BRIGhTMIND trial-motivating mechanism of action analysis plan:

Resting-state fMRI (v1.0 08/11/22)

Dr Paul M Briley[1], Dr Lucy Webster[2], Miss Hyerin Oh[3,4,5], Dr Stefan Pszczolkowski[3,4,5], Dr William J Cottam[3,4,5], Dr Catherine Kaylor-Hughes[1], Dr Sarina Iwabuchi[1], Dr Sudheer Lankappa[1,2], Prof. Dorothee P Auer[3,4,5], Prof. Peter F. Liddle[1], Prof. Richard Morriss[2,3]

[1]Institute of Mental Health, School of Medicine, University of Nottingham, Nottingham, UK

[2]Nottinghamshire Healthcare NHS Foundation Trust, Nottingham, UK

[3]NIHR Nottingham Biomedical Research Centre, Queen's Medical Centre, Nottingham, UK

[4]Sir Peter Mansfield Imaging Centre, University of Nottingham, UK

[5]Mental Health and Clinical Neurosciences, School of Medicine, University of Nottingham, UK

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Abbreviations

AI: anterior insula; **BRIGhTMIND**: Brain Image Guided Transcranial Magnetic in Depression; **cgiTBS**: connectivity-guided intermittent theta-burst stimulation; **DLPFC**: dorsolateral prefrontal cortex; **DMN**: default mode network; **DMPFC**: dorsomedial prefrontal cortex; **EC**: effective connectivity; **ECN**: executive control network; **FC**: functional connectivity; **fMRI**: functional magnetic resonance imaging; **HDRS-17**: Hamilton Depression Rating Scale (17-item version); **MRI**: magnetic resonance imaging; **ROI**: region of interest; **sgACC**: subgenual anterior cingulate cortex; **rTMS**: repetitive TMS; **TMS**: transcranial magnetic stimulation

Background

BRIGhTMIND is a randomised controlled trial comparing two types of transcranial magnetic stimulation (TMS) for treatment-resistant depression: standard repetitive TMS (rTMS) and connectivity-guided intermittent theta-burst stimulation (cgiTBS). The overall trial protocol has been published (Morriss et al., 2020).

In the trial, participants undergo clinical assessment, at which measures including the 17-item Hamilton Depression Rating scale (HDRS-17) are obtained. They then have baseline brain imaging, which includes 3-Tesla T1-weighted structural MRI and resting-state functional MRI. Within two weeks, they are randomised and begin one of the two types of treatment, which lasts 20 sessions spanning across 4-6 weeks.

Both types of TMS are delivered in the vicinity of left dorsolateral prefrontal cortex (DLPFC), a key component of the "executive control network" (ECN) of brain areas. The stimulation target for participants receiving standard rTMS is computed using the T1-weighted structural MRI by identifying the grey matter voxel closest to the "F3" international 10-20 system scalp location. The stimulation target for cgiTBS is determined from the structural and resting-state functional MRI, by identifying the grey matter voxel in the left ECN that exhibits greatest "effective connectivity" (EC) from the right anterior insula.

A detailed description of image analysis steps, including pre-processing and subsequent determination of target co-ordinates, as well as trial modification due to the COVID-19 pandemic, is given in the published BRIGhTMIND MRI analysis protocol (Pszczolkowski et al., 2021).

At 8 weeks following randomisation (i.e., shortly after treatment completion), participants have a clinical assessment including a repeat HDRS-17. At 16 weeks following randomisation, participants have another assessment and repeat brain imaging. There is also a final clinical assessment at 26 weeks.

Role of this analysis plan

To better understand the mechanism of action of TMS, and of any benefit of cgiTBS over standard repetitive TMS, we will examine sets of hypotheses derived from prior literature. These analyses will be prespecified and published in detailed analysis protocols. This protocol relates to the mechanistic hypotheses examinable with resting-state fMRI that motivated the BRIGhTMIND trial when it was commenced.

One such hypothesis concerns "functional connectivity" (FC) – correlations in the activities of two brain regions, a measure of inter-regional co-operation and communication. Specifically, that the

extent of *decrease* in FC between the left DLPFC and left dorsomedial prefrontal cortex (DMPFC, a component of the "default mode network" of brain areas) will be associated with *greater* mean clinical improvement (sustained post-treatment). Likewise, that FC between left DLPFC and left DMPFC will decrease to a greater extent in responders on the HDRS-17 than non-responders.

Another hypothesis concerns "effective connectivity" (EC) – the directed influence of one brain region on another, which can be calculated using Granger causality analysis. Specifically, that *greater* EC from the right anterior insula (AI) to the left DLPFC at baseline will be predictive of greater mean clinical improvement at the end of treatment.

Other researchers have found that greater baseline anti-correlation between the subgenual anterior cingulate cortex (sgACC) and left DLPFC predicts greater clinical improvement with TMS (Cash et al., 2021, 2019; Fox et al., 2012), and we will examine this hypothesis in a secondary analysis.

Required data

- T1-weighted structural MRI and resting-state functional MRI at baseline and, where available, 16 weeks
- Treatment group assignment (rTMS or cgiTBS)
- Participant age, sex, and study centre
- For each participant, information on treatments given and protocol deviations:
    - Number of treatment sessions completed
    - Number of sessions stopped partway through treatment
    - Whether final treatment session occurred more than six weeks after first treatment
    - Whether there were any changes in medications in BNF Chapter 4 between baseline and 16 weeks (including starting and stopping medications)
    - Whether ECT was delivered between baseline and 16 weeks
    - Whether psychotherapy was started between baseline and 16 weeks
    - Whether *any* major protocol deviations (defined according to the trial protocol) occurred between baseline and 16 weeks
- For each participant, the following questionnaire scores:
    - 17-item HDRS total score at all available time points
    - 6-item HDRS total score at all available time points
    - Beck Depression Inventory at all available time points
    - 16-item self-report Quick Inventory of Depression Symptoms (QIDS-SR-16) at all available time points
    - 9-item Personal Health Questionnaire (PHQ-9) at all available time points
    - Massachusetts Treatment Resistance category (mild, moderate, severe, as defined in trial protocol)
    - General Anxiety Disorder Questionnaire (GAD-7) total score
    - Childhood Trauma Questionnaire (CTQ) total score

Definitions of measures

- *Clinical improvement*
  Mean change in depression measure (e.g., 17-item HDRS total score) from baseline

- *Treatment response*
  Reduction in depression measure (e.g., 17-item HDRS total score) of 50% or greater compared to baseline

- *Functional connectivity (FC)*
  Time series will be extracted from two regions of interest (ROIs) using the fslmeants tool (part of the FSL software library). The first principal component of the time series of all voxels within an ROI will be taken as a representation of the overall time series for that ROI (note that the mean white matter and cerebrospinal fluid time courses will have already been regressed out of each voxel's time course; for analyses involving the sgACC, the global mean time course will have also been regressed out – see Data pre-processing). The first five time points will be discarded to allow magnetisation stabilisation and time series will be band-pass filtered between 0.01 and 0.1 Hz. Zero-lag ROI-to-ROI correlations will then be calculated using Pearson correlations between the times series, partialling out twenty-four head motion parameters (three translations and three rotations for current time point and one time point prior, and squares of these parameters). Correlations of interest will then be converted to *z*-scores using Fisher's *r*-to-*z* conversion. These *z*-scores will serve as the measures of FC.

- *Effective connectivity (EC)*
  Granger causality computed using the REST toolbox (Song et al., 2011), which runs under MATLAB. This provides a measure of directed (effective) connectivity, from one ROI (*x*, for example, right AI) to another ROI (*y*, for example, left DLPFC). The toolbox provides measures of the influence of *x* on *y* as well as *y* on *x*. As for the FC analyses, for the EC analyses, the first five time points will be discarded, and the twenty-four head motion parameters will be entered as covariates. No band-pass filter will be applied, as per the trial target-identification procedure. Effective connectivity values will be converted to z-scores using Fisher's *r*-to-*z* conversion, then the mean *z*-score output across all voxels in *y* will serve as the measure of EC.

- *Net outflow*
  The rAI-to-lDLPFC effective connectivity (rAI "outflow") *minus* the lDLPFC-to-rAI effective connectivity (rAI "inflow"), as used in Iwabuchi et al. (2019).

Included participants

Hypotheses will include trial participants with baseline T1-weighted structural MRI and resting-state fMRI data available that used the correct scanning parameters and passed quality control criteria (image criteria as detailed in Pszczolkowski et al.). Where 16-week imaging data are available, for these to be included they too should pass quality control criteria. We will exclude participants:

1. With the major protocol deviation, "Participant received incorrect study treatment", where this arose due to TMS being delivered to an unintended target (primarily cases where target co-ordinates were uploaded incorrectly to the neuro-navigation software)
2. That received fewer than fifteen, out of twenty, full treatments (a full treatment is defined as a treatment that was not terminated prematurely)
3. With greater than six weeks between the first and last treatment

Hypotheses – baseline connectivity as a predictor of response

Primary hypothesis

A1. 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 left DLPFC, and this relationship will be stronger in the cgiTBS group

Secondary hypotheses

A2. Greater clinical improvement on 17-item HDRS will be associated with more positive baseline *net outflow* from right AI to left DLPFC, and this relationship will be stronger in the cgiTBS group

A3. Greater clinical improvement on 17-item HDRS will be associated with more negative baseline FC between subgenual anterior cingulate cortex (sgACC) and left DLPFC across both treatment groups

Hypotheses – associations between connectivity change and clinical improvement

Primary hypothesis

B1. Reduction in left DLPFC – 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

Secondary hypotheses

B2. Reduction in left DLPFC – left DMPFC 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

B3. 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

B4. Reduction in *net outflow* from right AI to left DLPFC from baseline to 16-week follow-up will be associated with greater clinical improvement, and this relationship will be stronger in the cgiTBS group

B5. Increase in sgACC – left DLPFC FC (reduction in anti-correlation) from baseline to 16-week follow-up will be associated with greater clinical improvement, across both treatment groups

Exploratory analyses

The above hypotheses will be tested with other measures of depression used in the study to test robustness of findings, namely HDRS-6, BDI, PHQ-9 and QIDS-SR-16 total scores. Additionally, we will examine the impact of including baseline level of anxiety (GAD-7), and change in GAD-7, and CTQ total score, in the analyses (continuous variables).

To aid understanding of the findings from tests of hypotheses involving rAI, we will also compare change in rAI-cgiTBS target effective connectivity (from baseline to 16-week follow-up) between the cgiTBS and rTMS groups. To aid understanding of findings from the tests of hypotheses involving lDLPFC and lDMPFC, we will also examine change in functional connectivity between the two lDLPFC regions of interest (one more anteriorly-located than the other – see Regions of Interest section below) from baseline to 16-week follow-up. To aid understanding of findings from tests of hypotheses involving sgACC, we will also examine changes in functional connectivity between the sgACC and rAI from baseline to follow-up.

As part of the trial target identification pipeline, we compute a map of left DLPFC effective connectivity from rAI. The maximum of this map corresponds to the cgiTBS target. We will calculate effective connectivity as a function of distance from this maximum to examine whether optimal targets according to the trial target identification procedure are clearly unique or whether there are multiple, separate, potential targets within DLPFC.

Finally, for each participant, we will compute functional connectivity between each image voxel and 6-mm spherical seed regions centred on the intended stimulation target co-ordinates. We will compute these seed-region functional connectivity images for baseline and follow-up, and we will also compute the difference between the follow-up and baseline images. Using SPM12, we will compare baseline, and difference, seed-region functional connectivity images between responders and non-responders at sixteen weeks. For these analyses, we will use a significance threshold of $p < 0.05$ with family-wise error rate correction, and a minimum cluster size of twenty.

Sensitivity analyses

In sensitivity analysis I, we will test the above hypotheses after excluding participants with any form of major protocol deviation (defined according to the trial protocol, e.g., medication changes or psychotherapy during the treatment course).

In sensitivity analysis II, we will test the above hypotheses after excluding participants whose cgiTBS target lay outside the left middle frontal gyrus according to the Harvard-Oxford cortical atlas at 10% threshold (Makris et al., 2006).

Regions of interest (ROIs)

Each ROI for each participant will be masked with the participant's binarized grey matter mask (thresholded at 25% tissue probability as per Data Pre-processing)

- For hypotheses A1, A2, B3 and B4 (examining right AI-DLPFC connectivity), the ROI for right AI will be a 6-mm sphere centred on MNI co-ordinates x=30, y=24, z=-14 (McGrath et al., 2013), as used for computing cgiTBS target co-ordinates in the trial. The ROI for left DLPFC will be a 6-mm sphere centred on the cgiTBS target co-ordinates themselves (regardless of treatment group).

- For hypotheses B1 and B2 (examining DLPFC-DMPFC connectivity), two centroids for the left DLPFC ROI that are independent from the cgiTBS and rTMS co-ordinates will be examined in separate analyses: an anterior DLPFC centroid from Liston et al. (2014), x = -44, y = 40, z = 29, and a more posterior DLPFC centroid from Fair et al. (2009), x = -44, y = 22, z = 36 (after

conversion from Talairach to MNI co-ordinates). Due to the use of two analyses for each of these hypotheses, we will apply, for each term of the mixed model, a Holm-Bonferonni correction across the *p*-values from the two analyses (that is, we will use a significance threshold of 0.025 for the smallest of the two *p*-values, and then, if the smallest *p*-value is significant, a threshold of 0.05 for the largest of the two *p*-values). The centroid for the left DMPFC ROI will be taken from a seed used by Yeo et al. (2011) in their 7-network resting-state parcellation of the cortex, x = -7, y = 49, z = 18. Each of these centroids lies within the fronto-parietal (DLPFC seeds) or default mode (DMPFC seed) network in the Yeo et al. atlas. Further, the nearest nodes in the Power et al. (2011) resting-state atlas to these centroids are also assigned to the fronto-parietal, and default mode, networks, as appropriate.

- For hypotheses A3 and B5 (examining sgACC connectivity), the centroid for the left DLPFC ROI will the target co-ordinates used for a given participant in the trial. For the participants who received cgiTBS, this will be their cgiTBS co-ordinates. For participants who received rTMS, this will be the rTMS target co-ordinates (as the rTMS target was superficial, we will project it 6-mm deeper into the brain using the method of Jing et al. (2020), giving x = -38, y = 40, z = 29). The ROI for sgACC will be a 6-mm sphere centred on MNI co-ordinates x=6, y=16, z=-10 (Cash et al., 2019)

Statistical tests

These analyses will be conducted in SPSS. Diagnostic plots of model residuals, and the results of the Shapiro-Wilk test, will be used to determine whether variable transformations are required.

<u>Hypothesis A1 (primary)</u>

"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 left DLPFC, and this relationship will be stronger in the cgiTBS group"

- Examined using mixed effects models with HDRS-17 treatment response as the dependent variable and participant as a random effect
- Independent variables will be:
    - HDRS-17 time point
    - Baseline EC from right AI to left DLPFC
    - Treatment group (rTMS or cgiTMS)
    - *Age*
    - *Sex*
    - *MGH treatment resistance group*
    - *Study centre*
- We will incorporate the three interaction terms formed by the combination of baseline EC from right AI to left DLPFC with either, or both, of HDRS-17 time point and treatment group
- We will use a scaled identity structure variance-covariance matrix for the random effect (participant)

- Models will be estimated with restricted maximum likelihood. If any of the italicized predictors above are non-significant, they will be removed from the model, which will be re-fitted.

Hypothesis A2 (secondary)

"Greater clinical improvement on 17-item HDRS will be associated with more positive baseline net outflow from right AI to left DLPFC, and this relationship will be stronger in the cgiTBS group"

Analysis will be as for Hypothesis A, with EC from right AI to left DLPFC replaced by net outflow from right AI to left DLPFC (that is, EC from right AI to left DLPFC minus EC from left DLPFC to right AI)

Hypothesis A3 (secondary)

"Greater clinical improvement on 17-item HDRS will be associated with more negative baseline FC between subgenual anterior cingulate cortex (sgACC) and left DLPFC across both treatment groups"

Analysis will be as for Hypothesis A, with EC from right AI to left DLPFC replaced by FC between sgACC and left DLPFC.

Hypothesis B1 (primary)

"Reduction in left DLPFC – 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"

- Examined using mixed effects models with HDRS-17 treatment response as the dependent variable and participant as a random effect
- Independent variables will be:
    - HDRS-17 time point
    - Reduction in left DLPFC – left DMPFC FC from baseline to 16 weeks
    - Baseline left DLPFC – left DMPFC FC
    - Treatment group (rTMS or cgiTMS)
    - The other italicized variables as above
- We will incorporate the three interaction terms formed by the combination of reduction in left DLPFC – left DMPFC FC from baseline to 16 weeks with either, or both, of HDRS-17 time point and treatment group

Hypothesis B2 (secondary)

"Reduction in left DLPFC – left DMPFC 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"

- Examined using mixed effects models with left DLPFC – left DMPFC FC as the dependent variable and participant as a random effect
- Independent variables will be:

    - Imaging time point (baseline, 16 weeks)
    - 8-week HDRS-17 responder status (responder, non-responder)
    - 16-week HDRS-17 responder status (responder, non-responder)
    - 26-week HDRS-17 responder status (responder, non-responder)
    - Treatment group (rTMS or cgiTMS)
    - The other italicized variables as above
- We will incorporate the following interaction terms: imaging time point by 8- or 16- or 26-week responder status (2-way), imaging time point by treatment group (2-way), imaging time point by treatment group by responder status (3-way)

Hypothesis B3 (secondary)

"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"

- Examined using mixed effects models with HDRS-17 treatment response as the dependent variable and participant as a random effect
- Independent variables will be:
    - HDRS-17 time point
    - Reduction in rAI→lDLPFC EC from baseline to 16 weeks
    - Baseline rAI→lDLPFC EC
    - Treatment group (rTMS or cgiTMS)
    - The other italicized variables as above
- We will incorporate the three interaction terms formed by the combination of reduction in rAI→lDLPFC EC from baseline to 16 weeks with either, or both, of HDRS-17 time point and treatment group

Hypothesis B4 (secondary)

"Reduction in net outflow from right AI to left DLPFC from baseline to 16-week follow-up will be associated with greater clinical improvement, and this relationship will be stronger in the cgiTBS group"

Analysis will be as for Hypothesis B3, with rAI-to-lDLPFC FC replaced by net outflow from rAI to lDLPFC.

Hypothesis B5 (secondary)

"Increase in sgACC – left DLPFC FC (reduction in anti-correlation) from baseline to 16-week follow-up will be associated with greater clinical improvement, across both treatment groups"

Analysis will be as for Hypothesis B3, with rAI-to-lDLPFC FC replaced by sgACC – left DLPFC FC

Data pre-processing

Pre-processing of the structural and resting-state fMRI data will be with the latest version of the SPMIC-BRC pipeline (1.5.5, 23/08/21), which is freely available to download at github.com/SPMIC-UoN/BRC_Pipeline.

Pre-processing steps will be the same as those used during the trial for computing cgiTBS target co-ordinates, as detailed in the trial MRI protocol (Pszczolkowski et al., 2021). This is with the exception of the use of advanced EDDY slice-to-volume and volume-to-volume motion correction (Andersson et al., 2017), which we will use in place of the MCFLIRT six degrees-of-freedom volume-to-volume correction used in the trial. The SPMIC-BRC pipeline is based on tools from: SPM12, FSL, and Freesurfer. EDDY motion correction uses the NVIDIA CUDA Toolkit.

Specifically, structural pre-processing will be run with the SPMIC-BRC pipeline function "struc_preproc.sh". Steps will include: bias-field correction, brain extraction, tissue segmentation, and registration to standard space. Optional parameters given to this function will be: strongbias (bias correction enabled) and nodefacing (turns off automatic defacing since this was implemented prior to running the SPMIC-BRC pipeline in the XNAT database to which images are initially uploaded). Registration to standard space (MNI152) will be done via the default linear + non-linear (FSL FNIRT) method. Whole brain (FSL BET), and grey matter (GM), cerebrospinal fluid (CSF) and white matter (WM) masks (FSL FAST), produced as part of the structural pre-processing pipeline, will also be warped to standard space. WM and CSF images will be binarized at a tissue-probability threshold of 99% and the GM images at 25%.

Functional pre-processing will be run with the SPMIC-BRC pipeline function "fMRI_preproc.sh". Steps will include: EPI distortion correction, motion correction, intensity normalisation, slice-timing correction, temporal filtering, physiological noise removal, and registration to standard space. Optional parameters given to this function will be: mctype EDDY (EDDY motion correction in place of MCFLIRT6), dcmethod TOPUP (FSL TOPUP distortion correction), biascorrection SEBASED (bias field calculation from spin echo images), intensitynorm (turns on intensity normalisation), fwhm 5 (spatial size of image smoothing in mm), and tempfilter 100 (high-pass temporal filter in seconds). Finally, the mean time course of the BOLD signal from WM and CSF will be extracted, then regressed out of the rsfMRI time series (for analyses involving the sgACC, the whole brain mean time course will also be regressed out).

Quality control

All structural and functional MRI scans will undergo the same quality control process as used in the BRIGhTMIND stimulation target identification pipeline, and as detailed in Pszczolkowski et al. (2022). This involves use of the MRIQC v0.11.0 quality control XNAT container, with verification that: the average, and maximum, framewise displacement of BOLD images are not greater than 1 mm, and 3 mm, respectively; that BOLD images do not show long-lasting intensity changes or image artefacts; and that T1w images contain whole head coverage and do not contain incidental findings or image artefacts.

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