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Original Article

The effects of high-frequency repetitive transcranial magnetic stimulation on auditory hallucinations and working memory among patients with schizophrenia

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Abstract

Background and aims: Schizophrenia is one of the most complicated psychiatric disorders. Some afflicted patients show resistance to routine treatments. Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive brain stimulation technique with the potential to reduce symptoms among patients with schizophrenia. The aim of this study was to evaluate the effects of high-frequency rTMS on auditory hallucinations and working memory among patients with schizophrenia.

Methods: This experimental study was conducted using a pretest-posttest controlled design. The statistical population of the study consisted of all patients with schizophrenia and auditory hallucinations who referred to the outpatient psychiatric emergency department of Imam Hossein hospital, Tehran, Iran, in 2019. In total, twelve eligible patients were recruited through convenience sampling and randomly allocated to a control and an intervention group. Participants in the intervention group individually received rTMS in ten sessions, while their counterparts in the control group received no intervention during the study. Data were collected using the diagnostic interview, the screening questionnaire for rTMS, the Positive and Negative Syndrome Scale for schizophrenia, the Varieties of Inner Speech Questionnaire, and the Working Memory Measure. Data analysis was performed using univariate and multivariate analyses of covariance.

Results: The posttest mean score of auditory hallucination in the intervention group was significantly less than the control group, while the posttest mean score of working memory in the intervention group was significantly greater than the control group ($P<0.05$).

Conclusion: This study suggests the effectiveness of rTMS in significantly reducing auditory hallucinations and improving working memory among patients with schizophrenia.

Keywords: Repetitive transcranial magnetic stimulation, Auditory hallucinations, Working memory, Schizophrenia

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Introduction

Schizophrenia is one of the most bizarre and most complicated psychiatric disorders. It is characterized by severe alterations in perception, thinking, action, self-concept, and interpersonal communications (1). The symptoms of schizophrenia include paranoia, strange delusions, auditory hallucinations, disordered thinking and speech, and agitation (2).

Hallucination is one of the most annoying symptoms of schizophrenia for patients and their significant others. Hallucination has different types including auditory, visual, and tactile. Auditory hallucination, characterized by hearing sounds in the brain, is so prevalent that is considered as the main criteria for schizophrenia diagnosis (3). A hypothesis suggests that inner speech can be a major cognitive source for auditory hallucinations. Inner speech is a cognitive process with roles in auditory hallucinations and executive function and has relationship with working memory (4), planning (5), inhibition (6), and cognitive flexibility (7). Patients with schizophrenia experience alterations in cognitive functions such as speech perception, memory, planning, and attention. They usually talk with themselves or hear sounds in the brain (8). Evidence also shows alteration in working memory as a common characteristic of schizophrenia (9). By definition, working memory is the ability to keep information in the mind up to the end of an activity and is considered as a mental system for storing and processing information needed for a series of complex cognitive tasks (such as understanding and learning) (10).

Around 20%–30% of patients with schizophrenia and auditory hallucinations show resistance to routine treatments. Therefore, noninvasive brain stimulation techniques such as repetitive transcranial magnetic

stimulation (rTMS) have been used in recent years to manage auditory hallucinations among these patients. These techniques have potential positive effects on cognitive deficit among patients with auditory hallucinations (11). A meta-analysis showed that high-frequency rTMS improved cognitive function among patients with auditory verbal hallucinations (12). Moreover, a study reported the effectiveness of rTMS in significantly improving working memory and alleviating mood symptoms among patients with bipolar disorder (13). Another meta-analysis revealed that through affecting the left hemisphere of the brain, rTMS reduces medication-resistant auditory hallucinations and can be considered as an effective treatment option for afflicted patients (14). Similarly, several studies found the effectiveness of rTMS in significantly reducing auditory hallucinations and inner speech and improving working memory among patients with schizophrenia (9-15). The aim of this study was to evaluate the effects of high-frequency rTMS on auditory hallucinations and working memory among patients with schizophrenia.

Methods

This experimental study was conducted using a pretest-posttest controlled design. The statistical population of the study consisted of all patients with schizophrenia and auditory hallucinations who referred to the outpatient psychiatric emergency department of Imam Hossein hospital, Tehran, Iran, in 2019. Sampling was performed conveniently. Inclusion criteria were an age of 20–45 years, an intelligent quotient of more than 80, definite diagnosis of auditory verbal hallucinations according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), medication resistance determined by treatment failure with at least two different psychiatric medications (including at least one atypical medication), normal intracranial pressure, no instability in health status, no history of drug abuse, no serious medical disorder (such as cardiovascular disease or epilepsy), no risk of post-rTMS convulsion due to medical or neurological disorders, no pregnancy, no history of neurosurgery or cerebral injuries or disorders, no comorbid psychiatric disorder, and consent for participation. Patients were not included if they had metal medical instruments in the body such as cochlear implants, brain stimulation implants, vascular stents, and fracture fixation implants, due to the possibility of electrical damage during rTMS. In total, twelve eligible patients were selected and randomly allocated to a control (n = 6) and an intervention (n = 6) group.

Data collection instruments

Diagnostic interview

Diagnostic interview based on the DSM-5 criteria was used to determine and select eligible patients.

The screening questionnaire for rTMS

This questionnaire was used to select patients with low risk of rTMS (16).

The Positive and Negative Syndrome Scale for schizophrenia

This scale has thirty items in five subscales, namely negative symptoms (eight items), positive symptoms (six items), disorganization (seven items), excitement (four items), and depression and anxiety (five items). Items were scaled on a five-point scale as follows: 1: "Absent"; 2: "Mild"; 3: "Moderate"; 4: "Severe"; and 5: "Extreme". This scale was developed by Kay et al in 1990 for the comprehensive assessment of schizophrenia symptoms. In psychometric evaluation through factor analysis, Kay et al administered the scale to 240 patients with schizophrenia and found that the scale had two main factors, namely positive and negative syndromes which explained 36.1% of the total variance (17). The Cronbach's alpha of the scale in this research was 0.85.

Varieties of Inner Speech Questionnaire

This self-report questionnaire was developed in 2011 by McCarthy-Jones and Longden for assessing inner speech, disorganization, and different hallucinations (18) and was psychometrically evaluated by Alderson-Day et al in 2018 in the United Kingdom. McCarthy-Jones and Longden showed that inner speech had evaluative/motivational burden while the presence of other people in inner speech had positive relationship with anxiety. Moreover, they reported that susceptibility to auditory hallucinations had positive relationship with internal dialogue in inner speech. The questionnaire has eighteen items in four dimensions, namely self-talk, evaluative/motivational characteristics, condensed inner speech, and presence of other people in inner speech. Items are scaled on a six-point Likert scale from 1 ("Certainly does not apply to me") to 6 ("Certainly applies to me"). All dimensions have Cronbach's alpha values greater than 0.80 and test-retest correlation coefficients greater than 0.60 (19). The revised version of the questionnaire has 35 items and has Cronbach's alpha values greater than 0.80 (20). The Cronbach's alpha of the questionnaire in the present study was 0.87.

The Working Memory Measure

This test was developed by Daneman and Carpenter in 1980. It has 27 items in six two-, three-, four-, five-, six-, and seven-sentence parts. Each part has relatively difficult sentences which are irrelevant to each other. Sentences were read for participants and they were asked to listen to the sentences and then, determine their semantic accuracy (for assessing processing capacity) and write the last word of each sentence (for assessing storage capacity). Previous studies reported strong correlation between the score of this test and the scores of reading comprehension tests such as the scholastic aptitude test (r = 0.59) and tests involving fact retrieval (r = 0.72) and pronominal reference (r = 0.90) (6-8).

Intervention: high-frequency rTMS

Study intervention was high-frequency rTMS implemented in 10 sessions using an rTMS device. In rTMS, electromagnetic fields are used to affect the electrical activity of the brain. The electromagnetic field produced by the electromagnetic coil of the rTMS device passes the cranium and provides a strong and pain-free focal stimulation or inhibition to a small part of the brain (21). The rTMS device produces pulses with frequencies of 1–100 Hz. The stimulating or inhibitory effects of the pulses depend on their frequency. Pulses with low frequency have inhibitory effects, while pulses with high frequency have stimulating effects on neurons. Moreover, the effects of rTMS vary according to the characteristics of each patient. Although the mechanism of action of rTMS is not well known, some evidence suggests that rTMS exerts its effects through affecting neurotransmitters and neuron plasticity (21).

Results

The results indicated that all subjects in the study were male. The mean age of the intervention group was 35 ± 3.16. The mean age of the control group was 37 ± 1.21. The independent *t* test showed that the two groups were similar in terms of the desired variable. Also, 35% of the intervention group had under graduate and university education. In the control group, 35.5% had under graduate and university education. 20% of the intervention group were employed and 25% of the control group were also employed. Statistical tests showed that the two groups were not significantly different in terms of gender, level of education and occupation.

Table 1 shows the pretest and the posttest mean scores of auditory hallucinations and working memory. As

Table 1. The pretest and posttest mean scores of auditory hallucinations and working memory in the control and the intervention groups (n = 12)

Variables	Time	Groups	Mean	Standard deviation
Auditory hallucinations	Pretest	Intervention	93.42	18.12
		Control	94.20	17.33
	Posttest	Intervention	78.57	16.13
		Control	93.55	17.61
Working memory	Pretest	Intervention	11.24	6.75
		Control	11.82	4.02
	Posttest	Intervention	21.33	8.13
		Control	12.40	3.97

Table 2. The assumption of linearity between the pretest and the posttest mean scores of auditory hallucinations and working memory

Variables	Sums of squares	Df	Mean square	F	*P* value
Auditory hallucinations	19.352	2	9.676	1.265	0.098
Working memory	19.164	2	9.582	1.153	0.035

Table 3. The results of the Levine's test for the equality of variances

Variables	Levine's statistics	Df1	Df2	*P* value
Auditory hallucinations	1.452	1	38	0.302
Working memory	0.041	1	38	0.524

Table 2 shows, the relationship between the pretest and the posttest mean scores of auditory hallucinations and working memory was significant ($P < 0.05$). Thus, the linearity assumption was met.

The results of the Levene's test were insignificant ($P > 0.05$; Table 3), confirming the equality of variances before the intervention.

As Table 4 shows, the results of the multivariate analysis of covariance revealed significant between-group difference respecting the posttest mean score of at least one of the dependent variables ($P < 0.05$). Univariate analysis of covariance indicated that the study groups differed significantly from each other respecting the posttest mean scores of both auditory hallucinations ($F = 302.251$, $P = 0.001$) and working memory ($F = 1069.574$, $P = 0.001$) (Table 5).

Discussion

Study findings showed significant between-group differences respecting the posttest mean scores of auditory hallucinations and working memory which confirm the effectiveness of the high-frequency rTMS intervention in significantly reducing auditory hallucinations and improving working memory. In line with these findings, several earlier studies reported that rTMS significantly reduced auditory hallucinations and inner speech among patients with schizophrenia (4,5,7,9,22,23). Recent studies detected a region in the brain which contributes to the production of sounds among patients with schizophrenia and auditory hallucinations and reported that rTMS helped reduce the severity of auditory hallucinations among these patients (21). Auditory verbal hallucinations among patients with schizophrenia have different types. They are usually confusing and threatening and may be difficult to be differentiated from reality. Patients may hear one or several sounds which continuously criticize them. These sounds may be even the sounds of a dead relative or friend.

Study findings showed that the posttest mean score of working memory in the intervention group was significantly higher than the control group. Several earlier studies also showed the same finding (24-26). For example, a study showed that rTMS significantly improved working memory among young and older adults (19). Another study also showed that low-frequency rTMS slightly improved working memory among patients with Alzheimer's disease (12). The positive effects of rTMS on working memory may be due to the long-term potentiation mechanism, in which strong synaptic activity leads to strong synaptic transmission. Long-term

Table 4. The results of multivariate analysis of covariance for the posttest mean scores of auditory hallucinations and working memory

Effect	Value	F	Hypothesis df	Error df	*P* value	Eta squared
Pillai-Bartlett trace	0.973	603.284	3	34	0.0001	0.421
Wilks' lambda	0.027	603.284	3	34	0.0001	0.358
Hotelling-Lawley trace	35.487	603.284	3	34	0.0001	0.392
Roy's largest root	35.487	603.284	3	34	0.0001	0.403

Table 5. The results of univariate analysis of covariance for the posttest mean scores of auditory hallucinations and working memory

Source	Variables	Sum of squares	df	Mean square	F	*P* value	Eta squared	Power
Group	Auditory hallucinations	1574.625	1	1574.625	302.251	0.001	0.425	0.98
	Working memory	2540.951	1	2540.951	1069.574	0.001	0.547	0.99

potentiation is a well-accepted model of neural flexibility and is a fundamental assumption of learning and memory. In fact, it is a powerful technique for enhancing the effects of other interventions such as medication therapy. The other explanation for the positive effects of rTMS is mood improvement which is in turn associated with improved cognitive function. Previous studies reported that therapeutic interventions have positive effects on cognitive problems among patients with mood disorders (27). Of course, some scholars believe that rTMS independently improves the different aspects of cognitive function.

Conclusion

This study concludes that high-frequency rTMS is effective in significantly reducing auditory hallucinations and improving working memory among patients with schizophrenia. Given the serious side effects of psychiatric medications for patients with auditory hallucinations and impaired working memory, rTMS is recommended to improve treatment outcomes and reduce the need for medication therapy among these patients. Of course, further studies are still needed to provide firmer evidence respecting the effects of rTMS.

Authors' contribution

All authors significantly contributed to designing and conducting the study and drafting the manuscript.

Conflict of Interests

None is declared.

What does this paper contribute to the wider global clinical community?

- High-frequency rTMS is effective in significantly reducing auditory hallucinations and improving working memory among patients with schizophrenia.
- Psychiatrists and neurologists are recommended to consider rTMS for treating patients with schizophrenia and auditory hallucinations and thereby, reduce their symptoms and improve their personal, familial, and social health.

Ethical Approval

This study was approved by the Ethics Committee of Shahid Chamran University, Ahvaz, Iran (code: EE/99.3.02.133337/scu.ac.ir). Participants were ensured of their freedom to unilaterally withdraw from the study and the confidentiality of their information. Informed consent was obtained from all participants.

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