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Predicting prognosis in patients with first-episode psychosis using auditory P300: A 1-year follow-up study

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HIGHLIGHTS

- Biomarkers forecasting prognosis of psychosis are lacking.
- Auditory P300 amplitude were lower in patients with first-episode psychosis than controls.
- Higher baseline P300 amplitude was related to greater symptom and function improvement after 1-year.

ABSTRACT

Objective: To clarify the role of auditory P300 in predicting prognosis in patients with first-episode psychosis (FEP) during a 1-year follow-up.
Methods: Auditory P300 of 24 patients with FEP and 24 matched healthy control (HC) participants were measured at baseline. The clinical status of the FEP patients was assessed at baseline and reassessed after 1 year. P300 amplitudes and latencies among the groups were analyzed using repeated measures analysis of variance. Multiple regression analysis was conducted to assess the predictive value of P300 in patients with FEP during the 1-year follow-up.
Results: Auditory P300 amplitudes were significantly smaller in FEP patients than HCs. Higher baseline P300 amplitudes at CPz significantly predicted better improvements in the Positive and Negative Syndrome Scale total, positive, and general scores, as well as in the Global Assessment of Functioning and Brief Psychiatric Rating Scale.
Conclusions: P300 may predict improvements in symptoms, functional status, and overall psychiatric status in patients with FEP.
Significance: We first show that P300 amplitude at baseline predicts symptomatic and functional improvements after 1 year of treatment in patients with FEP. This finding may aid in effective interventions from the beginning of a psychotic episode to improve subsequent outcomes in clinical practice.

1. Introduction

Early intervention from the first episode is well known to be essential for favorable outcomes in patients with schizophrenia. Previous studies have shown that a shorter duration of untreated psychosis (DUP) is associated with better symptomatic and functional outcomes (Perkins et al., 2005). The DUP seems to affect quality of life, social functioning and cognitive function throughout the course of the illness and often throughout the patient's life (Ito et al., 2015). In this respect, appropriate management of patients during their first episode of psychosis for the purpose of preventing illness progression and recurrent episodes has been a great interest (McGorry et al., 2008; Sommer et al., 2016).

Although early treatment is important, the burden of side effects associated with antipsychotic medication is substantial (Young et al., 2015). Patients prescribed an antipsychotic agent may experience extrapyramidal symptoms and metabolic side effects (Tschoner et al., 2007; Rummel-Kluge et al., 2010), which greatly impair their quality of life. These side effects lead to poor adherence (DiBonaventura et al., 2012), which compromises treatment outcomes as a result of recurrence. As treatment responses

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and side effects vary among individuals (Haddad and Sharma, 2007; van den Oord et al., 2009), the treatment intensity and duration should be determined individually to achieve precision medicine, which aims to reduce the impact of side effects and enhance treatment outcome. However, factors that effectively and objectively predict treatment outcome for psychosis remain lacking. Thus, investigating biomarkers which predict prognosis will aid in effective treatment from the beginning of a psychotic episode to ensure a better treatment outcome and long-term prognosis (Hager and Keshavan, 2015).

Event-related potential (ERP), a neurophysiological marker, has been highlighted because it provides millisecond temporal resolution of brain activity, including cognitive and sensory processing (Luck et al., 2011). With a high temporal resolution, ERPs might sensitively reflect changes in brain dysfunction associated with pathophysiology in patients with schizophrenia (Javitt et al., 2008; Luck et al., 2011; Light and Swerdlow, 2015; Thibaut et al., 2015). In particular, the auditory P300 ERP component is one of the most widely studied neurophysiological markers of schizophrenia (Picton, 1992). P300 is considered to represent information processing associated with selective attention and contextual updates of working memory (Polich, 2012). Diminished P300 amplitude is consistently reported in schizophrenia patients (Ford, 1999; Bramon et al., 2004; Kim et al., 2018), which suggests pervasive impairments of selective attention and working memory function in schizophrenia. The P300 amplitude reduction is observed not only in chronic schizophrenia but also in first-episode psychosis (FEP) patients and subjects at clinical high risk (CHR) for psychosis (van der Stelt et al., 2005; Atkinson et al., 2012; Nagai et al., 2013). Moreover, P300 latency prolongation in schizophrenia has been reported (Ford, 1999). Increased rate of P300 latency prolongation with age compared to healthy controls was observed in chronic schizophrenia and patients with FEP (O'Donnell et al., 1995, Wang et al., 2003). As impaired P300 appears from the early stages of the disorder, it could be utilized as a promising biomarker that is predictive of treatment outcomes.

Although the P300 amplitude has been correlated with clinical symptoms, such as positive symptoms (O'Donnell et al., 1993; Gallinat et al., 2001; Higashima et al., 2003) negative symptoms (Ford et al., 1999; Mathalon et al., 2000a), and overall functioning (Strik et al., 1993) in cross-sectional studies, few studies have investigated whether auditory P300 could predict clinical outcomes or prognosis in patients with schizophrenia (Strik et al., 1996; Perlman et al., 2015; Turetsky et al., 2015). Moreover, in these studies, patients with chronic schizophrenia, whose P300 may have been significantly influenced by medication and the chronic course of the illness, were included (Coburn et al., 1998; Mathalon et al., 2000b), which made it difficult to elucidate the predictive value of P300. Only recent studies regarding at-risk individuals have elucidated the auditory P300 amplitude as a prognostic factor that predicts the transition to psychosis (van Tricht et al., 2010) and the improvement of negative and general symptoms over 2 years of follow-up in CHR individuals (Kim et al., 2015). However, there were no previous studies on whether P300 had predictive value in the prognosis of patients with FEP.

Thus, auditory P300 might be a promising predictive marker for prognosis, which could assist in the implementation of precision medicine in the treatment of patients with FEP. In this study, we aim to clarify the role of auditory P300 in predicting prognosis in first-episode psychosis (FEP) patients during a 1-year follow-up. First, we expected the replication of previous findings, which have consistently reported impaired P300 in FEP patients compared to healthy control (HC) subjects. In addition, we hypothesized that higher baseline P300 amplitudes would predict greater improvements in symptoms and functioning in FEP patients during the 1-year follow-up.

2. Methods

2.1. Participants

Twenty-four patients with FEP and 24 HCs matched for age and sex participated in this study. A patient with FEP was defined as an individual who was diagnosed with schizophrenia spectrum disorder within the recent two years and had their diagnosis confirmed with a clinical interview using the Structured Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Axis I Disorders (SCID-1). Patients with FEP were recruited by the inpatient and outpatient clinics in the Department of Psychiatry of Seoul National University Hospital (SNUH) and the Seoul Youth Clinic (www.youthclinic.org) (Kwon et al., 2012). All the patients underwent laboratory tests including complete blood count, electrolyte panel, and liver function tests. HCs were recruited through internet advertisements and excluded subjects with a past or current DSM-IV Axis I psychiatric history or family histories of schizophrenia within third-degree relatives. Based on thorough review of medical record or medical interview by qualified clinicians, it was confirmed that no participants had a history of substance abuse or dependence, severe head trauma or neurological disease, severe medical illness that interferes with ability to be tested, sensory impairments such as auditory or visual impairment, or intellectual disability (intelligence quotient [IQ] < 70) for both groups.

All study participants understood the study procedures and provided written informed consent according to the Declaration of Helsinki. This study protocol was approved by the Institutional Review Board of SNUH.

2.2. Demographic factors, clinical characteristics and medication usage

The demographic factors included age, sex, years of education, IQ, and handedness. IQ measurement and handedness were assessed using the Korean Wechsler Adult Intelligence Scale (Yum et al., 1992) and the Annett Handedness Inventory (Annett, 1967), respectively. The evaluation of DUP was based on the medical records of the patients and interviews with the patients and family members. Clinical statuses were measured at baseline and reassessed after a 1-year treatment using the Positive and Negative Syndrome Scale (PANSS), Global Assessment of Functioning (GAF) and Brief Psychiatric Rating Scale (BPRS) in the patients with FEP. Calculation of the changes in the symptoms and functional status were performed by subtracting the 1-year follow-up scores of the PANSS, GAF, and BPRS from the scores measured at baseline. The usage of antipsychotics was documented and converted into a daily olanzapine equivalent dose (Gardner et al., 2010), and the usage of other medications (antidepressants, mood stabilizers, and anxiolytics) was also recorded at baseline and at 1-year follow-up.

2.3. ERP measurement

The recording protocol of the electroencephalography (EEG) utilized in this study was identical to that previously used in our laboratory (Kim et al., 2015). EEGs were recorded during an auditory oddball task. The 3 trial blocks were presented during a half-hour recording session, and a several-minute of resting period was provided between the blocks. The participants were presented with a pseudorandom series of two types of stimuli, which differed in frequency, composed of standard/frequent stimuli (1000-Hz tones, 82% (820 of 1000 trials)) and target/infrequent stimuli (1500-Hz tones, 18% (180 of 1000 trials)). The auditory stimuli (80 dB; 10 ms rise/fall time; 50 ms duration) were presented binaurally via STIM2 sound generator (Neuroscan, El Paso, TX, USA) with a fixed intertrial interval of 1300 ms. The participants were required to press the button if the stimulus was the target stimulus. EEGs were continuously recorded by a Neuroscan SynAmps 128-channel system using 64 electrodes placed according to the 10/20 international system (Neuroscan, El Paso, TX, USA). The left and right mastoids were used as the reference. The EEG signals were digitized at a sampling rate of 1 kHz and filtered from 0.05 to 100 Hz online. Electrodes placed below and on the outer canthus of the left eye were used to obtain horizontal and vertical electro-oculogram (EOG). The impedance of all electrodes was less than 5 kΩ.

We used Curry 7 software (Compumedics, Charlotte, NC, USA) to analyze continuous EEG data. Bad channels, which contained persistent artifacts throughout the trials, were reconstructed using a linear interpolation of the surrounding channels (up to 7% per participant). The removal of eye movement artifacts was performed by utilizing an artifact reduction algorithm in the Curry 7 software (Semlitsch et al., 1986). The EEG data were re-referenced to a common average reference and filtered with a bandpass of 0.1–30 Hz. The data were subsequently epoched between 100 ms prestimulus and 900 ms poststimulus, and baseline corrected using the mean amplitude during 100 ms prior to stimulus onset. Only epochs with an adequate button press were included in the further analysis to maximize the effects of attention on the P300 ERP component. Epochs that contained EEG voltages exceeding ±75 μV were automatically rejected as artifacts, and the number of remaining epochs did not differ between the patients with FEP and the HCs ($t = -0.803$, $p = 0.426$, number of remaining epochs: 149.4 ± 26.0 vs. 142.5 ± 33.2, respectively). The P300 amplitude and latency were identified using a peak detection method which identifies the most positive deflection point between 250 and 500 ms poststimulus at 6 centro-parietal electrode sites (CP3, CPz, CP4, P3, Pz, and P4). Six electrodes were selected as P300 (P3b) shows maximal amplitude in the parietal area (Polich, 2007).

2.4. Statistical analysis

Independent samples t-test (equal variances) or Welch's t-test (unequal variances) for the continuous variables and $\chi 2$ analysis or Fisher's exact test for the categorical data were used to compare the demographic and clinical characteristics of the FEP patients and participants. For each test, the threshold for significance was set at $P < 0.05$. To investigate the group differences in the P300 amplitudes and latencies, repeated-measures analysis of variance (ANOVA) with the between-subject factor of group (FEP vs. HC) and the within-subject factor of electrode sites (CP3, CPz, CP4, P3, Pz, and P4) was performed. Furthermore, we compared the P300 amplitude and latency, respectively, at each site via independent samples t-test to identify the specific electrodes that showed significant group differences for P300. A Bonferroni corrected threshold of $P < 0.0083$ (0.05/6) for significance was used to account for multiple comparisons. To determine the factors that significantly forecasted symptoms or functional improvement in the FEP patients after 1 year of follow-up, simple regression analysis and multiple regression analysis with the backward selection method ($P > 0.1$ as the elimination criterion) were performed. For the multiple regression analysis, all the following factors, which were considered to be potential predictors of clinical outcomes, were initially included in the analysis: the P300 peak amplitude or latency at baseline, demographic factors including age, sex, handedness, level of education (education years) and IQ, DUP, PANSS total, positive, negative, general subscale scores, GAF or BPRS scores measured at baseline, and medication use during the 1-year follow-up (mean daily olanzapine equivalent dose of antipsychotics, antidepressant use (no use/use), mood stabilizer use (no use/use), and anxiolytic use (no use/use)). To exclude the possibility of multicollinearity between variables in the multiple regression analysis, multicollinearity test in SPSS was performed to verify whether the variance inflation factor (VIF) was less than 10. In addition, we performed an exploratory multiple regression analysis that included the time from the disease onset to the ERP study or the time from the first antipsychotic use to the ERP study as a potential predictor. To clarify whether P300 was significantly influenced by baseline medication status or sex in our study, we performed Mann-Whitney U tests to compare P300 according to medication status or sex at baseline in the patients (refer to the Supplementary material).

3. Results

3.1. Subject characteristics

Table 1 summarizes the demographic factors in the FEP patients and HCs, clinical characteristics and medication usage at baseline. Table 2 shows the changes in the symptoms and medication usage during the 1-year follow-up period. Five patients were drug-naïve, and 19 patients were prescribed atypical antipsychotics at the baseline. No differences were identified in age, sex, and handedness between the FEP patients and HCs. However, the HC subjects were more educated ($t = 2.488$, $p = 0.017$) and showed higher IQs ($t = 5.160$, $p < 0.001$) than the FEP patients. All patients with FEP were prescribed atypical antipsychotics during the follow-up period. The mean time (mean ± standard deviation) from the disease onset to the ERP study of the 24 FEP patients was 5.6 ± 3.9 months, and the average time from the first antipsychotic use to the ERP study of the medicated patients at baseline was 3.2 ± 3.5 months.

3.2. P300 amplitude of FEP and HC groups

Fig. 1(a) shows the grand averaged P300 waveforms. Fig. 1(b) displays the P300 peak amplitudes at the CPz and Pz electrode sites across the FEP and HC groups. Fig. 1(c) illustrates topographic maps of the P300 amplitudes of the FEP and HC participants. A repeated-measures ANOVA with the between-subject factor of group (FEP vs. HC) and the within-subject factor of electrode sites (CP3, CPz, CP4, P3, Pz, and P4) indicated a significant main effect of group ($F = 13.915$, $p = 0.001$) and electrode site ($F = 21.373$, $p < 0.001$) on the P300 amplitude at baseline. A significant group × electrode site interaction was observed ($F = 7.184$, $p < 0.001$). The independent samples t-tests with corrected p-values for multiple comparisons using the Bonferroni technique indicated that the P300 amplitudes at CPz ($p < 0.001$) and Pz ($p < 0.001$) were smaller in the FEP subjects compared to HCs. In terms of the P300 latency at baseline, no significant effect of group ($F = 0.387$, $p = 0.537$) was observed, but a significant effect of electrode site ($F = 5.108$, $p = 0.001$) and group × electrode interaction ($F = 6.098$, $p < 0.001$; Table 3) were present. The P300 peak amplitudes measured at the CPz and Pz electrode sites, which showed significant group differences between the FEP patients and HCs, were used as independent variables in the multiple regression analysis.

3.3. P300 amplitude at baseline predicts symptomatic and functional improvement

The simple regression analyses results are shown in the Supplementary material (Supplementary Table S1–S6). The multiple regression analysis showed that the improvement in the PANSS total score was predicted by the baseline P300 amplitude at CPz

Table 1
Demographic and clinical characteristics of the patients with first-episode psychosis (FEP) and healthy controls (HCs) at baseline.

	FEP ($N = 24$)		HC ($N = 24$)		Statistical analysis[a]	
	Mean	SD	Mean	SD	χ^2 or T	P
Age (years)	22.4	5.1	23.5	4.0	−0.813	0.420
Sex (male/female)	10/14		9/15		−0.087	0.768
Education (years)	13.3	2.1	14.6	1.6	−2.488	0.017[*]
IQ	98.0	13.7	118.2	13.4	−5.160	<0.001[**]
Handedness (right/left)	22/2		22/2		–	0.696
DUP (months)	3.1	3.2	–	–	–	–
PANSS						
Total	69.1	14.0	–	–	–	–
Positive symptoms	17.3	4.6	–	–	–	–
Negative symptoms	17.3	4.6	–	–	–	–
General symptoms	34.5	7.1	–	–	–	–
GAF	45.3	8.7	–	–	–	–
BPRS	46.4	8.6	–	–	–	–
Antipsychotics dose[b]	10.0	8.3	–	–	–	–
Medication use[c]						
Drug free	5 (20.9)		–	–	–	–
Antipsychotics	19 (79.1)		–	–	–	–
Antidepressants	4 (16.7)		–	–	–	–
Mood stabilizers	1 (4.2)		–	–	–	–
Anxiolytics	10 (41.7)		–	–	–	–

IQ, Intelligent Quotient; DUP, Duration of Untreated Psychosis; PANSS, Positive and Negative Syndrome Scale; GAF, Global Assessment of Functioning; BPRS, Brief Psychiatric Rating Scale.
[a] Independent t test or Welch's t test if the variances were not equal; $\chi 2$ analysis or Fisher's exact test for categorical data.
[b] Mean olanzapine equivalent dose.
[c] Number (percentage) of subjects who were prescribed each medication at baseline
[*] The mean difference is significant at the 0.05 level.
[**] The mean difference is significant at the 0.005 level.

Table 2
Change in symptoms as well as medication characteristics during 1 year of the patients with first episode psychosis (FEP).

	FEP ($N = 24$)	
	Mean	SD
Change in PANSS[a]		
Total	22.4	17.6
Positive symptoms	7.1	5.0
Negative symptoms	4.5	5.9
General symptoms	10.8	9.3
Change in GAF[a]	-21.6	13.7
Change in BPRS[a]	13.2	9.1
Antipsychotics dose[b]	13.9	12.6
Medication use[c]		
Antipsychotics	24 (100)	
Antidepressants	10 (41.7)	
Mood stabilizers	4 (16.7)	
Anxiolytics	19 (79.2)	

PANSS, Positive and Negative Syndrome Scale; GAF, Global Assessment of Functioning; BPRS, Brief Psychiatric Rating Scale.
[a] Which was calculated by subtracting scores at last follow-up point from scores at baseline.
[b] Mean olanzapine equivalent dose.
[c] Number (percentage) of subjects who were prescribed each medication during the follow-up period.

($\beta = 1.783$, 95% confidence interval [95%CI] = 0.421–3.145, $p = 0.013$), baseline PANSS total score ($\beta = 1.065$, 95%CI = 0.808–1.322, $p < 0.001$) and sex ($\beta = 9.738$, 95%CI = 2.842–16.634, $p = 0.008$). The P300 amplitude at CPz ($\beta = 0.956$, 95%CI = 0.512–1.399, $p < 0.001$), baseline PANSS positive score ($\beta = 1.173$, 95% CI = 0.955–1.390, $p < 0.001$) and benzodiazepine use ($\beta = -4.413$, 95%CI = −7.335 to −1.492, $p = 0.005$) significantly predicted a subsequent decrease in the PANSS positive score. A decrease in the PANSS general score was predicted by the baseline P300 amplitude at CPz ($\beta = 0.762$, 95%CI = 0.064–1.459, $p = 0.034$), baseline PANSS general score ($\beta = 1.108$, 95%CI = 0.844–1.372, $p < 0.001$), sex ($\beta = 4.141$, 95%CI = 0.497–7.784, $p = 0.028$) and antidepressant use ($\beta = 3.824$, 95%CI = 0.070 to 7.578, $p = 0.046$). Improvement in the GAF score was significantly forecasted by the P300 amplitude at CPz ($\beta = -2.364$, 95%CI = −4.490 to 3.145, p = 0.031) and baseline GAF score ($\beta = 0.804$, 95%CI = 0.150–1.458, $p = 0.019$). Changes in the BPRS were predicted by the P300 amplitude at CPz ($\beta = 0.829$, 95%CI = 0.122–1.536, $p = 0.024$), baseline BPRS ($\beta = 0.874$, 95% CI = 0.651–1.098, $p < 0.001$) and sex ($\beta = 4.318$, 95%CI = 0.564–8.071, $p = 0.028$; Table 4, Fig. 2). However, the baseline P300 amplitude at Pz did not predict the improvement of symptoms and functional outcome in the FEP patients during the 1-year follow-up period. The VIF of all the significant predictors in the multiple regression analyses were less than 10. Results of the exploratory regression analyses, which included the time from the disease onset to the ERP study or the time from the first antipsychotic use to the ERP study as an additional variable, are summarized in the Supplementary material (Supplementary Tables S7 and S8).

4. Discussion

The purpose of this study was to determine whether baseline P300 predicted prognosis, including the improvement of symptoms and functioning after 1 year of treatment in patients with FEP. In line with many previous studies (Salisbury et al., 1998; van der Stelt et al., 2005, Qiu et al., 2014), we also observed reduced P300 amplitudes in patients with FEP compared to HCs. In addition, the baseline P300 peak amplitudes in patients with FEP were predictive of the improvement of the PANSS total, positive, and general scores during a 1-year follow-up period. The baseline P300 amplitude was an independent predictor of improving the overall psychiatric status, as measured by the BPRS, and the global functional status, as measured by the GAF. Thus, patients with greater initial P300 amplitudes at CPz improved more in overall psychotic symptoms, positive symptoms, and general symptoms, as well as overall psychiatric symptoms and general functional outcomes, than patients with smaller baseline P300 amplitudes at CPz.

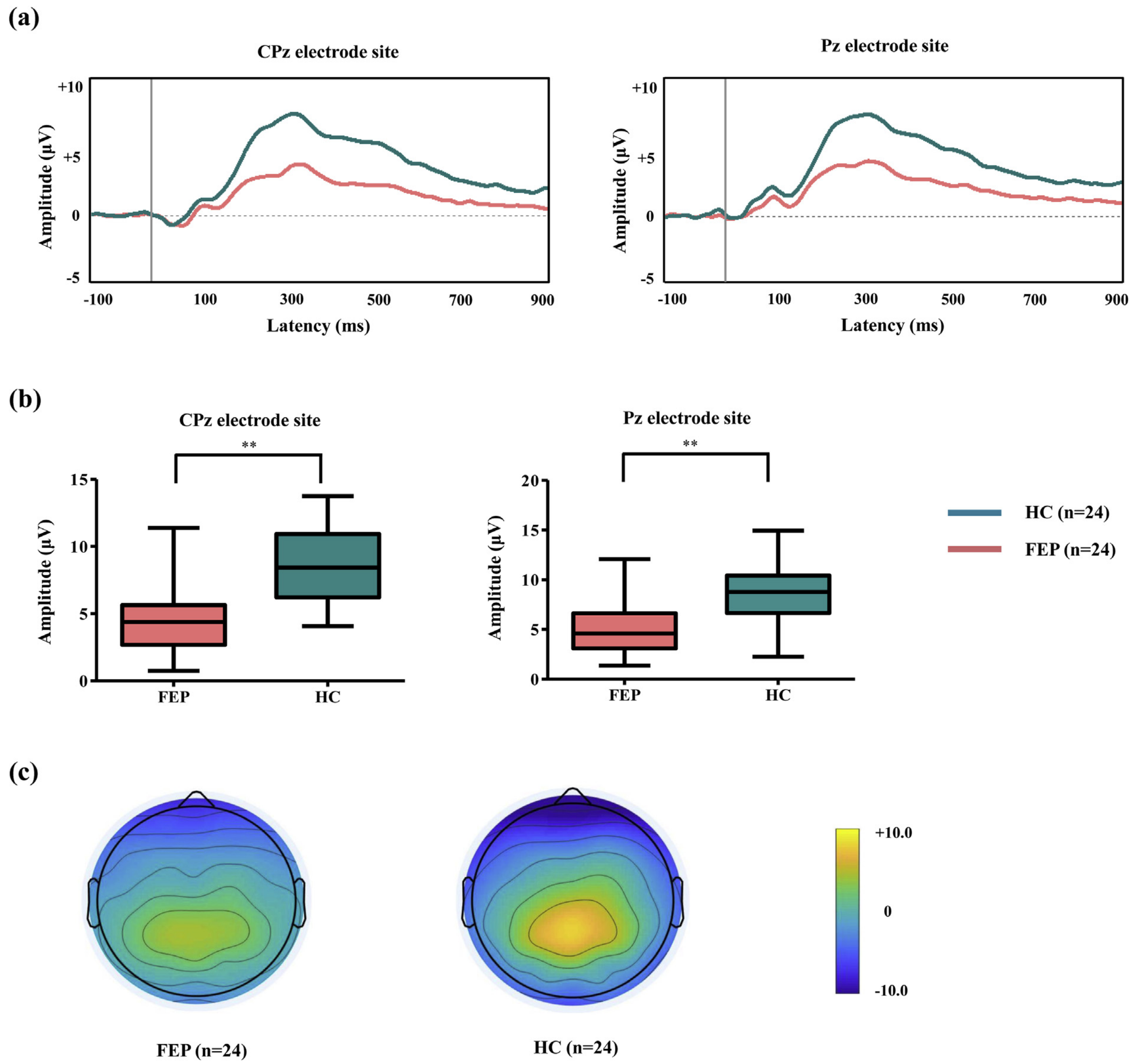

Fig. 1. (a) Grand-averaged P300 waveforms at CPz and Pz electrode sites in patients with first-episode psychosis (FEP) and healthy control (HC) subjects. (b) The P300 amplitudes at CPz and Pz electrode sites across the groups. The horizontal lines in the group indicate the means, and the vertical lines in the group indicate min to max. [**]indicates that the mean differences are significant at the 0.005 level. (c) Two-dimensional P300 topographic maps across FEP and HC groups.

Table 3
Means and standard deviations (SDs) of P300 peak amplitudes and latencies in patients with first-episode psychosis (FEP) and healthy controls (HCs) at surface electrodes.

Electrode sites	FEP (N = 24)		HC (N = 24)		Statistical analysis[a]	
	Mean	SD	Mean	SD	T	P[b]
Amplitude (μV)						
CP3	3.7	2.0	5.1	2.3	−2.108	0.041
CPz	4.6	2.7	8.6	2.8	−5.039	<0.001[*]
CP4	4.2	2.4	5.7	2.4	−2.172	0.035
P3	4.5	2.2	6.1	2.5	−2.413	0.020
Pz	5.2	2.7	8.6	3.2	−4.110	<0.001[*]
P4	4.2	2.3	5.9	2.5	−2.484	0.017
Latency (ms)						
CP3	405.5	59.4	352.7	53.5	3.237	0.002[*]
CPz	378.0	70.6	336.4	56.3	2.255	0.029
CP4	339.0	62.9	361.0	66.3	−1.180	0.244
P3	355.0	73.3	354.9	49.4	0.009	0.993
Pz	346.3	79.2	349.3	63.9	−0.142	0.887
P4	330.5	80.5	343.9	58.8	−0.660	0.513

[a] Independent t test or Welch's t test if the variances were not equal.
[b] Corrected p-value for multiple comparisons using the Bonferroni technique.
[*] Bonferroni corrected P value was significant at $P < 0.0083$ level.

Table 4
Multiple regressions predicting symptom improvement from baseline demographic characteristics, baseline clinical symptom severity, medication use and electrophysiological variable.

Outcome variables					95% CI		
Change in symptoms	Significant predictors	R^2	Beta	P	Lower	Upper	VIF
PANSS							
Total	P300 amplitude at CPz	0.836	1.783	0.013*	0.421	3.145	1.144
	Baseline PANSS total		1.065	<0.001**	0.808	1.322	1.110
	Sex		9.738	0.008*	2.842	16.634	1.032
Positive	P300 amplitude at CPz	0.872	0.956	<0.001**	0.512	1.399	2.005
	Baseline PANSS positive		1.173	<0.001**	0.955	1.390	1.425
	Benzodiazepines		−4.413	0.005*	−7.335	−1.492	2.076
General	P300 amplitude at CPz	0.840	0.762	0.034*	0.064	1.459	1.161
	Baseline PANSS general		1.108	<0.001**	0.844	1.372	1.110
	Sex		4.141	0.028*	0.497	7.784	1.089
	Antidepressants		3.824	0.046*	0.070	7.578	1.150
GAF	P300 amplitude at CPz	0.641	−2.364	0.031*	−4.490	−0.237	1.857
	Baseline GAF score		0.804	0.019*	0.150	1.458	1.849
BPRS	P300 amplitude at CPz	0.808	0.829	0.024*	0.122	1.536	1.048
	Baseline BPRS		0.874	<0.001**	0.651	1.098	1.082
	Sex		4.318	0.028*	0.564	8.071	1.041

PANSS, Positive and Negative Syndrome Scale; GAF, Global Assessment of Functioning; BPRS, Brief Psychiatric Rating Scale; VIF, Variance Inflation Factor.
* The mean difference is significant at the 0.05 level.
** The mean difference is significant at the 0.005 level.

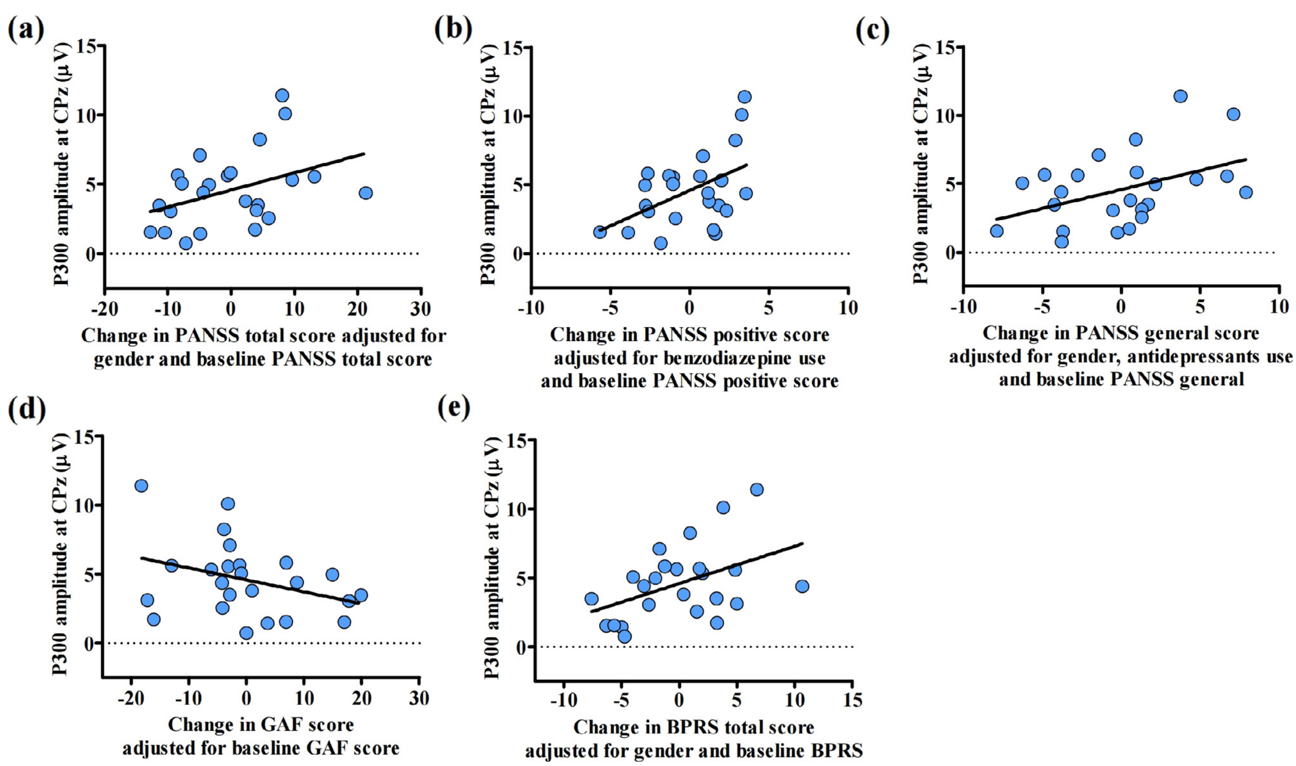

Fig. 2. The correlation between the baseline P300 amplitude at CPz and the change in the scores on the Positive and Negative Syndrome Scale (PANSS) (a) total, (b) positive, (c) general, and (d) the Global Assessment of Functioning (GAF), as well as (e) the Brief Psychiatric Rating Scale (BPRS) adjusted for significant predictors obtained from each multiple regression analysis.

Limited studies have examined whether the P300 amplitude was correlated with symptomatic or functional improvement in chronic schizophrenia patients (Strik et al., 1996; Perlman et al., 2015). Strik et al. reported that low amplitudes of P300, measured at the study index date, which was approximately 10 years after the onset of illness, were correlated with social functioning after an average of 2.4 years of follow-up (Strik et al., 1996). In Perlman et al., P300 was assessed 15 years after the first admission and was associated with global functioning and recovery during the course of the illness. As these studies measured P300 amplitudes a substantial number of years after the onset of psychosis, it might complicate the interpretation of whether the P300 impairment was the result of the clinical course of the illness, a medication effect, or a reflection of poor prognosis. As the P300 amplitude is influenced by the duration of untreated psychosis, illness chronicity, and medication usage (Coburn et al., 1998; van der Stelt et al., 2005; Wang et al., 2005), the assessment of patients with FEP is necessary to minimize these confounders. In our study, which investigated

FEP patients whose mean DUP was 3.1 months and whose average time from the disease onset to the ERP study was less than 6 months, we could minimize the impact of the duration of illness on P300. Moreover, considering the time from the first antipsychotic use to the ERP study was 3.2 months, on average, in medicated patients, P300 was recorded in a short period of time after the first antipsychotic use.

In accordance with previous studies that examined the association of P300 amplitudes and the total symptom severity or general symptoms in chronic schizophrenia over the course of the illness (O'Donnell et al., 1993; Ford et al., 1999; Mathalon et al., 2000a), we demonstrated that baseline P300 amplitudes predicted subsequent improvements in overall symptoms, as measured by the PANSS total and general symptom scores, as well as the BPRS score. Consistent with previous studies, which reported a relationship between P300 amplitudes and positive symptoms (Higashima et al., 2003; Turetsky et al., 2015), the P300 amplitudes predicted positive symptom improvement after one year. Hallucination and delusion may have resulted from a source monitoring failure and a loss of reality testing, which are related to impaired attentional capacity (Brebion et al., 1996; Qiu et al., 2014). Considering that reduced P300 represents impaired attentional capacity (Turetsky et al., 2009; del Re et al., 2015), less P300 impairment may imply less attentional dysfunction, thereby resulting in more positive symptomatic improvement after treatment than more severe P300 impairment. Thus, our results suggest that P300 may be a potential predictor of symptomatic improvement in patients with FEP.

In addition, the improvement in functional outcomes was significantly forecasted by the baseline P300 amplitudes in the FEP patients in the current study. Although Hamilton et al. recently reported that mismatch negativity (MMN) deficit, and not P300, was deferred in schizophrenia patients with high and low functioning (Hamilton et al., 2018), the chronicity of the study participants and cross-sectional design may have loosened the association between P300 and functional status. Because the current study evaluated P300 in FEP participants who were less affected by the disease chronicity with a longitudinal design in functional assessment, the current results may better define P300 as a predictor of functional improvement from the beginning of a psychotic disorder. Reduced P300 might be associated with impaired working memory (Rawdon et al., 2013), which strongly predicts functional outcome (Vesterager et al., 2012; Holshausen et al., 2014; Turetsky et al., 2015). Considering the inferior parietal lobe and temporoparietal junction, which have been suggested as candidate regions for P300 generation (Linden, 2005), are related to working memory functioning (Baldo and Dronkers, 2006; Ravizza et al., 2011), impaired P300 may imply that dysfunction of corresponding brain regions occurs from the beginning of psychosis (Qiu et al., 2014). As less impaired cognitive function at baseline predicts better functional and social outcomes in schizophrenia patients (Carlsson et al., 2006; Vesterager et al., 2012), it might be possible to presume that less disturbance of the P300 amplitude predicts a better outcome.

Because long-term functional outcomes are strongly predicted by the severity of negative symptoms (Fervaha et al., 2014), we expected a prediction of improvement in negative symptoms by P300, as in our previous report with clinical high risk (CHR) non-converters (Kim et al., 2015). However, in our study, the P300 amplitudes at baseline did not predict the improvement of negative symptoms. Previous cross-sectional studies (Ford et al., 1999; Mathalon et al., 2000a), which showed a correlation between P300 and negative symptoms, included patients with a long duration of illness. In contrast, our study included subjects in the early stages of psychosis who were less likely to experience negative symptoms and the extrapyramidal symptoms that mimic negative symptoms. This might have resulted in a negative result in our study. Furthermore, because our previous study, which reported that the initial P300 was predictive of improvement in negative prodromal symptoms, included CHR who did not convert to psychosis (Kim et al., 2015), the results differed from the current study, which included patients with established first-episode psychosis who were diagnosed with positive psychotic symptoms that were not prominent in CHR non-converters.

There are several limitations in this study. First, 19 FEP patients in the study were taking medications, which may have influenced the P300 measured at the baseline assessment. The results from previous studies are inconsistent with the effect of medication on P300. Although studies have reported that the reduced P300 amplitude was restored after treatments (Coburn et al., 1998; Korostenskaja and Kahkonen, 2009; Park et al., 2010), a meta-analysis showed that the P300 amplitude did not differ according to the medication status (unmedicated, low dose or high dose medication) in chronic schizophrenia (Jeon and Polich, 2003). Moreover, a recent meta-analysis regarding FEP patients showed that P300 is not affected by medication (Qiu et al., 2014). To clarify whether P300 was influenced by baseline medication in our study, we performed a Mann-Whitney U test to compare P300 between unmedicated ($N = 5$) and medicated ($N = 19$) patients at baseline (Supplementary Table S9). The results indicated that there was no difference in the P300 amplitudes according to the baseline medication status. However, as the effects of medications on P300 have not been clearly elucidated, caution is required when interpreting the current results. Second, although the clinical and functional assessments were followed-up 1 year after the baseline assessment, we only measured P300 at the baseline and not at the follow up. Thus, we could not investigate the longitudinal change of P300 in relation to symptomatic and functional improvements. Finally, the relatively small number of participants and the short duration of follow-up merit caution in the interpretation of these results. In particular, because the follow-up period is one year, it is difficult to determine the value of P300 as a long-term outcome predictor. To overcome these limitations, additional studies with large numbers of subjects and longer follow-up periods are necessary.

To the best of our knowledge, this study is the first investigation to show that P300 amplitudes measured at baseline in patients with FEP predict symptom and function improvements after 1 year of treatment, which suggests that auditory P300 may be a potential biomarker capable of predicting the symptomatic and functional prognosis in patients with a first psychotic episode. Predicting prognosis from the beginning of a psychotic disorder can provide valuable information to plan the treatment intensity and duration in individual patients and achieve better compliance and long-term outcomes. Although considerable challenges remain before this electrophysiological finding may be translated to clinical practice, the current findings suggest that auditory P300 may be a potential marker utilized for precision medicine, which encompasses personalized early intervention and treatment adherence improvement that may lead to better outcomes in real clinical practice. Future studies using P300 as a predictive biomarker in FEP patients in a larger sample are required to evaluate the validity and clinical significance. Furthermore, the neural basis of P300, which is related to the aspect of prognosis, should be further investigated to have clinical implications. Moreover, the development of a model for precision medicine using markers that are predictive of the prognosis of FEP, including auditory P300, is necessary to improve the quality of life of patients and reduce the socioeconomic burden of the disease.

Conflict of interest

None of the authors have potential conflicts of interest to be disclosed.

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Appendix A. Supplementary material

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