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Impaired error-related processing in patients with first-episode psychosis and subjects at clinical high-risk for psychosis: An event-related potential study

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Impaired error-related processing in patients with first-episode psychosis and subjects at clinical high-risk for psychosis: An event-related potential study

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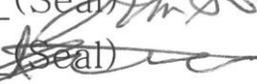
Abstract

Background: Impaired event-related potential (ERP) indices reflecting performance monitoring systems have been consistently reported in patients with schizophrenia. However, whether these impairments exist from the beginning of the early phase of psychosis, such as in first-episode psychosis (FEP) patients and individuals at clinical high risk (CHR) for psychosis, has not yet been clearly explored.

Methods: Thirty-seven FEP patients, 22 CHR subjects, and 22 healthy controls (HCs) performed a visual go/no-go task so that three ERP components associated with performance monitoring—error-related negativity (ERN), correct response negativity (CRN) and error positivity (Pe) —could be assessed. Repeated measures analysis of variance (ANOVA) with age and sex as covariates was used to compare ERN, CRN and Pe across groups.

Results: Repeated measures ANOVA with age and sex as

covariates revealed that FEP patients and CHR subjects showed significantly smaller ERN amplitudes at Fz (F = 4.980, p = 0.009) and FCz (F = 3.453, p = 0.037) electrode sites compared to those of HCs. Neither CRN nor Pe amplitudes showed significant group differences across FEP, CHR and HC groups.

Conclusion: These findings suggest that performance monitoring is already compromised during the early course of psychotic disorders, evident in FEP patients and CHR subjects, as reflected in the reduced ERN amplitude. Taken together, ERN could serve as a potential indicator of early stages of psychosis.

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List of Abbreviations

ERP: event-related potential

FEP: first-episode psychosis

CHR: clinical high risk

HC: healthy control

ERN: error-related negativity

CRN: correct response negativity

Pe: error positivity

ANOVA: analysis of variance

DUP: duration of untreated psychosis

SCID-I: Structured Clinical Interview for the Diagnostic and
Statistical Manual of Mental Disorders, Fourth Edition Axis I
Disorders

PANSS: Positive and Negative Syndrome Scale

SIPS: Structured Interview for Prodromal Symptoms

SOPS: Scale of Prodromal Symptoms

IQ: intelligence quotient

EEG: electroencephalography

DOI: duration of illness

Chapter 1. Introduction

1.1. Study Background

The ability to monitoring one's own performance is fundamental and pertinent for goal-directed behaviors in social functioning (Ullsperger et al., 2014); this ability enables individuals to integrate intended goals and real performances. Deficiency of performance monitoring, which has been consistently reported in patients with schizophrenia, is also related to impaired social functioning in patients with the disorder (Divilbiss et al., 2011). Furthermore, researchers have proposed that positive symptoms or thought disorders are caused by the inability to monitor behavior resulting from a discrepancy between internally generated action and externally induced action (Frith and Done, 1988, McGrath, 1991). Given these clinical implications for psychotic disorders, investigating the neural substrates of performance monitoring is essential for understanding psychotic disorders in depth.

To better comprehend the neural mechanism of performance monitoring, electrophysiological studies have identified 3 event-related potential (ERP) components associated with error-related

processing or monitoring systems, namely, error-related negativity (ERN), correct response negativity (CRN), and error positivity (Pe). ERN is a negative deflection of the ERP wave observed following an erroneous response, which is generally assessed with choice reaction time tasks (e.g., flanker, go/no-go paradigm, stroop tasks)(Falkenstein et al., 1991, Gehring et al., 1993). CRN is a smaller negative deflection following a correct response, which occurs at the same time course and location as ERN (Coles et al., 2001, Falkenstein et al., 2000), and it reflects conflict monitoring or partial error detection (Coles et al., 2001). Pe is a positive deflection observed between 250 – 450 ms after the onset of an error response, which is associated with conscious error awareness or motivation to correct errors (Endrass et al., 2007, Nieuwenhuis et al., 2001). Previous studies investigating these ERP components of performance monitoring consistently reported reduced ERN (Martin et al., 2018, Mathalon et al., 2002, Morris et al., 2008) and enlarged CRN (Mathalon et al., 2002, Morris et al., 2006) amplitudes in schizophrenia patients compared to those of healthy controls (HCs). With regard to Pe, most of the studies reported Pe amplitudes to be normal in schizophrenia (Mathalon et al., 2002, Horan et al., 2012), with a few exceptions reporting a reduction in amplitude (Perez et al.,

2012, Foti et al., 2012). Previous studies were performed in schizophrenia patients with a relatively long duration of illness (Mathalon et al., 2002, Morris et al., 2008); thus, the results may have been confounded by the effect of aging, medication exposure, and disease chronicity.

It is unclear whether the ERP components of performance monitoring are also impaired in the early stages of psychosis, such as in fist-episode psychosis (FEP) patients and in individuals at clinical high risk (CHR) for psychosis; hence, these components should be explored during the stages of psychosis since past findings from chronic schizophrenia patients may have been affected by potential confounders, such as disease chronicity, exposure to antipsychotics, and relatively old age. In addition, as it is well known that a shorter duration of untreated psychosis (DUP) is essential for a better schizophrenia prognosis(Perkins et al., 2005), investigation of biomarkers that could identify the patients in the earlier stages of the disorder would aid in efforts to improve clinical outcomes. However, there has been only one study that has explored ERP components related to performance monitoring across the FEP, CHR, and HC groups(Perez et al., 2012). In their seminal study, Perez *et al.*

(Perez et al., 2012) reported that FEP patients showed smaller ERN, larger CRN, and smaller Pe amplitudes compared to HCs, but CRN and Pe amplitudes in CHR subjects were comparable to those of HCs. Despite the clinical implication of performance monitoring impairments in early psychosis patients, to the best of our knowledge, no follow-up study has been reported after the Perez *et al.* (Perez et al., 2012) study was published.

Notably, it has been suggested that self-related stimuli could enhance ERP components associated with attentional processing (Gray et al., 2004, Tacikowski and Nowicka, 2010). Self-related stimuli, such as one's own name or face, are known to be processed mostly automatically, faster and more accurately than other types of stimuli (e.g., other's name or face stimuli)(Gray et al., 2004, Brédart et al., 2006). Attention is also associated with monitoring functions (Manna et al., 2010); this association could enable subjects to have better performance monitoring regarding self-relevant stimuli (e.g., the subject's own name stimuli) than for stimuli not related to the self (e.g., other's name stimuli). In addition, accurate self-appraisal and self-monitoring have been reported to be essential for preserving or providing good insight into psychosis (Kircher et al., 2003, Shad et

al., 2007). Since no previous studies have explored the effect of self-referential stimuli on ERP indices of monitoring systems in patients with psychotic disorders, we wanted to evaluate the effect of self-related stimuli (e.g., one's own name) on performance monitoring as measured by ERN amplitude.

1.2. Purpose of Research

The current study aimed to investigate whether ERP components (i.e., ERN, CRN, and Pe) that reflect performance monitoring are compromised in the early stages of psychosis (i.e., FEP and CHR) as indicated by the previous findings in chronic schizophrenia patients and in the Perez *et al.* study (Mathalon et al., 2002, Perez et al., 2012). In addition, for an exploratory purpose, we aimed to investigate the effect of self-related stimuli on impairments in error monitoring reflected in ERN amplitude in early psychosis patients. We hypothesized that FEP and CHR participants would show smaller ERN amplitudes, larger CRN amplitudes and intact Pe amplitudes compared to the amplitudes of HCs. We also expected that error monitoring would be improved when the self-related stimuli, which were the subject's own name in this study, were presented; this improvement would be reflected as an increase in ERN amplitude.

Chapter 2. Methods

2.1. Participants and Clinical Assessments

Thirty-seven FEP patients, 22 subjects at CHR for psychosis, and 22 HCs participated in this study. The participants in the FEP and CHR groups were recruited from the inpatient and outpatient clinics in the Department of Neuropsychiatry of Seoul National University Hospital (SNUH) and the Seoul Youth Clinic (www.youthclinic.org)(Kwon et al., 2012). The inclusion criteria for FEP subjects were as follows: 1) between the ages of 16 and 40; 2) diagnosis of schizophreniform disorder, schizophrenia or schizoaffective disorder using the Structured Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Axis I Disorders (SCID-1); and 3) psychotic disorder duration of less than 2 years. The severity of psychotic symptoms was assessed using the Positive and Negative Syndrome Scale (PANSS). CHR status was confirmed using the validated Korean version of the Structured Interview for Prodromal Symptoms (SIPS)(Jung et al., 2010, Miller et al., 2003) when subjects met at least one of the three established criteria for the prodromal psychosis state: 1) attenuated positive symptoms state (APS), 2) the presence of brief intermittent

psychotic symptoms (BIPS), and 3) genetic risk with deterioration (GRD). The severity of prodromal symptoms was assessed using the Scale of Prodromal Symptoms (SOPS). All of the clinical assessments were performed by certified psychiatrists. Prescribed medication at the time of ERP recording was obtained from the review of electronic medical records in both FEP and CHR participants. The dose of antipsychotic medication was calculated as the olanzapine equivalent dose (Gardner et al., 2010). HCs were recruited via internet advertisement and screened using SCID-I Nonpatient Edition (SCID-NP). HCs were excluded when they had any first- to third-degree biological relatives with a psychotic disorder. The common exclusion criteria for all groups were a diagnosis at any point in time of substance abuse or dependence, neurological disease or history of head injury accompanied by loss of consciousness, medical illness with documented cognitive sequelae, sensory impairments, or intellectual disability (intelligence quotient [IQ] < 70).

Written informed consent was obtained from all subjects after they were provided with a thorough explanation of the study procedure in the previous prospective cohort study (IRB no. H-1201-008-392). In the case of minors, their parents provided written informed consent, and youths provided written informed assent. The

study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of the Seoul National University Hospital (IRB no. H-2003-241-111).

2.2. Task and Procedure

All study participants performed a visual go/no-go task presented by STIM2 software (Neuroscan, ElPaso, TX, USA), in which they had to press a button as quickly as possible when they encountered a go stimulus and to refrain from pressing the button for a no-go stimulus. Each block included a pseudorandom series of go stimuli (70%) and no-go stimuli (30%), and two no-go stimuli were never presented in succession. Go stimuli included 10 names of former presidents in South Korea, and the no-go stimulus was the name of the current president in South Korea. In addition, we utilized an exploratory condition to test the effect of self-related stimuli on ERN. In this exploratory condition (i.e., own-name condition), 10 names of famous movie stars were presented as go stimuli, and the participant's own name was the self-related no-go stimulus. The main experimental condition with the names of former and current presidents (i.e., other-name condition) were used as the control condition in the exploratory study. Each stimulus was displayed for

200 ms, the intertrial interval was 1300 ms, and the task comprised 300 trials in each block. During the task procedure, a block of the other-name condition and own-name condition were presented twice in an alternating order; thus, the entire task included a total of 4 blocks and 1200 trials.
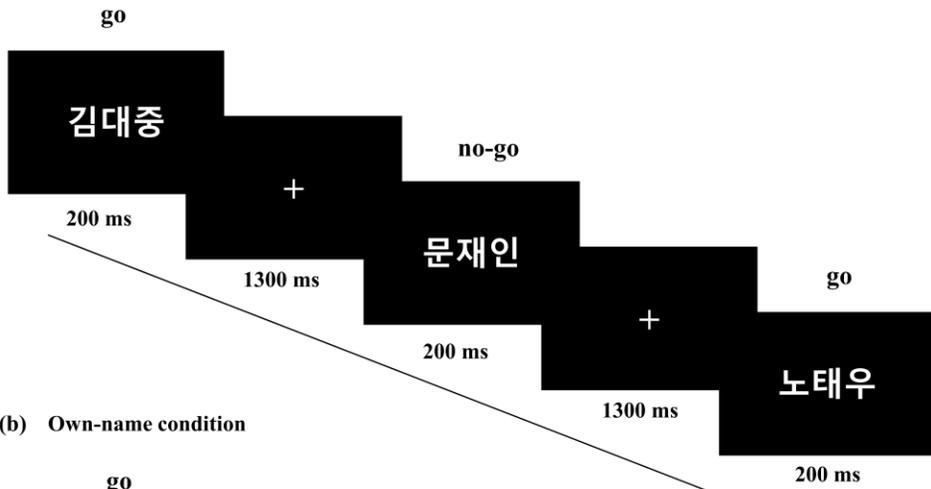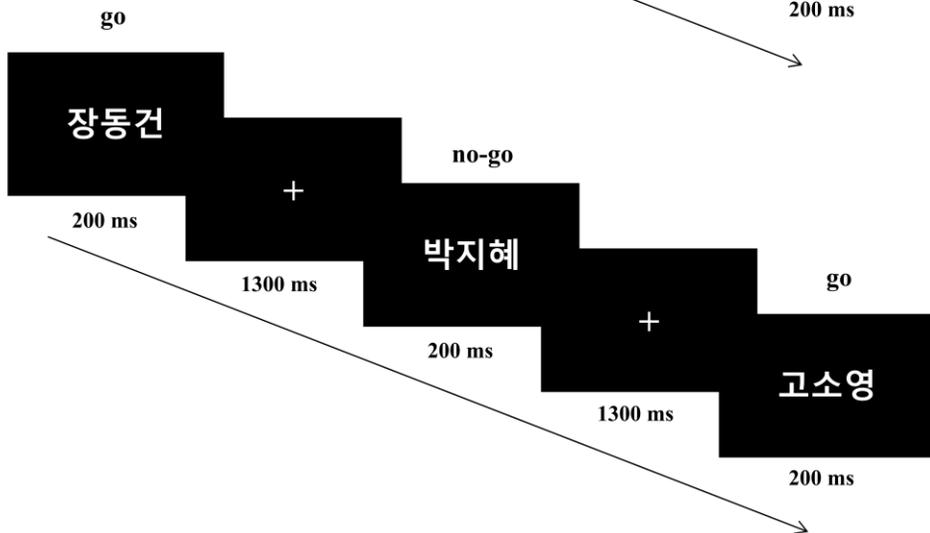
Figure 1. The trial sequence of the visual go/no-go task. (a) In the other-name condition, the names of former and current presidents are presented; the names of the former presidents are go stimuli, and the name of the current president is a no-go stimulus. (b) In the own-name condition, the participant's own name and the names of the famous movie stars are presented; the names of the famous

movie stars serve as go stimuli, and the participant's own name

serves as a no-go stimulus.

2.3. ERP Acquisition and Data Analysis

Continuous electroencephalography (EEG) data were acquired using a Neuroscan Synamps 2 system (Neuroscan, ElPaso, TX, USA) with a 128 channel Quik-cap based on a modified international 10-20 system during go/no-go task performance. The electrodes at each mastoid site served as reference electrodes. EEG data were digitized with a 1000-Hz sampling rate, and an online low pass filter of 100 Hz was applied. The ocular artifacts were monitored by recording the vertical and horizontal electro-oculograms using electrodes below and on the outer canthus of the left eye. The impedance for all electrodes was kept below 5 kΩ.

Curry 7 software (Compumedics, Charlotte, NC, USA) was used for ERP data analysis. The band channel was interpolated using the signal from adjacent electrode sites (up to 7% per participant). Eye-movement artifact reduction was performed by using the artifact reduction algorithm implemented in Curry 7 software(Semlitsch et al., 1986). Continuous EEG data were rereferenced to the common average reference data, bandpass filtered between 0.1 and 30 Hz, and divided into 1000 ms response-locked epochs between 100ms preresponse and 900 ms postresponse. Baseline correction was performed using the averaged voltage of the preresponse interval.

Epochs containing voltages exceeding ±75 μV were automatically rejected. All subjects had to have at least 11 error trials to be included in analysis. The number of remaining epochs from the main experimental condition (i.e., other-name condition) was not significantly different across the groups for all error trials (FEP group, 40.35 ± 22.46; CHR group, 46.50 ± 35.69; HC group, 31.27 ± 13.40; F = 1.849, p = 0.164) and correct trials (FEP group, 336.57 ± 62.97; CHR group, 296.91 ± 62.97; HC group, 328.36 ± 83.09; F = 2.318, p = 0.105). Detailed information regarding the number of remaining epochs in both the main experimental and exploratory conditions is presented in Table 1. The remaining epochs from error trials were averaged to calculate ERN and Pe, and epochs from correct trials were averaged to determine CRN. Based on prior studies, amplitudes of the ERN and CRN were measured from 6 fronto-central electrode sites (F3, Fz, F4, FC3, FCz, and FC4), defined as the largest negative peak between 0 ms and 150 ms after response onset. Pe was measured from 6 centro-parietal electrode sites (CP3, CPz, CP4, P3, Pz, and P4), defined as the largest positive peak between 250 ms and 450 ms postresponse.

Table 1. Group comparison of the number of epochs used for analysis in each condition.

	FEP (N=37)	CHR (N=22)	HC (N=22)	Statistical analysis[†] F	P
Other-name					
Error	40.35 ± 22.46	46.50 ± 35.69	31.27 ± 13.40	1.849	0.164
Correct	336.57 ± 62.97	296.91 ± 62.97	328.36 ± 83.09	2.318	0.105
Own-name					
Error	34.84 ± 22.96	45.45 ± 31.89	27.14 ± 12.38	3.159	0.048*
Correct	365.73 ± 64.86	335.55 ± 61.89	362.05 ± 57.48	1.502	0.229

Abbreviations: FEP, first-episode psychosis; CHR, clinical high risk; HC, healthy control.

[†] Analysis of variance with age and sex as covariates.

Data are presented as the mean ± standard deviation.

* The mean difference is significant at the 0.05 level.

2.4. Statistical Analysis

The demographic, clinical and behavioral data of the subjects were compared across the groups using analysis of variance (ANOVA). A x^2 test or Fisher's exact test was used to analyze the categorical data. For the main study, group comparisons of the amplitudes and latencies of the ERN and CRN were performed using a repeated measures ANOVA with 6 fronto-central electrode sites (F3, Fz, F4, FC3, FCz, and FC4) as the within-subject factor, and group (FEP, CHR, and HC) as the between-subjects factor, and with age and sex as covariates. Pe amplitudes and latencies were compared using a repeated measures ANOVA with 6 centro-parietal electrode sites (CP3, CPz, CP4, P3, Pz, and P4) as the within-subject factor, group (FEP, CHR, and HC) as the between-subjects factor, and with age and sex as covariates. A *post hoc* simple contrast test was used to reveal specific group differences. When a significant effect of group by electrode site was found, ANOVAs with age and sex as covariates were performed to reveal specific electrode sites that showed group differences in ERPs. For the statistical analysis of the exploratory study data, the main experimental condition with the names of former and current presidents (i.e., other-name condition) were used in the control condition for the comparison with the data

from the exploratory condition (i.e., own-name condition). Repeated measures ANOVA was conducted to reveal the effect of self-related stimuli on ERN amplitude at the Fz electrode site; for this ANOVA, condition was the within-subject factor (other-name condition and own-name condition) and group was the between-subjects factor (FEP, CHR, and HC), and age and sex were covariates. A *post hoc* simple contrast test was performed to find specific ERN differences across groups. When a significant group-by-condition interaction was found, a paired t-test was used to reveal the specific ERN difference across the conditions within each group. SPSS software ver. 25.0 (IBM Corp., Armonk, NY, USA) was used for the statistical analyses. The threshold for statistical significance was set at $p < 0.05$.

Chapter 3. Results

3.1. Subject Characteristics

Table 2 summarizes the demographic and clinical characteristics of all participants. Because there were significant group differences in age (t = 4.808, p = 0.011) and sex (χ^2 = 12.394, p = 0.002), age and sex were used as covariates for all statistical analyses for ERPs. The ratio of females to males was higher in the FEP group than in the CHR and HC groups. The groups did not differ significantly in years of education (F = 1.593, p = 0.210) or IQ (F = 0.956, p = 0.389). Patients with FEP were prescribed greater olanzapine equivalent doses of antipsychotics than CHR individuals (t = 5.548, p < 0.001) at the time of ERP measurement.

Table 2. Demographic and clinical characteristics of patients with first-episode psychosis (FEP), subjects at clinical high risk (CHR) for psychosis, and healthy controls (HCs).

	FEP (N=37)	CHR (N=22)	HC (N=22)	Statistical analysis[†] F or T or χ^2	P
Sex (male/female)	13/24	13/9	18/4	12.394	0.002[**]
Handedness (right/left)	35/2	21/1	19/3	1.723	0.422
Age (years)	22.46 ± 4.51	20.41 ± 3.58	19.59 ± 1.44	4.808	0.011[*]
IQ	102.95 ± 16.84	98.68 ± 11.81	104.32 ±11.61	0.956	0.389
Education (years)	13.78 ± 3.16	12.82 ± 1.68	12.82 ± 1.40	1.593	0.210
DOI (months)	7.47 ± 5.13				
PANSS					
Positive symptoms	14.43 ± 5.14	–	–	–	–
Negative symptoms	15.38 ± 6.92	–	–	–	–
General symptoms	28.49 ± 9.97	–	–	–	–
SOPS					
Positive symptoms	–	10.55 ± 5.39	–	–	–
Negative symptoms	–	10.55 ± 5.65	–	–	–
Disorganization	–	3.15 ± 2.98	–	–	–

General symptoms	–	6.80 ± 4.97	–	–	–
Prescribed medication[‡]					
Antipsychotics	32 (86.4)	0 (0.0)	–	11.663	<0.001[**]
Antidepressants	6 (16.2)	2 (8.6)	–	–	0.439
Mood stabilizers	1 (2.7)	0 (0.0)	–	–	0.437
Antipsychotic dose[§]	14.31 ± 12.06	0.00	–	5.548	<0.001[**]

Abbreviations: IQ, intelligence quotient; DOI, duration of illness; PANSS, positive and negative syndrome scale; SOPS, scale of prodromal symptoms.

[†] Analysis of variance, independent t test or Welch's t test if the variances were not equal, χ2 analysis or Fisher's exact test for categorical data.

[‡] Number (percentage) of subjects who were prescribed each medication at the time of the error-related negativity (ERN) measurement.

[§] Olanzapine equivalent dose of antipsychotics prescribed at the time of ERN measurement.

Data are presented as the mean ± standard deviation.

[*], the mean difference is significant at the 0.05 level.

[**], the mean difference is significant at the 0.005 level.

3.2. ERPs of Performance Monitoring

Figure 2(a) shows the grand-averaged ERN waveforms, and Figure 2(b) displays the peak ERN amplitudes across the FEP, CHR and HC groups. Figure 2(c) shows 2-dimensional topographic maps of the ERN amplitudes for the 3 groups. Table 3 presents group comparison results for the ERN amplitudes and latencies at each electrode site. A repeated measures ANOVA with 6 fronto-central electrode sites (F3, Fz, F4, FC3, FCz, and FC4) as the within-subject factor, group (FEP, CHR, HC) as the between-subjects factor, and with age and sex as covariates showed a significant main effect of group (F = 4.337, p = 0.016), but no significant effects of electrode site (F = 0.470, p = 0.686) and group by electrode site interaction (F = 1.366, p = 0.234) were present. The *post hoc* simple contrast test revealed that the ERN amplitudes at Fz in the FEP (p = 0.002) and CHR (p = 0.039) groups were smaller than those in the HC groups. There was no significant difference in ERN amplitudes between the FEP and CHR groups (p = 0.273). For ERN latencies, no significant effect of group (F = 2.437, p = 0.094), electrode site (F = 2.289, p = 0.058), or group by electrode site interaction (F = 1.474, p = 0.164) was found.

Figure 3(a) displays the grand-average CRN waveform at the

Fz electrode site and the group comparison of peak CRN amplitudes across the FEP, CHR, and HC participants. Figure 3(b) shows the grand-averaged Pe waveform at the Pz electrode site and group comparison of peak Pe amplitudes across the 3 groups. Table 4 demonstrates the results of the group comparison of CRN and Pe. In terms of CRN amplitudes, a repeated measures ANOVA with 6 fronto-central electrode sites (F3, Fz, F4, FC3, FCz, and FC4) as the within-subject factor, group (FEP, CHR, and HC) as the between-subjects factor, and with age and sex as covariates revealed that there was no significant effect of group ($F = 0.058$, $p = 0.944$) or electrode site ($F = 1.658$, $p = 0.166$) and no significant group by electrode site interaction ($F = 1.561$, $p = 0.144$). Regarding CRN latencies, there was no significant effect of group ($F = 0.213$, $p = 0.809$) or electrode site ($F = 0.927$, $p = 0.438$) and no significant group by electrode site interaction ($F = 0.683$, $p = 0.683$).

For Pe amplitudes, repeated measures ANOVA with 6 centro-parietal electrode sites (CP3, CPz, CP4, P3, Pz, and P4) as the within-subject factor, group (FEP, CHR, and HC) as the between-subjects factor, and with age and sex as covariates found that there was no significant effect of group ($F = 1.533$, $p = 0.222$) or electrode

site (F = 3.084, p = 0.224) and no significant group by electrode site interaction (F = 0.665, p = 0.693). In addition, no significant effect of group (F = 0.952, p = 0.391) or electrode site (F = 0.844, p = 0.483) and no significant group by electrode site interaction (F = 1.375, p = 0.218) was found for Pe latencies.

(a)

Fz electrode site

FCz electrode site

(b)

Fz electrode site

FCz electrode site

FEP (*n*=37)
CHR (*n*=22)
HC (*n*=22)

(c)

FEP   CHR   HC

+3.0
0
-3.0
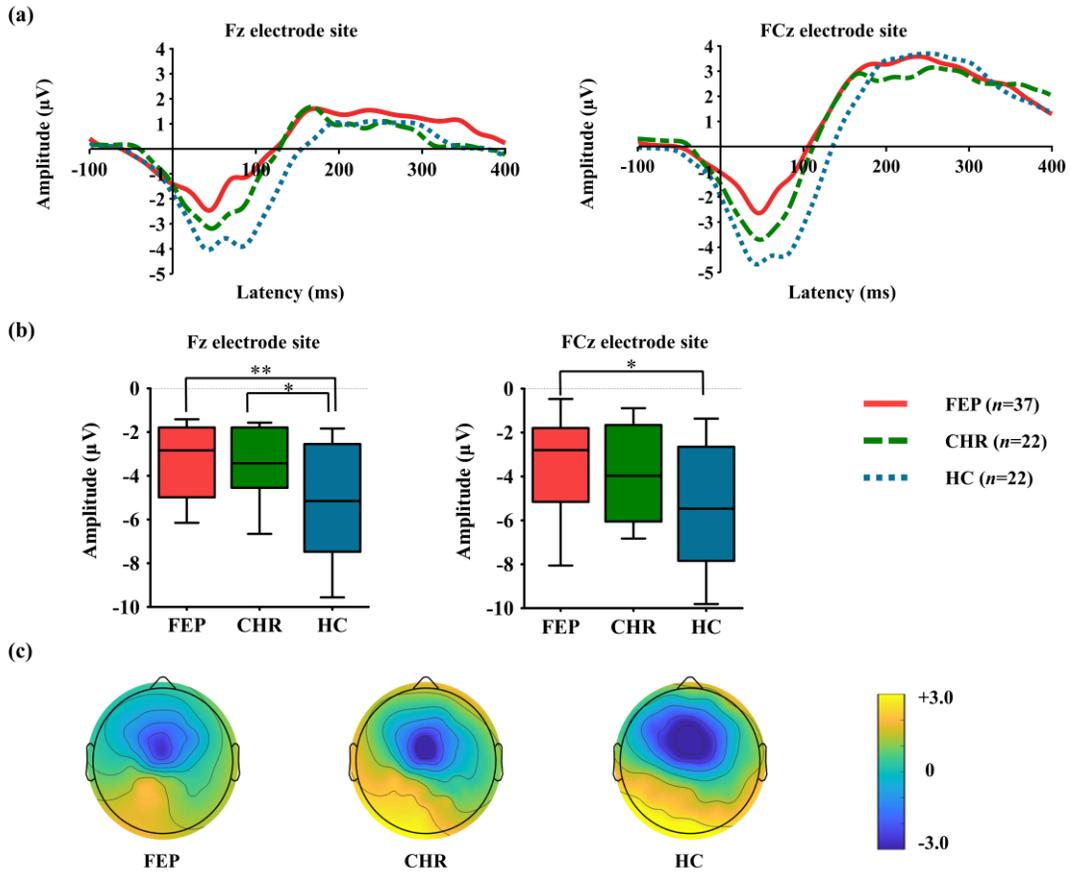
Figure 2. (a) Grand averaged waveforms of error-related negativity (ERN) at Fz and FCz electrode sites across the first-episode psychosis, clinical high risk for psychosis, and healthy control groups. (b) ERN amplitudes at the Fz and FCz electrode sites across the groups. The horizontal lines in the group indicate the means, and the vertical lines in the group indicate the 10th to 90th percentiles. * indicates that the mean difference is significant at the 0.05 level; ** indicates that the mean difference is significant at the 0.005 level. (c)

Two-dimensional topographic maps of ERN in the FEP, CHR and HC groups. The colored bar with numbers indicates the amplitude of ERN (μV).

Table 3. Error-related negativity (ERN) amplitudes and latencies measured at the surface electrodes in patients with first-episode psychosis (FEP), subjects at clinical high risk (CHR) and healthy controls (HCs).

Electrode sites	FEP (N=37)	CHR (N=22)	HC (N=22)	Statistical analysis[†]		Post hoc analysis[‡]		
				F	P	FEP vs CHR	FEP vs HC	CHR vs HC
ERN amplitude (μV)								
F3	−2.89 ± 1.60	−2.78 ± 1.66	−4.00 ± 2.96	2.831	0.065	0.927	0.034*	0.043*
Fz	−3.42 ± 1.73	−3.86 ± 3.03	−5.29 ± 3.14	4.980	0.009*	0.273	0.002**	0.039*
F4	−2.54 ± 1.91	−2.88 ± 1.89	−3.60 ± 2.75	2.197	0.118	0.411	0.040*	0.192
FC3	−2.13 ± 1.37	−2.56 ± 1.45	−3.32 ± 2.47	2.892	0.062	0.312	0.019*	0.151
FCz	−3.60 ± 2.78	−4.40 ± 3.96	−5.56 ± 3.51	3.453	0.037*	0.181	0.011*	0.177
FC4	−1.92 ± 1.23	−2.40 ± 1.63	−2.65 ± 2.18	2.682	0.075	0.137	0.027*	0.395
ERN latency (ms)								
F3	55.73 ± 40.14	48.05 ± 32.82	76.18 ± 48.96	3.406	0.038*	0.772	0.033*	0.018*
Fz	46.89 ± 41.87	47.64 ± 24.38	58.41 ± 39.96	0.224	0.800	0.698	0.759	0.510
F4	58.78 ± 42.04	62.09 ± 40.60	71.09 ± 48.95	0.713	0.493	0.716	0.242	0.407

	FEP	CHR	HC	F	P†	‡	‡	‡
FC3	50.57 ± 37.61	43.18 ± 31.41	62.41 ± 34.99	2.726	0.072	0.907	0.047*	0.038*
FCz	35.92 ± 46.13	47.41 ± 25.64	45.45 ± 32.68	0.245	0.783	0.506	0.907	0.620
FC4	42.46 ± 33.44	60.45 ± 27.57	67.14 ± 38.92	5.006	0.009*	0.030*	0.003**	0.336
Error rate (%)	20.06 ± 10.21	25.30 ± 16.93	16.20 ± 6.89	3.339	0.056	–	–	–
Response time (ms)	385.22 ± 72.13	361.27 ± 88.36	377.47 ± 64.65	0.705	0.407	–	–	–

Abbreviations: FEP, first-episode psychosis; CHR, clinical high risk; HC, healthy control.

† Analysis of variance with age and sex as covariates.

‡ P value of post hoc analysis using a simple contrast test.

Data are given as the mean ± standard deviation.

*, the mean difference is significant at the 0.05 level.

**, the mean difference is significant at the 0.005 level.
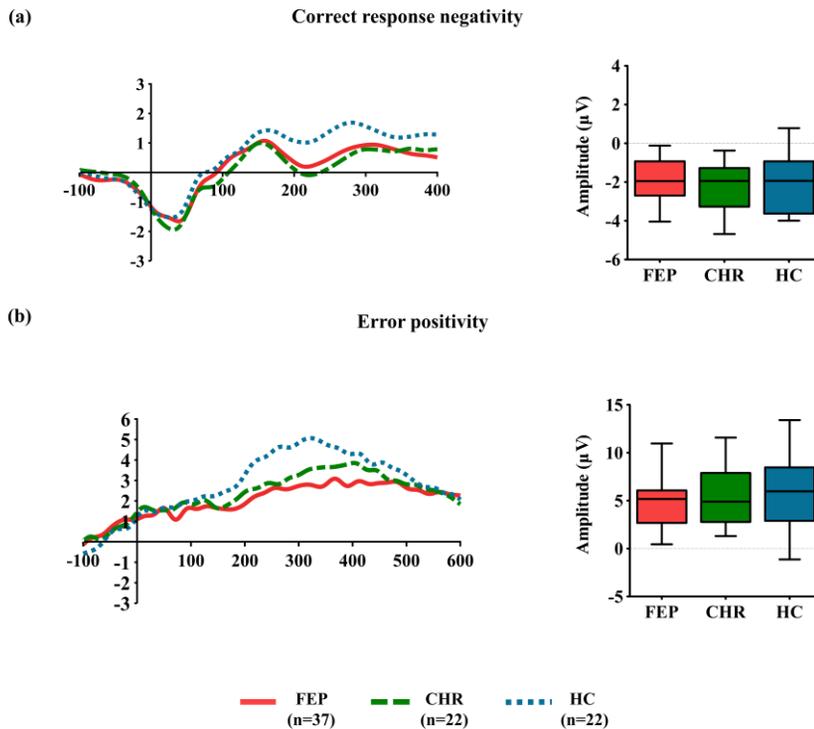
Figure 3. (a) Grand averaged waveforms of correct response negativity (CRN) and the comparison of the mean CRN amplitudes at the Fz electrode site across the first-episode psychosis, clinical high risk for psychosis, and healthy control groups. (b) Grand averaged waveforms of error positivity (Pe) and the comparison of the mean Pe amplitudes at the Pz electrode site across the three groups. The horizontal lines in the group indicate the means, and the vertical lines in the group indicate the 10th to 90th percentiles.

Table 4. Summary of mean amplitudes and latencies of correct-response negativity (CRN) and error positivity (Pe) at the surface electrodes across groups.

Electrode sites	FEP (N=37)	CHR (N=22)	HC (N=22)	Statistical analysis[†]	
				F	P
CRN amplitude (μV)					
F3	-1.98 ± 1.34	-2.10 ± 1.43	-1.44 ± 1.71	1.044	0.357
Fz	-1.95 ± 1.29	-2.23 ± 1.39	-1.93 ± 1.79	0.358	0.700
F4	-1.91 ± 2.06	-1.45 ± 1.25	-1.87 ± 2.05	0.549	0.580
FC3	-0.92 ± 0.95	-1.24 ± 0.95	-1.20 ± 1.26	0.351	0.705
FCz	-1.31 ± 1.32	-1.62 ± 1.49	-1.28 ± 1.33	0.641	0.529
FC4	-0.93 ± 1.09	-0.77 ± 0.98	-0.85 ± 0.96	0.138	0.871
CRN latency (ms)					
F3	35.38 ± 34.03	33.91 ± 23.27	32.18 ± 41.70	0.047	0.954
Fz	32.54 ± 29.40	33.55 ± 24.05	30.18 ± 35.50	0.116	0.863
F4	39.73 ± 38.11	32.50 ± 28.04	37.36 ± 44.86	0.148	0.863
FC3	22.41 ± 22.99	39.86 ± 24.24	34.23 ± 33.26	2.010	0.141
FCz	33.95 ± 24.63	30.00 ± 20.83	30.36 ± 35.06	0.038	0.963

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FC4	32.19 ± 30.25	39.05 ± 32.45	40.32 ± 41.29	0.894	0.413
Pe amplitude (μV)					
CP3	1.30 ± 1.77	2.06 ± 1.72	2.76 ± 2.40	2.355	0.102
CPz	4.66 ± 2.45	5.42 ± 3.32	6.07 ± 3.49	0.660	0.520
CP4	3.43 ± 2.06	3.96 ± 2.20	4.04 ± 3.02	0.584	0.560
P3	2.11 ± 2.43	2.87 ± 2.01	3.00 ± 3.32	1.049	0.355
Pz	4.32 ± 3.02	4.87 ± 2.91	6.16 ± 4.12	2.339	0.103
P4	3.42 ± 2.10	3.87 ± 2.17	3.90 ± 3.96	0.515	0.600
Pe latency (ms)					
CP3	346.11 ± 73.67	344.09 ± 68.23	343.32 ± 65.70	0.068	0.934
CPz	327.54 ± 69.83	355.73 ± 69.83	306.18 ± 49.10	3.248	0.044
CP4	355.14 ± 66.65	357.14 ± 63.02	330.73 ± 61.61	0.557	0.575
P3	349.73 ± 70.67	363.59 ± 67.12	346.86 ± 76.85	0.413	0.663
Pz	359.51 ± 72.43	363.32 ± 61.60	316.09 ± 57.18	2.744	0.071
P4	353.35 ± 67.92	356.18 ± 63.04	355.50 ± 72.68	0.353	0.703

Abbreviations: FEP, first-episode psychosis; CHR, clinical high risk; HC, healthy control.
[†] Analysis of variance with age and sex as covariates.
Data are presented as the mean ± standard deviation.

3.3. Effects of Participants' Own Names as Stimuli on ERN Amplitude

The exploratory study results are summarized in Table 5. Figure 4 displays grand-averaged ERN waveforms across the conditions (other-name condition and own-name condition) in each group. Repeated measures ANOVA with conditions as within subject factors (other-name condition and own-name condition), group as between subject factors (FEP, CHR, and HC), and with age and sex as covariates found no significant effect of group (F = 2.467, p = 0.092). However, a significant effect of condition (F = 7.133, p = 0.009) and a significant group by condition interaction (F = 5.929, p = 0.004) was found. Because there was a significant group by condition interaction, a paired samples t-test was performed to investigate whether there was a difference in ERN amplitude between conditions (other-name condition and own-name condition) within each group. There was no significant difference between conditions (other-name condition and own-name condition) in all 3 groups (FEP, t = 0.986, p = 0.331; CHR, t = -0.267, p = 0.792; HC, t = -1.994, p = 0.059).

Table 5. Summary of error-related negativity (ERN) peak amplitudes at the Fz electrode site for each group and condition.

	FEP (N=37)	CHR (N=22)	HC (N=22)	Statistical Analysis[†]	F	P
Peak ERN amplitudes (μV) for each condition						
Other-name	-3.42 ± 1.73	-3.87 ± 3.03	-5.29 ± 3.14	Group	2.467	0.092
Own-name	-3.65 ± 2.06	-3.75 ± 2.84	-4.44 ± 2.32	Condition	7.133	0.009**
Paired samples t-test	Other = Own	Other= Own	Other = Own	Group X Condition	5.929	0.004**
Peak ERN latency (ms) for each condition						
Other-name	46.89 ± 41.87	47.64 ± 24.38	58.41 ± 39.96		0.726	0.487
Own-name	38.70 ± 43.62	42.18 ± 20.15	43.36 ± 24.55		0.151	0.860

Abbreviations: FEP, first-episode psychosis; CHR, clinical high risk; HC, healthy control.

The other-name condition indicates that the names of current and former presidents were given, and in own-name conditions, the subject's own name and the names of famous actors were presented.

[†] Analysis of variance with sex and age covariates.

Data are presented as the mean ± standard deviation.

*The mean difference is significant at the 0.05 level.

Figure 4. Grand averaged error-related negativity waveforms at the Fz electrode site in patients with first-episode psychosis, subjects at clinical high risk and healthy controls at each condition.
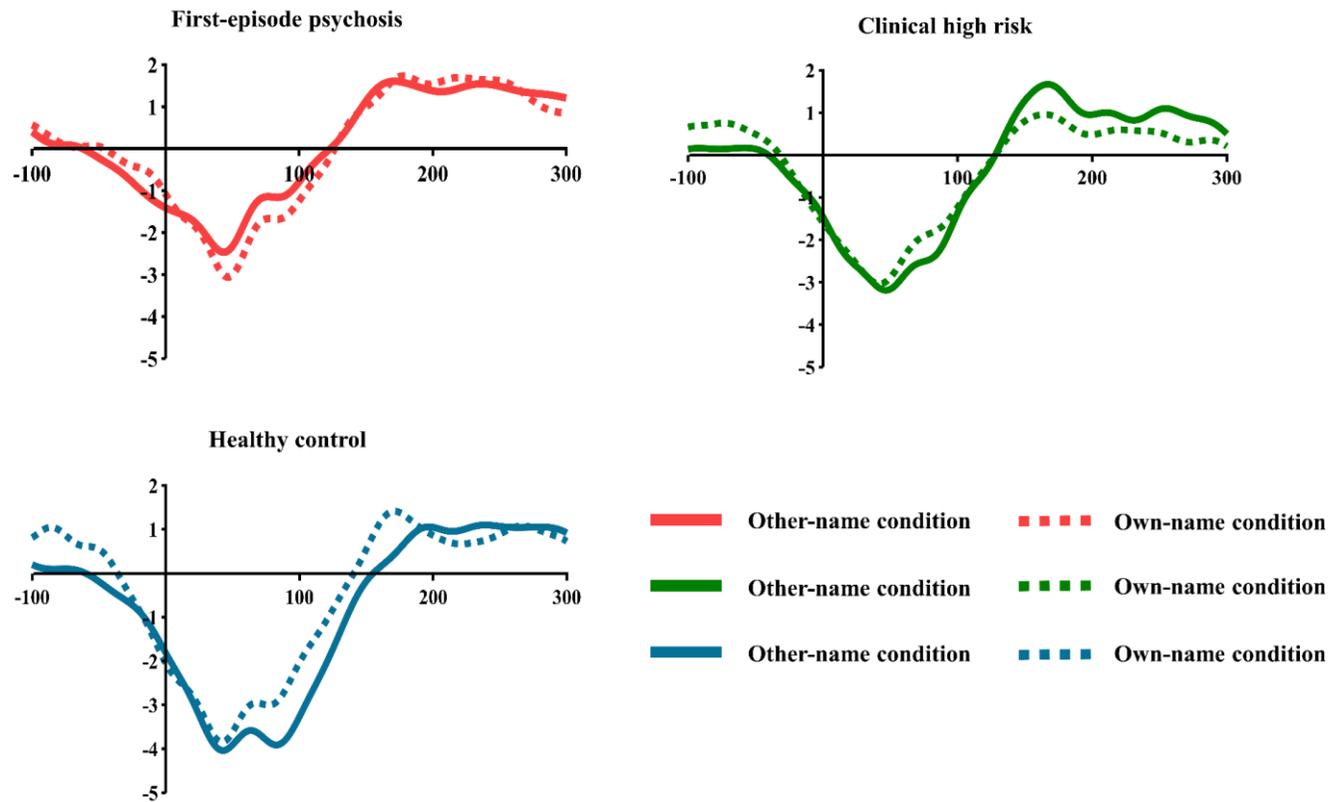
Chapter 4. Discussion

In the current study, we investigated whether ERP components associated with performance monitoring are impaired in the early phases of psychotic disorders such as FEP and CHR. We observed impaired ERN, intact CRN and Pe amplitudes in both FEP and CHR participants compared to the amplitudes of HCs. Exploratory experimental conditions were designed to investigate the effect of self-related stimuli on ERN amplitude did not yield significant results. The findings of the present study support the previous reports of Perez *et al*. (Perez et al., 2012) that error monitoring-related ERP components are impaired from the very beginning of the psychotic disorder. ERN may serve as a neurophysiological indicator of early stages of psychosis, such as FEP and CHR.

The present study found reduced ERN and intact CRN and Pe amplitudes in both FEP and CHR participants compared to the amplitudes of HCs. The finding of reduced ERN amplitudes in the FEP and CHR groups is similar to the existing literature in schizophrenia patients with a relatively long duration of illness (Martin et al., 2018, Mathalon et al., 2002, Morris et al., 2008) and

consistent with one study (Perez et al., 2012) that included FEP patients and CHR subjects. Our results suggest that cognitive processes such as automatic error detection are already impaired from the prodromal stage and that aberrant error-related processing is not the consequence of disease chronicity. Since there is a robust pattern of reduced ERN amplitude across various tasks in chronic schizophrenia patients compared to that of individuals at CHR for psychosis, deficiencies in error monitoring could be reflective of an important pathophysiology of the disease.

Unlike ERN amplitude, CRN amplitude did not differ across FEP, CHR, and HC groups in this study, which contrasts with the findings of previous studies that observed augmented CRN amplitudes in chronic schizophrenia (Mathalon et al., 2002, Morris et al., 2006) and FEP patients (Perez et al., 2012). Such a discrepancy might have resulted from the differences in the participant sample and behavioral task characteristics of our study and those of the previous studies. Unlike prior studies including chronic schizophrenia patients (Mathalon et al., 2002, Morris et al., 2006), we included FEP patients who were in the early stages of psychosis. In addition, the complexity of behavioral tasks might have contributed to the

difference. It has been shown that increased cognitive complexity of the task led to an increase in CRN amplitude, which may reflect increased uncertainty (Mathalon et al., 2009). Whereas we employed a relatively simple go/no-go task that might have yielded less uncertainty and did not have the consequential increase in CRN amplitude, Perez *et al*. (Perez et al., 2012) used a complex picture-word matching task and reported increased CRN amplitudes. Since CRN amplitude seems to reflect either a response comparison process(Vidal et al., 2000) or uncertainty associated with a response(Pailing and Segalowitz, 2004), similar correct answer rates and comparable CRN amplitudes in our study among FEP patients, CHR subjects, and HCs may have resulted from the relative simplicity of behavioral tasks. Such results may also indicate that some aspects of performance monitoring, as reflected by the CRN components, are at least partially intact in prodromal and early psychosis patients when performance of a relatively simple task is required.

Our study results of preserved Pe amplitude in FEP patients and CHR subjects compared with that of HCs were in line with the preponderance of previous studies showing normal Pe amplitude in

chronic schizophrenia patients (Mathalon et al., 2002, Horan et al., 2012). Incompatibility with the results of Foti *et al.* (Foti et al., 2012) and Perez *et al.* (Perez et al., 2012), which reported reduced Pe amplitude in chronic schizophrenia and FEP patients, respectively, might have arisen from the tasks differences. Pe is thought to reflect conscious error recognition because the Pe was larger or more pronounced during perceived errors than during unperceived errors (Endrass et al., 2007, Nieuwenhuis et al., 2001). The relatively simple task employed in the present study may have allowed the participants to recognize and perceive erroneous responses. Although both ERN and Pe are known to be related to error responses (Martin et al., 2018), the intact Pe amplitude but impaired ERN in the FEP and CHR groups may suggest that two indices represent different aspects of error processing (Falkenstein et al., 2000, Nieuwenhuis et al., 2001). This is supported by the fact that ERN is more specific to the immediate detection process of error monitoring (Falkenstein et al., 2000) whereas Pe is thought to reflect later, conscious recognition of an error (Nieuwenhuis et al., 2001). Our results show that individuals with early psychosis (i.e., FEP and CHR) have preserved conscious error awareness, while immediate error detection abilities are compromised.

As an exploratory experiment, we used a modified visual go/no-go task with the subject's own name to investigate the effect of self-related stimuli on error monitoring in early psychosis. We expected that self-related stimuli would enhance error monitoring reflected by an increased ERN amplitude, based on the previous literature that self-related processing is not only prioritized but is also efficacious (Gray et al., 2004, Brédart et al., 2006) and results in augmented P300 amplitudes in the general population. However, contrary to our initial expectation, ERN amplitude was not modulated by self-related stimuli in all 3 groups. One possible explanation is that participants' own name presented as a simple text may not have been sufficient as a self-related stimulus. Lee *et al.* (Lee et al., 2007) reported that pictures of an individual's own face were more efficiently processed than pictures of a famous person's face in schizophrenia patients. It remains to be addressed in future studies if varying levels of self-related stimuli (e.g., pictures with the participants' own face) result in enhanced performance monitoring in psychosis spectrum patients or if such stimuli do not have any enhancing effects in the patient population.

This study has several limitations. First, a small sample size

may be the cause of insufficient statistical power. Second, most of the FEP patients were taking antipsychotic medications at the time of ERP measurement. Several studies found that antipsychotics could attenuate the ERN amplitude (de Bruijn et al., 2006, Zirnheld et al., 2004), whereas others suggested that a small ERN amplitude might not be a result of antipsychotic medications (Bates et al., 2004, Houthoofd et al., 2013, Simmonite et al., 2012). Because the existing literature regarding the effect of antipsychotic medication on ERN amplitudes did not reach a definitive conclusion, the current study results should be interpreted while considering the potential effect of antipsychotic medication on ERN amplitudes did not reach a definitive conclusion, the current study results should be interpreted while considering the potential effect of antipsychotic medication on ERN amplitudes. Third, there were statistically significant differences in age and sex among the FEP, CHR, and HC groups in our study. Only one previous study found that adolescents (ages 13–14) have comparable ERN amplitudes to those of adults (ages 23–24)(Wiersema et al., 2007). In addition, males showed larger ERN and Pe amplitudes than females in one study (Larson et al., 2011). Therefore, we used age and sex as covariates to control the effect of age and sex on the amplitudes of the ERP components in group

comparison analysis. However, the results should be interpreted with caution because the possible confounders of age and sex were not matched across groups.

In this study, we investigated the neurophysiological indices of performance monitoring in early psychosis patients. ERN amplitudes were reduced from the prodromal stage to FEP, whereas CRN and Pe amplitudes were comparable to those of HCs. These results suggest that impairments in neurophysiological correlates of error monitoring occurs before the onset of psychotic disorders and are not the consequence of disease chronicity. These results add to the growing knowledge of the early course of schizophrenia and serve as evidence that ERN could be used as an indicator of psychotic illness from the prodromal stage. Future longitudinal studies with larger sample sizes are needed to test the ability of ERN to serve as a potential tool for predicting and promoting better prognoses of prodromal and early stages of psychotic disorders.

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국문 초록

서론: 조현병 환자에서 행동 모니터링 시스템을 반영하는 사건 관련 전위의 손상은 지속적으로 보고되었다. 그러나 비교적 질환의 초기 단계인 초발 정신증 환자군과 조현병 전구기 증상을 보이는 정신증 임상적 고위험군에서도 이러한 손상이 나타나는지는 아직 잘 알려지지 않았다. 따라서 본 연구에서는 사건 관련 전위를 통해 반영된 행동 모니터링의 저하가 초발 정신증 환자군과 정신증 임상적 고위험군에서부터 관찰되는지 알아보고자 한다.

방법: 37명의 초발 정신증 환자군, 22명의 정신증 임상적 고위험군, 22명의 정상 대조군이 연구에 참여하여 행동 모니터링과 관련된 3개의 사건 관련 전위 구성 요소인 오류 관련 음전위 (ERN), 정반응 관련 음전위 (CRN), 오류 양전위 (Pe)를 측정하였다. 또한 성별과 연령의 공변량 분석을 통해 보정한 뒤 각 구성 요소들의 진폭, 잠복기 등의 차이가 있는지 분석하였다.

결과: 초발 정신증 환자군과 정신증 임상적 고위험군에서 정상 대조군에 비해 Fz (F = 4.980, p = 0.009)전극 부위와 FCz (F = 3.453, p = 0.037) 전극 부위에서 오류 관련 음전위 (ERN)의 진폭이 현저하게 낮았고, 초발 정신증 환자군과 정신증 임상적 고위험군의 진폭은 서로 비슷한 정도

로 저하되어 있었다. 정반응 관련 음전위 (CRN)과 오류 양전위 (Pe)의 진폭은 세 그룹 모두 유의미한 집단 간 차이를 보이지 않았다.

고찰: 본 연구의 결과는 초발 정신증 환자군과 정신증 임상적 고위험군에서 오류 관련 음전위 (ERN) 진폭의 저하를 통해 질환의 초기 단계에서 이미 행동 모니터링이 손상되었음을 시사한다. 종합해보자면, 본 연구의 결과들은 오류 관련 음전위 (ERN)은 정신증의 초기 단계를 확인할 수 있는 잠재적인 임상지표로서의 가능성을 제시한다.