. Continuous but slightly better	Headache mild but continuous. Dizziness mild currently but can fluctuate. Nausea moderate prior to taking anti-sickness medication thus feeling better and no nausea presently
BRI1100	Pain above the right eye during stimulations	
BRI2021	Dry mouth	
BRI3037	Feeling very sleepy	
BRI3054	Increased flashbacks/panic/low mood	
BRI3058	Feeling over-stimulated	
BRI4024	Hot flush	
BRI4029		Metallic taste (teeth filling). Left face twitch. Tired. Hot
BRI4036	Eye throbbing/pain	

TABLE 63 Listing of uncommon side effects after TMS session 16

Trial ID	Uncommon side effect description	Details
Uncommon side effects after TMS session 16. Treatment group: rTMS		
BRI1028	Flickering in both eyes, PI advised retesting of MT and see if any different, if not, to continue and reassess next week with a view to moving target	
BRI1051	Pain behind left ear	
BRI1058	Tiredness ongoing	
BRI1079	Tiredness	
BRI1084	Backache	
BRI1096	Pins and needles in the back of the head	
BRI1097	Had an uncomfortable night sleep	
BRI1101	Anxiety, difficulty sleeping	Tinnitus is pre-existing, feels worse at present
BRI1111	Have been struggling to falls asleep for 3 days	
BRI3022	Mild tooth pain again. Over the weekend had bad headaches	
BRI3024	Feeling of bruised side of head	
BRI3056	Nerves twitching	
BRI4022	Left facial/upper teeth pain	
BRI4031		Sensitivity in tooth (capped) only during the treatment
BRI4037	Nose bleed 1 hour after lasting 10 minutes	Slight light headiness. When listening to speech it was delayed from other people
BRI4041	Hand tremors	Hand tremors are very minor, no other side effects evident
BRI4043	Tiredness	
Uncommon side effects after TMS session 16. Treatment group: cgiTBS		
BRI1013	Dazed, tired	
BRI1023	Feels forgetful. Tongue still feels swollen. Tired all the time	Tinnitus right ear
BRI1049	Sleepiness still continuing throughout day	
BRI1050	Sleepiness	Sleepiness – mild feeling of tiredness which feels continuous – headache – mild goes same day. Scalp discomfort – mild, goes same day. Dizziness – mild, goes same day. Jaw ache
BRI1067	Forgetfulness with words ongoing	
BRI1100	Discomfort above right eye during stimulations	
BRI2005		Reports tight band around head. Feelings of emotional blockage
BRI2008	Nightmares have returned	
BRI3037	Feeling sleepy	
BRI3054	Worsening low mood, lethargy	
BRI4029		Left-side face twitch. Hot. Confusion
BRI4036	Eye throbbing	
BRI4042		Face sensitivity on left-hand side where I have treatment

TABLE 64 Listing of uncommon side effects after TMS session 17

Trial ID	Uncommon side effect description	Details
Uncommon side effects after TMS session 17. Treatment group: rTMS		
BRI1039		
BRI1051	Sleepiness	
BRI1058	Tiredness ongoing	Warm discomfort on right side of head (like pins and needles)
BRI1079	Tiredness	
BRI1084	backache	
BRI1097	Uncomfortable night affecting sleep.	
BRI1108	Dry throat during treatment	
BRI1110	Pre-existing tinitis worse than usual	
BRI1111	Mood is a bit low, concerns about ending treatment this week	
BRI3024	Tenderness and feeling of bruising on side of head. Lasts 12–24 hours	
BRI4031	Sensitivity in tooth (capped) during the treatment	
BRI4037	Lightheadiness very surly for 3–4 hours after treatment	Still getting hot flashes and very little sleep due to TMS and also pain from Fibromyalgia
BRI4041	Hand tremors	Hand tremors very slight
BRI4043	Tiredness + memory word loss	
BRI5002		
Uncommon side effects after TMS session 17. Treatment group: cgiTBS		
BRI1023	Tongue still feels swollen. Exhausted	Tinnitus right ear
BRI1024	Stomach ache in the mornings only	
BRI1025		
BRI1050	Tiredness	
BRI1067	Forgetfulness with words ongoing.	
BRI1098	Brain fog	
BRI1100	Discomfort over right eye only during stimulations	
BRI2005		Tightness around head – very anxious
BRI2008	Nightmares – as experienced prior to treatment	
BRI3037	Feeling sleepy	
BRI3054	Low energy	
BRI3058	Exceedingly tired	
BRI4029		Tired. Forgetfulness. Metallic taste

TABLE 65 Listing of uncommon side effects after TMS session 18

Trial ID	Uncommon side effect description	Details
Uncommon side effects after TMS session 18. Treatment group: rTMS		
BRI1027		
BRI1039		
BRI1051	Sleepiness	None
BRI1058	Tiredness ongoing	
BRI1079	Really tired still	
BRI1084	Back discomfott but no worse continuous from 16 July	
BRI1111	Tiredness possibly due to being sat in the chair relaxing during session	
BRI3015	Facial nerve affected	
BRI3024	Bruised sensation on side of head for 12–24 hours. Dry eye on the side of head where the coil is placed	
BRI3033	Head vibrating	
BRI4030		Tingling left hand
BRI4031		Sensitivity to tooth (capped) only during treatment
BRI4041	Hand tremors	Only minor tremors evident
BRI4043	Tiredness and memory (loss of words, searching for right word)	
Uncommon side effects after TMS session 18. Treatment group: cgiTBS		
BRI1023	Tongue still feels swollen. Indigestion several days ago	Tinnitus right ear. Watering of eyes – possible allergy
BRI1024	Stomach ache, very tired	
BRI1049	Sleepiness	
BRI1050	Tiredness	
BRI1067	Forgetfulness with words ongoing	
BRI1086	Feeling faint, feeling hot and clammy	
BRI1098	Tiredness and brain fog	
BRI1100	Slight discomfort above right eye only during stimulations	
BRI1107	Anxiety	Reports anxiety has been noticeable since 29 December 2021
BRI2008	Retyrn of nightmares as prior to treatment	
BRI3013	Drowsiness	
BRI3037	Feeling sleepy	
BRI3054	Increased lethargy	
BRI4029		Hot. Confusion. Metallic taste. Sick
BRI5006		Slept a lot yesterday had a weeks gap since last treatment

TABLE 66 Listing of uncommon side effects after TMS session 19

Trial ID	Uncommon side effect description	Details
Uncommon side effects after TMS session 19. Treatment group: rTMS		
BRI1040	Extreme tiredness	
BRI1051	Ongoing tiredness	None
BRI1058	Tiredness ongoing	
BRI1079	Tired	
BRI1084	Back pain continuous from 16th but no worse. Mild	Neck discomfort pre-existing and no worse
BRI3015	Facial nerve affected	
BRI3017	Tired, sleepy, eyes hurt	
BRI3024	Bruised sensation on side of head for 12–24 hours. Dry eye on side of head where coil is placed	
BRI4022		Small amount of pain around left and right scalp, cheeks
BRI4031		
Uncommon side effects after TMS session 19. Treatment group: cgiTBS		
BRI1023		
BRI1049	Sleepiness	Sleepiness overall feeling of tiredness and spontaneously dropping off to sleep
BRI1050	Sleepiness	
BRI1067	Forgetfulness with words ongoing	Neck pain began on Monday, mild and not sure if connected to treatment
BRI1098	Tiredness – moderate and brain fog – mild	no
BRI1100	Discomfort above the right eye during stimulations	
BRI1107	Anxiety	
BRI3037	Feeling sleepy	
BRI4029		Hot. Metallic taste. Forgetfulness
BRI4042	Sensitivity face left-hand side	
BRI4045	More tired than normal	

TABLE 67 Listing of uncommon side effects after TMS session 20

Trial ID	Uncommon side effect description	Details
Uncommon side effects after TMS session 20. Treatment group: rTMS		
BRI1058	Tiredness ongoing	
BRI1079	Tiredness	
BRI1084	Backache – is not any worse and eases when moves position	
BRI1108	Numbness in back of head	

continued

TABLE 67 Listing of uncommon side effects after TMS session 20 (*continued*)

Trial ID	Uncommon side effect description	Details
BRI3015	Facial nerve affected	All side effects seem acceptable and easily managed with OTC analegesics if needed
BRI3017	Tired, sleepy	
BRI3024	Bruising sensation on side of head for 12–24 hours after session; and eye closest to coil is dry for about 12 hours after session	
BRI4022	Right face pain	
BRI4031		Sensitivity in tooth (capped) only during treatment
BRI4043	Tiredness	
Uncommon side effects after TMS session 20. Treatment group: cgiTBS		
BRI1023	Slight swollen tongue. Indigestion	Tinnitus right ear
BRI1050	Sleepiness	
BRI1067	Forgetfulness ongoing. Lethargy since start of week. Aching in tops of arms also since start of week.	Neck pain ongoing. Scalp discomfort/bruise feeling at stimulation target – gone as of this morning
BRI1100	Discomfort above the right eye during stimulations	
BRI1107	Anxiety	
BRI3037	Feeling sleepy	
BRI4029		Hot. Confusion/forgetfulness
BRI4036	Eye throbbing	

TABLE 68 The listing below corresponds to minor protocol deviations that fall under the category of 'Treatment adjusted as participant could not tolerate'

Trial ID	Treatment	Deviation date	Deviation reason	Additional details
BRI1010	rTMS	17 May 2019	Treatment adjusted as participant could not tolerate. (State adjustment)	
BRI1020	rTMS	18 July 2019	Treatment adjusted as participant could not tolerate. (State adjustment)	Treatment adjusted as participant could not tolerate any more than 39%. (Treated on original site with threshold reduced)
BRI1022	cgiTBS	22 July 2019	Treatment adjusted as participant could not tolerate. (State adjustment)	Treatment delivered on target at a lower percentage than motor threshold due to excessive jaw movement
BRI1027	rTMS	27 August 2019	Treatment adjusted as participant could not tolerate. (State adjustment)	Treatment target moved within 1 cm from original target as participant experienced pain and could not tolerate original target
BRI1028	rTMS	14 October 2019	Treatment adjusted as participant could not tolerate. (State adjustment)	Target moved on 17th treatment due to ongoing issue with flickering in eye, participant found this worse and chose to return to original site
BRI1032	rTMS	30 September 2021	Treatment adjusted as participant could not tolerate. (State adjustment)	Threshold reduced. Treatment to continue at original site with treatment dose of 47%

TABLE 68 The listing below corresponds to minor protocol deviations that fall under the category of 'Treatment adjusted as participant could not tolerate' (*continued*)

Trial ID	Treatment	Deviation date	Deviation reason	Additional details
BRI1033	rTMS	23 October 2019	Treatment adjusted as participant could not tolerate. (State adjustment)	Level of treatment reduced to 50% as participant experienced twitching jaw and neck at full dose. Also discomfort in left eye
BRI1036	cgiTBS	11 November 2019	Treatment adjusted as participant could not tolerate. (State adjustment)	Struggling with nausea and dizziness. Target moved, this did not help so moved back to original site and MT reduced down from 36% to 30%
BRI1040	rTMS	5 December 2019	Treatment adjusted as participant could not tolerate. (State adjustment)	Participant could not tolerate treatment on original site (reported jaw ache and toothache). As per protocol, target was adjusted, first it was moved back which did not help, this it was moved forward within 2 cm diameter of original site. The participant was able to tolerate this adjustment, therefore a new target was created in the forward position which was used for subsequent treatments
BRI1044	cgiTBS	27 December 2019	Treatment adjusted as participant could not tolerate. (State adjustment)	Target moved forward as original site was not tolerable and experience movement of the jaw
BRI1051	rTMS	24 February 2020	Treatment adjusted as participant could not tolerate. (State adjustment)	Participant began to experience dizziness and nausea during treatment number 5. The symptoms came on suddenly and treatment was paused. Reviewed by PI who advised decreased intensity of treatment and repositioning of the coil. This did not help so decreased intensity at original position. ECG carried out the following day prior to treatment and medical colleagues. MT retested and treatment carried out at a slightly lesser intensity
BRI1057	rTMS	7 September 2020	Treatment adjusted as participant could not tolerate. (State adjustment)	Participant could not tolerate above 40% treatment dose (dose should have been 60%). Dose lowered to 40%. Steps were followed on treatment CRF. Repositioning coil did not help with discomfort, therefore step 3 was followed and threshold was reduced with Stimguide set at original site. The participant was able to tolerate this
BRI1057	rTMS	23 September 2020	Treatment adjusted as participant could not tolerate. (State adjustment)	Participant initially could not tolerate full treatment dose based on motor threshold, and received treatments 1–11 at a reduced dose (40%) as this is the most she could tolerate. However she later expressed that she was finding the treatment much more tolerable and wanted to try to increase. PI was consulted and agreed to this plan. On 23 September 2020 the treatment was incrementally increased, and participant felt that she could now tolerate treatment at 52%. Treatment to continue at this level (this is still less than the dose determined by retesting MT on 6th treatment, which was 55%, making treatment dose 66%)
BRI1058	rTMS	8 September 2020	Treatment adjusted as participant could not tolerate. (State adjustment)	Treatment dose reduced at original site. Unable to tolerate full dose (should have been 76%), and adjusting position did not help. Reduced to 44%

continued

TABLE 68 The listing below corresponds to minor protocol deviations that fall under the category of 'Treatment adjusted as participant could not tolerate' (*continued*)

Trial ID	Treatment	Deviation date	Deviation reason	Additional details
BRI1061	rTMS	13 October 2020	Treatment adjusted as participant could not tolerate. (State adjustment)	Target moved back 1 cm in accordance with CRF due to participant not tolerating. Treated at full dose on new target. New target created on Stimguide
BRI1061	rTMS	15 October 2020	Treatment adjusted as participant could not tolerate. (State adjustment)	Treatment dose reduced from 54% to 49% as participant reported adverse reactions (including sickness and dizziness) after the previous treatment. Reduction in dose made under the advice of the PI
BRI1062	rTMS	3 November 2020	Treatment adjusted as participant could not tolerate. (State adjustment)	Participant could not tolerate full treatment dose. Change of position did not help. Treated at original site at reduced dose of 50% (should be 74%). Treatment was delivered at 50% up to and including treatment 5. MT% was retested on session 6 and remained unchanged (62%, indicating a treatment dose of 74%). At this point the participant expressed that he now felt he could tolerate the full dose. The dose was turned up to 74% in increments, and participant was able to tolerate. Treatments to continue at full dose of 74% from treatment 6 onwards unless another deviation occurs
BRI1074	rTMS	8 March 2021	Treatment adjusted as participant could not tolerate. (State adjustment)	Participant could not tolerate treatment when titrating dose on first treatment. Attempted to move coil position back and forward of original site (options 1 and 2 from treatment CRF), however neither of these options helped (participant experienced an intolerable level of discomfort during stimulations). Therefore the coil was positioned on the original site with reduced threshold (lower treatment power). Participant was randomised to RTMS and motor threshold on day one was determined to be 65%, which would mean a treatment percentage of 78%; however with the deviation he is now being treated on the original site with a treatment power of 44%, which is the highest level he could tolerate
BRI1076	rTMS	23 March 2021	Treatment adjusted as participant could not tolerate. (State adjustment)	Stimulation not tolerated at 77%. M/T 64%. Adjusted treatment as protocol forward and backward from original site with no benefit. Therefore treatment reduced at original site to 69%. Participant could not tolerate full dose due to jaw movement and scalp discomfit. Plan to deliver future treatment at 69%
BRI1079	rTMS	5 May 2021	Treatment adjusted as participant could not tolerate. (State adjustment)	Treatment dose reduced as participant could not tolerate. Changing position (steps 1 and 2) did not help. MT% was 51% treatment dose should have been 61%. However, participant could not tolerate above 53% treatment dose
BRI1081	cgiTBS	7 June 2021	Treatment adjusted as participant could not tolerate. (State adjustment)	MT was 83%, treatment dose should have been 66%. On the first treatment the dose was gradually increased to 66%, however participant found this intolerable. The following day (second treatment) the treatment was adjusted. Position was moved in accordance with SOP however this did not help. However, participant was able to tolerate treatment dose of 60% on the original target. Therefore treatment dose has been reduced to 60% and the plan is to continue the rest of the treatments at that level

TABLE 68 The listing below corresponds to minor protocol deviations that fall under the category of 'Treatment adjusted as participant could not tolerate' (*continued*)

Trial ID	Treatment	Deviation date	Deviation reason	Additional details
BRI1090	rTMS	23 August 2021	Treatment adjusted as participant could not tolerate. (State adjustment)	Motor threshold was 56%, treatment dose should have been 67%. However, participant could not tolerate this. Position changes (as per treatment CRF) did not help. Treatment dose was therefore reduced. Participant was able to tolerate 61% treatment dose. Treatment to continue at that level
BRI1097	rTMS	14 October 2021	Treatment adjusted as participant could not tolerate. (State adjustment)	Participant stated on day 2 she could not tolerate treatment due to discomfort. position change did not help, therefore reduced treatment dose on original site. this helped and participant agreed to continue at the reduced level. New treatment dose 52%
BRI2014	cgiTBS	26 June 2019	Treatment adjusted as participant could not tolerate. (State adjustment)	EEG cap used instead of navigation process
BRI2018	cgiTBS	7 August 2019	Treatment adjusted as participant could not tolerate. (State adjustment)	Option treatment location No 2. Stimguide reset to 1 cm forwards of the site (within 2 cm diameter of original site)
BRI2019	rTMS	7 August 2019	Treatment adjusted as participant could not tolerate. (State adjustment)	Treatment dose reduced to 45% from 79%, to be increased as per tolerance level. Stimguide reset 1 cm backward from the site
BRI2019	rTMS	9 August 2019	Treatment adjusted as participant could not tolerate. (State adjustment)	Increase in treatment dosage to 50%
BRI2019	rTMS	12 August 2019	Treatment adjusted as participant could not tolerate. (State adjustment)	Increase in treatment dosage to 55%
BRI2019	rTMS	15 August 2019	Treatment adjusted as participant could not tolerate. (State adjustment)	Coil moved 2 cm back and up to treat. V1 deviation form completed
BRI2019	rTMS	23 August 2019	Treatment adjusted as participant could not tolerate. (State adjustment)	Increase in treatment dosage to 60%
BRI2024	rTMS	08 November 2019	Treatment adjusted as participant could not tolerate. (State adjustment)	Moved from treatment site 2 cm
BRI2024	rTMS	12 November 2019	Treatment adjusted as participant could not tolerate. (State adjustment)	Reduced from 80% to 70% due to jaw movement
BRI2024	rTMS	13 November 2019	Treatment adjusted as participant could not tolerate. (State adjustment)	Lowered from 70% to 65% due to jaw movement

continued

TABLE 68 The listing below corresponds to minor protocol deviations that fall under the category of 'Treatment adjusted as participant could not tolerate' (*continued*)

Trial ID	Treatment	Deviation date	Deviation reason	Additional details
BRI2026	rTMS	3 December 2019	Treatment adjusted as participant could not tolerate. (State adjustment)	Due to unable to tolerate 72% and lowered to 60%
BRI2026	rTMS	11 December 2019	Treatment adjusted as participant could not tolerate. (State adjustment)	Motor threshold was 79%, participant was unable to tolerant, treatment threshold reduced to 65%
BRI2027	rTMS	2 December 2019	Treatment adjusted as participant could not tolerate. (State adjustment)	Reduced from 74% to 65%, participant was unable to tolerant treatment at 74%
BRI2027	rTMS	3 December 2019	Treatment adjusted as participant could not tolerate. (State adjustment)	Adjustment from 74% to 65% due to pain at the back of the eyes
BRI2027	rTMS	9 December 2019	Treatment adjusted as participant could not tolerate. (State adjustment)	Due to jaw movement at 74%, treatment threshold adjusted to 68% and moved back from target site by 2 cm
BRI2027	rTMS	24 December 2019	Treatment adjusted as participant could not tolerate. (State adjustment)	Participant was treated 2 cm away from treatment target site due to jaw movement
BRI2027	rTMS	27 December 2019	Treatment adjusted as participant could not tolerate. (State adjustment)	Participant was treated at 2 cm away from the target treatment spot due to jaw movement
BRI2029	cgiTBS	19 March 2020	Treatment adjusted as participant could not tolerate. (State adjustment)	Lowered treatment dose from 47% to 42%, replaced coil by 2 cm
BRI2029	cgiTBS	20 March 2020	Treatment adjusted as participant could not tolerate. (State adjustment)	Lowered from 42% to 38%, could not tolerate
BRI2029	cgiTBS	3 April 2020	Treatment adjusted as participant could not tolerate. (State adjustment)	Moved coil 2 cm from treatment site
BRI2029	cgiTBS	17 April 2020	Treatment adjusted as participant could not tolerate. (State adjustment)	Due to pain, coil was moved 2 cm from treatment site
BRI3006	rTMS	18 July 2019	Treatment adjusted as participant could not tolerate. (State adjustment)	Treatment target was moved 1 cm above due to participant not tolerating treatment on 18th session
BRI3006	rTMS	19 July 2019	Treatment adjusted as participant could not tolerate. (State adjustment)	Treatment target was adjusted but all options were uncomfortable, therefore treatment power was reduced by 2%

TABLE 68 The listing below corresponds to minor protocol deviations that fall under the category of 'Treatment adjusted as participant could not tolerate' (*continued*)

Trial ID	Treatment	Deviation date	Deviation reason	Additional details
BRI3024	rTMS	29 November 2019	Treatment adjusted as participant could not tolerate. (State adjustment)	Treatment tolerated 1 cm behind target at lower MT
BRI3034	cgiTBS	26 February 2020	Treatment adjusted as participant could not tolerate. (State adjustment)	
BRI3057	cgiTBS	25 January 2022	Treatment adjusted as participant could not tolerate. (State adjustment)	Coil moved 1 cm backwards/power reduced by 10%
BRI3057	cgiTBS	26 January 2022	Treatment adjusted as participant could not tolerate. (State adjustment)	Power reduced by 10%
BRI3057	cgiTBS	27 January 2022	Treatment adjusted as participant could not tolerate. (State adjustment)	Power reduced by 3%
BRI3059	rTMS	1 February 2022	Treatment adjusted as participant could not tolerate. (State adjustment)	Two stimulations done at 1 cm backwards; the rest at original site with power reduced by 20%
BRI3059	rTMS	2 February 2022	Treatment adjusted as participant could not tolerate. (State adjustment)	Power reduced by 20% for one stimulation, and the rest by 30%
BRI3059	rTMS	3 February 2022	Treatment adjusted as participant could not tolerate. (State adjustment)	Power reduced by 30%
BRI3059	rTMS	4 February 2022	Treatment adjusted as participant could not tolerate. (State adjustment)	Power reduced by 25% for 1 stimulation, the rest by 30%
BRI3059	rTMS	7 February 2022	Treatment adjusted as participant could not tolerate. (State adjustment)	Two stimulations done at MT with coil moved 1 cm upwards, the rest at 1 cm upwards with power reduced by 20%
BRI3059	rTMS	8 February 2022	Treatment adjusted as participant could not tolerate. (State adjustment)	Treatment done with 1 cm upwards with power reduced by 10%
BRI3059	rTMS	9 February 2022	Treatment adjusted as participant could not tolerate. (State adjustment)	Treatment done with coil 1 cm upwards and power reduced by 10%
BRI3059	rTMS	10 February 2022	Treatment adjusted as participant could not tolerate. (State adjustment)	Power done at MT for 1 stimulation, the rest reduced by 5% all with coil moved 1 cm upwards
BRI3059	rTMS	11 February 2022	Treatment adjusted as participant could not tolerate. (State adjustment)	Power reduced by 10% and completed with coil 1 cm upwards

continued

TABLE 68 The listing below corresponds to minor protocol deviations that fall under the category of 'Treatment adjusted as participant could not tolerate' (*continued*)

Trial ID	Treatment	Deviation date	Deviation reason	Additional details
BRI3059	rTMS	14 February 2022	Treatment adjusted as participant could not tolerate. (State adjustment)	Power reduced by 5% and completed with coil 1 cm upwards
BRI4004	rTMS	4 June 2019	Treatment adjusted as participant could not tolerate. (State adjustment)	Unable to tolerate treatment at session 16. Protocol followed, unable to tolerate moving coil. Agreed to deliver treatment at lower % of MT for last 5 sessions
BRI4004	rTMS	5 June 2019	Treatment adjusted as participant could not tolerate. (State adjustment)	Unable to tolerate treatment delivered at 120% of MT, Protocol followed. Unable to tolerate with coil moved. Agreed to deliver at 100% of MT
BRI4004	rTMS	6 June 2019	Treatment adjusted as participant could not tolerate. (State adjustment)	Unable to tolerate treatment delivered at 120% of MT. Protocol followed. Unable to tolerate. Coil moved. Agreed to deliver at 100% of MT
BRI4004	rTMS	7 June 2019	Treatment adjusted as participant could not tolerate. (State adjustment)	Unable to tolerate treatment at 120% of MT. Protocol followed. Unable to tolerate. Agreed to deliver at 100%
BRI4004	rTMS	10 June 2019	Treatment adjusted as participant could not tolerate. (State adjustment)	Unable to tolerate treatment delivered at 120% of MT. Protocol followed. Unable to tolerate. Coil moved. Agreed to deliver at 100% of MT
BRI4007	rTMS	1 July 2019	Treatment adjusted as participant could not tolerate. (State adjustment)	
BRI4022	rTMS	02 January 2020	Treatment adjusted as participant could not tolerate. (State adjustment)	Coil moved forward due to participant not being able to tolerate original position
BRI4042	cgiTBS	5 July 2021	Treatment adjusted as participant could not tolerate. (State adjustment)	Coil was moved backwards 1.9 cm from original site and new treatment target was created
BRI4044	rTMS	5 August 2021	Treatment adjusted as participant could not tolerate. (State adjustment)	Treatment dose titrated as patient did not tolerate maximum dose well in previous session. Titrated 20% below max dose for 25 trains, 10% below for 25 trains then maximum treatment dose for final 25 trains
BRI4044	rTMS	9 August 2021	Treatment adjusted as participant could not tolerate. (State adjustment)	Treatment dose delivered at 50% as participant could not tolerate treatment during previous session. Has been discussed with trial clinician
BRI4047	rTMS	22 September 2021	Treatment adjusted as participant could not tolerate. (State adjustment)	Treatment intensity gradually increased as per the request of the patient as he was struggling to tolerate. Treatment intensity increased every 15 trains, delivered at correct intensity level for the final 15 trains
BRI4047	rTMS	23 September 2021	Treatment adjusted as participant could not tolerate. (State adjustment)	Treatment threshold reduced as participant could not tolerate allocated treatment intensity. This has been discussed and agreed with the trial clinician
BRI4047	rTMS	30 September 2021	Treatment adjusted as participant could not tolerate. (State adjustment)	Treatment threshold reduced as participant could not tolerate allocated treatment intensity. This has been discussed and agreed with the trial clinician

TABLE 69 Patient-rated acceptability after TMS sessions

Patient-rated acceptability after each TMS session		rTMS	cgiTBS	Total
TMS session 1				
Overall, how acceptable was the TMS treatment?	Unacceptable. Negative effects outweigh benefits, *n* (%)	2 (1.6%)	0 (0.0%)	2 (0.8%)
	Unacceptable. Negative effects and benefits are about equal, *n* (%)	2 (1.6%)	0 (0.0%)	2 (0.8%)
	Neutral, unsure or waiting to find out, *n* (%)	81 (64.3%)	86 (67.2%)	167 (65.7%)
	Acceptable. Negative effects and benefits are about equal, *n* (%)	27 (21.4%)	29 (22.7%)	56 (22.0%)
	Acceptable. Benefit effects outweigh the negative effects, *n* (%)	14 (11.1%)	12 (9.4%)	26 (10.2%)
	Response not available, *n* (%)	0 (0.0%)	1 (0.8%)	1 (0.4%)
TMS session 2				
Overall, how acceptable was the TMS treatment?	Unacceptable. Negative effects outweigh benefits, *n* (%)	0 (0.0%)	1 (0.8%)	1 (0.4%)
	Unacceptable. Negative effects and benefits are about equal, *n* (%)	0 (0.0%)	1 (0.8%)	1 (0.4%)
	Neutral, unsure or waiting to find out, *n* (%)	81 (65.9%)	77 (61.6%)	158 (63.7%)
	Acceptable. Negative effects and benefits are about equal, *n* (%)	33 (26.8%)	33 (26.4%)	66 (26.6%)
	Acceptable. Benefit effects outweigh the negative effects, *n* (%)	9 (7.3%)	13 (10.4%)	22 (8.9%)
TMS session 3				
Overall, how acceptable was the TMS treatment?	Unacceptable. Negative effects outweigh benefits, *n* (%)	0 (0.0%)	1 (0.8%)	1 (0.4%)
	Unacceptable. Negative effects and benefits are about equal, *n* (%)	1 (0.8%)	2 (1.6%)	3 (1.2%)
	Neutral, unsure or waiting to find out, *n* (%)	69 (56.6%)	77 (60.6%)	146 (58.6%)
	Acceptable. Negative effects and benefits are about equal, *n* (%)	40 (32.8%)	33 (26.0%)	73 (29.3%)
	Acceptable. Benefit effects outweigh the negative effects, *n* (%)	12 (9.8%)	13 (10.2%)	25 (10.0%)
	Response not available, *n* (%)	0 (0.0%)	1 (0.8%)	1 (0.4%)
TMS session 4				
Overall, how acceptable was the TMS treatment?	Unacceptable. Negative effects outweigh benefits, *n* (%)	0 (0.0%)	1 (0.8%)	1 (0.4%)
	Unacceptable. Negative effects and benefits are about equal, *n* (%)	2 (1.6%)	3 (2.4%)	5 (2.0%)
	Neutral, unsure or waiting to find out, *n* (%)	71 (57.7%)	72 (56.7%)	143 (57.2%)
	Acceptable. Negative effects and benefits are about equal, *n* (%)	37 (30.1%)	35 (27.6%)	72 (28.8%)
	Acceptable. Benefit effects outweigh the negative effects, *n* (%)	13 (10.6%)	16 (12.6%)	29 (11.6%)

continued

TABLE 69 Patient-rated acceptability after TMS sessions (*continued*)

Patient-rated acceptability after each TMS session		rTMS	cgiTBS	Total
TMS session 5				
Overall, how acceptable was the TMS treatment?	Unacceptable. Negative effects outweigh benefits, *n* (%)	1 (0.8%)	1 (0.8%)	2 (0.8%)
	Unacceptable. Negative effects and benefits are about equal, *n* (%)	1 (0.8%)	3 (2.4%)	4 (1.6%)
	Neutral, unsure or waiting to find out, *n* (%)	64 (52.0%)	61 (48.0%)	125 (50.0%)
	Acceptable. Negative effects and benefits are about equal, *n* (%)	42 (34.1%)	43 (33.9%)	85 (34.0%)
	Acceptable. Benefit effects outweigh the negative effects, *n* (%)	15 (12.2%)	19 (15.0%)	34 (13.6%)
TMS session 6				
Overall, how acceptable was the TMS treatment?	Unacceptable. Negative effects and benefits are about equal, *n* (%)	1 (0.8%)	4 (3.1%)	5 (2.0%)
	Neutral, unsure or waiting to find out, *n* (%)	55 (45.1%)	53 (41.7%)	108 (43.4%)
	Acceptable. Negative effects and benefits are about equal, *n* (%)	48 (39.3%)	50 (39.4%)	98 (39.4%)
	Acceptable. Benefit effects outweigh the negative effects, *n* (%)	18 (14.8%)	20 (15.7%)	38 (15.3%)
TMS session 7				
Overall, how acceptable was the TMS treatment?	Unacceptable. Negative effects and benefits are about equal, *n* (%)	0 (0.0%)	3 (2.4%)	3 (1.2%)
	Neutral, unsure or waiting to find out, *n* (%)	53 (43.4%)	51 (40.2%)	104 (41.8%)
	Acceptable. Negative effects and benefits are about equal, *n* (%)	52 (42.6%)	54 (42.5%)	106 (42.6%)
	Acceptable. Benefit effects outweigh the negative effects, *n* (%)	17 (13.9%)	19 (15.0%)	36 (14.5%)
TMS session 8				
Overall, how acceptable was the TMS treatment?	Unacceptable. Negative effects outweigh benefits, *n* (%)	1 (0.8%)	0 (0.0%)	1 (0.4%)
	Unacceptable. Negative effects and benefits are about equal, *n* (%)	2 (1.6%)	2 (1.6%)	4 (1.6%)
	Neutral, unsure or waiting to find out, *n* (%)	45 (36.9%)	49 (38.9%)	94 (37.9%)
	Acceptable. Negative effects and benefits are about equal, *n* (%)	56 (45.9%)	48 (38.1%)	104 (41.9%)
	Acceptable. Benefit effects outweigh the negative effects, *n* (%)	18 (14.8%)	27 (21.4%)	45 (18.1%)
TMS session 9				
Overall, how acceptable was the TMS treatment?	Unacceptable. Negative effects outweigh benefits, *n* (%)	0 (0.0%)	1 (0.8%)	1 (0.4%)
	Unacceptable. Negative effects and benefits are about equal, *n* (%)	1 (0.8%)	1 (0.8%)	2 (0.8%)
	Neutral, unsure or waiting to find out, *n* (%)	45 (36.9%)	45 (36.0%)	90 (36.4%)

TABLE 69 Patient-rated acceptability after TMS sessions (*continued*)

Patient-rated acceptability after each TMS session		rTMS	cgiTBS	Total
	Acceptable. Negative effects and benefits are about equal, *n* (%)	53 (43.4%)	47 (37.6%)	100 (40.5%)
	Acceptable. Benefit effects outweigh the negative effects, *n* (%)	22 (18.0%)	31 (24.8%)	53 (21.5%)
	Response not available, *n* (%)	1 (0.8%)	0 (0.0%)	1 (0.4%)
TMS session 10				
Overall, how acceptable was the TMS treatment?	Unacceptable. Negative effects and benefits are about equal, *n* (%)	2 (1.7%)	2 (1.6%)	4 (1.6%)
	Neutral, unsure or waiting to find out, *n* (%)	42 (34.7%)	46 (37.1%)	88 (35.9%)
	Acceptable. Negative effects and benefits are about equal, *n* (%)	48 (39.7%)	41 (33.1%)	89 (36.3%)
	Acceptable. Benefit effects outweigh the negative effects, *n* (%)	29 (24.0%)	35 (28.2%)	64 (26.1%)
TMS session 11				
Overall, how acceptable was the TMS treatment?	Unacceptable. Negative effects outweigh benefits, *n* (%)	0 (0.0%)	1 (0.8%)	1 (0.4%)
	Unacceptable. Negative effects and benefits are about equal, *n* (%)	2 (1.7%)	1 (0.8%)	3 (1.2%)
	Neutral, unsure or waiting to find out, *n* (%)	42 (34.7%)	42 (33.9%)	84 (34.3%)
	Acceptable. Negative effects and benefits are about equal, *n* (%)	50 (41.3%)	45 (36.3%)	95 (38.8%)
	Acceptable. Benefit effects outweigh the negative effects, *n* (%)	27 (22.3%)	35 (28.2%)	62 (25.3%)
TMS session 12				
Overall, how acceptable was the TMS treatment?	Unacceptable. Negative effects outweigh benefits, *n* (%)	1 (0.8%)	0 (0.0%)	1 (0.4%)
	Unacceptable. Negative effects and benefits are about equal, *n* (%)	1 (0.8%)	1 (0.8%)	2 (0.8%)
	Neutral, unsure or waiting to find out, *n* (%)	40 (33.1%)	38 (31.1%)	78 (32.1%)
	Acceptable. Negative effects and benefits are about equal, *n* (%)	47 (38.8%)	49 (40.2%)	96 (39.5%)
	Acceptable. Benefit effects outweigh the negative effects, *n* (%)	32 (26.4%)	34 (27.9%)	66 (27.2%)
TMS session 13				
Overall, how acceptable was the TMS treatment?	Unacceptable. Negative effects outweigh benefits, *n* (%)	1 (0.8%)	0 (0.0%)	1 (0.4%)
	Unacceptable. Negative effects and benefits are about equal, *n* (%)	0 (0.0%)	2 (1.6%)	2 (0.8%)
	Neutral, unsure or waiting to find out, *n* (%)	43 (35.5%)	42 (34.4%)	85 (35.0%)
	Acceptable. Negative effects and benefits are about equal, *n* (%)	45 (37.2%)	45 (36.9%)	90 (37.0%)
	Acceptable. Benefit effects outweigh the negative effects, *n* (%)	32 (26.4%)	33 (27.0%)	65 (26.7%)

TABLE 69 Patient-rated acceptability after TMS sessions (*continued*)

Patient-rated acceptability after each TMS session		rTMS	cgiTBS	Total
TMS session 14				
Overall, how acceptable was the TMS treatment?	Unacceptable. Negative effects outweigh benefits, *n* (%)	1 (0.8%)	1 (0.8%)	2 (0.8%)
	Unacceptable. Negative effects and benefits are about equal, *n* (%)	2 (1.7%)	0 (0.0%)	2 (0.8%)
	Neutral, unsure or waiting to find out, *n* (%)	37 (30.6%)	38 (31.1%)	75 (30.9%)
	Acceptable. Negative effects and benefits are about equal, *n* (%)	44 (36.4%)	44 (36.1%)	88 (36.2%)
	Acceptable. Benefit effects outweigh the negative effects, *n* (%)	37 (30.6%)	39 (32.0%)	76 (31.3%)
TMS session 15				
Overall, how acceptable was the TMS treatment?	Unacceptable. Negative effects outweigh benefits, *n* (%)	1 (0.8%)	1 (0.8%)	2 (0.8%)
	Unacceptable. Negative effects and benefits are about equal, *n* (%)	1 (0.8%)	0 (0.0%)	1 (0.4%)
	Neutral, unsure or waiting to find out, *n* (%)	38 (31.4%)	40 (33.1%)	78 (32.2%)
	Acceptable. Negative effects and benefits are about equal, *n* (%)	46 (38.0%)	40 (33.1%)	86 (35.5%)
	Acceptable. Benefit effects outweigh the negative effects, *n* (%)	35 (28.9%)	40 (33.1%)	75 (31.0%)
TMS session 16				
Overall, how acceptable was the TMS treatment?	Unacceptable. Negative effects and benefits are about equal, *n* (%)	2 (1.7%)	2 (1.7%)	4 (1.7%)
	Neutral, unsure or waiting to find out, *n* (%)	34 (28.1%)	33 (27.3%)	67 (27.7%)
	Acceptable. Negative effects and benefits are about equal, *n* (%)	44 (36.4%)	46 (38.0%)	90 (37.2%)
	Acceptable. Benefit effects outweigh the negative effects, *n* (%)	41 (33.9%)	40 (33.1%)	81 (33.5%)
TMS session 17				
Overall, how acceptable was the TMS treatment?	Unacceptable. Negative effects outweigh benefits, *n* (%)	1 (0.8%)	0 (0.0%)	1 (0.4%)
	Unacceptable. Negative effects and benefits are about equal, *n* (%)	1 (0.8%)	1 (0.8%)	2 (0.8%)
	Neutral, unsure or waiting to find out, *n* (%)	29 (24.0%)	34 (28.1%)	63 (26.0%)
	Acceptable. Negative effects and benefits are about equal, *n* (%)	45 (37.2%)	42 (34.7%)	87 (36.0%)
	Acceptable. Benefit effects outweigh the negative effects, *n* (%)	45 (37.2%)	44 (36.4%)	89 (36.8%)
TMS session 18				
Overall, how acceptable was the TMS treatment?	Unacceptable. Negative effects and benefits are about equal, *n* (%)	1 (0.8%)	1 (0.8%)	2 (0.8%)
	Neutral, unsure or waiting to find out, *n* (%)	31 (25.8%)	33 (27.5%)	64 (26.7%)
	Acceptable. Negative effects and benefits are about equal, *n* (%)	42 (35.0%)	39 (32.5%)	81 (33.8%)

TABLE 69 Patient-rated acceptability after TMS sessions (*continued*)

Patient-rated acceptability after each TMS session		rTMS	cgiTBS	Total
	Acceptable. Benefit effects outweigh the negative effects, *n* (%)	46 (38.3%)	47 (39.2%)	93 (38.8%)
TMS session 19				
Overall, how acceptable was the TMS treatment?	Unacceptable. Negative effects outweigh benefits, *n* (%)	1 (0.8%)	0 (0.0%)	1 (0.4%)
	Unacceptable. Negative effects and benefits are about equal, *n* (%)	1 (0.8%)	1 (0.8%)	2 (0.8%)
	Neutral, unsure or waiting to find out, *n* (%)	30 (25.4%)	33 (27.7%)	63 (26.6%)
	Acceptable. Negative effects and benefits are about equal, *n* (%)	33 (28.0%)	36 (30.3%)	69 (29.1%)
	Acceptable. Benefit effects outweigh the negative effects, *n* (%)	53 (44.9%)	49 (41.2%)	102 (43.0%)
TMS session 20				
Overall, how acceptable was the TMS treatment?	Unacceptable. Negative effects outweigh benefits, *n* (%)	1 (0.9%)	0 (0.0%)	1 (0.4%)
	Unacceptable. Negative effects and benefits are about equal, *n* (%)	2 (1.7%)	2 (1.7%)	4 (1.7%)
	Neutral, unsure or waiting to find out, *n* (%)	24 (20.5%)	28 (23.3%)	52 (21.9%)
	Acceptable. Negative effects and benefits are about equal, *n* (%)	38 (32.5%)	37 (30.8%)	75 (31.6%)
	Acceptable. Benefit effects outweigh the negative effects, *n* (%)	52 (44.4%)	53 (44.2%)	105 (44.3%)

TABLE 70 Patient-rated acceptability measure at follow-up

Patient-rated acceptability at 8-, 16- and 26-week follow-up		rTMS	cgiTBS	Total
8-week follow-up				
Overall, how acceptable was the TMS treatment?	Unacceptable. Negative effects outweigh benefits, *n* (%)	3 (2.7%)	2 (1.8%)	5 (2.3%)
	Unacceptable. Negative effects and benefits are about equal, *n* (%)	6 (5.4%)	2 (1.8%)	8 (3.6%)
	Neutral, unsure or waiting to find out, *n* (%)	30 (27.0%)	31 (27.9%)	61 (27.5%)
	Acceptable. Negative effects and benefits are about equal, *n* (%)	26 (23.4%)	22 (19.8%)	48 (21.6%)
	Acceptable. Benefit effects outweigh the negative effects, *n* (%)	46 (41.4%)	54 (48.6%)	100 (45.0%)
16-week follow-up				
Overall, how acceptable was the TMS treatment?	Unacceptable. Negative effects outweigh benefits, *n* (%)	3 (2.7%)	1 (0.9%)	4 (1.8%)
	Unacceptable. Negative effects and benefits are about equal, *n* (%)	2 (1.8%)	1 (0.9%)	3 (1.4%)

continued

TABLE 70 Patient-rated acceptability measure at follow-up (*continued*)

Patient-rated acceptability at 8-, 16- and 26-week follow-up		rTMS	cgiTBS	Total
	Neutral, unsure or waiting to find out, *n* (%)	33 (29.7%)	29 (26.4%)	62 (28.1%)
	Acceptable. Negative effects and benefits are about equal, *n* (%)	25 (22.5%)	31 (28.2%)	56 (25.3%)
	Acceptable. Benefit effects outweigh the negative effects, *n* (%)	48 (43.2%)	48 (43.6%)	96 (43.4%)
26-week follow-up				
Overall, how acceptable was the TMS treatment?	Unacceptable. Negative effects outweigh benefits, *n* (%)	4 (4.0%)	3 (2.9%)	7 (3.4%)
	Unacceptable. Negative effects and benefits are about equal, *n* (%)	3 (3.0%)	2 (1.9%)	5 (2.5%)
	Neutral, unsure or waiting to find out, *n* (%)	22 (22.0%)	24 (23.3%)	46 (22.7%)
	Acceptable. Negative effects and benefits are about equal, *n* (%)	22 (22.0%)	24 (23.3%)	46 (22.7%)
	Acceptable. Benefit effects outweigh the negative effects, *n* (%)	49 (49.0%)	50 (48.5%)	99 (48.8%)

TABLE 71 Further facilitator, barrier, and acceptability quote examples

Acceptability	Quotes
The TMS experience	*Really glad that took part. Hopefully in long run could help.* Participant 90 verbatim comment *If benefits last, it will be well worth it.* Participant 64 verbatim comment *Nice to have same practitioners throughout.* Participant 10 verbatim comment *(TMS staff) found some quiz questions for me online as well so it was good, once we had established that, it was nice because it made it enjoyable and I got through it quicker, than just lying there.* Participant 1 qualitative interview *I remember saying to somebody that it's how I imagine going to a spa would be like, because there was a reclining chair, I had a pillow on my chest. I just took the time to read my book which is a treat in itself … an hour in the middle of the day to read, so it was lovely, it was really relaxing.* Participant 3 Qualitative interview *No longer finding it painful/uncomfortable like I did on the first day.* Participant 124 verbatim comment *I have found the treatment to be a lot less traumatic and invasive then I had imagined.* Participant 81 verbatim comment *There is a slight tingling sensation but nothing unpleasant at all, but perfectly acceptable and my natural scientific curiosity in effect led me to enjoy it as something new I never knew that magnets could well a magnetic field could generate psych feelings inside one's head.* Participant 6 qualitative interview *Overall positive – big time commitment; easy to comply with. No side effects.* Participant 10 verbatim comment
Variation in symptom changes	*TMS treatment has been life changing for me. It is the only thing that has worked. It has allowed me to come off my medication.* Participant 156 verbatim comment *I don't consider that I have received any therapeutic benefit from the TMS, and I understand that some people don't.* Participant 6 qualitative interview *I felt it did help me to start with, but it didn't last very long. It was only a short period that it seemed to work.* Participant 145 verbatim comment *Sleeping well. More concentration and less anxious.* Participant 46 Verbatim comment *Marginally improved in mood. Anxiety still very prominent. Having dips still in mood, especially in the mornings.* Participant 126 verbatim comment

TABLE 71 Further facilitator, barrier, and acceptability quote examples (*continued*)

Acceptability	Quotes
Lay theories of effectiveness	*I was getting up, getting washed, getting ready and going out the house every day [and] that was already having a bit of an uplift on how I was feeling.* Participant 12 qualitative interview *Although it may be the treatment, it may be the excellent conversations that have improved my mood.* Participant 41 verbatim comments *Really glad that took part. Hopefully in long run could help. Going through a difficult time seems like TMS would have worked if circumstances were different.* Participant 90 verbatim comment *The TMS treatment received from day to day felt variable, due to different staff members delivering the treatment. It felt like the location of treatment delivery was different, dependent on the person who delivered the treatment. Whilst some staff members were quick to readjust the coil when it moved out of parameter, other staff members were less concerned to do so. It was very off putting and felt like a flaw in the experimental design.* Participant 33 verbatim comment *Benefit definite though required more than research though, effects appear to be wearing off.* Participant 140 verbatim comment
Facilitators	**Quotes**
Hope	*It was sort of like exciting or interesting yes. That is how I felt about it. […] Well I suppose if I was feeling well, I would have still have been interested in the results or interested in speaking to people about it, especially because I was feeling my mood was very down at the time.* Participant 4 qualitative interview *To give me a sense of hope, the way my psychiatrist described the treatment study, it can be quite effective in some cases and in some cases, it could even offer a cure for resistant depression, obviously if there was a chance that that could help me then I was very keen to give it a go.* Participant 9 qualitative interview *I've looked at TMS before, seen the prices and thought that's out of my reach, so the prospect of being able to access the treatment without having to pay £3000 was wonderful.* Participant 3 qualitative interview
Influence of staff	*The staff at the treatment centre were really really professional tried to make me feel as comfortable as possible; when I went for my first treatment, I was very very nervous because I didn't know what to expect and things like that; the machine itself was a bit intimidating to look at but all the staff were really great and tried to make me feel really comfortable.* Participant 9 qualitative interview
Interest in new treatments	*Medication did not work. Therapy did not seem to work. Other things did not really work, so, you know, I just decided to try this one.* Participant 8 qualitative interview *It was more the case of we've tried so many things to that point that you know, almost the idea of something experimental seemed like a really really good idea.* Participant 9 qualitative interview *Part of the attractiveness of doing the trial, was that they said it was totally non invasive so you would be able to function as normally as you normally are afterwards.* Participant 1 qualitative interview
Altruism	*I did not know whether it would help me or not but it was quite a commitment as well. […] I was happy that I was contributing to a research study as well, because it is another positive way that I can help maybe others even if it could not help me.* Participant 1 qualitative interview
Barriers	**Quotes**
Commitment concerns	*The hassle of arranging everything around coming every day, that's the only thing and as I say I could do that because I'm self employed.* Participant 3 qualitative interview *There's the fear that you're going to become ill and not be able to meet not longer than four day gap, I had that at the back of my mind.* Participant 3 qualitative interview
Treatment-related concerns	*The only thing that I was a little of unsure of is where they had said there was a very small risk of having an epileptic fit, or seizure I should say, and that just concerned me a little bit if that were to happen I wouldn't be able to drive.* Participant 2 qualitative interview *Fear that it would be too painful, some people experience pain.* Participant 11 qualitative interview *I think for me actually being so anxious and stressed and depressed, it's almost in that order and time and I, therefore, would not want to like, I do not know, some might complicate that or make that worse.* Participant 15 qualitative interview

Appendix 4 Economic evaluation results supplemental information

TABLE 72 Missing data

Variable	Observed	Missing	% missing
Treatment group	255	0	0
Site	255	0	0
Baseline severe depression (HDRS)	255	0	0
Ethnicity	255	0	0
Female	255	0	0
Age	255	0	0
Baseline inpatient costs	255	0	0
Inpatient costs week 16	221	34	13
Inpatient costs week 26	205	50	20
Baseline outpatient costs	255	0	0
Outpatient costs week 16	221	34	13
Outpatient costs week 26	205	50	20
Baseline community costs	255	0	0
Community costs week 16	221	34	13
Community costs week 26	205	50	20
Baseline primary care costs	255	0	0
Primary care costs week 16	221	34	13
Primary care costs week 26	205	50	20
Mental health medication costs week 16	215	40	16
Mental health medication costs week 26	202	53	21
Baseline productivity costs	254	1	0
Productivity costs week 16	220	35	14
Productivity costs week 26	205	50	20
Baseline private services costs	255	0	0
Private services week 16	221	34	13
Private services week 26	205	50	20
Baseline over-the-counter medication costs	255	0	0
Over-the-counter medication costs week 16	224	31	12
Over-the-counter medication costs week 26	206	49	19
Baseline travel costs	255	0	0
Travel costs week 16	224	31	12
Travel costs week 26	206	49	19
Baseline EQ-5D	255	0	0

TABLE 72 Missing data (*continued*)

Variable	Observed	Missing	% missing
EQ-5D week 8	220	35	14
EQ-5D week 16	218	37	15
EQ-5D week 26	201	54	21
Baseline informal care days	254	0	0
Informal care hours week 16	219	34	13
Informal care hours week 26	198	50	20
Baseline informal care days off work[a]	254	0	0
Informal care days off work week 16[a]	219	34	13
Informal care days off work week 26[a]	198	50	20

a Depression-related status was complete for all reported cases of informal carers taking days off work.

TABLE 73 Observed resource use in total and by follow-up: rTMS

	Observed resource use – rTMS																			
	Total[a]					Baseline[b]					Week 16					Week 26				
	N	Mean	SD	Min	Max	*N*	Mean	SD	Min	Max	*N*	Mean	SD	Min	Max	*N*	Mean	SD	Min	Max
Inpatient hospital services																				
Acute psychiatric ward	98	0.33	3.23	0	32	127	0.83	8.20	0	92	111	0.29	3.04	0	32	101	0.30	2.99	0	30
Psychiatric rehabilitation ward	98	0.00	0.00	0	0	127	0.00	0.00	0	0	111	0.00	0.00	0	0	101	0.00	0.00	0	0
Long-stay ward	98	0.00	0.00	0	0	127	0.00	0.00	0	0	111	0.00	0.00	0	0	101	0.00	0.00	0	0
Psychiatric intensive care unit	98	0.00	0.00	0	0	127	0.00	0.00	0	0	111	0.00	0.00	0	0	101	0.00	0.00	0	0
General medical ward	98	0.03	0.22	0	2	127	0.01	0.09	0	1	111	0.03	0.21	0	2	101	0.00	0.00	0	0
Outpatient hospital services																				
Psychiatric outpatient visits	98	0.90	1.36	0	5	127	0.54	1.02	0	5	111	0.52	0.96	0	4	101	0.38	0.86	0	5
Psychologist visits	98	0.65	2.62	0	18	127	0.41	1.74	0	12	111	0.31	1.40	0	11	101	0.32	1.35	0	9
A&E attendances	98	0.16	0.51	0	3	127	0.09	0.29	0	1	111	0.10	0.40	0	3	101	0.05	0.22	0	1
Day hospital attendances	98	0.04	0.25	0	2	127	0.07	0.42	0	4	111	0.02	0.19	0	2	101	0.02	0.14	0	1
Non-psychiatric outpatient visits	98	0.48	1.06	0	5	127	0.12	0.39	0	2	111	0.35	1.38	0	13	101	0.22	0.70	0	4
Primary care (visits)																				
General practitioner (surgery)	98	1.72	2.67	0	20	127	1.31	1.78	0	9	111	1.06	1.71	0	12	101	0.68	1.40	0	8

continued

TABLE 73 Observed resource use in total and by follow-up: rTMS (*continued*)

	Observed resource use – rTMS																			
	Total[a]					Baseline[b]					Week 16					Week 26				
	N	Mean	SD	Min	Max	*N*	Mean	SD	Min	Max	*N*	Mean	SD	Min	Max	*N*	Mean	SD	Min	Max
General practitioner (home)	98	0.11	0.49	0	3	127	0.00	0.00	0	0	111	0.05	0.35	0	3	101	0.05	0.26	0	2
Practice nurse (at surgery)	98	0.48	1.32	0	10	127	0.25	0.67	0	4	111	0.29	1.07	0	10	101	0.20	0.69	0	4
District nurse	98	0.04	0.32	0	3	127	0.00	0.00	0	0	111	0.02	0.13	0	1	101	0.03	0.30	0	3
Community psychiatric nurse	98	1.87	5.49	0	32	127	1.09	3.63	0	24	111	1.24	4.49	0	30	101	0.70	2.00	0	11
Social worker	98	0.06	0.61	0	6	127	0.06	0.54	0	6	111	0.03	0.21	0	2	101	0.04	0.40	0	4
Occupational therapist	98	0.23	1.30	0	12	127	0.11	0.77	0	7	111	0.15	1.20	0	12	101	0.06	0.28	0	2
Advocate	98	0.04	0.40	0	4	127	0.03	0.28	0	3	111	0.04	0.38	0	4	101	0.00	0.00	0	0
Home help/care Worker	98	0.07	0.50	0	4	127	0.00	0.00	0	0	111	0.03	0.28	0	3	101	0.04	0.40	0	4
Community matron	98	0.00	0.00	0	0	127	0.00	0.00	0	0	111	0.00	0.00	0	0	101	0.00	0.00	0	0
Community services[c]																				
Day care centre	98	0.04	0.28	0	2	127	0.00	0.00	0	0	111	0.03	0.21	0	2	101	0.01	0.10	0	1
Drop-in centre	98	0.10	1.01	0	10	127	0.17	1.38	0	12	111	0.00	0.00	0	0	101	0.10	1.00	0	10
Specialist education facility	98	0.04	0.40	0	4	127	0.05	0.53	0	6	111	0.00	0.00	0	0	101	0.04	0.40	0	4
Sheltered workshop	98	0.00	0.00	0	0	127	0.00	0.00	0	0	111	0.00	0.00	0	0	101	0.00	0.00	0	0

a Costs from baseline to week 26.
b Up to 3 months prior to baseline.
c Full day appointments = 1; half-day appointments = 0.5.

TABLE 74 Observed resource use in total and by follow-up: cgiTBS

	Observed resource use – cgiTBS																			
	Total[a]					Baseline[b]					Week 16					Week 26				
	N	Mean	SD	Min	Max	*N*	Mean	SD	Min	Max	*N*	Mean	SD	Min	Max	*N*	Mean	SD	Min	Max
Inpatient hospital services																				
Acute psychiatric ward	100	0.00	0.00	0	0	128	0.26	2.31	0	25	110	0.00	0.00	0	0	104	0.00	0.00	0	0
Psychiatric rehabilitation ward	100	0.00	0.00	0	0	128	0.00	0.00	0	0	110	0.00	0.00	0	0	104	0.00	0.00	0	0
Long-stay ward	100	0.00	0.00	0	0	128	0.00	0.00	0	0	110	0.00	0.00	0	0	104	0.00	0.00	0	0
Psychiatric intensive care unit	100	0.00	0.00	0	0	128	0.00	0.00	0	0	110	0.00	0.00	0	0	104	0.00	0.00	0	0

TABLE 74 Observed resource use in total and by follow-up: cgiTBS (*continued*)

	Observed resource use – cgiTBS																			
	Total[a]					Baseline[b]					Week 16					Week 26				
	N	Mean	SD	Min	Max	*N*	Mean	SD	Min	Max	*N*	Mean	SD	Min	Max	*N*	Mean	SD	Min	Max
General medical ward	100	0.22	2.20	0	22	128	0.01	0.09	0	1	110	0.00	0.00	0	0	104	0.21	2.16	0	22
Outpatient hospital services																				
Psychiatric outpatient visit	100	0.61	1.32	0	8	128	0.50	1.12	0	7	110	0.32	0.87	0	6	104	0.33	0.66	0	3
Psychologist visit	100	0.26	1.57	0	14	128	0.51	2.06	0	12	110	0.08	0.61	0	6	104	0.17	1.05	0	8
A&E attendance	100	0.14	0.45	0	3	128	0.09	0.46	0	4	110	0.10	0.41	0	3	104	0.07	0.29	0	2
Day hospital attendance	100	0.05	0.22	0	1	128	0.05	0.30	0	3	110	0.01	0.10	0	1	104	0.04	0.19	0	1
Non-psychiatric outpatient visit	100	0.29	0.83	0	5	128	0.30	1.24	0	10	110	0.13	0.54	0	5	104	0.15	0.55	0	4
Primary care																				
General practitioner (surgery)	100	1.59	2.26	0	14	128	1.48	1.96	0	10	110	0.84	1.39	0	8	104	0.77	1.57	0	12
General practitioner (home)	100	0.11	0.53	0	4	128	0.02	0.15	0	1	110	0.04	0.38	0	4	104	0.07	0.35	0	2
Practice nurse (at surgery)	100	0.61	1.10	0	6	128	0.30	0.90	0	8	110	0.40	0.89	0	4	104	0.16	0.48	0	3
District nurse	100	0.00	0.00	0	0	128	0.01	0.09	0	1	110	0.00	0.00	0	0	104	0.00	0.00	0	0
Community psychiatric nurse	100	0.91	2.54	0	13	128	0.66	1.92	0	12	110	0.43	1.51	0	8	104	0.67	2.89	0	26
Social worker	100	0.01	0.10	0	1	128	0.01	0.09	0	1	110	0.00	0.00	0	0	104	0.01	0.10	0	1
Occupational therapist	100	0.11	0.72	0	7	128	0.25	1.63	0	17	110	0.07	0.38	0	3	104	0.06	0.50	0	5
Advocate	100	0.00	0.00	0	0	128	0.04	0.36	0	4	110	0.02	0.19	0	2	104	0.00	0.00	0	0
Home help/care worker	100	0.00	0.00	0	0	128	0.19	2.12	0	24	110	0.00	0.00	0	0	104	0.00	0.00	0	0
Community matron	100	0.00	0.00	0	0	128	0.05	0.53	0	6	110	0.00	0.00	0	0	104	0.00	0.00	0	0
Community services																				
Day care centre	100	0.00	0.00	0	0	128	0.37	2.31	0	20	110	0.00	0.00	0	0	104	0.10	0.98	0	10
Drop-in centre	100	0.62	6.20	0	62	128	0.29	3.10	0	35	110	0.29	3.05	0	32	104	0.29	2.94	0	30
Specialist education facility	100	0.00	0.00	0	0	128	0.00	0.00	0	0	110	0.00	0.00	0	0	104	0.00	0.00	0	0
Sheltered workshop	100	0.00	0.00	0	0	128	0.00	0.00	0	0	110	0.00	0.00	0	0	104	0.00	0.00	0	0

a Costs from baseline to week 26.
b Up to 3 months prior to baseline.

TABLE 75 rTMS observed costs

	rTMS observable costs																			
	Total cost[a]					Baseline[b]					Week 16					Week 26				
	N	Mean	SD	Min	Max	*N*	Mean	SD	Min	Max	*N*	Mean	SD	Min	Max	*N*	Mean	SD	Min	Max
Health service perspective																				
Intervention cost	127	1058.83	0	1059	1059	127	1059	0	1059	1059										
Equipment	127	42.37	0	42	42	127	42	0	42	42										
Staff	127	42.37	0	42	42	127	42	0	42	42										
Inpatient hospital services																				
Acute psychiatric ward	98	10.45	103	0	1024	127	52	547	0	6164	111	9	97	0	1024	101	19	191	0	1920
Psychiatric rehabilitation ward	98	0.00	0	0	0	127	0	0	0	0	111	0	0	0	0	101	0	0	0	0
Long-stay ward	98	0.00	0	0	0	127	0	0	0	0	111	0	0	0	0	101	0	0	0	0
Psychiatric intensive care unit	98	0.00	0	0	0	127	0	0	0	0	111	0	0	0	0	101	0	0	0	0
General medical ward	98	5.98	44	0	391	127	2	17	0	195	111	5	41	0	391	101	0	0	0	0
Other	98	0.00	0	0	0	127	4	41	0	457	111	0	0	0	0	101	5	46	0	457
Outpatient hospital services																				
Psychiatric outpatient visit	98	290.94	440	0	1620	127	173	331	0	1620	111	169	312	0	1296	101	122	278	0	1620
Psychologist visit	98	144.98	583	0	3996	127	91	387	0	2664	111	68	311	0	2442	101	70	299	0	1998
A&E attendance	98	48.40	152	0	889	127	28	87	0	296	111	29	120	0	889	101	15	65	0	296
Day hospital attendance	98	13.62	82	0	667	127	24	141	0	1334	111	6	63	0	667	101	7	47	0	334
Non-psychiatric outpatients visit	98	110.03	243	0	1147	127	27	90	0	459	111	81	316	0	2983	101	50	161	0	918
Other	98	115.85	287	0	1408	127	44	189	0	1610	111	50	178	0	1320	101	67	194	0	1194
Primary care																				
General practitioner (At Surgery)	98	67.65	105	0	785	127	52	70	0	353	111	42	67	0	471	101	27	55	0	314
General practitioner (at home)	98	12.18	54	0	326	127	0	0	0	0	111	6	38	0	326	101	5	28	0	217
Practice nurse (at surgery)	98	20.14	55	0	420	127	11	28	0	168	111	12	45	0	420	101	8	29	0	168

	rTMS observable costs																			
	Total cost[a]					Baseline[b]					Week 16					Week 26				
	N	Mean	SD	Min	Max	*N*	Mean	SD	Min	Max	*N*	Mean	SD	Min	Max	*N*	Mean	SD	Min	Max
District nurse	98	2.12	17	0	156	127	0	0	0	0	111	1	7	0	52	101	2	15	0	156
Community psychiatric nurse	98	2.33	9	0	57	127	1	7	0	63	111	1	6	0	48	101	1	5	0	45
Social worker	98	3.18	32	0	312	127	3	28	0	312	111	1	11	0	104	101	2	21	0	208
Occupational therapist	98	11.73	65	0	600	127	6	38	0	350	111	8	60	0	600	101	3	14	0	100
Advocate	98	1.25	12	0	123	127	1	9	0	92	111	1	12	0	123	101	0	0	0	0
Home help/ care worker	98	2.36	17	0	132	127	0	0	0	0	111	1	9	0	99	101	1	13	0	132
Community matron	98	0.00	0	0	0	127	0	0	0	0	111	0	0	0	0	101	0	0	0	0
Other	98	94.83	255	0	1557	127	49	164	0	1383	111	60	212	0	1557	101	31	96	0	563
Community services																				
Day care centre	98	1.59	11	0	78	127	0	0	0	0	111	1	8	0	78	101	0	4	0	39
Drop-in centre	98	3.98	39	0	390	127	7	54	0	468	111	0	0	0	0	101	4	39	0	390
Specialist education facility	98	0.04	0	0	4	127	0	0	0	0	111	0	0	0	0	101	0	0	0	4
Sheltered workshop	98	0.00	0	0	0	127	0	0	0	0	111	0	0	0	0	101	0	0	0	0
Other	98	19.63	140	0	1163	127	0	2	0	25	111	10	110	0	1163	101	8	76	0	761
Medication																				
Prescribed MH-related medicines	96	40.11	83	0	590	127	19	36	0	302	106	27	49	0	403	100	26	60	0	473
Societal perspectives																				
Travel	100	20.50	55	0	443	127	9	32	0	328	112	11	39	0	384	102	9	27	0	248
Productivity	98	1076.22	3480	0	22396	126	802	2094	0	11184	111	762	2474	0	14346	101	295	1169	0	8528
Over-the-counter medications	100	4.72	24	0	235	127	2	6	0	40	112	3	23	0	235	102	1	5	0	40
Private services	98	46.48	247	0	2240	127	70	294	0	2430	111	16	74	0	570	101	28	203	0	2000

continued

TABLE 75 rTMS observed costs (*continued*)

	rTMS observable costs																			
	Total cost[a]					Baseline[b]					Week 16					Week 26				
	N	Mean	SD	Min	Max	*N*	Mean	SD	Min	Max	*N*	Mean	SD	Min	Max	*N*	Mean	SD	Min	Max
Total costs																				
Health service perspective costs	94	2127.91	1098	1101	6249	127	1693	863	1101	7292	105	598	779	0	3441	99	432	512	0	2309
Societal perspectives costs	98	1148.43	3487	0	22472	126	883	2089	0	11200	111	793	2479	0	14386	101	333	1184	0	8587
Total costs	94	3316.53	4020	1101	24921	126	2573	2316	1101	13357	105	1421	2904	0	16677	99	758	1326	0	9568

a Costs from baseline to week 26.
b Up to 3 months prior to baseline.

TABLE 76 cgiTBS observed costs

	rTMS observable costs																			
	Total cost[a]					Baseline[b]					Week 16					Week 26				
	N	Mean	SD	Min	Max	*N*	Mean	SD	Min	Max	*N*	Mean	SD	Min	Max	*N*	Mean	SD	Min	Max
Public perspective																				
Intervention cost	127	1058.83	0	1059	1059	127	1059	0	1059	1059										
Equipment	127	42.37	0	42	42	127	42	0	42	42										
Staff	127	42.37	0	42	42	127	42	0	42	42										
Inpatient hospital services																				
Acute psychiatric ward	98	10.45	103	0	1024	127	52	547	0	6164	111	9	97	0	1024	101	19	191	0	1920
Psychiatric rehabilitation ward	98	0.00	0	0	0	127	0	0	0	0	111	0	0	0	0	101	0	0	0	0
Long-stay ward	98	0.00	0	0	0	127	0	0	0	0	111	0	0	0	0	101	0	0	0	0
Psychiatric intensive care unit	98	0.00	0	0	0	127	0	0	0	0	111	0	0	0	0	101	0	0	0	0
General medical ward	98	5.98	44	0	391	127	2	17	0	195	111	5	41	0	391	101	0	0	0	0
Other	98	0.00	0	0	0	127	4	41	0	457	111	0	0	0	0	101	5	46	0	457
Outpatient hospital services																				
Psychiatric outpatient visit	98	290.94	440	0	1620	127	173	331	0	1620	111	169	312	0	1296	101	122	278	0	1620

TABLE 76 cgiTBS observed costs (*continued*)

	rTMS observable costs																			
	Total cost[a]					Baseline[b]					Week 16					Week 26				
	N	Mean	SD	Min	Max	*N*	Mean	SD	Min	Max	*N*	Mean	SD	Min	Max	*N*	Mean	SD	Min	Max
Psychologist visit	98	144.98	583	0	3996	127	91	387	0	2664	111	68	311	0	2442	101	70	299	0	1998
A&E attendance	98	48.40	152	0	889	127	28	87	0	296	111	29	120	0	889	101	15	65	0	296
Day hospital attendance	98	13.62	82	0	667	127	24	141	0	1334	111	6	63	0	667	101	7	47	0	334
Non-psychiatric outpatients visit	98	110.03	243	0	1147	127	27	90	0	459	111	81	316	0	2983	101	50	161	0	918
Other	98	115.85	287	0	1408	127	44	189	0	1610	111	50	178	0	1320	101	67	194	0	1194
Primary care																				
General practitioner (at surgery)	98	67.65	105	0	785	127	52	70	0	353	111	42	67	0	471	101	27	55	0	314
General practitioner (at home)	98	12.18	54	0	326	127	0	0	0	0	111	6	38	0	326	101	5	28	0	217
Practice nurse (at surgery)	98	20.14	55	0	420	127	11	28	0	168	111	12	45	0	420	101	8	29	0	168
District nurse	98	2.12	17	0	156	127	0	0	0	0	111	1	7	0	52	101	2	15	0	156
Community psychiatric nurse	98	2.33	9	0	57	127	1	7	0	63	111	1	6	0	48	101	1	5	0	45
Social worker	98	3.18	32	0	312	127	3	28	0	312	111	1	11	0	104	101	2	21	0	208
Occupational therapist	98	11.73	65	0	600	127	6	38	0	350	111	8	60	0	600	101	3	14	0	100
Advocate (e.g. creative support)	98	1.25	12	0	123	127	1	9	0	92	111	1	12	0	123	101	0	0	0	0
Home help/ care worker	98	2.36	17	0	132	127	0	0	0	0	111	1	9	0	99	101	1	13	0	132
Community matron	98	0.00	0	0	0	127	0	0	0	0	111	0	0	0	0	101	0	0	0	0
Other	98	94.83	255	0	1557	127	49	164	0	1383	111	60	212	0	1557	101	31	96	0	563
Community services																				
Day dare centre	98	1.59	11	0	78	127	0	0	0	0	111	1	8	0	78	101	0	4	0	39
Drop-in centre	98	3.98	39	0	390	127	7	54	0	468	111	0	0	0	0	101	4	39	0	390

continued

TABLE 76 cgiTBS observed costs (*continued*)

	rTMS observable costs																			
	Total cost[a]					Baseline[b]					Week 16					Week 26				
	N	Mean	SD	Min	Max	*N*	Mean	SD	Min	Max	*N*	Mean	SD	Min	Max	*N*	Mean	SD	Min	Max
Specialist education facility	98	0.04	0	0	4	127	0	0	0	0	111	0	0	0	0	101	0	0	0	4
Sheltered workshop	98	0.00	0	0	0	127	0	0	0	0	111	0	0	0	0	101	0	0	0	0
Other	98	19.63	140	0	1163	127	0	2	0	25	111	10	110	0	1163	101	8	76	0	761
Medication																				
Prescribed MH-related medicines	96	40.11	83	0	590	127	19	36	0	302	106	27	49	0	403	100	26	60	0	473
Societal perspectives																				
Travel	100	20.50	55	0	443	127	9	32	0	328	112	11	39	0	384	102	9	27	0	248
Productivity	98	1076.22	3480	0	22396	126	802	2094	0	11184	111	762	2474	0	14346	101	295	1169	0	8528
Over-the-counter medications	100	4.72	24	0	235	127	2	6	0	40	112	3	23	0	235	102	1	5	0	40
Private services	98	46.48	247	0	2240	127	70	294	0	2430	111	16	74	0	570	101	28	203	0	2000
Total costs																				
Public perspective costs	94	2127.91	1098	1101	6249	127	1693	863	1101	7292	105	598	779	0	3441	99	432	512	0	2309
Societal perspectives costs	98	1148.43	3487	0	22472	126	883	2089	0	11200	111	793	2479	0	14386	101	333	1184	0	8587
Total costs	94	3316.53	4020	1101	24921	126	2573	2316	1101	13357	105	1421	2904	0	16677	99	758	1326	0	9568

a Costs from baseline to week 25.
b Up to 3 months before baseline.

TABLE 77 rTMS imputed costs

	rTMS imputed costs							
	Total cost		Baseline		Week 16		Week 26	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Health service perspective								
Intervention cost	2354.03	159	2354	159				
Inpatient hospital services	34.69	264	57	549	16	123	19	211
Outpatient hospital services	752.40	1368	387	641	431	1138	321	543
Primary care	210.15	360	121	188	131	302	79	131
Community services	24.09	165	7	54	13	132	11	88
Medication	55.28	127	19	36	29	74	26	69

TABLE 77 rTMS imputed costs (*continued*)

	rTMS imputed costs							
	Total cost		Baseline		Week 16		Week 26	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Societal perspectives								
Travel	19.88	53	9	32	11	40	9	26
Productivity	1085.05	3746	800	2093	820	2940	265	1140
Over-the-counter medications	4.65	26	2	6	3	24	1	6
Private services	50.34	278	70	294	20	101	30	231
Total costs								
Health service perspective	3430.63	1620	2303	1413	621	1287	455	664
Broader societal perspective	1159.91	3749	881	2088	855	2951	305	1151
Total costs	4590.55	4576	3183	2483	1476	3690	760	1377

TABLE 78 cgiTBS imputed costs

	cgiTBS imputed costs							
	Total cost		Baseline		Week 16		Week 26	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Health service perspective								
Intervention cost	2308.90	109	2309	109				
Inpatient hospital services	38.21	384	15	120	3136	2530	38	382
Outpatient hospital services	605.67	1604	410	790	362	1531	244	470
Primary care	192.82	319	119	186	124	259	69	114
Community services	38.08	263	47	242	24	155	14	124
Medication	81.96	184	49	182	52	122	30	73
Societal perspectives								
Travel	16.79	69	8	31	8	24	9	58
Productivity	903.38	3444	626	1849	743	2995	160	851
Over-the-counter medications	6.74	26	3	14	4	22	2	9
Private services	133.93	584	151	865	93	452	41	179
Total costs								
Health service perspective	3265.64	1766	2348	1286	562	1579	395	683
Broader societal perspective	1060.85	3534	788	2038	849	3053	212	871
Total costs	4326.48	4602	3136	2530	1410	4138	607	1192

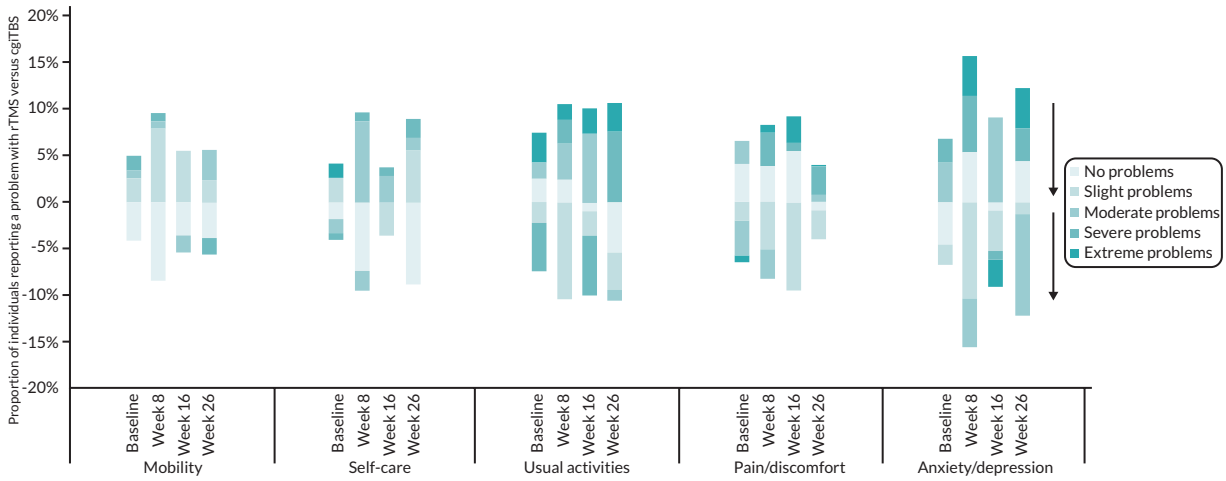

FIGURE 23 Differential severities in EQ-5D-5L responses between rTMS (> 0%) and cgiTBS (< 0%).

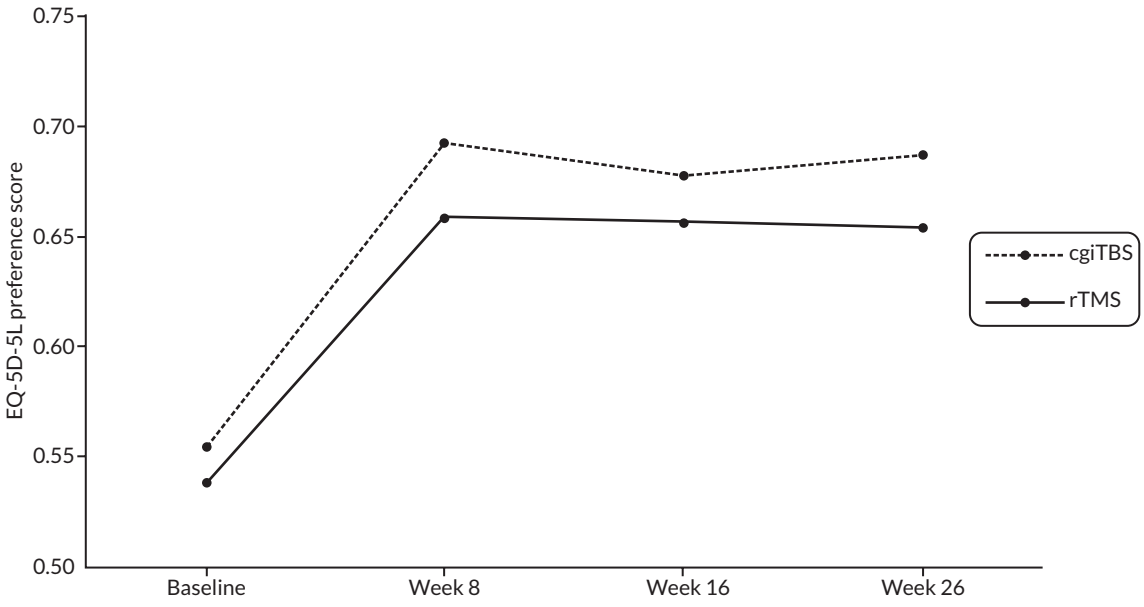

FIGURE 24 Average imputed EQ-5D-5L preference scores.

TABLE 79 Average imputed HRQoL and QALY outcomes by treatment arm and follow-up

	rTMS				cgiTBS				Difference			
	Baseline	Week 8	Week 16	Week 26	Baseline	Week 8	Week 16	Week 26	Baseline	Week 8	Week 16	Week 26
EQ-5D-5L	0.53798	0.66092	0.66036	0.65803	0.55405	0.69285	0.68145	0.69123	−0.01608	−0.03193	−0.02109	−0.03321
(Mapped) EQ-5D-3L	0.39471	0.54614	0.55286	0.55647	0.42185	0.58738	0.58007	0.59341	−0.02714	−0.04124	−0.02721	−0.03694
QALYs (EQ5D-5L)	0.31977				0.33272				−0.01296			
QALYs (EQ5D-3L)	0.26287				0.27952				−0.01665			

TABLE 80 Observed informal care

	Informal care											
	Total (*n* = 198)			Baseline (*n* = 255)			Week 16 (*n* = 221)			Week 26 (*n* = 205)		
	rTMS	cgiTBS	Difference	rTMS	cgiTBS	Difference	rTMS	cgiTBS	Difference	rTMS	cgiTBS	Difference
Total hours care	129.04	125.25	3.78	68.65	107.52	−38.87	73.66	80.01	−6.35	54.23	51.83	2.41
Days off work												
Total days	1.15	0.24	0.92	0.55	0.64	−0.09	0.96	0.94	0.02	0.06	0.15	−0.09
Depression-related days	1.12	0.20	0.93	0.54	0.62	−0.07	0.96	0.94	0.02	0.03	0.12	−0.09

TABLE 81 Base-case QALY regression (EQ-5D-3L)

Base-case QALY regression (EQ-5D-3L)	Coeff	Sd err	*t*	*p*	lci	hci
Treatment_grp	−0.0091794	0.0103391	−0.89	0.376	−0.02959	0.011231
EQ5D_3L_util_w0	0.2729923	0.0247968	11.01	0	0.223827	0.322158
Age	0.0004147	0.000366	1.13	0.258	−0.00031	0.001136
Female	0.0034417	0.0102218	0.34	0.737	−0.01673	0.023609
Ethnicity_BAME	−0.0109877	0.0188896	−0.58	0.562	−0.04828	0.026303
Site 2: nohant (ref Notts)	0.0444985	0.0180913	2.46	0.015	0.008716	0.080281
Site 3: London (ref Notts)	0.0049403	0.0135247	0.37	0.715	−0.02175	0.031633
Site 4: newcas (ref Notts)	−0.0049961	0.0144265	−0.35	0.73	−0.03348	0.023487
Site 5: 5oldham (ref Notts)	−0.0218496	0.0322262	−0.68	0.499	−0.08546	0.041756
Baseline_HDRS17_Severe	−0.0216018	0.0123921	−1.74	0.084	−0.04618	0.002972
Constant	0.1495569	0.0238116	6.28	0	0.102526	0.196587

TABLE 82 Base-case cost regression

	Coeff	Sd err	*t*	*p*	lci	hci
Treatment_group	177.302	191.1369	0.93	0.354	−197.479	552.0834
Age	1.970476	7.304498	0.27	0.787	−12.3639	16.30489
Female	−98.65704	200.9926	−0.49	0.624	−493.257	295.943
Ethnicity_BAME	−271.4768	337.276	−0.8	0.421	−933.332	390.3783
Site 2: nohant (ref Notts)	238.3407	331.3924	0.72	0.472	−411.534	888.2151
Site 3: London (ref Notts)	59.56257	245.3605	0.24	0.808	−421.532	540.6574
Site 4: newcas (ref Notts)	679.6804	307.2987	2.21	0.027	76.28058	1283.08
Site 5: 5oldham (ref Notts)	−422.1358	674.8757	−0.63	0.533	−1762.09	917.8186
Baseline_HDRS17_Severe	−52.14218	217.3775	−0.24	0.811	−479.261	374.9767
Constant	3118.38	383.4216	8.13	0	2366.473	3870.287

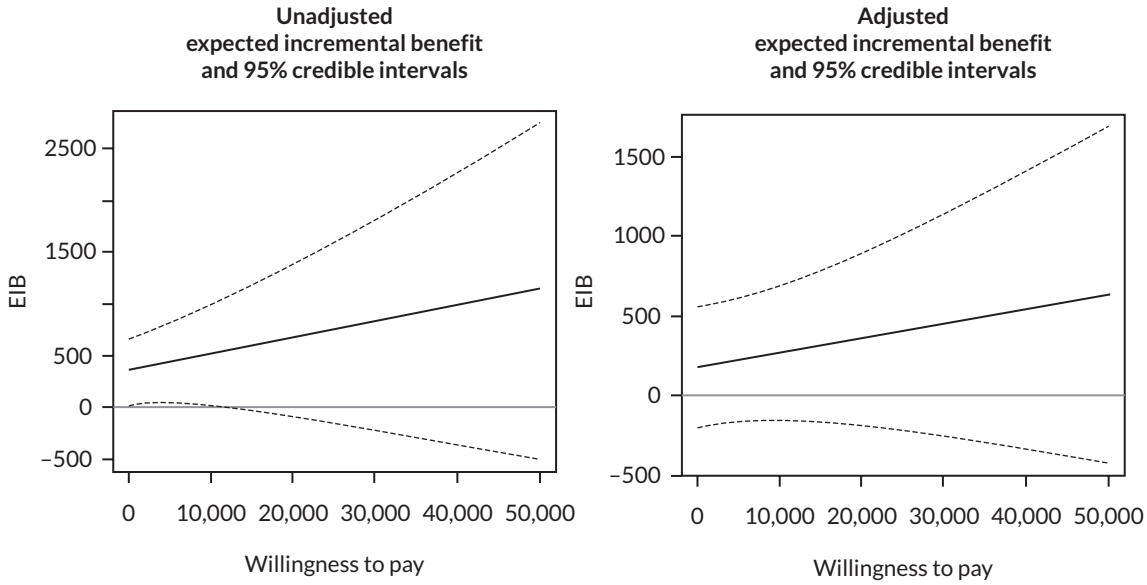

FIGURE 25 Base-case health service perspective expected incremental monetary benefit.

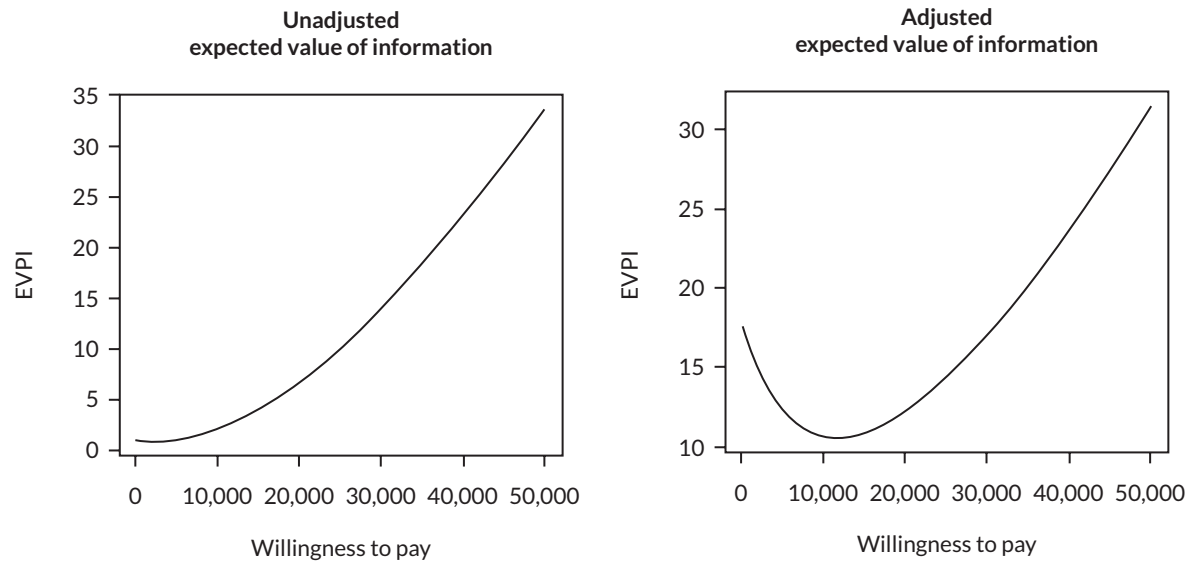

FIGURE 26 Base-case health service perspective EVPI.

Appendix 5 Mechanism-of-action results supplemental information

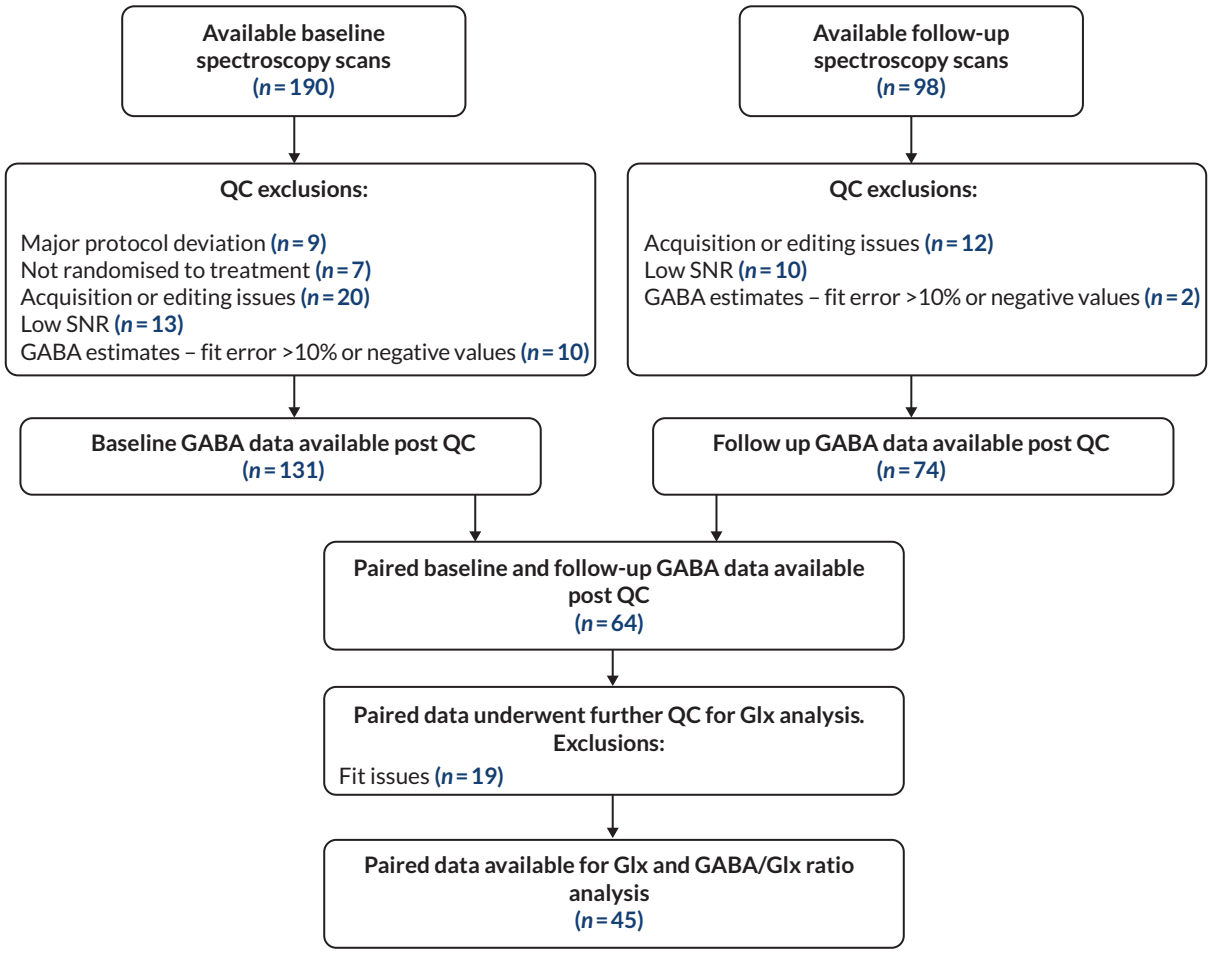

FIGURE 27 QC flowchart for MRS scans.

TABLE 83 MRS descriptives broken down by treatment arm and MRS scanner platform

Descriptive scanning information for baseline GABA+/Cr analysis *n* = 190						
	Nottingham GE scanners		Nottingham Phillips scanner		Newcastle Phillips scanner	
	rTMS *n* = 42	cgiTBS *n* = 39	rTMS *n* = 14	cgiTBS *n* = 16	rTMS *n* = 8	cgiTBS *n* = 12
Baseline GABA+/tCr	0.12 (0.01)	0.12 (0.01)	0.13 (0.02)	0.13 (0.01)	0.10 (0.01)	0.09 (0.01)
Baseline GABA+ Fit Error (%)	3.47 (1.08)	3.58 (1.04)	5.45 (2.17)	5.22 (1.44)	6.62 (1.85)	7.63 (1.91)
Baseline signal to noise ratio	149.80 (42.14)	155.38 (40.56)	216.11 (36.95)	213.19 (31.68)	107.01 (49.98)	98.41 (15.21)
Baseline Water linewidths	8.49 (1.36)	9.07 (1.66)	7.51 (0.55)	8.17 (1.45)	8.46 (1.06)	8.91 (0.63)

continued

TABLE 83 MRS descriptives broken down by treatment arm and MRS scanner platform (*continued*)

Descriptive scanning information for GABA+/Cr change analysis *n* = 63				
	Nottingham GE scanners		Nottingham Phillips scanner	
	rTMS *n* = 20	cgiTBS *n* = 21	rTMS *n* = 10	cgiTBS *n* = 12
GABA+/tCr change (follow-up minus baseline)	−0.008 (0.014)	−0.001 (0.014)	−0.001 (0.023)	0.009 (0.028)
GABA+ Fit Error (%) baseline/follow-up	3.47 (1.19)/ 3.27 (0.57)	3.41 (0.94)/ 3.52 (0.96)	5.25 (1.99)/ 5.44 (1.66)	5.14 (1.63)/ 4.06 (1.08)
Signal to noise ratio baseline/ follow-up	142.85 (51.94)/ 142.08 (32.65)	155.58 (46.33)/ 147.71 (29.87)	215.94 (40.15)/ 203.81 (62.23)	216.27 (36.61)/ 212.16 (62.23)
Water linewidths baseline/follow-up	8.29 (1.52)/ 8.76 (1.83)	9.20 (1.70)/ 8.89 (1.57)	7.60 (0.54)/ 7.86 (1.16)	8.30 (1.77)/ 8.12 (0.82)
Descriptive scanning information for Glx/tCr change and GABA/Glx ratio change analyses *n* = 45				
	Nottingham GE scanners		Nottingham Phillips scanner	
	rTMS *n* = 13	cgiTBS *n* = 13	rTMS *n* = 11	cgiTBS *n* = 8
Glx/tCr change (follow-up minus baseline)	0.004 (0.085)	−0.07 (0.19)	−0.01 (0.08)	−0.03 (0.07)
GABA/Glx ratio change (follow-up minus baseline)	−0.012 (0.025)	0.034 (0.082)	0.003 (0.017)	0.01 (0.03)
GABA+ Fit Error (%) baseline/follow-up	3.31 (1.21)/ 3.11 (0.52)	3.21 (0.64)/ 3.26 (0.75)	5.48 (1.91)/ 5.69 (1.49)	4.74 (1.43)/ 4.25 (1.12)
Signal to noise ratio baseline/follow-up	155.56 (56.12)/ 158.89 (24.21)	160.96 (39.08)/ 155.98 (25.21)	192.33 (40.24)/ 218.03 (39.89)	225.05 (31.05)/ 210.69 (30.49)
Water linewidths baseline/follow-up	7.67 (0.97)/ 7.76 (0.94)	8.36 (1.20)/ 8.51 (1.34)	7.59 (0.56)/ 7.80 (1.19)	7.73 (0.86)/ 8.34 (0.76)
Cramer Rao Lower Bounds baseline/ follow-up	8.38 (1.98)/ 7.85 (1.34)	8.92 (2.02)/ 10.23 (3.90)	4.55 (0.52)/ 4.64 (0.50)	4.50 (0.76)/ 4.63 (0.52)

TABLE 84 Pearson correlations between depression improvement and baseline GABA+/Cr by scanning platforms

	16-week PHQ-9 change	26-week PHQ-9 change	HDRS-17 change averaged over 8, 16, and 26 weeks	HDRS-6 change averaged over 8, 16, and 26 weeks
GE scanners Baseline GABA+/Cr	$r = 0.274$, $p = 0.030$	$r = 0.183$, $p = 0.154$	$r = 0.334$, $p = 0.010$	$r = 0.252$, $p = 0.056$
Phillips scanners Baseline GABA+/Cr	$r = 0.107$, $p = 0.478$	$r = 0.081$, $p = 0.608$	$r = -0.215$, $p = 0.172$	$r = -0.231$, $p = 0.142$

EME
HSDR
HTA
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PHR

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