BRIGhTMIND trial-motivating mechanism of action analysis plan:

MRS (v4.0 30/01/23)

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Abbreviations

MRS: magnetic resonance spectroscopy; **BRIGhTMIND**: Brain Image Guided Transcranial Magnetic in Depression; **cgiTBS**: connectivity-guided intermittent theta-burst stimulation; **DLPFC**: dorsolateral prefrontal cortex; **VOI:** Voxel of Interest**; ROI**: Region of Interest; **GABA:** Gamma-AminoButyric Acid; **Glx**: Glutamate + Glutamine, **LCModel**: Linear Combination of Model; **MEGA-PRESS**: MEGA-Point-RESolved Spectroscopy; **Cr:** Creatine; **LW**: Linewidth

Background

BRIGhTMIND is a randomised controlled trial and compares two transcranial magnetic stimulation (TMS) methods for treatment-resistant depression (TRD): standard repetitive TMS (rTMS) and connectivity-guided intermittent theta-burst stimulation (cgiTBS). The overall protocol for trial has been published (Morriss et al., 2020), modified with the COVID-19 pandemic (Pszczolkowski et al., 2022). In brief, the trial protocol includes clinical, psychometric and cognitive assessment and multimodal brain imaging at 3T at baseline and 16 weeks following rTMS or cgiTBS (20 sessions spanning across 4-6 weeks). Both types of TMS are delivered to the left dorsolateral prefrontal cortex (DLPFC), a key component of the "executive control network" (ECN) of brain areas. The selection of the stimulation target site was imaging-based for both treatment arms with different approaches. T1-weighted structural MRI was used to find the grey matter voxel the nearest to the "F3" international 10-20 system scalp location for the rTMS arm, while the target for the cgiTBS arm was decided from the structural and resting-state functional MRI, by finding the grey matter voxel in the left ECN, which shows the greatest "effective connectivity" (EC) from the right anterior insula.

All participants underwent MRI for neuronavigation at all four scanning sites (Nottingham, Newcastle, London and Manchester), and a subset of participants (those recruited for scanning at Nottingham or Newcastle) was also enrolled into the mechanistic proton MR spectroscopy (MRS) substudy, whereby GABA-edited MRS was acquired over the DLPFC at baseline and 16-weeks follow-up. Here, we summarise the rationale and hypotheses and describe processing details and changes from the original protocol plan and document the statistical analysis plan that will be followed for the MRS substudy.

Compared to the published protocol (Pszczolkowski et al., 2022), the MRS processing pipeline has been changed due to a compatibility issue in spectra processing pipeline across MRI vendors. Originally, we proposed to use an in-house MATLAB processing pipeline and LCModel to quantify metabolites based on experience with the main MRS platform. However, due to implementation challenges on other platforms and based on favourable in-house comparison between pipelines we decided to switch to GANNET, a MATLAB package to process spectra and quantify metabolites, which is in line with recent recommendations based on a thorough validation study across multi-sites and different vendors (Mikkelsen et al., 2017). We will, however, still report the LCModel derived results from a single-site, single vendor protocol for interest.

Glutamate and GABA are major excitatory and inhibitory neurotransmitters respectively and can be detected noninvasively detectable by MRS. However, MRS detectable glutamate and GABA levels are not direct read-outs of the respective neurotransmitter pool but there is strong supportive evidence that GABA levels co-vary with the extent of inhibitory activity while glutamate may index increased metabolic or excitatory activity. Due to the inability to separate glutamate from glutamine, commonly Glx (the estimated sum of glutamate and glutamine) is reported. GABA/Glx in particular

is an increasingly used index of the inhibitory/excitatory ratio which is considered to be robust in healthy brains.

In chronic stress and depression, there is well-documented impaired function of GABAergic and glutamatergic neurons in the PFC and hippocampus with some suggestion that GABA dysfunction may be the primary pathogenic mechanism (Duman et al., 2019). In people with depression, decreased frontal $GABA_B$ receptors and reduced GABA levels in the plasma, cortical and limbic brain areas were reported in preclinical and clinical studies (for a review, see Duman et al., 2019). Alterations of GABAergic transmission have long been considered as putative pathomechanism and treatment target in affective disorders (Kalueff & Nutt, 2007; Lloyd et al., 1989; Möhler, 2012). A recent meta-analysis of Glx MRS studies in depression (Moriguchi et al., 2019) shows overall reduction that medial prefrontal Glx/glutamate with some variation and possible link to medication state. Despite some reports of increased Glx, the overall parallel reduction of Glx and GABA cautions against use of GABA/Glx as marker of inhibitory/excitatory balance in people with depressions, which may explain the negative finding reported by Narayan et al., (2022) as they found no changes of medial prefrontal GABA/Glx after 8 weeks of escitalopram treatment, and no association with change in depression scores. By contrast, there is suggestive evidence that antidepressants and in particular short-acting agents like ketamine may restore a balanced GABAergic and glutamatergic neurotransmission as part of the antidepressant treatment efficacy (Silberbauer et al., 2020; Stone et al., 2012).

TMS related neurochemical changes were reported in few studies focusing on GABAergic or glutamatergic neurochemicals, with variable findings based on typically small sample sizes and differing TMS and MRS protocols in healthy controls and patients (Gonsalves et al., 2022). In rTMS responders who were TRD patients, GABA levels in the dorsolateral prefrontal cortex increased after rTMS treatment while no trend was observed in the non-responders (Levitt et al., 2019). A recent small MRSI study in TRD reported localised mPFC Glx increases after iTBS but no GABA changes (Spurny-Dworak et al., 2022). There is however some existing literature describing that frontal glutamatergic metabolites and GABA increases after high frequency left DLPFC rTMS in association with clinical improvement. Conversely, a recent study shows an increase of mPFC GABA post iTBS in acute bipolar depression that was unrelated to clinical improvement (Diederichs et al., 2021). Also, in our unreported MRS substudy of the pilot cgiTBS study in TRD (Iwabuchi et al., 2019) we found no GABA changes at 3 months post iTBS, but some suggestion of predictive power of baseline prefrontal GABA for HDRS-17 and Beck Depression Inventory (BDI) scores at 3 months. Moreover, GABA and HDRS-17 change between baseline and 3 months was moderately correlated suggesting an inverse relationship with clinical improvement. The negative relationship between GABA and HDRS-17 changes suggests that GABA increase may result in the clinical improvement in depression. Our pilot study also showed acute reduction of the ratio of prefrontal GABA/Glx after a single session of 3000 TBS pulses over the left DLPFC in healthy volunteers (Iwabuchi et al., 2017). The observed acute change pattern is well in line with the expected excitatory nature of iTBS but it is unknown whether chronic GABA/Glx changes would occur in healthy volunteers nor are there reports on acute changes in people with depression. Differences are however expected in neurobiological effects between healthy brains and patients with depression and between acute treatment effects and chronic neuroplastic changes with further likely differences between brain regions as well as recognised inter-individual variability ascribed to meta-plasticity (Kinjo et al., 2021). Taken together, there is strong evidence for impaired prefrontal GABAergic and glutamatergic neurotransmitter systems in depression, but conflicting evidence whether reversal of these neurochemical alterations (and in which brain regions) by TMS may be an important mechanism of its antidepressant efficacy.

Role of this analysis plan

To better understand the mechanism of action of TMS, and of any putative benefit of cgiTBS over standard repetitive TMS, we will examine a set of hypotheses derived from prior literature. Here, we describe the spectroscopic processing and statistical analysis plan.

The main study rationale is to assess whether clinical response to treatment is associated with GABA changes in the DLPFC.

Definitions of measures

- *Clinical improvement*
  Mean change in depression measure from baseline (17-item HDRS total score as primary measure); changes from baseline in BDI, QIDS-SR-16, PHQ-9 and GAD-7 will be used for exploratory analyses only)

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

- *Metabolite ratios*

GABA levels relative to Cr (GABA+/Cr), Glx levels relative to Cr (Glx/Cr) and GABA levels relative to Glx (GABA+/Glx as no macromolecule suppression). Glx and Cr will be estimated from non-edited spectra.

Primary hypotheses

1. Changes in depression symptoms on 17-item HDRS (16 weeks versus baseline) 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 decrease of HDRS (improvement).
2. Changes in depression symptoms on 17-item HDRS (26 weeks versus baseline) 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 decrease of HDRS (improvement).

3. 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.

Secondary hypotheses

1. GABA+/Cr will be increased after treatment compared to baseline for treatment responders across both treatment groups (a) and (b) GABA+/Cr increase will be higher in responders than in non-responders.

2. GABA+/Cr increase will be higher in cgiTBS compared to rTMS group (all patients).

3. Greater averaged and sustained clinical improvement on 17-item HDRS (averaged over 8,16 26-week follow-up) will be associated with more GABA+/Cr change across both treatment groups.

4. Greater averaged and sustained clinical improvement on 17-item HDRS (averaged over 8, 16 26-week follow-up) will be associated with lower GABA+/Cr at baseline across both treatment groups.

5. Glx/Cr will be increased after treatment compared to baseline for treatment responders across both treatment groups (a), and Glx/Cr increase will be higher in responders than in non-responders (b).

6. Glx/Cr increase will be higher in cgiTBS compared to rTMS group (all patients).

7. 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:

1. All 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

2. GABA+/Glx changes will be associated with clinical outcomes (17-item HDRS at 16 and 26 weeks).

3. GABA+/Cr and Glx/Cr changes correlate with rAI-DLPFC net outflow changes (16 weeks vs baseline).

4. GABA+/Glx is associated with rAI-DLPFC FC and net outflow (baseline and 16 weeks) with stronger association in treatment responders after treatment compared to baseline.

5. Clinical subtypes, especially TRD severity and comorbid anxiety are associated with changes in GABA+/Cr.

6. Treatment response is associated with changes in the association between intrinsic within and between brain network FC metrics and DLPFC GABA+/Cr, Glx/Cr and GABA+/Glx levels.

Required data

- MEGA-PRESS MRS and resting-state functional MRI at baseline and, where available, at 16 weeks
- Treatment group assignment (rTMS or cgiTBS)
- Participant age, sex, and study centre and MRS protocol/platform
- For each participant, whether protocol deviations were submitted on the basis of stimulation sequence or localisation method received
- For each participant, whether there were any changes in medications in BNF Chapter 4 between baseline and 16 weeks (including starting and stopping medications)
- For each participant, whether ECT was delivered between baseline and 16 weeks
- For each participant, whether they started psychotherapy between baseline and 16 weeks
- For each participant, whether any major protocol deviations occurred from baseline to 16 weeks
- 17-item HDRS total score at baseline, 8-week follow-up, 16-week follow-up and 26-week follow-up.
- 6-item HDRS total score at baseline, 8-week follow-up, 16-week follow-up and 26-week follow-up.
- Beck Depression Inventory at baseline, 8-week follow-up, 16-week follow-up and 26-week follow-up
- 16-item self-report Quick Inventory of Depression Symptoms (QIDS-SR-16) at baseline, 8-week follow-up, 16-week follow-up and 26-week follow-up
- 9-item Personal Health Questionnaire (PHQ-9) at baseline, 8-week follow-up, 16-week follow-up and 26-week follow-up
- Total score on the GAD-7 measure of anxiety
- Massachusetts Treatment Resistance category (mild, moderate, severe as defined in trial protocol

Regions of interest (ROIs) / Voxel of interest (VOI)

- For MRS, a voxel (20x45x30mm) was placed on the left DLPFC based on the individual T1 anatomical image acquired prior to the MRS session.
- Grey Matter (GM), White Matter (WM) and Cerebrospinal fluid (CSF) will be parcellated through GANNET segmentation with SPM12. The GM values will be covariates of no interest in the statistical analysis.

Sensitivity analyses

In order to examine whether quality of MRS affected the results, we will conduct sensitivity analyses to

- assess a potential effect from outliers in voxel position. For this, coverage of anatomical DLPFC (in percent) and overlap with TMS brain target within the individual MRS voxels will inform through the sensitivity analysis.
- assess spectral fitting quality effects. For this, only data with higher quality data fit will be used to repeat primary and secondary hypothesis with p<0.1 results.

Statistical tests

Primary Hypotheses

- The correlation between change in GABA+/Cr between baseline and 16 weeks (post minus pre-treatment) and clinical improvement will be tested by regression with the following covariates for P1 and P2:
    - *Age*
    - *Sex*
    - *Treatment group (rTMS or cgiTMS)*
    - *MGH treatment resistance*
    - *Baseline 17-item HDRS*
    - *Study centre*
    - *MRS platform (scanner/protocol)*
    - *MRS quality (GABA+ fitting error)*

P<0.01666 will be the level considered for statistical significance (p<0.05/3, i.e. 5% significance level with Bonferroni correction for 3 co-primary hypotheses). For missing data (e.g. due to poor spectra quality, participants' absence for the scanning or incompleteness of whole MRS sessions) we will take an available data approach, meaning individuals with enough data for a model will be included in that model's analysis.

- For P3, a mixed effects model will be used with participant as random effect to account for three repeated measures. Each participant will contribute up to 3 repeated outcome measures to the model in addition to the baseline HDRS-17 score. The model will be adjusted for the stratification and minimisation variables: baseline HDRS-17 score, baseline Massachusetts General Hospital Treatment Resistant Depression score, and study centre as part of the covariable detailed above. For missing data, we will take an available data approach, meaning individuals with enough data for a model will be included that model's analysis.

Secondary Hypotheses

Secondary hypotheses S2, S3, S5, S6, S7 will be analysed as above, for S1 and S4 we will use a mixed model

- A Linear mixed model will be used with GABA+/Cr as the dependent variables.
- Independent variables will be the *Treatment* response group, *Time* (pre-and post) and *Treatment* type
- Covariates of no interest include
    - *Age*
    - *Sex*
    - *MGH treatment resistance group*
    - *Study centre*
    - *MRS platform (scanner/protocol)*
    - *MRS quality (GABA+/Glx fitting error respectively)*

We will take an available data approach, meaning individuals with enough data for a model will be included in that model's analysis. For secondary analyses P<0.05 will be considered significant without Bonferroni correction.

The statistical analysis for primary and secondary hypotheses will be performed using a current version of either SPSS, SAS, Stata or R (for graphical illustrations). Diagnostic plots of model residuals, and the results of the Shapiro-Wilk test, will be used to determine whether variable transformations are required.

Exploratory hypotheses

Exploratory tests will be undertaking using current versions of either established advanced image analyses, SPSS, SAS, Stata or R (for graphical illustrations).

Included participants

All trial participants with baseline T1-weighted structural MRI, and MRS passing quality control criteria as detailed later in this document. We will include only participants that received the treatment to which they were assigned (that is, participants without protocol deviations on the basis of stimulation sequence or localisation method used).

Data processing

We originally planned to perform the entire MRS analysis using LCModel but during preprocessing noted that data from only one vendor was compatible for our in-house analysis pipeline. Due to time constraints, we then decided to use GANNET instead. Acquired spectra in the left DLPFC will thus be processed with GANNET MATLAB package (v 3.3.0) with the default setting. MEGA-PRESS origin will be set as 'JHU' in GANNET for Nottingham GE and Newcastle Philips data and 'Phillips' for Nottingham Philips. For completeness we will also report summary results from LCModel based GABA+/Cr estimates. In brief, GANNET processing uses time domain signals that will be frequency and phase corrected by spectral registration. 3-Hz exponential line broadening and zero-filling with a factor of 16 will be applied for filtration. Each pair of spectra (edited – non edited) will be aligned, and edited spectra will be subtracted from non-edited spectra to detect a GABA peak. The processed spectra will be averaged and fit to Gaussian function to the GABA and Glx peak at 3.0 and 3.8 ppm,

respectively. GABA peak will be modelled using a five-parameter Gaussian model (2.19 – 3.55 ppm) and water peak will be modelled using a Gaussian-Lorentzian function. Creatine and N-acetylaspartate will be modelled as two Lorentzians in the non-edited spectra. The integral Cr area in non-edited spectra will be used to calculate GABA+ ratio relative to Cr. Linewidths of water and NAA peak will be reported for quality control.

We are employing the best practice of Glx estimation from MEGA-PRESS or validated equivalence using the GANNET pipeline. Glx acquisitions from edit-off MEGA-PRESS spectra show significantly higher correlation with Glx levels acquired by Point RESolved Spectroscopy (PRESS) than Glx from edit-on MEGA-PRESS spectra (Maddock et al., 2018), hence we aim to measure Glx levels from edit-off spectra. Once the compatibility issue is addressed with our in-house pipeline, measured GABA from edited spectra and Glx and other metabolite levels from non-edited spectra will be reported using our in-house MATLAB pipeline and LCModel. All the MRS sequence parameters pinned down for the various acquisitions will be checked, and the sequence specific basis sets will be built in the future for the Glx measurements.

Quality control

For MRS, measurements with > 10% water referenced GABA+, Glx fit error (Sedley et al., 2015) will be excluded. Negative measurement will be also excluded. Fit error in GANNET is the standard deviation of the residual and shown in percentage of signal height.

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