Research report

rTMS in resistant mixed states: An exploratory study

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ABSTRACT

Background: Repetitive transcranial magnetic stimulation (rTMS) has shown efficacy in resistant unipolar depression, but its efficacy in bipolar disorders has not yet been extensively investigated. Mixed episodes are reported in up to 40% of acute bipolar admissions and are associated with severe psychopathology, comorbidity, high risk of suicide and poor treatment response. Right low-frequency rTMS (LF-rTMS) as an augmentation treatment might be effective for mixed states.
Methods: Forty patients were treated during a 4-week period with a mood stabilizer and subsequent rTMS (low frequency stimulation − 1 Hz – applied to the right Dorso-Lateral Prefrontal Cortex (DLPFC)) as add-on treatment for 3 weeks. Response to LF-rTMS was assessed by the Hamilton Depression Rating Scale (HAM-D), the Young Mania Rating Scale (YMRS) and the Clinical Global Impressions-Bipolar Version (CGIBP) subscales. ANOVA with repeated measures performed on HAM-D, YMRS and CGI-BP subscales "change from the preceding phase" and "severity of illness" showed a statistically significant time effect from the baseline to the endpoint.
Results: For the HAM-D there was a 46.6% responder rate, of which 28.6% was remitted, while for the YMRS there was a 15% responder rate, all of which was remitted.
Limitations: The open label-design of our study and the lack of a sham-controlled group represent a methodological limitation.
Conclusions: The results suggest that LF-rTMS on the right DLFC might be a potential augmentation strategy in the treatment of both depressive and manic symptoms in mixed states.

1. Introduction

Repetitive transcranial magnetic stimulation (rTMS) has demonstrated efficacy in treatment resistant depression and different protocols have been adopted and reported as effective and safe (Pascual-Leone et al., 1996; Padberg et al., 1999; Berman et al., 2000; Padberg et al., 2000; Garcia-Toro et al., 2001; Manes et al., 2001; Boutros et al., 2002; Loo et al., 2003; Miniussi et al., 2005; Avery et al., 2006; Speer et al., 2013; Baeken et al., 2013).

Manic and depressive states co-occur in bipolar disorder, characterizing a common, severe and complex clinical state. DSM-IV-TR classifies mixed states (MS) only in bipolar I disorder (BPI), requiring co-occurrence of syndromic manic and major depressive episodes. ICD-10 provides a less strict definition, and

recognizes that MS can occur also in bipolar II disorder (BP-II), requiring co-occurrence of "prominent" manic/hypomanic and depressive symptoms, or "rapidly alternating" opposite polarity episodes (very rapid cycling). MS are difficult to treat and are over-represented in treatment resistant subgroups. Mixed episodes are reported to occur in up to 40% of acute bipolar admissions and are associated with severe psychopathology, comorbidity, high risk of suicide and poor response to treatments (Benazzi, 2007). The severe psychopathology and the complexity of mixed states have important treatment implications. In particular the treatment of depressive symptoms in mixed states represents a clinical dilemma, mostly because antidepressants seem to worsen intraepisodic mood lability and switching (Post et al., 2003).

Several data support an antidepressant effect of both high-frequency rTMS (HF-rTMS) administered to the left Dorso-Lateral Prefrontal Cortex (DLPFC) (O'Reardon et al., 2007; Padberg and George, 2009), and low frequency rTMS (LF-rTMS) administered to the right DLPFC in depressed patients (Menkes et al., 1999). A recent meta-analysis suggested that both protocols are equally

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effective, but considering that right-sided LF-rTMS produces fewer side effects and is more protective against seizures, its clinical applicability shows greater promise (Fitzgerald et al., 2003; Pallanti et al., 2010; Chen et al., 2013). Despite in these studies bipolar patients were included, separate analyses have not been available for bipolar patients, but no switches to manic states have been reported (Ella et al., 2002). A first study of rTMS in bipolar depression (Dolberg et al., 2002) comparing active and sham rTMS found a statistically significant improvement in the real-stimulation group compared with the control group at week 2, but not at week 4 (the authors did not report parameters of stimulation). A subsequent study by Nahas et al. (2003) applied left prefrontal HF-rTMS in 23 depressed bipolar patients (2 had bipolar I disorder in a mixed state) and failed to find difference between sham and active stimulation on clinical outcome. However, three subjects in this acute study were followed during weekly maintenance treatment with rTMS for up to one year and maintained the improvement obtained in depressive symptoms for the whole period (Li et al., 2004). One sham-controlled trial (Tamas et al., 2007) and an open label trial (Dell'Osso et al., 2009a) found that LF-rTMS over the right DLPFC was effective in patients diagnosed with bipolar depression and no manic/hypomanic activation was detected during the treatment. Several studies investigated the efficacy of rTMS in manic bipolar patients reporting that HF-rTMS over the right DLPFC had positive effects in the treatment of mania (Girasu et al., 1998; Kaptsan et al., 2003; Michael and Erfurth, 2004; Saba et al., 2004; Praharaj et al., 2009).

Antidepressants, even administered with mood stabilizers in subsyndromic mixed states (number of manic symptoms > 2), seem not to hasten time to recovery. On the contrary, a higher risk of manic severity worsening has been reported compared with the treatment with mood stabilizers alone (Goldberg et al., 2007). Moreover there are few double blind, placebo controlled studies specifically designed to investigate treatments in bipolar MS (Freeman et al., 1992; Tohen et al., 1999). Rather, in many studies patients with MS have been considered as a subgroup of the total number of patients. Thus, even double blind, placebo-controlled studies have to be interpreted with caution.

To our knowledge currently there is a lack of data on rTMS treatment of mixed states, except for a single case report by Zeeuws et al. describing the case of a mixed patient, resistant to electro-convulsive therapy, successfully treated with intensive (5 sessions a day for 4 days) left-sided HF-rTMS (Zeeuws et al., 2011).

Taking into account the documented efficacy of rTMS in the treatment of bipolar depression and its low-risk to induce mania in bipolar depression (Zwanzger et al., 2002; Janicak et al., 2008; Xia et al., 2008), we will test rTMS as an augmentation to mood stabilizers for the acute treatment of mixed states. The aim of this study is to explore the efficacy of right LF-rTMS as augmentation treatment for mixed states in patients taking mood stabilizers, taking into account the rTMS effect on both manic and depressive symptoms.

The current study test the hypothesis that LF-rTMS over the right DLPFC could be effective in treating both depressive and manic symptoms in bipolar patients with a treatment resistant mixed state given our unpublished data on the effectiveness of low frequency rTMS over the right DLPFC on both depressive and sub-threshold manic symptoms in treatment-resistant depressed-patients (from Pallanti et al., 2010, unpublished data).

2. Materials and methods

2.1. Participants

Subjects were recruited at the Department of Psychiatry of the University of Florence and at the Institute of Neurosciences,

Florence. Eligible right-handed patients 18–65 years of age were invited to participate. The study included outpatients with bipolar disorder during a mixed index episode according to DSM-IV criteria (40 patients, 18 female/22 male, with a mean age respectively of $45,2 \pm 15,2$ and $44,9 \pm 14,2$) (American Psychiatric Association, 2000). All patients were non-responders to pharmacological treatment. Information to establish treatment resistance was based upon a review of outpatient and inpatient medical records and upon the report of the patient, family members, and prescribing psychiatrists. Non-response was defined as the presence of persisting mixed symptoms despite a trial of at least 16 weeks with 2 or more mood stabilizers and/or typical or atypical antipsychotics and or antidepressants in variable doses depending on symptoms patterns. The exclusion criteria were: (1) any additional psychiatric comorbidity, according to DSMIV criteria; (2) the inability to receive rTMS because of metallic implants, or history of seizures (personal or family history of seizure in first degree relatives); (3) substance abuse in the previous six months; (4) any major medical disease; (5) pregnancy; and (6) the inability or refusal to provide written informed consent. All patients were treated for at least 4 weeks before the stimulation with valproate (500–2500 mg/day) as a mood stabilizing agent. All subjects gave written informed consent to participate into the study after full explanation of the research protocol. Before starting patient recruitment, the study protocol received the internal Institutional Review Board approval.

2.2. Clinical assessment

At baseline subjects underwent a psychiatric interview conducted by senior psychiatrists (S.P. and S.A.), followed by a comprehensive clinical interview and review of past data. Diagnoses were performed using the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1997). After baseline assessment outcome measurements were repeated every week for the duration of the treatment by independent psychiatrists not directly involved in the treatment aspect of the study. A physical examination and screening laboratory tests were performed at baseline to rule out comorbid medical illness. Additional baseline data were obtained from the interview and review of hospital records including age, gender, duration of the current mixed episode, history of depression and ECT, treatment resistance as measured by the number of previous adequate courses of antidepressants and augmentation strategies, the number of previous mood episodes, and any suicide attempts. Safety and tolerability was monitored by assessing each week adverse events and vital signs.

2.3. Pharmacological treatment

For a 4-week period, patients were treated with a mood stabilizer effective in mixed states (valproate from 500 to 2500 mg/day) and subsequently received rTMS (low frequency stimulation – 1 Hz – applied to the right DLPFC) as add-on treatment on each weekday for 3 weeks. Valproate doses were kept constant during the 3-week rTMS treatment period. Valproate doses were individually determined by blood concentrations and side effects. The relatively short 4 weeks period of pre-rTMS valproate treatment was adopted according to studies suggesting an effectiveness of valproate in mixed states after 3 weeks of treatment (Freeman et al., 1992). Also, most patients included in the study had a prior history of valproate treatment during the current mixed episode.

2.4. rTMS treatment

rTMS sessions were conducted in a laboratory with physician personnel certified in basic life support and trained in the prompt

recognition and treatment of seizures and other medical emergencies. Emergency equipment such as oxygen, IV access tools, and emergency medications were available. Repetitive TMS was administered using a MAGSTIM rapid magnetic stimulator (Magstim Company, Ltd., Whitland, U.K.). We used a 70 mm figure eight shaped coil. The coils were alternated, in order to allow cooling during treatment sessions without interruption. Patients sat in a reclining chair with a headrest for stabilization of the head and wore protective earplugs. In the first session, and at the beginning of every week, the resting motor threshold (RMT) was determined. RMT was defined as the intensity required eliciting at least 5 MEPs of 50 µV in peak-to-peak amplitude with 10 consecutive stimulations, when the coil was placed over the optimal position to activate the abductor pollicis brevis muscle in both hands based on electromyographic recordings. The site of stimulation in the right DLPFC was located 5 cm anterior to the stimulation site for the contralateral abductor pollicis brevis in the parasagittal plane. During the treatment, three 140-sec trains will be applied at 1 Hz and at 110% of the right RMT over the right DLPFC, with a 30 sec inter-train interval (a total of 420 stimuli per session). These parameters are widely considered as safe. A full course, comprising 15 daily sessions, was administered on weekdays, beginning on Monday. The coil was held tangentially to the scalp with the handle pointing back and away from the midline at 45°.

2.5. Outcome measures

Primary outcome measures included the Hamilton Depression Rating Scale (HAM-D) (score range: 0–66) (Hamilton, 1960), the Young Mania Rating Scale (YMRS) (score range: 0–58) (Young et al., 1978) and the Clinical Global Impressions-Bipolar Version Scale (CGI-BP) (score range: 0–7) (Spearing et al., 1997). The CGI-BP represents a specifically modified CGI scale for the assessment of global severity of illness and relative changes in patients with bipolar disorder. The CGI-BP has three subscales, a general one, a manic and a depressive one, with seven severity degrees for each. A response was defined as a decrease ≥ 50% in both YMRS and HAM-D, and a significant or very significant score on the mania, depression, and overall bipolar illness index of the CGI-BP subscale "change from the preceding phase". Remission was defined as an YMRS score ≤ 12, and HAM-D score ≤ 8, and minimally- or not-ill score on the mania, depression, and overall bipolar illness indexes of the CGIBP subscale "severity of illness". The outcome measurements were performed at baseline (T0), after 5 stimulations (T1), after 10 stimulations (T2) and after 15 stimulations (T3, end of the third week). Each outcome questionnaire was administered before the daily session of rTMS. Our Institutional Review Board approved the study in accordance with the Helsinki Declaration of 1975. After a complete description of the study to the subjects, written informed consent was obtained.

2.6. Data analysis and statistics

Baseline demographic and clinical characteristics of the sample were tabulated with descriptive statistics. Baseline to endpoint change in outcome measures was analyzed using ANOVAs with repeated measures. Post-hoc tests were conducted with the Bonferroni adjustment for multiple comparisons across four different assessment times. The total numbers of responders (HAM-D and YMRS total score reduction ≥ 50% with respect to baseline) and remitters (HAM-D-total score ≤ 8 or YMRS ≤ 12) were also computed. For all the statistical analysis the alpha level of significance was set at 0.05, and was not adjusted. All the statistical analyses were performed using the SPSS software for Windows (version 14.0; SPSS, Chicago, IL, USA).

3. Results

Demographic and clinical characteristics of the sample are summarized in Table 1. All subjects ($n=40$) completed the three weeks of treatment. All subjects were treated for at least 4 weeks before the trial with an adequate and stable dose of valproate (plasma levels: 74.28 ± 23 mEq/L). ANOVA with repeated measures performed on HAM-D showed a statistically significant time effect ($F(3, 117)=22.51$; $p < 0.001$). The coefficient $\eta_2 = 0.36$ shows the magnitude of the effect size and post-hoc tests revealed that there was not a difference between T0 and T1, while there were significant differences between baseline and T2 (Bonferroni $= 4.56$; $p < 0.001$) and T3 (Bonferroni $= 5.5$; $p < 0.001$) (Fig. 1). ANOVA with repeated measures performed on YMRS showed a statistically significant time effect ($F(3, 117)=12.46$; $p < 0.001$) with coefficient $\eta2 = 0.24$. Post-hoc tests again showed significant differences between baseline and T2 (Bonferroni $= 3.18$; $p < 0.05$) and T3 (Bonferroni $= 4.27$; $p < 0.01$) (Fig. 1). The same results, both on the CGI-BP subscale "change from the preceding phase" ($F(2, 78)= 15.34$; $p < 0.001$ and $\eta2 = 0.28$) and "severity of illness" ($F(3, 117)= 27.14$; $p < 0.001$ and $\eta2 = 0.41$) (Figs. 2 and 3). Post-hoc tests for CGI-BP subscale "change from the preceding phase" showed a significant difference between T2–T3 and T0–T1 (Bonferroni $= 4.21$; $p < 0.001$) and between T2–T3 and T1–T2 (Bonferroni $= 4.42$; $p < 0.001$). The same tests for CGI-BP subscale "severity of illness" showed significant differences between the baseline and all the follow-up assessments: T0–T1 (Bonferroni $= 3.54$; $p < 0.01$), T0–T2 (Bonferroni $= 5.52$; $p < 0.001$) and T0–T3 (Bonferroni $= 6.13$; $p < 0.001$). For the HAM-D there was a 46.6% responder rate, of

Table 1
Baseline demographic and clinical characteristics of the sample.

Characteristics	Value ($N=40$)
Age (years), mean $\pm$ SD	F: 45.2 $\pm$ 15.2; M: 44.9 $\pm$ 14.2
Gender	F: 22/40; M: 18/40
Pharmacological therapy during TMS trial	Divalproex
	Dosage: 1050 $\pm$ 447.7 mg/day
	Plasma level: 74.28 $\pm$ 23 mEq/L
Duration of the illness (bipolar disoder), mean $\pm$ SD	15 $\pm$ 7.5 years
No. of episodes (manic/hypomanic and depressive), mean $\pm$ SD	5.35 $\pm$ 2.54
	No. of manic episodes: 1.15 $\pm$ 0.66
	No. of hypomanic episodes: 0.87 $\pm$ 0.64
	No. of depressive episodes: 1.62 $\pm$ 0.74
No. of hospitalizations, mean $\pm$ SD	1.5 $\pm$ 1.19
Duration (weeks) of the current episode, mean $\pm$ SD	13.4 $\pm$ 5.36
No. of pharmacological trials failed before entering the study, mean $\pm$ SD	4.72 $\pm$ 2.12
Presence of psychotic symptoms, (number of patients) (item 20 HAM-D)	14
No. of suicide attempts, mean $\pm$ SD	0.95 $\pm$ 0.99
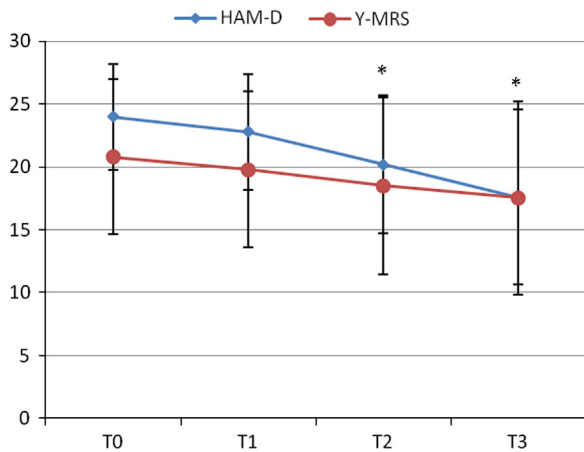
Fig. 1. Baseline to endpoint change of 21-items in the Hamilton Depression Rating Scale (HAM-D) and the Young Mania Rating Scale (Y-MRS). HAM-D and Y-MRS total scores are reported on the y-axis. Time is reported on the x-axis (T0=baseline, T1=after 5 stimulations, T2=after 10 stimulations, and T3=after 15 stimulations). Statistical measurements are presented as ANOVAs with repeated measures. The asterisks refer to post-hoc tests showing significant differences both for HAM-D and Y-MRS between baseline and T2 ($p < 0.001$ and $p < 0.05$, respectively) or T3 ($p < 0.001$ and $p < 0.01$, respectively). The error bars show the variability of the HAM-D and Y-MRS total scores at each time point.
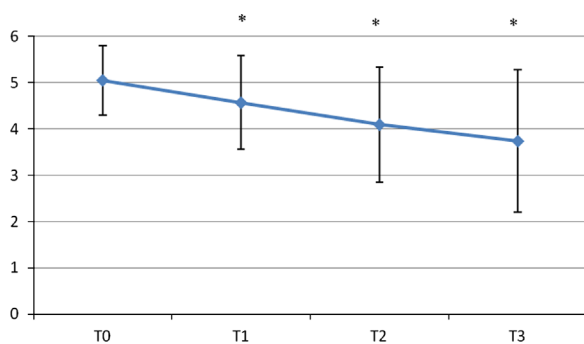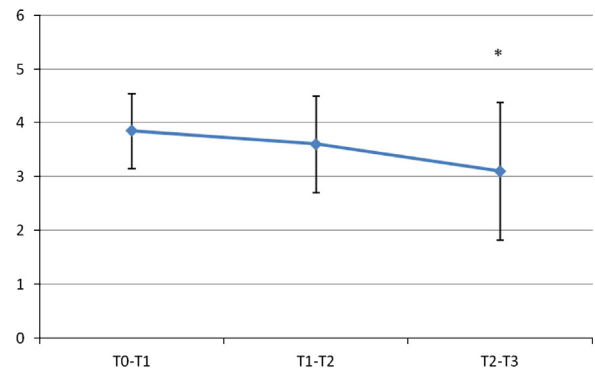

Fig. 2. T0 to endpoint changes of Clinical Global Impression Bipolar Version (CGI-BP) severity of illness. The CGI-BP total score is reported on the y-axis. Time is reported on the x-axis (T0=baseline, T1=after 5 stimulations, T2=after 10 stimulations, and T3=after 15 stimulations). Statistical measurements are presented as ANOVAs with repeated measures. The asterisks refer to post-hoc tests showing significant differences between baseline and all the follow-up assessments: T1 ($p < 0.01$), T2 ($p < 0.001$) and T3 ($p < 0.001$). The error bars show the variability of the CGI-BP (severity of illness) total scores at each time point.

which 28.6% was remitted, while for the YMRS there was a 15% responder rate, all of which was remitted. Finally, there were no serious adverse events reported by the patients during the study. Only 2 patients reported headache, 1 insomnia, and 2 pain on the site of the coil stimulation, limited to the first week of treatment. None of the patients developed manic/hypomanic episodes during the 3 weeks of treatment. Nor age, gender, valproate dosage and duration of illness were predictors of the response to LF-rTMS.

4. Discussion

This is the first open study to evaluate the use of rTMS in the treatment of mixed states, a common, severe and complex clinical state representing a therapeutic challenge for clinicians. In our study, all subjects completed the three weeks of treatment and only minimal side effects were reported for a small number of subjects. Moreover, no manic/hypomanic activation was detected during the three weeks, demonstrating that rTMS represents a potentially safe and well tolerated treatment.

Fig. 3. T1 to endpoint changes of Clinical Global Impression Bipolar Version (CGI-BP) change from the preceding phase. CGI-BP change from the preceding phase total scores is reported on the y-axis. Time is reported on the x-axis (T1=after 5 stimulations, T2=after 10 stimulations, and T3=after 15 stimulations). Statistical measurements are presented as ANOVAs with repeated measures. The asterisks refer to post-hoc tests showing significant differences between T2–T3 and T0–T1 ($p < 0.001$) and between T2–T3 and T1–T2 ($p < 0.001$). The error bars show the variability of the CGI-BP (change from the preceding phase) total scores at each time point. The Mauchly Test of Sphericity showed that the sphericity assumption is violated (Mauchly's $W=0.553$ and $p < 0.001$), and in the text the F value is reported according to the Greenhouse–Geisser correction.

Results from this study show that augmentation with LF-rTMS of the right DLPFC is effective in both depressive and manic symptoms in bipolar mixed patients in a 3-week treatment protocol (Fig. 1). We observed a 46.6% responder rate on HAM-D, of which 28.6% was remitted, while there was a 15% responder rate on YMRS, all of which was remitted, despite the CGIBP scores which showed a high severity of the acute mixed phase. Finally, there were no serious adverse events reported by the patients during the study. The choice of LF-rTMS was motivated by its lower risk of accidental seizure (Wassermann, 1996) and better tolerability (Loo and Mitchell, 2005). Regarding the site of stimulation, several neuropsychological and imaging studies highlighted the contrasting role in mood regulation between right and left hemispheres (Loo and Mitchell, 2005) and LF-rTMS on the right DLPFC has been shown to produce the same antidepressant effect as HF-rTMS on the left DLPFC both in unipolar depressed patients (Loo and Mitchell, 2005) and in bipolar depression (Tamas et al., 2007; Dell'Osso et al., 2009a, b). Although in several studies right HF-rTMS on the DLPFC in bipolar manic patients was found to be effective as an add-on to standard pharmacotherapy (Girasu et al., 1998; Kaptsan et al., 2003; Michael and Erfurth, 2004; Saba et al., 2004), our study is the first to show that right LF-rTMS on the DLPFC is an effective treatment on mixed symptoms after three weeks. The higher rate of response on depressive symptoms in our study seems to indicate that the beneficial effects of right DLPFC LF-rTMS in mixed patients are probably mainly driven by its antidepressant effect. Regarding the stimulation intensity, we choose a high intensity protocol (110% of RMT) since it has been associated with better results (Gershon et al., 2003), even though a systematic investigation of this parameter has yet to be performed. With regards to the duration of treatment, the present study is longer (three weeks) than many acute clinical trials with rTMS (two weeks). Indeed, studies reporting a rTMS course longer than two weeks have generally demonstrated continuous improvement over the third and fourth week (Loo and Mitchell, 2005; O'Reardon et al., 2007; Tamas et al., 2007; Dell'Osso et al., 2009a; Dell'Osso and Altamura, 2009b). In accordance with these studies, we observed a statistically significant reduction of both depressive and manic symptoms in the second and third week as measured by the HAM-D and by the Y-MRS (see Fig. 1). The number of stimuli per session delivered in the current study (420 stimuli/session) is the same we found to be effective and safe in our previous study on unipolar depression (Pallanti et al., 2010). Moreover, the current number of stimuli is in

line with the number of stimuli per session used in most clinical trials with rTMS applied to treat bipolar depression. Although in some studies, 300 stimuli per session (Dell'Osso et al., 2009a) and 100 stimuli per session (Tamas et al., 2007) were delivered in order to minimize the side effects, no dropouts and only mild side effects were registered in our trial.

Of note, our patients were all on valproate. To date, studies concerning the effect of valproate on cortical excitability demonstrate conflicting results (Nezu et al., 1997; Mulleners et al., 2002; Cantello et al., 2006; Li et al., 2009). A recent study with TMS comparing the effect of valproate and lamotrigine on resting motor threshold failed to find an increase on RMT with valproate (Li et al., 2009). However, a study on epileptic patients showed a reduced cortical excitability after chronic valproate administration (Cantello et al., 2006). Therefore, we cannot exclude the hypothesis that the clinical improvement could be due to the synergistic inhibitory effect on the cortical excitability of LF-rTMS (that has an inhibitory effect on the cortex) and valproate treatment. Further studies in mixed patients treated with different antiepileptic treatments are needed to clarify this issue.

We did not find any clinical predictor of response in our study. This is probably due to the small sample size and to the fact that we did not perform any imaging assessment before rTMS trial. Several studies suggested that baseline cortico-limbic perfusion (mainly hippocampus and amygdala) could predict the response to rTMS. Thus, future studies may address this issue including neuroimaging in the baseline assessments.

Finally, the current literature shows a different rTMS response depending on the age of the patient (over or under 60 years of age). Although our sample had a large age-span (F: 45.2 ± 15.2; M: 44.9 ± 14.2), there were no patients over age 60; thus, there is no clear evidence of a confounding effect in the large age-span.

5. Limitations of the study

The open label-design of our study and the lack of a sham-controlled group represents a methodological limitation. Therefore, we cannot rule out a putative placebo effect on our results. However, mixed and treatment-resistant mixed states usually have a poor response to treatment, a longer course of illness and a low rate of response to placebo (McIntyre and Yoon, 2012). Thus, if is unlikely that the observed improvement in our study was due solely to a spontaneous improvement in the episode.

A putative confounding factor could be a practice effect of completing the same test measure over time (e.g. HAM-D) (Laenen et al., 2009). One way to prevent a practice effect is the use of alternate forms of the HAM-D, but in this exploratory study we did not do so. Furthermore, we did not use any self questionnaire. Further sham-controlled studies should address these issues as well.

Nevertheless, this study suggests that rTMS in mixed states might be a potential efficacious and well tolerated augmentation strategy in the treatment of both depressive andmanic symptoms. Further sham-controlled studies in mixed state patients are needed toconfirm our results.

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