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Research report

Antidepressant effectiveness of deep Transcranial Magnetic Stimulation (dTMS) in patients with Major Depressive Disorder (MDD) with or without Alcohol Use Disorders (AUDs): A 6-month, open label, follow-up study

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ABSTRACT

Introduction: Co-occurrence of Major Depressive (MDD) and Alcohol Use Disorders (AUDs) is frequent, causing more burden than each disorder separately. Since the dorsolateral prefrontal cortex (DLPFC) is critically involved in both mood and reward and dysfunctional in both conditions, we aimed to evaluate the effects of dTMS stimulation of bilateral DLPFC with left prevalence in patients with MDD with or without concomitant AUD.

Methods: Twelve MDD patients and 11 with concomitant MDD and AUD (MDD+AUD) received 20 dTMS sessions. Clinical status was assessed through the Hamilton Depression Rating Scale (HDRS) and the Clinical Global Impressions severity scale (CGIs), craving through the Obsessive Compulsive Drinking Scale (OCDS) in MDD+AUD, and functioning with the Global Assessment of Functioning (GAF).

Results: There were no significant differences between the two groups in sociodemographic (age, sex, years of education and duration of illness) and baseline clinical characteristics, including scores on assessment scales. Per cent drops on HDRS and CGIs scores at the end of the sessions were respectively 62.6% and 78.2% for MDD+AUD, and 55.2% and 67.1% for MDD ($p < 0.001$). HDRS, CGIs and GAF scores remained significantly improved after the 6-month follow-up. HDRS scores dropped significantly earlier in MDD+AUD than in MDD

Limitations: The small sample size and factors inherent to site and background treatment may have affected results.

Conclusions: High frequency bilateral DLPFC dTMS with left preference was well tolerated and effective in patients with MDD, with or without AUD. The antidepressant effect of dTMS is not affected by alcohol abuse in patients with depressive episodes. The potential use of dTMS for mood modulation as an adjunct to treatment in patients with a depressive episode, with or without alcohol abuse, deserves further investigation.

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1. Introduction

Major Depressive Disorder (MDD) is the most prevalent lifetime psychiatric illness and one of the leading causes of disability in the developed countries (World Health Organization, 2000). In the National Comorbidity Replication Survey, lifetime prevalence of DSM-IV MDD was 16.2%, with a 12-month estimate of 6.6% (Kessler et al., 2003).

MDD impacts brain structure and function (Maletic et al., 2007). Impaired inter-hemisphere asymmetry has been shown in patients with depression (Maeda et al., 2000; Bajwa et al., 2008), while right lateralisation was higher in people scoring higher on the depression scale of the MMPI (Biondi et al., 1993). This suggests differential brain activity in patients with MDD, which can explain depressive symptoms like psychomotor retardation and executive function impairment (mainly related to dysfunctional dorsolateral prefrontal cortex [DLPFC]), feelings of guilt and hopelessness (principally hippocampal and amygdala dysfunction), anhedonia (dysfunction of the nucleus accumbens) and negative emotional judgment (mainly related to left–right imbalance) (Grimm et al., 2008; Koenigs and Grafman, 2009; Maletic et al., 2007).

Alcohol Use Disorders (AUDs) often co-occur with MDD (Schuckit, 2006; Boschloo et al., 2011). Half of treatment-seeking AUD patients have comorbid depression (Swendsen and Merikangas, 2000). Similarly, MDD treatment populations have up to 40% lifetime probability of developing AUD (Grant et al., 2004; Jane-Llopis and Matytsina, 2006).

Co-occurrence of AUD and MDD results in even greater disease-related burden than the separate disorders (Gadermann et al., 2012). People with comorbid AUD and MDD have high morbidity and mortality levels, functional impairment and increased suicide risk (Blanco et al., 2012). Not surprisingly, societal cost is substantial, owing to high levels of health-care service utilisation, inadequate treatment outcomes, high work absenteeism and lost productivity (Chisholm et al., 2003; Rehm et al., 2009).

Patients with co-occurring MDD and AUD often fail to respond sufficiently to drug trials (Baldwin and Simpson, 1997; McLoughlin et al., 2007). For this reason, alternative treatments are sought, and cortical excitability modulation techniques show promise in AUD (Nardone et al., 2012) and MDD (Bersani et al., 2013; Harel et al., 2014; Berlim et al., 2014).

The H-coil used for deep Transcranial Magnetic Stimulation (dTMS) allows deeper brain structure stimulation than the classical repetitive TMS 8-coil. The efficacy and safety of dTMS in patients with various neuropsychiatric disorders (Minichino et al., 2012; Bersani et al., 2013; Spagnolo et al., 2014) have already been assessed widely. dTMS received FDA approval for "the treatment of depressive episodes in adult patients suffering from Major Depressive Disorder who failed to achieve satisfactory improvement from previous anti-depressant medication treatment in the current episode" early in 2013 (Food and Drug Administration, 2013). As DLPFC is critically involved in both mood and reward mechanisms and was found to be dysfunctional in both MDD (Ye et al., 2012; Chang et al., 2011; Oh et al., 2012) and substance-abuse patients (Lang et al., 2008; Moreno-López et al., 2012; Bosch et al., 2013), we may speculate that dTMS focused on DLPFC may be clinically effective in treating patients with co-occurrence of MDD and AUD. Furthermore, reduced substance craving has been shown with both rTMS (Politi et al., 2008; Amiaz et al., 2009; Mishra et al., 2010) and dTMS (Rapinesi et al., 2013; Girardi et al., 2014), to point to an indication of TMS in addictions (Feil and Zangen, 2010). We expected either similar improvements in depression in patients with MDD alone and MDD comorbid with AUD or an interference of AUD with antidepressant response, given that substance use comorbidity with depression complicates the latter's response to treatment (Nunes et al., 1996). Based on our previous experience with patients affected by comorbid dysthymic disorder and AUD (Rapinesi et al., 2013; Girardi et al., 2014), we also expected a reduction in alcohol craving in patients with MDD with AUD.

The objective of the study was to compare short- and long-term effectiveness of dTMS stimulation of bilateral DLPFC with prevalence for the left hemisphere as add-on in patients with MDD with AUD vs. MDD without AUD, whose episode was not responding satisfactorily despite adequate antidepressant drug doses, which were left unchanged throughout the study. We also aimed to assess the short- and long-term effect of dTMS in alcohol craving in patients with coexisting MDD and AUD.

2. Materials and methods

2.1. Patients

The study was conducted at the Psychiatric Unit of the Sant'Andrea University Hospital, Sapienza University of Rome, and at the Day Hospital on Alcoholism of the Villa Rosa Hospital in Viterbo. Recruitment period was October 2011 to April 2013; 23 Caucasian consecutive patients (13 male, 10 female) with DSM-IV-TR MDD diagnosis (American Psychiatric Association, 2000) were enroled. Twelve had MDD only (mean age = 51.2 years, standard deviation [SD] ± 8.02) and 11 (mean age = 55.2 years SD ± 6.95 years) had concomitant MDD and AUD. Diagnoses were posed through the Structured Clinical Interviews for DSM-IV Axis I (SCID-I) (First et al., 2002) and II (SCID-II) (First et al., 1997). Reviewing each case retrospectively, all patients also met DSM-5 criteria for MDD (American Psychiatric Association, 2013) and those with comorbid AUD met DSM-5 criteria; three were rated as severe (≥ 6 criteria met) and eight as moderate (4–5 criteria present). All patients gave written informed consent for participation in the study and subsequent publication of results.

Inclusion criteria were as follows: a diagnosis of MDD; age 18–75 years; at least 5 years from first onset of illness (to ensure no bipolar depression cases were included); availability of reliable informants; unsatisfactory response to at least one adequate course of antidepressant treatment during the current episode, and wish to participate in the study. Exclusion criteria were as follows: concomitant use of substances other than alcohol (with the exception of nicotine and three or less daily cups of coffee/tea); specific contraindications to dTMS (history of seizures, pacemakers); axis I diagnosis other than MDD and AUD; having received TMS in the past 12 months.

All patients were on stable drug treatment from at least one month. In the MDD group 5 patients were on venlafaxine (average dose = 200 mg/day), 5 on citalopram (average dose = 20 mg/day), and 2 on sertraline (average dose = 100 mg/day). Nine received concomitant clonazepam (average dose = 1 mg/day), 2 lamotrigine (average dose = 150 mg/day), and 1 quetiapine (dose 100 mg/day), while in MDD with AUD 10 patients were on trazodone (average dose = 175 mg/day), 1 on duloxetine (dose 60 mg/day); 10 of them received concomitant diazepam (5 mg/day), and 1 olanzapine (2.5 mg/day).

Patients with concomitant MDD and AUD abstained from alcohol for at least one month before the first dTMS session; they underwent alcohol detoxification (5–20 mg/day diazepam, 75–150 mg/day trazodone, or a combination of the two). Their detoxification did not affect their mood condition.

2.2. Clinical measures

Patients were assessed through the Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960), the Clinical Global Impressions scale, severity (CGIs) (Guy, 1976), and the Global Assessment of Functioning Scale (GAF) (Endicott et al., 1976). These were

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completed by trained clinicians at baseline, (all scales) at the end of the first, second, third and fourth week of dTMS treatment (HDRS, and CGIs, but not GAF), and at the end of the 6-month follow-up period (all). Patients with comorbid MDD and AUD were also rated with the Obsessive Compulsive Drinking Scale (OCDS) (Anton et al., 1995) to assess their alcohol craving; the OCDS followed the same timeline as the HDRS and the CGIs in all patients.

HDRS is a 21-item scale, but only the first 17 are added to obtain the total score; single items are Likert, ranging 0–4 (8 items) or 0–2 (9 items); 0–7 is normal, 8–13 is mild depression, 14–18 moderate depression, 19–22 severe depression, and ≥ 23 very severe depression. A $\geq 50\%$ drop from baseline scores is commonly accepted as treatment response, while a ≤ 7 score is considered remission (Lecrubier, 2002). Certified clinicians with a 0.863 interrater reliability (Fleiss' κ) conducted HDRS interviews. The CGIs is a Likert scale ranging 1 (not at all ill) to 7 (extremely ill). Dropping to 1 or 2 (borderline ill) is considered an additional measure of clinical remission or response. The GAF is a "continuous" 1–100 scale subdivided in ten 10-point content layers; higher scores indicate better psycho-socio-occupational functioning. The OCDS is a self-rated scale, developed to measure obsessionality and compulsiveness related to craving and drinking behaviour; two subscale scores measuring specific cognitive aspects of alcohol craving are added to obtain the total score. Safety was measured through spontaneous reporting of side effects.

2.3. Deep TMS protocol

For dTMS sessions we used Brainsway's H1 coil deep TMS 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 (Roth et al., 2007). H1 coils were positioned over patient's scalp. The optimal spot on the scalp for stimulation of the right *abductor pollicis brevis* muscle was located, and the motor threshold established by delivering single stimulations to the motor cortex. The motor threshold, defined as the lowest stimulation intensity producing five motor evoked potentials (MEPs) of at least 50 μV in 5 of 10 stimulations, was measured by gradually increasing stimulation intensity. The site of stimulation was located 5.5 cm anterior to the point at which maximum stimulation of the *abductor pollicis brevis* muscle was reached. dTMS treatment was delivered by expert, trained, certified physicians (CR, VRF, PS, SDP) in trains of 20 Hz at 120% of the measured motor threshold. Each patient received 55 18 Hz trains per session at 120% of the measured motor threshold, with 2 s duration each and 20 s inter-train intervals, for a total of 1980 pulses per session. The complete cycle of the dTMS treatment consisted of five consecutive session days in a week for 4 consecutive weeks, for a total of 20 sessions amounting to 39,600 pulses for each patient. The study protocol has been approved by both local ethical committees.

2.4. Statistical analysis

SPSS version 19.00 (SPSS Inc., Chicago, IL, United States) was used for data analysis. Continuous variables were assigned as mean ± standard deviation, while discrete variables were assigned as numbers and percentages. Whether continuous variables complied with a normal distribution were checked with a Kolmogorov–Smirnov test. Whether the groups differed in terms of discrete variables were checked by Pearson's Chi Square test (χ^2). Since continuous variables did not comply with normal distribution, the Mann–Whitney *U* test was used for the two group comparisons. Then, a Wilcoxon signed rank test was used to assess whether clinical scales scores changed significantly from baseline to end of treatment in each group and in all patients. Statistical significance was set at p value < 0.05.

3. Results

3.1. Demographics and baseline clinical characteristics of the study groups

Baseline socio-demographic and clinical characteristics of the sample are summarised in Table 1. There were no significant differences between MDD and MDD+AUD in terms of age, sex distribution, years of education and duration of illness (Table 1) and in baseline scale scores. Scores on the HRDS ranged from 17 to 41 in the MDD+AUD group (median=28) and from 16 to 34 in the MDD group (median=26.5). Furthermore, both groups showed a moderate functional impairment (as measured with the GAF) and moderate-to-severe depressive symptoms (as measured with HDRS and CGIs) before initiating dTMS treatment (Table 1). Concomitant antidepressant, benzodiazepine and atypical antipsychotic treatment differed between MDD and MDD+AUD, with 7 patients in the MDD group receiving selective serotonin reuptake inhibitors and 5 a serotonin-noradrenaline reuptake inhibitor (SNRI), while all but one MDD+AUD patient received a serotonin/noradrenaline receptor-serotonin/D_4/histamine transporter inhibitor and the other a different SNRI; most MDD patients ($N=9$) took clonazepam while MDD+AUD were on diazepam, which was part of their detoxification programme. Two patients in the MDD group and none in the MDD+AUD group had the stabiliser antidepressant lamotrigine added in their treatment schedule, while one patient in each group took two different dibenzo-oxazepine atypical antipsychotics. Three patients in the MDD+AUD group had stage 1 treatment-resistant depression (failure to respond to one adequate trial of an antidepressant) and the other eight had stage 2 (failure to respond to two adequate antidepressant trials) (Nemeroff, 2007), compared to four MDD patients with stage 1 and eight with stage 2 treatment-resistant depression. The doses were adequate and equivalent in the two groups and could not account for results. Despite being taken since at least one month, no patient had reached a satisfactory response.

3.2. Clinical outcomes during and immediately after dTMS in the study groups

dTMS was associated with significant drops from baseline in HDRS and CGIs scores in both MDD and MDD+AUD groups and in

Table 1
Socio-demographic and clinical characteristics of the study groups.

	MDD+AUD ($n=11$)	MDD ($n=12$)	U/χ^2	p
Age (mean ± SD)	53.64 ± 7.94	51.2 ± 8.02	55.5	0.525
Sex (% males)	54.5	58.3	0.03	0.593
Years of education (mean ± SD)	10.73 ± 2.61	10.75 ± 3.65	65.5	0.976
Duration of illness (mean ± SD)	18.73 ± 7.58	17.33 ± 3.75	63.0	0.880
HDRS pre-dTMS	27.36 ± 6.15	26.75 ± 5.51	64.5	0.928
CGI pre-dTMS	6.00 ± 0.78	5.83 ± 0.84	58.0	0.651
GAF pre-dTMS	45.27 ± 3.77	45.58 ± 4.80	65.5	0.976

p-Values refer to Mann–Whitney *U* test for continuous variables and to the Chi-squared test for categorical variables. *p*-Values below the threshold of statistical significance (0.05) were not found, but would have been indicated in *italics*.
Abbreviations: MDD – Major Depressive Disorder; AUD – Alcohol Use Disorder; dTMS – deep Transcranial Magnetic Stimulation; HDRS – Hamilton Rating Scale for Depression; CGI – Clinical Global Impression; GAF – Global Assessment of Functioning.

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the entire group as a whole, as shown in Tables 2 and 3, and Fig. 1. HDRS scores dropped from baseline to the end of the 20 sessions (week 4) by 55.2% in MDD and by 62.6% in MDD+AUD, while CGIs scores dropped in the same time period by 67.1% in the MDD and 78.2% in the MDD+AUD group.

Depression, as assessed through the HDRS dropped faster in the MDD+AUD than in the MDD-only group. HDRS scores dropped significantly better in the MDD+AUD group than in the MDD the 2nd and 3rd week time-points; however, differences at the 4th week (post-dTMS) time-point were not significant, but nevertheless, a trend could be observed (Table 3). Improvement, as shown by decreased severity scores on the CGIs, was significantly better in the MDD+AUD group, compared to the MDD-only group starting from the first week and extending to the entire duration of the dTMS period (Table 3).

3.3. Six-month follow-up

All the included patients were followed and evaluated after six months in order to assess the long-term efficacy of the dTMS treatment. As shown in Table 3, the HDRS score in the MDD+AUD group was significantly lower than in the MDD group after six months form the dTMS treatment indicating that dTMS treatment efficacy might be higher in the treatment of comorbid depression and alcohol abuse. As well, the GAF score was significantly higher in the MDD+AUD group with respect to the MDD one. The higher MDD+AUD patients global functioning could be related to the higher improvement of the depressive symptoms after the dTMS treatment. Conversely, the CGI score after six months is not significantly different between the study groups.

Despite the higher efficacy in the MDD+AUD patients, the dTMS treatment improved significantly all the scale scores in both groups after the six months follow-up (Table 4).

3.4. Effect of dTMS on alcohol craving

Scores on the OCDS in DDM+AUD dropped from 23.83 ± 5.42 to 10.32 ± 1.86 at week 1, to 9.26 ± 2.16 at week 2, to 8.12 ± 1.99 at week 3, to 7.23 ± 2.31 at week 4 (end of the 20-session dTMS treatment); this was significant (Wilcoxon signed rank test, $Z = -2.236$; $p = 0.025$), and was maintained and potentiated during the 6-month follow-up (6.33 ± 2.58; Wilcoxon signed rank test, $Z = -2.91$; $p = 0.018$).

3.5. Response and remission

According to the at least 50% drop in HDRS scores from baseline response criterion, all MDD+AUD patients were responders at the end of the dTMS treatment period (100%) and at the 6-month

Table 2
Significant reduction in HDRS and CGI scores from baseline to end of dTMS treatment in each study group and in all participants.

	MDD+AUD ($n=11$)	MDD ($n=12$)	All patients ($n=23$)
HDRS [(Z); p]	(−2.94) *0.003*	(−3.06) *0.002*	(−4.20) *<0.001*
CGI [(Z); p]	(−2.98) *0.003*	(−3.09) *0.002*	(−4.24) *<0.001*

p-Values refer to the Wilcoxon signed rank test (*H0*: differences between pre-dTMS and post-dTMS follow-up values). p-Values below the threshold of statistical significance (0.05) are indicated in *italics*.
Abbreviations: MDD – Major Depressive Disorder; AUD – Alcohol Use Disorder; dTMS – deep Transcranial Magnetic Stimulation; HDRS – Hamilton Rating Scale for Depression; CGI – Clinical Global Impression; GAF – Global Assessment of Functioning.

Table 3
Comparison between the study groups scale scores during and after dTMS treatment.

	MDD+AUD ($n=11$)	MDD ($n=12$)	U/χ^2	p
HDRS 1 week	21.91 ± 5.80	25.17 ± 4.80	39.5	0.104
HDRS 2 weeks	16.64 ± 4.01	22.17 ± 5.31	27.5	*0.016*
HDRS 3 weeks	12.36 ± 2.73	16.33 ± 4.76	31.0	*0.032*
HDRS post-dTMS (4 weeks)	9.45 ± 2.30	12.75 ± 4.22	35.5	0.059
HDRS six-month follow-up	8.09 ± 2.91	13.67 ± 3.94	15.5	*0.001*
CGIs 1 week	2.81 ± 0.75	3.75 ± 0.87	28.5	*0.019*
CGIs 2 weeks	1.82 ± 0.60	3.50 ± 1.24	12.5	*<0.001*
CGIs 3 weeks	1.36 ± 0.51	2.33 ± 0.89	25.0	*0.011*
CGIs post-dTMS (4 weeks)	1.18 ± 0.41	1.92 ± 0.67	26.5	*0.013*
CGIs six-month follow-up	1.09 ± 0.30	1.33 ± 0.49	50.0	0.347
GAF six-month follow-up	92.36 ± 4.25	84.67 ± 6.01	19.5	*0.003*

p-Values refer to the Mann–Whitney U test for continuous variables and to the Chi-squared test for categorical variables. p-Values below the threshold of statistical significance (0.05) are indicated in *italics*.
Abbreviations: MDD – Major Depressive Disorder; AUD – Alcohol Use Disorder; dTMS – deep Transcranial Magnetic Stimulation; HDRS – Hamilton Rating Scale for Depression; CGI – Clinical Global Impression; GAF – Global Assessment of Functioning.

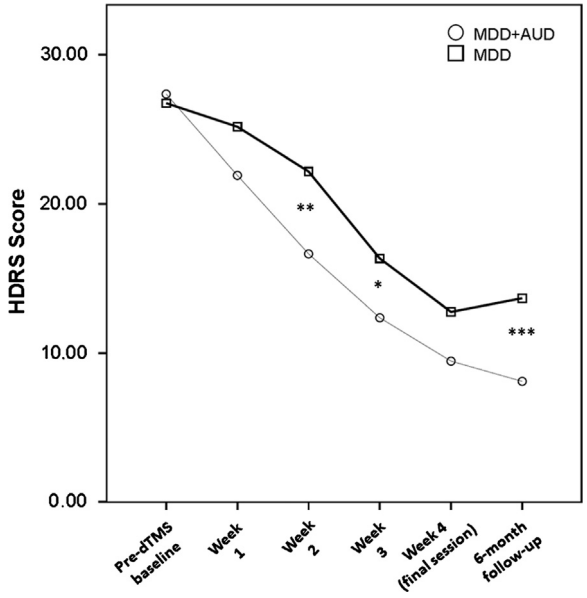

Fig. 1. Comparison of the HDRS total score during the study between the MDD+AUD and MDD-only groups. *$p < 0.05$; **$p = 0.02$; ***$p < 0.01$.

Table 4
Significant reduction in HAM-D and CGI scores and increase in GAF scores before and after the six month follow-up in each group and in all participants.

	MDD+AUD ($n=11$)	MDD ($n=12$)	All patients ($n=23$)
HDRS [(Z); p]	(−2.94) *0.003*	(−3.07) *0.002*	(−4.02) *<0.000*
CGIs [(Z); p]	(−2.97) *0.003*	(−3.11) *0.002*	(−4.26) *<0.000*
GAF [(Z); p]	(−2.94) *0.003*	(−3.07) *0.002*	(−4.20) *<0.000*

p-Values refer to Wilcoxon signed rank test (*H0*: differences between pre-dTMS and 6 months follow-up values). p-Values below the threshold of statistical significance (0.05) are indicated in *italics*.
Abbreviations: MDD – Major Depressive Disorder; AUD – Alcohol Use Disorder; dTMS – deep Transcranial Magnetic Stimulation; HDRS – Hamilton Rating Scale for Depression; CGI – Clinical Global Impression; GAF – Global Assessment of Functioning.

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follow-up (100%), while in the MDD-only group, 7 were responders at post-dTMS (58.33%) and 7 (not the same) at follow-up (58.33%). According to the less than 8 score on the HDRS criterion of remission, 3 MDD+AUD patients were remitters post-dTMS (27.27%) and 7 at the 6-month follow-up (63.64%), while none of the MDD-only patients were remitters post-dTMS (0%) and one was at the 6-month follow-up (8.33%). All MDD+AUD patients scored 1 or 2 on the CGIs scale post-dTMS (100%) and at follow-up, compared to 10 (83.33%) of the MDD-only group post-dTMS and all (100%) at follow-up.

3.6. Side effects

One MDD-only patient reported one day of headache during the second week that he did not attribute to the treatment. No other patient in either group reported any side effect.

4. Discussion

As expected in this study, dTMS was followed by improvement in depressive symptomatology and clinical status during the treatment cycle and at the end of it, as well as at a 6-month follow-up in both MDD-only and MDD+AUD adult patients who did not respond satisfactorily to appropriate treatment. We aimed to assess the antidepressant effect of add-on dTMS in patients with MDD. We also observed a fast reduction in craving, according to our expectations, which persisted in the long-term follow-up. We did not find the presence of AUD to hamper antidepressant response to 20 add-on sessions of dTMS delivered over bilateral DLPFC with left prevalence, in comorbid MDD patients; on the contrary, the onset of the antidepressant effect was faster in the MDD+AUD group and depressive outcome was better at the 6-month in the comorbid than in the MDD-only group (Table 3, Fig. 1). This is not easy to explain, as the two groups of patients were similar at baseline for clinical status, depression, and global functioning and were similarly resistant to the therapeutic effects of drug treatment they received, and which remained unchanged during the trial. We might hypothesise a site effect, which may have been masked by the comparability of obtained results. Even with the use of identical coils and apparatuses and personnel sharing, site effects are likely. We cannot assess the contribution to the observed variance of intergroup differences in drug regimens, to which patients in the two groups were similarly resistant; however, regimens were variable also intragroup, although in MDD+AUD they were more uniform; this is another possible confounder that might have contributed to a site effect, as more MDD+AUD were from the Viterbo site. We might speculate that people who were comorbid and obtained a prompt response for AUD, as shown by the fast decrease in craving, had earlier a lesser hurdle to overcome and this might have facilitated the response of depression to both dTMS and drugs. It should be stressed that comorbid people had also a better 6-month functioning outcome that could partly explain the better long-term antidepressant response; however, we cannot establish a cause–effect relationship. In one study, young adults with substance use disorder, the presence of MDD lowered their ability to control their substance use (Greenfield et al., 2012); it is possible that an initial improvement of depression in our MDD+AUD sample induced by dTMS has increased its ability to control alcohol use and this in turn has further reduced depression by triggering a positive feedback between the two conditions. Or it could be that DLPFC stimulation allowed better executive functioning, including the ability to establish hierarchical priorities, thus better control of substance craving (Boggio et al., 2008, 2009) and appraisal of negative emotions (Feeser et al., 2014; Ma, 2014; Silvers et al., 2014). Despite not showing higher impulsiveness levels, patients with AUD and depression/anxiety differ from patients with depression/anxiety alone and from healthy controls for a higher activation of the thalamus and putamen during an inhibitory task performance (Sjoerds et al., 2014). There is no evidence as yet, but if DLPFC stimulation could selectively correct this abnormality, this could confer an advantage to the comorbid sample in terms of response, but again, it could not explain the puzzlingly better 6-month outcome of the comorbid sample, compared to the MDD-only.

Craving for several substances has been shown to be reduced through DLPFC stimulation, including nicotine (Amiaz et al., 2009; Li et al., 2013; Pripfl et al., 2014), cocaine (Camprodon et al., 2007; Politi et al., 2008), and alcohol (Boggio et al., 2008). However, alcohol-related cues which increase craving, are likely to increase activity in the prefrontal cortex (Olbrich et al., 2006).

Even with the use of more stringent remission criteria in our study, our results compare favourably with the existing literature of dTMS in MDD (Levkovitz et al., 2009; Rosenberg et al., 2010a, 2010b). The reason could be that our sample was less treatment-resistant than those of previous reports. However, all our patients were on antidepressants for sufficient time and at sufficient doses for antidepressant effects to appear, although they did not meet the third-stage resistance of the Thase and Rush (1997) criteria for drug resistance. Furthermore, we obtained similar results for our MDD+AUD patients to those we previously reported for third-stage treatment-resistant patients with dysthymic disorder comorbid with AUD (Girardi et al., 2014).

4.1. Limitations

This was a two-centre, open-label study, with a small sample size that does not allow us to draw strong conclusions, and drug treatment heterogeneity and study site adding further possible confounders that, due to the small sample, could not be explored adequately. Our long-term follow-up was conducted without maintenance sessions; dTMS maintenance could have improved our outcomes, as rTMS was shown to reduce relapse/recurrence (Richieri et al., 2013). However, even without controlling for the effects of maintenance, our results were impressive and pointed to long-term effects of dTMS, six months after one single cycle, a longer follow-up than the one used by Richieri et al. (2013). Furthermore, we did not use sham dTMS control groups. The two groups did not differed for being taken care by staff, as the conditions between the two sites were similar and kept constant, with remarkable sharing of the personnel. Possible differences could have boosted Hawthorne-like placebo effects that could have been detected by using a sham. In spite of uncertainty as to the magnitude of the placebo effect of the various routes of administration and procedures, innovative technology and devices are likely to be endowed with higher placebo-like effects than other treatments (Kaptchuk et al., 2000), so it is possible that some of the responsiveness we obtained here could be due to the patients' idealisation of the procedure.

In this study we confirmed in patients with MDD the early and protracted antidepressant effect of 20 sessions of add-on dTMS we previously reported for patients with dysthymic disorder (Rapinesi et al., 2013; Girardi et al., 2014). We also confirmed the anti-craving potential of dTMS in patients with MDD with AUD. The effect occurred earlier in the comorbid sample, compared to MDD-only patients. We observed no relapse during a period of 6 months after the end of the dTMS cycle and no side effect attributable to the treatment.

5. Conclusions

The add-on of dTMS to standard treatment that had not elicited satisfactory treatment response was associated with significant and

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fast improvement of the clinical picture, which was faster in patients with both MDD and AUD than in patients with MDD only. Furthermore, reduced alcohol craving was found in the MDD+AUD group. Effects are maintained at the 6-month follow-up. Add-on dTMS appears to be a safe and effective treatment for otherwise unresponsive patients with MDD. It is possible that there was an interplay between neurobiological factors related to depression and factors related to abuse in the therapeutic effect of DLPFC stimulation, which resulted in mutual enhancement. Our data need replication in larger samples and using sham controls. The value of maintenance treatment needs to be better assessed. In fact, it was shown to prevent relapse/recurrence in less than five months, but we observed no relapse in six months.

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Conflict of interest

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