Efficacité et facteurs prédictifs de réponse de la stimulation magnétique transcrânienne dans la dépression résistante : étude naturalistique

Victor Naimi

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Pour obtenir le titre de
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Présentée et soutenue publiquement
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Sommaire

Efficacy of high frequency rTMS for non-responders to low frequency rTMS, a naturalistic study in treatment-resistant depression in a French academic center.

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ABSTRACT

Background: Repetitive transcranial magnetic stimulation (rTMS) is an effective therapy for treatment-resistant depression. High-frequency (HF) rTMS over the left prefrontal dorsolateral cortex is the most frequently used protocol, low-frequency (LF) rTMS over the right DLPFC seems to be as effective. Objective: In Montpellier university hospital, patients were first treated with LF-rTMS, and switched to HF-rTMS if they did not respond. A 6-months maintenance treatment was available for the responders. The aim of this study was to assess the efficacy of this protocol. Methods: 119 patients with treatment-resistant depression were treated between 2009 and 2020. Primary outcome was remission rate according to MADRS. Secondary outcomes were response and remission rates according to MADRS and BDI at the end of treatment, at the end of LF-protocol, and at the end of HF-protocol for patients who did not respond to LF. Clinical and demographic characteristics were analysed as potential predictor of response. Results: Response and remission rates were 47.6 and 22.9 % at the end of treatment, 31 and 17 % at the end of LF-protocol, 38.9 and 12.2 % at the end of HF-protocol. None of the baseline variables were found to be associated with a better response. Among patients who benefited from maintenance treatment, around 50% had relapsed at 6 months. Conclusion: These results encourage changing rTMS protocol in case of non-response to a first-line treatment, and highlight the benefits of maintenance treatment.

Keywords: transcranial magnetic stimulation; treatment-resistant depression; naturalistic; low-frequency rTMS; high-frequency rTMS

INTRODUCTION

La dépression est une maladie psychiatrique fréquente, on estime sa prévalence vie entière entre 15 et 20%. Elle est une cause majeure d'incapacité dans le monde, et augmente la morbidité et la mortalité. Les médicaments antidépresseurs sont le traitement de première ligne des dépressions modérées à sévères, cependant une proportion significative des patients ne répond pas à ces traitements. Les techniques de neuromodulation, en particulier l'électroconvulsivothérapie (ECT) et la stimulation magnétique transcrânienne répétée (rTMS) sont des alternatives intéressantes. La rTMS, bien que moins efficace que l'ECT, a l'avantage d'être mieux tolérée et de ne pas nécessiter d'anesthésie générale.

La dépression unipolaire résistante est généralement définie par l'absence de réponse à deux traitements antidépresseurs de deux classes différentes, à posologie et durée efficaces. Il n'y a pas de définition officielle de la dépression bipolaire résistante, cependant un groupe d'experts britanniques a récemment proposé de la définir par l'absence de réponse à deux lignes de traitement bien conduites. La dépression résistante entraine une augmentation de 35% de la mortalité par rapport à la dépression non résistante, il s'agit donc d'un problème majeur de santé publique.

La rTMS est une technique de neuromodulation non-invasive, basée sur l'induction d'un champ magnétique par une bobine, entraînant une dépolarisation neuronale. Pour le traitement de la dépression, deux protocoles sont principalement utilisés : rTMS haute-fréquence sur le cortex préfrontal dorsolatéral gauche, et rTMS basse-fréquence sur le CPFDL droit. Plusieurs méta-analyses d'essais cliniques randomisés ont démontré la supériorité de la rTMS versus placebo, dans la dépression résistante unipolaire et bipolaire. Cependant, il y a moins d'études naturalistiques, évaluant l'efficacité de la rTMS en population clinique de routine. Leurs résultats sont similaires à ceux des essais cliniques, avec un taux de réponse compris entre 30 et 60%. La plupart des études naturalistiques évaluent l'efficacité de la rTMS haute-fréquence.

Dans cette étude, un protocole adaptatif est utilisé, permettant aux patients de recevoir jusqu'à 60 séances de rTMS avec évaluation médicale toutes les 15 séances. Les patients n'ayant pas répondu à la rTMS basse-fréquence ont ensuite été traités par rTMS haute-fréquence. Elle évalue aussi l'efficacité d'un traitement de consolidation.

A Montpellier, la rTMS dans la prise en charge de la dépression résistante est utilisée depuis 2009. Les patients sont adressés par leur psychiatre traitant.

A notre connaissance, il s'agit de la première étude à évaluer l'efficacité de la rTMS haute-fréquence chez des patients n'ayant pas répondu à la basse-fréquence, ainsi que de la première à publier des résultats portant uniquement sur la basse-fréquence. Par ailleurs, elle comporte des données de traitement de consolidation, ce qui est rarement publié dans ce type d'étude.

INTRODUCTION

Depression is a common mental health disorder, with an estimated lifetime prevalence of 15 to 20%[1].It is a major cause of disability worldwide, and can increase morbidity and mortality.

Antidepressant medications are the first-line treatment for moderate to severe depressions, but it is estimated that a significant number of patients do not respond to these medications[2], making them candidates to neuromodulation procedures, electroconvulsive therapy (ECT) and repetitive transcranial magnetic stimulation (rTMS). Being the most studied, rTMS, even if less effective than ECT[3,4], has the advantage of being better tolerated and not requiring general anesthesia.

Unipolar resistant depression is commonly defined as the absence of response to two well conducted antidepressants from two different classes. There is no definition of bipolar pharmacoresistant depression, but a recent British expert group published a consensus, defining bipolar pharmacoresistant depression as the absence of response to two lines of well conducted treatments[5]. Treatment-resistant depression (TRD) has a mortality rate increased by 35% compared to non-resistant depression[6]. It is therefore a major public health issue.

Repetitive transcranial magnetic stimulation is a non-invasive neuromodulation process, which creates a magnetic field with a coil, inducing neuronal depolarization. For the treatment of depression, mainly two stimulation methods are used: high frequency (HF) over the left dorsolateral prefrontal cortex (DLPFC) or low-frequency (LF) over the right DLPFC. Several meta-analysis of multiple randomized control trials[7–22]) have demonstrated the superiority of rTMS over sham-stimulation, in unipolar and bipolar treatment-resistant depression.

However, there are only few naturalistic studies, evaluating efficacy of rTMS in treatment-resistant depression in routine clinical practice. Their results are consistent with randomized controlled trials, with response rates between 30 and 60 % in most of the studies[23–40].

In most of these naturalistic studies, high frequency rTMS over the left dorsolateral prefrontal cortex was used. The present study uses a duration-adaptative treatment design that allows patients to receive

up to 60 sessions of rTMS with medical assessment every 15 sessions. This study examines the efficacy of switching to HF rTMS for non-responders to LF rTMS and the efficacy of a maintenance treatment.

In Montpellier, rTMS has been used since 2009 for treatment-resistant depression. Patients are addressed by their referent psychiatrist.

This is, to our knowledge, the first study evaluating the efficacy of HF-rTMS for patients who did not respond to LF-rTMS, as well as the first naturalistic study assessing results for LF-rTMS only. Plus, it includes data from maintenance treatment, which is rarely reported in this type of study.

MATERIAL AND METHODS:

This is a naturalistic, observational, retrospective study, conducted in Montpellier University Hospital

Subjects:

Patients were eligible to the rTMS protocol if they were over 18, suffered from a major depressive episode according to DSM IV criteria, and did not respond to at least two antidepressant medications, with optimal dosage and duration. MADRS score at baseline had to be > 21.

Written informed consent was obtained from all participant.

Exclusion criteria were contraindication to rTMS (intra-cranial foreign object, non-stabilized epilepsy, cochlear implant, pacemaker, pregnancy, non-stabilized medical affection).

119 patients were included, all of them benefited from rTMS in Montpellier University Hospital between 2009 and 2020. Current treatment was not modified.

rTMS procedure:

First-line treatment was one cure of 15 sessions of low-frequency rTMS over the right prefrontal dorsolateral cortex. Then, depending on the clinical response, several options were considered: in case of excellent clinical response, a six-months consolidation treatment of LF rTMS was proposed. In case of minimal response but with a hope of better improvement, a second cure of 15 sessions of right LF rTMS

was proposed. In case of absence of response after one LF cure or insufficient response after 2 cures, a change of protocol was made, and one or two cures of 15 sessions of high-frequency rTMS over the left prefrontal dorsolateral cortex was undergone. In that case, if clinical response was satisfying, a six-months consolidation treatment was proposed; if not, rTMS was stopped. See figure 1.

All the therapeutical decisions were based on clinical criteria, and not on the scales used for the study.

Treatment parameters:

The medical device (Super Rapid 2 from Magstim company) has a CE label and has the FDA agreement for treatment-resistant depression.

LF rTMS was administered at 1 Hz over the right prefrontal dorsolateral cortex at 120% of motor threshold, patients received 6 trains of 60 seconds stimulation separated by 30-seconds inter train periods, for a session duration of 8 min 30 s and a total of 360 pulses. This protocol has proven its efficacy in a French multicenter trial[41]. HF rTMS was administered at 10 Hz over the left prefrontal dorsolateral cortex at 110% of motor threshold, patients received 40 trains of 5 seconds stimulation separated by 25-seconds intertrain periods, for a session duration of 20 minutes and a total of 2000 pulses. Sessions were daily or twice daily five days per week.

The resting motor threshold was determined using visual methods (visible contraction of the thumb) [42] and was reassessed every 15 sessions. Site of stimulation was determined, during the first years, using the 6 cm method (6 cm forward from motor site in a sagittal plan), then using the Beam-F3 method[43]. During the stimulation, the patient was instructed not to sleep and was allowed to talk with the nurse.

Outcome measures:

For the measurement of efficacy, Beck Depression Inventory (BDI)[44] and Montgomery-Adsberg Depression Rating Scale (MADRS)[45] scales were assessed before treatment, at the end of each 15 sessions, and in case of consolidation protocol, at 1, 3 and 6 months after the end of the initial protocol. Side effects were assessed by the nurse at each session and the physician every 15 sessions. Demographic information, diagnosis, treatment, treatment resistance, duration of the episode and of

the disease were collected by the physician during the first consultation.

Statistical analysis :

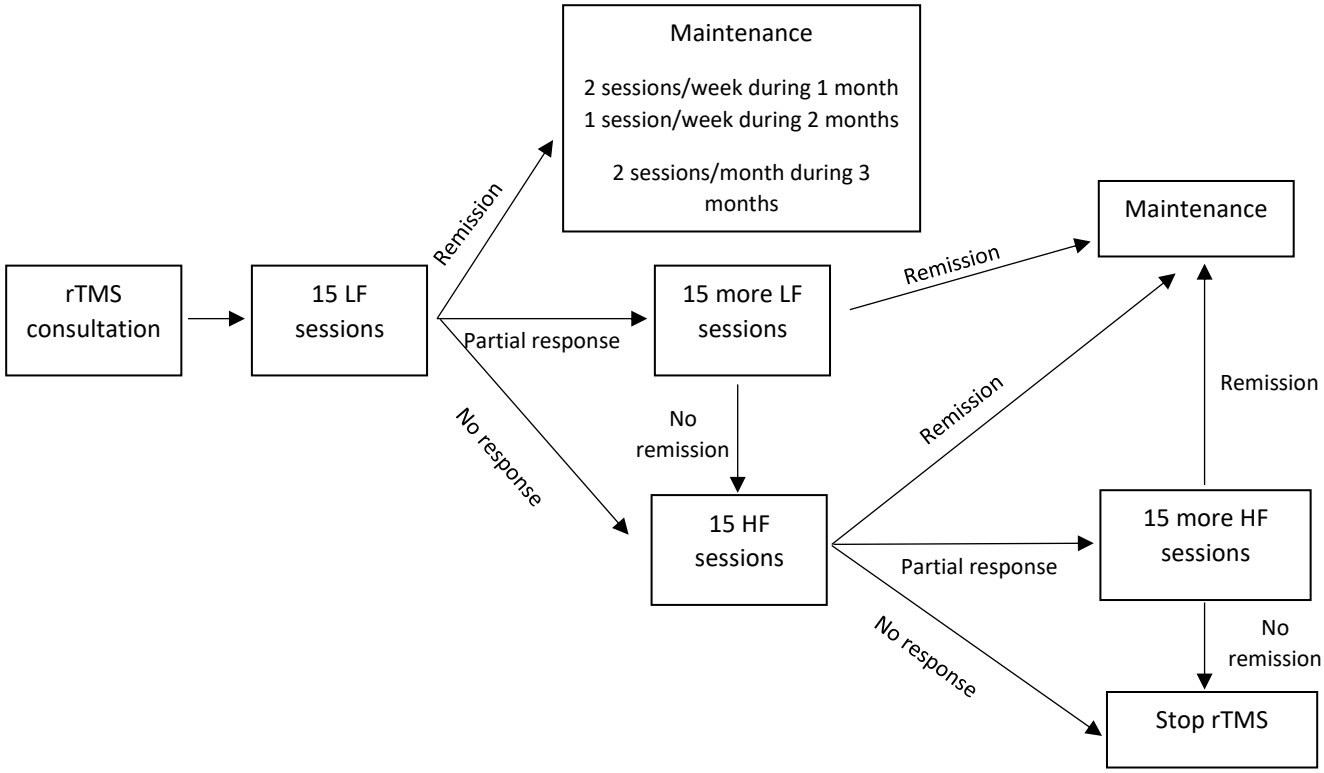
The primary outcome was the remission rate based on the MADRS. Remission was defined by a MADRS score ≤10. Secondary outcomes were response rate, defined by a >50 % reduction of MADRS score, remission and response rates based on the BDI score (remission if BDI < 15, response if 50% diminution of the BDI score), evolution on MADRS and BDI scores during the consolidation treatment, and predictive factors of response according to several criteria (age, gender, number of current antidepressant treatments, number of failed antidepressant or potentializing treatment in current episode, episode duration, disease duration, main diagnosis, baseline depression scores). Episode duration was analyzed as a qualitative variable (<24 months vs > 24 months), since the efficacy of rTMS in chronic depression seems to be uncertain[46].

For the descriptive analysis, qualitative variables were described with their numbers and associated percentage. Quantitative variables were described with their means and standard deviation.

Mean differences in the MADRS and BDI change post-treatment vs baseline were compared with a Student test for matched data.

For the analyses of potential predictive factors of response, Chi-square test was used for qualitative variables (main diagnosis, gender, episode duration); Wilcoxon test was used for quantitative variables (age, number of failed pharmacological treatments, baseline depression scores, number of current treatments, disease duration). All the analyses were performed with SAS 9.4 software.

Figure 1. rTMS protocol



Protocol used in Montpellier university hospital. All therapeutical decisions were based on clinical presentation, and not on MADRS or BDI depression scores.

RESULTS:

Demographic and clinical characteristics of study population

Baseline characteristics of study population are shown in table 1. One hundred and nineteen patients who received rTMS for the treatment of TRD between 2009 and 2020 were included, a majority were women with a median age of 52 years old. Bipolar disorder was the main diagnosis for 31 (26.7%) patients, unipolar disorder for 85 (73.3%). The mean number of failed pharmacological treatments (including antidepressants and mood stabilizers) was high at 8.

Table 1. Demographic and clinical characteristics of study population

Variable	Value
Age (mean ± SD)	**52 ± 13.3**
Age range	19-83
Gender	
Male	39 (33.3%)
Female	77 (66.7%)
Main diagnosis	
Bipolar depression	31 (26.7%)
Unipolar depression	85 (73.3%)
Failed pharmacological treatment during the current episode	**8 ± 4.3**
Duration of current episode (months)	**34 ± 33.5**
Disease duration (months)	**207 ± 146**
Baseline MADRS score	**31.6 ± 5.9**
Baseline BDI score	**36.9 ± 10.1**

Treatment outcomes

The average number of rTMS sessions across the acute phase was 32.7.

There was a statistically significant improvement of both MADRS and BDI scores from baseline at the end of the rTMS treatment (-12.9; $p < 0.0001$ and -12.85; $p < 0.0001$ respectively).

Regarding the primary outcome, MADRS remission rate at the end of rTMS-treatment (all protocols combined) was 22.9%. MADRS response rate was 47.6%. Response and remission rates according to the BDI were 46.4% and 33.7%, respectively.

In detail, at the end of low-frequency rTMS protocol, response and remission rates were 31% and 17% according to the MADRS; 29.1 % and 22% according to the BDI.

Among patients with an insufficient response to LF-rTMS and who were then treated with HF-rTMS,

response and remission rates were 38.9% and 12.2% according the MADRS, 34.8% and 25.5% according to the BDI.

Predictive factors of response, analysis of moderators of treatment outcome

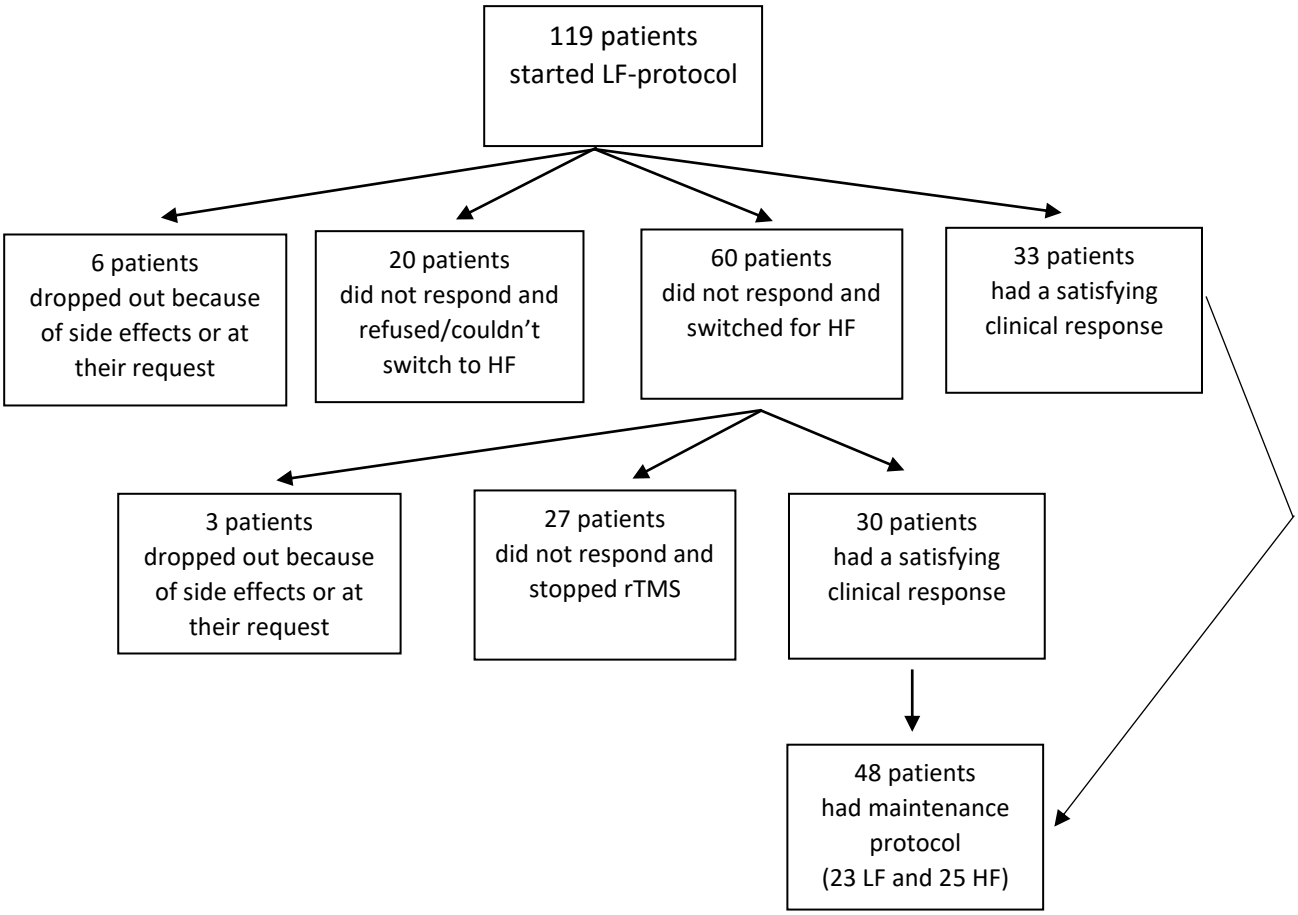
Among the analysed parameters (gender, age, main diagnosis, episode duration, disease duration, number of current treatments, number of failed pharmacological treatments, baseline MADRS score), none of them was associated with a significantly better response rate, in the univariate and multivariate analyses.

A comparison was made between the population that responded to HF-rTMS and the population that responded to LF-rTMS. Patients that responded to HF-rTMS had a higher mean number of failed pharmacological treatments during the episode (8.6 vs 6.3, $p<0.05$). There was no other difference in the clinical and demographical characteristics of the two populations.

Safety and tolerability

No serious adverse event occurred during the course of treatment, particularly no seizure. For 6 patients, poor tolerance caused a change in the protocol. Two patients had to stop rTMS because of side-effects during low-frequency protocol, two who were supposed to switch to high-frequency protocol did not because of mediocre tolerance of low-frequency, two had to stop high-frequency protocol (one of them switched back to low-frequency). Main side-effects were headaches and discomfort in the stimulation area.

Figure 2. Flowchart



Maintenance

Among the 48 patients who benefited from maintenance treatment, 16 maintained response or remission after 6 months of follow-up, 24 experimented relapse, 5 dropped out consolidation protocol before 6 months, 1 is still in the protocol. For the 2 remaining patients, data were insufficient to conclude.

Table 2. Treatment outcomes: categorical variables

	End of treatment	End of LF-protocol	End of HF-protocol
MADRS			
Response rate	47.6%	31%	38.9%
Remission rate	22.9%	17%	12.2%
BDI			
Response rate	46.4%	29.1%	34.8%
Remission rate	33.7%	22.2%	25.5%

Table 3. Treatment outcomes : continuous variables

Variables	Mean difference (SD)	P value
MADRS before and after treatment	12.90 (10.74)	<0.0001
BDI before and after treatment	12.85 (12.86)	<0.0001

DISCUSSION :

Results of this study show that rTMS is an effective therapy for treatment-resistant depression, and that therapeutical response to high-frequency rTMS can be high even in case of non-response to low-frequency rTMS. Naturalistic studies are important to assess the efficacy and acceptability of treatment in clinical practice due to non-research patients often having a high rate of psychiatric and somatic comorbidity. In this one, response and remission rates are consistent with those found in both sham-controlled randomized clinical trials and other naturalistic studies. Depending on the depression scales used, response rate is usually between 30 and 60%. This is higher than the 16.8 % response rate to a third-line pharmacological treatment, as reported in the STAR*D study(2).

European recommendations are in favour of rTMS treatment for major depressive disorder after failure of one well-conducted antidepressant medication[46].

Diminution of BDI and MADRS scores from baseline was highly significant, like in other rTMS studies.

The study population was similar to those found in other naturalistic studies for the mean age and gender ratio [29,31,32,35,37,40] but is different in terms of treatment resistance level (8 treatment failures) and episode duration (34 months) that implies a very difficult to treat population. Patients were often addressed by their referent psychiatrists after several years of therapeutical stagnation. In other similar naturalistic studies, the number of failed pharmacological treatments was either not reported or inferior ; 2 to 6,6 [26,29,32,38]. The relatively high response rate in this population suggests that rTMS can be an interesting treatment even for patients with a high level of resistance. Besides, there was no statistically significant difference in the response and remission rates according to the number of failed pharmacological treatment or the duration of current episode.

None of the other baseline sociodemographic or clinical characteristics were associated with a statistically better response or remission rate. This is consistent with the existing literature, most of the studies didn't find any reliable predictive response factors. Contradictory results exist concerning age, a higher age is sometimes found associated with a statistically significant lower response [29,47,48], sometimes not [30,31,34,35]. There are also contrasting results for baseline depression scores, a lower score [29] or on the contrary a higher score [35] can both be found to be a statistically significant predictive response factors.

Number of failed treatment during the episode is also sometimes found as a negative predictor of response to rTMS [48,49].

Several meta-analysis and naturalistic studies compared low-frequency rTMS over the right prefrontal dorsolateral cortex and high-frequency rTMS over the left prefrontal dorsolateral cortex [18,20,30,50], none of them found a statistically significant difference between the two protocols. LF-rTMS is usually better tolerated, with a lower risk of seizure in particular, that is why this was the first-line treatment in this protocol. Besides, the duration of a low-frequency rTMS session is shorter than a high-frequency session (8.30 vs 20 minutes) and is less likely to cause a coil overheat.

The response and remission rates in right-low frequency observed in this study are consistent with this, with results within the range of usually observed response/remission rates.

Among patients who did not respond to LF rTMS, around 40 % obtained a clinical response when switching to the high-frequency left protocol. This rate is interesting, because it is similar to response rate of patients who had never been treated with rTMS. We could have expected a lower response rate in that case. There may be two reasons to explain these results. First, the remission rate may depend on the number of sessions as shown by some studies[51]. Second, the TRD population is heterogeneous in terms of neurobiological underpinnings. A subgroup of TRD may be sensitive to LF rTMS and another subgroup may be sensitive to HF rTMS[52]. It would be useful to capture the predictive factors to response to one or another therapy. Outside of a slightly higher level of treatment-resistance in the HF-responders, our study did not find a difference in these two subgroups but future investigations may find biomarkers either electrophysiological or imaging.

To our knowledge, this is the first naturalistic study to analyse this protocol change. An open-label study found a 26% remission rate with right low-frequency rTMS among 81 patients who did not respond to left high-frequency rTMS[53].

Very few studies have been published about maintenance rTMS after acute rTMS treatment, and have inhomogeneous results. An open-label trial found a 71% relapse rate at one year with maintenance rTMS[55], another one 62% sustained response at 6 months[56]. Another trial compared the clinical evolution of 59 responders to acute rTMS, among them, over a period of 20 weeks, 37 had maintenance treatment, 22 did not. Relapse rate was significantly higher in the non-maintenance group (37.8% vs 81.8%)[57]. A randomized control trial evaluated efficacy of 8 months rTMS maintenance over 17 patients who responded to rTMS : depression score was significantly better in the active groupe between the first and fourth month[58].

In our study, at least 50% of the patients experimented relapse within the 6 months following acute rTMS treatment. One hypothesis is that a fornightly period between two rTMS session is insufficient to maintain the antidepressant effect.

No serious adverse effects, including seizure induction, occurred during the protocol. Adherence rate was high, only a few patients (4) interrupted rTMS because of adverse events (mostly headaches). rTMS is known to be a generally well tolerated treatment, with few side effects ; in a meta-analysis, there was no statistically significant difference in drop-out rates due to adverse event between active and sham rTMS groups [17].

The main limitation of this study was the loss of data due to the retrospective analysis, for many patients, especially those treated during the first years of the initiation of the protocol (between 2009 and 2013) when data were not recorded on computer. For example, for the main outcome measures, 8 patients could not be included in the analysis due to the absence of final MADRS score. Another limitation is the absence of comparison with a sham group, knowing that a part of the therapeutical response is likely due to other factors than rTMS. The presence of nurses during sessions is likely

responsible for part of the clinical benefit. It is known that placebo is part of response to rTMS, with significative effect on depression scores[55].

CONCLUSION :

In this naturalistic study, efficacy of rTMS among patients with treatment resistant depression is consistent with the published literature. For the non-responders to LF rTMS, HF rTMS seems to be an interesting treatment. None of the potential predictive factors analysed showed a significative difference in clinical response.

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Conflict of interest

Dr Attal reports speaker fees, advisory board and research grants from Otsuka, Lundbeck, Eisai, Janssen and Boehringer-Ingelheim. Dr Naimi, Macgregor and Peyre-Costa have no conflict of interest.

Contributors

Jerôme Attal confirmed the medical indication, assessed the motor threshold and evaluated the patients, designed the study and the data collection, revised the manuscript. Victor Naimi conducted the literature searches, wrote the first draft and made the data collection. David Peyre-Costa undertook the statistical analysis. Alexandra Macgregor and Delphine Capdevielle revised the manuscript. All authors contributed to and have approved the final manuscript.

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References:

1. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005 Jun;62(6):593–602.

2. Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, et al. Acute and Longer-Term Outcomes in Depressed Outpatients Requiring One or Several Treatment Steps: A STAR*D Report. Am J Psychiatry. 2006;13.

3. Eranti S, Psych MRC, Philpot M, Psych FRC. A Randomized, Controlled Trial With 6-Month Follow-Up of Repetitive Transcranial Magnetic Stimulation and Electroconvulsive Therapy for Severe Depression. Am J Psychiatry. 2007;9.

4. Berlim MT, Van den Eynde F, Daskalakis ZJ. EFFICACY AND ACCEPTABILITY OF HIGH FREQUENCY REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION (rTMS) VERSUS ELECTROCONVULSIVE THERAPY (ECT) FOR MAJOR DEPRESSION: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED TRIALS: Review: High Frequency rTMS versus ECT for Major Depression. Depress Anxiety. 2013 Jul;30(7):614–23.

5. Hidalgo-Mazzei D, Berk M, Cipriani A, Cleare AJ, Florio AD, Dietch D, et al. Treatment-resistant and multi-therapy-resistant criteria for bipolar depression: consensus definition. Br J Psychiatry. 2019 Jan;214(1):27–35.

6. Reutfors J, Andersson TM-L, Brenner P, Brandt L, DiBernardo A, Li G, et al. Mortality in treatment-resistant unipolar depression: A register-based cohort study in Sweden. J Affect Disord. 2018 01;238:674–9.

7. Berlim MT, Van den Eynde F, Daskalakis ZJ. A systematic review and meta-analysis on the efficacy and acceptability of bilateral repetitive transcranial magnetic stimulation (rTMS) for treating major depression. Psychol Med. 2013 Nov;43(11):2245–54.

8. Zhang YQ, Zhu D, Zhou XY, Liu YY, Qin B, Ren GP, et al. Bilateral repetitive transcranial magnetic stimulation for treatment-resistant depression: a systematic review and meta-analysis of randomized controlled trials. Braz J Med Biol Res. 2015 Mar;48(3):198–206.

9. Berlim MT, Van den Eynde F, Jeff Daskalakis Z. Clinically Meaningful Efficacy and Acceptability of Low-Frequency Repetitive Transcranial Magnetic Stimulation (rTMS) for Treating Primary Major Depression: A Meta-Analysis of Randomized, Double-Blind and Sham-Controlled Trials. Neuropsychopharmacol. 2013 Mar;38(4):543–51.

10. Berlim MT, Van den Eynde F, Daskalakis ZJ. High-Frequency Repetitive Transcranial Magnetic Stimulation Accelerates and Enhances the Clinical Response to Antidepressants in Major Depression: A Meta-Analysis of Randomized, Double-Blind, and Sham-Controlled Trials. J Clin Psychiatry. 2013 Feb 15;74(02):e122–9.

11. Kozel FA, George MS. Meta-Analysis of Left Prefrontal Repetitive Transcranial Magnetic Stimulation (rTMS) to Treat Depression: Journal of Psychiatric Practice. 2002 Sep;8(5):270–5.

12. Schutter DJLG. Quantitative review of the efficacy of slow-frequency magnetic brain stimulation in major depressive disorder. Psychol Med. 2010 Nov;40(11):1789–95.

13. Lam RW, Chan P, Wilkins-Ho M, Yatham LN. Repetitive Transcranial Magnetic Stimulation for Treatment-Resistant Depression: A Systematic Review and Metaanalysis. Can J Psychiatry. 2008 Sep;53(9):621–31.

14. Berlim MT, van den Eynde F, Tovar-Perdomo S, Daskalakis ZJ. Response, remission and drop-out rates following high-frequency repetitive transcranial magnetic stimulation (rTMS) for treating major depression: a systematic review and meta-analysis of randomized, double-blind and sham-controlled trials. Psychol Med. 2014 Jan;44(2):225–39.

15. Allan CL, Herrmann LL, Ebmeier KP. Transcranial Magnetic Stimulation in the Management of Mood Disorders. Neuropsychobiology. 2011;64(3):163–9.

16. Nguyen TD, Hieronymus F, Lorentzen R, McGirr A, Østergaard SD. The efficacy of repetitive transcranial magnetic stimulation (rTMS) for bipolar depression: A systematic review and meta-analysis. Journal of Affective Disorders. 2020 Oct;S0165032720328573.

17. Wei Y, Zhu J, Pan S, Su H, Li H, Wang J. Meta-analysis of the Efficacy and Safety of Repetitive Transcranial Magnetic Stimulation (rTMS) in the Treatment of Depression. 2017;29(6):15.

18. Mutz J, Vipulananthan V, Carter B, Hurlemann R, Fu CHY, Young AH. Comparative efficacy and acceptability of non-surgical brain stimulation for the acute treatment of major depressive episodes in adults: systematic review and network meta-analysis. BMJ. 2019 27;364:l1079.

19. Brunoni AR, Chaimani A, Moffa AH, Razza LB, Gattaz WF, Daskalakis ZJ, et al. Repetitive Transcranial Magnetic Stimulation for the Acute Treatment of Major Depressive Episodes: A Systematic Review With Network Meta-analysis. JAMA Psychiatry. 2017 Feb 1;74(2):143–52.

20. Leggett LE, Soril LJJ, Coward S, Lorenzetti DL, MacKean G, Clement FM. Repetitive Transcranial Magnetic Stimulation for Treatment-Resistant Depression in Adult and Youth Populations: A Systematic Literature Review and Meta-Analysis. Prim Care Companion CNS Disord. 2015;17(6).

21. Liu B, Zhang Y, Zhang L, Li L. Repetitive transcranial magnetic stimulation as an augmentative strategy for treatment-resistant depression, a meta-analysis of randomized, double-blind and sham-controlled study. BMC Psychiatry. 2014 Nov 30;14:342.

22. Gaynes BN, Lloyd SW, Lux L, Gartlehner G, Hansen RA, Brode S, et al. Repetitive transcranial magnetic stimulation for treatment-resistant depression: a systematic review and meta-analysis. J Clin Psychiatry. 2014 May;75(5):477–89; quiz 489.

23. Dunner DL, Aaronson ST, Sackeim HA, Janicak PG, Carpenter LL, Boyadjis T, et al. A Multisite, Naturalistic, Observational Study of Transcranial Magnetic Stimulation for Patients With Pharmacoresistant Major Depressive Disorder: Durability of Benefit Over a 1-Year Follow-Up Period. J Clin Psychiatry. 2014 Dec 24;75(12):1394–401.

24. Taylor SF, Bhati MT, Dubin MJ, Hawkins JM, Lisanby SH, Morales O, et al. A naturalistic, multi-site study of repetitive transcranial magnetic stimulation therapy for depression. Journal of Affective Disorders. 2017 Jan;208:284–90.

25. McGirr A, Van den Eynde F, Tovar-Perdomo S, Fleck MPA, Berlim MT. Effectiveness and acceptability of accelerated repetitive transcranial magnetic stimulation (rTMS) for treatment-resistant major depressive disorder: An open label trial. Journal of Affective Disorders. 2015 Mar;173:216–20.

26. Berlim MT, McGirr A, Beaulieu M-M, Turecki G. High frequency repetitive transcranial magnetic stimulation as an augmenting strategy in severe treatment-resistant major depression: A prospective 4-week naturalistic trial. Journal of Affective Disorders. 2011 Apr;130(1–2):312–7.

27. Fitzgerald PB, Benitez J, De Castella AR, Brown TL, Jeff Daskalakis Z, Kulkarni J. Naturalistic Study of the use of Transcranial Magnetic Stimulation in the Treatment of Depressive Relapse. Aust N Z J Psychiatry. 2006 Sep;40(9):764–8.

28. Fukuda AM, Tirrell E, Gobin AP, Carpenter LL. Repetitive Transcranial Magnetic Stimulation for depression relapse or recurrence: Naturalistic retreatment series outcomes. Brain Stimulation. 2019 Sep;12(5):1328–9.

29. Carpenter LL, Janicak PG, Aaronson ST, Boyadjis T, Brock DG, Cook IA, et al. TRANSCRANIAL MAGNETIC STIMULATION (TMS) FOR MAJOR DEPRESSION: A MULTISITE, NATURALISTIC, OBSERVATIONAL STUDY OF ACUTE TREATMENT OUTCOMES IN CLINICAL PRACTICE: Research Article: An Observational Study of TMS. Depress Anxiety. 2012 Jul;29(7):587–96.

30. Ciobanu C, Girard M, Marin B, Labrunie A, Malauzat D. rTMS for pharmacoresistant major depression in the clinical setting of a psychiatric hospital: Effectiveness and effects of age. Journal of Affective Disorders. 2013 Sep;150(2):677–81.

31. Frank E, Eichhammer P, Burger J, Zowe M, Landgrebe M, Hajak G, et al. Transcranial magnetic stimulation for the treatment of depression: feasibility and results under naturalistic conditions: a retrospective analysis. Eur Arch Psychiatry Clin Neurosci. 2011 Jun;261(4):261–6.

32. Aliño JJL-I, Jiménez JLP, Flores SC, Alcocer MIL-I. Efficacy of transcranial magnetic stimulation (TMS) in depression: naturalistic study. Actas Esp Psiquiatr. 2010 Apr;38(2):87–93.

33. Rachid F, Moeglin C, Sentissi O. Repetitive Transcranial Magnetic Stimulation (5 and 10 Hz) With Modified Parameters in the Treatment of Resistant Unipolar and Bipolar Depression in a Private Practice Setting: Journal of Psychiatric Practice. 2017 Mar;23(2):92–100.

34. Griffiths C, O'Neill-Kerr A, Millward T, da Silva K. Repetitive transcranial magnetic stimulation (rTMS) for depression: outcomes in a United Kingdom (UK) clinical practice. International Journal of Psychiatry in Clinical Practice. 2019 Apr 3;23(2):122–7.

35. Dowling NL, Bonwick R, Dharwadkar NP, Ng CH. Repetitive transcranial magnetic stimulation for major depression: A naturalistic observational study in an Australian private hospital. Psychiatry Research. 2020 Sep;291:113275.

36. Godfrey KE, Muthukumaraswamy SD, Stinear CM, Hoeh NR. An open-label feasibility study of repetitive transcranial magnetic stimulation (rTMS) for treatment-resistant depression in the New Zealand healthcare context. N Z Med J. 2019 25;132(1504):46–55.

37. Conelea CA, Philip NS, Yip AG, Barnes JL, Niedzwiecki MJ, Greenberg BD, et al. Transcranial magnetic stimulation for treatment-resistant depression: Naturalistic treatment outcomes for younger versus older patients. J Affect Disord. 2017 01;217:42–7.

38. Philip NS, Carpenter SL, Ridout SJ, Sanchez G, Albright SE, Tyrka AR, et al. 5Hz Repetitive transcranial magnetic stimulation to left prefrontal cortex for major depression. J Affect Disord. 2015 Nov 1;186:13–7.

39. Galletly CA, Carnell BL, Clarke P, Gill S. A Comparison of Right Unilateral and Sequential Bilateral Repetitive Transcranial Magnetic Stimulation for Major Depression: A Naturalistic Clinical Australian Study. The Journal of ECT. 2017 Mar;33(1):58–62.

40. Carnell BL, Clarke P, Gill S, Galletly CA. How effective is repetitive transcranial magnetic stimulation for bipolar depression? Journal of Affective Disorders. 2017 Feb;209:270–2.

41. Brunelin J, Jalenques I, Trojak B, Attal J, Szekely D, Gay A, et al. The Efficacy and Safety of Low Frequency Repetitive Transcranial Magnetic Stimulation for Treatment-resistant Depression: The Results From a Large Multicenter French RCT. Brain Stimulation. 2014 Nov;7(6):855–63.

42. Pridmore S, Fernandes Filho JA, Nahas Z, Liberatos C, George MS. Motor threshold in transcranial magnetic stimulation: a comparison of a neurophysiological method and a visualization of movement method. J ECT. 1998 Mar;14(1):25–7.

43. Beam W, Borckardt JJ, Reeves ST, George MS. An efficient and accurate new method for locating the F3 position for prefrontal TMS applications. Brain Stimul. 2009 Jan;2(1):50–4.

44. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry. 1961 Jun;4:561–71.

45. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry. 1979 Apr;134:382–9.

46. van Eijndhoven PFP, Bartholomeus J, Möbius M, de Bruijn A, Ferrari GRA, Mulders P, et al. A randomized controlled trial of a standard 4-week protocol of repetitive transcranial magnetic stimulation in severe treatment resistant depression. J Affect Disord. 2020 Sep 1;274:444–9.

47. Lefaucheur J-P, André-Obadia N, Poulet E, Devanne H, Haffen E, Londero A, et al. [French guidelines on the use of repetitive transcranial magnetic stimulation (rTMS): safety and therapeutic indications]. Neurophysiol Clin. 2011 Dec;41(5–6):221–95.

48. Aguirre I, Carretero B, Ibarra O, Kuhalainen J, Martínez J, Ferrer A, et al. Age predicts low-frequency transcranial magnetic stimulation efficacy in major depression. Journal of Affective Disorders. 2011 May;130(3):466–9.

49. Fregni F, Marcolin MA, Myczkowski M, Amiaz R, Hasey G, Rumi DO, et al. Predictors of antidepressant response in clinical trials of transcranial magnetic stimulation. Int J Neuropsychopharmacol. 2006 Dec;9(6):641–54.

50. Trevizol AP, Downar J, Vila-Rodriguez F, Thorpe KE, Daskalakis ZJ, Blumberger DM. Predictors of remission after repetitive transcranial magnetic stimulation for the treatment of major depressive disorder: An analysis from the randomised non-inferiority THREE-D trial. EClinicalMedicine. 2020 May;22:100349.

51. Cao X, Deng C, Su X, Guo Y. Response and Remission Rates Following High-Frequency vs. Low-Frequency Repetitive Transcranial Magnetic Stimulation (rTMS) Over Right DLPFC for Treating Major Depressive Disorder (MDD): A Meta-Analysis of Randomized, Double-Blind Trials. Front Psychiatry. 2018;9:413.

52. Beuzon G, Timour Q, Saoud M. Predictors of response to repetitive transcranial magnetic stimulation (rTMS) in the treatment of major depressive disorder. Encephale. 2017 Feb;43(1):3–9.

53. Speer AM, Benson BE, Kimbrell TK, Wassermann EM, Willis MW, Herscovitch P, et al. Opposite effects of high and low frequency rTMS on mood in depressed patients: relationship to baseline cerebral activity on PET. J Affect Disord. 2009 Jun;115(3):386–94.

54. McDonald WM, Durkalski V, Ball ER, Holtzheimer PE, Pavlicova M, Lisanby SH, et al. Improving the antidepressant efficacy of transcranial magnetic stimulation: maximizing the number of stimulations and treatment location in treatment-resistant depression. Depress Anxiety. 2011 Nov;28(11):973–80.

55. Fitzgerald PB, Grace N, Hoy KE, Bailey M, Daskalakis ZJ. An open label trial of clustered maintenance rTMS for patients with refractory depression. Brain Stimul. 2013 May;6(3):292–7.

56. Connolly KR, Helmer A, Cristancho MA, Cristancho P, O'Reardon JP. Effectiveness of transcranial magnetic stimulation in clinical practice post-FDA approval in the United States: results observed with the first 100 consecutive cases of depression at an academic medical center. J Clin Psychiatry. 2012 Apr;73(4):e567-573.

57. Richieri R, Guedj E, Michel P, Loundou A, Auquier P, Lançon C, et al. Maintenance transcranial magnetic stimulation reduces depression relapse: a propensity-adjusted analysis. J Affect Disord. 2013 Oct;151(1):129–35.

58. Benadhira R, Thomas F, Bouaziz N, Braha S, Andrianisaina PS-K, Isaac C, et al. A randomized, sham-controlled study of maintenance rTMS for treatment-resistant depression (TRD). Psychiatry Res. 2017;258:226–33.

59. Razza LB, Moffa AH, Moreno ML, Carvalho AF, Padberg F, Fregni F, et al. A systematic review and meta-analysis on placebo response to repetitive transcranial magnetic stimulation for depression trials. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2018 Feb;81:105–13.

SERMENT

En présence des Maîtres de cette école, de mes chers condisciples et devant l'effigie d'Hippocrate, je promets et je jure, au nom de l'Etre suprême, d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la médecine.

Je donnerai mes soins gratuits à l'indigent et n'exigerai jamais un salaire au-dessus de mon travail.

Admis dans l'intérieur des maisons, mes yeux ne verront pas ce qui s'y passe, ma langue taira les secrets qui me seront confiés, et mon état ne servira pas à corrompre les mœurs, ni à favoriser le crime.

Respectueux et reconnaissant envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.

Que les hommes m'accordent leur estime si je suis fidèle à mes promesses. Que je sois couvert d'opprobre et méprisé de mes confrères si j'y manque.

Résumé

La dépression est une maladie mentale fréquente (prévalence vie entière d'environ 15 à 20%) et invalidante, qui entraîne une augmentation de la morbi-mortalité. Les médicaments antidépresseurs constituent le traitement de première ligne de la dépression, cependant 20 à 40 % des patients n'obtiennent pas de réponse clinique satisfaisante, même avec plusieurs lignes de traitement bien conduites.
La stimulation magnétique transcrânienne répétée (rTMS) est une technique de neuromodulation non invasive ayant démontré son efficacité dans la dépression résistante unipolaire ou bipolaire au travers de nombreuses méta-analyses d'essais cliniques randomisés vs placebo, ainsi que d'études naturalistiques. Dans la plupart des études, un protocole de rTMS haute fréquence stimulant le cortex préfrontal dorsolatéral gauche est utilisé, d'autres études utilisent un protocole basse fréquence stimulant le cortex préfrontal dorsolatéral droit, les méta-analyses comparant ces deux protocoles ne retrouvant pas de différence significative.

Dans cette étude naturalistique rétrospective réalisée au CHU de Montpellier, les patients présentant une dépression pharmacorésistante étaient inclus dans un protocole de rTMS basse fréquence, puis en cas de réponse insuffisante le protocole était changé pour de la rTMS en haute fréquence. Le taux de réponse et de rémission étaient mesurés, et des facteurs sociodémographiques ou cliniques associées à une meilleure réponse recherchés.

Parmi les 119 patients inclus dans l'étude, 47,6% ont répondu à la rTMS, et 22,9 % étaient en rémission à la fin du traitement, selon l'échelle MADRS. Les taux de réponse et rémission à la fin du protocole de rTMS basse fréquence étaient de 31% et 17% respectivement. Parmi les patients n'ayant pas répondu à la rTMS basse fréquence et pour lesquels un protocole haute fréquence a été effectué, les taux de réponse et de rémission étaient de 38,9% et 12,2%. Parmi les facteurs sociodémographiques et cliniques recherchés (âge, sexe, diagnostic principal, durée de l'épisode, durée de la maladie, nombre de résistances médicamenteuses, nombre de traitements en cours, score MADRS initial), aucun n'était associé à une différence de réponse significative.

Cette étude, à notre connaissance la seule à étudier la rTMS haute fréquence chez des patients n'ayant pas répondu à la basse fréquence, retrouve des taux de réponse et de rémission comparables aux autres études randomisés ou naturalistiques analysant les résultats de la rTMS dans la dépression résistante. Malgré un niveau de résistance élevée (8 traitements en moyenne), la réponse à la rTMS est satisfaisante. Par ailleurs, le taux relativement élevé de répondeurs en haute fréquence en cas d'échec de la basse fréquence est en faveur de la poursuite du traitement par rTMS avec un protocole différent en cas de non-réponse à un premier protocole.

Mots clés : stimulation magnétique transcrânienne ; dépression résistante ; naturalistique ; rTMS basse fréquence ; rTMS haute fréquence