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Repetitive transcranial magnetic stimulation in schizophrenic patients reporting auditory hallucinations

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Abstract

Auditory hallucinations are experienced by 60–80% of person with schizophrenia and can often cause significant distress behavioural dyscontrol. The application of rTMS in the left temporoparietal cortex could modulate the neuronal activation and reduce the occurrence of auditory disperceptions. Sixteen schizophrenic patients (treated with atypical antipsycothic drugs) reporting auditory hallucinations were included in the study. Low frequency rTMS (1 Hz) was performed at the 90% of resting motor threshold (MT), during 4 sessions in four consecutive days for 15 minutes each application. Eight patients received active stimulation, while eight patients received sham stimulation. Scale for the assessment of positive symptoms (SAPS), scale for the assessment of negative symptoms (SANS) and a scale to asses the severity of the auditory hallucinations (SAH) were administered at the beginning and at regular intervals during the follow-up. The present study confirms the reduction in auditory hallucinations by means of rTMS. The main finding was the long-term reduction in auditory hallucinations in the active group, with a return to the baseline in the sham group. The negative symptomatology improved only in the later sessions and lasted during the follow-up. The improvements in auditory hallucinations and positive symptomatology increased and lasted during the follow-up till the end-point. These data suggest that this approach may lead to an alternative somatic intervention for auditory hallucination in patients with schizophrenia.

Keywords: Repetitive transcranial magnetic stimulation; Schizophrenia; Auditory hallucination; Primary auditory cortex; Motor cortex excitability

Auditory hallucinations are experienced by 60–80% of person with schizophrenia and can often cause significant distress behavioural dyscontrol.

According to many recent studies using functional magnetic resonance imaging (FMRI) [1,7], single photon emission computed tomography (SPECT) associated with regional cerebral blood flow (rCBF) [6,19], positron emission tomography (PET) [19], the left temporoparietal cortex has been implicated in the genesis of auditory hallucinations.

Repetitive transcranial magnetic stimulation (rTMS) is a new method able to induce alterations of neuronal activity that may affect cognition and mood [10].

The application of rTMS in the left temporoparietal cortex could modulate the neuronal activation and reduce the occurrence of auditory disperceptions.

Some studies have found that rTMS to left temporoparietal cortex is beneficial in curtailing auditory hallucinations [3,5,14] but one study did not [9].

In the present study, we performed low frequency rTMS to reduce the excitability of the left temporoparietal cortex with the aim to curtail auditory hallucinations.

Sixteen patients (11 men, 5 women, range: 21–53 years; mean age: 40.0 ± 10.1 years) with auditory hallucinations who satisfied the Diagnostic and Statistical Manual IV (DSM-IV) criteria for paranoid schizophrenia were included in the study (Table 1).

All patients were treated with atypical antipsychotic. The total amount of chlorpromazine equivalents of atypical

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Table 1
Characteristics of real and sham group and baseline symptom measures

	Real	Sham	*p*-Value
N	8	8	1.00
M:F	5 : 3	6 : 2	0.59
Age	39.1 ± 10.8	41.0 ± 9.9	0.76
ID	8.3 ± 2.3	8.0 ± 2.1	0.82
CPZ Eq	453.4 ± 30.2	473.1 ± 28.2	0.69
SAPS	101.0 ± 14.1	93.4 ± 10.9	0.25
SAH	8.5 ± 1.2	7.8 ± 0.8	0.16
SANS	79.4 ± 13.5	79.4 ± 8.0	0.98

N, number of patients; M, male; F, female; ID, illness duration (years); CPZ Eq, chlorpromazine equivalents (mg/days); SAPS, scale for the assessment of positive symptoms; SAH, scale for auditory hallucination; SANS, scale for the assessment of negative symptoms.

antipsychotic drugs was calculated according to the following factors: risperidone 2 mg = chlorpromazine 100 mg; olanzapine 5 mg = chlorpromazine 100 mg; quetiapine 75 mg = chlorpromazine 100 mg.

All of them reported more than 3 months auditory hallucinations, in spite of antipsychotic treatment.

The control group was composed by 10 men and 6 women (age range: 38–55 years; mean age: 46.67 ± 5.67 years).

All the subjects included in the study were all right handed, according to the Edinburgh Handedness Inventory (EHI) [12].

The study was approved by the local ethics committee and informed consent was obtained from all patients and all healthy volunteers.

rTMS was performed using a Super Rapid Magnetic stimulator (The Magstim Company Limited, Withland, South West Wales, UK) connected with a figure 8-shaped coil for a focal stimulation, applied on the left temporoparietal cortex. The resting motor threshold (MT) and the silent period (SP) were evaluated using a single pulse TMS stimulator (Magstim 200 stimulator) for each patient at the first day (day 1, before and after rTMS) and at the end of the sessions (day 4, after rTMS). Surface recording electrodes were placed over the first dorsal interosseus (FDI) muscle. The motor threshold (MT) was defined as the lowest TMS intensity able to induce motor responses of an amplitude >50 μV in the relaxed contralateral target muscle in approximately 50% of 10–20 consecutive stimuli, according to internationally established guidelines [15]. Cortical stimulation was performed with the coil placed tangentially to the scalp and lateralised on the examined hemisphere with the handle held backward. Stimulation was applied at the "hot spot" (i.e., the scalp position from which a contralateral MEP of maximal amplitude, minimal latency and lowest threshold was obtained), according to Rossini et al. [15] MEPs were amplified using a Medelec Premier (Oxford Instruments) system with gains of 100 μV and 5 mV/div (band pass, 30 Hz–3 kHz).

The silent period (SP) is a period of electromyographic silence following TMS delivered during maximal voluntary muscle contraction. The duration of the SP was estimated by the beginning of the MEP to the recovery of voluntary activity. TMS intensity was standardised at 30% above resting MT due to the great variability of SP related to stimulus intensity and level of muscle contraction. The analysis time was 500 ms. In each experimental condition, the mean SP duration of the five trials was calculated.

Low frequency rTMS (1 Hz) was performed at the 90% of resting MT, during four sessions in four consecutive days for 15 min each application. Eight patients (five men and three women; mean age, 39.1 ± 10.8 years) received active stimulation. The 8-shaped coil was placed tangentially to the left temporoparietal area with the handle pointed antero-medially 45° backward. The location of focal coil was given midway between the left temporal (T3) and parietal (P3) electroencephalogram electrode sites on the basis of the international 10–20 system. Scalp co-ordinates were determined on a tightly adjusted rubber cap placed over the patient's head with the two axis drawn from the temporo-parietal cortex and a diagonal cutting the 90° angle in two of 45° each. Eight patients (six men and two women; mean age, 41.0 ± 9.9, years) received sham stimulation, consisting in the 45° scalp application of the coil, able to induce scalp stimulation simulating the subjective sensation of real rTMS. All patients remained blind to their allocation for the duration of the study. Real rTMS and sham groups were matched for sex, age, education, duration of illness, chlorpromazepine equivalents (Table 1).

Symptom assessments were administrated at baseline (T1), after the fourth rTMS application (T2) and at each follow-up point of the trial [1st week after rTMS (T3), 2nd (T4), 3rd (T5), 4th (T6), 6th (T7), 8th (T8) week]. The Rating Scales performed in the experimental design were: scale for the assessment of positive symptoms (SAPS), scale for the assessment of negative symptoms (SANS) and a composite scale of 0–10 to asses the severity of the auditory hallucinations (SAH, Table 2). The rater conducting the clinical assessment was blind to stimulation condition (active versus sham), until the endpoint.

Social and demographic variables were analysed with chi-square for categorical and *t*-test for continuous data. Immediate effect of TMS treatment (real or sham) was assessed by comparing rating scales scores just before treatment and after the administration of TMS, by the means of a paired *t*-test. Changes from baseline were evaluated at each time point in each group separately by one-way ANOVA repeated measures. Rating scales data for each group were entered in an ANOVA repeated measures with time as within-subjects and group as between-subjects factors to compare the stability of the results. Mann–Withney test was used to compare the MT and SP scores of the patients and control group. All

Table 2
Scale for auditory hallucinations (SAH)

	None	Low	Moderate	Severe
Frequency	0	1	2	3
Suffering	0	1	1.5	2
Belief	0	1	1.5	2
Behavioural influence	0	1	2	3