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· Research Article ·

Effect of adjunctive treatment with repetitive transcranial magnetic stimulation on exploratory eye movements and negative symptoms in schizophrenic patients: a randomized, double-blind, sham-controlled study

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Background: The left dorsolateral prefrontal cortex (DLPFC) is one of the crucial areas in ocular control that may be involved in the abnormal Exploratory Eye Movements (EEM) seen in schizophrenia. Repetitive Transcranial Magnetic Stimulation (rTMS) to this same region of the brain is a promising adjunctive therapy for the negative symptoms of schizophrenia.

Objective: Assess the effects of rTMS stimulation on EEM abnormalities in schizophrenia and the relationship of changes in EEM to changes in the positive and negative symptoms of schizophrenia.

Methods: 46 inpatients with schizophrenia at the Shanghai Mental Health Center between June 2009 and February 2010 were randomly divided into an rTMS group ($n = 24$) and a sham rTMS group ($n = 22$). Both groups received standard antipsychotic medication. The rTMS group received five adjunctive rTMS treatments per week for four weeks using intermittent theta burst stimulation to the left dorsolateral prefrontal cortex. Patients were evaluated using blinded assessments of the Positive and Negative Syndrome Scale (PANSS) and tests of EEM, including number of eye fixations score (NEF), responsive search score (RSS), and the differentiation score (D), before and after the course of treatment.

Results: 23 patients in the intervention group and 19 patients in the control group finished the study. Both groups had significant decreases in symptoms after four weeks of treatment but at the end of the treatment period both the total PANSS score and the PANSS negative symptom score were significantly lower in the group that received adjunctive rTMS. The NEF score increased significantly (i.e., improved) in the real rTMS group after four weeks of treatment but not in the sham rTMS group. Neither group had significant changes in the RSS or D scores. However, the median percent change in the NEF score for the real rTMS group (10%) was not significantly greater than the median percent change in the sham rTMS group (19%).

Conclusion: Compared to standard antipsychotic therapy, a four-week course of antipsychotic medication with adjunctive rTMS was more effective in improving both the negative symptoms of schizophrenia and one component of the abnormal EEM seen in schizophrenia. High individual variability in responsiveness of EEM measures to treatment will necessitate relatively large samples to determine whether or not particular treatments are effective.

Keywords: Exploratory eye movement; Repetitive transcranial magnetic stimulation; Schizophrenia

1 Introduction

Abnormal eye movements in schizophrenia is a well documented phenomenon[1-3]. Many studies assess these abnormal eye movements by evaluating Exploratory Eye Movements (EEM), specific ocular movements seen when gazing at static images. Abnormal EEM are common in persons with a diagnosis of schizophrenia[4-6]. Kojima and colleagues[4] compared EEM in 145 patients with schizophrenia, 116 patients with depression and 124 normal controls; they found that the sensitivity and specificity of EEM to schizophrenia were both higher than 80% and that the two components of EEM—the Responsive Search Score (RSS) and the Number of Eye Fixations (NEF) score—were significantly lower in schizophrenia than in the other two groups. Moreover, and RSS was a very stable indicator of a diagnosis of schizophrenia that was not influenced by the administration of antipsychotic medications or changes in patients' symptoms;

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though some studies report that EEM measures may change with symptom improvement[7,8]. Other studies that highlight the potential utility of EEM as biological markers of schizophrenia include the finding that parents of persons with schizophrenia have low RSS scores[9] and the finding of a correlation of EEM with chromosome 22q11 —a heavily investigated candidate gene for schizophrenia[10].

Despite the fact that EEM abnormalities are one of the most well documented physical abnormalities seen in schizophrenia, few studies have assessed the biological basis for these abnormalities or the effect of treatment on EEM. Eye movements such as EEM are managed and regulated by the parietal, prefrontal and supplementary motor areas of the cerebrum. The dorsolateral prefrontal cortex (DLPFC) is one of the crucial areas in this ocular control[11], injuries in this area can lead to significant eye movement disorders[12]. Thus, one might hypothesize that changes which affect the prefrontal cortex might influence EEM.

Repetitive transcranial magnetic stimulate (rTMS) is a relatively new treatment in psychiatry that applies magnets to produce highly focused electrical currents that stimulate specific points in the brain[13]. rTMS to the DLFPC has been used as an adjunctive treatment for the cognitive deficits of schizophrenia[14] and for the positive and negative symptoms in schizophrenia[15]. To our knowledge no study has yet assessed the effect of rTMS on abnormal EEM and the relationship of rTMS-induced changes in EEM to clinical improvement. The present study aims to assess the effect of adjunctive treatment with rTMS to the left DLPFC on abnormal EEM in patients with schizophrenia who have prominent negative symptoms. We choose such subjects because of the relatively poor effectiveness of antipsychotic medications for negative symptoms and because some reports suggest that changes in the DLPFC are closely associated with the negative symptoms of schizophrenia[16].

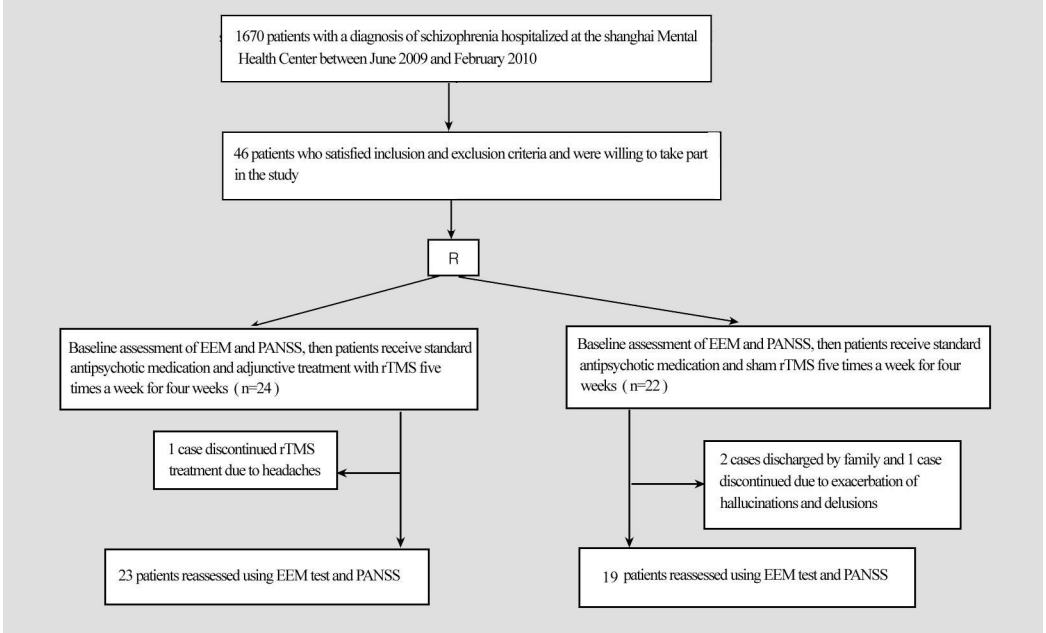
2 Methods

2.1 Subjects

Patients who took part in this study were all hospitalized patients with a diagnosis of schizophrenia at the Shanghai Mental Health Center of the Shanghai Jiao Tong University School of Medicine. Participants were recruited between June 2009 and February 2010.

Inclusion criteria: 1) meets diagnostic criteria for Schizophrenia using the Diagnostic and Statistical Manual for Mental Disorders, 4th edition (DSM-IV); 2) 18 to 55 years of age; 3) negative symptom factor score of the Positive and Negative Syndrome Scale (PANSS) ≥ 20; 4) on a stable medication regimen; and 5) had not previously participated in an EEM assessment. Exclusion criteria: 1) prior suicidal or violent behavior; 2) contraindications for rTMS treatment such as metal implants in the body or medical history of migraine, seizure, or abnormal EEG; 3) diseases affecting eye movements; 4) significant cardiac, pulmonary, or other serious illness; 5) mental retardation; 6) comorbid substance abuse; and 7) currently pregnant or breast feeding. (See Figure 1).

Figure 1. Flowchart of enrollment and treatment of subjects



EEM=Exploratory Eye Movements; PANSS=Positive and Negative Symptom Scale; rTMS=repetitive Transcranial Magnetic Stimulation

Eligible subjects were randomized to rTMS therapy or sham rTMS therapy based on a computerized algorithm, the result for each subject was provided to the rTMS technician the first time the patient entered the rTMS treatment room. The treatment protocol was approved by the Ethics Committee of Shanghai Mental Health Center. All of the subjects or their accompanying family members signed informed consent for the treatment.

2.2 Research Methods

2.2.1 Repetitive transcranial magnetic stimulation

The circular magnet version of the Magpro X100 transcranial magnetic stimulator produced by the Medtronic Company in Denmark was used in the study. The treatment protocol was based on that reported by Grossheinrich and colleagues[14], the position for treatment was the left DLPFC, a treatment session involved administering a total of 2400 pulses over a 22-minute period using an intermittent theta burst stimulation pattern with a stimulus frequency of 50 Hz and strength of 80% of the patient's motor threshold. One treatment session was completed five days a week for four consecutive weeks (a total of 20 sessions). In the sham rTMS treatment patients were placed in the rTMS apparatus for 22 minutes and exposed to similar sounds as those experienced by rTMS but the magnets were not activated.

2.2.2 EEM test method

We assessed EEM using the DEM-2000 eye movement detector produced by the Shanghai Dikang Biotechnology Company, which automatically records the trajectory of eye movements and analyzes the data. Subjects sit comfortably in a chair and gaze at a small screen in front of them. The distance between the subject's eyes and the screen was 25 cm in order to keep the angle for moving the eyes from the left border to the right border at 33 degrees. The first S shaped figure (S1) was displayed on the screen for 15 s and subjects were asked to carefully observe the figure. The instrument automatically records the number of eye fixation (NEF) points in the 15 s. Subsequently two slightly different S shaped figures (S2 and S3) are displayed on the screen for 15 s, and the subject is again asked to carefully observe the figures and repeatedly asked "is there any other difference between this figure and the first figure" until the subject answers "no difference". The instrument divides S2 or S3 into seven regions, the number of regions the subject fixes on over a 5-second interval is recorded as the 'responsive search score' (RSS). The highest RSS score for each image was seven and the maximum score for the two figures is 14[14]. Higher NEF and RSS scores indicate better eye movement functioning. A discriminant score — the 'D score' — is also computed by combining the NEF and RSS results (D = 10.265 − 0.065 * NEF + 0.871 * RSS). The technician who conducted the EEM tests was blind to the treatment status of the patients.

2.2.3 Assessment of psychotic symptoms

The Chinese version of the PANSS was used to assess patients' psychotic symptoms at baseline and after 4 weeks of treatment. This instrument is used widely in China and has good internal consistency (Cronbach α = 0.87)[17]. The evaluating researchers were blind to the treatment status and EEM results of the subject they evaluated.

2.3 Statistical analysis

All data were analyzed using SPSS 15.0 software. Demographic data for the groups were compared using t-tests and Chi Square tests. Paired t-tests were used to compare the before versus after changes in PANSS and the EEM test scores (NEF, RSS and D scores). Several of the before-versus-after percent change scores had skewed distributions so change scores were compared using median tests.

3 Results

3.1 Subjects

In total 46 patients with schizophrenia satisfied inclusion criteria and 42 patients completed the 4-week trial. Four subjects dropped out in the first week of the trial, 1 patient from the intervention group refused to continue rTMS because of transient headaches during the treatment sessions, 2 control group subjects were discharged from the hospital by their family members for reasons unrelated to the rTMS treatment, and one control group subject stopped because of an exacerbation of hallucinations and delusions that required changing his medication regimen. The discontinuation rate in the two groups was not significantly different (4.1% vs. 13.6%, $\chi^2 = 0.38$, $P > 0.05$).

The 23 subjects in the intervention group who completed the trial included 16 males and 7 females, their mean (SD) age was 37.4 (11.8) years (range 23-55), their mean duration of education was 12.0 (2.2) years, their median (IQR) duration of illness was 17 (6-23) years (range 1-34 years), and the median duration of their current hospitalization was 11 (6-25) months (range 0.5-68 months). Their primary medication treatment was a follows: 5 received a mean dose of 4.4 (0.6) mg/d risperidone, 5 received 20 mg/d olanzapine, 4 received a mean dose of 22.5 (8.0) mg/d aripiprazole, 2 received a mean dose of 550.0 (70.7) mg/d quetiapine, and 7 received a mean dose of

332.1 (±23.1) mg/d clozapine.

The 19 subjects in the control group who completed the trial included 11 males and 8 females, their mean (±SD) age was 39.7 (±13.3) years (range 18-52), their mean duration of education was 11.0 (±2.6) years, their median (±IQR) duration of illness was 13 (±9-22) years (range 2-32 years), and the median duration of their current hospitalization was 12 (±9-26) months (range 0.5-58.5 months). Their medication treatment was as follows: 9 received a mean dose of 4.0 (±2.0) mg/d risperidone, 2 received 20 mg/d olanzapine, 3 received a mean dose of 23.3 (±11.6) mg/d aripiprazole, 2 received a mean dose of 550.0 (±70.7) mg/d quetiapine, and 4 received a mean dose of 312.5 (±75.0) mg/d clozapine.

The differences in gender, age, years of education, duration of illness, length of hospital stay, category of antipsychotics, and calculated dosages of antipsychotics (using chlorpromazine equivalents) were not statistically different between the two groups. Seven subjects in the real rTMS group and eight subjects in the sham rTMS group also received a second antipsychotic (data provided on request). All subjects remained on the same dose of the same antipsychotic medication throughout the 4-week trial.

3.2 Assessment of rTMS therapeutic efficacy

As shown in Table 1, the total PANSS scores and the subscale scores in the real and sham rTMS groups were not significantly different at baseline. After four weeks of antipsychotic treatment with or without adjunctive rTMS treatment, the total PANSS scores and the positive symptoms score, negative symptoms score and general pathology score all decreased significantly in both groups. At the end of treatment the total PANSS score and the PANSS negative symptom score were significantly lower in the rTMS group than in the sham rTMS group; the PANSS general pathology score and the PANSS positive symptom score were also lower in the rTMS group but the differences did not reach statistical significance. The median percent change scores after the four weeks of treatment are shown in Table 2; the median drop in negative symptoms score and in the total PANSS score was significantly greater in the real rTMS group.

Table 1. Mean (±SD) PANSS subscale and total scores and Exploratory Eye Movement (EEM) test scores before and after adjunctive treatment with rTMS or sham rTMS

	Baseline Assessment				Assessment after four weeks of treatment				Before vs. after rTMS		Before vs. after Sham rTMS	
	rTMS (n=23)	Sham rTMS (n=19)	t-value	P-value	rTMS (n=23)	Sham rTMS (n=19)	t-value	P-value	Paired t-test	P-value	Paired t-test	P-value
PANSS SCORES												
Positive symptom score	14.17 (±3.83)	13.47 (±2.99)	−0.65	0.052	11.57 (±2.71)	12.11 (±2.79)	−1.65	0.107	4.16	<0.001	3.31	0.004
Negative symptom score	25.91 (±3.19)	26.95 (±2.46)	1.16	0.254	22.22 (±4.63)	24.95 (±2.84)	−2.89	0.006	8.20	<0.001	5.85	<0.001
General pathology score	34.52 (±3.60)	34.53 (±3.99)	0.00	0.997	28.61 (±4.59)	30.53 (±3.84)	−1.90	0.065	7.71	<0.001	6.64	<0.001
Total PANSS score	74.61 (±5.84)	74.95 (±6.56)	0.18	0.861	62.39 (±9.42)	67.58 (±7.14)	−2.49	0.017	7.69	<0.001	7.84	<0.001
EEM SCORES												
Number of eye fixations	22.87 (±8.34)	23.00 (±8.57)	0.05	0.960	26.91 (±7.23)	20.95 (±10.01)	−2.24	0.030	−2.33	0.036	0.58	0.571
Responsive search score	4.52 (±2.00)	4.68 (±1.64)	0.28	0.778	4.96 (±1.94)	5.16 (±1.30)	0.06	0.960	−0.83	0.417	−0.99	0.337
Discriminant (D) score	4.94 (1.79)	4.75 (1.46)	−0.37	0.714	4.26 (1.97)	4.41 (1.36)	0.48	0.636	1.37	0.183	0.70	0.492

PANSS = Positive and Negative Symptom Scale; EEM = Exploratory Eye Movements; rTMS = repetitive Transcranial Magnetic Stimulation

Table 2. Percent change in PANSS and EEM scores after four weeks of real or sham rTMS adjunctive treatment

	real rTMS (n = 23)		sham rTMS (n = 19)		Chi square for median test	p2value
	median	IQR	median	IQR		
PANSS SCORES						
Positive symptom score	−18	(−25 ~0)	−11	(−16 ~0)	0.10	0.757
Negative symptom score	−13	(−21 ~ −8)	−7	(−11 ~ −4)	7.79	0.005
General pathology score	−16	(−24 ~ −12)	−12	(−15 ~ −6)	1.47	0.226
Total PANSS score	−17	(−21 ~ −8)	−9	(−13 ~ −6)	4.71	0.030
EEM SCORES						
Number of eye fixations	10	(−3 ~43)	−19	(−44 ~50)	2.40	0.121
Responsive search score	0	(−20 ~50)	20	(−25 ~50)	1.47	0.226
Discriminant (D) score	−14	(−40 ~12)	−6	(−40 ~33)	0.10	0.757

PANSS = Positive and Negative Symptom Scale; EEM = Exploratory Eye Movements; rTMS = repetitive Transcranial Magnetic Stimulation; IQR = interquartile range

3.3 EEM results

Table 1 also shows that the differences in base2line NEF, RSS, and D scores between the two groups were not statistically significant. After four weeks of treatment the number of eye fixations (NEF) score increased (i. e., improved) signifi2cantly in the group that received adjunctive rTMS but the RSS and D scores did not change signifi2cantly and none of the three measures changed sig2nificantly in the group that received sham rTMS. Table 2 shows that the real rTMS group had a me2dian percent increase in the NEF score of 10% after four weeks of adjunctive rTMS treatment and the sham rTMS group had a median decrease of 19% in the NEF score over the same period; but this difference was not statistically significant due to the very wide range in the distribution of the percent change scores for the EEM measures.

4 Discussion

4.1 Main findings

Similar to our previous report on adjunctive treatment of schizophrenia with rTMS[14], this study found that the addition of rTMS as an adjunctive treatment to standard antipsychotic treatment signif2icantly improves the outcome for negative symp2toms (as assessed by PANSS) after four weeks of treatment.

We also found that after four weeks of adjunc2tive treatment with rTMS one of the measures of abnormal EEM in schizophrenia − number of eye fixations (NEF)) had improved significantly. But there was no improvement in the other measures of EEM (RRS and D scores) and the use of antipsy2chotic medications without adjunctive rTMS did not result in improvements in any of the measures of EEM. This result is relevant to the debate about whether or not abnormal EEM in schizophrenia can improve with treatment[1,8]; it suggests that NEF is a state characteristic that can change over time while RSS is a trait characteristic that does not change o2ver time.

But our finding of improvement in NEF with adjunctive rTMS treatment needs to be replicated in larger samples. Despite a 29% difference in the be2fore2versus2after percent change scores between the real and sham rTMS groups (+10% vs −19%), this difference was not statistically significant due to the very wide range in the percent change scores for the NEF measure. Thus the high individual vari2ability in the responsiveness of these scores to treat2ment necessitates large samples to determine whether or not treatment is effective. This high vari2ability in responsiveness may be one of the reasons for conflicting results in previous studies about ab2normal EEM in schizophrenia.

4.2 Limitations

The major deficiency of the present study was the relatively small sample size and the relatively short duration of adjunctive rTMS treatment. Given the wide number of potential confounding factors simple randomization may not have adequately balanced the two groups. To minimize the effect of potentially imbalanced groups we also used the be2fore versus after change scores to compare the effi2cacy of the two treatment modalities (antipsychotic medication with or without adjunctive rTMS). One subject withdrew from the intervention group for

reasons apparently related to the rTMS treatment (reported headache during the treatment) and three other subjects were dropped from the control group for reasons unrelated to the rTMS treatment; given the small proportion of dropouts (8.7%) we did not include these treatment failure results in the analysis. The drawings used for the EEM tests were the same at baseline and at four weeks after starting treatment; this could have affected the second evaluation but there is unlikely to be much carry-over learning effect over the 4-week interval between the two tests and the use of similar procedures in both groups means that any learning effect would be similar in both groups and, thus, have little effect on the overall results about differences between the two treatment conditions.

4.3 Implications

The 5-day-per-week treatment schedule for rTMS used in this study may make this impractical in routine clinical care, but the importance of negative symptoms to the social dysfunction experienced by many patients with schizophrenia and the replicated effectiveness of rTMS in treating these difficult to treat symptoms justifies further research of this new treatment modality. Among several other issues, the optimal duration of treatment and interval between treatment sessions are yet to be determined.

The fact that stimulation of the left dorsolateral prefrontal region was associated with increased NEF scores supports the notion that this region is involved in the EEM abnormalities seen in schizophrenia. Nemoto and colleagues[18] used fMRI to assess regional brain functioning during completion of a visual exploration task similar to the EEM test and detected a significant bilateral activation in the prefrontal cortex and thalamus in normal subjects that was deficient in patients with schizophrenia. Our findings are consistent with this result. Whether abnormal EEM is a byproduct of generalized dysfunction of the prefrontal cortex in schizophrenia or has a more specific etiologic relationship to schizophrenia remains to be determined.

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对照研究

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左侧前额叶背外侧区(dorsolateral prefrontal cortex DLPFC 是调控眼球运动的关键区域, 很可能与精神分裂症的异常探索性眼球运动(exploratory eye movement EEM 有关。重复经颅磁刺激(repetitive transcranial magnetic stimulation rTMS 刺激大脑的这个区域有可能辅助治疗精神分裂症阴性症状。

目的 评估 rTMS 干预对精神分裂症者 EEM 异常的影响, 以及 EEM 变化与精神分裂症阳性和阴性症状变化之间关系。

方法 在上海市精神卫生中心住院的46 位精神分裂症患者于 2009 年 6 月至 2010 年 2 月参加本研究。患者被随机分为 rTMS 真刺激组(研究组, 24 例) 和 rTMS 伪刺激组(对照组, 22 例)。两组均接受标准抗精神病药治疗。rTMS真刺激组每周接受5 次 rTMS 干预, 持续 4 周, 应用 θ 短阵快速脉冲刺激(intermittent theta burst stimulation iTBS 模式刺激左侧 DLPFC。于治疗前及治疗 4 周末应用阳性与阴性症状量表(Positive and Negative Syndrome Scale, PANSS) 盲法评定患者的精神症状和进行 EEM 检查, EEM 检查指标包含凝视点数(number of eye fixations score, NEF) 、反应探索分(the responsive search score, RSS) 和判别值(differentiation score, D)。

结果 研究组 23 例和对照组 19 例完成研究。经 rTMS 干预4 周后, 两组的症状均有明显减轻, 但是, 接受 rTMS 辅助治疗患者组的 PANSS 总分及 PANSS 阴性症状因子分明显低于对照组。4 周后, rTMS 真刺激组的 NEF 分较治疗前有明显升高(改善), 而 rTMS 伪刺激组的 NEF 分未见明显升高; 两组治疗前后 RSS 及 D 值的变化均不明显。但是, rTMS 真刺激组的 NEF 中位数变化的百分数(+10%), 并没有显著性高于 rTMS 伪刺激组的 NEF 中位数变化的百分数(-19%)。

结论 与标准药物治疗相比, 接受 4 周 rTMS 刺激左侧前额叶背外侧区辅助治疗的精神分裂症患者的阴性症状更轻, 异常探索性眼球运动 EEM 有一成份也有提高。EEM 指标对于治疗的反应方面存在高度个体化变异, 这表明需要相对较大的样本来判断特殊治疗是否有效。

【关键词】 探索性眼球运动 重复经颅磁刺激 精神分裂症