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Cerebellar repetitive transcranial magnetic stimulation (rTMS) for essential tremor: A double-blind, sham-controlled, crossover, add-on clinical trial

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ABSTRACT

Background: There is controversial evidence about the effect of cerebellar low-frequency stimulation in patients with essential tremor (ET).
Objectives: In this study we assessed safety and effectiveness of 1 Hz (low-frequency) cerebellar repetitive transcranial magnetic stimulation (rTMS) on tremor severity in patients with essential tremor in a sham-controlled crossover trial.
Methods: A total of 23 patients assigned into two groups to receive either sham (n = 10) or rTMS (n = 13) treatment, with crossing over after a two-month washout period. Intervention consisted of 900 pulses of 1 Hz rTMS at 90% resting motor threshold or the same protocol of sham stimulation over each cerebellar hemisphere for 5 consecutive days. Tremor severity was assessed by Fahn-Tolosa-Marin (FTM) scale at baseline and at days 5, 12 and 30 after intervention. The FTM consists of 3 subscales including tremor severity rating, performance of motor tasks, and functional disability. Carry-over and treatment effects were analyzed using independent samples *t*-test.
Results: There was no significant improvement in the total FTM scores in rTMS compared to the sham stimulation on day 5 ($p = 0.132$), day 12 ($p = 0.574$), or day 30 ($p = 0.382$). Similarly, FTM subscales, including tremor severity rating, motor tasks, and functional disability did not improve significantly after rTMS treatment. Mild headache and local pain were the most frequent adverse events.
Conclusion: Although cerebellar rTMS seems to have acceptable safety when used in ET patients, this study could not prove any efficacy for it in reduction of tremor in these patients. Larger studies are needed to evaluate efficacy of this therapeutic intervention and to provide evidence about the optimal stimulation parameters.

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Introduction

Essential tremor (ET) is one of the most common adult movement disorders with a prevalence rate of 0.9% in general population. ET presents typically with a postural kinetic tremor in the limbs, voice, chin, or neck [1]. Tremor usually worsens with age leading to increased disability of patients as well as loss of their independence. Despite detrimental effects on quality of life of patients, medications traditionally used as the first-line treatment for ET are neither effective enough nor completely safe in a considerable number of patients [2,3]. Although deep brain stimulation (DBS) and other surgical procedures such as thalamotomy may provide better unilateral tremor control, they are invasive [4,5] and many patients prefer not to select surgical therapeutic options. Altogether, currently there are very few effective non-invasive safe therapeutic strategies for treatment of this common neurological disorder.

The presence of cerebellar features in ET such as kinetic/intention tremor [6], cerebellar gait features [7,8], dysarthria [9], eye movement abnormalities [10], as well as reports of tremor improvement after cerebellar stroke [11,12] among others [13], highlight the role of cerebellum in pathogenesis of tremor in ET. Although current evidence does not support the presence of a single central oscillator for ET [14,15], cerebellar overactivation has been demonstrated by functional imaging studies of ET patients [16] and an altered connectivity of the cerebello-thalamo-cortical (CTC) connections in ET currently seems to be an agreed paradigm [17–20]. Overall, the above mentioned studies make the cerebellum a reasonable target for ET therapeutic interventions.

It has been known for decades that a conditioning electrical or magnetic stimulus delivered to the cerebellum inhibits the primary motor cortex excitability, contralateral to the cerebellar stimulus, probably via CTC connections [21–23]. This effect was known as cerebellar inhibition (CBI). Subsequent studies showed that CBI can be modulated by cerebellar repetitive transcranial magnetic stimulation (rTMS) or transcranial direct current stimulation (tDCS). These modulatory effects last at least for 30 min [24–26]. Gironell et al. showed that a single session of 1 Hz cerebellar rTMS (30 trains of 10-s duration) can reduce tremor severity in ET patients when assessed within 5 min of intervention but not after 60 min [27]. A more durable reduction of tremor has been reported by Popa et al. after 5 consecutive daily sessions of 1 Hz cerebellar rTMS [28]. They showed that the functional connectivity of the CTC network increases significantly in ET patients after 5 sessions of 1 Hz cerebellar rTMS. However, this study was not sham-controlled. Larger sham-controlled studies are necessary before application of these promising results to the clinical practice since trials using tremor as the outcome measure are prone to large placebo effects [29,30]. For the first time we assessed the efficacy of multiple sessions of bilateral low-frequency cerebellar rTMS in reducing tremor in ET patients in a double blind sham controlled trial with crossover design.

Methods

Cognitively normal patients aged more than 18 years old with diagnosis of classical ET based on Movement Disorder Society (MDS) criteria [31] were included in this prospective randomized double-blind, sham-controlled, 2 by 2 crossover, add-on clinical trial. At the time of recruitment for this study, the new MDS tremor classification [32] was not available. However, on retrospective application of the new diagnostic criteria, all patients included in this study fulfilled the new ET criteria except one patient who had a tremor duration of 2 years at the first visit. Our sample included no ET plus subjects based on the new definitions. Patients who had any contraindications for exposure to the magnetic field as well as those with a history of seizure were excluded from the study. Eligibility was assessed in 37 patients of whom 23 were included and randomized into either "Sham-rTMS" (n = 10; sequence 1) or "rTMS-Sham" (n = 13; sequence 2) sequences. In the sequence 1, patients received sham stimulation for 5 consecutive days (period 1) and after a two-month washout period received rTMS for another 5 consecutive days (period 2). In the sequence 2, patients received same interventions in a reverse order (i.e. rTMS in period 1 and sham stimulation in period 2) (Fig. 1). In every session, rTMS or sham stimulation was first delivered to the right occipital area followed by the stimulation of the left side with a 5 min interval.

In active arm, patients received 900 daily pulses of 1 Hz rTMS on 90% of resting motor threshold (RMT) over each cerebellar hemisphere for 5 consecutive days. RMT was measured based on the stimulation intensity that produced only 5 visible contractions out of 10 stimulations in abductor pollicis brevis muscle of the dominant hand. The stimulation intensity was further adjusted based on

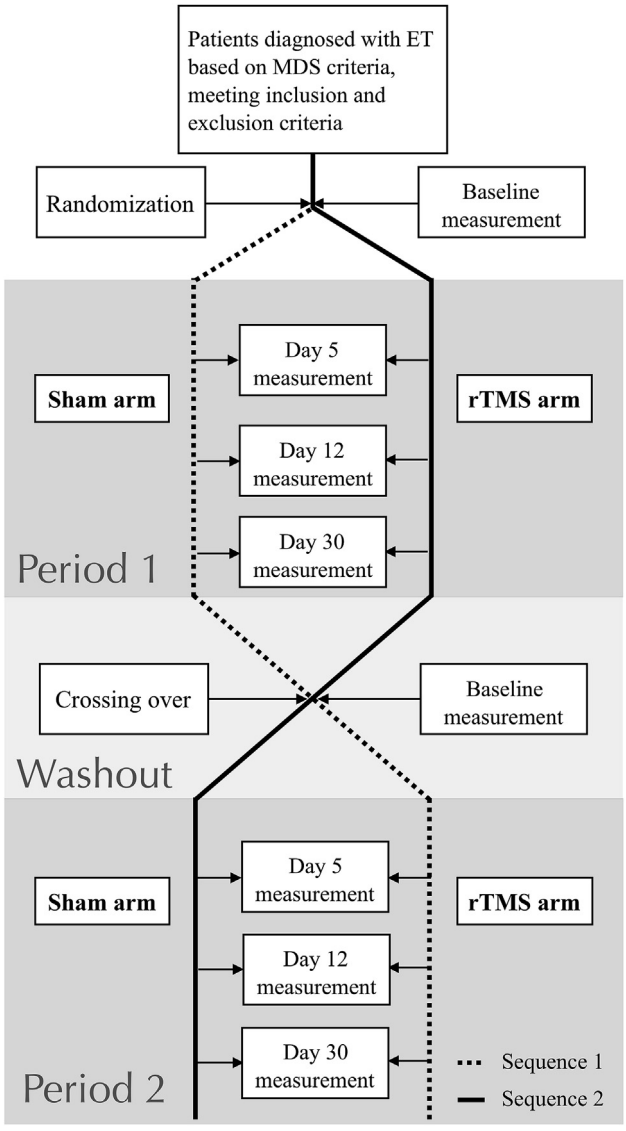

Fig. 1. Study design.
ET: Essential tremor; MDS: Movement Disorders Society; rTMS: repetitive transcranial magnetic stimulation.
Modified with permission from Shoeibi and Olfati, 2016 [36].

the measured distances between motor or cerebellar cortices and scalp, using the data obtained from the baseline magnetic resonance imaging (MRI) of each patient [33]. Baseline MRI included a T1-MPRAGE 3D sequence at 1 mm thickness. Distances were measured using Osirix MD software. RMT adjustment was performed using the following formula: Adjusted RMT = mRMT + m × ($D_{Cerebellum}$ - D_{M1}), where mRMT is the measured RMT in percentage of stimulator output, D_{M1} is the scalp-motor cortex distance, $D_{Cerebellum}$ is the scalp-cerebellar cortex distance, and m is the distance-effect gradient, calculated as ~2.8% by Stokes et al. [33]. Magnetic stimulation was delivered using a Neuro-MS/D variant 2 (therapeutic) device (Neurosoft Ltd., Ivanovo, Russia) with a 2 × 100 mm winding diameter angulated figure of eight coil. Peak magnetic field generated by this coil is 1.6 T at 100% stimulus amplitude. On each side, coil was positioned at $^1/_3$ distance from inion to the mastoid process. This positioning was based on previous studies that showed effective stimulation of the cerebellum using this area [26,34]. Use of this proportion of distance between the two landmarks to select the target in lateral cerebellum allowed us to adjust for skull size. Coil was angulated 45° towards midline with a caudal to rostral current flow.

Sham stimulation was performed with the same protocol using an inactive coil mounted with a small device producing 300 ms-long pulses of low intensity (up to 2 mA) electrical stimulation with simulation of rTMS sound. It was intended to induce an electrical sensation over the scalp delivered by 10 mm gold disc electrodes (one cathode and one anode). This sham stimulation was considered passive since no significant neuromodulatory effect has been reported for this protocol of electrical stimulation [35]. Patients were allowed to continue their previous tremor medications and instructed not to change their medication/dosage at least one month prior and during the study. The methods have been described with more details elsewhere [36]. Clinical effects were assessed using the Fahn-Tolosa-Marin (FTM) clinical scale which includes three subscales of (A) tremor location/severity rating, (B) specific motor tasks, and (C) functional disability [37]. FTM scores range from 0 to 160 with higher scores indicative of more severe tremor. The first subscale includes rating of resting, postural and intention tremor amplitudes in various anatomic locations including limbs, head/neck, tongue, voice, and trunk. The second subscale evaluates performance of motor tasks, including writing, spiral drawing, and pouring. The third subscale assesses tremor-related functional disability in daily living activities including speaking, eating, drinking, hygiene, dressing, writing, working, and social activities. A neurologist (HA) blinded to the intervention type performed measurements at baseline, day 5 (after the 5th rTMS/sham session), day 12 (7 days after the 5th rTMS/sham session), and day 30. Adverse events were recorded at every visit or upon patient report.

Baseline characteristics were analyzed using independent samples *t*-test and Chi square/Fisher's exact tests. Considering the crossover nature of this study firstly we assessed first order carryover effect. For this purpose, difference of baseline responses (measured total and subscale FTM scores) between the two periods were calculated separately for each subject. Results were compared between the two sequences using independent samples *t*-test. For evaluation of the second order carryover effect, differences between baseline and day 30 were calculated for each subject-period. Independent samples *t*-test was used to assess second order carryover effect [38]. First and second order carryover effects were not significant at 10% level (see Results for more information). This allowed us to assess the treatment effect, response differences of the two periods at each time point, using independent samples *t*-test [38]. One-sample Kolmogorov-Smirnov test showed that all variables have normal distribution. A significance level of 5% was assumed at this analysis. R 3.3.3 software was used to run these analyses.

All patients signed a written consent in advance of the intervention. Study was approved by our institutional Research Ethics Board (approval code: ir.mums.sm.rec.1394.353) and was conducted in accordance with the international declaration of Helsinki. Study was registered in ClinicalTrials.gov (identifier: NCT02704793) and IRCT.ir (identifier: IRCT2015100824428N1).

Results

All 23 patients received their intended treatments. One patient did not complete the first period and was excluded from analysis of the main outcome in both treatment periods. Three patients did not attend only their second periods (Fig. 2).

Of twenty-three patients 14 (64%) were male. Mean age of participants was 60 ± 15.38 years. Mean tremor duration was 17.4 ± 12.51 years. Six patients (26.1%) had no family history of ET in first degree relatives. All patients had hand tremor. Other locations for tremor in decreasing frequency included legs (78.3%), head (30.4%), tongue (26.1%), trunk (17.4%), voice (8.7%), and face (4.3%). Baseline and demographic data are shown in Table 1. There was no significant difference in tremor duration, severity of tremor based on baseline FTM scale, and use of tremor medications between the two sequences at baseline. Scalp-to-cerebellar cortex distance was significantly larger in the rTMS-sham sequence compared to the sham-rTMS sequence ($p = 0.03$). However, adjusted resting motor thresholds were not significantly different between the two sequences.

Treatment tolerability was generally good. A total of 12 adverse events occurred in 11 patients during the study which were generally mild. These include 3 headaches (1 during rTMS and 2 during sham periods), 3 local pain during rTMS, 2 visual disturbances during rTMS, one neck spasm during rTMS, one episode of light-headedness during rTMS, one episode of dizziness during rTMS, and one transient ischemic attack (TIA)-like episode during sham period. We did a comprehensive evaluation of the TIA-like event which presented as mild (MRC grade 4) left hemiparesis lasting about 2 h in a hypertensive elderly participant. Patient noticed a left-sided weakness at the end of the last sham stimulation over the left occipital area. Patient had completed both rTMS and sham periods before the TIA-like episode occurred and he continued to attend follow-up visits on days 12 and 30. An MRI with diffusion weighted (DWI) and map of apparent diffusion coefficient (ADC) sequences was performed a few hours after symptom resolution which was essentially normal. We deemed that this event was unrelated to the study interventions. All headache as well as local pain and light-headedness episodes were mild, lasted no more than a few hours and improved spontaneously. Visual disturbances were in the form of nonspecific blurring of vision with normal examination of eye movements which lasted less than 1 h. Bilateral neck spasm occurred at the last day of rTMS treatment (first period). Symptom resolved within 2 days without medical treatment. None of these episodes caused discontinuation of treatment except for the dizziness episode, which was accompanied with worsening of a preexisting anxiety disorder. In this patient anxiety, and not the dizziness episode, was the prime cause of treatment discontinuation. Gait and coordination examination was normal. In the sham periods, patients reported non-irritating electrical sensation at the site of stimulation which faded after a few minutes.

First and second order carryover effects were not significant at the 10% level when assessed for total ($p = 0.547$ and $p = 0.939$ respectively) or subscale FTM scores (tremor severity rating: $p = 0.408$ and $p = 0.265$, motor task: $p = 0.342$ and $p = 0.198$, functional disability: $p = 0.176$ and $p = 0.697$, respectively).

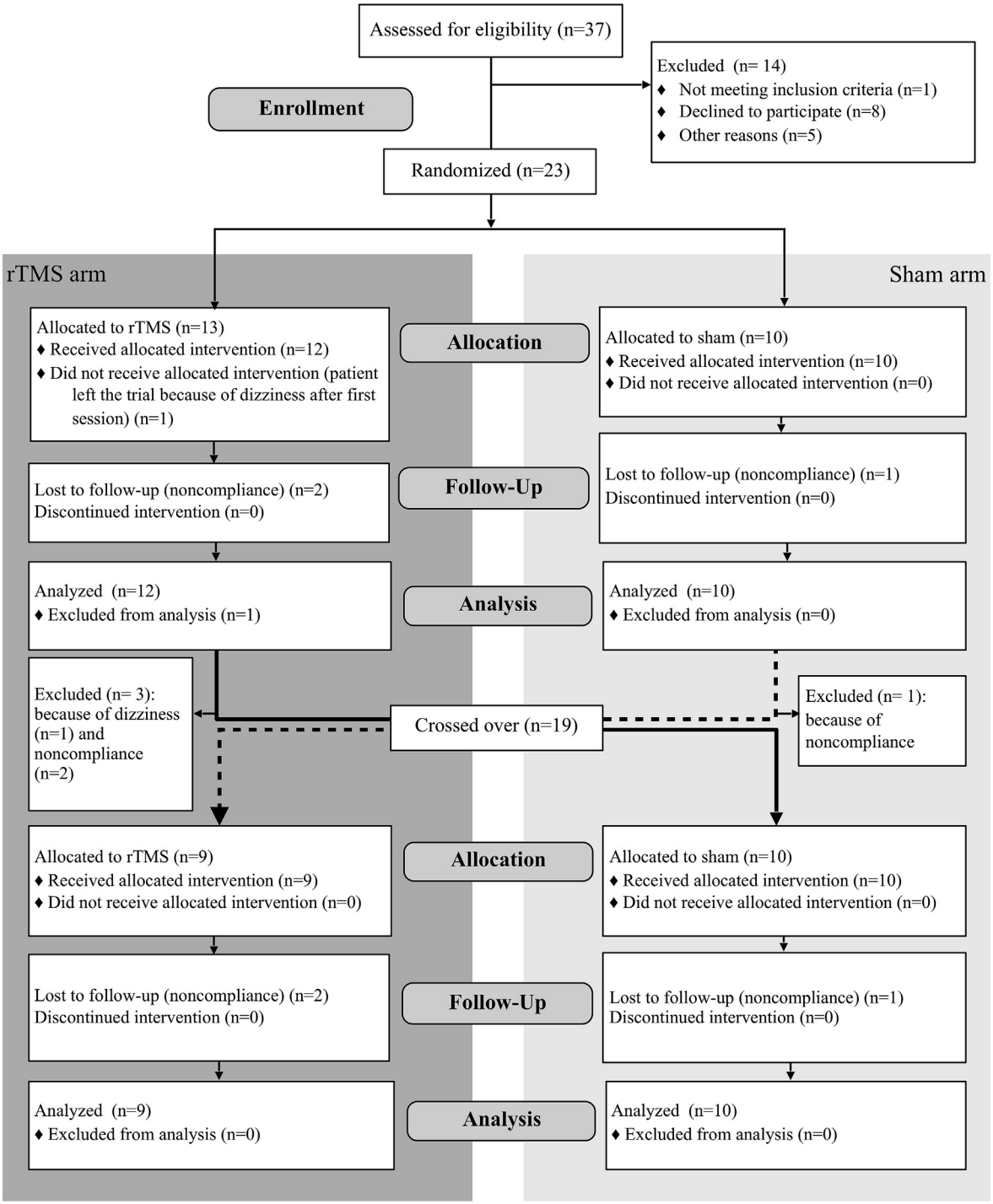

Fig. 2. Flow diagram of participants through the study.
rTMS: repetitive transcranial magnetic stimulation.

Tremor severity decreased in all four sequence-periods after application of either rTMS or sham on day five (Table 2). A large placebo effect (i.e. 70% or more reduction in tremor severity based on total FTM scores on day 5 compared to the baseline) was observed in one patient of sequence 1. Such placebo response has been reported in a previous study of rest tremor in Parkinson's disease patients [30] and in a meta-analysis of placebo response in patients with essential tremor [29]. To avoid confounding by this outlier we removed this placebo responder from the analysis for the treatment effect.

No aspect of tremor improved significantly at any time point after application of cerebellar rTMS.

For the total FTM score the treatment difference (rTMS effect - sham effect) was not significant on day 5 ($p = 0.132$, confidence interval (CI): 2.1 to 0.3), day 12 ($p = 0.574$, CI: 0.5 to 0.8), or day 30 ($p = 0.382$, CI: 0.7 to 1.8) (Fig. 3). Similarly, treatment difference was

Table 1
Baseline characteristics of the patients.

		Number (%) or Mean (±SD)		P value
		rTMS-Sham sequence	Sham-rTMS sequence	
Gender	Male (%)	7 (58.3)	7 (70)	0.67
Age (SD)		60.3 (±9.4)	59.3 (±21.1)	0.88
Tremor duration (SD)		17.9 (±11.6)	16.1 (±14.1)	0.74
Use of tremor Medication (%)	Yes	10 (83.3)	6 (60)	0.35
	No	2 (16.7)	4 (40)	
Family history (%)	Yes	8 (66.7)	8 (80)	0.65
	No	4 (33.3)	2 (20)	
Total FTM score		26.8 (±12.3)	35.6 (±23.4)	0.30
FTM subscale A score (tremor severity rating)		9.0 (±4.6)	10.5 (±8.0)	0.59
FTM subscale B score (motor tasks)		10.6 (±5.5)	15.2 (±10.0)	0.22
FTM subscale C score (functional disability)		7.3 (±3.4)	9.9 (±6.9)	0.26
Scalp-to-motor cortex distance (mm)		14.8 (±2.9)	14.9 (±3.1)	0.91
Scalp-to-cerebellar cortex distance (mm)		19.7 (±2.1)	17.1 (±3.1)	0.03
Measured resting motor threshold (%)		58.8 (±11.7)	61.3 (±17.2)	0.73
Adjusted resting motor threshold (%)		74.7 (±10.7)	66.8 (±9.0)	0.15
Calculated stimulation intensity (%)		67.2 (±9.5)	60.3 (±7.8)	0.16

SD: standard deviation; rTMS: repetitive transcranial magnetic stimulation; FTM: Fahn-Tolosa-Marin.

Table 2
Mean FTM scores (total and subscale).

	Seq	Period 1				Period 2			
		Baseline	Day 5	Day 12	Day 30	Baseline	Day 5	Day 12	Day 30
Tremor Severity Rating	TS	9.0 ± 4.6	6.6 ± 3.6	5.6 ± 2.6	6.2 ± 2.5	6.8 ± 4.3	5.3 ± 4.9	5.6 ± 4.3	6.3 ± 5.1
	ST	10.5 ± 8.0	6.9 ± 5.9	8.0 ± 6.3	7.9 ± 5.7	6.6 ± 4.0	6.4 ± 3.9	6.3 ± 4.2	5.8 ± 3.2
Performance of Motor Tasks	TS	10.6 ± 5.5	9.8 ± 6.8	10.0 ± 5.8	11.1 ± 6.1	10.0 ± 6.6	8.5 ± 5.9	8.9 ± 5.6	10.2 ± 6.0
	ST	15.2 ± 10.0	12.7 ± 9.1	13.5 ± 9.4	13.6 ± 8.3	12.2 ± 8.3	10.6 ± 7.6	11.1 ± 8.2	11.3 ± 8.4
Functional Disability	TS	7.3 ± 3.4	6.1 ± 3.4	5.8 ± 3.4	5.5 ± 2.9	5.6 ± 3.1	5.1 ± 2.9	4.8 ± 2.2	5.0 ± 3.1
	ST	9.9 ± 6.9	8.9 ± 6.2	8.8 ± 6.2	8.7 ± 6.1	8.3 ± 5.6	7.7 ± 5.9	7.4 ± 5.7	7.2 ± 5.5
TOTAL	TS	26.8 ± 12.3	22.4 ± 12.1	21.5 ± 10.5	22.8 ± 10.4	22.4 ± 13.5	18.9 ± 12.4	19.3 ± 10.6	21.5 ± 13.2
	ST	35.6 ± 23.4	27.8 ± 20.0	30.3 ± 20.1	30.2 ± 19.4	27.1 ± 16.7	24.7 ± 15.6	24.9 ± 16.8	24.3 ± 16.0

Figures are mean ± standard deviation. Seq: sequence; TS: rTMS-sham sequence; ST: sham-rTMS sequence.

not significant for FTM subscales including tremor severity rating [day 5 (p = 0.148, CI: 1.3 to 0.2), day 12 (p = 0.663, CI: 0.4 to 0.6), and day 30 (p = 0.509, CI: 0.5 to 1.0)], performance of motor tasks [day 5 (p = 0.955, CI: 0.7 to 0.7), day 12 (p = 0.466, CI: 0.3 to 0.7), and day 30 (p = 0.459, CI: 0.4 to 0.9)], and functional disability [day 5 (p = 0.053, CI: 0.8 to 0.0), day 12 (p = 0.580, CI: 0.6 to 0.3), and day 30 (p = 0.874, CI: 0.4 to 0.5)].

These effects were symmetrical when appendicular tremor severity rating and motor task subscales were analyzed separately on each side of the body. Cerebellar rTMS did not improve midline tremors at any time point.

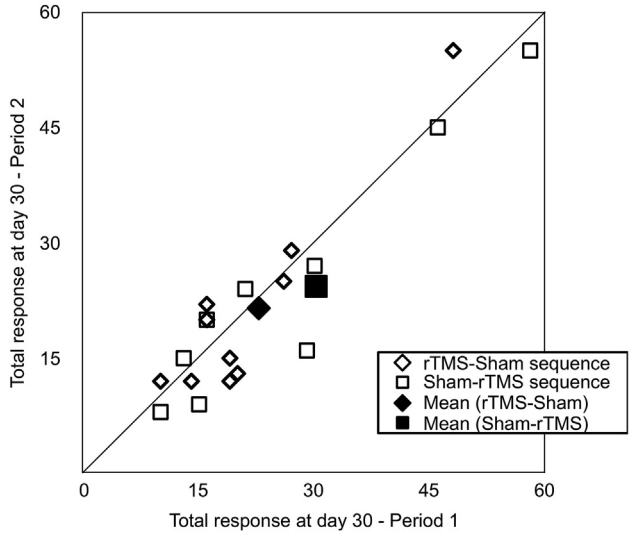

Fig. 3. Total Fahn-Tolosa-Marin scores during each study period. Sets of points for both treatment periods are depicted on this graph. The centroid of each group is shown with a larger solid character. The centroids are placed on one side of the line which is the evidence of no treatment effect.
rTMS: repetitive transcranial magnetic stimulation.

Discussion

In this double-blind sham-controlled trial we assessed the effect of a course of 5 consecutive daily low-frequency rTMS sessions over cerebellar hemispheres on patients with essential tremor. Overall, no significant effect of rTMS was observed on any aspect of tremor at any time point. In a previous uncontrolled study [28], Popa et al. reported a significant long-lasting decrease in all aspects of tremor after application of the same rTMS protocol as our study in 11 ET patients which was accompanied by improved CTC network connectivity in functional MRI studies. We did not observe such prolonged effect of cerebellar rTMS in our sample. Although tremor severity based on total FTM scores increased less from day 5 to day 30 in rTMS periods compared to sham periods, this was not statistically significant. In a recent parallel-designed single-blinded randomized, sham-controlled study of a similar 1 Hz cerebellar rTMS [39], Shin et al. reported no improvement in either total or subscale FTM scores measured immediately after intervention and 4 weeks later in 22 ET patients. Our study benefits from a double-blind and crossover design which improves the power while also providing control for various confounders.

A number of limitations should be considered while evaluating results of our study. There is an inherent difficulty in measuring severity of tremor. Variabilities occur both inter- and intra-individually. Various factors including caffeine use [40,41], anxiety [42], and fatigue [43] could potentially account for some of these variabilities. We tried to address the issue of inter-individual variability using a crossover design. Another limitation of our study was the fact that we did not use any neuronavigation technique to localize the site of stimulation, so we cannot exclude the possibility of improper coil positioning. However, this can also be considered as a strength of this study regarding the fact that this setting might better reflect a real clinical practice situation, along with add-on nature of our study. Moreover, RMT measurement was based on visually perceptible muscle contraction which seems to be prone to over-estimation especially in elderly patients with joint problems [44]. Measuring tremor with more objective tools, such as accelerometer, could possibly allow detecting smaller changes in tremor severity. In addition, there are limitations in the use of subscales of the second version of FTM scale since their clinimetric properties are not yet known [45–47].

Special attention should be given to the degree of placebo effect observed in this study. A considerable fall in the FTM scores, comparing baseline to the 5th day, was evident in the sham periods, especially when the sequence was starting with the sham (sequence 2). Although we conclude that our sham stimulation was effective in generating a placebo effect, this may entail that a larger sample with a more rigorous design is probably needed to confidently differentiate between placebo and treatment effects. In fact, a previous study showed that more than half of the patients with tremor-dominant Parkinson's disease experience at least 70% improvement of their rest tremor amplitude after receiving placebo [30]. Significant placebo response has been also reported in patients with essential tremor [29]. In our study one patient in the sham-rTMS sequence showed at least 70% reduction in tremor severity, comparing day 5 to the baseline total FTM scores, after sham stimulation (period 1). This could be accountable for a major part of the placebo response we observed at the sequence 2. We removed this outlier form analysis of the treatment effect to avoid its confounding effect. Finally our results show that this study is underpowered and future studies should consider recruiting larger samples to detect possible therapeutic effects.

Our findings show that 1 Hz cerebellar rTMS is a relatively safe technique when used in ET patients, however, we could not show any therapeutic effect of this modality in these patients. Considering that the safety of cerebellar rTMS in ET patients have been shown in multiple studies [27,28,39] including the present study, and in the view of limitations of the current and previous studies, it might be acceptable to proceed to evaluation of low frequency cerebellar rTMS in larger samples with a design involving multiple courses of treatment before revisiting of the original hypothesis. Future studies should recruit larger samples of ET patients and exploit more rigorous designs to address the issue of the placebo effect and other limitations.

Declaration of competing interest

None.

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