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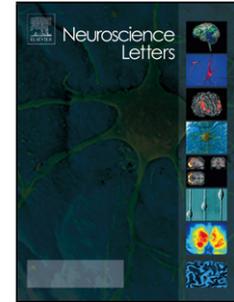
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Title page

Add-on high frequency deep transcranial magnetic stimulation (dTMS) to bilateral prefrontal cortex in depressive episodes of patients with Major Depressive Disorder, Bipolar Disorder I, and Major Depressive with Alcohol Use Disorders.

Short running head: dTMS in depressive episodes

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Appendix

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Highlights

- Deep transcranial magnetic stimulation (dTMS) proved effective in depression
- We added dTMS to ineffective ongoing treatment to people with depression
- Patients had major depression with or without alcohol use or bipolar-I depression
- All groups showed symptom improvement after add-on dTMS with no adverse events

Abstract

Background: Dorsolateral prefrontal cortex (DLPFC) is critically involved in mood and alcohol use disorders. *Objective:* We aimed to investigate the safety of intervention with add-on bilateral prefrontal high-frequency deep transcranial magnetic stimulation (dTMS) and between-group differences in treatment response in patients with different types of depressive episodes, including major depressive episodes in the course of major depressive disorder (MDD), bipolar disorder, type I (BD-I), and MDD with alcohol use disorder (MDAUD). *Methods:* We conducted a 6-month open-label study, involving 82 patients with DSM-5 Depressive Episode. Of these, 41 had diagnosis of MDD, 20 BD-I, and 21 MDAUD. All patients received standard drug treatment and add-on dTMS over the bilateral DLPFC with left prevalence for four weeks, with five sessions in each week. We rated mood state with the Hamilton Depression Rating Scale (HDRS) at baseline, one-month, and six-month follow-up visits. *Results:* Mean total HDRS scores dropped from 22.8 (SD=5.9) at baseline to 10.4 (SD=3.6) at 1 month, to 10.0 (SD=4.5) at 6 months, while response/remission were 70.73% (*N*=58) and 19.51% (*N*=16) at 1 month and 76.83% (*N*=63) and 32.93% (27) at 6 months, respectively, with no between-group differences. No patient experienced any side effects. *Conclusions:* High-frequency DLPFC dTMS was well tolerated and did not significantly differ on improvement of depression in MDD, BD-I, and MDAUD.

Keywords: Major Depressive Disorder; Bipolar Disorder; Alcoholism; Dorsolateral Pre-Frontal Cortex (DLPFC); deep Transcranial Magnetic Stimulation (dTMS); Treatment of depression.

Introduction

Major Depressive Disorder (MDD) is the most prevalent psychiatric illness lifetime and a leading cause of disability in developed countries [1]. In the National Comorbidity Replication Survey, lifetime prevalence of MDD was 16.2%, with a 6.6% 12-month estimate [2]. Alcohol use disorder (AUD) often co-occurs with MDD [3,4], which results in even greater burden of disease than each disorder alone, and higher probability of resistance to pharmacological treatments, leading to the need for complementary therapies [5].

Bipolar disorder is common in psychiatric practice; its estimated prevalence ranges from 0.5 to 5% in community samples [6]. Depressive episodes in BD-I are related to grossly dysfunctional symptoms, and first-line treatments may be in some cases ineffective, treatment-resistance being twice as high as unipolar depression [7]. Antidepressant drugs, which constitute the mainstay of treatment for unipolar depression, have limited efficacy and are related to adverse effects in BD-I, particularly with regard to possible switch to manic episodes [8]. In addition, BD-I pharmacotherapy has side effects that limit treatment adherence and produce long-term clinical comorbidities. These issues highlight the need for developing new treatment strategies that could combine efficacy with acceptability and tolerability/safety [9].

Dorsolateral prefrontal cortex (DLPFC) is dysfunctional in mood disorders [10-12] and substance use disorder [13]. Neuroimaging studies point to an imbalance hypothesis of depression, which postulates prefrontal asymmetry with relative hypoactivity in the left DLPFC, associated with relative hyperactivity in the right DLPFC [14]. Cortical excitability modulation techniques showed efficacy in MDD with or without AUD [15-17] and in bipolar disorder [18,19]. Patients with depressive episodes were consistently found to benefit from excitatory high-frequency deep transcranial magnetic stimulation (dTMS) over the bilateral DLPFC with left prevalence [20]. dTMS received approval from the United States Food and Drug Administration since 2013 for treatment-resistant depression. It is also authorized for the treatment of MDD in Israel (since 2013) and Europe (since 2014) as add-on or monotherapy. The dTMS device (Brainsway Ltd., Jerusalem, Israel) utilizes a unique coil design, the H-coil, which enables stimulation of deeper and larger brain areas compared to standard TMS coils. The H-coil induces an effective magnetic field 3-6 cm deep from the skull, which can reach subcortical areas, as compared to about 1.5 cm when using standard TMS coils [21].

We aimed to investigate the safety of bilateral DLPFC high-frequency dTMS, added onto standard treatments in depressive episodes. We also investigated clinical between-group symptom differences in patients with MDD, BD-I, and MDAUD. Our primary hypothesis was that add-on dTMS would be well tolerated. Our secondary hypothesis was that all groups would present

improvement in their depressive symptoms at the end of the acute intervention phase (four weeks of treatment) and after a 6-month follow-up.

Materials and Methods

Patients

The study was conducted at the Psychiatric Unit of the "Sant'Andrea" University Hospital, Sapienza University of Rome. We recruited a sample of 82 patients (44 men, 38 women) with depressive episodes between October 2011 and March 2016. Of these, 41 right-handed adult outpatients (22 men, 19 women; mean age 51.44 years, SD=10.84) met DSM-5 criteria for depressive episodes in MDD (MDD group). Twenty right-handed outpatients (11 men, 9 women; mean age 57.85 years, SD=8.189) were affected by a depressive episode in BD-I (BD-I group). Twenty-one right-handed outpatients (11 men, 10 women; mean age 54.38 years, SD=7.18) had a diagnosis of depressive episode in MDD and Alcohol Use Disorder (MDAUD group). We obtained written consent from all participants after having them informed fully about the aims of the treatment and its mechanisms. This study was carried-out in accordance with the Principles of Human Rights, as adopted by the World Medical Association at the 18th WMA General Assembly, Helsinki, Finland, June 1964 and subsequently amended by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013.

In the whole sample, different patients were included in two of our previous studies: 12 MDD and 11 MDAUD (Rapinesi et al. 2015a) [16]; 4 MDD and 4 BD-I patients (Rapinesi et al. 2015b) [18]. Exclusion criteria included minor (≤17) or advanced age (≥65 years), other concurrent substance use disorders except nicotine dependence, neurological (epilepsy, dementia, cerebral edema, Parkinson's disease) or organic illnesses (major cardiovascular disorders and hypertension, diabetes, malignancy, renal failure), specific contraindications to dTMS (history of seizures and carrying a pacemaker), and having received dTMS in the past 12 months.

All patients were on medications for at least one month (80 for at least two months to two different drugs given at adequate doses; 2 [one with BD and one with MDAUD] were not responding for just one month), to which they were poorly responsive or unresponsive (less than 50% drop in Hamilton Depression Rating Scale [HDRS]); treatment remained unchanged for the entire duration of the study.

In the MDD group, patients were on antidepressants (32 patients), or antidepressants and mood stabilizers (3), or antidepressants and atypical antipsychotics (6). In the BD-I group, patients were on antidepressants (1), or antidepressants and mood stabilizers (8), or antidepressants, mood

stabilizers and atypical antipsychotics (3), mood stabilizers and atypical antipsychotics (7). in the alcohol-abstaining MDAUD group, patients were on antidepressants (2), or antidepressants and mood stabilizers (5), or antidepressants, mood stabilizers and atypical antipsychotics (11), antidepressants and atypical antipsychotics (3). All dosages were according to the average clinical prescriptions.

Assessments

We diagnosed patients with the Structured Clinical Interview for DSM-5 – Research Version (SCID-5-RV) [22]. We used the 17-item HDRS [23] for assessing depressive symptoms. We assessed adverse events during control visits, in which we investigated the presence of an adverse event and its relationship with the stimulation. We performed all clinical assessments at baseline, treatment week 4, and 6-month follow-up. All doctors who carried out dTMS were specifically trained. Interrater reliability between physicians was good (Cohen's kappa=0.87).

Deep TMS Treatment

The dTMS sessions were conducted using Brainsway's H1 coil dTMS System (Brainsway, Har Hotzvim, Jerusalem, Israel). The H1 coil is designed to elicit neuronal activation in medial and lateral prefrontal regions, including the orbitofrontal cortex, with a preference for the left hemisphere [21]. The H1 coils were positioned over the patient's scalp. The optimal spot on the scalp for stimulation of the right *abductor pollicis brevis* muscle was located, and the motor threshold (MT) was established by delivering individual stimulations to the motor cortex. MT was measured by gradually increasing stimulation intensity (using single pulse mode, applying 1 pulse every 5 seconds [0.2 Hz]) and recording electrical activity in the *abductor pollicis brevis* with surface electrodes. MT was defined as the lowest stimulation intensity, which produced five motor evoked potentials of at least 50 μV in 5 of 10 stimulations. The coil was then placed 5.5 cm anterior to the motor spot (i.e., corresponding to the prefrontal cortex), and spatial coordinates were recorded with markings on a cap placed on the patient's head to ensure placement reproducibility. dTMS treatment was delivered by a trained physician in trains of 20 Hz at 120% of the measured MT. Each dTMS session consisted of 55 trains with a 2-second duration each and an inter-train interval of 20 seconds. The complete cycle of the dTMS treatment consisted of five consecutive session days in a week for four consecutive weeks, for a total of 20 sessions for each patient. The treatment was well tolerated by all patients.

Adopted response/remission criteria

In our study we adopted the classical response criterion of a drop of at least 50% from baseline in HDRS scores. Remission was a total HRDS score of 7 or less. We examined response and remission rates both at the end of the treatment and at the 6-month follow-up.

Statistical analysis

We compared the baseline socio-demographic and clinical characteristics of the three groups of patients (MDD; BD-I; MDAUD) with one-way ANOVA for continuous variables (i.e., *age*) and Chi-squared test for categorical variables (i.e., *gender*). We measured score changes of psychopathological measure (HDRS) between baseline and 1-month and 6-month follow-up. We performed a One-Sample Kolmogorov-Smirnov Test that showed normal value distribution at each timepoint. Changes were then analysed by repeated measures analysis of variance (ANOVA), with diagnosis as between-subject factor, and time (baseline, 1-month, 6-month) as repeated-measures factor. Sphericity assumption was tested through Mauchly's Test, which showed significance (p=0.02; ε=0.912). On this basis, we used the Greenhouse-Geisser correction for the repeated measures ANOVA. *Post hoc* multiple comparisons were performed with Tukey's HSD Test to assess between-group differences at each timepoint. Cut-off for statistical significance was set at p<0.05. All *P* values were two-tailed. We used the IBM SPSS Statistics 24.0 (Armonk, New York, IBM Corporation, 2016) for all analyses.

Results

All patients tolerated the stimulation without complications or adverse effects. Baseline sociodemographic characteristics and mean total HDRS scores of the study sample are shown in Table 1. The groups significantly differed for the variable "age" (F=3.176; p=0.047), and *post hoc* Tukey HSD showed significant mean age differences between MDD and BD-I groups (p=0.039), and no differences between MDD and MDAUD groups (p=0.478), and BD-I and MDAUD groups (p=0.469). The three groups did not differ in gender composition and in HDRS mean values at each timepoint (see Table 1).

Table 1 around here, please

We found significant within-subjects main effect of treatment time (F=289.266; p<0.001), while we did not find any significant within-subjects time *x* diagnosis interaction (F=1.294; p=0.278). Repeated measures ANOVA showed that the mean total HDRS scores reductions in all groups significantly increased over time during add-on dTMS treatment and at the last follow-up. HDRS

scores reductions from baseline were significant at T2 ($p<0.001$) and T3 ($p<0.001$). No significant differences were found between T2 and T3. *Post hoc* Tukey HSD showed no significant between-group differences in HDRS score trends during treatment. No patient has manifested clinical hypomanic or manic episodes during the 6-month study period. Mean changes in HDRS scores across time are shown in Figure 1.

Figure 1 around here, please

Response/remission rates at the end of the dTMS treatment period and at the 6-month follow-up. At the end of the treatment period, response rate was 70.73% (response in 58 patients), while it was to 76.83% (63 patients) at the 6th month of follow-up. Remission rates were 19.51% (16 patients) at the end of the 1-month dTMS treatment period and 32.93% (27 patients) at the 6-month follow-up. We reported number of responses and remissions per gender and diagnoses in Table 2. We found a significant difference in follow-up remission number, which was higher in the MDAUD group (χ^2=7.89; p=0.019).

Table 2 around here, please

Discussion

In this study we presented safety data on dTMS applied over bilateral DLPFC with left prevalence in a sample of patients with MDE. Our analyses would support previous reports of antidepressant efficacy of add-on dTMS in treating depression in patients with MDD, with or without AUD [15-18, 20], bipolar disorder [24,18,19], and severe treatment-resistant depression [25].

The significant decrease in HDRS scores could be related to a substantial antidepressant effect of dTMS after the end of 20 sessions. We demonstrated significant improvements in depressive symptoms as early as four weeks following treatment initiation persisting at the 6-month follow-up. The safety and side effect profiles emerging from this study bear similarity to those previously reported [26-29]. The high compliance observed in our study and the absence of adverse events suggest that dTMS treatment was well tolerated.

Our findings match those of different repetitive transcranial magnetic stimulation (rTMS) studies. rTMS showed efficacy in unipolar [30] and bipolar depression [31,32], and in mixed mood episodes [33], although augmentation rTMS showed some side effects, including hypomanic switch [34]. Depression type (unipolar or bipolar) had no significant effect on rTMS response [35]. The findings

from our study point to a similar conclusion for dTMS. It remains unclear which brain stimulation methods correlates with best clinical responses in the treatment of depressive and mixed episodes of mood disorders. However, comparing Rostami's et al. (2017) [35] results with ours, we found a 70.73% response rate at the end of the dTMS treatment period, which compares favourably with the results of the Tehran group (45% overall response rate). However, their response criteria were not the same as ours, as they used the Beck Depression Inventory to rate their patients' depression, while we used the above mentioned HDRS criterion. Forthcoming studies should focus on comparing the antidepressant effects of dTMS and conventional rTMS with head-to-head randomised and controlled designs.

The fact that all patients in our study have maintained the improvement of depressive symptoms after six months without maintenance dTMS may be due to a progressive increase of the effect of maintenance drug treatment, to a possible long-term effect of dTMS, or to a combination of these supposed items or to the addition of other yet undiscovered factors. This topic should be further studied. Overall, our data are in line with studies suggesting that the dTMS antidepressant effects in MDD last for up to 12 months after treatment initiation, even without subsequent dTMS maintenance treatment. However, dTMS maintenance treatment (recall sessions) has been associated with reduced depressive episode relapses [18], and another recent report showed that a significant number of acute dTMS treatment course nonresponder patients affected by resistant depression finally responded with continued treatment [36]. Our results need replication in larger samples, with sham- and maintenance-dTMS assessing treatment efficacy in the long run.

Limitations of the study. This was a one-center, open-label study, and its limited sample size reflects this fact. Despite our long-term follow-up, we did not control for possible effects of maintenance dTMS treatment, which could possibly reveal an end-point between-group differences. Furthermore, the study did not include a sham dTMS control group, and the three groups differed for number of encounters with the operators, which can be linked with possible Hawthorne-like placebo effects of the procedure [37].

Conclusion

dTMS added on standard drug treatment was safe for treatment of depressive episodes, and was followed by significant improvement in depressive symptomatology in patients with depression in MDD, BD-I, or MDAUD. In the last group, the antidepressant effect of dTMS was not affected by alcohol use. Depression improvement were maintained at the 6-month follow-up. These findings provide support to add-on dTMS as potentially efficacious and well tolerated in resistant depression patients receiving adequate pharmacotherapy. Further studies assessing long-term outcomes, factors

that influence treatment response, and biomarkers for treatment response prediction will provide useful data to optimise treatment safety, while maximizing benefits.

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Figure caption

Figure 1

Error bars: 95% CI
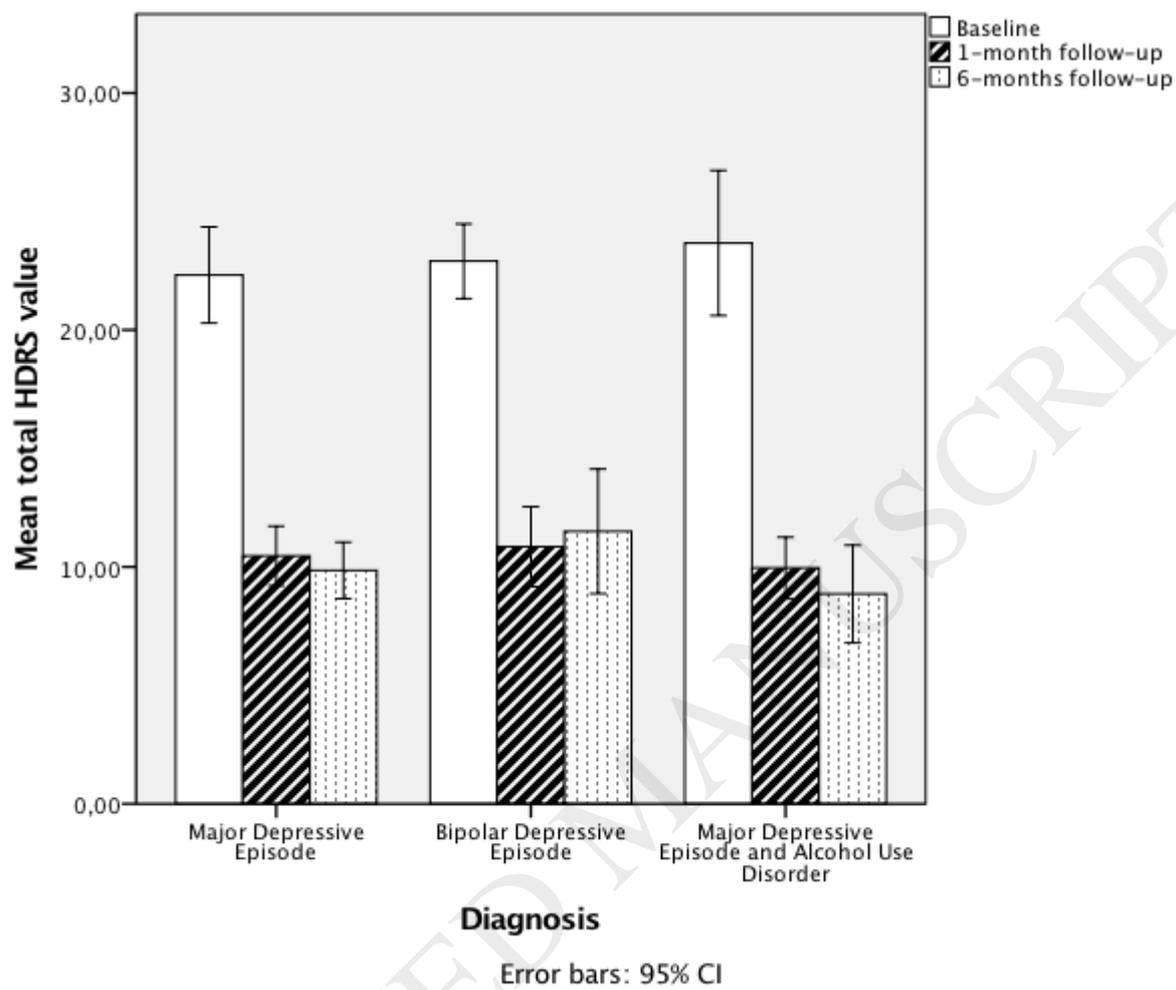
Table 1. Sociodemographic and clinical characteristics of the three samples.

Variable	MDD group (N=41)	BD group (N=20)	MDAUD group (N=21)	Test (value)	*p**
Mean Age, years (SD)	51.44 (10.84)	57.85 (8.189)	54.38 (7.18)	One-way ANOVA (F=3.176)	0.047*
Gender, male/female ratio	22/19	11/9	11/10	Chi-squared test	0.986
Mean baseline HDRS score (SD)	22.32 (6.42)	22.9 (3.37)	23.67 (6.73)	One-way ANOVA (F=0.364)	0.696
Mean 1-month HDRS score (SD)	10.46 (3.99)	10.85 (3.6)	9.95 (2.85)	One-way ANOVA (F=0.316)	0.730
Mean 6-month HDRS score (SD)	9.85 (3.77)	11.5 (5.61)	8.85 (4.53)	One-way ANOVA (F=1.834)	0.166

Abbreviations: BD, bipolar disorder; HDRS, Hamilton Depression Rating Scale; MDAUD, major depressive episode comorbid with alcohol use disorder; MDD, major depressive disorder; SD, standard deviation.

Table 2. Response and remission rates in patients treated with add-on dTMS.

	Response at treatment end	Response at follow-up	Remission at treatment end	Remission at follow-up
All patients (rate)	58 (70.73%)	63 (76.83%)	16 (19.51%)	27 (32.93%)
Gender m/f	34/24	36/27	11/5	16/11
Diagnosis				
MDD	27	32	7	9
BPD	16	15	2	6
MDAUD	15	16	7	12
Pearson chi-squared	1.306	0.077	3.862	7.89
p	0.52	0.962	0.145	*0.019*