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CLINICAL TRIAL REPORT

Optimal Treatment of Magnetic Seizure Therapy (MST) in Patients with Clozapine-Resistant Schizophrenia (CRS)

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Objective: The study aims to compare the clinical efficacy and cognitive side effect of magnetic seizure therapy (MST) and modified electroconvulsive therapy (MECT) on clozapine resistant schizophrenia (CRS).

Methods: Sixteen patients with CRS were enrolled in this randomized, parallel-group, controlled clinical trial. Patients were randomly allocated to receive 10 sessions of add-on MST or MECT over 4 weeks (1:1 ratio) and continued clozapine therapy during the study. Efficacy and neurocognition were assessed at baseline, 4-week and 8-week follow-up.

Results: (1) Clinical efficacy: MST significantly improved symptoms of schizophrenia from baseline to 4 weeks, as shown in PANSS total ($p = 0.009$), PANSS positive ($p = 0.026$), PANSS negative ($p = 0.031$) and PANSS general psychopathology ($p = 0.023$); we also observed significant reductions in PANSS total ($p = 0.049$) and PANSS positive ($p = 0.037$) at 8-week follow-up. MECT group also witnessed clinical improvement from baseline to 4-week in PANSS total ($p = 0.035$) and PANSS positive ($p = 0.001$); significant reduction in PANSS positive was also observed at 8-week follow-up ($p = 0.041$). From baseline to 8 weeks, PANSS negative had greater reduction in MST group compared with MECT group ($p = 0.042$). (2) Neurocognition: Pre-and post-treatment data showed no significant cognitive adverse effects in both groups. Immediate memory is better in patients who received MST than MECT at 4-week follow-up ($p = 0.030$).

Conclusion: In this pilot study, MST and MECT equally improved positive symptoms of CRS, while MST was more effective in relieving negative symptoms. Evidence showed negligible cognitive side effects in MST, with less adverse effect on immediate memory than MECT. As a promising alternative to MECT, MST requires further research in larger clinical population.

Keywords: clozapine resistant schizophrenia, CRS, modified electroconvulsive therapy, MECT, magnetic seizure therapy, MST, clinical efficacy, neurocognition

Introduction

Schizophrenia is a chronic serve disease with high morbidity and disability. The global disease burden survey revealed by lancet in 2019 shows that the number of patients with schizophrenia increased from 14.2 (million cases) in 1990 to 23.6 (million cases) in 2019, a corresponding increase of 63.7%.[1] Of which, 20–30% developing to treatment-resistant schizophrenia (TRS).[2] Clozapine is the most effective and the only evidence-based antipsychotic for TRS, but only one-third of patients respond to clozapine.[3] Patients with TRS who are resistant to clozapine treatment are termed clozapine resistant schizophrenia (CRS). Clozapine-resistant schizophrenia (CRS) is defined by the Treatment Response and Resistance in Psychosis (TRRIP) Working Group as persistence of either positive, negative, or cognitive symptoms of schizophrenia of at least moderate severity after an adequate trial of clozapine.[4]

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Multiple pharmacological enhancing strategies have been explored for CRS patients, such as the combination of a second antipsychotic drug, antidepressants, mood stabilizers, aglutaminergic drugs, but no convincing efficacy has been shown.[5–8] Due to the limited evidence-based pharmacological treatments for CRS, it remains severe and persistent symptoms, relapses and hospitalizations. Some evidence indicates that only marginal benefits for pharmacological clozapine combination after insufficient response to clozapine monotherapy.[5,9] New lines of research are needed to explore alternative forms of therapeutic schedule for CRS.

Electroconvulsive therapy (ECT) is reported to be an efficacious treatment option for CRS, but mostly positive symptoms are more likely to benefit from ECT.[10,11] For the management of clozapine refractory positive symptoms, clozapine augmentation with ECT was advised by 92.1% and with rTMS was suggested by 10% of the participants.[4] For the management of clozapine refractory negative symptoms, augmentation with ECT was advised by 21.6% and with rTMS was advised by 9.1% of the surveyed experts.[4] In the case of symptomatic improvement, 71.1% of the survey participants suggested ECT maintenance treatment for the positive symptoms and 40.8% of the surveyed experts suggested ECT maintenance treatment for the negative symptoms. For suicidal ideation symptoms and aggressive symptoms, ECT is also an offered augmentation strategy.[4] However, the biggest obstacle to the application of ECT comes from patients, families, and healthcare providers due to its fear, stigma, and cognitive effects.[12] Such side effects like cognitive deficits and, in particular, memory impairment can range from mild or negligible in some patients up to severe and distressing in others.[13–15] In patients receiving clozapine treatment, high-frequency rTMS in the dorsolateral prefrontal cortex and low-frequency rTMS in the temporal parietal cortex have been proven to be safe, but their efficacy in treating CRS is still uncertain.[16] An analysis of existing strategies for enhancing the efficacy of clozapine treatment found that ECT is effective for refractory positive symptoms of clozapine, with evidence level B, while rTMS enhancing treatment only meets the C-level criteria.[17] The above evidence indicates that ECT has a promise clinical efficacy but unneglected cognitive side effects. RTMS has good cognitive security, but its efficacy is limited. Thus, there is a need for new treatment alternatives for patients with CRS. One such option is magnetic seizure therapy (MST).

Magnetic seizure therapy (MST) is another emerging neuromodulation treatment which induces therapeutic seizures through the use of high-frequency repetitive transcranial magnetic stimulation.[18,19] It was first introduced by Lisanby in preclinical studies[20] and subsequently used for the first time in major depression disorder.[21] The magnetic fields used in MST are unimpeded and focal, thus provide directed and focal stimulation which is not like the ECT. This may account for the reports of absent or minimal effects of MST on neurocognitive function.[22] The hope for MST is to match the clinical efficacy of ECT but with fewer adverse effect because MST is mediated by a different mechanism of action and a more focal treatment target in the brain structures.[23,24] There is few evidence for this with regard to MST as a treatment for schizophrenia. However, it has not yet been established whether MST has the same antipsychotic effects as ECT in CRS.

Treatment of CRS represents a major challenge for clinicians. Thus, we assess the clinical and cognitive effects of MST in patients with CRS. We explored the association of MST with cognition on MST for CRS. We hypothesized that MST would be associated with clinically meaningful rates of remission and have fewer side effects than ECT.

Methods

Participants

Patients were recruited from Shanghai Mental Health Center in China (clinicaltrials.gov registration number: NCT02926976). The inclusion criteria were as follows: (1) 18–55 years old; (2) Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) diagnosis of schizophrenia; (3) fails to respond to ≥2 adequate, in terms of dose (400–600mg/d, equivalent dose of chlorpromazine) and duration (at least 6 weeks), trials of first-line antipsychotic medication; (4) persistence of either positive, negative, or cognitive symptoms of schizophrenia of at least moderate severity after an adequate trial of clozapine (300–600 mg/d, clozapine plasma concentration >350ng/mL, at least 6 weeks); (5) the following items of PANSS scale (delusion, hallucination, suspicion, conceptual disorder, abnormal thinking content), at least one of the items has a score ≥4 (moderate), the CGI-severity score was at least moderate (≥4).[25]

Exclusion criteria included: (1) severe physical disease, substance abuse or alcohol dependence; (2) currently pregnancy or lactating; (3) any implants in the head, cardiac pacemakers, cochlear implants, or other implanted electronic devices; (4) Those who have received MECT within 6 months or have failed to MECT in the past; (5) HAMD score >18 or have depressive symptoms judged by doctors.

Ethical Considerations

The study was approved by the Ethics Committee of the Shanghai Mental Health Center (2016–32). All subjects obtained informed consent, voluntarily participated in the study, and signed a written informed consent form. This study has been conducted in accordance with the Declaration of Helsinki.

Study Design

This is an add-on therapy study, in which patients were randomized to receive MECT or MST enhanced therapy based on clozapine treatment after enrollment. During the process, participants are required to maintain the original clozapine treatment, and adjust the dosage of clozapine according to the needs of the condition, but it must be ensured that between 300 mg and 600mg/day. Other antipsychotic drugs, antidepressants, and mood stabilizers were forbidden. Once the first trial of MST/MECT begins, the clozapine dose cannot be adjusted until to 8-week follow-up.

Interventions

In addition to treatment as usual, patients were randomly received with MST/MECT for 4 weeks, with 3 sessions per week for the first 2 weeks and 2 sessions per week for the following 2 weeks, totally 10 sessions. Before either intervention, patients received intravenous atropine (0.5mg/time) to increase heart rate and reduce airway secretions, followed by injection of etomidate (0.21–0.3mg/kg) and propofol (1.82–2.44 mg/kg) until the eyelash reflex disappeared. A mask was administered for pressurized oxygen inhalation, and succinylcholine (1mg/kg) was used as a muscle relaxant. During the process, relevant indicators such as the duration of EEG seizures and the inhibition index after seizures were recorded.

MST was administered with a MagPro X100 with MagOption MST (MagVenture A/S, Denmark) at 100 hz and 100% output. Due to the possibility that the seizure threshold may increase with the duration of treatment, the titration method was used to determine the duration of the magnetic stimulation; the duration began at 4 seconds and extended by 4 seconds in each subsequent session up to a maximum of 20 seconds. If the seizure duration was less than 15 seconds in a certain session, the increment of the stimulation duration was 8 seconds during the next session. If no seizures were generated, an extra stimulation lasting for 20 seconds was administered immediately. Studies had demonstrated the effectiveness of the titration method in generating seizure activity among patients with schizophrenia.[26] Magnetic stimulation was delivered via two conical coil with its midline on the vertex to achieve maximum output power.

The magnetic stimulation was delivered via a twin coil with its midline on the vertex. Keep the distance from the central of the coil to the midpoint of the line connecting the tragus and outer canthus of the eye to be equal. The MECT was administered using the Thymatron System IV device (Somatics, USA). Stimulate with a wave width of 1.0 ms, and the charge based on age and weight (maximum set charge of 100%: 504 mC). The frequency was 10–70 hz, increased by 10 hz (with a maximum frequency of 140 hz for 0.25 ms pulses). The pulse width was 0.25–1.5 ms, in increments of 0.25 ms. The treatment duration was 0.14–8.0 s, increasing in equal charge.

Assessments

Demographic measures were collected at baseline. Symptoms of schizophrenia were measured using the PANSS, and assessments were performed at baseline,4-weeks and 8-weeks from the first MST/MECT. The Repeatable Battery for the Assessment of Neuropsychological Status were employed to measure the cognitive effects. The response rate was defined as not less than a 20% reduction in the PANSS total score in TRS, a 25% reduction rate in the PANSS total score was defined as effective.[27] The RBANS consists of 12 subtests that form five age-adjusted index scores, including immediate memory, visuospatial function, language, attention, and delayed memory.

Eight patients were able to complete the RBANS (5 in MST group and 3 in MECT group) at the baseline, while the other eight patients were unable to complete due to psychiatric symptoms. At the follow-up end-timepoint evaluation, 2 individuals in the MST group and 2 individuals in the MECT group completed the RBANS. Due to the limited amount of data during the 8-week follow-up evaluation period, the data at this stage was not included in statistical analysis. The response rate was defined as not less than a 20% reduction in the PANSS total score. A delayed memory deficit was defined as a ≥10% reduction in the RBANS delayed memory score.[28]

Randomization and Blinding

Stratified Blocked Randomization procedures were performed. Subjects were randomly assigned to the MST and MECT groups in a 1:1 ratio. This ensures that the number of subjects in the two groups is equal. The randomization list was computer generated. The MST technician was aware of the group allocation but was not involved in any clinical or cognitive assessment. Neither the participant nor the rater was aware of the group allocation.

Data Analysis

SPSS 22 was used to perform the Statistical analyses. Chi-square test, independent *t*-test, and Mann–Whitney *U*-test were used to compare the demographic and clinical characteristics between the two intervention groups. When a cell in the four-fold table had an expected count of <5, Fisher's exact test was used instead of the Chi-square test.

Repeated measurement were utilized to investigate the within-group time effect (baseline/post-treatment/follow-up) and the between-group time × group (MST/MECT) interaction on psychotic symptoms and cognitive functions, with the individual differences as a random effect of slope and intercept, and the antipsychotic dosage as a covariate.

Results

Initially, 31 participants with CRS were assessed for eligibility. Ultimately, 18 patients were selected for randomization, and 16 of these individuals received the MST/MECT intervention. All these 16 participants successfully completed treatment and part of them finished the follow-up. Please refer to Figure 1 for the CONSORT chat, Table 1 for the baseline participant characteristics.

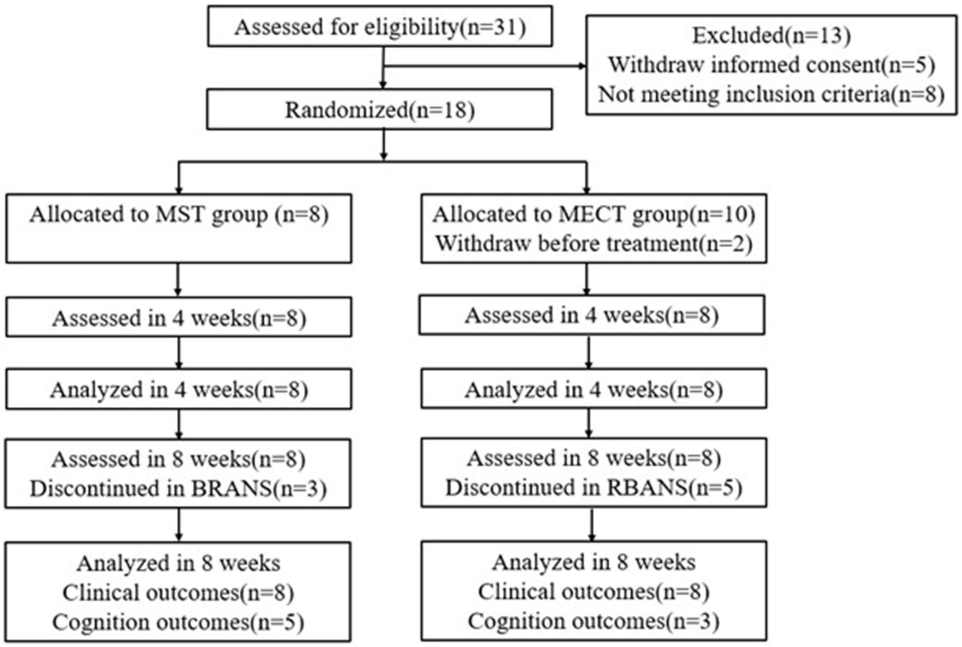

Figure 1 CONSORT chart for MST/MECT participant flow, allocation, and randomization. Adapted from Schulz KF, Altman DG, Moher D for the CONSORT Group (2010). CONSORT 2010 Statement: Updated Guidelines for Reporting Parallel Group Randomised Trials. *PLoS Med.* 2010;7(3): e1000251. Creative Commons.

Table 1 Demographic and Clinical Characteristics of MST Group and MECT Group

	MST (N=8)	MECT (N=8)	F/χ^2	p
Age (years)	35.50±11.45	37.25±9.92	0.147	0.749
Sex (M/F)	6/2	4/4	1.067	0.302
Education (years)	12.50±3.07	10.88±3.64	0.122	0.351
Illness duration	14.13±6.42	14.63±8.47	0.227	0.896
Clozapine plasma Concentration (ng/mL)	421±229.39	531.42±423.91	4.506	0.589
Chlorpromazine equivalent dose(mg)	371.43±50.89	331.25±69.11	0.771	0.228
PANSS-total	97.00±21.67	89.37±15.11	2.388	0.428
PANSS-P	26.37±6.23	24.25±4.86	0.130	0.460
PANSS-N	26.00±8.54	22.00±7.54	0.171	0.337
PANSS-G	44.88±11.27	43.13±7.02	3.608	0.715
CGI-SI	5.14±0.90	4.86±0.90	0.000	0.563

Notes: Values are presented as Mean (SD).
Abbreviations: PANSS, Positive and Negative Syndrome Scale; CGI-SI, Clinical Global Impression-Severity.

Demographic and Clinical Characteristics

Thirty-one patients were screened, eighteen clozapine-resistant patients were eventually recruited. All the participants were randomized into two groups (8 patients in the MECT group and 10 in the MST group). Two patients of the MST group were excluded from the final analysis: one patient was excluded because of the brain tumor after the MRI scan; another patient dropped out because of unwilling to continue hospitalization for financial reason. The demographic and clinical characteristics of the participants are detailed in Table 1. There were no significant differences in age, gender, education or PANSS score at the baseline between the two groups. All the patients were being treated with clozapine until the end of the experiment.

Comparison in Clinical Outcomes

All the 16 patients completed the 10 sessions of the MECT/MST. Repeated measurement analysis of variance was used to analyze the total score and various subscales of PANSS in two groups. However, there was no statistically significant difference in the main effects of inter-group variables in PANSS total score and subscale scores ($p>0.05$). The interaction between intra-group and inter-group variables of PANSS negative scores is significant ($F=5.308$, $p=0.014$). The main effect of the intra-group variable of PANSS positive score is significant ($F=12.775$, $p<0.001$) (Figure 2). Further paired *t*-tests were performed on both groups before and after treatment. After 4 weeks of intervention, the total PANSS score ($p=0.009$), positive PANSS score ($p=0.026$), negative PANSS score ($p=0.031$), and general pathological PANSS score ($p=0.023$) in the MST group significantly decreased. The total PANSS score ($p=0.049$) and positive PANSS score ($p=0.037$) were still significantly reduced during the follow-up evaluation period compared to baseline. For the MECT group, the total PANSS score ($p=0.035$) and PANSS positive score ($p=0.001$) significantly decreased after 4 weeks of intervention. The effect of PANSS positive score ($p=0.041$) continued until 8 weeks of follow-up (Figure 2 and Figure 3). Direct comparisons between MECT and MST did not reveal any significant changes in psychotic symptoms.

As for the D-value of the ΔPANSS score, it showed that there was no significant difference in the ΔPANSS score between the two groups at the end of treatment. However, at the 8-week follow-up evaluation period, the negative ΔPANSS score of the MST group was significantly greater than that of the MECT group ($p=0.042$).

Comparison in Cognition Outcomes

Five participants of the MST group and three participants of the MECT group were capable of receiving the RBANS at the baseline. The remaining eight participants failed to perform the tests due to their marked psychotic symptoms. Paired *t*-tests were conducted on the two groups, and there was no statistically significant difference in cognitive scores before and after treatment ($p> 0.05$). The MECT group showed marginal impairment in immediate memory ($p = 0.069$). The

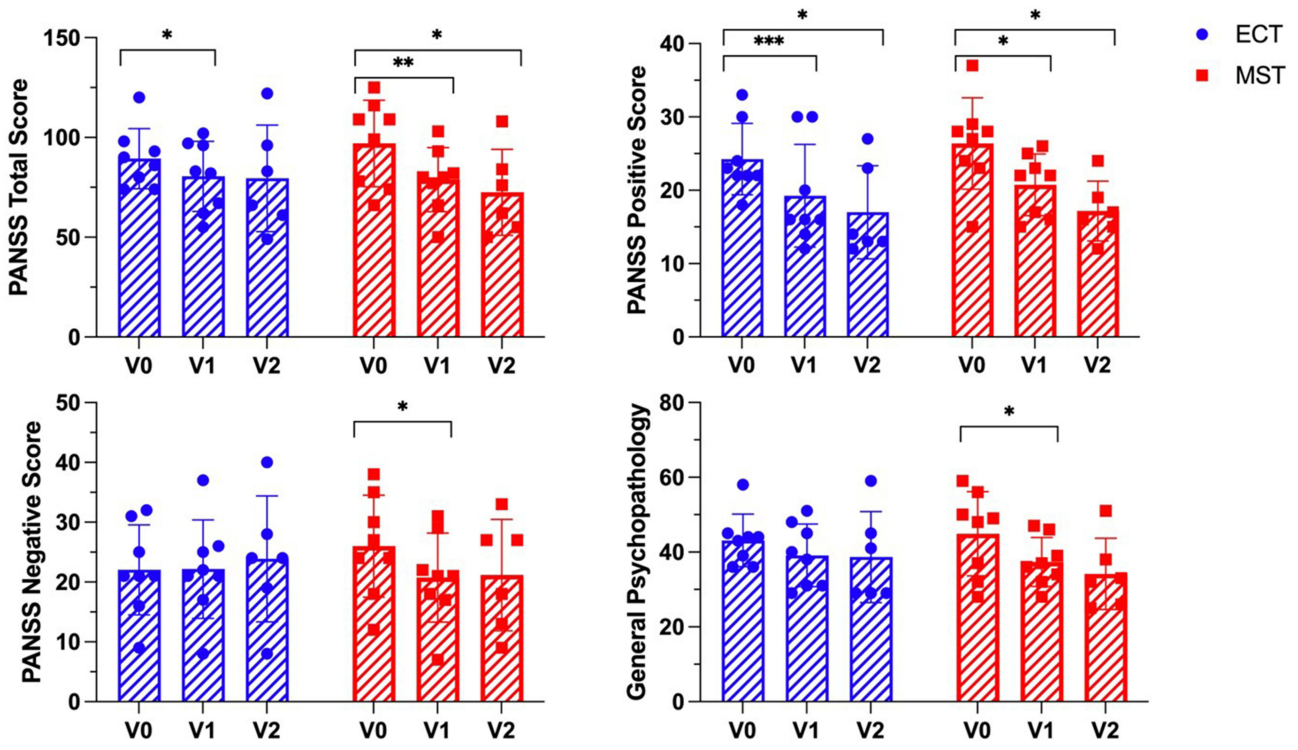

Figure 2 Changes of PANSS scores pre- (V0) and post- (V1: week 4, V2: week 8) within the two groups. Each dot represents one subject. PANSS, Positive and Negative Syndrome Scale; ***p = 0.001, **p < 0.01; *p < 0.05.

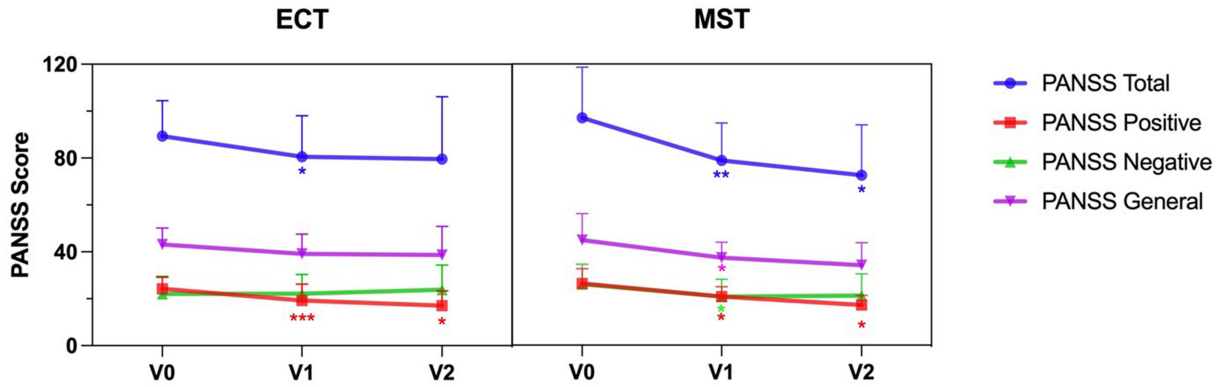

Figure 3 PANSS score changes with time in MECT/MST groups (V0: before intervention; V1: at the end of the treatment; V2:8-weeks follow-up); ***p=0.001; **p<0.01; *p<0.05.

independent sample *t*-test showed that the baseline MST group had significantly lower attention scores than the MECT group (p=0.001), and at the end of treatment, the MECT group had significantly lower immediate memory scores than the MST group (p=0.030) (Figure 4).

Discussion

There have been multiple comparative studies on the efficacy and cognitive impact of MST and MECT in patients with refractory depression, confirming the feasibility of MST as an alternative treatment for MECT.[23,29,30] However, the safety and effectiveness of MST in treating schizophrenia, especially CRS, has not yet been significantly identified. This study is an open label, randomized, parallel controlled clinical trial that compares the efficacy and cognitive adverse reaction of MST and MECT for patients with CRS for the first time. The results showed that MST can significantly improve

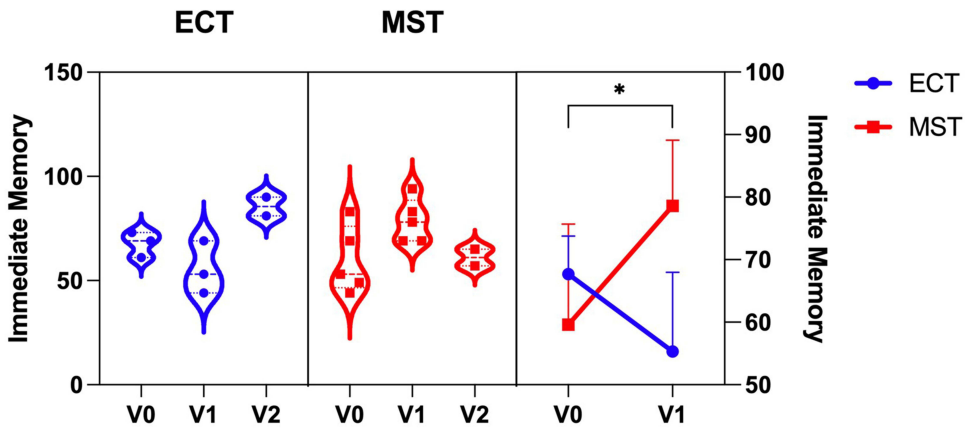

Figure 4 Changes of immediate memory scores pre- (V0) and post- (V1: week 4, V2: week 8) within the two groups. Each dot represents one subject. *p < 0.05.

psychiatric symptoms in the acute phase as MECT. Especially MST has unique therapeutic advantages in negative symptoms and cognition.

There are indications that ECT may enhance the response to antipsychotics, and combination with antipsychotics is superior to that of antipsychotics treatment alone. The combination with clozapine is particularly supported by evidence.[31] Our study also indicated that the combination of clozapine and MECT can significantly improve the positive symptoms of CRS patients, supporting the effectiveness of MECT enhanced antipsychotic effect in CRS. The CRS patients also showed significant improvement in positive symptoms in the following 4 weeks, which indicates that not all patients require MECT maintenance treatment that consistent with previous reports.[32] A study has found that there is a positive correlation between changes in gray matter volume in the right parahippocampal gyrus/hippocampus and positive scores on the PANSS scale. This suggests that ECT may induce brain plasticity through changes in gray matter volume, possibly targeting the marginal brain regions to improve positive symptoms in patients with schizophrenia.[33] In our study, MST showed comparable efficacy in improving positive symptoms to MECT, demonstrating significant acute-phase treatment effects and maintaining efficacy 4 weeks after treatment. In previous studies, a 25 hz MST significantly reduced the total PANSS score and positive symptom score.[34] This study experimented a higher magnetic stimulation frequency, confirming that a 100 hz MST is equally effective for positive symptoms. Study in refractory depression patients showed that 100 hz MST affects regional brain glucose metabolism and may exert therapeutic effects through the limb-cortical pathway.[35] Neurobiological research on schizophrenia also found anatomical and functional abnormalities in the limbocortical structure,[36] which may provide an explanation for the therapeutic mechanism of MST in schizophrenia.

As we know that most antipsychotics are used to release positive symptoms, and the treatment of negative symptoms is very difficult, which largely causes damage to health, social function, and life treatment.[37,38] Previous studies have shown that ECT add-on therapy hardly reduces PANSS negative symptom scores.[39–41] Our study is consistent with most studies, which suggest that the combination of clozapine and MECT therapy does not lead to improvement in negative symptoms in CRS patients. However, the decrease in PANSS negative scores after MST intervention reflects the improvement of negative symptoms in CRS patients during the acute phase of MST treatment, and the treatment effect even extends to 4 weeks after the end of treatment. This discovery is exciting, but the experimental sample size is small and this result needs to be repeated in larger samples. Negative symptoms of schizophrenia are related to changes in prefrontal cortex activity, suggesting that electric stimulation on the prefrontal cortex may be an effective treatment for negative symptoms.[42] Compared with the extensive stimulation of ECT, MST is more concentrated, inducing seizures locally in the prefrontal cortex,[43] which may be used to explain the effect of MST on negative symptoms.

Studies have confirmed that high-frequency rTMS can significantly release the negative symptoms of schizophrenia,[44–46] and there have been reports of delayed effects on the improvement of negative symptoms.[47] This is the first report on the improvement of negative symptoms by MST. An fMRI study showed that patients receiving

10 hz rTMS in the left dorsolateral prefrontal cortex had an increased volume in the left hippocampus, parahippocampal gyrus and precuneus, which predicted improvement in negative symptoms compared to pseudo stimulation.[48] As a result, researchers believed that the heterogeneity of the clinical response of negative symptoms of schizophrenia to high-frequency rTMS may be related to the plasticity of brain structures, especially the left hippocampus and precuneus. Researchers also found that high-frequency bilateral prefrontal rTMS may influence Glx concentration in the prefrontal cortex of patients with schizophrenia, observing an increase of Glx concentration in the active treatment group and a decrease of Glx concentration in the sham group.[49] Therefore, they concluded that high-frequency rTMS may increase metabolism in the prefrontal cortex and may be a potential neural mechanism of rTMS. MST is a modified magnetic therapy with higher frequency and intensity based on rTMS, which may also have a specific therapeutic effect on negative symptoms. The underlying neural mechanism may be related to the above factors.

When considering ECT, the first thing that comes to mind is its cognitive side effects. This study used RBANS to test the cognitive function changes before and after treatment. It was found that neither ECT nor MST showed significant cognitive deterioration after acute-phase treatment. This is consistent with the results of MST treatment for depression, and there is no evidence to suggest any cognitive impairment in patients after 100 hz MST treatment.[29] Animal experiments have confirmed the neurocognitive safety of MST, attributed to its concentration effect, particularly highlighting the potential role of the hippocampus. Electrophysiological studies of animal models have shown that the current and epileptic seizures caused by MST are mainly located in the targeted surface cortical areas, and rarely spread to deep brain structures such as the hippocampus, providing evidence to support the hypothesis.[50–52] Compared with MST, MECT showed poorer immediate memory in our study. The immediate memory score in the RBANS test comes from two sub tests: vocabulary learning and story recall, which are scored based on the number of repeated words and the number of key words in the story, mainly reflecting the short-term memory ability after obtaining information. Short term memory is an important result of the evolution of the human cognitive system and plays an important role in language processing and language information learning.[53] Recent evidence suggests that short-term memory requires coordination of multiple brain regions, and damage to the hippocampus can affect the coordination.[54] Our results support the view that the impact of MST on temporal lobe, especially hippocampal function, is smaller than that of MECT, consistent with the evidence of local brain current distribution in previous studies.

In this study, none of the patients reported serious adverse events. Two participants reported adverse reactions to headache or dizziness and recovered in a few hours. There were no clinically significant changes in electrocardiogram and blood indicators, which provides evidence support for the clinical application of MST and MECT in CRS patients.

There are some limitations of the study as follows. Firstly, the small sample size, especially who completed the cognitive measurements is small. Some negative results, such as no significant cognitive differences, may be due to Class II errors caused by small sample sizes. Given the strong clinical heterogeneity of small samples, it will be crucial to replicate these effects in larger samples in the future. Secondly, this study is an open label study without pseudo stimulus control, and the significant clinical improvement in the research results may be due to the overestimation of actual effects brought about by open labels. Finally, the follow-up period of this study is 8 weeks, and more long-term follow-up can be conducted in the future.

Conclusion

Noninvasive neurostimulation with MST or MECT may equally improve the positive symptoms of CRS, while MST was more effective in the negative symptoms. MST demonstrated evidence for negligible cognitive side effects, with less effect on immediate memory than MECT. Further study in larger clinical populations is needed.

Data Sharing Statement

The authors confirm that the data supporting the findings of this study are available within the article. The data are not publicly available due to ethical restrictions.

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Disclosure

The authors report no conflicts of interest in relation to this paper.

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