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Intermittent theta burst stimulation (iTBS) versus 10 Hz high-frequency repetitive transcranial magnetic stimulation (rTMS) to alleviate treatment-resistant unipolar depression: A randomized controlled trial (THETA-DEP)

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ABSTRACT

Background: Recently intermittent theta burst stimulation (iTBS) proved to be non-inferior to conventional repetitive transcranial magnetic stimulation (10 Hz rTMS) in unipolar depression after failure of one antidepressant trial, but to date no randomized control trial assessed the ability of iTBS to improve depression level and quality of life in more resistant features of depression with a long-term (6 month) follow-up in comparison to 10 Hz rTMS.

Objectives/Hypothesis: The aim of our study was to compare the efficacy of 10 Hz rTMS and iTBS in treatment-resistant unipolar depression on response rates (50% decrease of MADRS scores at one month from baseline) and change in quality of life during a 6-month follow-up. In addition, we investigated whether some clinical features at baseline were associated with the response in the different groups.

Method: Sixty patients were randomized in a double-blind, controlled study at the University Hospital Center of Nantes, and received 20 sessions of either rTMS or iTBS applied to the left dorsolateral prefrontal cortex targeted by neuronavigation. Statistical analysis used Fischer's exact test and Chi-square test as appropriate, linear mixed model, and logistic regression (occurrence of depressive relapse and factors associated with the therapeutic response).

Results: Included patients showed in mean more than 3 antidepressants trials. Response rates were 36.7% and 33.3%, and remission rates were 18.5% and 14.8%, in the iTBS and 10 Hz rTMS groups respectively. Both groups showed a similar significant reduction in depression scores and quality of life improvement at 6 months. We did not find any clinical predictive factor of therapeutic response in this sample.

Conclusion: Our study suggests the clinical interest of iTBS stimulation (which is more time saving and cost-effective as conventional rTMS) to provide long-lasting improvement of depression and quality of life in highly resistant unipolar depression.

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1. Background

According to the World Health Organization, unipolar depression will be the leading cause of disability and premature mortality worldwide by 2030 [1]. However, antidepressants remain insufficiently effective: 40% of patients do not respond to initial treatments, and 20% of depressions are resistant to pharmacological treatments [2]. Even in cases of initial remission, the STAR*D study observed a relapse rate of 43% a year after treatment [3,4]. Currently, the gold standard for treatment-resistant depression (TRD) remains electroconvulsive therapy (ECT), especially in the presence of life-threatening conditions, high suicidal risk, or depression with psychotic symptoms [5]. In parallel, within the last decade, repetitive transcranial magnetic stimulation (rTMS) has assumed an increasingly important role in the depression treatment armamentarium [6,7]. Response rates for rTMS vary, on average, from 40% to 60% [8,9]. Among responders to an initial course of rTMS, the response rate is ~60% at 3 months, and approximately 30%–50% at 6 and 12 months [10–12]. This treatment, in combination with antidepressants, is currently considered effective for unipolar TRD and has the advantage of being well tolerated [13–15]. Recent meta-analyses show the superiority, when compared with placebo treatments, of several brain stimulation techniques: high-frequency rTMS (HF-rTMS) and intermittent theta-burst stimulation (iTBS) of the left dorsolateral prefrontal cortex (DLPFC), low-frequency rTMS of the right DLPFC, and sequential bilateral stimulation [14,15].

The technique most studied is 10 Hz HF-rTMS, approved by the US Food and Drug Administration (FDA) in 2008. Most recent European guidelines give a Level A rating to evidence in support of its efficacy. On the basis of a large multicenter noninferiority study showing equivalence between the TMS protocol of O'Reardon et al. (10 Hz frequency; typical session duration of 37.5 min, for 3000 pulses) and iTBS, the latter obtained FDA approval in 2018 [11,16–18]. The very high frequency of TBS (50 Hz) mimics endogenous theta rhythms, promotes brain plasticity, induces long-term potentiation [19], and may recruit networks involved in depression physiopathology that oscillate at 50 Hz [20]. There is a growing effort in the field to enhance rTMS cost-effectiveness through time-saving protocols [21], and in this regard, iTBS is particularly promising [22]. The efficacy of iTBS in unipolar [23] or bipolar [24] depression is increasingly a topic of investigation. However, though superiority of iTBS to sham treatment has been demonstrated [25–27], this technique is the subject of fewer studies than for 10 Hz rTMS stimulation, and European guidelines assign a Level B rating to the evidence in its support [6]. In addition, long-term effects following 12 weeks of iTBS, compared to those for 10 Hz rTMS, are still unknown [16].

The main clinical predictors of positive outcomes identified for iTBS and Left High Frequency rTMS in the Three-D Study were lower baseline depression scores [28,29], older age, lack of benzodiazepine use [28], fewer past treatment failures, lower baseline anxiety and current employment [29]. It is not yet known if there is a difference in the antidepressant responses to iTBS and 10 Hz rTMS for particular clinical features (e.g., prominent anhedonia, retardation, anxiety, or apathy).

While Blumberger et al., [16], targeting the left DLPFC, found iTBS to be noninferior to 10 Hz rTMS in patients who had failed one to three trials of antidepressants, it is not clear if the same would hold for patients with higher levels of treatment resistance. Moreover, there is a scarcity of data on the longitudinal effects of iTBS after 3 months and its impact on sustained quality of life, which is the most desirable outcome from the patient's perspective [30].

The primary objective of our study [31] was to compare the efficacy of iTBS and 10 Hz rTMS applied to the left DLPFC in patients having an episode of TRD. The primary outcome was the response rate at the end of the treatment (week 4) relative to baseline (i.e., inclusion). Secondary objectives were to describe the rate of remission, quality of life, and level of depression at 1, 3, and 6 months, and to identify characteristics (e.g., anxiety, anhedonia, apathy, and psychomotor retardation) associated with therapeutic response using psychometric and clinical measures.

2. Methods

2.1. Study design

We conducted a randomized two-arm parallel-design single-center trial at Nantes University Hospital in Nantes, France (see Bulteau et al. [31] for flowchart). Patients were randomly assigned to the iTBS or 10 Hz rTMS group (1:1) using a computer program integrated into the electronic Case Report Form (e-CRF). During the screening visit (V1), a patient information leaflet was provided, the consent form was collected, and the candidate was checked against exclusion and inclusion criteria. The baseline visit (V2) had to take place $\leq$72 h before the first session of 10 Hz rTMS or iTBS (V3). Investigators assessed patients once a week during the course of treatment (V4 to V7), and then 1 (V8), 3 (V9), and 6 (V10) months after the last brain stimulation session. Patients were called during the second, fourth, and fifth months to maintain contact and remind them of their next appointment, to avoid loss to follow-up. The study took 33 months, including 24 months for enrollment and ~34 weeks for the follow-up stage.

2.2. Participants

We randomized 60 patients between the ages of 18 and 75 who were diagnosed with major depressive disorder per the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), had total Montgomery–Åsberg Depression Rating Scale (MADRS) scores above 20 [32], and were considered treatment-resistant (i.e., failure to respond to two treatment programs using different antidepressants at normally effective dosages over a 6-week period during current depressive episode). Antidepressants at inclusion were continued at stable dosages throughout the course of iTBS or 10 Hz rTMS treatment. Each subject included had to be able to understand information given; make decisions; participate voluntarily; complete required questionnaires; take oral medications alone or with assistance, throughout the period of the study; and return to the research center for following visits.

The following exclusion criteria were applied: DSM-5–based diagnosis of bipolar I or II disorder, schizophrenia, substance use disorder, or major neurocognitive disorder; modification of benzodiazepine dosage during the preceding 3 months (due to difficulty tapering and possible effect on cortical excitability); ongoing mood-altering treatment (e.g., thyroid extracts, interferon, corticosteroids); previous ECT that failed to resolve current episode; treatment with anticonvulsant other than lamotrigine; contraindications to magnetic resonance imaging (MRI) or rTMS; history of convulsions; progressive neurological or neurosurgical disorder; presence of in situ device (e.g., pacemaker or implantable defibrillator); being a minor; having been deprived of freedom by a court or administrative decision, hospitalized without consent, or placed under guardianship; pregnancy; or being a woman of childbearing age who has not been using contraception. We did not exclude anxiety disorders as they are known to be frequently associated with unipolar TRD in daily clinical practice. In the event of a serious adverse event or exacerbated symptoms of depression, unblinding was permitted, and the patient could receive the appropriate care and remain in the study for follow-up.

2.3. Procedures

Before treatment, each patient had an MRI scan (Siemens 1.5T scanner; sequences: diffusion, T1 3D, FLAIR 2D and T2 rapid, SWI) to rule out any neurological disorder and mark the stimulation target using neuronavigation software (Nexstim eXimia). The target was the left DLPFC, corresponding to the junction between Brodmann areas 9 and 46, as determined by patients' 3D-MRI imagery and neuroanatomy [33,34]. For rTMS, a figure-eight coil (Cool B65) and a MagPro X100 stimulator (Dantec Company, Copenhagen, Denmark) were employed. A Natus Keypoint (Natus, Middleton, WI, USA) was used for daily recording of the resting motor threshold (RMT), defined as the intensity required to elicit $\geq$5 out of 10 consecutive motor evoked potentials with a 50-μV peak-to-peak amplitude when the coil is placed over the "hot spot" of the left primary cortex (site of maximal stimulation of the abductor pollicis brevis muscle) [35].

For 10 Hz rTMS, the following parameters were used: 110% of RMT; 10 Hz pulses; 20-min session; 4 s per train; 28-s intertrain interval; 1600 pulses per day (40 trains of 40 pulses each) [36]; for iTBS: 80% of RMT; 50 Hz pulses; 600 pulses per day. In both trial arms, participants had one session each weekday for 4 weeks, for a total of 20 sessions. During 10 Hz rTMS or iTBS sessions, participants were instructed to keep their eyes open and relax.

2.4. Randomization and blinding

During the baseline visit, participants meeting criteria for inclusion were randomly assigned to the two groups (1:1) by a computerized random number generator with a permuted block design, without stratification or minimization, $\leq$72 h before the initial 10 Hz rTMS or iTBS session. No one but the research nurses who delivered the treatments knew whether patients received rTMS or iTBS. Raters, but not operators, were blinded to treatment allocation. Patients did not know which group they belonged to, were not informed of exact rTMS parameters and session duration, and did not speak to each other near the time of the session. Both treatments were presented as effective.

2.5. Assessments

During the baseline visit, the patient's sociodemographic data (i.e., age, gender, laterality, professional status, and marital status); Body Mass Index (BMI); medical history, including duration of current depressive episode, psychiatric history, treatments prescribed, and degree of prior therapeutic resistance according to the Maudsley Staging Method [37]; and basal personality, according to Cloninger's Temperament and Character Inventory [38] were recorded.

The following variables were measured at inclusion, at the end of the brain stimulation treatment course, and then at 1, 3 and 6 months after the last session: intensity of depression, using MADRS, 13-item Beck Depression Inventory (BDI-13) [39], and Clinical Global Impression–Severity (CGI-S) [40] assessments (higher scores indicating greater severity); and quality of life, with the 36-Item Short-Form Health Survey (SF-36), a scale validated in 160 countries [41] (higher scores indicating better quality of life). Side effects were assessed clinically at each appointment through a systematic interview conducted by the rater.

In addition to anamnestic and sociodemographic data, potential treatment response predictors were anhedonia, assessed using the Snaith-Hamilton Pleasure Scale (SHAPS) [42]; apathy, using Starkstein's Apathy Scale (SAS) [43]; certain moods, anxiety, retardation, suicidal ideation, and other signs of depression, evaluated with the French HARD diagram [44]; and scores on Widlöcher's Depressive Retardation Scale (ERD) [45]. All were measured at inclusion, at the end of the brain stimulation treatment course, and 1 month after the last session. Age, the number of failed antidepressant treatments, and benzodiazepine use were also analysed as variable potentially associated with non-response (NB: as benzodiazepine dosage did not satisfy the log-linear assumption, we used a binary variable—i.e., patient either received or did not receive benzodiazepines—for univariate and multivariate analysis).

2.6. Statistical analysis

At the end of a course of iTBS or 10 Hz rTMS, response was defined as a MADRS score 50% lower than at baseline. A MADRS score less than 8 was deemed indicative of remission. At the time of study design (before the first large study published in 2018), we anticipated a response rate of 25% in the 10 Hz rTMS group [18] and 60% in the iTBS group [46], in light of pilot studies. Assuming a 5% (two-sided) type I error and 80% power, 60 participants were needed.

Our final analysis applied the principle of intention to treat (ITT). Data for continuous variables were summarized by means and standard deviations in the case of normal distributions; otherwise, by medians and interquartile ranges. Qualitative data were summarized by numbers and percentages for each category. Descriptive analyses, including point estimates and 95% confidence intervals, were performed for all variables.

Response and remission rates for each group were compared using a chi-square or Fisher's exact test, as appropriate. We calculated odds of response and their 95% confidence intervals. To analyze change in quantitative variables over time, we applied random effects models, including random intercept and slope, and fixed time, group, and interaction effects. We used logistic regression models to analyze and compare the occurrence of depressive relapse in both groups during the 6 months following the final iTBS or HF-rTMS session, and to search for response predictors. Fisher's exact test was used to compare adverse effects between the two groups.

Missing data were described in terms of frequencies and corresponding percentages, according to group and point in time. Imbalance in missing data percentages between treatment groups was evaluated by a Fisher's exact test. Distribution of missing data over time in both groups was assessed with a Kaplan-Meier estimator, and compared by a log-rank test. For ITT analysis of the primary outcome, missing data were imputed by the worst-case scenario (i.e., failure defined as <50% decrease in MADRS score at the end of 20 sessions), except for one patient who missed only one visit. During the blind review, we decided to impute the missing data for this patient using the mean of all of his MADRS scores since the start of the treatment course. Analyses were performed with SAS v. 9.4 (SAS Institute, Cary, NC, USA). The level of significance was set to 5%.

2.7. Ethics

This study was approved by the French drug and medical device regulatory agency (ANSM) (DMDPT-BLOC/MM/2014-AO1918-39/MS 1); and by the local Nantes Ouest IV Ethics Committee, on December 1, 2015 (05/15; TLT/BB CPP no. 738/2015; ID-RCB no. 2014-AO1918-39). It was conducted in accordance with the Declaration of Helsinki (2013) and French legislation (Public Health Code, Articles L1121–160 and L1126-7). All participants gave written informed consent (informational letter and consent form, v. 2, approved on January 12, 2015).

3. Results

In all, 60 patients were randomized in the study, 30 allocated to each treatment group as illustrated in the CONSORT flow diagram Fig. 1. Baseline sociodemographic, clinical, and psychometric data are summarized in Table 1. As expected with randomization, patients' characteristics were well balanced between the groups.

The sample was predominantly female (n = 41, 68.3%); mean age was 52.3 years (SD: 13.4); and most participants were right-handed (n = 59, 98.3%). There were 56 (93.3%) patients treated with antidepressants; 36 (60%), with benzodiazepines; 23 (38.3%), with potentiation agents, such as antipsychotics; and 13 (21.7%), with mood stabilizers (e.g., lithium or lamotrigine, the use of other anticonvulsants being an exclusion criterion).

Of the 60 participants, 54 completed the stimulation sessions (10 Hz rTMS: 27 [90%]; iTBS: 27 [90%]). Numbers of patients present at follow-up appointments were 53 at 1 month (10 Hz rTMS: 27 [90%]; iTBS: 26 [87%]), 49 at 3 months (10 Hz rTMS: 25 [83%]; iTBS: 24 [80%]; and 39 at 6 months (10 Hz rTMS: 21 [70%]; iTBS: 18 [60%]). Distributions of missing data were not significantly different between groups (p = 0.5067) as shown in Fig. 2.

After imputation of missing data (except for one patient who missed a single visit), response rates—our primary outcome measures— were 33.3% for 10 Hz rTMS and 36.7% for iTBS and were not significantly different between groups as shown in Table 2. Rates of remission were 14.8% for 10 Hz rTMS and 18.5% for iTBS group, with no difference between groups detected by the Fisher's exact test (OR: 0.769; 95% CI: 0.134 to 4.101; p = 1.000).

Fig. 3 summarizes changes in mean MADRS, BDI-13, and CGI-S scores, which did not significantly differ over time between groups. After 28 weeks, mean scores in both groups were significantly lower than at baseline (MADRS, estimated difference: −0.2611, 95% CI: −0.3794 to −0.1427, p < 0.0001; BDI-13, estimated difference: −0.1078, 95% CI: −0.1876 to −0.0280, p = 0.009; CGI-S, estimated difference: −0.1722, 95% CI: −0.2527 to −0.0918, p < 0.0001). Trajectories of mood changes according to MADRS and BDI-13 scales over time in responders and non responders are also represented in Fig. 3. The rate of sustained responses after the end of treatment at each measurement point during the follow-up are detailed in Table 3.

HARD, ERD, SHAPS, and SAS scores dropped significantly at the 1-month follow-up appointment (Table 4) but did not differ significantly between groups—with the exception of the apathy score (SAS), which showed greater improvement in the iTBS group (estimated difference: 3.1573, 95% CI: 0.1303 to 6.1842, p = 0.0413).

Our mixed linear regression analyses found no significant difference in overall SF-36 scores between groups after 6 months. However, the physical functioning (PF), role functioning-physical (RE), vitality (VT), social functioning (SF), mental health (MH), role functioning-emotional (EP), and mental component summary (MCS) scores improved significantly. No significant changes were seen in bodily pain (BP), general health (GH), and physical component summary (PCS) scores. SF-36 results (Table 4 and Fig. 4) were thus independent of the protocol applied.

There were 2 adverse effects of moderate to severe intensity reported by participants: asthenia (10 Hz rTMS: 2 [6%]; iTBS: 4 [13%]) and headaches (10 Hz rTMS: 1 [3%]; iTBS: 5 [17%]). Fisher's exact test detected no significant difference between groups for asthenia (OR: 0.47; 95% CI: 0.0394 to 3.600; p = 0.6708) or headaches (OR: 0.1769; 95% CI: 0.0035 to 1.7331; p = 0.1945).

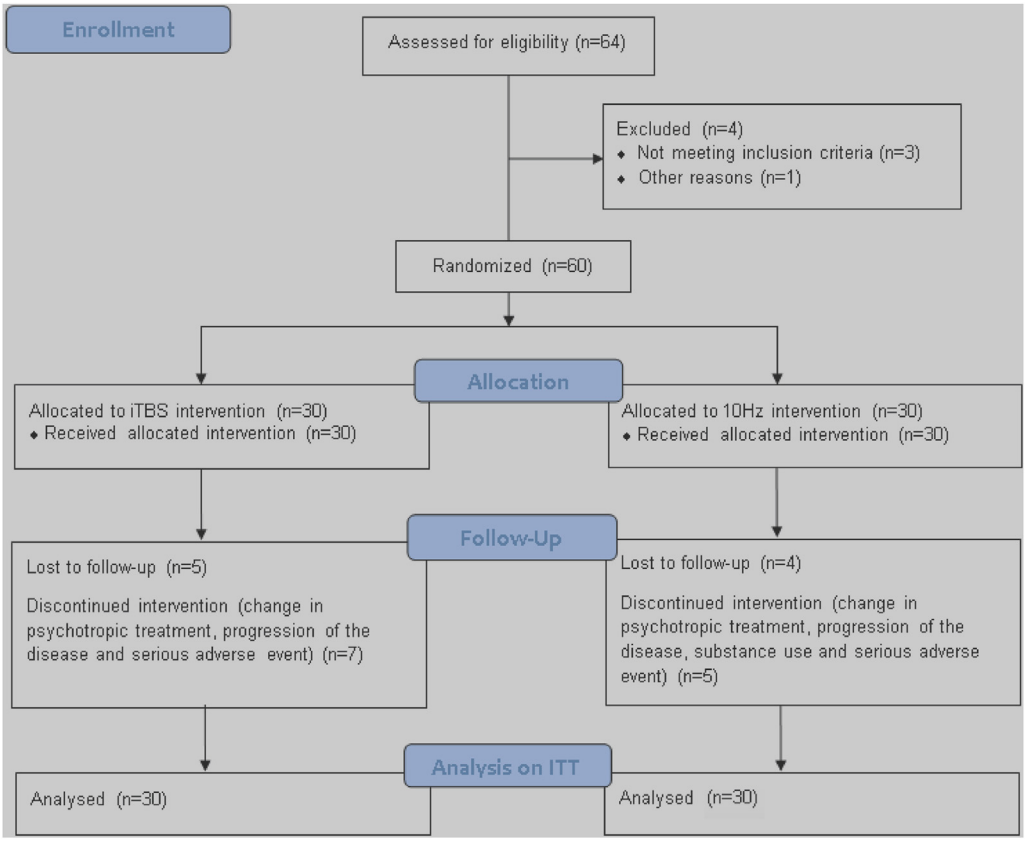

Fig. 1. CONSORT flow diagram of participants enrollment.
10 Hz rTMS: high frequency repetitive Transcranial Magnetic Stimulation; iTBS: intermittent ThetaBurst stimulation; ITT: Intention To Treat.

Table 1
Baseline sociodemographic and clinical characteristics of study sample. Quantitative data expressed as means (standard deviations) for normal distributions, and medians (interquartile ranges) otherwise. Categorical data expressed as numbers of patients (%).

	10 Hz rTMS ($n = 30$)	iTBS ($n = 30$)
Age in years	48.5 (14.7)	56.1 (10.9)
Male sex	12 (40.0%)	7 (23.3%)
Right-handed	30 (100.0%)	29 (96.6%)
BMI	26.8 (6.2)	27.2 (5.9)
Marital status		
Married	12 (40.0%)	14 (46.6%)
Widowed	0 (0.0%)	1 (3.3%)
Single	11 (36.6%)	2 (6.6%)
Divorced	7 (23.3%)	13 (43.3%)
Professional status		
Invalidity	24 (80.0%)	19 (63.3%)
Medical history		
Previous ECT	2 (6.6%)	3 (10.0%)
Previous rTMS	3 (10.0%)	2 (6.6%)
Previous psychotherapy	8 (26.6%)	8 (26.6%)
Family history of mood disorders	23 (76.6%)	16 (53.3%)
Attempted suicide	8 (26.6%)	14 (46.6%)
Number of suicide attempts	1.0 (1.5–3.0)	1.0 (1.5–3.0)
Number of hospitalizations	1.0 (0.0–4.0)	2.0 (1.0–5.0)
Previous depressive episodes	2.0 (0.0–8.0)	2.0 (1.0–7.0)
Current episode duration		
Months	20.0 (6.0–72.0)	19.0 (12.0–44.0)
Number of antidepressant trials for the current episode		
Min-Max	[2.0; 9.0]	[2.0; 12.0]
Mean (SD)	3.4 ± 1.6	3.9 ± 2.2
2	9 (30.0%)	10 (33.3%)
3	11 (36.6%)	5 (16.6%)
≥4	10 (33.3%)	15 (50.0%)
Clinical measures at baseline		
MADRS	27.3 (3.3)	29.8 (6.6)
BDI-13	17.0 (5.6)	19.3 (8.3)
CGI (total)	17.4 (4.9)	19.5 (4.8)
MSM	8.7 (2.2)	9.0 (1.9)
HARD (total)	7.5 (2.0)	9.0 (2.6)
SAS	22.3 (6.8)	25.6 (6.6)
SHAPS	6.1 (4.0)	7.1 (4.0)
ERD	22.4 (7.0)	25.2 (9.4)
MoCA	26.1 (2.5)	26.0 (3.0)
SF-36: Physical Functioning	64.5 (23.8)	60.5 (28.0)
SF-36: Role Functioning–Physical	0.0 (0.0–25.0)	0.0 (0.0–25.0)
SF-36: Bodily Pain	52.4 (30.8)	48.7 (29.2)
SF-36: General Health	37.1 (14.6)	37.2 (20.3)
SF-36: Vitality	18.6 (14.2)	20.8 (18.7)
SF-36: Social Functioning	24.5 (17.5)	24.5 (20.4)
SF-36: Role Functioning–Emotional	0.0 (0.0–0.0)	0.0 (0.0–0.0)
SF-36: Mental health	27.3 (13.6)	25.7 (19.0)
SF-36: Physical Component Score	44.3 (9.3)	43.5 (11.1)
SF-36: Emotional Component Score	21.0 (6.5)	21.2 (9.2)
TCI: Novelty Seeking	50.2 (10.9)	49.5 (12.9)
TCI: Harm Avoidance	43.6 (12.6)	43.5 (11.6)
TCI: Reward Dependence	47.6 (10.7)	51.0 (13.8)
TCI: Persistence	56.0 (15.2)	57.3 (25.7)
TCI: Self-Directedness	50.3 (11.2)	49.4 (13.2)
TCI: Cooperativeness	43.1 (12.7)	43.7 (12.4)
TCI: Self-Transcendence	44.4 (17.5)	50.1 (14.6)
Use of benzodiazepines at baseline		
No	11 (36.6%)	11 (36.6%)
Yes	19 (63.3%)	19 (63.3%)
Dose >2 mg lorazepam equivalent	3 (10.0%)	7 (23.3%)
Min-Max (mg)	[0.0; 5.5]	[0.0; 6.0]
Mean (SD)	0.9 ± 1.2	1.2 ± 1.5

BDI-13, 13-items Beck Depression Inventory; CGI, Clinical Global Impression; ERD, Echelle de Ralentissement Dépressif (Depression Retardation Scale); 10 Hz rTMS, high-frequency repetitive transcranial magnetic stimulation; iTBS, intermittent theta-burst stimulation; MADRS, Montgomery-Åsberg Depression Rating Scale; MoCA, Montreal Cognitive Assessment; MSM, Maudsley Staging Model; SAS, Starkstein Apathy Scale; SF-36, 36-item Short-Form Health Survey; SHAPS, Snaith-Hamilton Pleasure Scale; TCI, Cloninger's Temperament and Character Inventory.

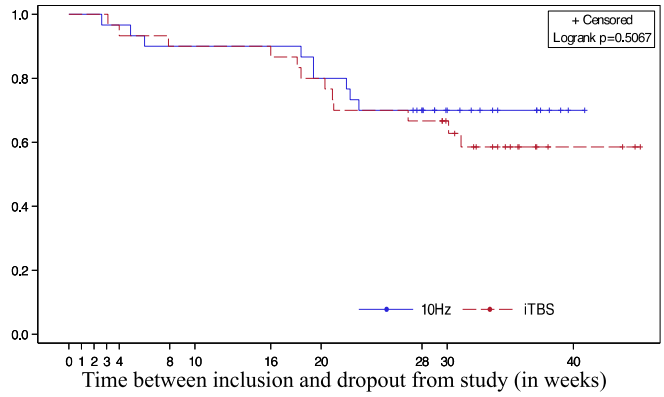

Fig. 2. Kaplan-Meier estimator of survival distribution of missing data over time for 10 Hz rTMS and iTBS groups, compared by logrank test.

There were 2 covariates associated with lack of response to treatment (i.e., <50% improvement relative to baseline) in univariate analyses: high BDI-13 scores (OR: 1.12; 95% CI: 1.02 to 1.23; $p = 0.0191$) and high SHAPS scores (OR: 1.18; 95% CI: 1.01 to 1.38; $p = 0.0357$). However, no factor was associated with lack of response after multivariate regression ($p > 0.2$). Some variables indicated a possible influence in the direction of lowering response rates: age (+1 year: OR 0.99; 95% IC (0.94–1.05)); BDI score (+1point: OR 0.88; 95% IC (0.77–1)); benzodiazepine use (yes *vs* no: OR 0.56; 95% IC (0.16–1.92)), but none of those variables in this multivariate model proved to have a significant effect on treatment response ($p = 0.7517$; $p = 0.0563$; $p = 0.3537$ respectively).

4. Discussion

Our randomized rTMS study aimed to compare iTBS to 10 Hz rTMS in terms of efficacy and tolerance with a high level of evidence. It failed to demonstrate superiority of iTBS to 10 Hz rTMS in TRD. Although this was not a noninferiority study, the response and remission rates for both groups were similar, which is in line with Blumberger's findings of iTBS and 10 Hz rTMS equivalence [16]. Such equivalence would give iTBS the advantages of shorter sessions, enabling more patients to be treated without difference in efficacy, and greater cost-effectiveness. A cost analysis has shown iTBS to be more economical than 10 Hz rTMS: average costs per patient were, respectively, US$1108 and US$1,844, while average costs per remission were US$3695 and US$6146 [22].

One strength of our study is its demonstration that improvement in clinical scores, including quality of life, can be maintained over the 6 months following a course of treatment. However, with the exception of SAS scores, which showed greater improvement following iTBS, results of assessments did not significantly differ between groups. By all scales, we observed a clear subsidence in depression during the month of stimulation, followed by stabilization of symptoms. This sustained improvement may be multifactorial (e.g., long-lasting TMS effect, regularity of appointments during the study, or change in psychotropic prescription based on appraisal of clinician following rTMS courses), but brain stimulation may also have acted as a trigger initiating a process of improvement in depressive symptoms. Improvements in quality of life concerned most SF-36 domains, including mental health, but also physical, emotional, and social functioning, which patients prioritize [47]. Regarding quality of life, our findings were similar to those of Giaccobe et al. [48] even if they used different scales (Quality of Life Enjoyment and Satisfaction Questionnaire and Sheehan Disability Scale) and recruited a different population (mean number of failed antidepressant treatments: <3 for Giaccobe et al.; >3 in our study). Self-reported quality of life according to the SF-36, significantly and continuously improved in both groups (no significant difference between them) during long-term follow-up. Given that a gain of 3 points in each domain is considered clinically significant [49], patients reaped major clinical benefits: their quality of life increased by 0.1–0.7 points per week (depending on domains as reported in Table 3) i.e., by 2.4–16.8 points in 24 weeks.

Our study also confirms a high rate of treatment compliance (~90%), as previously reported for TMS [18], in both groups. In contrast, medication adherence is estimated to be ~50% [50,51]. Both brain stimulation procedures were well tolerated without serious adverse effects, and although headaches may were more frequent in iTBS patients, dropout rates were similar for both groups.

No factors (i.e., sex, age, duration of illness, psychiatric history, history of attempted suicides, intensity of depression, degree of therapeutic resistance, apathy, anhedonia, personality dimensions, or quality of life, treatments) were found to predict absence of treatment response in our study. Thus, symptomatology was not found to predict response and may not be important in deciding between the type of brain stimulation. Nevertheless, clinicians must remember that, in the event of suicidal crises, psychotic symptoms, and life-threatening or severe TRD episodes, ECT is still the most appropriate treatment.

Response rates, as determined by MADRS scores following a 4-week course of TMS, were 33.3% for 10 Hz rTMS and 36.7% for iTBS at the end of treatment, while remission rates were 14.81% for 10 Hz rTMS and 18.52% for iTBS. These rates are lower than those observed after 6 weeks of treatment by Blumberger et al., who reported rates of 40%–50% for response and about 20%–30% for remission, with no significant differences between groups [16]. For comparison, treatment of TRD with pramipexol or esketamine is associated with ~50% response and ~30% remission [52,53]. One reason for this may be that patients received only 20 sessions over 4 weeks. Interestingly, if we consider the response rates at week 4 described in the secondary analysis of the THREE-D trial by Kaster et al., for the 3 groups that showed improvement over time (i.e., rapid responders, linear responders with lower baseline symptoms, and linear responders with higher baseline symptoms), the rate of response is 45% and the rate of remission ~13%, in line with our results [28].

This suggests the need for ≥30 sessions for optimal treatment, keeping in mind that, if the goal is to achieve remission, a mode of 35–45 sessions may be required, with some patients needing even 60 sessions [54].

Table 2
Response rates (50 % reduction in MADRS score) by treatment group after 4 weeks.

Therapeutic response	iTBS (n = 30)	10 Hz rTMS (n = 30)	Total (n = 60)	% difference (95% CI)	p-value
	12 (36.7%)[a]	10 (33.3%)[a]	22 (35.0%)[a]	−6.7 (−31.0 to 17.7)	0.789

[a] Number and percentage after imputation of missing data at V7 for 6 patients: for five of these patients, maximum bias method applied; for sixth patient, intermittent missing datum at V7 substituted by mean of MADRS scores at V6, V8, V9, and V10. CI, confidence interval; HF-rTMS: high-frequency (10-Hz) repetitive transcranial stimulation; iTBS, intermittent theta-burst stimulation; MADRS, Montgomery–Åsberg Depression Rating Scale.

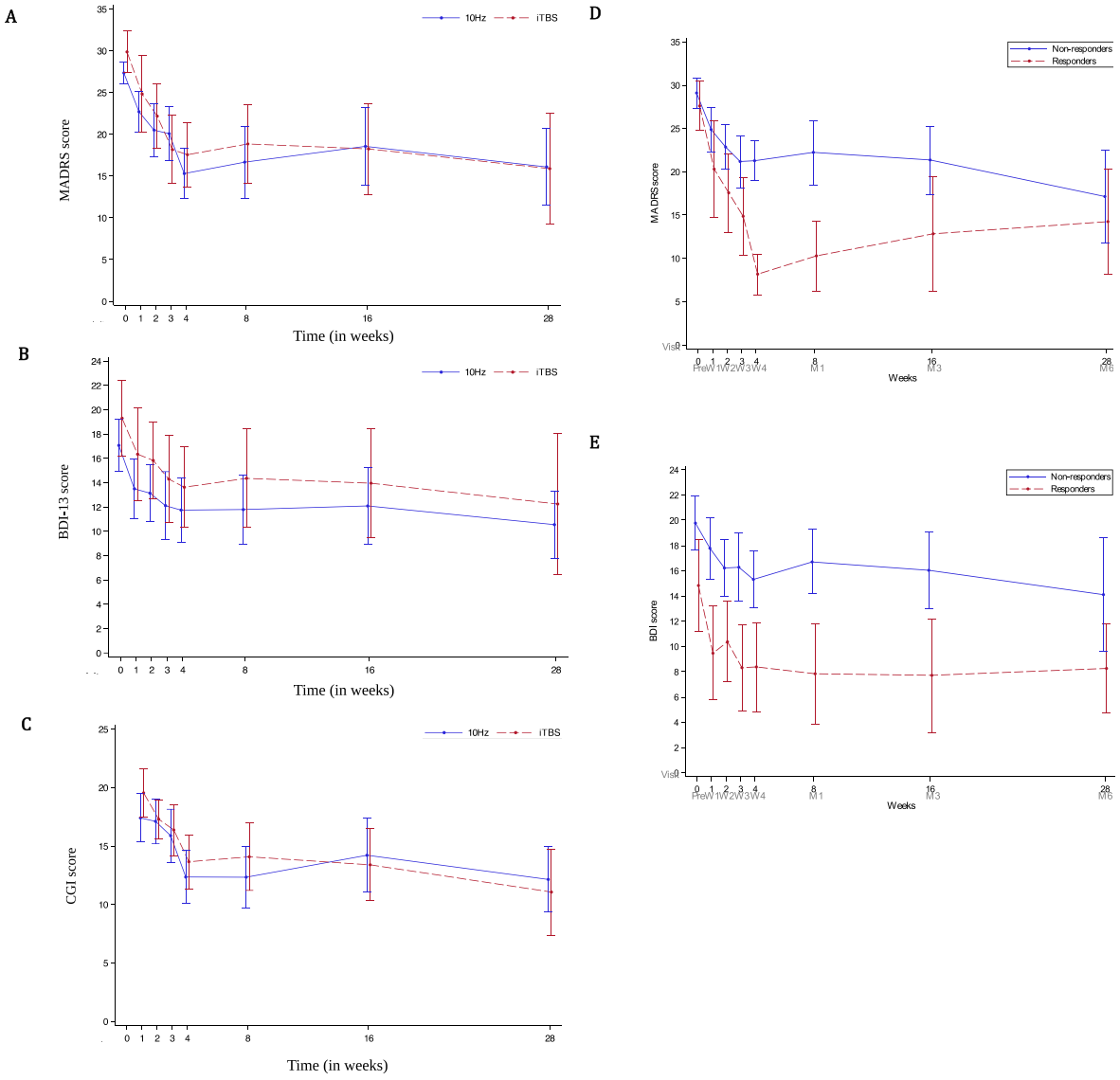

Fig. 3. Changes in (A) MADRS, (B) BDI-13, and (C) CGI scores over time in 10 Hz HF-rTMS and iTBS groups. Changes in MADRS (D) and BDI-13 (E) in responders and non-responders whatever the treatment. Data expressed as means with 95% confidence intervals.

Table 3
Maintenance of the response during the 6 months' follow-up.

		10 Hz rTMS	iTBS	Total
Patients responders at V7 (end of treatment)		**N = 10**	**N = 10**	**N = 20**
Response maintained at V8 (M1) since V7	Yes	9 (90.0%)	7 (70.0%)	16 (80.0%)
	No	1 (10.0%)	3 (30.0%)	4 (20.0%)
Response maintained at V9 (M3) since V7	Yes	4 (40.0%)	4 (40.0%)	8 (40.0%)
	No	6 (60.0%)	6 (60.0%)	12 (60.0%)
Response maintained at V10 (M6) since V7	Yes	3 (30.0%)	3 (30.0%)	6 (30.0%)
	No	7 (70.0%)	7 (70.0%)	14 (70.0%)
Patients non-responders at V7 but responders at V8		**N = 3**	**N = 4**	**N = 7**
Response maintained at V9 (M3) since V8 (M1)	Yes	2 (66.6%)	2 (50.0%)	4 (57.1%)
	No	1 (33.3%)	2 (50.0%)	3 (42.8%)
Response maintained at V10 (M6) since V8 (M1)	Yes	2 (66.6%)	1 (25.0%)	3 (42.8%)
	No	1 (33.3%)	1 (33.3%)	4 (57.1%)

1100 Hz10 Hz rTMS, high-frequency repetitive transcranial magnetic stimulation; iTBS, intermittent theta-burst stimulation. M1, M3, M6: one month, three months and six months after the 4 weeks of TMS treatment respectively. V7: end of the 4 weeks of TMS treatment.

Table 4
Changes in clinical scales from baseline to 6-month follow-up appointment, comparing both groups, using mixed linear regression model.

		Estimate	Lower 95% CI	Upper 95% CI	*p-value*
SF-36 Physical Functioning	iTBS vs. 10 Hz rTMS	−4.13	−15.06	6.79	0.4553
	Time (+1 week)	0.32	0.11	0.52	0.0035
SF-36 Role Functioning−Physical	iTBS vs. 10 Hz rTMS	−0.15	−14.17	13.87	0.9834
	Time (+1 week)	0.59	0.013	1.16	0.0452
SF-36 Bodily Pain	iTBS vs. 10 Hz rTMS	−6.08	−18.13	5.96	0.3195
	Time (+1 week)	0.19	−0.080	0.47	0.1607
SF-36 General Health	iTBS vs. 10 Hz rTMS	1.06	−6.77	8.88	0.7893
	Time (+1 week)	0.10	−0.093	0.30	0.2977
SF-36 Vitality	iTBS vs. 10 Hz rTMS	3.48	−4.70	11.65	0.4016
	Time (+1 week)	0.40	0.14	0.66	0.0029
SF-36 Social Functioning	iTBS vs. 10 Hz rTMS	0.21	−8.20	8.63	0.9602
	Time (+1 week)	0.70	0.39	1.02	<.0001
SF-36 Role Functioning−Emotional	iTBS vs. 10 Hz rTMS	2.19	−9.00	13.37	0.6994
	Time (+1 week)	0.75	0.23	1.27	0.0053
SF-36 Mental Health	iTBS vs. 10 Hz rTMS	−0.97	−9.50	7.57	0.8230
	Time (+1 week)	0.34	0.10	0.59	0.0073
SF-36 Mental Component Score	iTBS vs. 10 Hz rTMS	0.97	−3.53	5.48	0.6701
	Time (+1 week)	0.26	0.10	0.42	0.0014
HARD-Mood	iTBS vs. 10 Hz rTMS	1.11	−0.17	2.39	0.0870
	Time (+1 week)	−0.38	−0.52	−0.25	<.0001
HARD-Anxiety	iTBS vs. 10 Hz rTMS	−0.22	−1.43	0.99	0.7156
	Time (+1 week)	−0.29	−0.41	−0.17	<.0001
HARD-Retardation	iTBS vs. 10 Hz rTMS	0.53	−0.98	2.05	0.4796
	Time (+1 week)	−0.43	−0.57	−0.29	<.0001
HARD-Danger	iTBS vs. 10 Hz rTMS	0.93	−0.07	1.93	0.0665
	Time (+1 week)	−0.24	−0.35	−0.14	<.0001
HARD, total	iTBS vs. 10 Hz rTMS	2.27	−1.56	6.09	0.2392
	Time (+1 week)	−1.35	−1.74	−0.96	<.0001
ERD	iTBS vs. 10 Hz rTMS	3.09	−0.87	7.04	0.1225
	Time (+1 week)	−1.13	−1.47	−0.80	<.0001
SHAPS	iTBS vs. 10 Hz rTMS	0.56	−1.32	2.43	0.5529
	Time (+1 week)	−0.24	−0.37	−0.12	0.0003
SAS	iTBS vs. 10 Hz rTMS	3.16	0.13	6.18	0.0413
	Time (+1 week)	−0.52	−0.79	−0.26	0.0002

SF36: Short Form (36) Health Survey, assessing Quality of Life; ERD, Echelle de Ralentissement Dépressif (Depression Retardation Scale); SAS: Starkstein Apathy Scale; SHAPS: Snaith-Hamilton Pleasure Scale.

Our results are nevertheless encouraging because every patient in our study had experienced ≥2 antidepressant treatment failures (57% with 2−3 failures and 43%, >3 failures) with a mean number of failure of 3.7 (±1.9) above the cut-off of 3 (higher than those of patients in the study by Blumberger et al.). The mean MSM score was >8, indicating a high resistance level. Reneses et al. [55] have associated such scores with “severe, persisting and unremitting illness as judged on symptoms, neurocognition and disability criteria”, making reference to the Hetrick staging model [56]. In addition, the difference in our results might be explained by a lower number of sessions (≤20), which may bias results towards fast responders, and by the severity of the depressive episode at baseline (BDI-13 score: >16; MADRS score: ~30) [28]. The percentage of TRD patients prescribed benzodiazepines over prolonged periods was high (60%) in our sample, which is concordant with the observation that exposure to benzodiazepine could be a marker of a difficult-to-treat condition justifying additional augmentation therapies [57]. Seven patients received doses of >2 mg lorazepam/day. We didn't find any significant effect of the presence of benzodiazepine at baseline on response rates after treatment. While, as suggested by Kaster et al. [28], this may have contributed to a lower response rate, Fitzgerald et al. [58] raise doubts as to whether benzodiazepines negatively affect TMS outcomes. Distinguishing the respective effects of anxiety, comorbid anxiety disorder, and benzodiazepine on TMS efficacy remains a challenge. Benzodiazepine use and anxiety disorders should not be exclusion criteria for TMS studies: rTMS decreases anxiety associated with depression [59] and has shown comparable efficacy in cases of comorbid anxiety disorders [60].

The selected intensity of 80% of RMT should not have hindered TBS efficacy since a recent large study (n = 300) found no difference in response between sub- and supra-threshold intensities (80% and 120%, respectively) for bilateral TBS in patients with TRD [61]. Optimization of iTBS efficacy is ongoing. Recently, a preliminary open-label study applying an accelerated iTBS protocol that used functional-connectivity MRI to target the area of the left DLPFC most anticorrelated with the subgenual anterior cingulate cortex, observed a remission rate of 86.7% [23]. Finally, Williams et al. treated highly refractory depression with high-dose theta-burst TMS (18,000 pulses in 10 sessions over 5 days) and reported a remission rate of 83%, though performance on clinical assessments 2 weeks after treatment revealed that its effects had dwindled [62].

A potential limitation was that the trial was not strictly double-blind since operators knew which treatments they administered. Furthermore, it is unlikely, but not impossible, that patients could infer the treatment received, resulting in partial unblinding. A few patients received lamotrigine. This was allowed in our study because off-label use of lamotrigine for treatment-resistant unipolar depression is not uncommon [63]. Nevertheless, there is considerable evidence suggesting that neurophysiological effects of TMS can be modified by lamotrigine [64,65]. It is thus not excluded that lamotrigine may alter intended effects of 10 Hz rTMS and iTBS.

Returning to the question of cost-effectiveness, previous analyses for iTBS mainly focused on direct cost. Currently, the estimated annual cost of depression is €14 billion in France [66] and €92 billion in Europe [67]. Elements contributing to this expenditure include comorbidities such as substance abuse, suicide and suicide attempts, inadherence to care, somatic multi-morbidities,

Fig. 4. Changes in SF-36 scores (quality of life) over time in HF-rTMS (A) and iTBS (B) group.
(*) indicates significant improvement at 6-month follow-up and (**) indicates a trend at 6-month follow-up with a p-value = 0.053 using mixed linear regression. Data are means in each SF-36 sub-scores. Endpoint: after 20 sessions. 1 and 6 months: 1 and 6 months after the last session respectively.

loss of production, work stoppages, greater burden on health-care system, impaired quality of life, and the social and professional consequences thereof [68,69]. All of these factors must be integrated into health-economic studies for cost-utility analysis of brain stimulation protocols [21,70].

Our inability to identify clinical predictors of response to iTBS or 10 Hz rTMS suggests we should investigate other potential predictors, including neuropsychological test scores, performance on objective psychomotor objective assessments [71–74], and measures of cortical excitability [75–78].

5. Conclusion

This study in patients with severe, unipolar TRD found iTBS and 10 Hz rTMS to be equally effective, contributing to the international literature suggesting the same. In both groups, levels of depression fell and quality of life rose after treatment, with improvements still observed 6 months later, irrespective of baseline symptomatology. Our findings add to evidence in support of shorter TMS protocols such as iTBS in clinical practice.

Availability of data and materials

All supporting data are available from authors upon reasonable request.

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CRediT authorship contribution statement

Samuel Bulteau: Conceptualization, Methodology, Validation, Investigation, Writing – original draft, Writing – review & editing, Visualization, Project administration, Funding acquisition. **Andrew Laurin:** Investigation, Writing – original draft, Writing – review & editing. **Morgane Pere:** Formal analysis, Data curation, Visualization. **Guillemette Fayet:** Methodology, Project administration, Writing – review & editing. **Veronique Thomas-Ollivier:** Methodology, Project administration, Writing – review & editing, Visualization. **Thibault Deschamps:** Writing – review & editing, Visualization. **Elisabeth Auffray-Calvier:** Resources, Investigation. **Nicolas Bukowski:** Writing – original draft, Writing – review & editing. **Jean-Marie Vanelle:** Supervision, Writing – review & editing. **Véronique Sébille:** Methodology, Validation. **Anne Sauvaget:** Conceptualization, Investigation, Project administration, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors have no conflict of interest to declare.

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