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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

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Scientific summary

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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.

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