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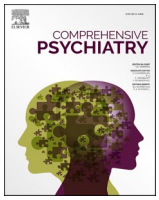

Acceptability, tolerability and safety of the BRIGhTMIND trial: Connectivity-guided intermittent theta-burst stimulation versus F3-repetitive transcranial magnetic stimulation for treatment-resistant depression

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ABSTRACT

Background: The BRIGhTMIND study was a double-blind RCT comparing repetitive transcranial magnetic stimulation at a standard simulation site (the "F3" location given by the International 10–20 system, F3-rTMS) versus connectivity-guided intermittent theta burst stimulation (cgiTBS) for treatment-resistant depression. This present study reports the acceptability, safety, and tolerability of F3-rTMS versus cgiTBS.

Methods: The present study used quantitative and qualitative methods. Two hundred fifty-four participants were included in the quantitative BRIGhTMIND acceptability and safety analysis ($n = 126$ F3-rTMS, $n = 128$ cgiTBS). Qualitative analysis included interviews for 15 participants ($n = 7$ F3-rTMS, $n = 8$ cgiTBS) and 582 written comments made by any participant randomised to the BRIGhTMIND trial regarding their experience of TMS and the study. Statistical analyses were used to explore differences between F3-rTMS and cgiTBS, as well as associations between acceptability, impression of change and safety. Qualitative data was analysed using an inductive thematic framework approach.

Outcomes: Acceptability, TMS benefits/negative effects and impression of improvement ratings did not differ across the two treatment protocols, with ratings maintained long-term (71.4 % rated TMS acceptable, 48.8 % indicated benefits of TMS outweighed negative effects and 52.2 % feeling somewhat or much better at 26 week follow-up $n = 203$). Impression of improvement was positively associated with acceptability and TMS benefits. Qualitative themes included participants' TMS experience, TMS response variability, and lay theories of effectiveness. Safety profiles were comparable between F3-rTMS and cgiTBS, with 74.5 % of participants ($n = 190/254$) experiencing at least one adverse event possibly, probably, or definitely related to TMS. The majority of adverse events were transient and mild, with a sizeable number requiring simple treatments or small adjustments to TMS intensity and coil positioning. The F3-rTMS group had a significantly greater proportion of participants that required small adjustments to TMS to tolerate treatment compared to the cgiTBS group. Serious adverse events were rare, with one serious event in each treatment arm possibly related to TMS (F3-rTMS- psychotic episode, cgiTBS-manic episode).

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Conclusion: F3-rTMS and cgiTBS are comparably safe, tolerable and highly acceptable interventions for treatment-resistant depression. BRIGhTMIND systematically collected data from a large sample, providing evidence to meet the information needs of patients, clinicians and policy makers.

1. Introduction

Major depressive disorder (MDD) is a leading cause of disability [1], with 20–30 % of people with MDD not responding to two or more pharmacological treatments, known as treatment-resistant depression (TRD) [2,3]. Alternative treatments for TRD include transcranial magnetic stimulation (TMS) which delivers magnetic pulses over the scalp to alter neural circuit activity. In TRD, TMS is commonly delivered over the left dorsolateral prefrontal cortex (DLPFC) using high frequency repetitive TMS (rTMS) over 20–30 daily sessions [4]. An alternative form of administering the TMS is theta burst stimulation (TBS), including "excitatory" intermittent theta burst (iTBS) and "inhibitory" continuous theta burst stimulation (cTBS) protocols [5]. It has been suggested that iTBS has been associated with more favourable response rates in depression than cTBS [5].

rTMS and iTBS are shown to be equally effective in TRD [6], with sustained improvements observed six months after treatment [7,8]. In addition, iTBS is more cost effective than rTMS due to requiring shorter administration time, thus increasing treatment capacity [9]. More recent therapeutic approaches have utilised the shorter administration time of iTBS to devise accelerated and personalised protocols using magnetic resonance imaging (MRI) with some evidence of therapeutic benefit [10]. However, it is also important to explore patients' experience, satisfaction and factors associated with tolerability, to optimise adherence, therapeutic outcomes and implementation of such treatments [11].

Treatment acceptability can be seen as a multifaceted construct ranging from before, during and after participating in a health intervention, balancing positive and negative aspects of the intervention [12]. It encompasses affective attitude, burden, ethicality, intervention coherence, opportunity costs, perceived effectiveness, and self-efficacy of patients and those delivering the interventions [12]. Since it is a complex construct that includes value-based judgements that might vary among individual patients, clinicians and policy makers, then a range of quantitative and qualitative data is required to address their information needs.

Acceptability of TMS in depression has been widely reported on in relation to treatment adherence, with no differences in dropout rates for rTMS or TBS protocols compared to sham protocols [13,14]. Other facets of TMS acceptability in particular comparing rTMS and iTBS have been less studied. One telephone survey showed individuals with depressive illness had positive views about TMS, found it to be an acceptable treatment and preferable to the prospect of receiving more invasive electroconvulsive therapy [15]. Further, preliminary qualitative work has highlighted the experience of TMS (including physical response to treatments), mindfulness and awareness experienced during sessions, and the importance of the rapport with the clinicians is associated with acceptability in TRD [16]. From a practitioner perspective, providing a relaxing and comfortable environment, engaging in constructive therapeutic conversations as well as supportive long-term management, has been highlighted as improving the patient experience [17].

Related to acceptability is the tolerability and safety of health interventions. While TMS is low risk in terms of safety and generally well-tolerated [18], it is important to explore and understand factors associated with the incidence and severity of treatment-emergent adverse events. Distressing adverse events reported with TMS in depression studies typically include headaches, discomfort at stimulation site, pain at stimulation site, dizziness, insomnia, anxiety, tinnitus and muscle twitching, with only headaches and discomfort at stimulation site significantly higher in active TMS versus sham [19]. Typically, these are reported to be generally mild and transient [19]. More serious adverse events with the potential for harm including the risk of syncope, seizures, suicide attempts and mood switches to hypomania in active TMS are considered rare [19]. Reviews also show adverse event profiles are similar between rTMS and iTBS protocols, however further randomised controlled trials are needed, particularly of novel TMS protocols [20,21]. For instance, the large THREE-D trial further indicated significantly higher pain scores for iTBS compared to rTMS when both were delivered at 120 % resting motor threshold (rMT) [22]. Therefore, further exploration of such protocols are imperative, any may help inform practice guidelines and assist in weighing up the risks and benefits for individual treatment decisions.

In a small pilot study of 27 TRD patients, individualised connectivity guided iTBS (cgiTBS) based on maximum effective connectivity from the right anterior insula (rAI) to left DLPFC led to a non-significant increased response in depression symptoms at 3 months than rTMS using the same personalised, neuronavigated approach (89 % versus 44 % in 18 completers) [23]. Consequently, BRIGhTMIND a large double-blind randomised controlled trial in TRD, examined whether cgiTBS based on the aforementioned targeting method would show superior clinical efficacy compared to standard left DLPFC (operationalised as the F3 EEG recording site on the scalp) structural MRI neuronavigated repetitive transcranial magnetic stimulation (F3-rTMS) [8]. Theoretically, iTBS might induce long-term potentiation in more distal brain areas compared to rTMS [24]. Therefore, connectivity-guided iTBS rather than connectivity-guided rTMS was selected. Further considering structural MRI neuronavigated iTBS is non-inferior to structural MRI neuronavigated rTMS [7,22], any differences between the two arms would have been due to personalisation rather than the form of TMS.

Here within, we report on a secondary objective of the BRIGhTMIND study using qualitative and quantitative data to investigate the acceptability, impression of change, adverse event profiles, and tolerability of cgiTBS versus F3-rTMS. Further exploring participants' subjective experiences and the associations between the acceptability and safety/tolerability facets. This is pertinent considering the comparison of different TMS protocols (particularly including novel personalised target sites) on treatment acceptability facets other than adherence, and safety/tolerability remains underexplored. We anticipated that cgiTBS would be associated with greater perceived improvement and higher acceptability compared to F3-rTMS. Furthermore, based on prior literature we expected cgiTBS and F3-rTMS to be equally safe and tolerable.

2. Method

The BRIGhTMIND trial received research ethics committee approval and health research authority approval from the East Midlands Leicester Central Research Ethics Committee (no. 18/EM/0232). All participants gave written informed consent.

2.1. Study design

Two hundred and fifty-five participants were randomised to the BRIGhTMIND trial ($n = 127$ F3-rTMS, $n = 128$ cgiTBS). The trial design and methods are outlined in two published trial protocols [25,26]. Clinical efficacy results and reporting of serious adverse events are detailed in Morriss et al. [8]. Briefly, participants completed a telephone screening, baseline assessment, baseline magnetic resonance imaging (MRI), 20 sessions of TMS over 4–6 weeks, follow-up assessments at 8, 16 and 26 weeks post randomisation and a 16 week repeat MRI scan.

Eligible participants were aged ≥18 years and diagnosed with current major depressive disorder (DSM-5 criteria-[27]), that was rated as moderate to severe (≥16 on the 17-item GRID Hamilton Depression Rating Scale [28]) and resistant to treatment (≥ 2 Massachusetts General Hospital Staging Score [29] which was adapted for new treatment options [25]).

Exclusion criteria included a history of bipolar disorder or depression secondary to other mental health disorders; neurological conditions; standard MRI contraindications; major unstable medical illness under investigation/treatment; change in prescribed medication in 2 weeks before the baseline assessment; current use of lamotrigine gabapentin or pregabalin; intermittent benzodiazepines or hypnotics (or daily prescription >5-mg diazepam equivalents, >7.5-mg zopiclone equivalent); history of TMS treatment, high risk of suicidality; other TMS treatment complicating factors (e.g. irremovable facial piercings or hairstyles impeding coil placement); clinical trial involvement at time of consent or 6 months previously; unable to read or understand English.

Two participants entered the study in error, one was judged at risk of suicidality at baseline and one participant with a history of a transient ischaemic attack 20 years beforehand. Both participants completed treatment and the study with no incidents and were retained in the study analysis. There was no difference in the primary outcome between the novel cgiTBS arm and the F3-rTMS arm, with a sustained substantial improvement in depression symptoms (an average of >7 points on the GRID-HDRS-17 at 8, 16 and 26 weeks) [8].

2.2. Interventions

Participants received twenty daily sessions of cgiTBS or F3-rTMS over 4–6 weeks (3000 pulses per session) via a Magstim Horizon Performance Stimulator with StimGuide Navigated TMS package, using a 70 mm figure-of-eight coil. Resting motor threshold (rMT) was determined at the first treatment session and tested again on the sixth treatment session for both treatment arms.

CgiTBS was delivered at 80 % rMT, with 50-Hz bursts of three pulses repeating every 200 ms (5-Hz). Bursts were presented in 10-s cycles (2 s stimulation, 8 s rest), with twenty cycles per run (600 pulses per run). Five runs were delivered each session with 5-min inter-run intervals. The cgiTBS brain target was determined using the participant's baseline rsFMRI scan and defined based on Granger Causality Analysis as the location within the lDLPFC receiving maximal effective connectivity from the right anterior insula (MNI co-ordinates: $x = 30$ mm, $y = 24$ mm, $z = -14$ mm) [25,26].

F3-rTMS was delivered using the widely used protocol, with 75 × 4-s trains of 10 Hz interspersed by 26-s intertrain intervals at 120 % rMT [30]. The brain target was determined using the participants' structural MRI to target a standard MNI co-ordinate (x = −41, y = 43, z = 32 mm), which was selected a priori as the parenchymal voxel closest to the "F3" site in a standard brain.

Therefore, the number of pulses per session, duration of session, and number of sessions were identical between the treatment arms. However, the rMT was lower in the cgiTBS arm, as is standard to improve the tolerability of iTBS. The two groups further differed in stimulation frequency (iTBS or rTMS) and site of stimulation (resting state effective connectivity versus structural MRI).

2.3. Acceptability

At each TMS session and 8, 16 and 26 week post-randomisation follow-ups, participants completed a 5-point Likert acceptability measure designed for the BRIGhTMIND study (1 = "unacceptable negative effects outweigh benefits", 2 = "unacceptable negative effects and benefits about equal", 3 = "neutral, unsure or waiting to find out", 4 = "acceptable benefits and negative effects about equal", 5 = "acceptable benefits outweigh negative effects").

They also completed an adapted version of the patient global impression of change measure (PGIC [31]) at the same time points. This was measured on a 5-point Likert scale (1 = "much worse", 2 = "somewhat worse", 3 = "just the same", 4 = "somewhat better", 5 = "much better"). The modified PGIC (mPGIC) was adapted based on the advice of our Patient and Public Involvement Lived Experience Advisory Panel of people who have experienced severe depression, some of whom also had received rTMS before. The change was to reflect language that patients would use (i.e. "better" rather than "improved", "a bit" rather than "minimally" and "just the same" rather than "no change").

A proportion of participants from both treatment groups were selected and invited to complete a semi-structured qualitative interview to provide their views on the treatment received (see Appendix A for interview questions). This purposive sampling aimed to capture participants from both treatment arms across study sites, reflecting a mix of demographic characteristics and adherence/non-adherence to treatment and follow-up assessments. Interviews were carried out face-to-face or via telephone between October 2019 and March 2022 by researchers working on the main BRIGhTMIND study.

Participants were also given the option after each TMS session and follow-up appointment to provide written open-ended comments on their experience of the treatment and the study, which were also used in the qualitative analysis.

2.4. Safety and tolerability

Safety checks were made by TMS staff immediately before each treatment session, checking alcohol consumption, medication checks for hypnotics, benzodiazepines, gabapentin, pregabalin or lamotrigine, checking for severe anxiety and general feelings of being unwell (including COVID-19 symptoms).

Participants completed a self-report side effects checklist after every TMS session, including the following common side effects (headaches, scalp discomfort, dizziness, jaw ache, nausea, watering eyes and tinnitus). Participants were also asked to tick an uncommon side effects box if they experienced any other side effects not listed above, and provide open-ended comments to describe these uncommon side effects.

The self-report side effect checklists contributed to the recording of adverse event (AE logs) which were recorded by the BRIGhTMIND study staff. The AE data is reported here within as it was verified by the research team.

AEs and serious AEs (SAE) were recorded using internationally agreed definitions [32]. Seizures were reported as SAEs with all further treatment stopped. Syncope was recorded as an AE, and only as an SAE if the event required hospital admission. Any participant with high risk of suicidality or developing a SAE was referred to relevant clinical services. For safety reasons, participants with worsening depression at 16 and 26 week follow-ups were reviewed by clinical experts in treatment resistant depression.

BRIGhTMIND study staff recorded the details of the event, start/stop date and outcome of the AE. Principal investigators (psychiatrists at each site) made the decisions on severity of AEs (mild, moderate, severe or fatal), relatedness (not related, unlikely, possible, probably or definitely related), expectedness (yes or no) and whether the AE was serious (yes or no). Decisions on treatment (none, concomitant medication, non-drug therapy, combination of concomitant medication and non-drug therapy) as well as actions (none, study interrupted, study discontinued) were made by TMS clinical staff with consultation of the psychiatrist principal investigators.

An external independent data monitoring ethics committee reviewed all un-blinded accumulating data on trial conduct and participant safety and reported their recommendations with regards to the trial continuing to the trial steering committee. All SAEs were reported to the sponsor (Nottinghamshire Healthcare NHS Foundation Trust, UK).

A standard operating procedure was developed for participants unable to tolerate the cgiTBS or F3-rTMS protocols as per the MRI data, to maximise tolerability of TMS protocols and reduce risk of drop out and

lack of adherence (see Appendix A for standardized adjustment steps).

2.5. Data analysis

Our published statistical analysis plan states that comparison of quantitative acceptability and safety outcomes by treatment arm would be reported descriptively [33]. However, we conducted additional exploratory statistical analyses here to determine if there were significant differences between the cgiTBS and F3-rTMS groups and associations between acceptability, impression of change and safety.

Chi-squared or Fisher Exact tests were used to compare the proportion of participants (cgiTBS versus F3-rTMS) on *acceptability ratings* (unacceptable, neutral, acceptable), *benefits/negatives of TMS* (negatives outweigh benefits, benefits and negatives about equal/neutral, benefits outweigh negatives), *impression of change* (much worse, somewhat worse, just the same, somewhat better, much better), *experiencing AEs* (yes or no) and requiring *tolerability adjustments* (yes or no). Friedman tests were used to assess whether acceptability, benefits/negatives of TMS and impression of change differed across the 20th treatment session, 8, 16 and 26 week follow-up (treatment groups collapsed). Correlation analysis was used to examine the associations between impression of change, acceptability, benefits/negatives of TMS and number of AEs (Spearman correlations for associations between ordinal variables only, Kendall's tau correlations for associations between continuous and ordinal variables). Statistical tests were performed in IBM SPSS Statistics (v28.0.1.1), were two-tailed, with alpha set to 0.05. As this was an exploratory analysis, corrections of multiple comparisons were not applied.

Qualitative interviews and recorded written comments on participants' experience of treatment were pooled across treatment groups and analysed using an inductive thematic framework approach [34]. Interview transcripts were repeatedly read by two researchers (CB and LW) for data familiarity [35], with the first several transcripts independently coded by both researchers for consistency and reliability [36], with CB reading and coding further transcripts. The two aforementioned researchers and qualitative principal investigator (LT) organised the codes into an overarching framework of themes and subthemes. The framework of themes and quotes were presented to our Lived Experience Advisory Panel, who aided with refinement and interpretation of themes. Coding and themes were input into a framework matrix using NVivo 12. The written comments were initially coded by LW, with CB reviewing codes, to examine whether any additional subthemes/themes could be identified. Following this, the framework and naming of themes was further refined and approved by the qualitative analysis team.

3. Results

3.1. Sample

In total 255 participants were randomised to the BRIGhTMIND trial (F3-rTMS $n = 127$; cgiTBS $n = 128$) and 91.8 % of participants completed all twenty TMS sessions. Completion rates for the 8, 16, and 26 week follow-ups were 87.5 %, 87.8 %, and 80.8 % respectively. A flowchart of participants through the trial can be found in supplemental Fig. 1. One participant in the F3-rTMS group was excluded from the safety and acceptability analysis after being withdrawn before any treatment was provided due to experiencing a suspected two-second seizure during the first motor threshold testing. Demographic and clinical characteristics for the 254 participants are included in the safety population are reported in Table 1.

The duration of current major depressive episodes was calculated using the date of randomisation and start date of the episode. Other employment includes part-time, sheltered, voluntary employment and higher education.

Table 1
Sample characteristics.

		F3-rTMS	cgiTBS
		$n = 126$	$n = 128$
Age- years, Mean (SD)		43.8 (13.1)	43.7 (15.0)
Gender, *n* (%)	Men	64 (50.8 %)	58 (45.3 %)
	Women	62 (49.2 %)	70 (54.7 %)
Ethnicity, *n* (%)	White British	105 (83.3 %)	108 (84.4 %)
	White Other	10 (7.9 %)	8 (6.3 %)
	Asian or Asian British	6 (4.8 %)	6 (4.7 %)
	Mixed	3 (2.4 %)	4 (3.1 %)
	Black or Black British	1 (0.8 %)	0 (0 %)
	Chinese	0 (0 %)	1 (0.8 %)
	Other	1 (0.8 %)	1 (0.8 %)
Employment/Education, *n* (%)	Full time	38 (30.2 %)	37 (28.9 %)
	Other employment	36 (28.6 %)	26 (20.3 %)
	Retired	13 (10.3 %)	17 (13.3 %)
	Unemployed	39 (31.0 %)	48 (37.5 %)
Baseline HDRS-17, Mean (SD)		24.0 (4.8)	22.9 (4.7)
Baseline GAD-7, Mean (SD)		13.4 (4.7)	13.1 (4.6)
Antidepressant use at baseline *n* (%)		93 (73.8 %)	104 (81.3 %)
MGH treatment resistance category *n* (%)	Low: 2–3.5	42 (33.3 %)	45 (35.2 %)
	Medium: 4–6	35 (27.8 %)	37 (28.9 %)
	High: ≥ 6.5	49 (38.9 %)	46 (35.9 %)
Duration of current major depressive episode (months), Median (IQR)		69.1 (27.4–127.6)	79.3 (24.9, 163.3)

Abbreviations: F3-rTMS = F3 repetitive transcranial magnetic stimulation; cgiTBS = connectivity guided intermittent theta burst stimulation; HDRS-17 = 17-item Hamilton Depression Rating Scale; GAD-7 = Generalised Anxiety Disorder Questionnaire; MGH-S = Massachusetts General Hospital Staging Score.

3.2. Quantitative acceptability

Acceptability ratings were available for 237 participants at the 20th TMS session, $n = 222$ at the 8 week, $n = 221$ at the 16 week, and $n = 203$ for the 26 week follow-up (Fig. 1). No significant differences (proportion of participants) were found between the two treatment groups for acceptability, benefits/negatives of TMS, or mPGIC at the 20th treatment session or three follow-up time points ($ps > 0.1$). Acceptability increased over the course of TMS (Supplemental Fig. 2), and out of the 237 participants at the 20th treatment session, 75.9 % ($n = 180$) rated TMS acceptable, 21.9 % ($n = 52$) were neutral, with 2.1 % ($n = 5$) finding treatments unacceptable. For these participants, 44.3 % ($n = 105$) reported benefits of TMS outweighed negatives, 55.3 % ($n = 131$) rated benefits and negatives about equal/neutral, and 0.4 % ($n = 1$) suggested negatives of TMS outweighed benefits. At the 20th treatment session mPGIC showed that 18.6 % of participants ($n = 44$) felt much better, 46.8 % ($n = 111$) felt somewhat better, 31.2 % ($n = 74$) felt the same, 3.0 % ($n = 7$) felt somewhat worse, and 0.4 % ($n = 1$) felt much worse.

For both treatment groups combined, rates of acceptability (X^2 [3, 187] = 8.65, $p = 0.03$, post hoc comparison all $ps > 0.05$), benefits/negatives of TMS (X^2 [3, 187] = 0.35, $p = 0.95$) and mPGIC (X^2 [3, 187] = 9.64, $p = 0.02$, post-hoc comparisons all $ps > 0.05$) were maintained between the final 20th treatment session and three follow-up time points. Positive associations were observed between mPGIC at the final

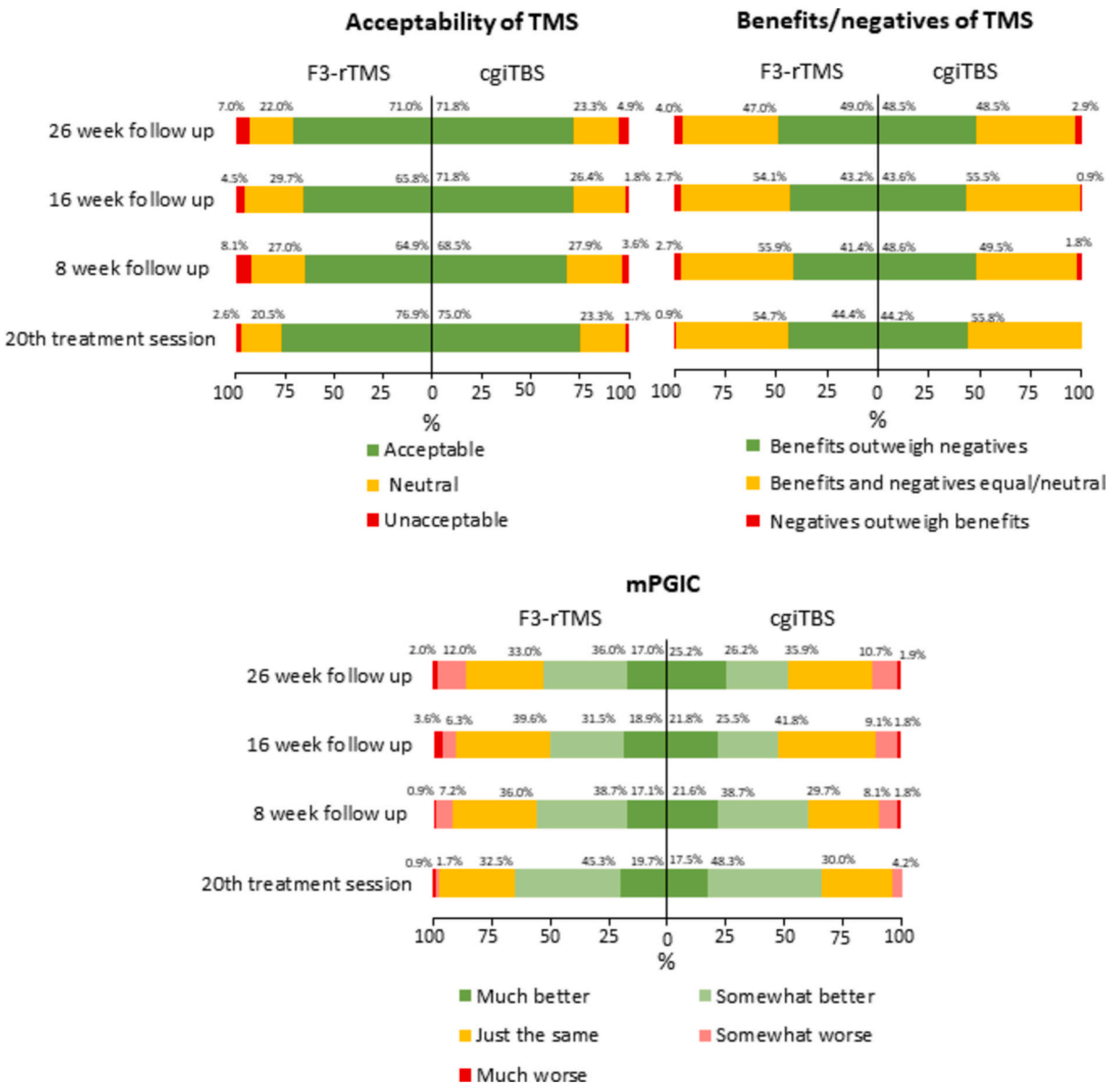

Fig. 1. Acceptability, positives/negative effects of TMS and mPGIC at the 20th treatment and 8, 16 and 26 week follow-ups.

treatment session and both acceptability and benefits/negatives of TMS at the final treatment session and 8, 16 and 26 week follow-up points (*acceptability*- $r = 0.59$, $r = 0.57$, $r = 0.44$, $r = 0.35$; *benefits/negatives of TMS*- $r = 0.67$, $r = 0.64$, $r = 0.55$, $r = 0.46$, all *ps* < 0.001, 20th TMS session, 8 week, 16 week and 26 week follow-up respectively).

Our findings overall suggest that TMS is acceptable in the short and longer term for individuals with treatment-resistant depression, with greater self-reported improvement associated with higher acceptability and TMS benefits outweighing negatives.

3.3. Qualitative acceptability

Fifteen participants who were randomised to treatment completed qualitative interviews (cgiTBS, $n = 8$; F3-rTMS, $n = 7$). A further 582 written comments made by 171 participants randomised to the BRIGhTMIND trial, regarding their experience of TMS and the study were also included in the qualitative analysis. Three main acceptability themes were identified from the data; (i) *The TMS experience (ii) TMS response variability,* (iii) *Lay theories of effectiveness.* See Table 2 for detailed descriptions of themes and illustrative quotes.

3.4. Adverse events

3.4.1. Adverse events unrelated or unlikely to be related to TMS or the study

Overall, 263 adverse events were recorded as being unrelated or unlikely to be related to the study, affecting 101 (39.8 %) participants (F3-rTMS $n = 51/126$; cgiTBS $n = 50/128$, X^2 [1, 254] $= 0.05$, $p = 0.82$). The majority of AEs were mild in severity (73.3 %, 193 AEs) see supplemental Table 1. Of these 263 AEs, 14 were recorded as serious AEs, including two fatal and twelve further SAEs requiring hospital admission ($n = 7$ severe and $n = 5$ moderate severity) [8]. The two fatal AEs included one myocardial infarction and one opiate poisoning, with both participants dying close to the 26 week follow-up assessment, with both reported as unlikely to be related to TMS treatments [8].

3.4.2. Adverse events possibly, probably or definitely related to TMS

In total, 190 (74.5 %) of participants experienced at least one AE that was possibly, probably or definitely related to TMS treatment (F3-rTMS $n = 96/126$; cgiTBS $n = 94/128$, X^2 [1, 254] $= 0.72$, $p = 0.61$). There were 1573 of these AEs recorded (F3-rTMS = 715 AEs; cgiTBS = 858

Table 2
Acceptability theme details and illustrative quotes.

The TMS experience	Illustrative quotes
A preference for TMS over previously tried treatments was reported in those with perceived improvements. Some participants who reported no improvement found TMS acceptable, whereas others found treatment less acceptable due to side effects and lack of response. Several individuals indicated that the significant commitment of attending twenty daily sessions would be acceptable if there were sustained improvements. The supportive and caring nature of TMS staff helped participants feel more comfortable and at ease. They preferred when there was a continuity of the same staff throughout the course of treatment and felt the treatment varied with more infrequent or different staff. One participant suggested that more frequent staff training was needed as their experience of TMS was *"less straightforward"* with staff who provided it less frequently (Participant 42 cgiTBS written comment). The physical sensation of TMS was sometimes described as unusual or unexpected, with some participants suggesting they felt "tingling" or "tapping" on the scalp. There was also variability in physical discomfort, ranging from no discomfort through to TMS feeling painful. Participants reported that tolerability improved over the treatment course.	➢ *"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 F3-rTMS written comment) ➢ *"The length of the treatments were long for the benefits provided"* (Participant 30 F3-rTMS written comment) ➢ *"The team that I worked closely with were very supportive and helpful - they made my time there easier"* (Participant 141 F3-rTMS written comment) ➢ *"I think that relationship really helped me to ensure my attendance […] I reckon that if I was seeing a different person every day and having to explain my story again, that would be a bit problematic"* (Participant 10 cgiTBS qualitative interview) ➢ *"Tapping feeling was fine - not uncomfortable"* (Participant 148 cgiTBS written comment) ➢ *"Very painful - but worth trying it, prepared to do again"* (Participant 11 F3-rTMS written comment) ➢ *"Initially I wasn't expecting the feeling of the TMS and it was a lot easier to tolerate over the weeks"* (Participant 50 cgiTBS written comment)

TMS response variability	Illustrative quotes
There was also inter-individual variability in treatment benefits. Perceived improvements were first noticed over the course of the twenty treatment sessions, with some participants reporting improvements only after completing the TMS course. Responses ranged from subtle to significant, with reports of sustained improvements at the 26 week follow-up. Others witnessed treatment effects wearing off over time, from immediately after TMS completion to across the 8, 16 and 26 week follow-up time points. While some reported improvements in overall depression, others described noticing improvements in specific symptoms. This included mood, sleep, cognitive abilities, anxiety/irritability, motivation, suicidal thoughts and physical symptoms such as headaches.	➢ *"It was a very slow process, but […] I could feel it after a week or so that something was happening." (Participant 7 cgiTBS qualitative interview)* ➢ *"The TMS treatment has really worked well for my anxiety and depression. Every two to three days I notice improvement even now after 17 sessions" (Participant 87 F3-rTMS written comment)* ➢ *"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 F3-rTMS written comment)* ➢ *"Improved concentration. Less anxiety. Improved sleep" (Participant 46 cgiTBS written comment)*

Lay theories of effectiveness	Illustrative quotes
Participants provided a variety of their own explanations and interpretations for the perceived effectiveness of TMS. For a number of participants, they related improvements directly to the TMS, others felt improvements were due to a combination of TMS and other factors such as psychological therapy, medications, and environmental changes. There were also suggestions that having a very regular routine required for the treatment and interacting with TMS staff may have also had therapeutic benefits. Several participants reported a lack of confidence in the level of treatment received, due to the perception of inconsistent coil placement across sessions, and of coil movement away from the scalp and target location during treatments. Neuronavigation data indicated the median distance and angle difference from first and subsequent sessions was about 0.5 cm and 7° for both treatment groups [8]. Some participants proposed that environmental stressors may have impeded their response to TMS. There was also the perception that receiving more TMS sessions could have led to greater improvements for a number of individuals, and those with perceived short-lived benefits expressed the need for further top-up treatments.	➢ *"I think it's probably a combination of the factors really, but yes, to feel so quickly better I put down mainly to the RTMS, yeah" (Participant 2 F3-rTMS qualitative interview)* ➢ *"so just purely going along for half an hour or an hour five days a week and meeting with the people who are doing the treatment was in itself a bit of a mood lifting experience" Participant 6 cgiTBS qualitative interview* ➢ *"Even though it was in the same place every time sometimes it would feel like it was better connected […] than other times like the pulse was stronger" (Participant 12 cgiTBS qualitative interview)* ➢ *"I'd like to think I could get more treatments in the future for a greater benefit." (Participant 65 F3-rTMS written comment)*

AEs). The frequency of AEs for both treatment groups were positively skewed (Supplemental Fig. 3), and the median number of these AEs for F3-rTMS and cgiTBS were 3.0 (IQR = 1–7) and 2.50 (IQR = 0–8) respectively ($U = 7749.5, p = 0.59$.) The twenty TMS sessions were to be completed in 4–6 weeks (28–42 days). Collapsed across both treatment groups, Fig. 2 shows that the start date of AEs decreased over time, with a minimal number of AEs starting 43 days or more after randomisation (1.9 %, 30 AEs). Of the 1573 AEs possibly, probably or definitely related to TMS, the majority were transient with 65.7 % (1033 AEs) resolved the same day, 10.6 % (167 AEs) within 1 day, 8.8 % (139 AEs) within 2–6 days and 7.9 % (124 AEs) in 1–4 weeks. Ninety-nine AEs (6.3 %) took 4 weeks or longer to resolve, with the duration of 0.7 % (11 AEs) classed as unknown, continuing, or unobtainable. No significant association was observed between number of TMS sessions completed and number of AEs possibly related to TMS ($r = 0.05, p = 0.44$).

Exploration of specific AEs demonstrated profiles were comparable between the F3-rTMS and cgiTBS groups (Table 3), with the exception of a greater proportion of cgiTBS participants experiencing fatigue (15.6 % $n = 20/128$, versus F3-rTMS, 7.1 % $n = 9/126$). Of the 254 participants included in the safety population, over half experienced head pain/ headache/ scalp discomfort (62.6 %, $n = 159$), with this the most reported AE, followed by neck pain, jaw ache/mouth pain, dizziness/light headedness, nausea and watering eyes (Table 3). Eleven percent of participants experienced tinnitus (10.6 %, $n = 27$). Further AEs of interest which affected less than 10 % of participants, included mood disturbances (7.9 %, $n = 20$) and cognitive complaints (5.1 %, $n = 13$). The majority of AEs were mild in severity (94.9 %, 1493 AEs), with 4.6 % moderate (73 AEs) and 0.4 % severe (7 AEs).

Just 7.2 % (113 AEs) possibly, probably or definitely related to TMS, required treatment such as concomitant medication, non-drug therapy or a combination of both. There were 33 AEs requiring treatment for 15 F3-rTMS participants and 80 AEs for 19 cgiTBS participants (X^2 [1, 254] $= 0.47, p = 0.49$). In terms of severity, 5.9 % (93 AEs) were mild, 1.0 % (16 AEs) moderate, and 0.3 % (4 AEs) severe (Supplemental Table 1). Two of these severe AEs, one each in cgiTBS and F3-rTMS groups, were reported as serious, with both participants requiring hospitalisation (manic episode and a psychotic episode with severe anxiety and depression). The psychotic episode occurred 1 month post the course

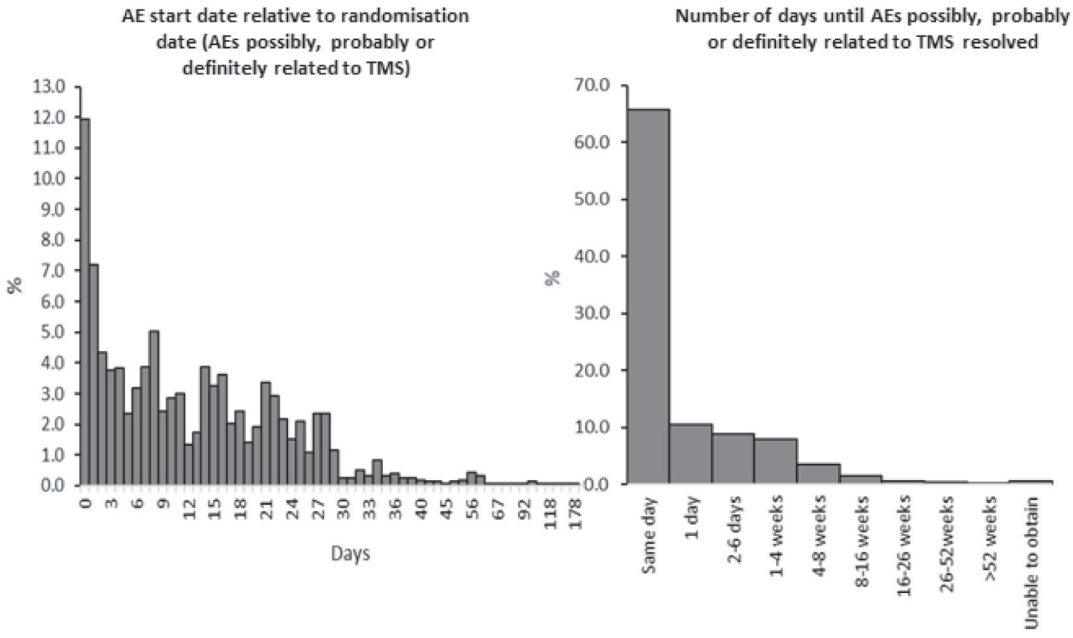

Fig. 2. Start date and number of days to resolve AEs possibly probably or definitely related to TMS.

Table 3
Specific profiles for AEs possibly probably or definitely related to TMS.

	Number of participants affected		Test of differences (Number of participants)	Total number of AEs (including serious)		AE severity (including serious)		
	F3-rTMS (n = 126)	cgiTBS (n = 128)		F3-rTMS	cgiTBS	Mild	Moderate	Severe
Head pain/headache/ scalp discomfort	83 (65.9 %)	76 (59.4 %)	$X^2 = 1.15$, $p = 0.28$	295 (18.8 %)	373 (23.7 %)	641 (40.8 %)	25 (1.6 %)	2 (0.1 %)
Jaw ache/mouth pain	42 (33.3 %)	32 (25.0 %)	$X^2 = 2.14$, $p = 0.14$	109 (6.9 %)	99 (6.3 %)	203 (12.9 %)	5 (0.3 %)	0 (0 %)
Neck pain	40 (31.7 %)	40 (31.3 %)	$X^2 = 0.01$, $p = 0.93$	104 (6.6 %)	90 (5.7 %)	192 (12.2 %)	2 (0.1 %)	0 (0 %)
Dizziness/light-headedness	31 (24.6 %)	32 (25.0 %)	$X^2 = 0.01$, $p = 0.94$	55 (3.5 %)	91 (5.8 %)	140 (8.9 %)	5 (0.3 %)	1 (0.1 %)
Nausea	24 (19.0 %)	17 (13.3 %)	$X^2 = 1.56$, $p = 0.21$	38 (2.4 %)	28 (1.8 %)	65 (4.1 %)	1 (0.1 %)	0 (0 %)
Watering eyes	21 (16.7 %)	16 (12.5 %)	$X^2 = 0.89$, $p = 0.35$	32 (2.0 %)	31 (2.0 %)	63 (4.0 %)	0 (0 %)	0 (0 %)
Tinnitus	11 (8.7 %)	16 (12.5 %)	$X^2 = 2.05$, $p = 0.15$	25 (1.6 %)	56 (3.6 %)	77 (4.9 %)	4 (0.3 %)	0 (0 %)
Mood disturbance	11 (8.7 %)	9 (7.0 %)	$X^2 = 0.26$, $p = 0.62$	15 (1.0 %)	14 (0.9 %)	22 (1.4 %)	5 (0.3 %)	2 (0.1 %)
Limb/trunk abnormal sensations	9 (7.1 %)	8 (6.3 %)	$X^2 = 0.08$, $p = 0.78$	15 (1.0 %)	9 (0.6 %)	24 (1.5 %)	0 (0 %)	0 (0 %)
Fatigue	9 (7.1 %)	20 (15.6 %)	**$X^2 = 4.52$, $p = 0.03$**	12 (0.8 %)	33 (2.1 %)	43 (2.7 %)	2 (0.1 %)	0 (0 %)
Cognitive complaints	4 (3.2 %)	9 (7.0 %)	$X^2 = 1.94$, $p = 0.16$	4 (0.3 %)	13 (0.8 %)	10 (0.6 %)	7 (0.4 %)	0 (0 %)
Sleep difficulties	3 (2.4 %)	4 (3.1 %)	$X^2 = 0.13$, $p = 0.72$	3 (0.2 %)	5 (0.3 %)	4 (0.3 %)	4 (0.3 %)	0 (0 %)
Syncope	2 (1.6 %)	0 (0 %)	*$p = 0.25$	2 (0.1 %)	0 (0 %)	0 (0 %)	2 (0.1 %)	0 (0 %)
Vomiting	1 (0.8 %)	1 (0.8 %)	*$p = 1$	1 (0.1 %)	1 (0.1 %)	1 (0.1 %)	1 (0.1 %)	0 (0 %)
Visual distortion	1 (0.8 %)	2 (1.6 %)	*$p = 1$	1 (0.1 %)	3 (0.2 %)	4 (0.3 %)	0 (0 %)	0 (0 %)
Nosebleed	1 (0.8 %)	0 (0 %)	*$p = 0.50$	3 (0.2 %)	0 (0 %)	3 (0.2 %)	0 (0 %)	0 (0 %)
Other physical complaints	1 (0.8 %)	3 (2.3 %)	*$p = 0.62$	1 (0.1 %)	4 (0.3 %)	1 (0.1 %)	4 (0.3 %)	0 (0 %)
Self-harm	0 (0 %)	2 (1.6 %)	*$p = 0.50$	0 (0 %)	4 (0.3 %)	0 (0 %)	3 (0.2 %)	1 (0.1 %)
Dissociative seizures/ collapsing	0 (0 %)	1 (0.8 %)	*$p = 1$	0 (%)	4 (0.3 %)	0 (0 %)	3 (0.2 %)	1(0.1 %)

Abbreviations: F3-rTMS = F3 repetitive transcranial magnetic stimulation; cgiTBS = connectivity guided intermittent theta burst stimulation.

TMS, and the manic episode after the 14th treatment session, with no further TMS provided [8]. One participant in the cgiTBS group also reported episodes of loss of consciousness. These events occurred outside of the TMS sessions and were confirmed by neurology as being dissociate seizures, rather than epileptic seizures, therefore not recorded as serious AEs [8]. TMS sessions were discontinued for this participant. One further participant in the cgiTBS group also had an episode of vertigo rated as severe, which commenced 37 days post randomisation and took 59 days to resolve. The majority of the AEs requiring treatment were resolved the same day or within 6 days (95 AEs), with 5 AEs taking 1–4 weeks to resolve and 13 AEs taking 4 weeks or longer.

An additional two participants in the F3-rTMS group also experienced an episode of syncope. No treatment was required, however TMS was suspended for that particular day, but with completion of the remainder of their TMS courses without further incident [8].

The number of adverse events possibly, probably or definitely related

to TMS, including AEs requiring treatment or AEs lasting more than 6 days, were not significantly associated with acceptability or mPGIC at the 20th treatment session or three follow-up time points (*ps* > 0.05). Post-hoc exploratory analysis of our recently published response trajectories [37], revealed members of improver classes found TMS more acceptable than those assigned to a non-improvement class or worsening class. The worsening group experienced significantly more AEs possibly, probably or definitely related to TMS compared to improver classes and non-improvers. The delayed-moderate improvement trajectory also had significantly more AEs compared to non-improvers (See appendix A for further details including response trajectory definitions).

3.4.3. Adverse events possibly, probably or definitely related to study MRI scan

Fourteen additional AEs were possibly, probably or definitely related to the study MRI scans (Supplemental Table 1) and were experienced by 4.3 % of participants (F3-rTMS $n = 2$; cgiTBS $n = 9$). This occurred for nine participants at the baseline scan and two participants for the 16 week repeat follow-up scan. All AEs were mild in severity, with the exception of one severe serious AE, with the participant admitted to hospital for nausea and vomiting following the baseline MRI scan [8]. This participant also experienced nausea, head discomfort and vomiting following the 16 week MRI scan which were mild in severity. There were a further 3 AEs for headaches, 3 AEs for limb/trunk pain, 2 AEs for tinnitus and 2 AEs for neck pain.

3.5. Tolerability

A significantly greater number of participants in the F3-rTMS group compared to cgiTBS group (23.0 % $n = 29/126$ versus 7.0 % $n = 9/128$) adjusted treatment as they were unable to tolerate the TMS protocol (X^2 [1, 254] = 12.75, $p = 0.0004$). Nineteen participants had a stimulation intensity reduction only (F3-rTMS $n = 16$; cgiTBS $n = 3$), seven participants had adjustments to site of stimulation only (F3-rTMS $n = 4$; cgiTBS $n = 3$), nine participants had a combination of stimulation intensity reduction and adjustments to site of stimulation, occurring either at the same session or at different sessions (F3-rTMS $n = 7$; cgiTBS $n = 2$) and for three participants, no information on tolerability adjustments were available (F3-rTMS $n = 2$; cgiTBS $n = 1$). Of the 33 participants requiring treatment for possible, probably or definitely related AEs, six adjusted treatment for tolerability (F3-rTMS $n = 3$; cgiTBS $n = 3$). Adjustments occurred across the twenty sessions, although this number decreased over time (See Supplemental Table 2).

On occasion, TMS clinicians tried to go back to correct stimulation intensity and correct target site but could only do so infrequently. Six of the twenty-eight participants that required stimulation intensity reduction, did go on to have an increase in stimulation intensity at a later point in their treatment course, however this was still below the expected intensity threshold. For participants requiring reduction in percentage of the rMT (F3-rTMS $n = 23$; cgiTBS $n = 5$), stimulation was delivered on average at $M = 99.9$ % rMT ($SD = 13.9$, *range* = 67.3 to 119.1) for F3-rTMS participants and $M = 75.0$ % rMT ($SD = 4.6$, *range* = 69.2 to 79.9) for cgiTBS participants. At session 6, rMT was retested, with eight participants having a decrease in rMT compared to session 1, eight participants having an increase and twelve participants with rMT remaining the same. Therefore, rMT was averaged between session 1 and session 6. Stimulation intensity information was not available for two of these F3-rTMS participants. Impression of change, clinical efficacy (HDRS-17) and acceptability ratings did not significantly differ between those with and without a stimulation intensity reduction.

Of the 254 participants included in the safety population, 20 participants (7.9 %) did not receive all twenty TMS sessions (F3-rTMS $n = 11$; cgiTBS $n = 9$; X^2 [1, 254] = 0.26, $p = 0.62$). See Appendix A for further details.

Total number of AEs and severity percentages are based on total number of possible, probable or definitely related AEs (*n* = 1573). *Fisher Exact test used instead of chi squared test where an expected frequency was <5

4. Discussion

The current study investigated the acceptability, safety and tolerability, of cgiTBS versus F3-rTMS for adults with treatment-resistant depression using a variety of quantitative and qualitative data. Both TMS protocols were comparable in acceptability, safety and tolerability with the exception of the F3-rTMS group requiring more minor adjustments to TMS intensity and coil positioning. Although overall adverse events were common, they were also mostly mild and of short duration. A sizeable number required simple treatments or minor adjustments to TMS. Serious adverse events were rare with high treatment acceptability, tolerability and completion of all 20 TMS sessions. The burden of attendance at the hospital site delivering TMS was perceived to be outweighed by some evidence of improvement even if there were a number of adverse events, with some qualitative data suggesting routine and interactions required for treatment may have been beneficial in and of themselves.

Consistent with prior research, adverse event profiles were comparable between cgiTBS and F3-rTMS, with head pain/headache/scalp discomfort the most commonly frequently reported AE [20,21]. The majority of participants experienced at least one AE that was possibly probably or definitely related to TMS (74.5 %), which were largely mild and transient in nature. However, as previously observed, tolerability improved and the number of emergent AEs decreased over the course of treatment [22,38]. A sizeable proportion of AEs that were possibly related to the TMS treatment, required simple additional treatment or small adjustments to the TMS site or percentage of rMT applied. However, these AEs were mostly mild in severity, and largely resolved within 0–6 days. At least 4.3 % of participants experienced an AE that was possibly related to the study MRI scans, however this number may be underreported, considering BRIGhTMIND research staff were not always in attendance of the full MRI scanning duration. Furthermore, of the 254 participants included in the safety population, at least 1.2 % discontinued TMS treatments due to lack of tolerability/side effects. This number could have been greater had the TMS staff not been attentive or made slight adjustments to the treatment protocol. This is particularly pertinent considering that the number of completed TMS sessions predicted depression outcomes across both treatment protocols in our study [8].

Fatigue was significantly greater in the cgiTBS group versus F3-rTMS, but this result should be interpreted with caution in light of the number of statistical tests conducted. The THREE-D trial reported significantly higher pain ratings in iTBS versus rTMS with both protocols delivered at 120 % rMT [22], but we found that more participants in the F3-rTMS group required adjustments in order to tolerate treatments. We therefore suggest that our current finding of more participants in the F3-rTMS group requiring adjustments was likely the result of the higher stimulus dose (120 % rMT) compared to the lower stimulus dose (80 % rMT) in the cgiTBS group. Reduction in stimulation intensity was not associated with acceptability, impression of change or clinical efficacy. Therefore, future trials, particularly using suprathreshold MT's, may look to ramp up stimulation intensity to the individuals' rMT during sessions, slightly adjust the percentage of motor threshold applied or treatment site if required [39], or use alternative methods to determine stimulation intensity such as heart rate variability [40].

The rates of tinnitus in the BRIGhTMIND trial (10.6 %) were higher than those reported in the THREE-D trial (1 %) [22]. Recent work has demonstrated accelerated iTBS and HF-rTMS can exceed daily TMS noise exposure inducing significant cochlear alterations in those with poor earplug fit [41]. All participants were advised to wear ear plugs, but these findings further emphasise the significant importance of using well fitted approved hearing protection to reduce the chances of temporary or permanent hearing changes. Further factors that can affect the

amount of sound reaching patient ears include the duration, pattern, and intensity of TMS pulses, closeness of the coil to ear, and coil contact with the head [42,43,44]. We recommend TMS clinicians provide patients with tutorials for how to use ear plugs, and conduct a quick noise test to check ear plugs are well fitted. TMS clinicians should also wear earplugs [44] and receive annual hearing checks. We further suggest that hearing safety of longer durations of rTMS/TBS/ accelerated TMS protocols and the use of personalised target sites needs further exploration for patients and TMS clinicians.

In addition, a small proportion of participants reported experiencing cognitive difficulties (e.g. brain fog and feeling spaced out) and emotional distress (e.g. increased anxiety/agitation) during treatment sessions. This is contrary to our clinical findings and other studies of the cognitive enhancing and anxiolytic effects in MDD following a course of TMS [8,45,46]. However, it is plausible that for some patients during TMS treatments, transient impairments in cognitive performance and increased anxiety may be observed, as has been found in healthy controls [47,48,49]. Future studies may wish to measure cognitive performance and anxiety symptoms during a course of treatments as well as follow-up, to determine the short-term and longer-term cognitive and anxiolytic effects of TMS.

Treatment acceptability and impression of change were comparable between protocols, and maintained over the 26 week follow-up. These findings further extend on studies that report high levels of treatment adherence as a measure of TMS acceptability [13,14], and are in line with the high treatment satisfaction ratings for rTMS in adolescent depression [38]. Our post-hoc exploratory analysis showed a trajectory of participants feeling worse had significantly greater AEs, alongside our qualitative findings, this may suggest it is only those that have both a lack of response and side effects that find TMS less acceptable given the burden of attending the hospital for 20 treatment sessions.

A consistent acceptability theme emerging from the literature is the importance of rapport between patients and TMS staff [16,17,38]. However, to our knowledge, the patients' subjective experience regarding theories of effectiveness and the detailed description of response variability for TMS treatment are unique to this current study. These findings do however correspond with the identification of differential TMS response trajectories [37,50,51,52] and symptom cluster responses [53], with suggestions that different symptoms may preferentially respond to different TMS targets within the prefrontal cortex [54]. Notably, some BRIGhTMIND participants had the perception that receiving more treatment sessions could have led to better response, in line with our previous finding that the proportion of participants feeling somewhat (or, much) better was still increasing at the 19th and 20th treatment session [8]. This also supports recent quantitative evidence that for most, courses of greater than 30 sessions may be required for adequate response [55]. To further optimise treatment benefit, some patients may also require potential augmentations to TMS [56,57] or top up treatments [58].Some participants also reported a lack of confidence in treatment they received due to the perception of inter and intra-session coil movement and placement. However, variability in stimulated location was relatively small [8], and we also found that a small amount of inter-session variability might be associated with stronger clinical response [37]. If this latter finding can be replicated it may suggest high precision is not necessary, in which case this should be relayed to patients so that they are not fearful of even the smallest of adjustments.

Overall this study demonstrates that cgiTBS and F3-rTMS were comparable in terms of acceptability and safety and are in line with our clinical efficacy findings [8]. In general iTBS is advantageous over rTMS as it requires less administration time, with the practical advantage of it being suitable for accelerated courses of treatment [10]. At present, the evidence indicates MRI/rsFMRI neuronavigated iTBS or rTMS leads to substantial long term improvement lasting 26 weeks or more [7,8]. However, it is unclear whether non-neuronavigated iTBS or rTMS would also lead to long term improvement, with the current literature focused on the immediate clinical efficacy of MRI neuronavigated versus non-neuronavigated TMS [59,60]. Consequently, a RCT comparing longer-term clinical efficacy and acceptability of neuronavigated and personalised iTBS or rTMS which is more expensive and less convenient versus non-navigated and non-personalised iTBS or rTMS is required.

4.1. Strengths and limitations

A strength of this study is the systematically collected data in a large sample drawn from five sites. This can be used to give accurate figures for the prevalence, severity and course of adverse events across 20 sessions of F3-rTMS or cgiTBS as well as the acceptability and impression of change of such treatments. Placebo responses to TMS in depression are considered large [61], and factors influencing this effect are relatively unexplored or speculative. Different sham TMS techniques do not influence outcomes, and thus the placebo effect has essentially been described as a psychosocial context effect [61]. A strength of our study is that participants describe this effect very well, suggesting routine, treatment change, hope, expectancy and TMS staff support may yield some therapeutic benefit. The size of this non-TMS effect is difficult to estimate given the lack of sham treatment group, and whilst we have previously given reasons to think at least part of the benefit was likely due to TMS treatment [8], it is important to acknowledge these non-TMS effects. Limitations include exclusion of certain medications/doses which may limit generalisability to usual clinical practice. As this work was exploratory we ran a large number of statistical analyses, therefore future replication is required. Finally, a very large sample would be required to estimate the true incidence of SAEs such as seizures. Therefore, it is important that data from RCTs are aggregated and checked alongside routine collected naturalistic data to arrive at more precise estimates of SAEs.

5. Conclusion

The current study provides further evidence that iTBS and rTMS are safe, tolerable and highly acceptable treatments for TRD with further insights to the different facets contributing to the acceptability of TMS.

BRIGhTMIND study and LEAP team membership

The BRIGhTMIND team consists of the named authors and also; D. Auer, P. Bates, A. Blamire, L. Booth, C. Brookes, W. Cottam, E. Cox, L. Davison, R. De Vai, D. Dos Santos, M. Douglas-Bailey, J. Eastham J. Gledhill, D. Harding, M. Hamie, L. Ingram, S. Iwabuchi, M. James, C. Kaylor-Hughes, M. Keane, N. Khalifa, P.F. Liddle, M. Liddell, S. Marner, R. McNaughton, M. Mistry, H. Oh, A. O'Neill-Kerr, J. Ooi, J. Parikh, S. Pszczolkowski, I. Reid, J. Rivera, S. Simpson, J. Stone, Y. Walters, A. Willis and T. Willis.

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Data availability

Demographic, clinical outcome, and treatment variables used in the current study will be made available on the University of Nottingham data repository (https://rdmc.nottingham.ac.uk).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.comppsych.2024.152544.

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