Original Articles

The Efficacy and Safety of Low Frequency Repetitive Transcranial Magnetic Stimulation for Treatment-resistant Depression: The Results From a Large Multicenter French RCT

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ARTICLE INFO

ABSTRACT

Context: The aim of this study was to assess whether the combination of low frequency repetitive transcranial magnetic stimulation (rTMS) and venlafaxine (150–225 mg/day) is effective and safe for treatment-resistant unipolar depression (TRD).
Method: In a multicenter (18 centers) randomized double blind controlled trial with three arms, 170 patients were allocated to receive active rTMS combined with active venlafaxine ($n = 55$), active rTMS combined with placebo venlafaxine ($n = 60$) or sham rTMS combined with active venlafaxine ($n = 55$). The patients received once daily sessions of active or sham 1 Hz rTMS applied over the right dorsolateral prefrontal cortex (360 pulses/day delivered at 120% of the resting motor threshold) for two to six weeks; rTMS was combined with active or sham venlafaxine (mean dose: 179.0 ± 36.6 mg/day). The primary outcome was the number of patients who achieved remission, which was defined as an $HDRS_{17}$ score < 8.
Results: We reported a similar significant antidepressant effect in the 3 groups ($P < 10^{-6}$), with a comparable delay of action and a comparable number of remitters at the endpoint (28% in the combination group, 41% in the rTMS group and 43% in the venlafaxine group; $P = 0.59$).
Conclusion: Low frequency rTMS appears to be as effective as venlafaxine and as effective as the combination of both treatments for TRD. Because of its short session duration (the duration of one session was 8.5 min) and its safety, slow rTMS might be a useful alternative treatment for patients with TRD.

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Introduction

Major Depressive Disorder (MDD) is a disabling, expensive and very frequently occurring disorder that tends to recur (in 50–85% of cases) or become resistant and chronic (in at least 20% of the cases), despite a wide range of treatment approaches. In 2010, it became the second cause of morbidity in the world [1]. Typically, the first line treatment consists of pharmacological approaches using

antidepressants (e.g., selective serotonin reuptake inhibitors (SSRIs)). Antidepressant treatments are moderately effective, and one patient in three achieves an adequate response to an initial antidepressant trial prescribed at the appropriate dose and duration [2]. Symptoms remain after a second line treatment in 50% of the cases of response failure to the initial treatment (e.g., the use of another pharmacological class of antidepressants such as serotonin–norepinephrine reuptake inhibitors (SNRIs) or a combination of different pharmacological classes). Antidepressant medications could be associated with adverse effects. There is a need to develop alternative novel or complementary approaches to alleviate treatment-resistant depression (TRD). Among them, there is evidence that repetitive transcranial magnetic stimulation (rTMS) could be effective in the acute treatment of TRD (for a review see [3,4]).

TMS is the delivery of a brief current pulse in a coil placed over the scalp of subjects to modulate cortical activity. Depending on the parameters of the stimulation, the effect of the stimulation on cortical excitability could outlast the stimulation period. Based on neuroimaging studies that suggest an imbalance between the frontal activities in MDD, two primary lines of rTMS protocols have been developed to achieve remission in TRD, as follows: i) high frequency (HF) rTMS applied over the left dorsolateral prefrontal cortex (DLPFC) and ii) low frequency (LF) rTMS applied over the right DLPFC.

Meta-analyses, single center and multicenter studies have, in most cases, supported the hypothesis of an antidepressant effect of these rTMS protocols in TRD. The use 2–6 weeks of HF rTMS applied over the left DLPFC [5,6] was approved in October 2008 by the Food and Drug Administration as a treatment of an MDD resistant to at least one antidepressant medication. The stimulation parameters consist of delivering 3000 pulses at a frequency of 10 Hz and at an intensity of 120% of the motor threshold (MT) for a total duration of 37.5 min. The latter could be uncomfortable, and because HF protocols could be associated with an increased risk of adverse effects [7], debate remains concerning the optimal stimulation parameters; LF rTMS could be a suitable alternative protocol [8]. There is growing evidence that LF rTMS applied over the right DLPFC is as effective as HF rTMS applied over the left DLPFC in the treatment of TRD and more effective than sham [4,9–19]. LF rTMS could be as effective as second line antidepressant treatments (such as SNRIs, [20]). Three recent meta-analyses [8,21,22] have reported that LF rTMS provided meaningful clinical benefits comparable to those of antidepressants and to HF rTMS protocols. These authors reported that LF rTMS causes fewer side effects and less serious adverse events, including seizures, and necessitates a lower total number of stimulations (and thus, shorter session duration) than HF rTMS for a comparable antidepressant effect [8,21,22].

To optimize the efficacy of rTMS in the treatment of TRD, several authors have proposed combining rTMS with antidepressant medications with the aim of accelerating the onset of action and increasing the therapeutic effect. Despite the fact that several studies did not support the superiority of the adjunction of rTMS to an antidepressant [23–25], the superiority of the combined approach was supported in other studies predominantly using HF rTMS in combination with SSRIs or tricyclic drugs [26–29]. The lack of clear results concerning the potential efficacy of the combined approach merits further investigation because combination strategies with other types of brain stimulation have been reported to be effective (with ECT [30]; with tDCS [31]).

We developed a double blind three-arm sham-controlled study to investigate the clinical effect of right-sided LF rTMS as a monotherapy or combined with a second line standard antidepressant medication in the treatment of TRD (i.e., an SNRI, venlafaxine at 150–225 mg/day [32]). The two strategies (pharmacological and

stimulation) were initiated at the identical time, and the number of responders was compared at the end of the study period, which was 6 weeks after the initiation of the treatment. We hypothesized the superiority of the combined strategy compared with venlafaxine only and with rTMS only as measured by the number of patients who achieved remission at the endpoint.

Method

Study design

We report results from a large multicenter randomized controlled trial. The study was conducted at 18 study sites in France and Monaco, with active enrollment from May 2008 to July 2012. The study was approved by the ethics committee (CPP Sud-Est 6, France, #AU732), and the participants provided their written informed consent before entering the study.

The participants were recruited by physician referral to the hospital. The participants were identified by a number delivered by a centralized computer-generated randomization code to determine real or sham stimulation and real or placebo venlafaxine conditions. Randomization was stratified for the center at enrollment. The patients were randomly allocated to one of the following three arms of the study (1:1:1):

- one group received active rTMS combined with placebo venlafaxine (referred to as the "*rTMS group*" in the manuscript)
- the second group received sham rTMS combined with active venlafaxine (referred to as the "*venlafaxine group*")
- the third group received active rTMS combined with active venlafaxine (referred to as the "*combination group*")

The study included a lead–in phase, an acute phase and a follow-up phase (Fig. 1).

Lead–in phase

The lead–in phase comprised a withdrawal phase (progressive dosage decrease of current medications including benzodiazepines lasting from 1 to 3 weeks depending on the patients' current medications) and a washout phase (1 week with no-treatment). Stability of symptoms was required during this 1-week no-treatment lead–in period (from screening to baseline; see Fig. 1), with a 17-item Hamilton Depression Rating Scale (HDRS$_{17}$; [33]) total score of at least 20 at baseline and a decrease in score of less than 25% from that observed at the screening assessment.

Acute double-blind treatment phase

The acute phase consisted of a 2–6-week acute treatment period with daily active or sham rTMS and active or sham venlafaxine depending on the randomization process. The duration of this phase lasted until patients achieved remission (i.e., HDRS$_{17} < 8$). Active venlafaxine ER at 75 mg was started during this phase, which was, in most cases, the Friday before the first rTMS session (D-3), and the participants were asked to take one capsule of venlafaxine ER at 75 mg per day for 3 days (until D1). On Monday morning (D1), on the first day of the rTMS session, the participants were asked to take two capsules per day (150 mg/day). The treatment was maintained for 4 weeks (until D28), and when necessary, based on the clinical judgment of the blind investigator, the dose could be increased to 3 capsules per day for the next 2 weeks of the acute treatment phase (225 mg/day).

Follow-up (ongoing) phase

At the end of the acute double-blind treatment phase, the treatment parameters allocated by the randomization were
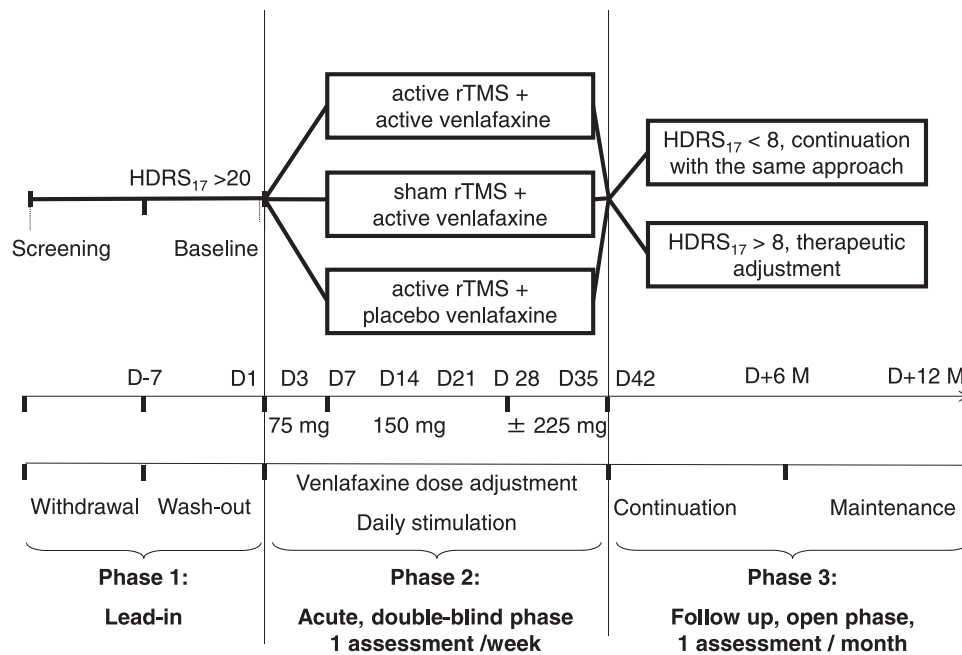
Figure 1. Overview of the study design and the 3 phases of the protocol (lead−in, acute, follow-up). Additional details on the study design were provided in the Supplementary Material 1.

maintained for the patients in remission (HDRS$_{17}$ < 8). The patients who were not in remission and who had not received active rTMS could then cross over to an open-study to receive 1 Hz rTMS (with the identical stimulation parameters used in this protocol). Finally, a 10 Hz rTMS protocol applied over the left DLPFC [5] was proposed to the patients who did not achieve remission and had received 1 Hz rTMS in the double blind phase.

Throughout the protocol and independently of the phase they were in, hydroxyzine or cyamemazine could be administered to the participants in case of major anxiety.

Participants

One-hundred and seventy patients were recruited in this study. The participants presented with a single episode or recurrent unipolar non-psychotic major depressive disorder (MDD), according to the DSM IV criteria and confirmed by a psychiatrist during a structural interview using the MINI 5.0. The participants had to present with an HDRS$_{17}$ > 20 despite receiving antidepressant treatment at an efficacious dosage for at least 6 weeks. Prior antidepressant treatment during the current and past episodes was assessed. The exclusion criteria were age under 18, other axis I disorders (except for anxiety disorders), substance use disorder (except for nicotine), somatic or neurological disorders, failure to respond to venlafaxine during the current depressive episode, pregnancy, previously received rTMS, and rTMS contraindications [4].

rTMS protocol

Depending on the investigation center, the stimulations were performed using a Magpro ×100 (Mag2Health, France) or a Magstim Super rapid (Inomed, France) stimulator system with a 70-mm figure-eight coil. The stimulation intensity was set at 120% of the resting motor threshold (RMT). The RMT was identified 3 days before the first stimulation session as the minimum magnetic field strength required to produce left thenar muscle activation by single TMS pulses delivered to the contralateral motor cortex for at least 5

of 10 trials [34]. The coil placement to the defined DLPFC stimulation was 6 cm anterior to the motor cortex hotspot. The stimulation site was outlined on a cap, which was repositioned at each rTMS session.

Stimulation consisted of 6 trains of 1-min duration separated by 30-sec inter-train "off" periods. The frequency of stimulation was 1 Hz, and the total duration of one rTMS session was 8 min 30 s. The patients received one daily session on 5 consecutive working days from Monday to Friday for at least 2−6 weeks (until remission).

Sham procedure

The sham stimulation consisted of the identical rTMS procedure; the RMT for the participants was determined at the screening visit (D-3). Determining the RMT 3 days before the start of stimulation allowed not changing the type of coil (active-sham) between the RMT assessment and the stimulation session in the presence of the participant, depending on the randomization. Sham stimulations were delivered at the identical location using a commercial figure-eight sham coil. The sham coil was similar in weight, external appearance and acoustic properties to the actual coil when it was activated; however, it did not produce the identical tactile sensation. To improve the blinding of the participants, a local electrical stimulation was delivered over the ipsilateral supraorbital area with two disposable 30-mm EMG electrodes (located on the FP2 and F8 electrode sites according to the 10/20 EEG International System). Brief electrical stimulations were synchronized at an identical frequency to the rTMS stimulator (1 Hz) using a TENS Stimulator (Cefar Primo Pro, Sweden). The intensity of the electrical stimulation was set at 2 mA in the sham condition and at 0.5 mA in the active condition. The integrity of the blinding of patients was assessed and confirmed by specific questionnaires administered to the participant and the investigator at the end of the blinding period (50% of the patients in the active TMS group believed that they were in the active TMS group; 70% of the patients in the sham TMS group believed that they were in the active TMS group).
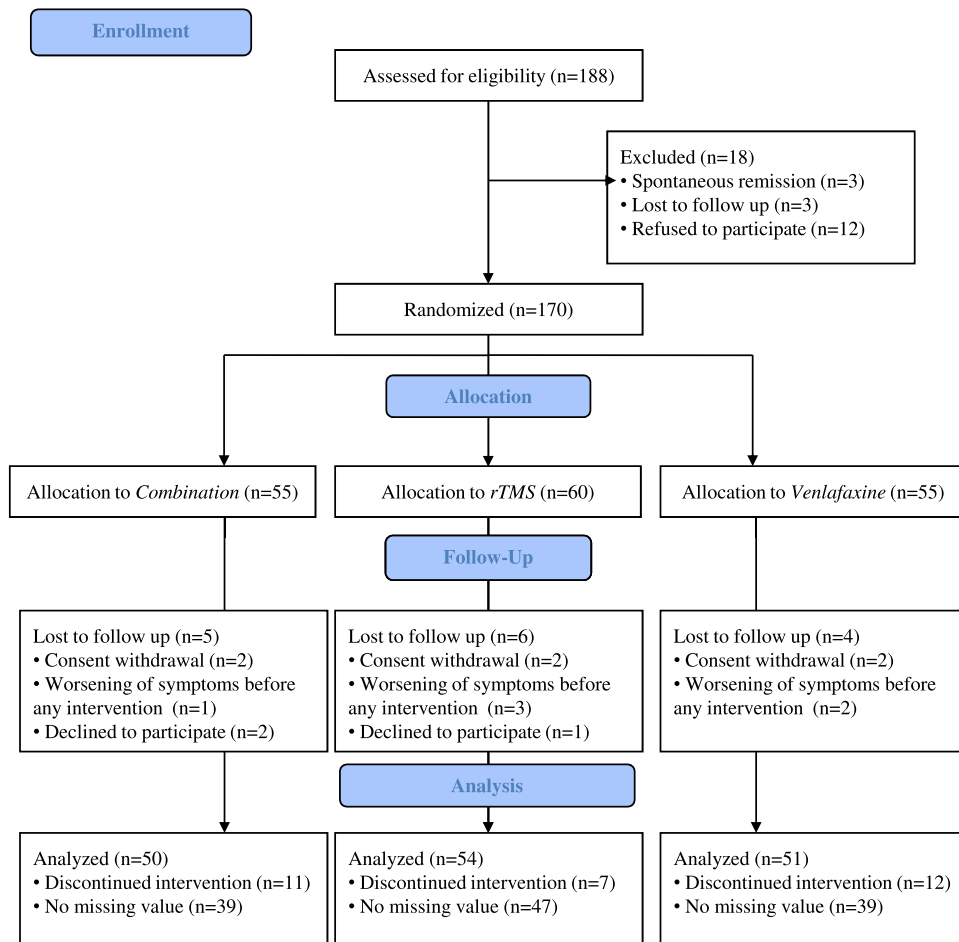
Figure 2. The CONSORT flow diagram of the study.

Clinical assessments

The clinical assessments were performed by blind investigators-raters at each center. Prior to the assessments, joint training sessions on the use of different scales were organized to verify the inter-rater reliability of the ratings.

Primary outcome

The primary efficacy outcome was the number of patients who achieved remission (defined as an HDRS$_{17}$ score <8) at the end of the acute double blind treatment phase.

Secondary outcomes

The secondary depression continuous efficacy outcomes were the HDRS$_{17}$, the 13-item self-evaluated Beck Depression Inventory (BDI$_{13}$; [35]) and the 10-item Montgomery and Asberg Depression Rating scale (MADRS$_{10}$; [36]) scores measured throughout the study. Additionally, the number of responders defined as a reduction of at least 50% from the baseline scores on the HDRS$_{17}$ was evaluated. At the inclusion and endpoint, the global clinical status and anxiety were assessed [Supplementary Material 1].

Safety assessment

Safety was assessed at each session according to a structural interview, and serious adverse events were systematically recorded by a blind rater.

Statistical analysis

The analyses were performed on a strict intention-to-treat sample of the evaluable patients defined in the protocol as patients with a baseline assessment and at least one post-rTMS score. The analyses were conducted in a last-observation carried forward (LOCF) manner through the indicated time points. The null hypothesis for the primary outcome was tested with analyses of the proportions (Chi square analysis). The effects on the continuous variables (secondary analysis) were tested using an analysis of variance (ANOVA). The significance level was set at $P < 0.05$. The baseline comparison between the groups was analyzed using chi square for the qualitative variables (e.g., sex, smoking status) and with Kruskal Wallis ANOVA for the continuous variables. The analyses were conducted on the 3 arms of the study.

The sample size was initially calculated using data from previous rTMS and venlafaxine studies by requiring a 90% power level for detecting a difference of 20% in the number of remitters between the double active group and the other groups based on the standard method.

Results

Participants

One-hundred and eighty-eight patients were initially recruited, and 170 were randomized after the lead–in phase. Among the 170

Table 1
The demographic and clinical characteristics of the participants at inclusion. The results are given as the mean (standard deviation).

	rTMS	Venlafaxine	Combination	P
n (at inclusion)	60	55	55	
Drop out before any intervention	6	4	5	1[b]
n (ITT analysis)	54	51	50	
Male/female	20/34	16/35	16/34	0.80[b]
Age (years)	53.3 (11.3)	56.2 (9.9)	54.2 (11.9)	0.57[a]
Education level (years)	11.7 (3.1)	12.1 (3.4)	12.5 (3.6)	0.49[a]
Handedness (right)	49	47	46/	0.77[b]
Smokers (yes/ex-smokers/no)	16/8/30	13/11/27	19/11/20	0.44[b]
Comorbidity with axis II (n)	17	15	13	0.91[b]
Illness duration (years)	16.2 (11.7)	20.5 (11.2)	17.3 (12.1)	0.07[a]
Ongoing episode duration (months)	15.4 (16.1)	21.9 (21.7)	14.4 (14.5)	0.07[a]
Failure of previous AD (n)	2.2 (1.5)	2.7 (1.7)	2.7 (2.2)	0.27[b]
Venlafaxine increase to 225 mg/d	14	11	14	1[b]
n drop out during protocol (discontinuation rate)	7 (13%)	12 (23%)	11 (22%)	1[b]
HDRS$_{17}$	25.8 (3.6)	25.8 (3.4)	26.1 (3.9)	0.84[a]

rTMS: repetitive transcranial magnetic stimulation; HDRS$_{17}$: Hamilton Depression Rating scale.
[a] Kruskal–Wallis ANOVA.
[b] Chi square test.

participants, 155 had at least one post baseline assessment and were analyzed in the full intention-to-treat analysis. The primary sample consisted of 60 patients who were randomized to the *rTMS group*, 55 to the *venlafaxine group* and 55 to the *combination group*. Because 15 patients dropped out from the study before the start of the rTMS session, the final sample (analyzed sample) consisted of 54 patients in the *rTMS group*, 51 in the *venlafaxine group* and 50 in the *combination group* (see Fig. 2).

The patients had a high level of resistance (mean: 2.5 ± 1.8 previous treatment failure; range 1–12), 33% had one failed treatment, 29% had 2 failed treatments and 38% had at least 3 failed treatments. The mean duration of the current episode was 14.1 ± 17.8 weeks (a median index of 9). A total of 73 patients were current smokers. The sample was composed of 103 females and 52 males, with a mean age of 54.5 ± 11.5 years and an educational level of 12.11 ± 3.4 years. The patients presented a mean HDRS$_{17}$ score of 25.86 ± 3.7 at baseline. Investigators could increase the venlafaxine dosage from 150 mg to 225 mg/day, and the number of subjects receiving the highest dose of venlafaxine was similar in the 3 groups (mean dose: 179.0 ± 36.6 mg/day). No difference was reported for the socio-demographic and clinical characteristics at baseline between the 3 groups (Table 1).

Primary outcome

There was no difference between the 3 groups in terms of the number of patients who achieved remission (HDRS$_{17}$ < 8) at the endpoint (Table 2, Fig. 3), with 41% of remitters in the *rTMS group*, 43% in the *venlafaxine group* and 28% in the *combination group* (P = 0.59).

Secondary depression outcomes

We reported a significant decrease of depression over time as measured by the HDRS$_{17}$ scores in the three groups ($F_{(6,912)} = 128.7$;

$P < 10^{-6}$) (Fig. 4, Table 3). The ANOVA revealed no difference between the groups regarding the continuous efficacy outcome measures assessed by HDRS$_{17}$ ($F_{(12,912)} = 0.36$; $P = 0.97$), MADRS$_{10}$ ($F_{(12,912)} = 0.47$; $P = 0.93$) or BDI$_{13}$ ($F_{(12,912)} = 0.52$; $P = 0.90$). Additionally, a significant decrease in depression scores over time was observed with MADRS$_{10}$ ($F_{(6,912)} = 128.7$; $P < 10^{-6}$) and BDI$_{13}$ ($F_{(6,912)} = 53.7$; $P < 10^{-6}$).

We found no difference between the 3 groups in terms of the number of responders defined as a decrease of at least 50% in the HDRS$_{17}$ score from baseline to endpoint, with 59% of the responders in the *rTMS group*, 60% in the *venlafaxine group* and 54% in the *combination group* ($P = 1$).

Covariate analysis revealed that number of failed treatment ($F_{(12,912)} = 0,36$; $P < 0,9771$) and illness duration ($F_{(12,912)} = 0,44$; $P < 0,9495$) have no effect on depression outcome.

Safety outcomes

There was no difference between the 3 groups regarding the number and the gravity of adverse events. We reported 12 serious adverse events, with 7 in the *venlafaxine group*, 3 in the *combination group* and 2 in the *rTMS group*. The most common adverse event was an exacerbation of depressive symptoms requiring the hospitalization of 5 participants. No deaths, no suicide attempts and no seizures were reported. There was no difference in the rate (13–23%) of discontinuation during the protocol (drop out during follow up, Table 1).

Discussion

This study is the first large, multisite, randomized controlled trial of daily LF (1 Hz) rTMS applied over the right prefrontal cortex in patients with treatment-resistant major depression compared to standardized antidepressant treatment. We report that the combination of LF rTMS and venlafaxine is not more efficient than

Table 2
The number of novel remitters defined as HDRS$_{17}$ < 8 in each of the 3 treatment groups at each visit.

	Week 1		Week 2		Week 3		Week 4		Week 5		Week 6		End point[a]	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
rTMS	0	0	4	7.4	1	1.9	6	11.1	4	7.4	7	13.0	22	40.7
Venlafaxine	0	0	2	3.9	6	11.8	4	7.8	6	11.8	4	7.8	22	43.1
Combination	0	0	1	2.0	5	10.0	3	6.0	3	6.0	2	4.0	14	28.0

[a] We reported no significant difference between the groups in terms of the number of remitters at the endpoint (Chi square test: $P = 0.59$).
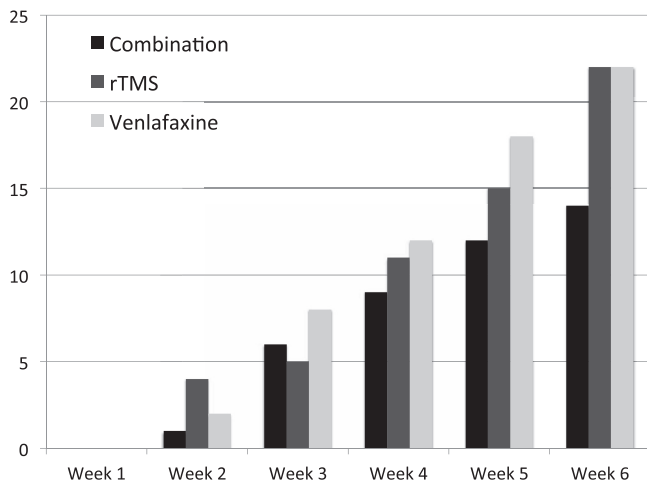
Figure 3. The number of participants achieving remission (HDRS$_{17}$ < 8) in each of the 3 groups from Week 1 to Week 6. We reported no significant difference between the groups.

venlafaxine only and rTMS only. LF rTMS appears to be as efficient as venlafaxine and as the combination of venlafaxine and rTMS in the treatment of TRD. In the *rTMS group*, we observed a mean reduction of 43% in the HDRS$_{17}$ score, 40% of remitters and 59% of responders at the endpoint (week 6). These results corroborate those from the studies that investigated LF rTMS in MDD and suggested the efficacy of LF rTMS in TRD [14,17–19]. Regarding the respective effects of rTMS and venlafaxine, our results corroborate those of previous studies. Using slightly different parameters of stimulation (600 stimulations per session, 100% MT) and of venlafaxine (from 75 to 375 mg/day), Bares et al. [20] described comparable efficacy of LF rTMS and venlafaxine measured with MADRS$_{10}$ (33% of responders and 19% of remitters) after 4 weeks of treatment.

These results support the use of rTMS as a monotherapy for the treatment of TRD and corroborate the results of previous HF
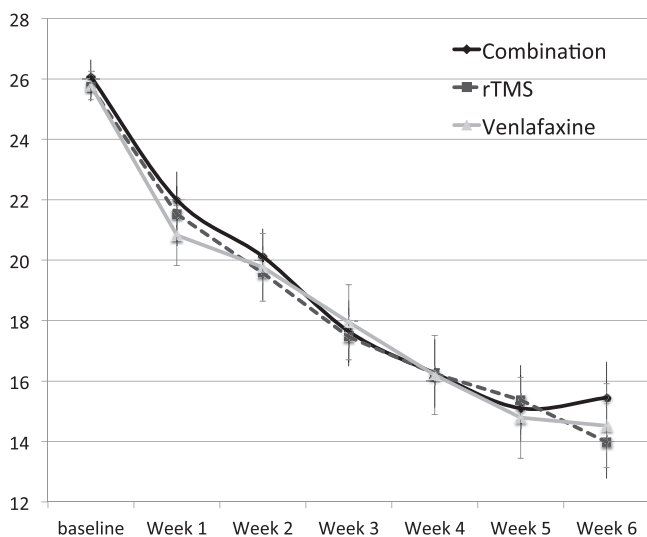
rTMS [5,6] and LF [8,21,22] studies. Previous studies with HF left prefrontal rTMS [5,6] reported lower remission rates (15%) and response rates (24%) measured with HDRS$_{17}$ than in the current LF study. The duration of one stimulation session in our LF rTMS protocol (8.5 min) is shorter than that in the HF rTMS protocols (37 min) [5,6]. Compared with the current HF rTMS parameters, which are highly time-consuming for the patients and practitioners, LF rTMS appears to be a suitable approach for therapeutic management of TRD. Numerous safety studies have reported that LF rTMS is safer than HF rTMS. Using LF rTMS in 104 patients with TRD, we observed neither manic/hypomanic shifts nor seizure induction, whereas such side effects have been described following HF rTMS [4,37]. We observed a low discontinuation rate (13% in the *rTMS group*, 23% in the *venlafaxine group* and 22% in the *combination group*) and no skin discomfort, confirming that rTMS was well tolerated. Our results indicate that LF rTMS is well tolerated and allows for stimulation sessions of short duration.

Contrary to our initial hypothesis, the combination strategy was not more effective than venlafaxine only and rTMS only. Previous studies had reported the efficacy of the combination of rTMS with pharmacotherapy. These studies primarily used HF rTMS in combination with SSRIs or tricyclics. Because SNRIs are characterized by a different mechanism of action because they block both serotonin and norepinephrine reuptake, it could be hypothesized that this mechanism of action is not additive (or synergistic) to the mechanism of the action of LF rTMS. Venlafaxine enhances cortical activation [38], whereas SSRIs depress paired-pulse facilitation [39], as revealed by TMS studies. Previous studies had investigated the combination of HF rTMS and venlafaxine; however, the results were mixed [25,27]. The mechanisms of action of intermittent or continuous HF and LF rTMS applied over the DLFPC are unclear, which limits the comparison of these approaches. The selection of venlafaxine as an antidepressant is based on studies reporting the efficacy of venlafaxine as a second line treatment after failure of an SSRI [32,40,41]. It could be hypothesized that the venlafaxine dosage (150 *vs* 225 mg/day) could have influenced the susceptibility of the brain to rTMS and subsequently the treatment efficacy. We observed that the venlafaxine dosage had no effect on the treatment outcome in the combination group ($P = 0.12$; data not shown). In our study, venlafaxine was initiated three days before the first rTMS session; in numerous previous add-on studies, rTMS was delivered in cases in which the participants had failed to respond to pharmacological treatment, and this treatment was maintained during the rTMS sessions. These differences might in part explain the discrepancies between studies; the optimum time to initiate pharmacology and rTMS and the optimal pharmacological dosage are under debate. Finally, our result is in accord with a recent meta-analysis suggesting that LF rTMS delivered in monotherapy is associated with higher rates of remitters than those in combination therapy [8].

This study has several strengths and limitations. First, regarding the sham procedure, venlafaxine and placebo venlafaxine were delivered in identical capsules. The active and sham rTMS sessions were conducted with identical active and sham TMS coils, respectively, in combination with an electric stimulator to induce comparable skin sensations during the rTMS sessions. The standardization of the pharmacological treatment for all the participants was an important strength of this study. The participants were medicated only with venlafaxine, and no concomitant medications were administered during the acute treatment phase. Standardization of the medication limits the uncontrolled pharmacological interactions that might have biased previous rTMS studies. The level of resistance (2.5 ± 1.8 failures for the current episode) in the three groups is

Figure 4. The evolution of the Hamilton Depression Rating scale (HDRS$_{17}$) scores throughout the study period in each of the 3 groups. There was no difference between the groups at baseline. The ANOVA revealed no significant difference between the groups (Group × Time interaction $F_{(12, 912)}$; $P = 0.9$) and a significant time effect revealing a decrease in the HDRS$_{17}$ scores in the 3 groups ($P < 10^{-6}$).

Table 3
The evolution (%) of the depression rating scale scores throughout the study period. There was no difference between the groups at baseline for each of the 3 scales. The ANOVA revealed no significant difference between the groups (Group $\times$ Time interaction $F_{(12, 912)}$; $P = 0.9$) and a significant decrease in the 3 groups ($P < 10^{-6}$) for the Hamilton Depression Rating scale ($HDRS_{17}$), the Beck Depression Inventory (BDI_{13}) and the Montgomery and Asberg Depression Rating Scale ($MADRS_{10}$).

	Baseline	%	Week 1	%	Week 2	%	Week 3	%	Week 4	%	Week 5	%	Week 6	%
$HDRS_{17}$														
rTMS	25.8	100	21.5	83.6	19.6	76.0	17.5	67.8	16.2	63.1	15.4	59.7	14.0	54.3
Venlafaxine	25.8	100	20.8	80.8	19.8	76.7	17.9	69.6	16.2	62.8	14.8	57.3	14.3	55.4
Combination	26.1	100	22.0	84.4	20.1	77.2	17.6	67.7	16.3	62.4	15.1	57.9	15.4	59.3
$MADRS_{10}$														
rTMS	32.8	100	27.8	84.8	25.6	78.1	22.7	69.2	17.7	53.9	19.5	59.4	17.9	54.5
Venlafaxine	32.7	100	26.7	81.7	24.9	76.2	22.0	67.3	18.5	56.4	18.3	56.0	18.0	54.9
Combination	33.5	100	29.6	88.3	26.6	79.5	23.6	70.4	18.1	54.1	20.8	62.0	20.1	60.0
BDI_{13}														
rTMS	21.4	100	17.6	82.2	17.2	80.1	15.6	72.8	14.8	68.9	13.8	64.1	13.0	60.5
Venlafaxine	20.7	100	14.9	72.1	15.4	74.5	13.2	63.9	12.7	61.5	12.1	58.4	12.0	58.1
Combination	20.8	100	17.7	85.1	15.9	76.3	15.4	74.0	14.4	69.1	14.0	67.4	13.8	66.1

higher than in previous large studies of HF rTMS, supporting the role of rTMS in high level TRD (e.g., 1.6 failures [5,6]). Our target location was 6 cm anterior to the MT location along an antero-posterior line, whereas in previous studies, the target location was generally defined as 5 cm anterior to the MT location along an oblique plane with a rotation point at approximately the tip of nose of the patient [5]. This location 6 cm anterior to the MT location appears to more accurately target the coil over the DLPFC (BA 9/46), the theoretical cortical target, and to reduce the premotor stimulation in BA6 [42]. The stimulation intensity (120% MT) is the intensity recommended to obtain the optimum results in term of remission [43]. Our study is one of the first to stimulate at such a high intensity with right-sided LF rTMS. Regarding the sample size, 170 patients were included, which is a large effective size compared to that in previous rTMS studies, particularly in studies using low frequency. Only patients with MDD were included, with bipolar disorder patients being excluded. We reported that a relative few number of stimulations per session (360 stimulations) efficiently decreased the depression scores. This result is in agreement with a recent meta-analysis, which reported that depression scores were significantly lower in the rTMS studies, with fewer stimuli per session [44].

One important limitation of this study is the three-arm design without a double-placebo arm. This design was used predominantly for ethical reasons as well as for the following reasons: previous studies have reported the superiority of LF rTMS compared to placebo [9,13] and the non-inferiority of LF rTMS compared with venlafaxine [20]; and each of the approaches (rTMS and venlafaxine) has been reported to be more effective than a placebo in large RCTs (see, respectively [5,6] and [32,41,42]). The authors acknowledge that their primary hypothesis could not be confirmed and that definite conclusions regarding the efficacy of LF rTMS in depression could not be drawn because of the lack of a placebo-medication and sham-TMS group. That the observed effects were spontaneous and unrelated to treatment could not be excluded, although this result appears to be highly unlikely given the high level of treatment resistance in this sample.

Conclusion

Because no significant difference was observed between the groups, our results suggest that LF rTMS is a suitable alternative as monotherapy for the treatment of TRD. Daily stimulation sessions could be continued over a 6-week period without any serious adverse event.

Author contribution

Drs. Poulet and Brunelin had access to the full data of this study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Benhadira, Brunelin, Galinowski, Januel, Poulet, Rachid. Acquisition of data, inclusion of participants, clinical assessment: Attal, Gay, Haffen, Jalenques, Januel, Poulet, Szekely, Trojak and the members of the STEP group. Management of data, study survey: Brault, Schott-Pethelaz. Analysis of data: Brault, Brunelin, Schott-Pethelaz. Interpretation of data: Brunelin, Haffen, Poulet, Szekely. Drafting the manuscript: Brunelin, Haffen, Poulet, Rachid, Szekely. All of the authors participated in the revision and approved the final version of the manuscript.

Conflict of interest disclosure

None reported.

Funding/support

Role of the sponsor

The funding sources had no role in the design and conduct of the study, the data collection management, analysis and interpretation of the data, drafting or submission of the manuscript.

Acknowledgment

TROJAK, Vincent MEILLE, CHU Dijon, Hôpital Général—Service de Psychiatrie et d'Addictologie, 21000 Dijon; Thierry BOUGEROL, David SZEKELY, Mircea POLOSAN, Clinique Universitaire de Psychiatrie, Pôle Psychiatrie-Neurologie, Centre Hospitalier Universitaire, Grenoble, France, Physiopathologie du Cytosquellette, Grenoble Institut des Neurosciences, Université Joseph Fourier, Grenoble, France; Maxime BUBROVSZKY, Hôpital Fontan—CHRU Lille, 59000 Lille; Abderrafi AÏT-AMEUR, ASM Limoux, 11200 Lézignan-Corbières; Raphaelle RICHIERI, C.H. Sainte Marguerite, 13000 Marseille; Jerome ATTAL, CHU—Hôpital La Colombière, 34000 Montpellier; Michel BENOIT, Hôpital Pasteur—CHU Nice, 06000 Nice; André GALINOWSKI, Thierry GALLARDA, Marion PLAZE, Hôpital Sainte Anne—Service Hospitalo-Universitaire de Santé Mentale et de Thérapeutique, 75014 Paris; Némat JAAFARI, Nicolas LAFAY, Jean Yves ROTGE, CHU de POITIERS, 86000 Poitiers; Bruno MILLET, Cecilia NAUCZYCIEL, CHU— CH Guillaume Régnier 35000 Rennes; Florence THIBAUT, Gaël FOULDRIN, CHU Charles Nicolle—Service Hospitalo-Universitaire de Psychiatrie, 76000 Rouen; Dominique JANUEL, René BENADHIRA, EPS de Ville Evrard—Unité de Saint-Denis, 93200 Saint-Denis, Catherine MASSOUBRE, Stéphane BILLARD, Aurélia GAY, CHU St Etienne—Hôpital Nord, 42055 St Etienne cedex; Irena CUSSAC, Centre Hospitalier Princesse Grace, Monaco, Monaco, 98000, Fady RACHID, 7 Place de la Fusterie 1204 Genève, Suisse.

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.brs.2014.07.040.

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