Efficacy of repetitive transcranial magnetic stimulation in drug-resistant schizophrenics

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Background
Despite the advances in pharmacological treatment of schizophrenia, the results are unsatisfactory. Therefore, the search for new antipsychotic drugs and the development of novel treatments for schizophrenia are critical. Transcranial magnetic stimulation is one of the tools that may help schizophrenic patients.

Aim of the study
To evaluate the efficacy of repetitive transcranial magnetic stimulation (r-TMS) in the treatment of drug-resistant schizophrenic patients.

Patients and methods
This study included 40 drug-resistant schizophrenic patients. In a random, double-blind placebo-controlled study, 30 patients were treated by 15 r-TMS sessions to both the left dorsolateral prefrontal cortex and the left temporoparietal cortex for 3 weeks. Ten patients were randomly subjected to sham stimulation (placebo group). Before and after the treatment sessions, all patients were assessed using the Positive and Negative Syndrome Scale, the Calgary Depression Scale for Schizophrenia, and cognitive tests.

Results
r-TMS could significantly improve only the negative symptoms. The positive symptoms, general psychopathology, and cognitive functions did not show any significant changes. The sham (placebo group) did not show any significant changes in schizophrenic symptoms and cognitive functions.

Conclusion
r-TMS can be a useful add-on treatment that helps to improve negative schizophrenic symptoms in drug-resistant patients.

Keywords:
negative syndrome, resistant schizophrenics, transcranial magnetic stimulation

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Introduction

Treatment for schizophrenia remains unsatisfactory. Current available antipsychotic drugs leave many symptoms of the illness untreated and induce unacceptable side effects, high rate of intolerability, metabolic side effects, and early discontinuation (Stone and Pilowsky, 2007; Cipriani *et al.*, 2009). Estimates indicate that 20–45% of schizophrenia patients respond only partially to antipsychotic agents and 5–10% of them are totally nonresponsive (Pantelis and Lambert, 2003).

Patients with treatment-resistant schizophrenia tend to have prominent negative and cognitive symptoms. These nonresponsive symptoms over multiple schizophrenia dimensions pose a significant burden on the patients and their caregivers. Clozapine, the best choice for the treatment of refractory symptoms of schizophrenia, fails to achieve remission in some cases. One-third of patients whose previous pharmacological treatment failed also show incomplete responses to clozapine. Therefore, the development of new treatment options is necessary and worth investigating (Paton *et al.*, 2007; Oh and Kim, 2011).

Repetitive transcranial magnetic stimulation (r-TMS) is a safe and a noninvasive method of changing neuronal activity in the cerebral cortex, using electric currents induced by magnetic fields (Wassermann and Lisanby, 2001). It is believed to work by modifying cortical excitability, with high-frequency or fast r-TMS (5–20 Hz) exerting an activating effect on neuronal circuits and slow r-TMS (1 Hz) exerting an inhibitory effect (Haraldsson *et al.*, 2004; Saba *et al.*, 2006).

Studies suggest that repetitive r-TMS may be useful in the treatment of refractory auditory hallucinations. Applied at a low frequency (1 Hz) to the left temporoparietal cortex (TPC), it has been shown to reduce the frequency, attentional salience, and loudness of auditory hallucinations (Hoffman *et al.*, 2000, 2005; Fitzgerald *et al.*, 2005).These studies are based on the ability of r-TMS to decrease cortical excitability and thus reduce regional overactivity associated with auditory hallucinations (Chen *et al.*, 1997; Wassermann and Lisanby, 2001). Hoffman *et al.* (2000, 2005) show that repeated sessions of 1 Hz r-TMS delivered to the left temporoparietal area suppressed auditory hallucinations, in some cases for weeks after stopping treatment.

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There is evidence showing that r-TMS can be considered an effective treatment option for negative symptoms of schizophrenia. Freitas *et al.* (2009) found that the effect of high-frequency r-TMS in the treatment of negative symptoms of schizophrenia seems to be mild to moderate. To date, r-TMS has been more successful in the treatment of refractory auditory hallucinations than for negative symptoms (Stanford *et al.*, 2011).

Neither the European Medicines Agency nor the Food and Drug Administration has approved r-TMS for the treatment of negative symptoms of schizophrenia (Prikryl and Kucerova, 2013).

Aim of the study

The aim of the present study is to evaluate the efficacy of r-TMS in the treatment of drug-resistant schizophrenic patients.

Patients and methods

The present study included 40 men, right-handed patients meeting the *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed., Text Revision, criteria for schizophrenia (American Psychiatric Association, 2000). Schizophrenia was diagnosed using the Mini International Neuropsychiatric Interview (Sheehan *et al.*, 1998). This interview was translated and validated into Arabic by Ghanem *et al.* (1999). They attended the psychiatry outpatient and inpatient services of Tanta University Hospitals (Egypt) from August 2010 to April 2012.

All patients were drug resistant. Treatment-resistant schizophrenia can be defined on the basis of little or no symptomatic response to multiple (≥ 2) antipsychotic trials of an adequate duration (≥ 6 weeks) and at a therapeutic dose range (Lehman *et al.*, 2004). All the patients studied were on their medication during the study.

Thirty patients completed the course of real r-TMS. Ten patients were randomly (one every three patients) chosen for sham stimulation (as a placebo group). The TMS was performed by a psychiatrist who was completely blinded to the clinical data of the patients.

The exclusion criteria were patients with a previous history of neurological disease (including seizure) or head trauma, internal electrical devices, an unstable medical condition, unable to provide informed consent, or difficulty communicating because of cognitive dysfunction, mental retardation, current substance abuse, or dependence. Patients with a history of electroconvulsive therapy in the last 6 months were excluded. Illiterate individuals were excluded as they cannot complete the cognitive evaluation.

The study was carried out independent of any institutional influence and was not funded. After approval of the study by the Ethical and Research Committee of Tanta University, Faculty of Medicine, the study procedures were explained to the patients and written consent was obtained. The study procedures were explained and written consent was obtained.

Clinical assessment

All patients were assessed before and after treatment using the Positive and Negative Syndrome Scale (PANSS) (Kay *et al.*, 1987), the Calgary Depression Scale for Schizophrenia (CDSS), and cognitive tests.

PANSS (Kay *et al.*, 1987) was designed to measure the severity of psychopathology in adult patients with schizophrenia, schizoaffective disorder, and other psychotic disorders. The theoretical frame for the construction of the PANSS was the assumption of two distinct subtypes of schizophrenia. Type I is characterized by florid (positive) symptoms such as delusions or hallucinations and type II is characterized by deficit (negative) symptoms such as blunted affect or social withdrawal. The scale distinguishes three dimensions: seven items constitute a positive subscale, seven items constitute a negative subscale, and 16 items constitute a general psychopathology subscale. Each symptom is rated on a seven-point scale (from 1 to 7), with scores ranging from 7 to 49 for the PANSS and from 16 to 112 for the General Psychopathology Scale.

The presence of depression among schizophrenic patients was assessed using the CDSS. The scale is a nine-item structured interview scale developed by Addington *et al.* (1990) to assess depression in schizophrenics. This scale seems to achieve a useful degree of separation between the measures of depressive, negative and extrapyramidal symptoms in patients with schizophrenia (Addington *et al.*, 1994). All patients had a total CDSS score PANSS of 6 or less to avoid the presence of depression among the patients studied (all patients with a CDSS score >6 were excluded).

Cognitive assessment

Trail making test B

This is a measure of visual conceptual and visual motor tracking skills focusing on divided attention, ability to shift, and mental flexibility (Reitan, 1992).

Benton Visual Retention Test

The Benton Visual Retention Test assesses visual perception, visual memory, and visual constructive abilities (Benton, 1992).

Wechsler Adult Intelligence Test

A comprehensive test of cognitive ability using subscales of general knowledge, similarities, picture completion, and block design. The intelligence quotient score of the four subscales was used (Melika, 1987).

Protocol for repetitive transcranial magnetic stimulation

Thirty patients were treated by real r-TMS and 10 patients were subjected to sham stimulation as a control (placebo) group.

To deliver the r-TMS, we used a Magstimrapid2 TMS machine (Magstim Ltd, Whitland, Wales) and a figure-of-eight coil (diameter of each wing 70 mm, peak magnetic field 2.2 T). At baseline, we assessed each patient's motor threshold using the visualization of movement method, defining motor threshold as the lowest stimulation intensity capable of inducing a visible finger movement by the abductor pollicis brevis in at least half of 10 primary motor

cortex stimulations (Pridmore *et al.*, 1998). We localized the areas for stimulation using the international 10–20 system defining the left dorsolateral prefrontal cortex (DLPFC) as F3 and the left TPC as the midpoint between T3 and P3. All patients underwent 15 sessions of r-TMS for 3 weeks, with five consecutive sessions at 2-day intervals. Initially, we provided patients stimuli with intensities of 80% of their individual motor thresholds and increased it up to 100% if the patient did not complain of an intolerable tingling sensation in the scalp. Each session consisted of 40 trains starting every 30 s: 20 trains of 10 Hz r-TMS to the left DLPFC with a 3-s duration and 20 trains of 1 Hz r-TMS to the left TPC with a 30-s duration (totaling 9000 pulses at high frequency and 9000 pulses at low frequency during the trial). This method comprised two consecutive modes of stimulation: high-frequency stimulation to the left DLPFC and low-frequency stimulation to the left TPC (Chen *et al.*, 1997; Chouinard *et al.*, 2003).

The ineffectiveness of the sham r-TMS was ensured by adjusting the location of the stimulation coil. It formed an angle of 90° against the surface of the head, which was sufficient to prevent stimulation of the brain cortex. Blinding of patients was also ensured using a background sound that occurs during the real stimulation.

Statistical analysis

All data were recorded, tabulated, and analyzed on SPSS (version 17; SPSS Inc., Chicago, Illinois, USA). Descriptive statistics were obtained as means and SD. Student's *t*-test was used for independent data. Qualitative data were analyzed using Pearson's χ^2-test. *P*-value was used to indicate the level of significance. A *P*-value less than 0.05 was considered significant.

Results

The age of the studied patients ranged between 24 and 51 years (mean ± SD = 38.5 ± 8.26). There was no significant difference between the r-TMS group and the sham group in terms of age ($t = 0.97$, $P = 0.35$). The duration of the illness among patients was 5.11 ± 2.53 years. There was no significant difference between the two groups in the duration of the schizophrenic illness ($t = 0.69$, $P = 0.5$). Also, the number of hospitalizations among the two groups was not significantly different ($t = 1.93$, $P = 0.07$). All demographic data are presented in Table 1.

The baseline total PANSS score of patients in the r-TMS group (79.3 ± 14.3) and the placebo (sham) group (76.7 ± 22.5) was not significantly different ($t = 0.34$, $P = 0.77$).

None of the patients reported any serious side effects; only five patients in the r-TMS group reported mild to moderate severity of headache that responded well to analgesics and completed the sessions of treatment.

Response to real repetitive transcranial magnetic stimulation

Among patients of the r-TMS group, the PANSS negative score showed a significant response (20% reduction of symptoms) to active treatment than the sham group ($P = 0.04$). Eleven patients (46.67%) in the r-TMS group showed 20% or more reduction of the score of negative symptoms, whereas only one patient (10%) in the sham group responded to the sessions. The total PANSS score, PANSS positive score, or general psychopathology scores did not show a significant response to r-TMS in comparison with the sham group (Table 3).

The total PANSS score of patients in the r-TMS group was 79.3 ± 14.3 and after r-TMS, it became 72.9 ± 15.6, and the difference was nonsignificant ($t = 1.65$, $P = 0.105$). After r-TMS sessions, the score of positive symptoms did not change significantly ($t = 1.04$, $P = 0.3$); before treatment, it was 19.10 ± 9 and after treatment it was 16.93 ± 7. The score of negative symptoms was significantly ($P = 0.04$) reduced from 22.2 ± 11 to 17 ± 8.46. The score of general psychopathology was reduced by r-TMS from 39.7 ± 8.9 to

Table 1 Demographic data of the studied patients

	r-TMS group (30 patients)	Sham group (10 patients)	*t*	*P*
Age (years)	39.30 ± 7.85	36.10 ± 9.42	0.97	0.35
Duration of illness (years)	5.55 ± 2.17	4.97 ± 2.66	0.69	0.50
Number of hospitalizations	3.07 ± 1.64	1.9 ± 1.66	1.93	0.07

All data are mean ± SD.
r-TMS, repetitive transcranial magnetic stimulation.

Table 2 Effects of repetitive transcranial magnetic stimulation on schizophrenic symptoms and cognitive tests

	Before treatment (mean ± SD)	After treatment (mean ± SD)	*P*
Total PANSS score	79.3 ± 14.3	72.9 ± 15.6	0.11
Positive symptoms	19.10 ± 9	16.93 ± 7	0.3
Negative symptoms	22.2 ± 11	17 ± 8.46	0.04*
General psychopathology	39.7 ± 8.9	36.67 ± 9.6	0.2
Trail making B test	96.9 ± 16.4	92.7 ± 14.8	0.3
BVM number of correct cards	6.73 ± 1.44	6.13 ± 1.46	0.1
BVM number of errors	4.63 ± 1.69	4.10 ± 1.54	0.2
Verbal IQ	85.57 ± 7.69	88.83 ± 9.85	0.2
Performance IQ	89.93 ± 9.73	92.3 ± 10.7	0.4
Full-scale IQ	87.13 ± 8.25	88.03 ± 8.04	0.7

IQ, intelligence quotient; PANSS, Positive and Negative Syndrome Scale.

Table 3 Response to both repetitive transcranial magnetic stimulation and sham stimulation

	r-TMS group (30 patient number) [*n* (%)]	Sham group (10 patient number) [*n* (%)]	*P*
Total PANSS	13 (43.33)	3 (33.33)	0.46
Positive symptoms	8 (26)	1 (10)	0.27
Negative symptoms	11 (46.67)	1 (10)	0.04*
General psychopathology	9 (30)	2 (20)	0.5

PANSS, Positive and Negative Syndrome Scale; r-TMS, repetitive transcranial magnetic stimulation.
*Significant difference $P<0.05$.

36.38 ± 4, and the difference was statistically nonsignificant ($P = 0.2$).

The full scale, verbal, and performance intelligence quotient scores did not change after the use of r-TMS; the difference between scores before and after treatment was not significant ($P>0.05$). Also, the results of both Trail making and Benton visual memory were not significantly changed by r-TMS. Thus, the use of r-TMS did not significantly affect the score of the cognitive tests used (Table 2).

Results of the sham group

The total PANSS score was 76.7 ± 22.5 and after treatment it became 74.9 ± 20.1; the difference was not significant ($t = 0.19$, $P = 0.9$). The score of positive symptoms was 19.4 ± 9.79 before treatment and 15.10 ± 7.64 after treatment. The negative symptoms were 22.80 ± 8.11 and became 18.20 ± 9.76; the general psychopathology score was 40.1 ± 14 and became 37 ± 14.7. The difference between total PANSS and all of the subscale scores was not significant ($P<0.05$). All the cognitive tests were not significantly changed by sham sessions.

Discussion

In the present study, 15 sessions of r-TMS to both the left DLPFC and the left TPC within 3 weeks improved negative symptoms and did not affect other parameters of PNSS in the treatment of drug-resistant schizophrenics.

Oh and Kim (2011) used the same r-TMS protocol as the present study and they found that r-TMS was effective in reducing the total score of PNSS and scores of the positive and negative subscale, whereas the general psychopathology was not significantly changed. The size sample was small (the study included only 10 patients, and only seven patients completed the study) and there was no sham group.

Poulet *et al.* (2005) found that low-frequency r-TMS applied to the left TPC in patients with resistant auditory hallucinations appeared efficient in reducing those symptoms in schizophrenia. The use of r-TMS is associated with reduction of auditory hallucinations with slow TMS over the auditory cortex and an improvement in psychotic symptoms after 2 weeks of high-frequency TMS over the left prefrontal cortex (Rollnik *et al.*, 2000; Hoffman *et al.*, 2005).

As shown by meta-analysis of Freitas *et al.* (2009), low-frequency r-TMS to the left TPC does not seem to be a suitable protocol for the treatment of positive symptoms other than auditory hallucinations. Moreover, these results are in agreement with previously reported meta-analytic findings of the lack of a significant improvement in overall positive symptoms (Aleman *et al.*, 2007). Probably, a major reason for such a poor outcome is the targeted site. Positive psychotic symptoms, other than hallucinations, have been associated with dysfunctions in the orbitofrontal cortex (Baas *et al.*, 2008; Premkumar *et al.*, 2008). Furthermore, altered distribution of the OFC sulcogyral pattern in schizophrenics and a smaller left middle orbital gyrus, strongly associated with worse positive formal thought disorder, have been described recently (Nakamura *et al.*, 2007). A role for the medial temporal lobe in positive psychotic symptoms was also suggested, whereas the lateral temporal cortex is involved in hallucinations (Whalley *et al.*, 2007). This suggests that positive psychotic symptoms, such as delusions, might be better addressed if brain regions other than the TPC are targeted.

Prikryl *et al.* (2007) concluded that augmentation of antipsychotics with a high-frequency stimulation of the left prefrontal cortex with 15 stimulation sessions was effective in reducing the severity of the negative symptoms in patients with schizophrenia. Also, Cordes *et al.* (2010) found that 10 Hz r-TMS 10 times within 2 weeks could produce significant improvement in negative symptoms.

Mogg *et al.* (2007) reported that real r-TMS was not found to be better than sham r-TMS in alleviating negative symptoms of schizophrenia. Other investigators found no difference between real and sham r-TMS on negative symptoms (Holi *et al.*, 2004).

In contrast to the negative results found when targeting positive symptoms with high-frequency r-TMS to the DLPFC, the treatment of negative symptoms with this approach has yielded somewhat more encouraging results. There have been a series of small parallel design trials. In several studies, there were no differences between the active and the sham groups (Holi *et al.*, 2004; Novák *et al.*, 2006; Mogg *et al.*, 2007). However, four studies have shown a significant advantage of active over sham stimulation (Hajak *et al.*, 2004; Jandl *et al.*, 2005; Goyal *et al.*, 2007; Prikryl *et al.*, 2007). This is in agreement with the present study.

Conclusion

The use of high-frequency r-TMS to the DLPFC and low-frequency r-TMS to the TPC is a useful add-on tool that may help in treatment of negative symptoms of drug-resistant schizophrenic patients; it has no effects on positive symptoms. It does not affect the cognitive function among drug-resistant schizophrenic patients.

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Conflicts of interest

There are no conflicts of interest.

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