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Research paper

Motor cortex repetitive transcranial magnetic stimulation in major depressive disorder - A preliminary randomized controlled clinical trial

Yu-Ting Hu [a,b,1], Xi-Wen Hu [a,1], Jin-Fang Han [a], Jian-Feng Zhang [c], Ying-Ying Wang [d], Annemarie Wolff [b], Sara Tremblay [b], Dusan Hirjak [e], Zhong-Lin Tan [a,*], Georg Northoff [a,b,**]

[a] Affiliated Mental Health Center and Hangzhou Seventh People's Hospital, Zhejiang University School of Medicine, Hangzhou, China
[b] Institute of Mental Health Research, University of Ottawa, Ottawa, Canada
[c] Center for Brain Disorders and Cognitive Sciences, Shenzhen University, Shenzhen, China
[d] Institute of Psychological Sciences, College of Education, Hangzhou Normal University, Hangzhou, China
[e] Department of Psychiatry and Psychotherapy, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany

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ABSTRACT

Background: Repetitive transcranial magnetic stimulation (rTMS) at left dorsolateral prefrontal cortex (lDLPFC) is commonly used in major depressive disorder (MDD), even though its therapeutic efficacy is limited. Given that many MDD patients show psychomotor retardation, we aim to examine whether the left motor cortex (lMC) as a novel rTMS target would provide effective and well-tolerated treatment as being comparable to lDLPFC-rTMS.
Methods: In this prospective double-blind randomized single-center study, 131 MDD patients were randomly assigned to the lDLPFC or lMC group and were treated with 10 Hz rTMS (90 % motor threshold) applied twice daily for 4000 pulses continuously over five days. The primary endpoint was the Hamilton Depression Scale (HAMD) total score change after treatment.
Results: After the five-day rTMS treatment, there was no significant difference in both HAMD reduction rate (lDLPFC 59.3 % ± 20.4 %, lMC 51.3 % ± 26.3 %, $P = 0.10$) and adverse effects ($P = 0.79$) between 48 (73.8 %) lMC subjects and 51 (77.3 %) lDLPFC subjects. Furthermore, the lMC study group showed stable HAMD scores at follow-up compared to their endpoint scores ($P = 0.08$).
Limitations: Sham-control group was not included and the sample size was small. Therefore, our results should be seen as exploratory and preliminary.
Conclusions: The preliminary good therapeutic response, comparability, and tolerability of lMC-rTMS suggest lMC a potential and more easily accessible rTMS target. Together, our findings raise the possibility of symptom-specific rTMS in motor cortex (psychomotor retardation) or lDLPFC (cognitive deficits). This warrants larger clinical trials of rTMS in MDD with symptom-specific stimulation targets.

1. Introduction

Major depressive disorder (MDD) is one of the leading causes of disability worldwide (Disease et al., 2018), with one in six adults experiencing it in their lifetime (Otte et al., 2016). Conventional pharmacological interventions for MDD, for example, using venlafaxine and duloxetine, show large individual differences along with sometimes varying degrees of unfavorable adverse effects including digestive disorders, weight gain, sexual dysfunction, etc. (Davidson, 2010). As an alternative option, non-invasive transcranial magnetic stimulation (TMS), a neuroelectrophysiological technique that emerged in recent decades, has attracted clinical attention (Barker et al., 1985). By using repetitive stimulation with different frequencies, namely repetitive TMS (rTMS), the purpose of exciting or inhibiting the local cerebral cortex can be achieved. rTMS was quickly applied in MDD therapy commonly at high frequency, e.g., 10 Hz or theta burst, to the left dorsolateral prefrontal cortex (lDLPFC) (George et al., 2010; O'Reardon et al., 2007). However, not all patients respond to this FDA-approved lDLPFC-rTMS

* Correspondence to: Z.-L. Tan, Affiliated Mental Health Center and Hangzhou Seventh People's Hospital, Zhejiang University School of Medicine, Hangzhou 310013, China.
** Correspondence to: G. Northoff, Institute of Mental Health Research, University of Ottawa, Ottawa, ON K1Z 7K4, Canada.
E-mail addresses: zhonglt@mail.ustc.edu.cn (Z.-L. Tan), georg.northoff@theroyal.ca (G. Northoff).
[1] The authors contributed equally.

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treatment, in which the response rate was recently reported as 47 % by Blumberger et al. (Blumberger et al., 2018). Recent studies have mainly focused on alternative regions within the prefrontal cortex like dorsomedial or orbital areas as they are related to the affective and cognitive symptoms of MDD (Dunlop et al., 2020; Fettes et al., 2017). Therapeutic results of these alternative treatment targets are not satisfactory (Dunlop et al., 2020; Fettes et al., 2017), though, as they range below those in lDLPFC-rTMS. Hence, other regions beyond lDLPFC and prefrontal cortex may be probed for rTMS treatment in MDD. This is the goal of our study.

In addition to affective and cognitive symptoms, MDD also features psychomotor retardation (Sobin and Sackeim, 1997) - one of the nine core symptoms for MDD diagnosis (DSM 5th ed., 2013; Loo et al., 2008). Research demonstrated decreased cerebral blood flow (Yin et al., 2018) and altered global activity (Lu et al., 2022) in the primary motor cortex in those MDD patients suffering from psychomotor retardation. Further, abnormal neurophysiological inhibition including abnormal excitation-inhibition balance has been reported in motor cortex of acute MDD (Levinson et al., 2010; Radhu et al., 2013). Most interestingly, antidepressant response of lDLPFC-rTMS treatment in MDD has been shown to go along with corresponding increase of excitability in motor cortex (Oliveira-Maia et al., 2017). Finally, one recent study demonstrated that rTMS in premotor cortex of MDD (and schizophrenia) patients with psychomotor slowing shows high therapeutic effects (Walther et al., 2020). Together, these findings render the motor cortex a promising candidate target region for effective, easily applicable, and well tolerated rTMS treatment in MDD.

The primary aim of our study was to assess the therapeutic potential of the motor cortex as a novel target region for rTMS treatment in MDD patients when compared to the standard target, lDLPFC. Therefore, we conducted a double-blind randomized single-center trial to compare the effects of rTMS applied to the left motor cortex (lMC) with those in lDLPFC-rTMS. In order to preliminarily investigate a rapid clinical effectiveness, we performed a short-term twice daily 10 Hz rTMS for five consecutive days based on previous successful protocols (well-organized in a review by Lefaucheur et al. (2014)) and our recent study (Zhang et al., 2021). The primary endpoint was the change of the 17-item Hamilton Depression Scale (HAMD) total score after five days of rTMS.

We first hypothesized that lMC-rTMS induces a significant reduction in depressive symptom severity. Secondly, we hypothesized that lMC-rTMS effects are comparable to lDLPFC-rTMS outcomes. Thirdly, targeting specifically the motor cortex, we hypothesized that lMC-rTMS improves psychomotor retardation just as good if not better than lDLPFC-rTMS. Finally, based on the application of TMS to motor cortex in various physiological studies (Hill et al., 2016; Spampinato and Celnik, 2021), we hypothesized that lMS-rTMS is well tolerated, as measured by self-recorded adverse effects.

2. Material and methods

2.1. Participants

The present trial was registered with the Chinese Clinical Trial Register (http://www.chictr.org.cn/), for which the registration number is ChiCTR2000040616. Participants were recruited from in- and outpatients of the Affiliated Mental Health Center, Zhejiang University School of Medicine, China. All the participants provided written informed consent, which was in accordance with the 1964 Declaration of Helsinki, for this rTMS trial and for the use of their clinical information for research purposes. All procedures of the ethical standards of the Affiliated Mental Health Center, Zhejiang University School of Medicine, were complied with.

Inclusion criteria were 1) right-handed adults; 2) who had a Mini-International Neuropsychiatric Interview confirmed diagnosis of MDD; 3) whose current episode of MDD showed a HAMD score of at least 18. None of the study patients did receive psychotherapy during the entire study. All patients were on stable medication at least one-week preceding study inclusion and the medication remained unchanged during rTMS treatment. Exclusion criteria included 1) pregnancy; 2) bipolar affective disorder; 3) schizophrenia spectrum disorders or any other psychiatric comorbidities; 4) previous systematic rTMS treatment or modified electroconvulsive therapy (MECT); 5) severe somatic diseases including neurological or immunological illness, acute myocardial ischemia etc.; 6) the presence of a cardiac pacemaker, intracranial implant, or metal in the body. Participants were numbered according to the order of entry, and were randomly assigned to groups receiving rTMS treatment at either the lDLPFC or the lMC using simple randomization based on Excel-generated random numbers.

2.2. rTMS procedures

TMS was delivered with a Rapid2 stimulator equipped with a figure-of-eight D70 Air Film Coil (Magstim, UK). The resting motor threshold (RMT) was determined for each participant prior to the initial TMS session. In brief: participants were seated in a comfortable chair with armrests and maintained relaxation. The coil was positioned tangentially to the head and approximately 45° to the midline. Surface electromyography was used to record the motor evoked potential (MEP) from the abductor pollicis brevis (APB) muscle in the right index finger. RMT was defined as the intensity of a single TMS pulse that was able to elicit at least five MEPs, with an amplitude of at least 50 μV, in ten consecutive trials (Kujirai et al., 1993; Rossini et al., 1994). The lMC region was defined as the position to elicit maximal MEPs in the right APB muscle; the position over lDLPFC was determined in the standard way as 5 cm anterior from the lMC region (Herwig et al., 2001). Based on the evidence-based guidelines on the therapeutic use of rTMS by Lefaucheur et al. (2014), our rTMS parameters were set as follows: 10 Hz, 90 % RMT, 5s on and 20s off, 2000 pulses per session, two sessions per day with an interval between three to 6 h for five consecutive days (from Day 1 to Day 5). The well-trained rTMS physician was blind to the clinical assessments.

It should be noted that the participants were informed that they would be assigned to one of two rTMS treatments for different brain areas, but not instructed where the exact locations were. Therefore, the allocation was considered to be blind to the participants due to their lack of previous rTMS treatment experience. Moreover, by using subthreshold stimulation (90 % RMT), the thumb movement that might attract the attention of participants in the lMC group was rarely observed by the rTMS physician. These can be supported by sham-controlled rTMS studies in chronic neuropathic pain (Lefaucheur et al., 2004a) and Parkinson's disease (Lefaucheur et al., 2004b), where the motor cortex was the common target.

2.3. Clinical assessments

The HAMD (Hamilton, 1960), 21-item Beck Depression Inventory-2nd edition (BDI-II) (Beck et al., 1996), 14-item Hamilton Anxiety Scale (HAMA) (Hamilton, 1959), and 20-item Beck Hopelessness Scale (BHS) (Beck and Steer, 1993) were obtained each day from baseline (Day 0) to the endpoint (Day 5). The primary outcome was the reduction rate of HAMD scores after five-day rTMS treatment from the baseline, i.e., % (Day 0–Day 5). Besides, BDI, HAMA, and BHS were regarded as the secondary outcome measures for further assessing the presence and severity of depressive symptoms in the present study. HAMD score reduction $\geq$50 % was defined as a response; HAMD score $<$8 was defined as remission (Blumberger et al., 2018). HAMD and HAMA scales were administered by a board-certified psychiatrist who was blind to the treatment allocation; BDI and BHS were self-reported questionnaires. Adverse effects were assessed after each day's rTMS treatment by asking the participants the items of the Treatment Emergent Symptom Scale (NIMH, 1985). We mainly focused on the most TMS-related adverse effects, such as seizures, dizziness, and headache; any other self-reported

discomforts were also recorded.

2.4. Statistical analysis

A minimum sample size of 64 in each group was required to achieve 80 % power at two-tailed 5 % significance level (α = 0.05) with a

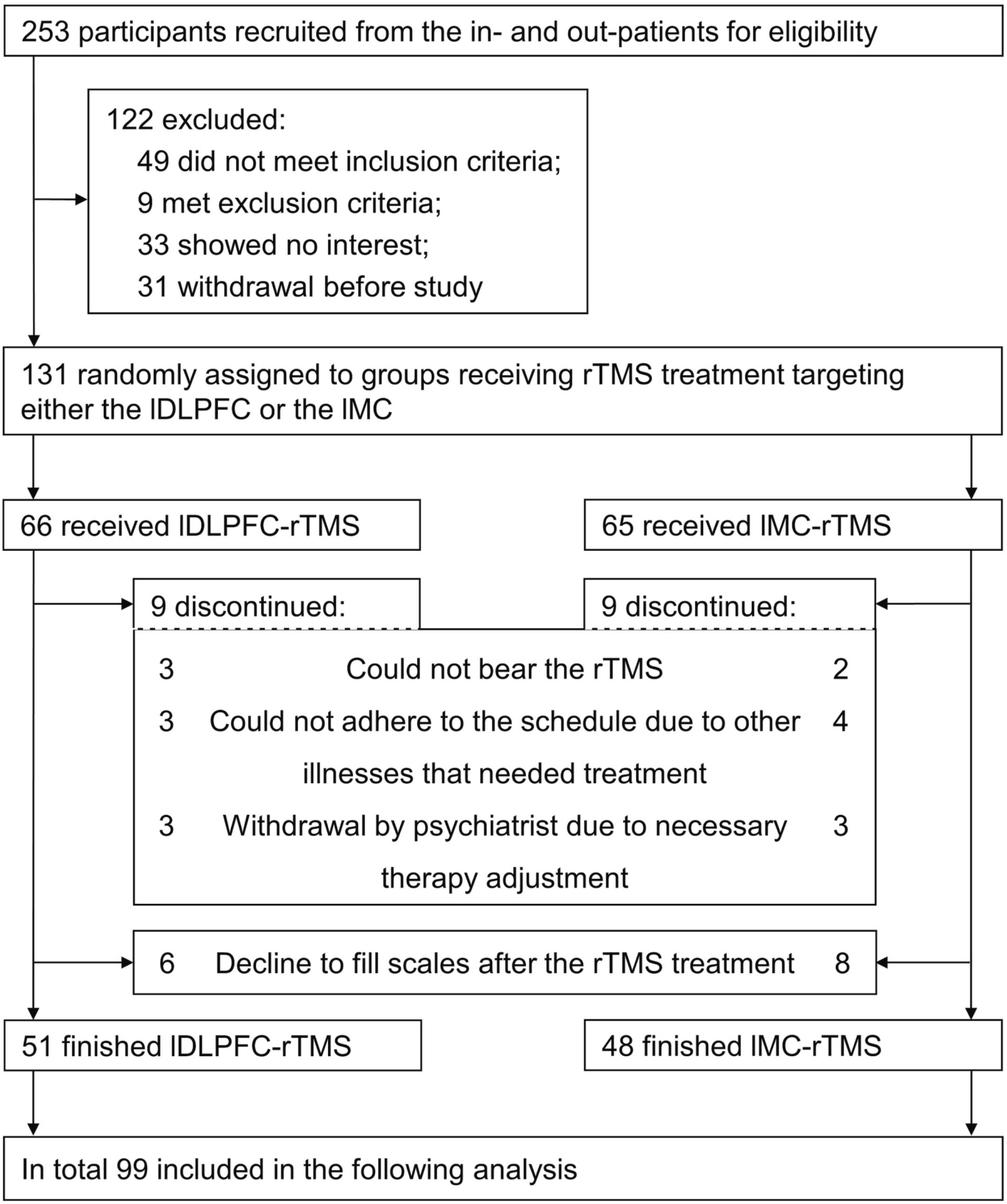

Fig. 1. Study profile.

medium effect size of 0.5, based on the standard Student's *t*-test, which was used to compare the reduction rates of all four depressive severity scales at the endpoint in the lDLPFC and lMC groups. For further confirmation, the baseline-adjusted differences of scales between the two groups were estimated by ANCOVA, with the Day 5 scores as the dependent variable and Day 0 scores as the covariate. In order to observe the dynamic changes in the severity of depression between the two groups over the five-day treatment period, two-way repeated measures ANOVA was conducted. In addition, Pearson Chi-Square test was used to compare the sex proportions, and Fisher's Exact test was used to compare the medication differences, proportion of dropouts and adverse effects between the two groups. The paired *t*-test was performed for analyzing the follow-up scores. Statistical analyses were conducted with GraphPad Prism 8.2.1 and SPSS 20.0. $P < 0.05$ was considered to be significant.

3. Results

3.1. Inclusion and dropout rates

253 MDD patients were enrolled, of whom 122 were ineligible according to our criteria or declined to participate. The remaining 131 patients (aged 18–65 years) were randomly assigned to receive the treatment. Nine (13.6 %) of 66 in the lDLPFC group and nine (13.8 %) of 65 in the lMC group discontinued the treatment during the five days. Five (three and two in each group) could not tolerate bear the rTMS due to noise or mild headache; seven (three and four in each group) were interrupted due to other rTMS-unrelated medical ailments; the rest participants (three in each group) discontinued by their psychiatrists due to necessary antidepressant therapy adjustments. In addition, six patients from the lDLPFC group and eight from the lMC group declined to fill out the depressive severity scales after five days of rTMS treatment. No significant difference in the number of dropouts for different reasons was found between the two groups ($P = 0.96$). See Fig. 1 for the detailed trial profile. Finally, 51 (77.3 %) participants from the lDLPFC group and 48 (73.8 %) from the lMC group completed the five-day rTMS treatment and were included in the following analysis. Age, sex, education year, and medication use did not differ between lDLPFC and lMC groups, see detailed demographic and clinical characteristics of participants in Table 1.

3.2. lMC-rTMS shows similar efficacy to lDLPFC-rTMS on alleviating depressive symptoms in MDD

3.2.1. Primary outcome measure

After five days of rTMS treatment, 25 (52.1 %) participants from the lMC group showed response with 10 of them meeting the HAMD criteria for remission. As the primary outcome measure, the HAMD reduction rate was found to be similar between the lDLPFC (59.3 % ± 20.4 %) and lMC (51.3 % ± 26.3 %) groups ($P = 0.10$).

3.2.2. Secondary outcome measure

Consistent results were also observed in the reduction rate of BDI (55.4 % ± 32.9 % and 45.9 % ± 32.3 %, $P = 0.15$), as well as of HAMA (58.7 % ± 22.8 % and 57.2 % ± 20.7 %, $P = 0.74$), and BHS (35.0 % ± 38.9 % and 24.5 % ± 36.8 %, $P = 0.17$) between the lDLPFC and lMC groups (also see Table 1).

By performing ANCOVA, the HAMD scores at the end of rTMS treatment (Day 5) showed an estimated baseline-adjusted difference of 1.85 points between the two groups. This indicates a greater HAMD reduction in the lDLPFC group, but the difference was not significant compared with the lMC group ($P = 0.15$, Table 1). For the other three scales, the results were similar to that of the HAMD (see Table 1).

Furthermore, the mean value of retardation symptoms reflected in HAMD item 8 was alleviated by 53.0 % in the lMC group, and by 53.9 % in the lDLPFC group ($P = 0.72$).

Table 1
Demographic data and depression severity scores.

	lMC ($n = 48$)	lDLPFC ($n = 51$)	Comparison between groups
Women	38 (79.2 %)	37 (72.5 %)	$\chi2 = 0.51$, $P = 0.44$
Age (years)	25.48 (8.2)	28.29 (9.8)	$P = 0.13$
Education years	14.15 (2.3)	13.80 (2.7)	$P = 0.56$
Drugs for treatment	47 (97.9 %)	47 (92.2 %)	
Antidepressant	41 (85.4 %)	42 (82.4 %)	
Antianxiolytic	27 (56.3 %)	33 (64.7 %)	
Antipsychotic	30 (62.5 %)	33 (64.7 %)	$P = 0.78$
Mood stabilizer	6 (12.5 %)	5 (9.8 %)	
Hypnotics	1 (2.1 %)	4 (7.8 %)	
Baseline scores (day 0)			
HAMD	26.27 (4.2)	26.16 (4.9)	$P = 0.84$
BDI	30.35 (7.8)	29.43 (10.3)	$P = 0.54$
HAMA	20.00 (4.9)	19.94 (6.1)	$P = 0.76$
BHS	13.23 (4.7)	12.22 (3.8)	$P = 0.08$
Endpoint scores (day 5)			$^{\#}$baseline-adjusted differences
HAMD	12.67 (6.9)	10.76 (6.4)	$^{\#}P = 0.15$
BDI	16.75 (10.9)	13.14 (11.3)	$^{\#}P = 0.12$
HAMA	8.56 (4.8)	8.18 (5.8)	$^{\#}P = 0.71$
BHS	9.85 (5.5)	7.67 (5.1)	$^{\#}P = 0.10$
Reduction rates (% (day 0 - day 5))			
HAMD	51.3 % (26.3 %)	59.3 % (20.4 %)	$P = 0.10$
BDI	45.9 % (32.3 %)	55.4 % (32.9 %)	$P = 0.15$
HAMA	57.2 % (20.7 %)	58.7 % (22.8 %)	$P = 0.74$
BHS	24.5 % (36.8 %)	35.0 % (38.9 %)	$P = 0.17$
Follow-up scores			Comparison with day 5
HAMD	8.57 (8.0)	\	$P = 0.08$
BDI	15.00 (13.9)	\	$P = 0.63$
HAMA	5.14 (4.7)	\	$P = 0.008$
BHS	9.00 (5.2)	\	$P = 0.36$

Note: Data was presented as the number of patients in each group (%) or the mean value (standard deviation). $^{\#}$Comparsion was estimated after baseline adjustment by ANCOVA. $P < 0.05$ was considered to be significant.

3.2.3. Interaction between rTMS effectiveness and time

The two-way repeated measures ANOVA revealed that the interaction between the effects of target (lDLPFC or lMC) and time (five-day course) on scores was not significant in HAMD ($F(5,93) = 1.30$, $P = 0.27$), nor in BDI ($F(5,93) = 1.45$, $P = 0.22$), HAMA ($F(5,93) = 0.33$, $P = 0.90$), and BHS ($F(5,93) = 1.88$, $P = 0.11$). These findings demonstrate that the changes in the severity of depressive symptoms in the two groups during the five-day period were consistent (see Fig. 2). Importantly, the main effect of time was significant, as the HAMD scores were gradually significantly decreased in both groups ($F(5,93) = 90.65$, $P < 0.001$, Fig. 2A). Consistent results were also observed in the changes of BDI ($F(5,93) = 41.83$, $P < 0.001$, Fig. 2B), HAMA ($F(5,93) = 89.20$, $P < 0.001$, Fig. 2C) and BHS ($F(5,93) = 14.62$, $P < 0.001$, Fig. 2D). The main effect of the target was not significant in either of the scales ($P \geq 0.18$).

3.2.4. No effects of medication

It should be noted that none of the reduction rates of our depressive severity scales shows a significant correlation with medication use during the course of rTMS treatment in both lDLPFC and lMC groups (Spearman's test, $P \geq 0.20$); therefore, drug-related effects on symptom reduction, complementing those of rTMS, were not considered to be crucially effective in our cohort. This is supported by the recommendation from Lefaucheur et al. that there is possibly no differential antidepressant efficacy between rTMS therapy conducted alone versus combined with antidepressants (Berlim et al., 2014; Lefaucheur et al., 2020). We further checked the patients who were medication free (four in lDLPFC group, one in lMC group), none showed extra high or low reduction rates.

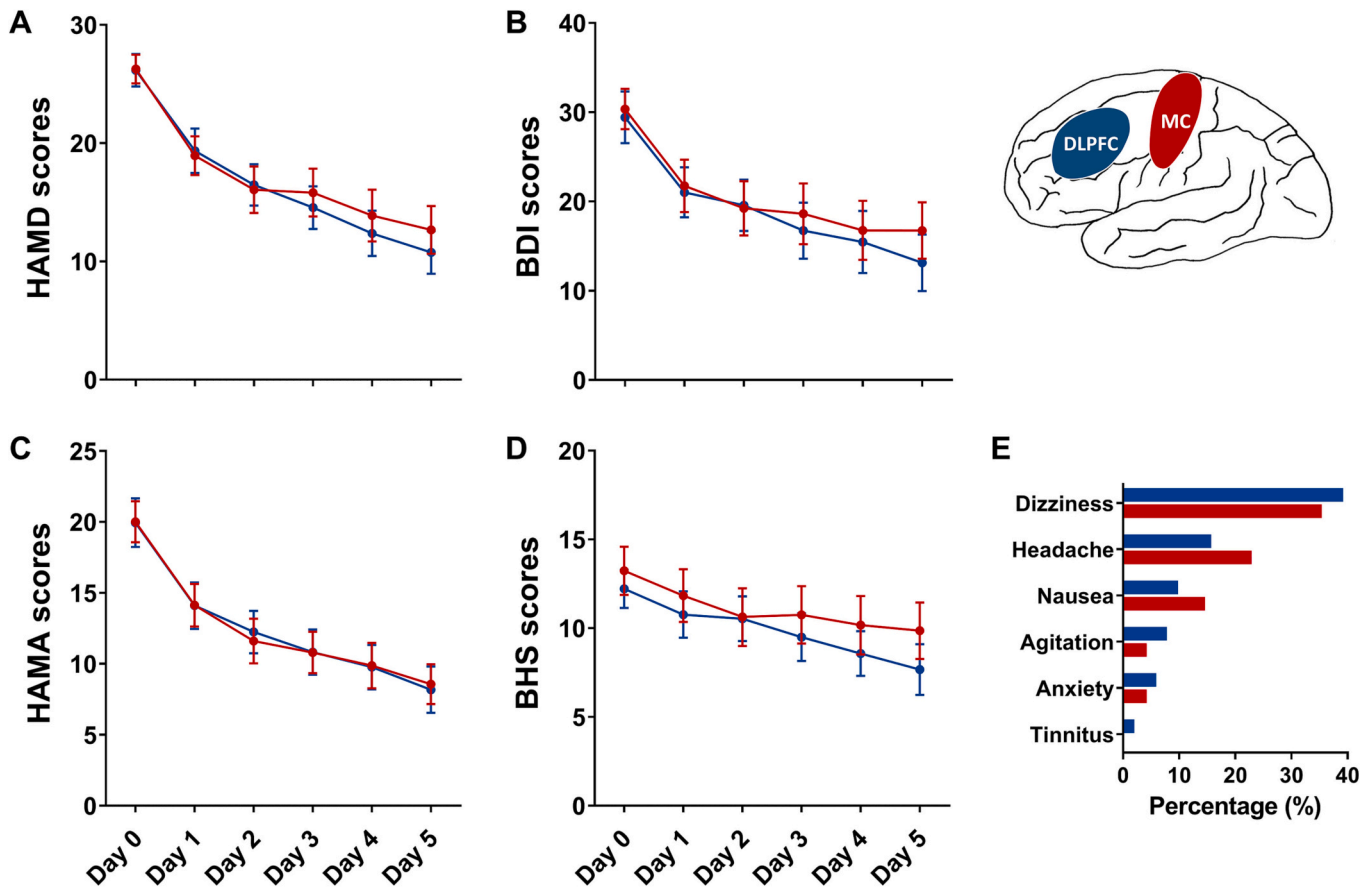

Fig. 2. Changes in the depression severity scores and adverse effects during the five-day rTMS treatment in the lDLPFC and lMC groups. **(A)** HAMD, **(B)** BDI, **(C)** HAMA, and **(D)** BHS scores gradually changed from baseline (Day 0) to the endpoint (Day 5) ($P < 0.001$); while the difference over time between the two groups were not significant ($P \geq 0.11$). **(E)** No significant difference in proportion of adverse effects was observed in the lMC group when compared with the lDLPFC group ($P = 0.79$). Data were mean scores with lower and upper 95 % confidence intervals.

3.3. lMC-rTMS shows similar frequency of adverse effects as lDLPFC-rTMS

The lMC-rTMS treatment was well-tolerated, there were no seizures, and no participants showed problems with memory or attention. All the self-reported adverse effects were very mild and transient, with dizziness the most common adverse effect, which was a complain for 17 (35.4 %) participants. In addition, 11 (22.9 %) participants felt a headache. The comparable numbers in the lDLPFC group were 20 (39.2 %) and 8 (15.7 %) respectively. The other adverse effects included nausea, agitation, and anxiety. There was no significant difference in the proportion of adverse effects when compared with the lDLPFC group ($P = 0.79$, Fig. 2E).

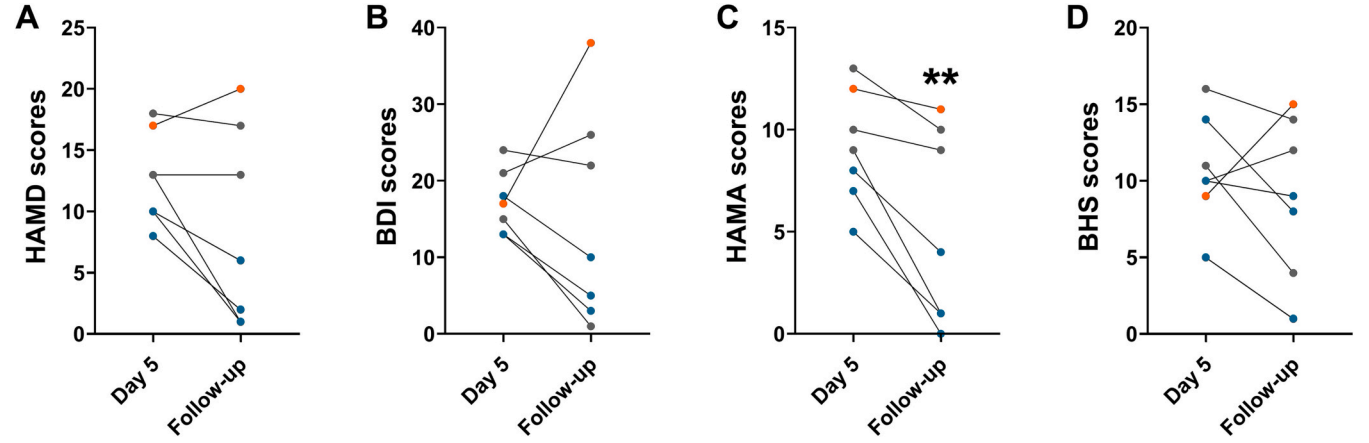

Fig. 3. Comparison of depressive severity scores of participants in the lMC group at follow-up and on Day 5. **(A)** HAMD, **(B)** BDI, and **(D)** BHS scores were unchanged ($P \geq 0.08$), while **(C)** HAMA scores were significantly decreased ($P = 0.008$). Three responders were indicated by blue dots and the relapser was presented in orange. $P < 0.05$ was considered to be significant, $^{**}P < 0.01$. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3.4. lMC-rTMS shows lasting antidepressant effect

The follow-up investigation was performed after three months of rTMS treatment. The effect of lMC-rTMS on alleviating depressive symptoms were maintained at follow-up, as the scores were unchanged in HAMD ($P = 0.08$), BDI ($P = 0.63$) and BHS ($P = 0.36$), and decreased in HAMA ($P = 0.008$) when compared with Day 5 (Table 1). Three of the seven subjects were responders who all showed decreased scores in the follow-up (indicated by blue dots, Fig. 3). Only one subject reached a score higher than 18 on the HAMD scale and was considered as relapsed (indicated by orange dots, Fig. 3).

4. Discussion

To our knowledge, this is the first randomized controlled clinical trial that applied rTMS to the motor cortex in MDD and compared it with the effects of lDLPFC-rTMS. Our findings confirm the hypotheses. First, we found lMC-rTMS to be highly therapeutically effective yielding high HAMD reduction, our primary endpoint. Secondly, therapeutic effects of lMC- and lDLPFC-rTMS were comparable showing the effectiveness of our novel rTMS treatment targets. Thirdly, we observed significant improvement in psychomotor retardation in lMC-rTMS of MDD. Finally, lMC-rTMS was well tolerated showing no major side effects in any of the patients. Therefore, our findings provide hint that the motor cortex might be a potential novel and easily accessible rTMS target.

Overall, the various lines of evidence of implicating the motor cortex in the pathophysiology of MDD including its severe psychomotor symptoms have led us to conduct a lMC-rTMS treatment on MDD. During the treatment, the HAMD scores significantly decreased while the proportion of participants showing a response was 52.1 %, with those 24.8 % met the criteria for a remission of MDD. These percentages were similar than those in previous studies using lDLPFC-rTMS (George et al., 2010; O'Reardon et al., 2007). Further, we observed similar reduction rates of the depressive severity scales in the lMC group when compared with the lDLPFC group ($P \geq 0.10$). Although participants from the lDLPFC group showed a nominal reduction in the depressive severities after baseline adjustment compared to those in the lMC group, the differences were not statistically significant ($P \geq 0.10$).

Our results further underline the key role of the motor cortex in pathophysiology and psychopathology of MDD. The functioning of the nervous system requires a dynamic balance of cortical excitation and inhibition, and studies have found hypoexcitability in the motor cortex in MDD patients as measured by TMS (Khedr et al., 2020; Levinson et al., 2010). That is also well in line with neuroimaging studies observing reduced metabolism (Yin et al., 2018) as well as decreased neural activity being directly related to psychomotor retardation (Lu et al., 2022). This is further supported by the observation of abnormal biochemical, e.g., dopaminergic and serotinergic modulation of the motor cortex resulting in psychomotor retardation in MDD and bioplar disorder (Conio et al., 2020; Magioncalda et al., 2020; Martino et al., 2020; Northoff et al., 2021). The present study extends these findings to the therapeutic realm showing the therapeutic efficacy of rTMS stimulation of the motor cortex in MDD. That is specified by our observation of the high degree of therapeutic reversal of psychomotor retardation in our lMC-rTMS study.

We further examined the subscales of our four clinical scales. The scores of one HAMD subscales indicating 'sleep disturbance' (items 4, 5, and 6) decreased more in the lMC group (2.40 ± 1.98) than in the lDLPFC group (1.60 ± 2.12) (Mann-Whitney, $P = 0.05$), which implies a better recovery of sleep-related symptoms in the lMC group. This may suggest a link between the motor cortex and sleep quality in MDD.

Several limitations of the present study need to be mentioned. We did not include a sham-control group for lMC-rTMS in our comparison of this novel treatment target with the standard lDLPFC-rTMS. Secondly, we did not assess psychomotor retardation in a more detailed way by for instance using the motor agitation and retardation scale (Sobin et al., 1998) or Salpetriere retardation rating scale (SRRS) (Widlöcher et al., 1989). Thirdly, the link of rTMS therapeutic efficacy to specific psychopathological symptoms like psychomotor retardation (motor cortex) or working memory deficits and/or goal-orientation (DLPFC) remains open. Fourthly, our sample size was rather small. Therefore, our results should be considered as exploratory and preliminary rather than providing definite findings that can be translated into clinical application. Fifthly, no neuronal or neurophysiological measures of for instance neural (fMRI or EEG) or biochemical (MRS) activity of the motor cortex (and lDLPFC) were obtained in the present study. Therefore, we strongly acknowledge future rTMS studies using neuroimaging in order to compare structural and functional changes within different brain regions after rTMS treatment. For instance, one may want to compare the rTMS effects of the motor cortex with those of the recently introduced occipital cortex rTMS (Zhang et al., 2021).

In conclusion, we demonstrate good therapeutic response of lMC-rTMS associated with only mild adverse effects. Given that lMC-rTMS shows comparable therapeutic effects as the lDLPFC-rTMS in our study, the motor cortex renders its potential as a rTMS target in MDD. This may especially be relevant in those MDD patients with strong psychomotor retardation as that is related to the motor cortex. Hence, albeit tentatively, this opens the specter of a symptom-based selection of rTMS therapeutic targets. MDD patients with strong psychomotor retardation may benefit more from rTMS in motor cortex while those exhibiting cognitive deficits (like in working memory and/or executive function) may better be stimulated with rTMS in lDLPFC. We therefore conclude that further efforts need to be made through larger clinical trials of lMC-rTMS in MDD accompanied by multimodal neuroimaging to achieve a more comprehensive and clinically applicable outcome.

CRediT authorship contribution statement

Y.H., J.Z., A.W., S.T., D.H., and G.N. wrote the manuscript. Z.T., and G.N. designed the research. X.H., J.H., Y.W., and Z.T. performed the research. Y.H., and G.N. analyzed the data.

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Declaration of competing interest

All authors declared no competing interests for this study. There are no other disclosures.

Acknowledgments

None.

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