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Maintenance Repetitive Transcranial Magnetic Stimulation (rTMS) Weakly Improved Treatment Effect in Patients with Treatment-Resistant Schizophrenia Who Responded to maintenance ECT and Adjunct Olanzapine Treatment – A Pilot Study

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Abstract

Background: Maintenance treatment with electroconvulsive therapy (ECT) and adjunct antipsychotics can alleviate symptoms of treatment-resistant schizophrenia (TRS), although cognitive impairment is a side effect. Transcranial magnetic stimulation (TMS) has alleviated symptoms and improved cognitive impairment caused by maintenance ECT treatment. This study aimed to investigate long-term treatment effects of maintenance repetitive TMS combined with maintenance ECT and Olanzapine (MTEO) treatment strategy on TRS patients.

Methods: Eighty TRS patients underwent MTEO or sham-MTEO treatments for 112 weeks. Severity of illness and patient cognition were evaluated with Positive and Negative Syndrome Scale (PANSS) and MATRICS Consensus Cognitive Battery (MCCB), respectively. Global functional connectivity density (gFCD) was used to assess alterations in brain activity.

Results: Compared to the sham-MTEO group, the MTEO group exhibited an increase in mean MCCB total score [140.8 ± 17.5 vs. 165.5 ± 10.2, respectively; $P < 0.05$]. Compared to baseline, reductions in PANSS scores were significant in both groups. Also compared to baseline, a marked increase in gFCD was only observed in the left prefontal lobe, parietal lobe, and insular lobe in the MTEO group (FWE correct, $P < 0.01$). The sham-MTEO group exhibited an increase in gFCD in the temporal lobe and anterior cingulated cortex at baseline. In the striatum, gFCD decreased in both groups.

Conclusions: This novel MTEO treatment for TRS patients improved cognitive ability based on PANSS and MCCB scores, and this improvement may be related to increased brain activity in the prefontal, parietal, and insular lobes. Thus, further study of this treatment approach is warranted.

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INTRODUCTION

The prevalence of treatment-resistant schizophrenia (TRS; also referred to as treatment refractory schizophrenia) is currently about 30% among patients with schizophrenia [1, 2]. Over the past 40 years, strategies to improve the treatment of TRS have been pursued [3]. While different strategies have been tested, the treatment effect achieved has remained less than ideal [4, 5]. According to many guidelines for the treatment of schizophrenia, electroconvulsive therapy (ECT) with adjunct clozapine can improve treatment effects [6-9]. However, approximately 30% of patients with TRS are not responsive to this treatment approach, or they cannot tolerate the side effects of clozapine [10-20]. Within this context, Lally et al. have proposed that novel strategies to treat TRS should be pursued, especially for patients who are not responsive to clozapine combined with ECT [21]. Continued ECT treatment refers to strategies which are administered following a course of acute ECT for up to 6 months, with an aim of preventing relapse. Maintenance

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ECT can then be administered following continued ECT treatment and is intended to prevent recurrence [22, 23]. Some studies have reported that maintenance ECT with adjunct antipsychotic medications has improved the treatment effect of ECT for TRS [24-26].

To date, olanzapine remains the first-line antipsychotic treatment recommended for TRS patients who cannot tolerate the side effects of clozapine. For example, one side effect of clozapine is granulocytopenia [27-29]. In addition, it has been reported that olanzapine improves the emotional cognition of TRS patients compared with clozapine [30]. Interestingly, maintenance ECT with adjunct clozapine has been reported to improve the treatment effect of TRS even in patients who are not responsive to clozapine [6-21]. Taken together, these important findings support maintenance ECT with adjunct olanzapine for treatment of TRS, especially in patients with TRS who are not responsive to clozapine, those who experience serious side effects of clozapine, and those who have contraindications to clozapine [31].

It has been proposed that impaired cognition induced by maintenance ECT treatment should be investigated. In particular, maintenance ECT with adjunct antipyschotic treatment has been suggested [24-26]. Many studies have reported that repetitive transcranial magnetic stimulation (rTMS) can improve cognitive impairment caused by ECT, or ECT with adjunct antipsychotic treatment, in patients with TRS [32-38]. Recently, neuroimaging studies showed that after ECT treatment, cognitive-related brain regions, such as the prefrontal lobe, parietal lobe, insular lobe, and hippocampus, exhibit a decrease in neural activity [39-41]. However, rTMS has been shown to improve cognitive ability in patients with schizophrenia [42-45]. Inspired by these milestone findings, we postulate that maintenance ECT with adjunct olanzapine in combination with rTMS may further improve treatment effect and cognitive impairment in TRS patients.

To test this hypothesis, we have conducted a pilot study to investigate the effect of maintenance rTMS +maintenance ECT + olanzapine treatment strategy (defined here as MTEO therapy) on TRS patients. Both Positive and Negative Syndrome Scale (PANSS) and MATRICS Consensus Cognitive Battery (MCCB) scores were compared between the MTEO therapy group and the sham group. Comparisons were also made for both groups before and after treatment. Global functional connectivity density (gFCD) has been characterized as a useful tool for investigating functional activity and regional metabolism in the brain [46-48]. Therefore, in this study, we adopted gFCD as an objective index to assess the effects of the MTEO treatment strategy

METHODS

Participants

In this pilot study, TRS patients were enrolled from Wenzhou Seventh People's Hospital. Multiple inclusion criteria were established for participation. First, the following three criteria for TRS [modified from those proposed by Kane et al. (1988)] needed to be met: 1) an absence of good functioning within the previous five years (determined from a review of patient medical records); 2) being non-responsive to at least two antipsychotic drugs from different chemical classes for at least 4-6 weeks each at doses equivalent to 5 mg/day risperidone or ≥ 400 mg chlorpromazine (based on a review of patient medical records and assessments conducted by a professional psychiatrist), 3) and exhibiting moderate to severe psychopathology, particularly suspiciousness, conceptual disorganization, hallucinatory behavior, and/or delusions (defined by PANSS, GAF scores). In addition, TRS was considered if patients underwent two trials (4-6 weeks duration each) with two different antipsychotics at adequate doses and still presented recurrent mood symptoms, persistent psychotic symptoms, suicidal ideation or repeated suicide attempts, uncontrolled aggressive behavior, moderate-severe cognitive impairment, or moderate-severe negative symptoms [48]. Criteria for participation also included: compatibility with maintenance ECT and adjunct antipsychotics treatment (including olanzapine and clozapine), no intolerance to side effects potentially induced by clozapine, compatibility with maintenance rTMS treatment, no previous exposure to rTMS, no history of psychiatric or neurologic disease or other health problems, an absence of metal implants (including fixation elements, cardiac pacemaker, or artificial joints) in any part of the body, particularly in the head or neck, no tattoos, right-handedness (according to Edinburgh Handedness Inventory), and an IQ ≥ 80 (defined by Wechsler Intelligence Scale). Exclusion criteria were: (1) no risk of metabolic syndromes [47, 48], (2) moderate to severe physical disease (i.e., respiratory, cardiovascular, endocrine, neurological, liver, or kidney disease), (3) receiving current ECT, (4) a history of loss of consciousness for more than 5 min for any reason, (5) left-handedness, as determined by the Annett Hand Preference Questionnaire, (6) any magnetic resonance imaging (MRI) contraindication, including claustrophobia, and (7) an IQ < 80. The Ethics Committee of Wenzhou Seventh Peoples Hospital approved this study (IRB No. 2015-1101, date: 11-09-2015). Each participant provided a signed informed consent.

Between January 2016 and January 2018, a total of 80 patients with TRS were recruited to undergo treatment and MRI. However, MRI data from only 56 patients could be used in our analysis. Therefore, this subset of patients was distributed between the MTEO and sham groups. Clinical and social-demographic information for our cohort are presented in Table 1. For comparisons regarding brain functional activity, we adopted our previous healthy samples (n = 30) from our database as healthy controls (all of them were recruited from the communities of Wenzhou by advertisement between 2016 and 2018).

Illness Symptoms Assessment

PANSS was adopted to assess symptoms of TRS [49], while

MCCB was adopted to assess the cognitive ability of TRS patients [50].

Maintenance ECT with Adjunct Olanzapine Treatment Procedure

Upon initial admission, some patients had received olanzapine at a dose up to 20 mg/day before ECT treatment. For the duration of the study, the dose of olanzapine was fixed. ECT was conducted twice a week for 112 weeks, for a total of 224 sessions. Standard premedication included atropine, rocuronium, and propofol. A Thymatron® System IV (Somatics LLC, Venice, FL, USA) applied an electrical dose which was determined according to the seizure threshold of the patient. The pulse width was 0.5-ms at a frequency of 60 Hz. The duration of the stimulus was 7.5-s and 900 mA current was applied. In addition, bifrontotemporal stimulation was applied. Initially, ECT was applied at 40% stimulation strength. However, in the absence of effective convulsions, the stimulation strength was increased to 80% and an effective seizure duration of 20–40 s was achieved. Acute ECT was performed for the first five weeks of the study. Continued ECT was subsequently maintained for an additional 27 weeks. Maintenance ECT was then completed after a total of 112 weeks, for a total of 224 sessions [23]. During this 112-week treatment period, the dose of olanzapine administered was fixed and side effects induced by ECT and olanzapine were carefully monitored by doctors adopted multiple methods.

Maintenance rTMS Treatment Procedure

For 112 weeks, rTMS was performed twice a week for a total of 224 sessions. According to updated safety guidelines [51], high-frequency rTMS was administered with a Magstim Rapid device with a 70-mm figure of eight air-film coil (Magstim, Whitland, UK). Stimulation was performed at 100% of resting motor threshold intensity at 20-Hz frequency. The stimulation was applied for 10 s, with an inter-train interval of 90 s. A total of 2,000 pulses/session were applied. According to standard procedure, the coil was placed over the left dorsolateral prefrontal cortex, with the TMS coil positioned 5.0 cm rostrally from the area of the right thumb [52].

Sham Maintenance rTMS Treatment Procedure

Sham rTMS was performed twice a week for 112 weeks, for a total of 224 sessions. The procedure used was the same as that established for the maintenance rTMS treatment group, with the key exception that a sham stimulus was applied [53].

MRI Data Acquisition

MRI data were collected with a 3.0-Tesla Discovery MR750 MR system (General Electric, Milwaukee, WI, USA). A GE Healthcare Discovery MR750 3T MRI system with an eight-channel phased-array head coil (General Electric, Milwaukee, WI, USA) was used to perform functional MRI (fMRI). To perform imaging, participants were asked to lay in a supine position and restrict head movements. The following imaging parameters were used: 45-ms echo time (TE), 2,000-ms repetition time (TR), 4-mm thick slices with a 0.5-mm gap (32 total slices), field-of-view (FOV), 90° flip angle, and a 64×64 acquisition matrix. Parallel imaging and SENSitivity Encoding (SENSE; with a SENSE factor of 2) were used for all scans. To obtain images, a three-dimensional, high-resolution turbo-fast echo T1-weighted sequence was used. The latter included the following parameters: 3.2-ms/8.2-ms TE/TR, a total of 188 1-mm thick slices with no gap, 256 × 256 FOV, 12° FA, and 256×256 acquisition matrix [54].

fMRI Data Pre-Processing

Resting-state fMRI scans were processed by using Statistical Parametric Mapping 8 (SPM8; http://www.fil.ion.ucl.ac.uk/spm). The first ten scan volumes were discarded to allow stabilization of the scanner and for patients to acclimate to testing conditions. The remaining volumes were corrected for slice timing and motion artifacts. All of the fMRI data were checked to ensure that both rotational and translational motion thresholds (2° and < 2 mm, respectively) were obeyed. Mean blood oxygen level-dependent signals of white matter and the ventricles were excluded. In addition, six motion parameters and data with specific-volume framewise displacement values > 0.5 were excluded from analysis. Bandpass frequencies (0.01–0.08 Hz) were used to filter data. Individual structural images were co-registered to the mean functional image. By using linear registration, transformed structural images were co-registered to the Montreal Neurological Institute (MNI) space. Motion-corrected functional volumes were spatially normalized to the MNI space by using parameters estimated during linear co-registration. The functional images obtained were subsequently re-sampled into 3-mm cubic voxels for further analysis [55].

gFCD Calculations

For each voxel, gFCD was calculated by using a customized Linux script. To explore functional connectivity between voxels, Pearson's linear correlation was used. The correlation coefficient threshold was $r > 0.6$. The gFCD for any given voxel (x0) was determined with a growth algorithm which included the total number of functional connections [k(x0)] between x0 and all of the other voxels. This procedure was applied to each voxel. Each gFCD value was divided by the mean value of all the included voxels to increase normality of the distribution. A Gaussian kernel (6×6×6 mm^3) was used to spatially smooth the gFCD maps in order to minimize the impact of anatomical differences between participants, age, gender, illness duration, and education level which all regressed out as covariants [56].

Statistical Analyses

The paired t-test was used to compare changes in PANSS and MCCB scores, and in gFCD before and after treatment. The paired t-test was applied three times during the study period, and alterations at the end of the 112-week treatment period were compared to baseline. The Mann-Whitney test was also used to identify differences between

the MTEO group and sham group. P-values less than 0.05 were considered significant [56, 57]. In this pilot study, we hypothesized that MTEO treatment can: 1) alleviate symptoms of TRS, 2) improve cognitive impairment of TRS, and 3) lead to alterations in gFCD.

Flowchart of This Pilot Study

RESULTS

Based on the inclusion criteria established for this pilot study, a total of 60 patients were recruited to participate. However, only 57 patients completed the study. Among these 57 patients, full MRI data could only be obtained for 39 patients. Therefore, the latter were divided into a MTEO group (n = 16) and a sham MTEO group (n = 23). A summary of patient characteristics is presented in Table 1. At the endpoint of the study, five patients in the MTEO group exhibited a deterioration in positive symptoms for 1~2 weeks. This was alleviated by adding ECT treatment once a week during the period of symptom deterioration. In the sham group, ten patients also exhibited a deterioration in positive symptoms over 1~2 weeks. Similarly, this was alleviated with ECT treatments which were performed once a week during period of symptom deterioration. Meanwhile, the negative symptoms of both groups were stable throughout the study period. The PANSS scores for positive symptoms were reduced between the MTEO group and sham group (Table 2). Five patients in the MTEO group reported weak headaches, while none of the patients in the sham group reported side effects (Table 2).

Table 1. Sociodemographic information and PANSS/MCCB scores at baseline presented as mean (SD).

Variable	MTEO group	Sham group	Mann-Whitney	*P*-value
Baseline	N = 16	N = 23		
Age (y)	39.0 (2.0)	33.8 (2.9)	0.005	0.998
Education level (y)	12.5 (0.3)	12.0 (15.0)	0.221	0.887
Illness duration (y)	15.2 (4.0)	12.4 (2.5)	6.879	< 0.001
Total PANSS score	85.5 (5.1)	86.7 (3.9)	0.633	0.228
Positive PANSS score	46.0 (8.5)	47.5 (6.0)	0.411	0.549
Negative PANSS score	39.5 (4.3)	39.0 (3.5)	0.317	0.689
MCCB total score	175.8 (15.2)	175.6 (9.3)	0.522	0.490
MCCB Speed Processing	30.0 (4.5)	32.0 (7.7)	0.571	0.481
MCCB Attention	30.0 (5.4)	29.0 (4.5)	0.103	0.925
MCCB Working Memory	24.2 (8.5)	23.5 (4.7)	0.958	0.050
MCCB Verbal Learning	24.2 (8.5)	25.0 (3.0)	0.315	0.590
MCCB Visual Learning	20.5 (2.5)	22.2 (2.40)	0. 299	0.700
MCCB Problem Reasoning	22.0 (9.5)	24.0 (6.5)	1.250	0.011
MCCB Social Cognition	24.9 (8.5)	23.9 (8.7)	0.730	0.222

Table 2. Alterations in PANSS and MCCB scores between the MTEO and sham groups after treatment presented as mean (SD).

Variable	MTEO group	Sham group	Mann-Whitney	*P*-value
Number of patients	N = 16	N = 23		
PANSS score	75.5 (9.5)	78.0 (5.1)	1.007	0.049
Positive PANSS scores	36.0 (8.7)	39.7 (6.5)	1.411	0.039
Negative PANSS scores	39.5 (5.7)	39.0 (4.2)	0.192	0.713
MCCB total score	182.2 (9.2)	172.8 (105.5)	5.200	< 0.001
MCCB Speed Processing	35.0 (4.5)	31.5 (2.5)	2.571	< 0.001
MCCB Attention	27.0 (2.0)	25.0 (4.5)	0.403	0.552
MCCB Working Memory	19.5 (4.3)	26.0 (6.5)	-1.853	0.001
MCCB Verbal Learning	25.5 (8.5)	22.8 (3.7)	0.315	0.590
MCCB Visual Learning	25.2 (2.0)	22.0 (4.2)	1. 299	0.009
MCCB Problem Reasoning	25.0 (10.5)	22.5 (5.6)	1.250	0.011
MCCB Social Cognition	25.0 (4.7)	23.0 (4.7)	0.730	0.222
Positive symptoms relapse rate	31.3% (5/16)	34.8% (8/23)	1.599	0.015

In this pilot study, we observed that most of the MCCB scores for the MTEO treatment group increased, except the working memory score which decreased, compared to the sham group (Table 2). When MCCB scores were compared with baseline, the same pattern was observed. Meanwhile, PANSS scores for the MTEO treatment group exhibited a slight reduction (11.8%) over the two years of the study period (Table 3). For the sham group, almost all of the MCCB items' scores were reduced compared to baseline (Table 4). In addition, PANSS scores for the sham group were reduced by 10.03% after the study period. (Tables 1-4). Overall, both the MTEO and sham treatments weakly alleviated the psychotic symptoms of our patients, with their positive symptoms mainly affected. In contrast, no significant effect on the negative symptoms in both groups was observed. According to the MCCB, working memory remained impaired after two years of maintenance rTMS treatment. Meanwhile, cognitive impairments exhibited differing extents of improvement in the MTEO group.

A comparison of gFCD between the healthy controls at baseline and the sham group showed no significant differences. However, some regions of the brain did exhibit alterations. For example, hypoactivity in the frontal lobe, parietal lobe, temporal lobe, and occipital lobe was observed in the MTEO group. These hypoactive regions were also observed in the sham group, as well as additional hypoactivity in the hippocampus (Figure 1A). Following treatment, the MTEO group exhibited significant increases

in gFCD in the prefontal lobe, parietal lobe, temporal lobe, insular lobe, and anterior cingulate compared to the sham group (Figure 1B). However, compared to baseline, the increases in gFCD in the MTEO group were most notable in the left prefontal lobe, parietal lobe, and insular lobe (Figure 1C). Meanwhile, the sham group exhibited an increased in gFCD in the temporal lobe and anterior cingulated cortex compared to baseline (Figure 1C). In the striatum, both groups exhibited a decrease in gFCD compared to baseline (Figure 1D).

Table 3. Alterations in PANSS and MCCB scores in the MTEO group (N = 16) between baseline and after treatment presented as mean (SD).

Variable	Pretreatment	After treatment	Mann-Whitney	*P*-value
PANSS score	85.5 (5.1)	75.5 (9.5)	1.007	0.049
Positive PANSS scores	46.0 (8.5)	36.0 (8.7)	1.411	0.039
Negative PANSS scores	39.5 (4.3)	39.5 (5.7)	0.192	0.713
MCCB total score	175.8 (15.2)	182.2 (9.2)	12.501	< 0.001
MCCB Speed Processing	30.0 (4.5)	35.0 (4.5)	4.888	< 0.001
MCCB Attention	30.0 (5.4)	27.0 (2.0)	5.258	< 0.001
MCCB Working Memory	24.2 (8.5)	19.5 (4.3)	-4.007	< 0.001
MCCB Verbal Learning	24.2 (8.5)	25.5 (8.5)	0.855	0.120
MCCB Visual Learning	20.5 (2.5)	25.2 (2.0)	4.544	< 0.001
MCCB Problem Reasoning	22.0 (9.5)	25.0 (10.5)	2.314	0.005
MCCB Social Cognition	24.9 (8.5)	25.0 (4.7)	0.820	0.2119

Table 4. Alterations in PANSS and MCCB scores in the sham group (N = 23) between baseline and after treatment presented as mean (SD).

Variable	Pretreatment	After treatment	Mann-Whitney	*P*-value
PANSS score	86.7 (3.9)	78.0 (5.1)	3.250	< 0.001
Positive PANSS scores	47.5 (6.0)	39.7 (6.5)	3.987	< 0.001
Negative PANSS scores	39.0 (3.5)	39.0 (4.2)	0.100	0.990
MCCB total score	175.6 (9.3)	162.3 (10.5.5)	5.540	< 0.001
MCCB Speed Processing	32.0 (7.7)	31.5 (2.5)	3.250	< 0.001
MCCB Attention	25.0 (9.5)	25.0 (4.5)	0.125	0.905
MCCB Working Memory	23.5 (4.7)	16.0 (6.5)	9.250	< 0.001
MCCB Verbal Learning	25.0 (3.0)	22.8 (3.7)	2.310	0.034
MCCB Visual Learning	22.2 (2.40)	22.0 (4.2)	0.112	0.888
MCCB Problem Reasoning	24.0 (6.5)	22.5 (5.6)	1.035	0.047
MCCB Social Cognition	23.9 (8.7)	23.0 (4.7)	0.995	0.061

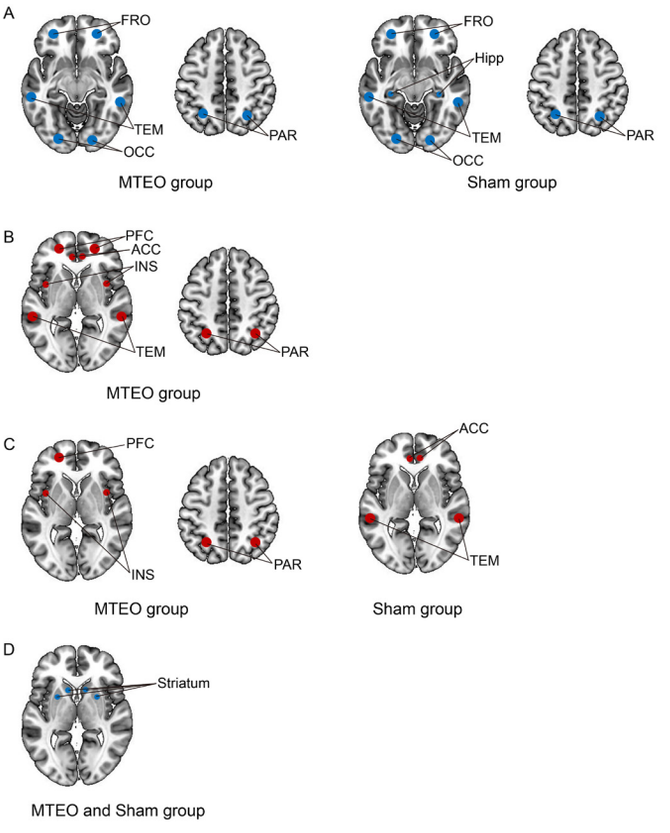

Figure 1. Alterations in gFCD in the MTEO and Sham groups. A, Compared to healthy controls and sham groups at baseline, hypoactivity was detected in the frontal lobe (FRO), parietal lobe (PAR), temporal lobe (TEM), and occipital lobe (OCC) in the MTEO group, with additional hypoactivity detected in the hippocampus (Hipp) in the sham group. B,) In the MTEO group, significant increases gFCD are detected in the prefrontal lobe (PFC), parietal lobe (PAR), temporal lobe (TEM), insular lobe (INS), and anterior cingulate (ACC) compared to the sham group after MTEO treatment. C, In the sham group, significant increases gFCD are detected in the left prefrontal lobe (PFC), parietal lobe (PAR), and insular lobe (INS) in the MTEO group compared to baseline, and significant increases in the temporal lobe (TEM) and anterior cingulated cortex (ACC) are detected in the sham group compared to baseline. D, Significant increase gFCD are detected in the striatum compared to baseline in the MTEO and Sham groups.

DISCUSSION

In this pilot study, we initially observed long-term effects of MTEO treatment on patients with TRS, especially patients non-responsive to clozapine treatment. After analyzing the data obtained, we have four main findings.

First, we initially observed that MTEO treatment reduced the duration of positive symptom deterioration and the ratio of these affected patients compared to the sham treatment group. These findings suggest that maintenance of rTMS can enhance the antipsychotic effects of maintenance ECT with adjunct olanzapine treatment. In previous studies, a higher frequency of rTMS treatment alleviated symptoms of TRS, especially auditory verbal hallucinations and negative symptoms [58-62]. However, in the present study, maintenance treatment enhanced the additional ECT treatment sessions to alleviate TRS symptoms, while maintenance rTMS did not enhance maintenance ECT and adjunct antipsychotics to alleviate negative symptoms of TRS. It has previously been observed that ECT can rapidly alleviate positive symptoms of TRS, and can also effectively alleviate negative symptoms which rarely respond to ECT treatment, clozapine, or olanzapine [7, 63-65]. However, in our sample, all of the patients manifested positive and negative symptoms, with the positive symptoms being predominant. Thus, despite our hypothesis that MTEO treatment strategies should alleviate negative symptoms, this was not observed in our cohort.

Secondly, we observed in the MTEO intervention group that the MCCB scores of some patients increased, while the scores of other patients decreased. When a comparison was made between baseline and two years after MTEO treatment for individual patients in this group, we observed that almost all of the MCCB scores had increased. This finding indicates that maintenance rTMS improved the cognitive impairment of these patients. However, we also observed that some items within the MCCB, especially the Working Memory score, were decreased when we compared the final MCCB scores to baseline in both groups. We postulate that this phenomenon is related to side effects of ECT, since previous studies have reported that ECT induces impairment of memory function, and this impairment can manifest as a long-term effect [7, 61-65].

Third, we observed an increase in gFCD mainly in the frontal, parietal, and insular lobes, while a decrease in gFCD was observed in the striatum. Previous studies have reported that the frontal-parietal lobe and insular lobe are pivotal components of cognitive processing circuit/networks. Our findings suggest that maintenance rTMS can improve brain functional activity in cognitive processing-related brain regions, consistent with available literature [66-68]. More notably, compared to baseline, both groups exhibited a decrease in gFCD in the striatum. These findings are consistent with previous studies which have shown that ECT can reduce functional connectivity between the striatum and other brain regions in patients with schizophrenia [69, 70].

Fourth, and possibly the most important finding in this pilot study, we observed that a reduction in PANSS scores in the MTEO treatment group did not significantly differ from the PANSS scores of the sham and baseline groups. Moreover, while both the MTEO and sham treatment groups exhibited significant reductions in PANSS scores, the reduction did not exceed 30% in either group. We postulate that this phenomenon is a manifestation of TRS, and may indicate that these patients are extremely resistant to treatment [4, 71, 72]. Thus, this latter group of patients should be further studied in order to investigate possible treatment strategies.

Many studies have reported that rTMS treatment alleviates cognitive function impairment in patients with schizophrenia. For example, Mogg et al. showed that 10 Hz high-frequency rTMS induces a significant improvement in verbal learning among patients with schizophrenia [73]. Another study reported that at least six months of rTMS treatment is needed to improve MCCB performance [74]. Our pilot findings support the latter finding, and they further demonstrate that six months is a sufficient treatment time for rTMS to alleviate cognitive impairment.

Limitations

There are at least six limitations associated with this pilot study. First, we only recruited TRS patients who had contraindications for clozapine and combined ECT treatment. Clozapine is recognized as a gold standard for discriminating TRS. Once identified, it is recommended that TRS patients receive ECT in combination with clozapine. Considering that the side effects of clozapine limit its administration to all TRS patients, we included olanzapine in our treatment protocol. Thus, the selection of patients to receive olanzapine as an alternative to clozapine may represent a selection bias which influenced our findings. In future studies, we are interested in comparing our present method to the method recommended by Polese et al. [72]. Second, we only compared MRI data twice during the two year duration of this pilot study. In future studies more frequent MRI scanning should be performed to obtain more data. Third, we included both maintenance rTMS and ECT in our treatment method, which has rarely been reported in the literature. Hence, these pilot findings should be carefully considered. Fourth, to our knowledge, this is the first study to apply both maintenance rTMS and ECT for long-term treatment. The results for treatment of TRS are not excellent. For example, PANSS scores were reduced above 50, while the MCCB total score increased 30%. Thus, further study is needed to identify effective treatments for TRS. Fifth, use of gFCD as an objective index was both a strength and a weakness of our pilot study. It is possible that long-term interval MRI data are influenced by many factors. Hence, we recommend that MRI data be acquired once every six months in future studies to improve this limitation. Sixth, the findings of the present study are consistent with those of previous studies where ECT is found to be an effective treatment method for TRS, yet it impairs cognitive ability. Previous studies have further

demonstrated that rTMS can alleviate cognitive impairment induced by ECT. Hence, in the present study we adopted this method for alleviating cognitive impairment of rTMS. We observed that gFCD alterations were improved by rTMS. However, the small sample size of our pilot study represents a limitation of our findings. Another important limitation of the present findings is that ECT and rTMS (high frequency) can induce epileptic effects. Thus, when applying both of these two methods, patients' epileptic threshold must be closely monitored in order to avoid inducing epileptic disease and brain impairment.

CONCLUSION

To our knowledge, this pilot study represents the first investigation of maintenance rTMS plus maintenance ECT and long-term olanzapine treatment for TRS patients. Maintenance rTMS treatment improved cognitive ability among our TRS patients, and this improvement may be related to alterations in brain activity. For example, an increase in brain activity was observed in the prefontal, parietal, and insular lobes. Simultaneously, we observed that PANSS and MCCB scores were altered in the TRS patients which showed improvement. However, the alterations only reflected an alleviation of TRS symptoms in 10–11.8% of our patients who received MTEO treatment, and 3.64% exhibited improved cognitive impairment. Taken together, these findings provide valuable insight for the design of future studies.

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Data availability statement: The datasets generated and analysed during the present study are available from the corresponding author on reasonable request.

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