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Research paper

Cognitive outcomes of TMS treatment in bipolar depression: Safety data from a randomized controlled trial

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ABSTRACT

Background: Bipolar depression (BD) is a highly prevalent condition associated with marked cognitive deficits that persist even in the euthymic phase of the illness. Pharmacological treatments for BD might further aggravate cognitive impairment, highlighting the need of developing interventions that present cognitive safety. In this study, we evaluated the cognitive effects of H1-coil (deep) transcranial magnetic stimulation (TMS) in patients with treatment-resistant bipolar depression.

Methods: Fourty-three patients were randomized to receive 20 sessions of active (55 trains, 18 Hz, 120% resting motor threshold intensity) or sham rTMS within a double-blind, sham-controlled trial. A battery of 20 neuropsychological assessments, grouped in 6 domains (attention and processing speed, working memory and executive function, inhibitory control, language, immediate verbal memory, and long-term verbal memory) was performed at baseline and after 4 and 8 weeks of trial onset. Depressive symptoms were assessed with the 17-item Hamilton Rating Scale for Depression.

Results: Cognitive improvement was shown for all cognitive domains. It occurred regardless of intervention group and depression improvement. For the language domain, greater improvement was observed in the sham group over time. No correlations between depression (at baseline or during treatment) and cognitive improvement were found.

Limitations: Absence of healthy control group.

Conclusion: The results of this exploratory study provide evidence on the cognitive safety of H1-coil TMS for BD patients. Putative pro-cognitive effects of rTMS in BD were not observed and thus should be further investigated.

1. Introduction

Bipolar disorder is a highly disabling condition with a worldwide prevalence of 2–3% (Ferrari et al., 2016). Depressive episodes are more frequent, prolonged, and incapacitating compared with manic ones (Judd et al., 2002), therefore representing the greatest burden of this disorder. Patients with bipolar depression (BD) present cognitive deficits in several domains, such as processing speed, attention, working memory, verbal memory, and problem solving (Depp et al., 2012). These deficits are associated with poor illness outcome and partly explain the burden of the disease (Baune and Malhi, 2015). In fact, cognitive impairment persists even in euthymic phases and might be, although less severe, qualitatively similar compared to the deficits observed in patients with schizophrenia (Daban et al., 2006).

However, available pharmacological treatments for BD do not sufficiently address cognitive symptoms. For instance, anticonvulsant and antipsychotic drugs often lead to psychomotor retardation and memory decline (Gualtieri and Johnson, 2006; Harvey et al., 2007); whereas lithium effects are mixed, improving some cognitive domains while decreasing the performance in others (Malhi et al., 2016). A recent non-

Abbreviations: BD, bipolar depression; rTMS, repetitive transcranial magnetic stimulation; DLPFC, dorsolateral prefrontal cortex; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; MINI, Mini-International Neuropsychiatric Interview; HDRS-17, Hamilton Depression Rating Scale, 17-items; YMRS, Young Manic Rating Scale

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pharmacological strategy is cognitive or functional remediation, which is based on several neurocognitive training strategies designed for tackling the core cognitive bipolar disorder deficits. Positive results have been demonstrated for cognitive remediation (Torrent et al., 2013); although negative findings were also reported (Demant et al., 2015). Moreover, the intervention requires staff training and patient commitment.

Another non-pharmacological strategy is repetitive transcranial magnetic stimulation (rTMS), a therapy that modulates brain activity via electromagnetic pulses discharged through a coil placed over the patient's head (Rosa and Lisanby, 2012). TMS produces magnetic fields with flux lines perpendicular to the plane of the coil. The figure-of-eight coil, which is usually employed for therapeutic purposes, produces a relatively "conic" and focal field, with the sum of the field lines induced by each loop of the eight producing a more intense magnetic field in the center of the "8". The width of the magnetic field corresponds to the size of the coil; whereas its deepness is usually limited to 2 cm or less, as the magnetic flux density falls off with the square of the distance from the stimulating coil (Rosa and Lisanby, 2012). For depressive disorders, rTMS is applied over the dorsolateral prefrontal cortex (DLPFC), a brain area whose connectivity and function are impaired in depression. The DLPFC is a key hub of the frontoparietal network, a set of regions responsible for cognitive control and emotion regulation (Kaiser et al., 2015). The role of the DLPFC in modulating cognitive control has been shown in single rTMS sessions in healthy volunteers (Vanderhasselt et al., 2006). In fact, rTMS over the DLPFC is an effective treatment for unipolar and bipolar depression, but with only moderate efficacy (Brunoni et al., 2017; McGirr et al., 2016); while rTMS effects on cognition are small(Martin et al., 2017).

Currently, numerous efforts are being made to optimize rTMS and increase its therapeutic efficacy. One recent, novel approach is H1-coil ("deep") rTMS, which is designed to stimulate deeper and larger brain volumes using a coil that produces less focal and wider electromagnetic fields (Zangen et al., 2005). According to phantom models, suprathreshold fields are induced by the H1-coil at depths of up to 4 or 5 cm along the lateral-medial and antero-posterior axes (Roth et al., 2007).

This coil characteristic can be advantageous for mood disorder treatment as connectivity of the DLPFC with the subgenual cingulate gyrus influences rTMS treatment response (Fox et al., 2012). H1-coil rTMS is effective for unipolar depression (Levkovitz et al., 2015), and a phase II randomized, sham-controlled trial from our group suggested that it is also effective for BD (Tavares et al., 2017). Although there is some evidence that H1-coil rTMS has beneficial effects on cognitive domains (Levkovitz et al., 2009), this has not been systematically evaluated.

Another concern is cognitive impairment. Although previous studies in mood disorders showed that rTMS does not impair cognitive performance (Tortella et al., 2014), there is insufficient information for the H1-coil.

Considering these issues, we investigated the cognitive effects of a treatment course of H1-TMS for BD. To this end, we employed a battery of standardized neuropsychological tests that were selected to assess adverse neuropsychological effects. Our hypothesis was that H1-rTMS would not produce cognitive adverse effects in BD patients. Moreover, we also explored whether H1-rTMS could increase cognitive performance in the investigated domains.

2. Methods

2.1. Design

The present study reports the effects of H1-rTMS on cognitive assessments performed in a recently published randomized, double-blind, sham-controlled trial that investigated the efficacy of H1-coil rTMS for bipolar depression (Tavares et al., 2017). The trial (clinicaltrials.gov identifier: NCT01962350) was approved by the local and national ethics committee and conducted at the Institute of Psychiatry, Clinics Hospital of the University of São Paulo between July 2013 and July 2016. All participants signed informed consent forms.

The trial lasted 8 weeks, encompassing 4 weeks of 20 daily TMS sessions (excluding weekends) and a follow-up of 4 weeks with no TMS sessions. Allocation concealment was done using sequentially numbered cards inserted in the TMS machine to perform active or sham stimulation. The cards were controlled by a secretary not directly involved in the research. Participants and staff were fully blinded to allocation status.

2.2. Subjects

Fifty adult (18–65 years-old) patients diagnosed with type I or II bipolar disorder in an acute depressive episode were recruited. Diagnoses were performed by board-certified psychiatrists according to DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th edition) criteria and confirmed using the Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998).

Patients presented a depressive episode of at least moderate severity corresponding to a Hamilton Depression Rating Scale, 17-items (HDRS-17) $\geq$17 (Hamilton, 1960). Exclusion criteria included other psychiatric disorders (such as unipolar depression, schizophrenia, substance dependence, dementias and others); neurologic disorders (such as stroke, traumatic brain injury, epilepsy and others); severe personality disorders; presence of manic symptoms at baseline and/or a score on the Young Manic Rating Scale (YMRS) $>$12 points; presence of psychotic symptoms; acute suicidal symptoms; rapid-cycling bipolar disorder; pregnancy; and specific contraindications for H1-coil rTMS.

Only patients without concomitant antidepressant drug medication (i.e., selective serotonin reuptake inhibitors, tricyclic antidepressants, dual inhibitors, and others) were included. This was done because (1) antidepressant drug treatment is usually not recommended for most patients in BD (Yatham et al., 2013) and (2) to avoid confounding effects of the antidepressant treatment in our trial.

All patients were on a stable pharmacological regimen and presented resistant depression, defined as the failure to achieve remission after $\geq$2 first-, second- or third-line therapies according to the CANMAT recommendations (Yatham et al., 2013). Benzodiazepine drugs were allowed at a maximum of 3 mg/day of lorazepam or equivalent.

2.3. rTMS parameters

TMS sessions were delivered using an H1-coil investigational device from Brainsway (Brainsway Ltd, Jerusalem, Israel), as previously reported (Tavares et al., 2017). In this system, both active and sham coils were built inside the same helmet to achieve effective cooling and allocation concealment during stimulation. The coil was positioned over the left DLPFC, found 6 cm anteriorly to the hotspot, which is the optimal location on the scalp to achieve motor evoked potentials.

The active stimulation session consisted of 55 trains at 18 Hz and 120% motor threshold intensity pulses (total of 1980 pulses/day or 39,600 pulses per treatment). For the sham stimulation, the sham coil mimicked the scalp sensations and acoustic artifacts of the active stimulation.

2.4. Assessments

Demographic and clinical assessments were performed by the trained staff using instruments to evaluate symptoms of depression, anxiety, and mania, as well as rTMS adverse effects, as described elsewhere (Tavares et al., 2017).

A battery of neuropsychological tests, lasting approximately 120 minutes, was administered to each patient at baseline and after 4 and 8 weeks. The neuropsychological tests were applied in the afternoon (2

Table 1
Battery of neuropsychological assessments used in the study.

Domain	Test	Range	Outcome	Direction
Attention and processing speed	Trail making test—A (Lezak et al., 2004)	0–300 s	test completion speed	Negative
	Stroop color (Lezak et al., 2004)	0-∞ s	test completion speed	Negative
	Digit symbol-coding (WAIS-III) (Wechsler and Nascimento, 2004)	0–133 points	symbol-code correct matching	Positive
	Digit span forward (WAIS-III) (Wechsler and Nascimento, 2004)	0–16	maximum span	Positive
	Stroop word (Lezak et al., 2004)	0-∞ s	test completion speed	Negative
Inhibitory control	Stroop interference (Lezak et al., 2004)	0-∞ s	test completion speed	Negative
	Wisconsin card Sorting Test (Lezak et al., 2004)	0–64 points	numbers of perseverative errors	Negative
	Iowa gambling task (Bechara et al., 1997)	0–100	number of cards chosen in each deck	Negative for bad decks / Positive for good decks
Working memory and executive function	Rey-Osterrieth Complex Figure (Lezak et al., 2004)	0–36	number of correct responses	Positive
	Cubes (WAIS-III) (Wechsler and Nascimento, 2004)	0–14	numbers of correct responses	Positive
	Wisconsin card sorting test - hits (Lezak et al., 2004)	0–64 points	total scores	Negative
	Trail making test—B (Lezak et al., 2004)	0–300 s	test completion speed	Negative
	Digit Span Backward (WAIS-III) (Wechsler and Nascimento, 2004)	0–16	maximum span	Positive
	Sequence of number and Letters (WAIS-III) (Wechsler and Nascimento, 2004)	0 −21	total score	Positive
Language	FAS verbal fluency (Tombaugh et al., 1999)	0- ∞	number of words	Positive
	Animal verbal fluency (Tombaugh et al., 1999)	0- ∞	number of words	Positive
Immediate verbal memory	Wechsler memory scale (Wechsler, 1987)	0–25	total score	Positive
	RAVLT (Paula et al., 2012)	0–15	remembered word list	Positive
Long-term verbal memory	Wechsler memory scale (Wechsler, 1987)	0–25	total score	Positive
	RAVLT (Paula et al., 2012)	0–15	remembered word list	Positive

Battery of tests used in our study. A “positive” direction means that higher values indicate higher performance; a “negative” direction indicates that higher values indicate lower performance. WAIS III, Wechsler Adult Intelligence Test-III; RAVLT, Rey Auditory Verbal Learning Test.

pm–5 pm) and the rTMS sessions in the morning (8 am–11 am) as to avoid any possible acute rTMS effects on cognition. All tests were applied by trained psychologists. We only used tests that had been previously validated for the Portuguese language. The tests assessed six different cognitive domains: attention and processing speed, inhibitory control, working memory and executive function, language, and immediate and long-term memory (Table 1).

2.5. Statistical analyses

Analyses were performed in Stata 14 (StataCorp, College Station, TX, USA) using the per protocol data (i.e., patients who completed the trial). The significance level was 5% and unadjusted for multiple comparisons since this was an exploratory study. Baseline characteristics were described as means and standard deviations or frequencies and compared between groups using the t test or the Chi-square test for continuous or categorical variables, respectively.

The first step was to convert the individual patients’ test scores on each instrument, asymmetrically distributed, in normalized z-scores. Next, we derived composite scores of the 6 cognitive domains evaluated in our neuropsychological battery (attention, inhibitory control, working memory and executive function, language, and immediate and long-term auditory memory). For all composite scores, higher values indicated better performance. The approach of using composite variables, as used in a previous study (Schulze et al., 2016), was performed to reduce the number of false positive findings due to multiple comparisons and to provide a more meaningful interpretation of the cognitive effects of H1-coil TMS. Nonetheless, considering the positive results of a recent meta-analysis of rTMS in depression for the trail making tests Part A and B (Martin et al., 2017), we additionally performed post-hoc analyses for these variables.

Several mixed models (command *mixed* in Stata) were performed. The cognitive domain was the dependent variable. Group (active or sham), time (baseline, week 4, week 8) and their interaction were the independent variables. Contrast tests were then performed to express the effects of group, time, and their interaction. Subject was the random-effects variable. Age, gender, depression scores, and years of schooling were introduced as independent co-variates as cognitive performance might vary according to them. We did not adjust for other potential confounding variables such as medication use due to the low sample size and the low number of patients using a given medication. Moreover, the distribution of variables was balanced between groups.

In addition, we evaluated whether the assessed cognitive domains at baseline predicted depression improvement. Analyses of variance (ANOVAs) were performed with depression change (baseline minus endpoint scores) as the dependent variable; and group, the cognitive domain and their interaction as independent variables. Models were adjusted for age, gender, and education.

Finally, we performed Pearson's correlations between depression improvement and cognitive improvement (baseline minus endpoint scores) to explore correlations between these variables.

3. Results

3.1. Overview

Out of 50 patients, 43 finished the study (23 and 20 in the sham and active groups, respectively). All patients who completed the trial performed the neuropsychological assessments. Main trial results are described elsewhere (Tavares et al., 2017). Briefly, we found that active stimulation was superior to sham at week 4 but not at week 8. The clinical, demographic and cognitive variables at baseline are described in Table 2.

3.2. Neuropsychological performance

All cognitive domains improved over time ($p < 0.001$) (Fig. 1) (Table 3). There were no interactions between time and group for the cognitive domains, except for language (Table 4). For this domain, although at endpoint no group difference was found (chi-squared = 0.57, $p = 0.44$), the contrast that compared group difference between endpoint and baseline was significant (chi-squared = 6.05, $p = 0.01$), showing a relative greater increase in performance of sham vs. active over time. Moreover, we found no interaction between group and time

Table 2
Baseline characteristics of the sample.

	Sham rTMS (n = 23)	Active rTMS (n = 20)	p
Clinical and demographic variables			
Gender (% Female)	18 (78)	15 (75)	0.81
Age, mean (SD)	40.6 (9)	41.2 (11.7)	0.86
Years at school, mean (SD)	15.2 (4.4)	14.1 (3.7)	0.36
Ethnicity (% Caucasian)	3 (14)	3 (15)	0.94
Income (R$), mean (SD)	4272 (3417)	5105 (3840)	0.47
Depression characteristics			
Bipolar disorder I, n (%)	13 (56)	9 (45)	0.45
Bipolar disorder II, n (%)	10 (44)	11 (55)	
Depression duration, mean (SD)	10.5 (10.4)	11.8 (14.7)	0.75
Depression episodes, mean (SD)	2.5 (1.2)	2.2 (1.2)	0.42
Hamilton Depression Rating Scale, 17-items, mean (SD)	25.2 (3.7)	26 (5.1)	0.53
Treatment history, n (%)			
First-line therapy	20 (87)	17 (85)	0.85
Lithium	13 (56)	12 (60)	0.82
Quetiapine	7 (30)	7 (35)	0.75
Valproate	4 (17)	5 (25)	0.4
Lamotrigine	8 (35)	5 (25)	0.48
Benzodiazepine	6 (26)	9 (45)	0.19
Cognitive domains, composite z-scores, mean (SD)			
Attention and processing speed	−0.24 (1.01)	−0.18 (0.79)	0.82
Inhibitory control	−0.16 (0.72)	−0.36 (0.57)	0.32
Working memory and Executive Function	0.06 (0.37)	−0.27 (0.7)	0.07
Language	−0.22 (0.9)	−0.14 (0.94)	0.76
Immediate memory	−0.35 (0.83)	−0.47 (0.71)	0.6
Long-term memory	−0.36 (0.79)	−0.39 (0.76)	0.92

SD, standard deviation. First-line therapy represents patients using treatments recommend by the CANMAT guidelines as first-line for bipolar depression (Yatham et al., 2013).

for the trail making tests Part A (F = 0.23, p = 0.79) and B (F = 0.26, p = 0.77).

In addition, depression scores at baseline were not associated with cognitive improvement.

3.3. Cognitive predictors of improvement

The interactions between treatment group and the domains of attention (F = 1.06, p = 0.3), inhibitory control (F = 2.17, p = 0.15), working memory and executive function (F = 1.81, p = 0.19), language (F = 0.12, p = 0.73), immediate memory (F = 0.03, p = 0.87), and long-term memory (F = 0.01, p = 0.91) were not significant. Therefore, no cognitive domain predicted the response to H1-coil rTMS compared to sham stimulation.

In addition, no correlations between depression and cognitive improvement were found (all ps > 0.44).

4. Discussion

In this randomized, placebo-controlled trial investigating deep TMS treatment for bipolar depression, cognitive improvement in all domains was observed. This improvement occurred over time and regardless of the allocation group. The results support our hypothesis that H1-coil TMS over the DLPFC for BD is safe in terms of cognitive outcomes.

Interestingly, for the language domain, the sham group presented a significant improvement over time, compared to the active group (p = 0.045). A similar (although non-significant) trend was also observed for long-term memory (p = 0.08). These findings should be interpreted with caution, considering that (1) multiple analyses were done and not corrected for multiple comparisons and (2) endpoint scores were not significantly different between groups. Considering these limitations, our findings could indicate that active TMS reduced the practice effects for these domains. Here, it should be noted that the

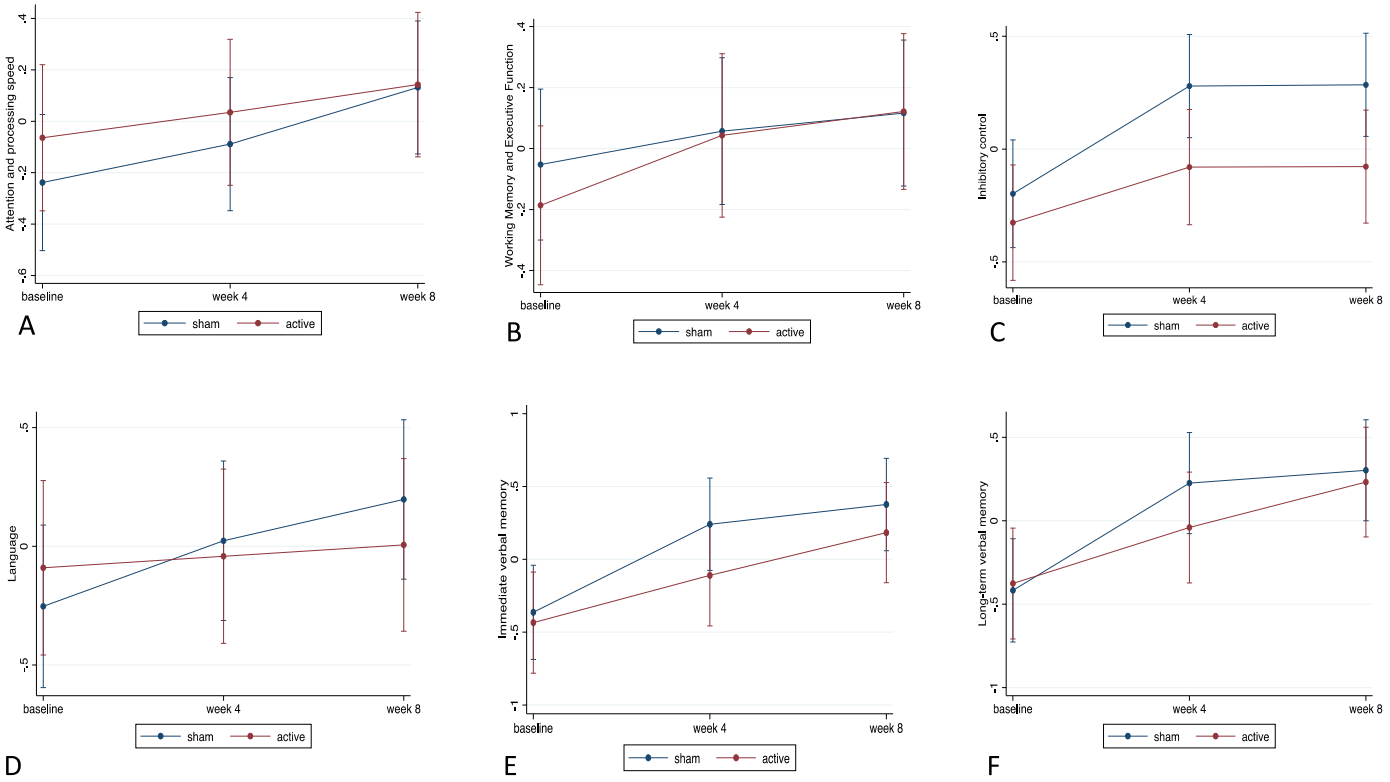

Fig. 1. Cognitive changes over time in active vs. sham rTMS groups.
The figure displays the cognitive changes over time in active and sham H1-rTMS for 6 cognitive domains: (a) attention and processing speed; (b) working memory and executive function; (c) inhibitory control; (d) language; (e) immediate verbal memory; (f) long-term verbal memory. Bars represent + −1 SD.

Table 3
Scores of the neuropsychological tests over time in active and sham groups.

	Baseline		Week 4		Week 8	
	Sham	Active	Sham	Active	Sham	Active
Attention						
Stroop color	15.9 (6.3)	14 (3.6)	16 (6.4)	14.2 (3.3)	14.4 (5.2)	14.5 (4)
Digit span forward *	7.7 (2.4)	8.3 (2.4)	8.5 (2.6)	8.6 (2.5)	8.7 (2.4)	9.4 (2.9)
Trail making test—A	45 (18.5)	49.5 (20.1)	35.2 (14.5)	39.6 (13.8)	32 (9.4)	33 (14)
Digit symbol-coding *	59.9 (20.5)	58.9 (18.7)	61.3 (16.7)	61.6 (22)	66.2 (16.2)	60.4 (20.6)
Stroop word	19 (7.4)	18.9 (5.8)	18.4 (6)	17.5 (3.8)	17.1 (6)	18.2 (4)
Inhibitory control						
Stroop interference	28.6 (11.9)	27.8 (7.7)	26.2 (9.8)	28.1 (7.1)	24.6 (10.3)	27 (7.8)
Wiscosin card sorting	13 (7.8)	15.4 (7.2)	8.8 (7)	11.1 (5.5)	8.5 (6.5)	12 (7.8)
Iowa gambling task	1.9 (21)	−7.4 (21)	16.2 (24.5)	−3.6 (20.7)	11.4 (28.9)	−3.3 (28.6)
Working memory						
Rey-Osterrieth complex figure	31.9 (3.7)	31.2 (5.5)	32.5 (4.1)	32.6 (3.9)	32.8 (3.6)	32.1 (3.8)
cubes *	31.1 (11.5)	29 (11.9)	30.5 (11.2)	32.4 (12)	34.2 (10.3)	33.7 (13.2)
Wiscosin card sorting	40.4 (10.8)	38.4 (10.2)	44.8 (15.3)	40.8 (11.6)	47.3 (12.3)	42.3 (11.9)
Trail making test—B	87.7 (36.5)	102 (51.8)	87.5 (36.7)	94.5 (40.7)	76.2 (42.5)	94 (49.3)
Digit span backward *	5.3 (2.3)	5.5 (2.8)	5.7 (2.4)	6.1 (2.9)	5 (2.3)	6.2 (2.9)
Sequence of number and letters *	8.5 (2.9)	7.7 (2.4)	9.2 (3)	8.8 (3.4)	8.9 (2.6)	9.5 (3.7)
Language						
FAS verbal fluency	30 (11.3)	31.4 (10.9)	33.8 (13)	31.9 (11.3)	36.7 (11.1)	35.5 (13.1)
Animal verbal fluency	16.6 (4.7)	16.8 (5.7)	17.8 (4.9)	17.3 (4.8)	18.3 (4.3)	16.2 (4.8)
Immediate verbal memory						
Wechsler memory scale	19 (7.2)	18.6 (5.1)	23.3 (8.1)	20.5 (5.3)	24.3 (8.7)	23.3 (6.3)
RAVLT - ΣA1-A5	47 (12.4)	44.3 (10.5)	53.8 (12.7)	50.3 (12.3)	58.1 (11.9)	54.2 (13.4)
RAVLT—A6	8.8 (3)	8.5 (3.3)	11.4 (3.3)	9.6 (3.2)	11.2 (3.2)	10.2 (3.5)
Long-term verbal memory						
Wechsler Memory Scale	16.6 (7.3)	16.2 (5.7)	22.3 (8.7)	18 (4.8)	23.8 (7.8)	21.4 (6.2)
RAVLT—A7	9 (3)	8.5 (3.5)	11.3 (3.1)	9.6 (3.5)	11.5 (3.1)	10.7 (3.5)
RAVLT-recognition	13.1 (1.7)	13.3 (1.7)	13.8 (1.8)	13.9 (1.4)	13.8 (2)	14 (1.4)

The table shows the raw mean (Standard Deviation) values of the neuropsychological tests used in our study according to treatment group and over time. (*) Based on the Wechsler Adult Intelligence Scale, 3rd edition (WAIS-III).

deep TMS field is large and could have modulated other left-hemisphere brain areas than the DLPFC that are associated with the cognitive outcomes evaluated, such as inferior frontal, temporal and hippocampal regions, thereby possibly inducing "virtual brain lesions" (Silvanto and Cattaneo, 2017). Nonetheless, if such effects occurred, they were temporary, as the endpoint scores were not different between groups. This hypothesis should be explored in further studies testing different parameters of stimulation and outcomes, as discussed below.

To the best of our knowledge, this is the first study that evaluated the cognitive safety of H1-coil TMS for BD. Therefore, our results cannot be directly compared to other studies. Notwithstanding, a recent meta-analysis of sham-controlled trials that assessed the cognitive effects of rTMS in patients with unipolar and bipolar depression (Martin et al., 2017) found improvement only for the trail making tests A and B, but not for the other evaluated tests (e.g., digit span, digit symbol, the Stroop tests, and others). In contrast, we observed no specific effects for the trail making tests. Nevertheless, we cannot disentangle whether the different findings between Martin et al. study and ours occurred due to our low sample size or specificities of the illness (i.e., bipolar vs. unipolar disorder) or the intervention (standard vs. H1 coil).

We found no correlation between changes in depression scores and changes in cognition. Theoretically, it could be expected that patients presenting larger depression improvement would also present greater cognitive improvement. Nonetheless, our results are in agreement with a recent study that also found no correlation between these variables when employing a non-pharmacological intervention—total sleep deprivation—for treating BD (Poletti et al., 2014). This might suggest that cognitive deficits are trait-like features in bipolar disorder rather than symptoms that occur only during the acute phases of the illness.

In addition, no cognitive domain predicted antidepressant response. To date, only a few predictors of rTMS response for BD have been identified, including younger age, low refractoriness, and presence of cognitive-affective symptoms (Cohen et al., 2010; Rostami et al., 2017). In contrast, there are several candidates of predictors of antidepressant response to rTMS in unipolar depression, including genetic, molecular and neuroimaging markers (for a review, see (Silverstein et al., 2015)). This reinforces the need of further research in this topic for BD.

Table 4
Mixed model results for the main and interaction effects of the factors time, group, time x group and depression.

	Time		Group		Time *x* Group		Depression	
	Chi-squared	p	Chi-squared	p	Chi-squared	p	Coef	p
Attention and processing speed	17.1	**<0.001**	0.32	0.57	1.9	0.38	−0.009	0.07
Inhibitory control	16.9	**<0.001**	3.8	0.051	2.7	0.25	0.001	0.86
Working memory and Executive Function	12.4	**0.002**	0.08	0.78	1.78	0.41	−0.005	0.91
Language	9.9	**0.007**	0.02	0.89	6.2	**0.045**	−0.001	0.81
Immediate memory	65.7	**<0.001**	0.83	0.36	4.11	0.13	−0.002	0.66
Long-term memory	63.3	**<0.001**	0.21	0.64	5.1	0.08	0.003	0.56

Significant results ($p \leq 0.05$) are highlighted in bold. Models were adjusted by age, gender, depression scores, and years of schooling.

4.1. Methodological considerations

Our study presents some limitations. First, we did not include a healthy control group, which would have been useful to evaluate to which extent our patients were impaired at baseline, and whether they "normalized" after treatment. Second, the neuropsychological battery might have not been sensible enough to detect specific cognitive improvements. For instance, studies using noninvasive brain stimulation that showed superiority of active vs. sham stimulation generally used computerized tests such as the *n*-back task and others (Oliveira et al., 2013; Tortella et al., 2015). Other cognitive domains that have been successfully modulated by brain stimulation, such as social cognition (Donne et al., 2011), were not tested in the present study. Third, due to ethical reasons, participants were not unmedicated, although pharmacotherapy use was balanced between groups. Lastly, overall cognitive improvement over time can be attributable to practice effects. In fact, the tests used are vulnerable to practice effects as they are relatively simple and patients were tested 3 times in a short interval (Calamia et al., 2012).

The sham-controlled design is a study strength. It allowed us to verify that cognitive improvement occurred in both active and sham groups, indicating that the effects were not caused by the intervention. In fact, most studies suggesting pro-cognitive effects of brain stimulation are limited by their open-label design (Tortella et al., 2014). In addition, we used a comprehensive neuropsychological battery, authorizing us to conclude that H1-coil rTMS presents cognitive safety for the domains evaluated.

4.2. Clinical and research implications

Our study shows that H1-coil TMS is a safe intervention for BD from a cognitive perspective. This is clinically important since cognitive dysfunction is common and debilitating in such patients, persisting even after adequate treatment (Yatham et al., 2013). In fact, certain drug classes such as antipsychotic medications can increase cognitive dysfunction due to their direct effects on psychomotor speed and sedation (Yatham et al., 2013). Pharmacotherapy can also indirectly contribute to cognitive dysfunction via weight gain and cardiovascular comorbidities, which are related to cognitive dysfunction (Yatham et al., 2013). Therefore, the safety and efficacy of H1-coil TMS (Tavares et al., 2017) suggest that this intervention is an interesting option for BD treatment.

From a research perspective, our findings foment further studies exploring rTMS interventions for cognitive improvement in BD. A critical issue is defining the optimal brain area to be stimulated to promote cognitive enhancement. Although most studies focused on the DLPFC, other regions might also play a critical role in cognition and mood enhancement. One of them is the dorsomedial prefrontal cortex (DMPFC), which is a node where cortical networks for cognitive control and affect regulation converge (Phillips and Swartz, 2014). In fact, an open-label study revealed promising findings on mood and cognition improvement of rTMS over the DMPFC in depressed subjects (Schulze et al., 2016). Moreover, future studies could investigate whether H1-rTMS can promote cognitive enhancement in healthy subjects, a topic that has not been systematically addressed.

Studies should also be properly designed to assess cognitive enhancement. Possible approaches could be: (1) using more sensitive and specific instruments to detect cognitive changes—for instance, the n-back task; (2) selecting specific populations with cognitive impairment as to avoid ceiling effects on cognition; (3) combining rTMS with other non-pharmacological approaches—for instance, cognitive remediation—to enhance the effects of both interventions (Tortella et al., 2014).

Finally, further research should examine whether the rTMS effects in unipolar and bipolar depression are different. Although pro-cognitive enhancement effects of rTMS for unipolar depression are modest, such patients are less cognitively impaired than those with BD. Thus, it is possible that the latter group benefits more from rTMS (Redlich et al., 2014).

5. Conclusion

In this randomized controlled trial, deep (H1-coil) rTMS did not lead to cognitive side effects in patients with bipolar depression. This suggests that deep rTMS is a safe antidepressant intervention in bipolar patients, who usually present marked cognitive impairment. Nonetheless, further research on the topic is needed, as for some domains the practice effects seemed to operate more evidently in the sham compared to the active group.

Conflict of interest

The authors have no conflict of interest to disclose.

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Author's contribution

M.L.M., A.R.B. designed the work.

M.L.M., A.F. collected study data.

M.L.M., M.M., L.V., ARB performed the statistical analyses and interpreted the data.

All authors revised the work and provided important intellectual content.

All authors approved the final version of the manuscript.

Supplementary materials

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