Effects of Repetitive Transcranial Magnetic Stimulation Treatment on Event-Related Potentials in Schizophrenia

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Abstract

Background: Repetitive transcranial magnetic stimulation (rTMS) and event-related potentials (ERPs) are a noninvasive technique that widely used in neurophysiological field. Although rTMS has shown clinical utility for a number of neurological conditions, Recently, there was little understanding of the efficacy of rTMS on Schizophrenia (SZ) and the change of ERP between before and after rTMS treatment. The objective of this study was to investigate the characteristics of N400, mismatch negativity (MMN), and P300 before and after treatment with rTMS in SZ.

Methods: One hundred and twenty-seven SZ patients hospitalized in Shanghai Mental Health Center from March 2015 to July 2017, divided into two groups (85 patients were recruited as rTMS group and 42 were recruited as sham rTMS [ShrTMS] group) and 76 normal controls (NCs) who were the staff and refresher staff in our hospital were recruited at the same time. A Chinese-made rTMS and a Runjie WJ-1 ERPs instrument were used in the present experiment. N400 was elicited by congruent and noncongruent Chinese idioms. At rTMS treatment, N400, P300, and MMN characteristics were compared with those before treatment and NC group.

Results: Compared with NC, the SZ patients exhibited delays in N400, P300, and MMN latency and decreased N400, P300, and MMN amplitudes in their frontal area (P < 0.05). After 25 rTMS treatments, N400 amplitudes in the frontal area (elicited by idioms with same phonetic and different shape and meaning and with different phonetic, shape, and meaning) were increased in the SZ patients (P < 0.05). However, there was no significant change in N400 before and after treatment with ShrTMS in SZ patients (P > 0.05). Amplitudes for MMN and target P300 also increased in SZ patients after rTMS treatment (P < 0.05).

Conclusions: Based on our preliminary findings, we believe that the combined usage of N400, MMN, and P300 could be a valuable index and an electrophysiological reference in evaluating the effects of rTMS treatment in SZ patients.

Key words: Frontal Area Repetitive Transcranial Magnetic Stimulation; Mismatch Negativity; N400; P300; Schizophrenia

INTRODUCTION

Event-related potentials (ERPs) and repetitive transcranial magnetic stimulation (rTMS) technologies have been introduced into the neurophysiological field in recent years and are widely used in the treatment of schizophrenia (SZ), depression, and other mental disorders. N400 is a major component of ERP, which is a common research tool used in the cognitive science field, including linguistic cognition. Mismatch negativity (MMN) is a component of ERP and is identified as an active discrimination stimulus during the experiment, reflecting the automatic recognition process of the standard and deviant stimuli in participants. Although rTMS has shown clinical utility for a number of neurological conditions, we have only limited understanding of how rTMS influences ERP in SZ. Recently, we evaluated the N400, P300, and MMN characteristics before and after treatment with rTMS in SZ patients as follows.

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**Methods**

**Ethical approval**

The research was approved by the Ethics Committee of the Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine and was carried out on the basis of the Helsinki Declaration, revised in 1983. Informed consent was obtained from all of the participants.

**Subjects**

One hundred and twenty-seven SZ patients were recruited in this experiment divided into two groups (85 patients were recruited as rTMS group and 42 were enrolled as sham rTMS [ShrTMS] group), and 76 volunteers were recruited as normal control (NC) group.

**Schizophrenia group**

One hundred and twenty-seven SZ patients who were hospitalized in Shanghai Mental Health Center from March 2015 to July 2017 were recruited for the present research study. Inclusion criteria of SZ included patients had been diagnosed with SZ according to the Chinese Classification of Mental Disorders-3, revised third edition. Exclusion criteria included severe dementia and organic disease, metal implant, past traumatic brain injury or epilepsy history, with significant extrapyramidal side effects, and without receipt of advanced electoconvulsive therapy.

Of the 127 SZ patients, 61 were males and 66 were females. The range of the age was 19–51 years, with a mean age of 31 ± 9 years. The patients had an average education length of 15.9 ± 2.8 years and an illness duration of 0.5–2.2 years (median of 1.5 years). The participants received either single risperidone treatment (112 cases, dosage: 2–6 mg/d) or combined common internal medicines such as antidiabetics and hypotensor drugs but not any other antipsychotic treatments (15 cases). All the participants were required to withdraw from antipsychotic drugs for 3–7 days before enrollment, with an average of 4–6 days. All the participants were divided into two groups (85 patients treated with real rTMS and 42 cases received ShrTMS).

**Normal control group**

Seventy-six healthy adult volunteers who were the staff and refresher staff in our hospital were recruited as NCs from March 2015 to July 2017. The inclusion criteria included with no history of neurological problems or taking psychoactive medications, with no somatic disease, without any mental disorders before, and were in fine mental condition. A total of 76 volunteers (40 males and 36 females) were recruited with an age range from 20 to 53 years (mean age 33 ± 13 years) and an average education length of 16.1 ± 3.0 years.

There were no significance differences in gender, age, and education background between SZ and NC groups (P > 0.05). Informed consent was obtained from all guardians of the participants. The study received full Research Ethics Board approval.

**Stimuli**

**Event-related potentials recording**

The experiments were carried out in a shielded soundproof room with a weak background light of 2 lux. All the participants took up a position with clinostatism, were relaxed and had their eyes facing forward. The participants were asked to stay awake and maintain attention during the experiments. The Guangzhou Runjie WJ-1 type ERP instruments were applied in the test to record the N400 component. The recording electrodes were located in the frontal area (FZ), central area (CZ), and parietal area (PZ). The electrode at the FZ was the recording electrode and was placed according to the international 10/20 system. The location of two lobes was reference electrode and the Fpz location was grounding electrode.

**N400**

The stimuli consisted of 76 Chinese idioms in a sequence and were chosen from the “Chinese Idioms Dictionary.”(7) The fourth character of each idiom in the stimulus sequence served as a target word which was either correct or incorrect. Hence, the idioms could be divided into two groups: the correct group and the incorrect group (38 idioms in each group). Thirty-eight idioms with a congruent fourth word were the correct group, for example, “爱不释手.” However, in the other group, the fourth character of Chinese idiom is completely different with the fourth character of correct Chinese idiom including there is no similarity in pronunciation, shape, and meaning, which called incongruent, for example, “触目惊泰（心）.” The idioms were presented in a random sequence with a rule, and any group of idioms could not be presented more than 3 consecutive times. The participants were asked to press the “No” key if the idiom was incongruent and “Yes” if it was congruent.

**Mismatch negativity and P300**

The oddball paradigm was applied in the task. The standard stimulus was 500 Hz with 80 dB pure tone, and the deviant stimulus was 2000 Hz with 85 dB pure tone. The appearance probability of the standard and deviant stimuli was 0.8 and 0.2, respectively. Two types of stimuli were presented 200 times in total in each cycle. During the first cycle, the participants were not asked to memorize the appearance times of the deviant stimuli, for the MMN test, while in the second cycle, the participants were required to memorize the appearance times of the deviant stimuli, for the P300 test. The unified instructions were given before the ERP experiments and were carried out by the fixed researchers. The electrical activity of the artifacts could be automatically excluded by the software installed in the computer.

**Repetitive transcranial magnetic stimulation**

The rTMS instrument was produced by Reed company (Wuhan, China), with a coil of “8” type. The participants received rTMS treatment for 5 weeks, for a total of 25 times. Each treatment included 30 series of stimuli, with 50 stimuli per series. The stimulation location...
was on the left dorsolateral frontal lobe. The stimulus had a frequency of 10 Hz and an intensity of 110% motor threshold (MT).

**Sham repetitive transcranial magnetic stimulation**

The angle of the ShrTMS coil plane and scalp was 90°. The patients will feel the knocking sense on their scalp which is similar to real stimulus, but the effect is invalid. The antipsychotic dose remained unchanged during the treatment period.

**Measurement**

The measurement indexes were the latency and amplitude of N400, P300, and MMN. MMN was an elicited ERP and calculated as deviated stimulus minus standard stimulus. It was a maximum negative phase wave located at the latency range from 100 to 250 ms. P300 was the maximum positive phase wave located at the ERP wave latency range from 250 to 450 ms and was elicited by the deviant stimulus itself. The peak latency and baseline peak amplitude of N400, P300, and MMN were measured, respectively.

**Clinical assessment**

The Positive and Negative Syndrome Scale (PANSS) and Scale for the Assessment of Negative Symptoms (SANS) were used to evaluate the clinical effects of rTMS on SZ. The PANSS is composed of four subscales including a positive scale (P score, 7 items), negative scale (N score, 7 items), general psychopathology scale (G score, 16 items), and additional symptoms (3 items). Each item was rated from “1” to “7” degrees in PANSS, with a range of no symptoms to extremely serious symptoms. A higher score indicated that the patient had more serious mental symptoms. In the present study, additional symptom scores were not calculated into the total score. The SANS contained 24 items and each item is rated with 6 degrees. The five subscales were emotional, dull or poor thinking, lack of will, lack of social interest, and attention disorders, respectively.

**Statistical analysis**

All data were analyzed using the Software SPSS version 13.0 (SPSS Incorporated, Chicago, IL, USA). Data were presented as a mean ± standard deviation, where intergroup comparisons were performed using an independent samples t-test, while within-group comparisons used the paired t-test. Pearson correlations were used to assess the relationships between N400, P300, MMN, and clinical scales. P < 0.05 was considered statistically significant.

**RESULTS**

**The change in N400 in patients before and after treatment with real and sham repetitive transcranial magnetic stimulation**

Eighty-five patients were examined by N400, respectively, before the first treatment of rTMS (before treatment) and after 25 treatments of rTMS (after treatment). It can be seen from Table 1 that N400 changed after rTMS treatment in the SZ group. After the treatment, N400 amplitude increased and was elicited by congruent idioms with same phonics and different shape and meaning and incongruent idioms with different phonics, shape, and meaning (P < 0.05). When compared to before treatment with rTMS, there were no significant changes in N400 latency elicited by congruent and incongruent idioms (P > 0.05). However, there were no significant changes in N400 before and after treatment with ShrTMS in patients (P > 0.05).

**Variation of Positive and Negative Syndrome Scale and Scale for the Assessment of Negative Symptoms before and after treatment in 85 SZ patients stimulation by rTMS**

There was no significance difference in the scores before and after treatment according to the P value. When compared to their values before treatment, the N score, G score, T score, and SANS score were significantly decreased after treatment [Table 2]. There was no significant correlation between the latency and amplitude of N400, P300, MMN, and the PANSS score and SANS score before and after treatment (P > 0.05).

**Comparison of N400 index**

Compared to the NC group, the N400 latency elicited by congruent idioms with same phonics and different shape and

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**Table 1: The change of N400 in patients before and after treatment with 85 real rTMS and 42 ShrTMS stimulation (mean ± SD)**

| Items                      | Wave                  | rTMS Before | rTMS After | ShrTMS Before | ShrTMS After | t    | P    |
|----------------------------|-----------------------|-------------|------------|---------------|--------------|------|------|
| Same phonics, different    | Latency (ms)          | 388.0 ± 43.0| 385.0 ± 37.0| 386.0 ± 38.0 | 390.0 ± 41.0 | 0.93 | >0.05|
| shape and meaning          | Amplitude (µV)        | 5.9 ± 4.5   | 7.6 ± 3.9*  | 5.8 ± 3.7     | 6.2 ± 4.3    | 2.71 | <0.05|
| Congruent                  |                       |             |            |               |              |      |      |
| Incongruent                | Latency (ms)          | 424.0 ± 33.0| 426.0 ± 29.0| 427.0 ± 31.0  | 425.0 ± 24.0 | 1.03 | >0.05|
| Amplitude (µV)             | 5.5 ± 3.7             | 5.6 ± 3.9   | 5.6 ± 4.1   | 5.4 ± 3.8    |              |      |      |
| Different phonics, shape   | Latency (ms)          | 425.0 ± 52.0| 419.0 ± 49.0| 422.0 ± 48.0  | 427.0 ± 46.0 | 1.39 | >0.05|
| and meaning                | Amplitude (µV)        | 2.9 ± 1.0   | 3.2 ± 2.1   | 3.0 ± 1.8    | 2.8 ± 1.4    | 1.64 | >0.05|
| Congruent                  |                       |             |            |               |              |      |      |
| Incongruent                | Latency (ms)          | 477.0 ± 41.0| 479.0 ± 43.0| 476.0 ± 38.0  | 481.0 ± 44.0 | 1.11 | >0.05|
| Amplitude (µV)             | 5.2 ± 3.3             | 6.9 ± 3.3*  | 5.3 ± 3.4   | 5.1 ± 3.6    |              |      | <0.05|

† Compared with before treatment with real rTMS in the patient, *P<0.05; Compared to before and after treatment either with real rTMS or ShrTMS, P<0.05. rTMS: Repetitive transcranial magnetic stimulation; ShrTMS: Sham rTMS; SD: Standard deviation.
meaning was delayed in the SZ group ($P<0.05$). Meanwhile, the latency and amplitude of N400 elicited by congruent idioms with different phonic, shape, and meaning were delayed in the SZ patients, and the N400 amplitude elicited by incongruent idioms with different phonic, shape, and meaning was reduced ($P<0.05$).

Eighty-five patients were examined by N400, respectively, before the first treatment of rTMS (before treatment) and after 25 treatments of rTMS (after treatment). It can be seen from Table 3 that N400 changed after rTMS treatment in the SZ group. After the treatment, N400 amplitude increased and was elicited by congruent idioms with same phonic and different shape and meaning and incongruent idioms with different phonic, shape, and meaning ($P<0.05$). When compared to before treatment with rTMS, there was no significant change in N400 latency elicited by congruent and incongruent idioms ($P>0.05$).

**Comparison of P300 and mismatch negativity latency and amplitude**

Compared to the NC group, the latency and amplitude of MMN decreased ($P<0.05$–0.01) and the P300 target amplitude also decreased in the SZ group ($P<0.05$). P300 and MMN latencies and amplitudes were compared, respectively, before and after rTMS treatment in the SZ group. The results showed that P300 and MMN amplitude increased after rTMS treatment, which was in coincidence with clinical recovery ($P<0.05$). However, there was no significance statistical difference in P300 target latency and MMN latency between pre- and post-treatment ($P>0.05$) [Table 4].

**Discussion**

SZ is a serious and highly prevalent mental illness and ranks fourth in the social burden among all diseases worldwide. Thus, several researchers around the world have put tremendous effort into investigating the etiology, pathogenesis, diagnosis, and treatment of SZ.[11] In current study, we used rTMS combined antipsychotic drug to treat SZ patients and assess the efficacy through ERP.

rTMS is a neurophysiological technique which was developed and used in SZ treatment for about 20 years. The main treatment for SZ involves antipsychotic drugs. Although the efficacy of atypical antipsychotic drugs on positive SZ symptoms has been confirmed by various clinical trials, these drugs actually have a poor effect on negative symptoms. In fact, most antipsychotic drugs have adverse reactions which, sometimes, maybe unbearable for SZ patients. To date, no treatment or adjuvant therapy has shown a sustained clinical improvement in negative SZ symptoms.[9] Meta-analysis suggested that, in comparison to the first generation of antipsychotic drugs, the second generation of antipsychotic drugs had a similar effect on negative symptoms, instead of being more effective. The clinical symptoms of SZ, including both negative and positive symptoms, are closely related to cognitive impairment, which is associated with injury in brain, frontal, and subcortical connections.[9] rTMS can affect near and relatively distant cortical function around the stimulation, thereby achieving reconstruction of regional cortical function. Meanwhile, the biological effects can be sustained for a period of time after the intermittence of stimulation. It has become a favorable tool to study the function of neural network reconstruction and explore the treatment efficacy on negative symptoms of SZ.[10,11] In previous studies, we found that the PANSS score was significantly decreased after treatment with real or ShrTMS, especially in the real rTMS group, suggesting that rTMS can improve mental

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**Table 2: Variation of PANSS and SANS scale before and after treatment in 85 patient group (mean ± SD)**

| Items        | Before treatment | After treatment | t    | P     |
|--------------|------------------|-----------------|------|-------|
| PANSS P score| 15.0 ± 4.8       | 14.3 ± 5.1      | 1.10 | >0.05 |
| PANSS N score| 24.1 ± 4.5       | 17.9 ± 6.1*     | 5.79 | <0.01 |
| PANSS G score| 30.4 ± 5.2       | 27.5 ± 4.7*     | 3.17 | <0.05 |
| PANSS T score| 69.6 ± 16.3      | 59.5 ± 17.8*    | 4.29 | <0.01 |
| SANS score   | 49.5 ± 13.4      | 28.9 ± 6.8*     | 9.41 | <0.01 |

Compared to before treatment *P<0.05. PANSS: Positive and Negative Syndromes Scale; SANS: Scale for Assessment of Negative Symptoms; SD: Standard deviation.

**Table 3: Comparison of the latency and amplitude of N400 among 85 SZs before and after treatment and 76 NCs (mean ± SD)**

| Items                     | Category       | Wave | NC | SZ             | Before | After | t     | P     |
|---------------------------|----------------|------|----|----------------|--------|-------|-------|-------|
| Same phonic, different    |                |      |    |                |        |       |       |       |
| shape and meaning         |                |      |    |                |        |       |       |       |
| Congruent                 | Latency (ms)   | 379.0 ± 39.0 | 385.0 ± 37.0 | 0.93 | >0.05 |
| Amplitude (µV)            | 6.3 ± 4.0      | 5.9 ± 4.5 | 7.6 ± 3.9* | 2.71 | <0.05 |
| Incongruent               | Latency (ms)   | 428.0 ± 30.0 | 426.0 ± 29.0 | 1.03 | <0.05 |
| Amplitude (µV)            | 5.2 ± 3.9      | 5.5 ± 3.7 | 5.6 ± 3.9 | 0.91 | >0.05 |
| Different phonic, shape   |                |      |    |                |        |       |       |       |
| and meaning               |                |      |    |                |        |       |       |       |
| Congruent                 | Latency (ms)   | 413.0 ± 48.0 | 419.0 ± 49.0 | 1.39 | <0.05 |
| Amplitude (µV)            | 5.2 ± 4.0      | 2.9 ± 1.0* | 5.2 ± 2.1* | 1.64 | <0.05 |
| Incongruent               | Latency (ms)   | 479.0 ± 43.0 | 479.0 ± 43.0 | 1.11 | <0.05 |
| Amplitude (µV)            | 7.9 ± 3.2      | 5.2 ± 3.3* | 6.9 ± 3.3* | 2.61 | <0.05 |

Compared to the NC group, *P<0.05, †P<0.01; Compared between before and after treatment with rTMS in SZ group, ‡P<0.05, †‡P<0.01. NCs: Normal controls; SZ: Schizophrenia; SD: Standard deviation.
symptoms. Our findings also affirmed that rTMS could be an effective way to treat SZ.\[^{[10]}\] The main therapeutic mechanism may be related to the role that rTMS plays in the left dorsolateral prefrontal cortex, where increased flow perfusion at the stimulation site could speed up metabolism, ultimately improving executive function.\[^{[12]}\]

N400 is one of the most important components of ERP\[^{[14]}\] and is widely used in the cognition process and related psychological activities. Since the 1990s, when Koyama\[^{[13]}\] first reported that N400 amplitude decreased in SZ, there is abundant evidence in the literature to show that N400 amplitude is decreased and N400 latency is delayed in SZ.\[^{[1,7,13,14]}\] Most of these reports used phonetic words as stimuli, especially in English. Due to cultural and language restraints,\[^{[13,14]}\] these results may not be particularly applicable to the Chinese. In the current study, we discuss N400 elicited by Chinese idioms ending with congruent or incongruent Chinese characters and we found that the amplitude of N400 was stable, large, and high when elicited by different phonic, shape, and meaning. In comparison to the control group, the N400 latency was delayed in the SZ group when elicited by congruent idioms with same phonic and different shape and meaning. The latency and amplitude of N400 were decreased in the SZ group when elicited by congruent idioms with different phonic, shape, and meaning. N400 amplitude elicited by incongruent idioms was decreased as well in this group. It indicated that Chinese idiom is suitable to Chinese patients, avoiding cultural difference, which was consistent with abroad investigation and was the same to the previous studies that N400 was suitable for application in patients with SZ.\[^{[15]}\]

The measurement of MMN in our research was obtained from the average brain wave induced by the deviated stimulus minus the average brain wave induced by the standard stimulus, located in the 100–250 ms negative phase wave after the appearance of the beginning auditory deviant stimuli, which was different from highly repetitive standard sound stimulation. Therefore, it is considered as one of the indexes reflecting the auditory and memory system and reflects an automatic processing of the brain’s response to external stimuli.\[^{[9]}\] The data of P300 and MMN in the patient group showed that, in comparison to the NC group, MMN latency was delayed and MMN amplitude was decreased, while the P3 target wave in the P300 was also decreased in the SZ group. The changes in the N400, P300, and MMN components in the ERP were similar to results reported in the foreign literature.\[^{[1,7,13,14,16-18]}\] In the 1990s, Roth reported that the P300 amplitude was decreased in SZ, and other studies have also shown that P300 amplitude is decreased and latency is delayed in these patients.\[^{[16-18]}\] MMN is a new component of ERP which was developed on the basis of P300 and founded by Naatanen et al.\[^{[6]}\]

Some of the recruited SZ patients were inpatients; although rTMS can improve the latency and amplitude of N400, P300, and MMN in SZ patients, further follow-up studies need to be conducted to provide direct evidence related to the cognitive function of patients.

Compared to research from abroad, the present study has made some progress in the field.\[^{[19]}\] SZ is a chronic mental disorder, involving long-term duration of treatment. Based on results from our previous research studies, we prolonged the time for rTMS therapy and chose the dorsolateral prefrontal cortex as the stimulation site with 110% MT. Our current results showed that the P300, MMN, and N400 amplitudes recovered after 25 treatments of rTMS. These findings indicated that cognitive disorder was responsible for the sustained symptoms of SZ, and that P300, MMN, and N400 could efficiently reflect the patients’ cognitive function.\[^{[19]}\] In addition, we theorized that a combination of antipsychotic drugs and rTMS could have an effect on the negative symptoms of SZ. The academic research and clinical application potential of rTMS were improved through the addition of N400, MMN, and P300 for evaluating its clinical efficacy in SZ. We believe that ERP is more sensitive to the dynamic changes in advanced cognitive function in the cerebral cortex of SZ patients over time and can be used as a reliable and objective tool to determine their short- and medium-term prognosis.

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### Conflicts of interest

There are no conflicts of interest.

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### Table 4: Comparison of P300 and MMN indexes among 85 SZs before and after treatment and 76 NCs (mean ± SD)

| Items  | Wave  | NC     | Before     | After     | t     | P  |
|--------|-------|--------|------------|-----------|-------|----|
| P300-P3| Target latency (ms)  | 331.0 ± 17.0 | 338.0 ± 16.0 | 1.64 | >0.05 |
|        | Target amplitude (µV) | 7.6 ± 4.8 | 5.3 ± 2.1*‡ | 3.31 | <0.05 |
| MMN    | Latency (ms)         | 209.0 ± 30.0 | 220.0 ± 39.0 | 1.07 | <0.05 |
|        | Amplitude (µV)       | 8.3 ± 3.4  | 5.5 ± 3.1*‡ | 4.01 | <0.05 |

Compared to the NC group, \( P < 0.05, \) \( P < 0.01; \) Compared between before and after treatment with rTMS in SZ group, \( * P < 0.05, \) \( \) \( \) \( \)$P < 0.01. NCs: Normal controls; SZ: Schizophrenia; SD: Standard deviation; MMN: Mismatch negativity.
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