

Follow-up of N400 in the Rehabilitation of First-episode Schizophrenia

Xiang-Dong Du¹, Guang-Ya Zhang¹, Yong Yang¹, Zhe Li¹, Wen Pan¹, Guang-Zhong Yin¹, Ri-Xia Dong¹, Hai-Jun Gai¹, Gang Ye¹, Jian-Gong Yang¹, Ying Yuan¹, Neng-Rong Pan¹, Wei-Qin Li¹, Xiao-Wen Xu¹, Xing-Shi Chen²

¹Department of Psychiatry, Suzhou Psychiatric Hospital, Suzhou, Jiangsu 215008, China

²Department of Electrophysiology, Shanghai Mental Health Center, Shanghai JiaoTong University, Shanghai 200030, China

Abstract

Background: The N400 component of event-related potentials (ERP) has recently drawn widespread attention at home and abroad. This study was to explore the relationship between N400 changes and risperidone treatment and rehabilitation in first-episode schizophrenia (FES).

Methods: ERP component N400 was recorded by Guangzhou Runjie WJ-1 ERP instruments, in 58 FES before and 6 months, 15 months after risperidone treatment, and in 62 normal controls. The patients' syndromes were assessed by Positive and Negative Syndrome Scale (PANSS). And the stimuli are Chinese sentences with matching (congruent) or mismatching (incongruent) ending words.

Results: N400 latencies were prolonged, and amplitudes were decreased in Cz, Pz, Fz, C3, C4, in FES compared with in NC, before treatment. The prolonged N400 latencies and decreased amplitudes were negatively correlated with the patients' positive scale and total scale of PANSS. There are significant differences of N400 amplitudes and latencies in 6 months and 15 months follow-up after treatment. Before treatment, 6 months and 15 months after treatment, N400 latencies are 446 ± 35 ms, 440 ± 37 ms, 414 ± 31 ms ($F = 9.72$, $P < 0.01$) in incongruent situation; N400 amplitudes are 5.2 ± 4.6 μ V, 5.7 ± 4.8 μ V, 7.3 ± 5.0 μ V ($F = 2.06$, $P > 0.05$) in congruent situation, and 8.5 ± 5.9 μ V, 10.1 ± 5.0 μ V, 11.9 ± 7.0 μ V ($F = 3.697$, $P < 0.05$) in incongruent situation.

Conclusions: N400 could be used to predict the effects of treatment of schizophrenia to some degree. The linguistic and cognitive impairment in schizophrenia can be improved by antipsychotic drugs.

Key words: Chinese Sentence; Effects of Treatment; Events Related Potentials; N400; Schizophrenia

INTRODUCTION

The N400 component of event-related potentials (ERP) has recently drawn widespread attention at home and abroad. Its clinical value is that, not only is it most frequently used to assess diseases associated with linguistic disorder in the department of neurology and psychiatry,^[1,2] but also, to effectively improve patients' linguistic disorder has become an important candidate target of the research and development on the new generation of anti-psychotic drugs.^[3,4] This research enrolled patients with first-episode schizophrenia (FES), who had never taken any antipsychotic drugs before, and carried out a 1-year follow-up on them. This way, we could eliminate the cross-effect among different antipsychotic drugs and draw some conclusions on N400 changes in FES patients and its clinical value.

METHODS

Subject

The patient group included a total of 58 patients of the Han Nationality, who were out-patients and in-patients with FES in Shanghai Mental Health Center Affiliated to School of Medicine, Shanghai JiaoTong University from January 2009 to February 2014. The criteria of enrollment were: (1) The schizophrenic patients had no history of antipsychotic treatment and visited Shanghai Mental Health Center for the first time in their life, (2) the symptoms fitted the diagnostic criteria of schizophrenia in the Chinese Classification of Mental Disorders-3 and the Diagnostic and Statistical Manual of Mental Disorders-IV, (3) mother language: Chinese, fluent in spoken and written Mandarin, (4) they had no organic mental health disorders, psychotic diseases other than schizophrenia, or history of substance dependence.

The 58 patients consisted of 30 males and 28 females. Age: 19–51 years, mean age: 29.5 ± 7.3 years, and average education

Access this article online

Quick Response Code:



Website:
www.cmj.org

DOI:
10.4103/0366-6999.162499

Address for correspondence: Prof. Xing-Shi Chen,
Department of Electrophysiology Shanghai Mental Health
Center, Shanghai JiaoTong University, Shanghai 200030, China
E-Mail: chenxingshi2008@163.com

years: 16.3 ± 2.9 years. Disease course: 0.6–2.5 years (beginning from the moment when the patients' relatives firstly found them strange until their enrollment into the group), median: 1.6 years. Their Positive and Negative Syndrome Scale (PANSS) total score at the moment of enrollment was 104.3 ± 11.7 .

The normal controls (NCs) consisted of the volunteers from Shanghai Mental Health Center affiliated to School of Medicine of Shanghai JiaoTong University, Shanghai JiaoTong University School of Medicine and the communities nearby from January 2009 to February 2014. The criteria of enrollment were: (1) No physical diseases were found during the physical examination, (2) the complete blood count, biochemical routine, and chest radiograph showed no abnormality, (3) the candidates received psychiatric interviews to insure that they had never had any mental disorder before and were then in good mental health, (4) the candidate's second-degree and third-generation relatives had no history of psychosis, (5) mother language: Chinese, fluent in spoken and written Mandarin, education level: College degree and above. A total of 62 candidates, 33 males and 29 females, were enrolled. Age: 19–50, mean age: 29.6 ± 6.6 , and average education years: 16.7 ± 2.2 years.

There was no significant difference in sex, age, nationality, or education level between the two groups ($P > 0.05$). Both groups had no visionary or auditory disorders. The patients or their guardians have all been informed and signed on the informed consent forms.

Methods

Stimuli

The task is consisted of 76 sentences in Chinese. The sentences were presented in random sequence. The last word of each sentence is the target word, which classifies the sentence into one of the two groups, matching (congruent) or mismatching (incongruent). When the logical and semantic relationship between the target word and the main body of the sentence is highly expected, the sentence is congruent. For example, "In the coffee, I put sugar" is congruent. Otherwise, if the expected probability of this relationship is zero, the sentence is incongruent. For example, "In the coffee, I put a dog" is incongruent. The stimuli are presented word by word. Among the 76 sentences, 31 are congruent, and 45 are incongruent. All the words in the stimuli are high-frequency Chinese words, whose frequency of use is higher than 30 times per 10,000. Their number of strokes is between 4 and 14.

Presentation of the stimuli

We referred to the Chinese sentence tests of Zhou *et al.*^[5] and Yang *et al.*^[6] The eyes of the subjects kept parallel with the words, with a distance of 1 m to the screen.

Process of the test

The subject sits comfortably on a chair. Before the test sets off, the subject is verbally informed of the nature and requirements of the test. Below is the verbal instruction:

Some Chinese sentences will present on the screen in front of you. At the end of the countdown, the test will set off.

During the test, please try to avoid blinking and keep silence. Judge carefully whether the word that lastly appears in the sentence is semantically correct until the screen turns black. After the test ends, your number of correct and incorrect answers will be shown (if the sentence is incongruent, the subject clicks on "NO;" if it is congruent, the subject clicks on "YES").

Recording areas

The Guangzhou Runjie WJ-1 ERP instruments were used in the test. In accordance with the International 10–20 system, the electrodes at Fp1, Fp2, Fz, F3, F4, Cz, C3, C4, Pz, P3, P4, O1, O2, F7, F8, T3, T4, T5, T6, FP locations were grounding electrodes. The electrodes at A1, A2 locations (at two ears) were reference electrodes. The electrode resistance was $<5 \text{ k}\Omega$. The wave filtering was between 0.53 and 60 Hz. The analyze time window of N400 was set to be 1100 ms. The waves whose amplitude were bigger than $75 \mu\text{V}$ due to eye movements or other factors were eliminated. The collected data were kept on the hard disk of the computer for further use.

Medication

All the patients were medicated only with risperidone (Xian-Janssen Pharmaceutical Ltd., Risperdal). The combination use of other anti-psychotic drugs was prohibited.

The therapeutic effect was evaluated with the PANSS before treatment, 6 months after treatment, and 15 months after treatment. The primary evaluation index is the reduction rate of PANSS total score at the end of 6 months after treatment. It is calculated as below:

$$\text{Reduction rate} = (\text{PANSS total score before treatment} - \text{PANSS total score after treatment}) / \text{PANSS total score before treatment} \times 100\%$$

Statistical analysis

The maximal N400 latencies and amplitudes at Fz, Cz, and Pz were detected for each congruent or incongruent ERP. The instrument has the function of automatic elimination of artifact and noise abatement. All data were automatically detected, calculated, and presented by the digital cursor of this instrument. The data were processed with SPSS version 11.0 (SPSS Incorporated, Chicago, USA). The *t*-test analyzed inter-group differences of N400 components. The *F* test analyzed changes in the FES group between before and after treatment. The correlation between N400 components of the FES group and PANSS scores was calculated with Spearman correlation analysis. *P* values <0.05 were considered statistically significant.

RESULTS

A comparison of N400 components between FES and NC before treatment

Compared with NCs, N400 latencies in the patient group at the 5 locations were significantly prolonged before treatment. In both congruent and incongruent situations, N400 latency

at Cz was more prolonged in the patient group than NCs. The changes in N400 latency in the patient group were alike at Fz, Pz, C3, and C4 locations [Table 1].

Compared with NCs, N400 amplitudes in the patient group at the 5 locations were significantly decreased before treatment. In both congruent and incongruent situations, N400 amplitude at Cz was smaller in the patient group than NCs. The changes in N400 amplitude in the patient group were alike at Fz, Pz, C3, and C4 locations.

The correlation (*r*) between PANSS and N400 at Cz in FES patients

After risperidone treatment, the symptoms were significantly improved in schizophrenia patients. Positive scores, negative scores, and general psychopathology scores, and total scores were significantly decreased at 6 and 15 months after treatment [Table 2].

At Cz location, the prolongation of N400 latency was negatively correlated with PANSS positive symptoms score (-0.463 , $P = 0.032$), and the decrease of N400 amplitude was negatively correlated with PANSS positive symptoms score (-0.431 , $P = 0.008$) and PANSS total score (-0.382 , $P = 0.023$).

Follow-up of N400 in FES patients

Among the 58 FES patients, we carried out follow-up on 52 of them 6 months after treatment, and on 45 of them 15 months after treatment. The loss to follow-up was due to the fact that some patients lived outside Shanghai or had moved away. As shown in Table 2, 6 months after the risperidone

treatment, the 58 FES patients' psychotic symptoms did not significantly alleviate, and there was no significant difference in N400 latency or amplitude between then and before treatment. However, 15 months after the treatment, their psychotic symptoms began to alleviate (PANSS total score 29.5 ± 3.3 , reducing rate $>50\%$), and N400 began to improve: N400 latency moved forward and N400 amplitude increased. There was a significant difference in N400 latency and amplitude ($P < 0.05$) [Table 3].

DISCUSSION

As an endogenous component of ERP, N400 reflects the linguistic and cognitive process of the brain and has increasingly received widespread attention. Ever since the 1990's when Koyama *et al.*^[7] firstly reported N400 changes in schizophrenic patients, quite an amount of repeated research has found decreased N400 amplitude and prolonged

Table 2: PANSS scores of schizophrenia patients at baseline, 6 months, and 15 months

Groups	Baseline	6 months	15 months	F	P
PS	16.4 ± 7.2	11.9 ± 3.3 [†]	9.3 ± 2.1 ^{†*}	7.459	0.000
NS	23.8 ± 11.5	15.4 ± 5.6 [†]	13.2 ± 5.9 [†]	9.603	0.000
GPS	42.7 ± 18.2	24.2 ± 14.3 [†]	21.9 ± 8.3 [†]	11.023	0.000
TS	88.1 ± 24.1	52.6 ± 19.3 [*]	48.3 ± 16.4 ^{**}	9.287	0.000

Compared with before treatment: * $P < 0.05$, [†] $P < 0.01$. Compared with 6 months after treatment: [‡] $P < 0.05$. PANSS: Positive and Negative Syndrome Scale; PS: Positive scores of PANSS; NS: Negative scores of PANSS; GPS: General psychopathology scores of PANSS; TS: Total scores of PANSS.

Table 1: Comparison of N400 latency and amplitude in congruent and incongruent situations, 62 NCs and 58 FES (mean ± SD)

Location	Group	Latency (ms)		Amplitude (μV)	
		Congruent	Incongruent	Congruent	Incongruent
Cz	NC	358.1 ± 32.1	409.5 ± 28.8	8.6 ± 5.1	13.4 ± 6.7
	FES	394.4 ± 44.6	446.3 ± 35.1	5.3 ± 4.5	8.6 ± 5.8
	<i>t</i>	4.97	6.26	2.84	4.31
	<i>P</i>	<0.01	<0.01	<0.05	<0.01
Fz	NC	380.5 ± 28.6	398.5 ± 29.6	8.4 ± 4.8	12.9 ± 6.8
	FES	389.9 ± 30.9	434.0 ± 44.1	8.6 ± 4.0	9.6 ± 5.4
	<i>t</i>	1.84	5.25	0.19	3.09
	<i>P</i>	>0.05	<0.01	>0.05	<0.05
Pz	NC	352.7 ± 32.9	416.6 ± 34.9	9.5 ± 5.0	11.9 ± 6.4
	FES	384.8 ± 45.1	429.4 ± 42.5	6.3 ± 4.1	10.0 ± 6.1
	<i>t</i>	4.21	1.56	3.88	1.59
	<i>P</i>	<0.01	>0.05	<0.01	>0.05
C3	NC	389.1 ± 37.8	401.3 ± 32.9	8.7 ± 4.7	12.3 ± 5.9
	FES	396.3 ± 40.7	429.0 ± 36.1	9.1 ± 4.9	9.3 ± 6.6
	<i>t</i>	0.87	4.39	0.23	2.69
	<i>P</i>	>0.05	<0.01	>0.05	<0.05
C4	NC	356.4 ± 35.9	411.9 ± 31.6	9.8 ± 5.1	11.2 ± 6.8
	FES	353.2 ± 38.2	442.6 ± 38.1	5.4 ± 4.0	12.3 ± 5.6
	<i>t</i>	0.306	4.69	4.58	0.81
	<i>P</i>	>0.05	<0.01	<0.01	>0.05

SD: Standard deviation; NC: Normal control; FES: First episode schizophrenia.

Table 3: A comparison of N400 components in congruent and incongruent situations, FES, before and after treatment (Cz) (mean ± SD)

Groups	Number of subjects	Latency (ms)		Amplitude (µV)	
		Congruent	Incongruent	Congruent	Incongruent
Before	58	394.4 ± 44.6	446.3 ± 35.1	5.3 ± 4.5	8.6 ± 5.8
6 months	52	394.9 ± 42.5	438.8 ± 36.5	5.8 ± 4.7	9.8 ± 5.0
15 months	45	386.4 ± 31.9	412.5 ± 31.3 ^{‡§}	7.4 ± 5.0*	11.8 ± 7.0 ^{‡*}
<i>F</i>		0.39	8.97	2.07	3.71
<i>P</i>		>0.05	<0.01	>0.05	<0.05

Compared with before treatment: * $P < 0.05$, [‡] $P < 0.01$. Compared with 6 months after treatment: [‡] $P < 0.05$, [§] $P < 0.01$. FES: First episode schizophrenia; SD: Standard deviation.

N400 latency in schizophrenic patients. N400 has become a long-term research topic. Currently, sentence stimuli are most frequently used in N400 tests.^[1,3,5-12]

The operational paradigm of this study accords with the recording standards and publication criteria of ERP proposed by the Society for Psychophysiological Research.^[13] This study selected the FES patients, who had never taken anti-psychotic drugs and whose disease course was <2 years, so that the cross-effect of multiple factors on the cerebral function, such as anti-psychotic drugs, nondrug treatments (e.g., electro-convulsive therapy), and long-term disease course, could be eliminated and the dynamic progression of the disease could be observed. In this study, the data collected on N400 show that: (1) Latency – Compared with NCs, N400 latencies in the patient group at the 5 locations were significantly prolonged before treatment. In both congruent and incongruent situations, N400 latency at Cz was more prolonged in the patient group than NCs. The changes in N400 latency in the patient group were alike at Fz, Pz, C3, and C4 locations. (2) Amplitude – Compared with NCs, N400 amplitudes in the patient group at the 5 locations were significantly decreased before treatment. In both congruent and incongruent situations, N400 amplitude at Cz was smaller in the patient group than NCs. The changes in N400 amplitude in the patient group were alike at Fz, Pz, C3, and C4 locations. The results of this study are the same as that of Grillon *et al.*^[12] The decreased N400 amplitude means that schizophrenic patients cannot make correct semantic expectations face to irrelevant semantic stimuli, which suggests that the patients' impaired semantic information process function could lead to the worsening of speed and accuracy in making semantic expectations. The prolonged N400 latency means that the information process of stimuli in schizophrenic patients is slowed down or easy to interrupt.

Andrews reported that the positive symptoms score of thought and attention disorder was negatively correlated with the average N400 amplitude in a time-window of 300–500 ms.^[1] Until now, it is unclear if N400 reduction relates to real-world functioning and recovery.^[14,15] This study found that the prolongation of N400 latency and decrease of N400 amplitude were negatively correlated with PANSS total score and positive symptoms score. This suggests that

N400 latency and amplitude change with the progression of the disease, and thus reflect the seriousness of schizophrenia.

Is N400 a trait marker, a state marker, or a mix of the two in schizophrenia? The follow-up in this study plays an important role in verifying the nature of this marker. The follow-up in this study shows that there was a significant difference in N400 changes between patients with notable psychotic symptoms and patients whose symptoms have alleviated. The follow-up included N400 aberration data from before treatment until the disappearance or alleviation of symptoms. The aberration of N400 is a state marker that indicates the existence of schizophrenia. As the disease ameliorates, N400 gradually turns normal. Therefore, the aberration of N400 is a state marker that indicates the onset and seriousness of the disease, and the impairment of N400 might be one of the important pathogenetic factors of schizophrenia. Currently, there is a lack of biological markers to facilitate the clinical diagnosis of psychotic diseases. N400 has been used as a candidate electroencephalologic marker in a series of research on schizophrenia.^[2]

Currently, in Europe and North-America, N400 has been used in the acologic and pharmacological research on neuropsychiatric drugs.^[16,17] In our study, we found that during the early stage of treatment, the antipsychotic drug did not have a great influence on N400. This result was the same as that of Hokama *et al.*^[9] In other words, N400 in schizophrenic patients is relatively stable at the beginning of the medical treatment, and thus, clinical examinations on N400 are feasible after a short period of medical treatment.^[18] The mechanism of this result remains to be studied. Since all of the schizophrenic patients in this study only took risperidone, further follow-up needs to be carried out on patients who take other antipsychotic drugs in order to see if the same conclusion could be reached.

There are several limitations in the present study. First, as only risperidone was used in the treatment of schizophrenia, the results may not suit to other situations. Second, the materials used in this study are Chinese sentences, which may also cause some bias when inferring the results to phonetic materials.

N400 reflects the word cognition process and its time resolution is high. Therefore, it can be used as a cognitive

electrical potential with clinical value to assess multiple diseases associated with linguistic disorder. During the recent years, the combination of N400 and the neuroimaging technique has opened up a whole new field for the research on N400 as well as on language. In addition, if the research on N400 could combine the knowledge of genetics, molecular biology, psychopharmacology, and psychotic symptoms, it will help to fully understand this potential biological marker of N400 and the mechanism of cerebral dysfunction in schizophrenia.^[19,20] That will be our future field of research.

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Received: 15-02-2015 **Edited by:** Li-Min Chen

How to cite this article: Du XD, Zhang GY, Yang Y, Li Z, Pan W, Yin GZ, Dong RX, Gai HJ, Ye G, Yang JG, Yuan Y, Pan NR, Li WQ, Xu XW, Chen XS. Follow-up of N400 in the Rehabilitation of First-episode Schizophrenia. *Chin Med J* 2015;128:2215-9.

Source of Support: Nil. **Conflict of Interest:** None declared.