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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.

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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 subthreshold 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

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