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Task-related functional magnetic resonance imaging-based neuronavigation for the treatment of depression by individualized repetitive transcranial magnetic stimulation of the visual cortex

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To determine whether repetitive transcranial magnetic stimulation (rTMS) of the visual cortex (VC) provides effective and well-tolerated treatment and whether magnetic resonance imaging (MRI) measures functional change of the VC as a biomarker of therapeutic effect in major depressive disorder (MDD), we performed a sham-controlled, double-blind, randomized, three-arm VC rTMS treatment study in 74 MDD patients. Neuronavigated rTMS (10 Hz, 90% of resting motor threshold, 1,600 pulses over 20 min twice per day) was performed over the VC for five days. Clinical outcome was measured by Hamilton Depression Rating Scale (HAMD-24) at days 0, 1, 3, 5 and after terminating rTMS, with follow-up at four weeks. MRI was measured at days 0 and 5. The individualized group exhibited the greatest change in HAMD-24 scores after VC rTMS for 5 days (F=5.53, P=0.005), which were maintained during follow-up period (F=4.22, P=0.016). All patients reported good tolerance. Changes in VC task-related functional MRI correlated with symptomatic reduction in the individualized group. Treatment reduced the initially abnormal increase in resting state functional connectivity from the VC to the pre/subgenual anterior cingulate cortex at day 5, especially in the individualized group. We demonstrated therapeutic potential and good tolerance of VC rTMS in MDD patients, indicated by biomarkers of fMRI measurement.

major depressive disorder, visual cortex, functional magnetic resonance imaging, repetitive transcranial magnetic stimulation, neuronavigated, individualized treatment

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INTRODUCTION

Major depressive disorder (MDD) is among the most common and severe mental disorders, having a lifetime prevalence of 11.1% (Bromet et al., 2011). Nearly one third of the world's MDD population is accounted for in China (Baxter et al., 2016). Repetitive transcranial magnetic stimulation (rTMS) over the left dorsolateral prefrontal cortex (lDLPFC) (Otte et al., 2016; Ridding and Rothwell, 2007) has been approved by the Food and Drug Administration (FDA) for the clinical treatment of MDD, yet such a treatment has been shown to be limited, with only a 29.3% response rate in MDD patients (Berlim et al., 2014) combined with adverse effects (e.g., feelings of pain and headache) (Janicak et al., 2008; O'Reardon et al., 2007). This experience argues for other potential rTMS treatment targets beyond the lDLPFC (Downar and Daskalakis, 2013; Dunlop et al., 2015), navigated and individualized rTMS coil positioning (Schönfeldt-Lecuona et al., 2010), or novel rTMS treatment protocols (e.g., accelerated rTMS or theta burst stimulation protocols) (Blumberger et al., 2018; Stubbeman et al., 2018).

As a region beyond the prefrontal cortex and its different subregions (Bakker et al., 2015; Downar and Daskalakis, 2013; Downar et al., 2014; Fettes et al., 2018; Niu et al., 2020; Schulze et al., 2018), the visual cortex (VC) may be a potential candidate target for the rTMS treatment of MDD. The primary VC (V1) projects to the pulvinar and superior colliculus (Zhao et al., 2014; Zhou et al., 2016) which regulate emotional behavior via the amygdala and striatum (Yu et al., 2016). Importantly, these regions have all been implicated in MDD (Alcaro et al., 2010; Kaiser et al., 2015; Northoff et al., 2011). Notably, the VC exhibits abnormalities in MDD with increased resting state/task-related activities (Le et al., 2017; Northoff et al., 2018), together with reduced inhibitory gamma-aminobutyric acid (GABA) concentrations (Sanacora et al., 2004; Sanacora et al., 1999). These changes in the VC could also predict response to therapeutic interventions, including antidepressant drugs (Furey et al., 2013; Keedwell et al., 2009), electroconvulsive therapy (ECT) (Sanacora et al., 2003), and cognitive behavioral therapy (Abdallah et al., 2014). More recently, light therapy (Lam et al., 2016; Sit et al., 2018) has been hypothesized to recruit the VC in addition to various up-stream regions, including the habenula, thalamus, pulvinar, amygdala and others, all of which are implicated in both emotion (Huang et al., 2019) and MDD (Alcaro et al., 2010; Kaiser et al., 2015; Northoff et al., 2011). Together, these results suggest that the VC may represent a highly promising target region for effective rTMS treatment in MDD.

Of note is recent empirical evidence demonstrating abnormal perception of time in depressed subjects (Stanghellini et al., 2017). Furthermore, yet another study indicated that abnormal outer time perception in depression is related to abnormal neuronal capability specifically in the occipital cortex (Northoff et al., 2018). Together, these studies suggest that, in addition to its role in the processing of emotion (as described above), abnormal neural activity in the visual cortex is related to the processing of the passage of time. For that reason, within the paradigm of functional magnetic resonance imaging (fMRI), we have tested for neural differences in slow and fast applications of both emotional and neutral stimuli, especially for neutral stimuli presented by "slow" and "rapid" images, which eliminates any interference of "emotion" in the present study.

Therefore, in the present study, neuronavigated rTMS was firstly utilized to target individual VC regions identified through task-guidance (as measured by fMRI) as a treatment in MDD patients (individualized group). To determine whether the VC represents a novel therapeutic target region for rTMS treatment in MDD, we conducted a sham-controlled randomized double-blind three-arm therapy study, in which the groups that were compared included real or sham rTMS targeting of structural MRI-based V1 (standard or sham groups). Moreover, to monitor and track the treatment effects of VC rTMS and understand the underlying network mechanisms, resting state and task-related fMRI were obtained both prior to (day 0) and after (day 5) treatment (Supplementary Method 1 in Supporting Information).

RESULTS

Baseline characterization

At the baseline (day 0), there were no significant differences in age, gender or years of education between the MDD patients and healthy control (HC) subjects (all $P>0.05$), or clinical features between the three treated groups (Table 1; Table S1 in Supporting Information).

Clinical outcome measures

After acute treatment with rTMS (day 5), a significant difference (compared with day 0) was observed in the HAMD-24 score of each treated MDD group (all $P<0.001$, individualized group: $t=14.498$; standard group: $t=14.408$; sham group: $t=6.865$). The individualized group had a higher number of responders (16/24; 66.67%) than in either the standard (10/27; 37.04%) or sham (9/23; 39.13%) groups (Figure 1A), but there was no significant difference ($\chi^2=5.368$ $P=0.068$). Over the treatment period, a significant interaction between the treatment and time point ($F=5.53$, $P=0.005$) was observed using the linear mixed model, indicating that trends in improvement in HAMD-24 scores were different among the three groups. A significant interaction between treatment and time point was also observed

Table 1 Baseline clinical characteristics and assessment of subjects that completed the whole research study[a)]

	MDD patients				Healthy controls (n=30)
	Individualized group (n=24)	Standard group (n=27)	Sham group (n=23)	Total (n=74)	
Age, years (SD)	31.71 (12.92)	31.33 (12.77)	31.61 (10.45)	31.54 (11.99)	33.67 (12.77)
Female (%)	13 (54.1)	17 (62.9)	13 (56.52)	43 (58.11)	18 (60.00)
Education, years (SD)	12.92 (2.77)	11.67 (3.88)	12.43 (3.80)	12.31 (3.52)	12.80 (3.70)
Age of onset, years (SD)	29.50 (13.31)	27.74 (12.13)	25.13 (7.55)	27.50 (11.33)	NA
First episode (%)	19 (79.17)	17 (62.96)	16 (69.57)	52 (70.27)	NA
Relapse (%)	5 (20.83)	10 (37.04)	7 (30.43)	22 (29.73)	NA
Drug-naïve (%)	14 (58.33)	13 (48.15)	16 (69.57)	43 (58.11)	NA
Drug-free (≥2 weeks) (%)	10 (41.67)	14 (51.85)	7 (30.43)	31 (41.89)	NA
Smoking (%)	7 (29.17)	4 (14.81)	2 (8.70)	13 (17.57)	5 (16.67)
Family history of mental disease (%)	5 (20.83)	12 (44.44)	9 (39.13)	26 (35.14)*	1 (3.33)
Baseline HAMD-24 scores (SD)	33.79 (6.31)	35.81 (7.90)	35.70 (9.28)	35.12 (7.85)*	2.20 (2.47)

a) Data represent means (standard deviation) or the number of participants in each group (% of total). *, $P \leq 0.001$ (total MDD patients vs. healthy controls). MDD: major depressive disorder; HAMD-24: 24-item Hamilton Depression Scale.

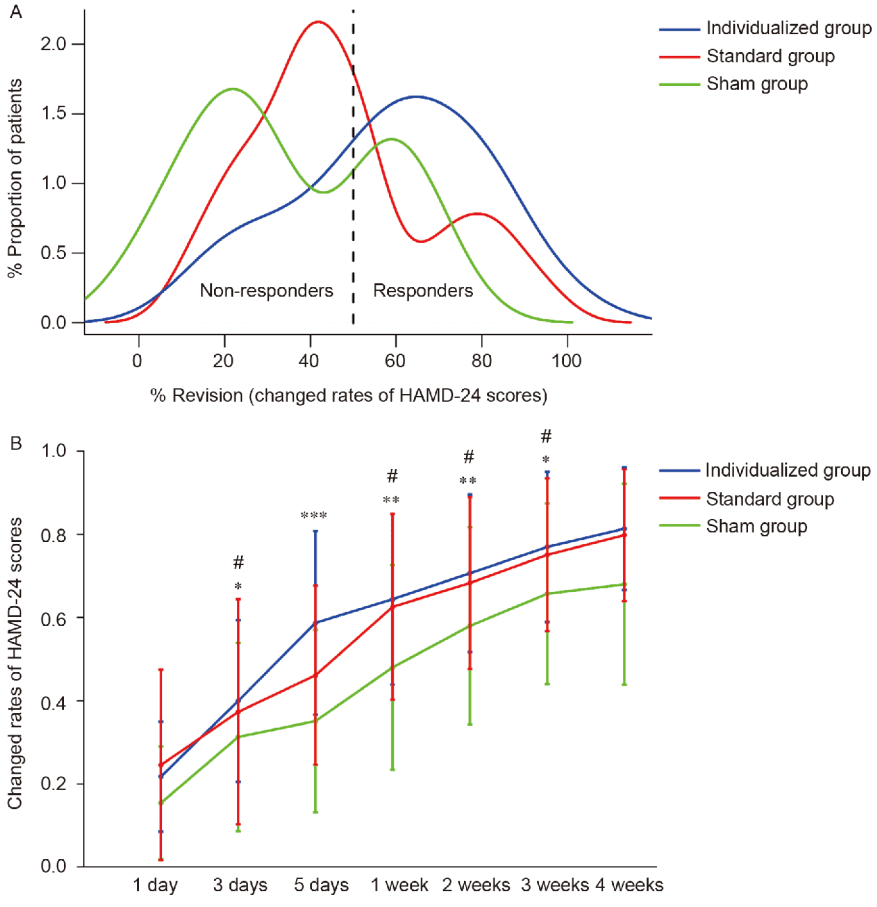

Figure 1 Therapeutic effect of rTMS among three treatment groups of MDD patients. A, The distribution of numbers of responders and non-responders after 5 days' rTMS treatment in three groups. B, Changed rates of HAMD-24 scores during the rTMS treatment and follow-up period. *, P<0.05; **, P<0.01; ***, P<0.001 (individualized group vs. sham group). #, P<0.05; ##, P<0.01 (standard group vs. sham group).

during the follow-up period (F=4.22, P=0.016). In addition, we further compared the changed rate in HAMD-24 score among the different groups at different time points. Compared with the sham group, the changed rate in HAMD-24 score was significantly improved at day 5 (P<0.001), week 1 (P=0.003) and week 2 (P=0.009) in the individualized group

(Figure 1B).

Tolerance, safety, and adverse effects of visual cortex rTMS

All subjects tolerated VC rTMS well, with no subjects prematurely terminating the rTMS study due to side effects (Table 2). The reported adverse effects included mild headache, slight dizziness, fatigue, somnolence, and abnormal facial sensations (Table 2). Notably, none of the MDD subjects undergoing VC rTMS reported feelings of pain or severe headache during treatment as described in DLPFC-based studies (Padberg and George, 2009). Nor did any subject report blurred vision, visual hallucinations, or photopsia, although these have previously been associated with VC TMS stimulation (Meyer et al., 1991; Salminen-Vaparanta et al., 2014; Samaha et al., 2017).

fMRI measures

Resting state fMRI

Both healthy and MDD subjects exhibited positive resting state functional connectivity (rsFC) of the VC with pre/subgenual anterior cingulate cortex. The MDD group (n=74) exhibited increased rsFC from the VC to anterior regions, especially the pre/subgenual anterior cingulate cortex at day 0 (Figure 2A(a, b, c); Figure S1A in Supporting Information). Conversely, rsFC from the VC to various posterior regions, including the right superior temporal gyrus (RSTG), right lingual gyrus (RLG) and cuneus (CUN) in MDD patients was less than that of healthy controls (Figure 2A(a, b, c); Figure S1A in Supporting Information). Following VC rTMS treatment, rsFC from the VC to those regions, including the pre/subgenual anterior cingulate, returned to a normal state, as in the healthy controls, i.e., increased or decreased, respectively, for the different connectivities at day 5, particularly in the individualized group (Figure 2A(d); Figures S1B and S2 in Supporting Information).

Task-related fMRI

At baseline, task-evoked activity in the VC was significantly higher in all MDD subjects (n=74) compared with the HC group (Figure 2B(a, b); Figure S3 in Supporting Information). After rTMS treatment for 5 days, the most significant reduction in VC task-evoked activity was observed at day 5 in the individualized group, a decrease which was also strongly correlated with HAMD-24 score reduction (days 0–5) (Figure 2C). Conversely, neither a reduction in VC task-evoked activity nor a correlation with reduction in depression score was observed in either the standard or sham groups (Figure S4 in Supporting Information).

DISCUSSION

The present study demonstrated that the individualized and standard groups exhibited a greater effect on the reduction of HAMD-24 score than the sham group both in the treatment period and follow-up period, suggesting that VC rTMS treatment efficiently reduced clinical symptoms in MDD patients. Regrettably, because the present study was designed for investigating a short-term, rapid (5 day) antidepressant effect for MDD, no significant difference in the efficacy of rTMS treatment was observed between the individualized group and the standard group during the treatment period, but a trend of better efficacy of treatment was detected in the individualized group at the conclusion of treatment. Therefore, a further study will be designed in which the length of treatment is extended to verify whether individualized treatment has significant efficacy compared with the standard left V1 treatment. In addition, targeted VC is well tolerated in all subjects with none reporting major adverse

Table 2 Adverse events treated by rTMS among subgroups of MDD patients[a)]

	Number of MDD patients reporting each adverse event, No. (%)*		
	Individualized group (n=24)	Standard group (n=27)	Sham group (n=23)
Headache/pain	3 (12.50)	2 (7.41)	3 (13.04)
Dizziness	2 (8.33)	4 (14.81)	2 (8.70)
Fatigue	0 (0)	1 (3.70)	0 (0)
Somnolence	2 (8.33)	3 (11.11)	2 (8.70)
Photopsia	0 (0)	0 (0)	0 (0)
Blurring of vision	0 (0)	0 (0)	0 (0)
Visual hallucination	0 (0)	0 (0)	0 (0)
Abnormal facial sensation	1 (4.17)	0 (0)	0 (0)
Abnormal sensation in eyes or nose	0 (0)	0 (0)	0 (0)
Abnormal sensation in tooth or jaw	0 (0)	0 (0)	0 (0)

a) Data represent numbers of participants in each group (% of total).*, P>0.05 for Fisher's exact test of each pair of comparisons. rTMS, repetitive transcranial magnetic stimulation; MDD, major depressive disorder.

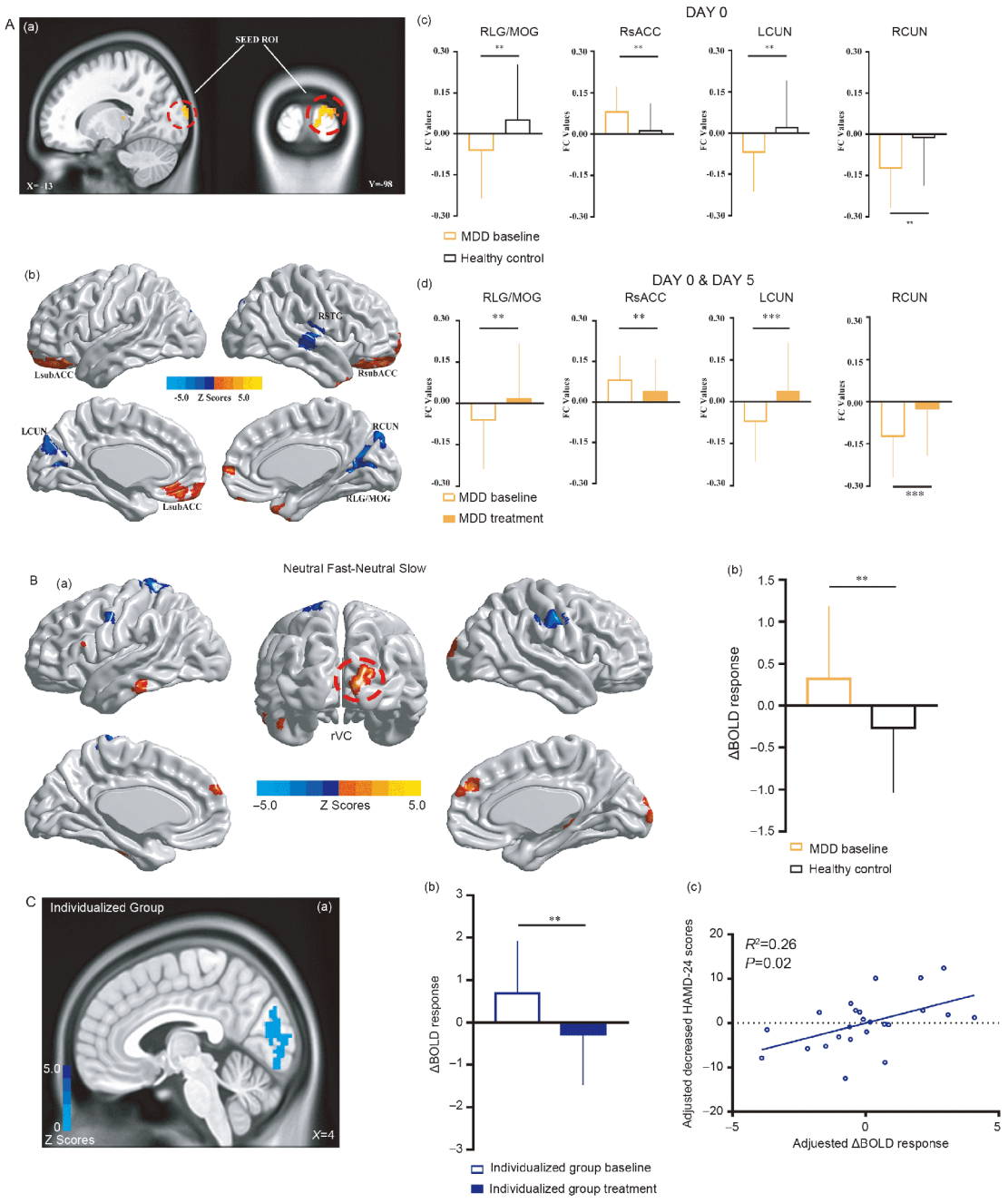

Figure 2 Results of resting state and task-related fMRI in MDD patients and healthy controls. A, Resting state functional connectivity (rsFC) from the visual cortex to the remaining brain regions. (a) As a region of interest (ROI), the visual cortex was extracted from the activated brain region of the visual cortex, demonstrating a significant increase in the BOLD response to the task (neutral fast minus neutral slow picture viewing) in 74 MDD subjects compared with 30 HCs at baseline; (b) Brain regions illustrated changes in the visual cortex FC (VCFC) at rest in all MDD patients (at baseline, i.e., day 0) compared with HCs (P<0.05, whole brain correction with AlphaSim, number of voxels: 169). Bright color indicates increased rsFC and blue color indicates decreased rsFC in MDD compared with HCs; (c) Numerical representation of the significant difference in VCFC between the two groups at day 0; (d) Numerical representation illustrating the significant change in VCFC on day 5 compared with day 0 in 74 MDD patients. B, BOLD response to the task between MDD patients and HCs at baseline (day 0), the task indicated by neutral fast minus neutral slow picture viewing. (a) Brain regions of the visual cortex demonstrated a significant difference in BOLD activity during the task at baseline (day 0) in MDD compared with HCs (P<0.05, small volume correction, number of voxels: 26). Color bar represents z scores; (b) Quantitative representation of differential BOLD task-related activity from group-level in the right visual cortex at baseline (day 0) in MDD patients compared with HCs. C, BOLD response to the task in MDD group with individualized rTMS treatment. (a) Brain regions in the visual cortex demonstrated that task-related BOLD activity decreased significantly at day 5 compared with day 0 in the MDD subgroup (P<0.05, whole brain correction with AlphaSim, number of voxels: 169); (b) Quantitative representation of change in BOLD activity (day 5–day 0) in MDD subjects with individualized rTMS treatment; (c) Change in BOLD signal (ΔBOLD=BOLD day 5–BOLD day 0) in the visual cortex were positively correlated with decrease in HAMD-24 total score in the MDD subgroup, the adjusted value was controlled for age, gender and years of education. sACC, subgenual anterior cingulate cortex; CUN, cuneus; STG, superior temporal gyrus; LG/MOG, lingual gyrus/middle occipital gyrus; HCs, healthy controls; MDD, major depressive disorder; L, left; R, right; BOLD, blood oxygen level dependent; VC, visual cortex.

effects such as severe pain, major headache, blurred vision, or visual hallucination. Resting state and task-related fMRI, serving as neuroimaging-related outcome measures, observably demonstrated abnormalities (day 0 compared with the HCs) and normalization (day 5) in both resting state visual–pre/subgenual cingulate functional connectivity and task-related VC activity, particularly in the individualized group, with reduction in VC activity correlated with symptomatic improvement. Together, this study suggests improved therapeutic efficacy of individualized VC rTMS for MDD patients. Furthermore, our data indicate involvement of the VC in the depressive neural circuitry which may thus be used as a biomarker of therapeutic effect.

The present study firstly established which VC region to target with rTMS in each individual through the use of blood oxygen level-dependent (BOLD) signals in task-related fMRI for the treatment of MDD patients, in which the visual-related task was designed based on our original hypothesis of dysfunction of objective time perception in MDD (Northoff et al., 2018). However, in only one previous study was individualized rTMS used to stimulate the hemi-DLPFC which had lower metabolic activity as determined by positron emission tomography (PET), which demonstrated no therapeutic benefit to MDD patients (Herwig et al., 2003). Furthermore, in order to solve the problem of precise positioning and further improve the treatment effect, neuronavigated rTMS was used in each MDD group, even if the efficacy of the technique remains uncertain, as indicated in six previously published papers on MDD studies (Dunlop et al., 2015; Fitzgerald et al., 2009; Hayasaka et al., 2017; Herwig et al., 2003; Paillère Martinot et al., 2010; Stubbeman et al., 2018). Importantly, to enhance the scientific basis and impartiality of assessment of the treatment effect, we conducted a sham-controlled randomized double-blind three-arm therapy study, in which the groups we compared included both real and sham structural MRI-based rTMS targeting of the left V1. For the first time, we directly targeted the region of the VC exhibiting the most increased BOLD activity and correlated this with depressive symptoms and treatment response. In summary, the strict design and technological innovations further supported the reliability of the results in the present study.

In addition to its therapeutic effect, VC rTMS was well tolerated with a low level of adverse effects (Table 2). Subjects reported no severe pain or major headache as reported previously with DLPFC rTMS treatment (Janicak et al., 2008; O'Reardon et al., 2007), nor any drowsiness or vomiting, typical side effects of pharmacological therapy (Carvalho et al., 2016). In addition, the study reported no blurred vision, flash illusions or phosphenes which have previously been observed during visual cortex TMS stimulation (Meyer et al., 1991; Salminen-Vaparanta et al., 2014; Samaha et al., 2017). It is possible that the 90% resting motor cortex threshold (RMT) 16,000 pulse protocol with 10 Hz rTMS treatment is insufficient to induce aberrant activity in the visual cortex, and therefore appears to be a clinically safe procedure.

The main finding from the study was that VC rTMS rapidly improved depressive symptoms with better efficacy in the individualized treatment, in which the therapeutic effect remained apparent for two weeks after the final rTMS treatment. Notably, at baseline, the BOLD activity of the targeted VC region was clearly higher in the MDD group than in HC, with the degree of increase closely correlating to the severity of depressive symptoms. Greater change in signal normalization was related to greater therapeutic effect, particularly in the individualized MDD group. These findings are direct evidence that supports the hypothesis that the VC is involved in the pathophysiology of MDD and that the change in BOLD activity may be a potential biomarker of neuroimaging for MDD and the effect of treatment.

The present resting state fMRI data in both healthy and MDD subjects demonstrate VC functional connectivity with, in particular, the pre- and subgenual anterior cingulate cortex, the latter region being implicated in mood, self-consciousness, and MDD (Bermpohl et al., 2006; Dunlop et al., 2015; Mayberg et al., 1999; Northoff, 2016; Northoff et al., 2011; Zhu and Hu, 2018). These regions were normalized following five days of rTMS treatment. Based on these findings, we hypothesize that VC rTMS exerts a network effect by "normalizing" the pre-/subgenual network rsFC with the VC through regions that have a potential mediating function, such as the thalamus/pulvinar, striatum, insula, and amygdala, all of which have been implicated in MDD (Alcaro et al., 2010; Avery et al., 2014; Dunlop et al., 2015; Kaiser et al., 2015; Northoff et al., 2011; Wiebking et al., 2011; Wiebking et al., 2015; Wiebking and Northoff, 2015; Wu et al., 2020; Young et al., 2018). Whether this is a direct effect of rTMS stimulation itself, directly related to symptom reduction, or an indirect secondary effect following the reported resting state network reorganization remains to be elucidated.

Despite the positive conclusions reached in the present study, there are nevertheless some limitations. Firstly, although a large sample of MDD subjects (n=74) was initially included, it was not possible to avoid having a relatively small number in each of the three treatment arms. Even though the individualized group clearly demonstrates the strongest treatment effect from rTMS, the results nonetheless suffer from analysis of a small number of subjects (n=24). Secondly, unlike the case of DLPFC rTMS, treatment-resistant MDD subjects were not included so that: (i) the effect of rTMS independent of ongoing antidepressant therapies was evaluated; (ii) the general feasibility of VC treatment for depressive symptoms was explored. However, a lack of concurrent antidepressant patient treatment limited the per-

iod of rTMS to only five days and on subjects suffered only mild-to-moderate depression. Future trials of rTMS VC stimulation with concurrent antidepressant drugs are required. Thirdly, large-scale clinical trials of VC rTMS in MDD including its comparison with DLPFC rTMS are required to further validate the clinical efficacy of the VC rTMS procedure. In addition, the peak coordinates in the individual group varied greatly across subjects, possibly limiting the generality of current findings. In the future, we should improve the design of visual-related task to eliminate any interference factor so that the individual activity measured by task-fMRI further focuses on the region of visual cortex, even in the same hemisphere.

In conclusion, the study suggests that VC rTMS has potential as a treatment target in acute MDD patients. Furthermore, our data indicate the potential role of the visual cortex in dysfunctional neural circuitry of MDD and may therefore serve as a biomarker of therapeutic efficacy in MDD.

MATERIALS AND METHODS

Participants

The study was approved by the local ethics research board of the Second Affiliated Hospital at Xinxiang Medical University and Affiliated Zhongda Hospital of Southeast University. It has been registered with the Chinese Clinical Trial Registry (http://www.chictr.org.cn/enIndex.aspx), for which the registration number is ChiCTR1800014392. We initially recruited a cohort of 90 adult MDD subjects (aged 18–55 years) who were suffering depressive episodes, of which 80 were randomly assigned to three individual rTMS treatment groups and included in an analysis of Intention-To-Treat (ITT) for therapeutic effect. However, a total of 16 subjects were excluded from the final neuroimaging analysis (Table 1, Figure 3; Table S1, Supplementary Method 2 in Supporting Information). An independent group of age- and gender-matched healthy subjects (n=30) was recruited as a HC group (Table 1). Inclusion criteria included: (i) presence of a current depressive episode in accordance with the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) using diagnostic criteria for major depressive disorders as: (a) established by the assessing psychiatrist, and (b) confirmed with a standardized structured clinical interview for DSM-IV Axis I disorders (SCID-I); (ii) clinical symptoms of depression as measured by a HAMD-24 score ≥18; (iii) drug-naïve or free of antidepressant drug treatment longer than 2 weeks prior to their first rTMS treatment session, termed for short "drug-free". Exclusion criteria were: (i) any other psychiatric disorder, or a mental disorder caused by a physical illness or substance abuse or a personality disorder; (ii) history of traumatic brain injury, epilepsy or other known organic lesion of the central nervous system; (iii) presence of psychotic symptoms during the depressive episodes; (iv) presence of active suicidal behavior; (v) history of endocrine disease or blood, heart, liver, kidney dysfunction, another medical disorder such as diabetes, or pregnancy; (vi) less than six months of ECT or rTMS therapy, or having contraindication to rTMS or MRI; (vii) current use of antidepressant pharmacological therapy; (viii) therapy with lorazepam greater than 2 mg (or equivalent), mood stabilizer, or any anticonvulsant.

Randomization and blinding

Patients were initially allocated a subject number as they entered the study. An independent member of staff, otherwise uninvolved with the research program, allocated a single computer-generated random number (1, 2, or 3 representing individualized, standard, or sham, respectively) to each subject, after initial MRI investigation (day 0). Researchers involved in the clinical assessment were blind to the rTMS allocation, while the rTMS physician was blind to all clinical assessments. The researchers involved in rTMS and clinical assessment did not participate in data analysis. The confidential allocation of each subject to a treatment group was revealed for data analysis only after the last subject had completed the study.

Treatment—visual cortex rTMS

The three treatment arms were distinguished according to the precise VC target region, e.g., individualized vs. standard/sham, or real vs. sham rTMS. The individualized rTMS target region in the VC was determined based on task-related fMRI, represented by the peak voxel of increased BOLD activation in the VC during neutral fast minus neutral slow image viewing (Table S2, Supplementary Methods 3 and 7 in Supporting Information). Conversely, the target region in both the standard and sham groups was determined on the basis of structural MRI focusing on the left V1 region of the visual cortex (Figure S5 in Supporting Information). Each treatment session used real-time MRI neuronavigation using a Visor neuronavigation system (Rogue Research Inc. Montreal, North America) for precise coil positioning. The VC target region was determined in each subject by reverse co-registration based on the Montreal Neurological Institute (MNI) stereotactic coordinate system (x, y, z). The rTMS treatment was performed using a Magstim Rapid stimulator system with a figure-of-eight coil (standard double 70 mm stimulating coil) (The Magsitim Company Ltd, UK). The RMT was determined for each participant using visual observation of elicited movement (minimum intensity for 5 movements in 10 trials) in accordance with standard clinical practice (Herwig et al., 2001). rTMS stimulation parameters were: 10 Hz frequency at 90% RMT; 4 s on then 26 s off for

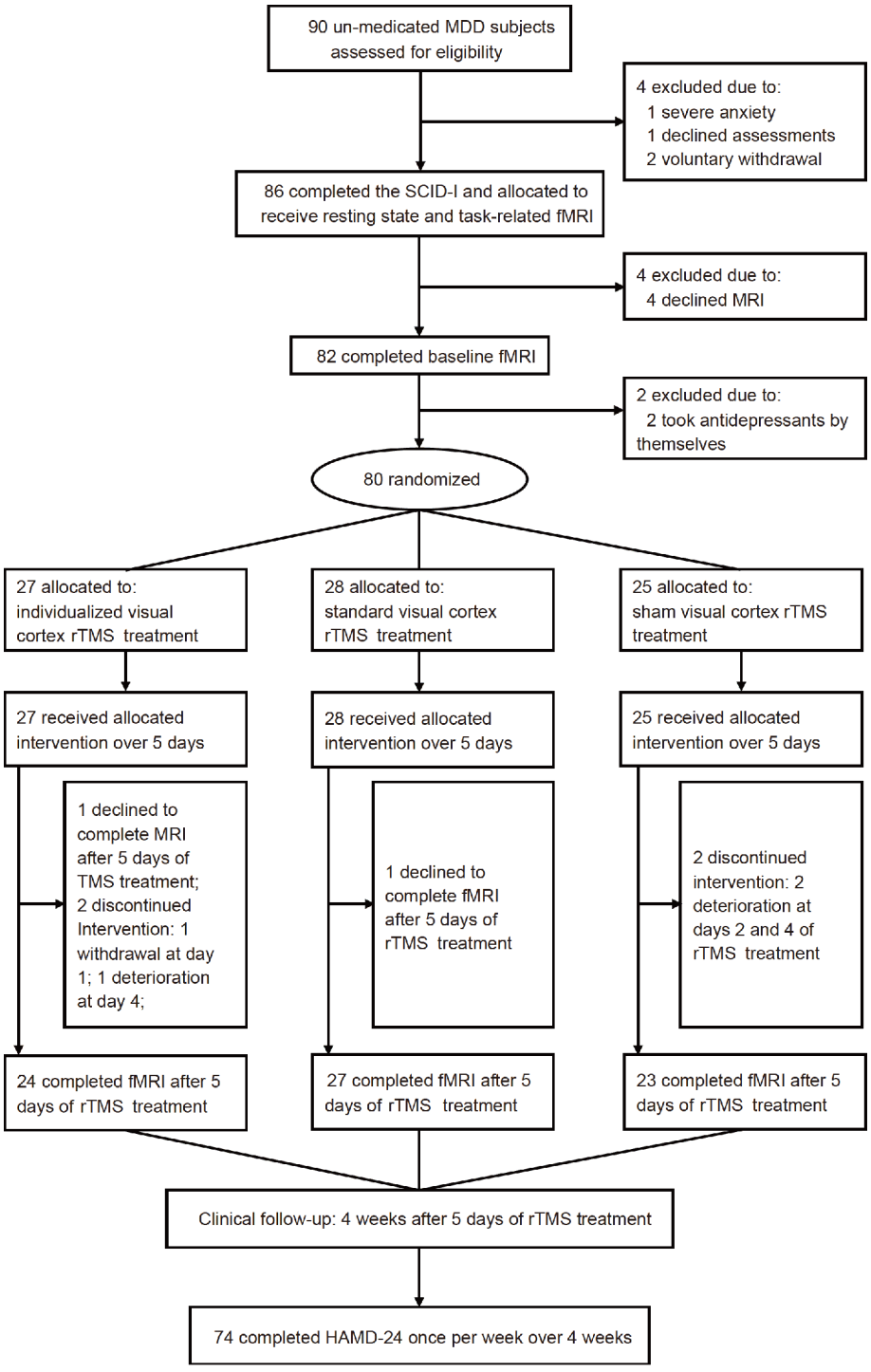

Figure 3 Flow diagram of study design in MDD patients. MDD, major depressive disorder; MRI, magnetic resonance imaging; rTMS, repetitive transcranial magnetic stimulation.

20 min, resulting in 1,600 pulses per session twice daily for 5 days, a total of 16,000 pulses for the treatment period. The sham treatment was delivered by turning the coil through 90°.

Clinical assessment

The measured clinical outcome was change in HAMD-24 score between day 0 (prior to MRI scan and rTMS treatment), and days 1, 3, and 5 (during rTMS treatment), and each week for the subsequent 4 weeks after the 5 days' rTMS treatment period. Participants with at least 50% improvement in their HAMD-24 scores were defined as responders (Blumberger et al., 2018). In addition, adverse events that were self-reported during the whole treatment period were

recorded.

Measures of resting state and task-related fMRI

Neuroimaging measures included resting state and task-related fMRI data before and after rTMS treatment. Resting state (eyes open) imaging was obtained for 5.7 min (342 volumes with a repetition time (TR)=1 s). Subjects then underwent a task procedure consisting of a 2×2 factorial design (emotional/neutral X slow/fast) (Figure S6 in Supporting Information). In particular, the present study initially focused on the analysis of neutral stimulation by slow or rapid viewing.

Data acquisition

Experimental scans were conducted and data acquired using a Magnetom Verio (A Tim System) 3.0T superconducting magnetic resonance imaging system produced by Siemens (Siemens, Erlangen, Germany). A 12-channel parallel acquisition head coil was used for signal reception. Details of the scanning parameters and quality control process of the MRI scanning are presented in Supplementary Method 4 in Supporting Information.

Data analyses

Data preprocessing of subjects was conducted using the SPM12 toolkit (http://www.fil.ion.ucl.ac.uk/spm), and the data analyzed using Analysis of Functional NeuroImages (AFNI) (http://afni.nimh.nih.gov/afni) and MATLAB version 7.10 (The MathWorks, Inc., Natick, MA, USA) software. Data analyses in the resting state focused on rsFC using the VC as a seed region to investigate its seed-based whole-brain voxel-wise rsFC with the rest of the brain, including the anterior prefrontal regions such as the pre/subgenual anterior cingulate cortex as they are typically involved in mood, self-consciousness, and MDD. VC seed-based whole-brain voxel-wise rsFC in MDD was compared with healthy subjects at day 0, while differences in rsFC for all three MDD treatment groups at days 0–5 were calculated in those regions that exhibited significant differences at day 0 (see Supplementary Methods 5 and 6 for details on rsFC analyses including head motion and global signal regression and Table S3 in Supporting Information). A voxel-wise threshold for whole brain correction (P<0.05) with 169 contiguous voxels was used for group-level analysis (3dClustSim (newest version), AFNI). All t-test analyses controlled for age, gender, years of education and raw gray matter volume for each subject. Analogous group comparisons were conducted in the case of task-evoked activity for contrast: neutral fast vs. neutral slow for healthy controls vs. all three MDD groups at day 0 in addition to all MDD groups at day 5 (including the difference at days 0–5). The threshold was set at P<0.05 (voxel-wise, whole brain correction) using the newest version of 3dClustSim, AFNI. Finally, whole-brain voxel-wise regression analysis was used to relate neutral fast vs. neutral slow task-evoked activity at day 5 (and days 0–5) with the reduction in HAMD-24 scores (days 0–5) in all three treatment groups (voxel-wise, whole brain-corrected, P<0.05).

Statistical analysis

The aim of the present study was to identify whether the mean change in HAMD-24 score was different among the three groups at day 5 and whether the effect of the treatment was sustained during the follow-up period. Two linear mixed models were used to analyze the trend in changed rate in HAMD-24 score among the three treatment groups over the treatment (day 1, 3, and 5) and follow-up periods (weeks 1, 2, 3, and 4). We calculated the changed rates of HAMD-24 score during treatment and follow-up periods using (baseline score—each point-in-time of score)/baseline score. In both models, treatment, its duration and their interactions were used as factors, while the baseline HAMD-24 score (day 0), age, gender, and years of education were used as covariates. Furthermore, the changed rate in HAMD-24 scores was estimated among the three treatment groups at different time points. Paired t-tests and one-way ANOVA were utilized to compare differences in HAMD-24 scores between baseline (day 0), after rTMS treatment (day 5), and during clinical follow-up (once per week over 4 weeks) within each treatment group or among the three groups, as appropriate.

Continuous variables are presented as means and standard deviations (SD). Categorical variables are presented as frequency and percentage. The normality of the distribution of data was evaluated using a Kolmogorov-Smirnov test. For continuous variables, independent sample t-test and one-way ANOVA were used for the comparison among groups, while a paired t-test was used for comparisons between different time points within each group. For categorical variables, chi-squared or Fisher's exact tests were performed. Quoted significance levels represent two-tailed tests, for which P<0.05 was regarded as significant. All statistical analyses were performed using SPSS V16 software (SPSS, Inc., USA). In addition, details of MRI-related analysis are presented in the Supplementary Materials.

Compliance and ethics *The author(s) declare that they have no conflict of interest. This study conformed with the Declaration of Helsinki of 1975 (as revised in 2008) concerning human and animal rights.*

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SUPPORTING INFORMATION

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