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Original article

# Augmentative repetitive Transcranial Magnetic Stimulation (rTMS) in the acute treatment of poor responder depressed patients: A comparison study between high and low frequency stimulation

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ABSTRACT

*Background:* While the efficacy of repetitive transcranial magnetic stimulation (rTMS) in Major Depressive Disorder (MDD) is well established, the debate is still open in relation to bipolar depression and to a possible different effectiveness of high vs. low stimulation. The present study was aimed to assess and compare the efficacy and tolerability of different protocols of augmentative rTMS in a sample of patients with current Major Depressive Episode (MDE), poor drug response/treatment resistance and a diagnosis of MDD or bipolar disorder.

*Methods:* Thirty-three patients were recruited in a 4-week, blind-rater, rTMS trial and randomised to the following three groups of stimulation: (1) ($n = 10$) right dorsolateral prefrontal cortex (DLPFC) 1 HZ, 110% of the motor threshold (MT), 420 stimuli/day; (2) ($n = 10$) right DLPFC, 1 Hz, 110% MT, 900 stimuli/day; (3) ($n = 13$) left DLPFC, 10 Hz, 80% MT, 750 stimuli/day.

*Results:* Twenty-nine patients completed the treatment, showing a significant reduction of primary outcome measures (HAM-D, MADRS and CGI-S total scores: $t = 8.1$, $P < 0.001$; $t = 8.6$, $P < 0.001$; $t = 4.6$, $P < 0.001$ respectively). No significant differences in terms of efficacy and tolerability were found between high vs. low frequency and between unipolar and bipolar patients. Side effects were reported by 21% of the sample. One of the 4 dropouts was caused by a hypomanic switch.

*Conclusions:* Augmentative rTMS appeared to be effective and well tolerated for the acute treatment of unipolar and bipolar depression with features of poor drug response/treatment resistance, showing a comparable effectiveness profile between protocols of high and low frequency stimulation.



## 1. Introduction

Traditionally used in neurophysiology as a research tool to investigate neuronal excitability [26], transcranial magnetic stimulation (TMS) has since been employed in different neuropsychiatric conditions, as treatment for major depression, schizophrenia and anxiety disorders, neurodegenerative and movement disorders, tinnitus as well as chronic pain and stroke rehabilitation [2,39,25]. TMS' mechanism of action lays on the application of non invasive electrical stimulation to the cerebral cortex by means of magnetic pulses [15]. Within the brain, the magnetic fields generated by a special coil convert into an electrical current that is supposed to produce long-term effects, modulating neuronal activity in a targeted area of dysfunctional cortex [15].

Repetitive TMS (rTMS) is conventionally directed at the level of the dorsolateral prefrontal cortex (DLPFC) in mood disorders, in light of several neurophysiological and neuroimaging studies documenting specific dysfunctions at such level [9,51]. For instance, an imbalanced activity of the frontal lobes in depressed patients and, in particular, a hypofunction of the left lobe caused by excessive inhibition exerted by the overactive right lobe, have been reported [46]. For such reason, low frequency stimulation (LF-rTMS, $\leq 1$ Hz) of the right DLPFC is supposed to exert neural inhibition, while high frequency stimulation (HF-rTMS, $> 1$ Hz) on the left hemisphere the opposite effect [40].

In 2008, TMS has been approved by the U.S. Food and Drug Administration for the treatment of "adult patients who have failed to achieve satisfactory improvement from one prior antidepressant medication at or above the minimal effective dose

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and duration in the current episode" [29]. Even at the current time, however, certain parameters of stimulation and other factors related to the way TMS is administered still represent critical aspects to be better defined, in order to increase chances of treatment response [27]. In fact, it has been pointed out that the available clinical data in the field derive from studies conducted with heterogeneous design and samples of patients with mixed clinical presentation [27]. Despite such limitations, a consistent body of evidence endorsed rTMS antidepressant efficacy and safety in the treatment of major depressive disorder (MDD) [17], including recent meta-analyses comparing active vs. sham stimulation [3,4,24,16].

On the other hand, rTMS efficacy in bipolar depression has been poorly investigated so far, with solid evidence still lacking [14]. From this perspective, a number of open studies showed positive effect for rTMS in depressed patients with bipolar disorder (BD) [33,19,50], and such result has been confirmed in few double-blind, sham-controlled studies with limited samples [32,11,47].

With respect to different parameters of stimulation, frequency has been assessed in several studies comparing the efficacy of HF and LF treatment. For instance, Hadley et al. [19] stressed the potential of HF-rTMS in rapidly reducing suicidal ideation, similarly to electro-convulsive therapy (ECT). Furthermore, two recent studies [7,35] evaluated the effectiveness of rTMS as maintenance treatment after acute ECT, reporting encouraging results [25].

Recently, a meta-analysis conducted on 8 randomised controlled trials (RCTs) showed a comparable antidepressant efficacy for HF and LF-rTMS [6]. A similar conclusion was drawn by another group additionally observing that LF-rTMS might show a more beneficial tolerability profile (e.g., milder discomfort at the level of the site of stimulation, lower risk of seizure induction) [4]. A similar result was observed even when the technique was provided in augmentation [12]. In addition, the potential ability for HF-rTMS to accelerate and improve the clinical response to antidepressants was reported in a recent meta-analysis conducted with 6 RCTs [4].

In light of the above, the primary aim of the present study was to assess and compare the efficacy and tolerability of three different protocols of augmentative rTMS, in a sample of patients with current moderate to severe major depressive episode (MDE) and a diagnosis of MDD or BD, with features of poor response/treatment resistance to standard treatments.

## 2. Methods

Thirty-three in- and out-patients with MDD or BD and current MDE, according to DSM-IV-TR criteria [1], were recruited. To be included in the study, patients were required to have shown a partial response, or to have not responded at all, to at least one (i.e., poor response) or more (i.e., treatment resistance) adequate antidepressant treatment (at therapeutic doses for at least 8 weeks) during the current episode.

For bipolar depression, the condition of poor drug response/resistance included adequate treatment with lithium or mood stabilizer plus lamotrigine or quetiapine at therapeutic dose ranges [38].

Partial response was defined as a reduction between 25% and 50% on the Hamilton Depression Rating Scale, 21 items (HAM-$D_{21}$) total score, compared to baseline and absent response as a $\leq$ 25% reduction [34]. Patients' condition of partial responder to previous pharmacological treatment or treatment-resistant was retrospectively assessed during the screening visit. Psychopharmacological treatment had to be maintained unchanged for the 4 weeks preceding TMS.

Exclusion criteria comprised the presence of neurological disorders (epilepsy or familiarity for epilepsy, previous significant head injuries, brain surgery and loss of consciousness for at least 15 minutes), pregnancy or lactation, significant medical and/or psychiatric comorbidities, substance abuse in the last 3 months, presence of pacemaker or any other electrical stimulation device, metallic clips, severe cardiac disorders, hypertension and sleep apnoea.

Diagnoses were obtained by trained psychiatrists through a structured clinical interview based on DSM-IV criteria [13] during which patients' socio-demographic and clinical characteristics were collected. These included age, age at onset, gender, diagnostic subtype (in case of BD), comorbidity, duration of illness and duration of untreated illness (DUI). When considering comorbidity, the disorder assessed for study inclusion had to be the primary one, i.e. providing the primary motivation to seek treatment and responsible for the most significant distress.

Patient recruitment took place from 2008 to 2014, after study protocol was approved by the local Ethics Committee.

Patients were planned to receive a total of 20 sessions of rTMS (5 sessions per week for 4 weeks), being randomised to 3 different protocols, with stimulation parameters chosen within those recommended by recently published International Safety Guidelines [41]:

- right DLPFC, LF-rTMS (1 Hz), 110% of Motor Threshold (MT), 7 trains of 60 seconds each (420 stimuli per session) interspersed by 1 minute of pause;
- right DLPFC, low frequency (1 Hz), 110% of MT, continuous, 15 minutes of treatment (900 stimuli per session);
- left DLPFC, high frequency (10 Hz), 80% of MT, 15 trains of 5 seconds each, interspersed by 25 seconds of pause (750 stimuli per session).

Before starting the stimulation, the identification of the resting MT and, consequently, of the targeted stimulation area was performed, according to standard procedures [23]. MT was considered as the minimum TMS intensity sufficient to produce a predefined motor-evoked potential in the contralateral abductor pollicis brevis in at least 50% of trials [42]. The position of the target area of stimulation (the DLPFC) was defined as 5 cm anterior to the aforementioned region of the motor cortex, in a parasagittal line [14].

Patients were daily monitored during TMS sessions in order to assess safety and tolerability of the procedure, using spontaneously reported side effects and adverse events and rates of termination for any of them.

The following psychometric scales were used as primary outcome measures: Hamilton Rating Scale for Depression (HAM-D, 21 items) [21], Montgomery Asberg Depression Rating Scale (MADRS) [31], Clinical Global Impression- Severity Scale [18], whereas as secondary outcome measures: Hamilton Anxiety Rating Scale (HAM-A) [20], Young Mania Rating Scale (YMRS) [49] and Sheehan Disability Scale (SDS) [45]. All psychometric scales were administered at baseline (T0) and at the end of each week of treatment (T1, T2, T3 and T4, respectively) in a blind-rater design. Raters, in fact, were distinct from clinicians providing the treatment and only administered psychometric scales without receiving information about the type of treatment (i.e., HF vs. LF-rTMS) patients were receiving.

Descriptive analyses were performed for the total sample and comparative analyses between groups were conducted using $Chi^2$ test in order to assess the homogeneity of patients groups. Efficacy analyses were restricted to patients who at least completed the first two weeks of treatment. Tolerability analyses were performed both for patients who completed treatment and for the total sample, including drop-outs.

For the quantitative analysis, student *t*-test for paired samples was used to analyse totals cores of primary (HAM-$D_{21}$, MADRS,