PSYCHIATRIA ET NEUROLOGIA JAPONICA

Frontier of Psychiatry

Longitudinal Evaluation of Visual P300 in a Group at High Risk of Psychosis: An Event-related Potential Study

Naoya Oribe[1,2], Yoji Hirano[2], Takefumi Ueno[1,2], Toshiaki Onitsuka[2]

1 Department of Clinical Research, National Hospital Organization, Hizen Psychiatric Medical Center

2 Department of Neuropsychiatry, Graduate School of Medical Sciences, Kyushu University

Psychiatria et Neurologia Japonica 123: 629-639, 2021

Abstract

[Purpose] We previously reported abnormalities of P300 and N200 in visual oddball tasks and a progressive decrease in the P300 amplitude in patients with first-episode schizophrenia at the 1-year follow-up. A decreased P300 amplitude and normal P1/N1 were also observed in subjects in the high-risk group (CHR), but it remains unclear whether these components change over time. In the present study, visual P300, P1, N1, and N200 in CHR were evaluated longitudinally. [Methods] Visual event-related potentials (ERPs) were recorded twice in CHR (n=19) and healthy controls (HC, n=28), at the baseline and 1-year follow-up. Participants silently counted infrequent target stimuli ('x') among standard stimuli ('y') presented on a screen while we recorded 64 channels of EEG. [Results] In this study, no CHR developed schizophrenia from the baseline to 1-year follow-up. At both time-points, CHR showed a decreased visual P300 amplitude and significantly delayed latency compared with HC. In addition, CHR subjects with more exacerbated positive symptoms showed a decrease in amplitude at both time-points. P1, N1, and N200 did not differ between the groups. [Conclusion] CHR showed a decrease in the P300 amplitude in response to visual stimuli. This finding was observed in subjects who had not developed psychosis by the time of the 1-year follow-up. The

association between the visual P300 amplitude and symptoms suggests that visual P300 may be an important indicator of pathophysiological disturbances underlying clinical symptoms of CHR.

Keywords: high-risk group, EEG, longitudinal study, P300, schizophrenia

Introduction

Recent studies on schizophrenia focused on its early detection, particularly in patients who experienced their first episode of schizophrenia, but also in patients who are considered to be at high risk of developing schizophrenia due to clinical symptoms and a high genetic risk 57). Importantly, individuals at high risk of developing psychosis already have some psychiatric symptoms and are often receiving treatment to alleviate them 24)25). Studies of event-related potentials (ERPs) may be important to assess neurophysiological changes in the early stages of schizophrenia, including early sensory processing and later working memory processes. The sensory evoked components, P1 and N1, are mainly considered indicators of early stages of perceptual processing, and their abnormalities in schizophrenia may be independent of abnormalities in P300 54). Visual N200 is elicited by task-related stimuli and considered to be an indicator of stimulus probability and classification 39)48). Visual N200 is often reported to be abnormal in schizophrenic patients independently of P300 11)18)19)47)62).

P300, which peaks approximately 300-500 ms after the presentation of target stimuli, is evoked by an oddball paradigm in which subjects discriminate between frequently presented standard stimuli and rarely presented target stimuli. Auditory P300 is considered to reflect complex cognitive functions such as working memory and attention 46), and abnormalities have been repeatedly reported in patients with schizophrenia 8). Impairment of auditory P300 has also been reported in clinical high-risk (CHR) patients 9)14)21)44)59). Fusar-Poli, P. et al. evaluated auditory P300 longitudinally in CHR and found that P300 deficits did not change over time 23). Auditory P300 may be a predictor of transition to psychosis 27)38)60) and improvement in negative and general symptoms 34). The authors of the former study also measured ERPs at 18 months and found no progressive changes in P300 in subjects who had

transitioned to psychosis 61).

Recently, Hamilton, H.K. et al. reported in a multicenter study that the smaller the auditory P300 amplitude, the shorter the time to psychosis onset 27).

Although most P300 studies focused on auditory stimuli, P300 in response to visual stimuli has also been studied. It has been suggested that visual P300 is more sensitive to "state" in schizophrenia, while auditory P300 has been found to be more sensitive to "trait" 17)36). Our previous study also revealed that the visual P300 amplitude is progressively decreased in patients with first-episode schizophrenia 41). Reports of visual P300 in CHR are limited 35)40). In patients with first-episode schizophrenia, abnormalities of P300 and N200 were noted in a visual oddball task, and a progressive decrease in the P300 amplitude was noted at the 1-year follow-up 40)41). Furthermore, in CHR, a decrease in the visual P300 amplitude and an increase in latency were reported in addition to the absence of P1 and N1 abnormalities 40). However, it is not yet clear whether these ERP components change over time in CHR. In the following, we report the results of a one-year follow-up study to evaluate visual P300 and P1, N1, and N200 in CHR over time.

I. Methods and Results

1. Subjects

The sample consisted of 19 CHR and 28 healthy controls (HC). Subjects were recruited as part of the Boston CIDAR Study 7), with CHR recruited through referrals from clinicians or local hospitals and clinics, and HC through newspaper and website advertisements. The study was approved by the Ethics Review Board of Harvard Medical School, Beth Israel Deaconess Medical Center, Cambridge Hospital, Brigham and Women's Hospital, Massachusetts General Hospital, and Veterans Affairs Boston Healthcare System. All study participants (or their legal guardians if under 18 years of age) provided written informed consent prior to study participation and received payment for their participation. All HC from the prior study 41) (n=24) participated in this study, and an additional 4 HC were newly recruited for both baseline and follow-up assessments. In addition, 15 of the 23 CHR subjects from the previous study participated in this study 40). Eight CHR subjects from the previous study did not participate in the current study because of: (1) dropout (n=5), (2) too short a measurement interval (n=2), and (3) excessive artifacts/noise in EEG data (n=1). Four additional CHR subjects were recruited and underwent both baseline and follow-up assessments. Note that 13 CHR and 23 HC in this study were also

included in our previous study 42). Exclusion criteria for all subjects were: sensory-motor impairments such as muscular impairment, hearing loss, or uncorrected visual impairment; neurological impairment; medical illness that significantly impairs neurocognitive function; diagnosis of intellectual disability; less than 5th grade education if under 18 years of age or less than 9th grade education if over 18 years of age; not fluent in English; DSM-IV substance abuse in the past month; DSM-IV substance dependence excluding nicotine in the past 3 months; current suicidal behavior; prior electroconvulsive therapy within the past 5 years for CHR and prior electroconvulsive therapy for HC; and other family-testing participation. In addition, subjects with measurement intervals of less than 6 months and excessive artifact/noise on EEG after artifact rejection (see above for the number of subjects excluded) were excluded from subsequent analyses. Substance use was assessed using the Substance Use Disorders module of the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID) and a questionnaire developed by our group. We examined the temporal relationship between substance use and prodromal symptoms to determine whether substance use was a likely cause (as with other psychiatric symptoms).

CHR was assessed using the Scale of Prodromal Symptoms (SOPS, included in the Structured Interview for Prodromal Syndromes (SIPS)) 37). The exclusion criteria for the CHR group were a DSM-IV diagnosis of psychotic disorder, and the presence of substance-induced or other medically-induced progressive symptoms. All but one participant met criteria for attenuated positive symptoms (APS), and one participant met criteria for genetic risk and deterioration syndrome (GRD). Of the participants who met criteria for APS, one met criteria for GRD and another met criteria for schizoid personality disorder. None of the CHR subjects developed schizophrenia within 1 year of the first EEG measurement included in the study. CHR included the following additional diagnoses at the baseline: major depressive disorder (n=6), major depressive disorder and attention-deficit/hyperactivity disorder (n=1), type II bipolar disorder (n=3), type II bipolar disorder and eating disorder (n=1); and at follow-up: major depressive disorder (n=6), type II bipolar disorder (n=2), type II bipolar disorder and eating disorder (n=1), and cannabis abuse (n=1). HC were from the same geographic area as CHR and had comparable age, sex, race and ethnicity, handedness, and parental socioeconomic indicators. HC were

excluded if they had: a current major DSM-IV-TR Axis I disorder or history of psychosis, major depression (recurrent), bipolar disorder, obsessive-compulsive disorder, post-traumatic stress disorder, or developmental disability; HC with a history of psychiatric hospitalization, exacerbations, schizotypal personality disorder or other cluster A personality disorder, first-degree relatives with psychosis, or current or past antipsychotic use were also excluded. Other past psychotropic medications were allowed, but subjects had to have been off of them for at least 6 months prior to entering the study, with the exception of abortive medications such as sleeping pills and anti-anxiety medications.

At the baseline, 5 of 19 CHR were receiving atypical antipsychotics, with chlorpromazine equivalents of 80.7 ± 106.9 mg (range: 6.7-266.7 mg) 56)65). The number of subjects who received other psychotropic drugs were as follows: mood stabilizers = 2, antidepressants = 7, anxiolytics = 6. At the follow-up, 4/19 CHR were receiving atypical antipsychotics with chlorpromazine equivalents of 84.2±123.1 mg (range: 6.7-266.7 mg). The number of patients receiving other psychotropic medications was as follows: mood stabilizers=2, antidepressants=6, and anxiolytics=5. Drug doses were similar between the two time-points (t=1.36, P=0.19).

Handedness was assessed using the Annett Handedness Questionnaire 1).

Premorbid intellectual ability was estimated using the Reading subtest of the Wide Range Achievement Test-4 64), and current intellectual ability was estimated using the Vocabulary and Block Design subtest of the Wechsler Abbreviated Scale of Intelligence 63). Parental socioeconomic indicators were assessed using Hollingshead's two-factor index 30). All subjects were assessed with the Global Assessment of Functioning Scale (GAF). The Spatial Span subtest of the Wechsler Memory Scale-III, a behavioral visual working memory test, was also administered. In addition, CHR symptoms were assessed with SOPS. All demographic and clinical data are summarized in Table 1. EEG was measured using the same experimental paradigm and protocol at the baseline and follow-up.

2. Experimental paradigm

Subjects were instructed to silently count infrequent (20%) target stimuli (letter 'X', 1.8 x 2.0 cm, total count: 36) presented mixed with standard stimuli (letter 'Y', 1.8 x 2.0 cm, total count: 144). The letter was white and displayed in the center of a black computer screen approximately 100 cm away from the subject's eyes. The stimulus duration was 82 ms, and the stimulus interval

was 976 ms (SuperLab 4.2, Cedrus Corporation, San Pedro, USA).

3. Acquisition and processing of EEG data

EEG was recorded using a 64-channel Active-Two system (BIOSEMI B.V., Amsterdam, Netherlands) with custom-made electrode caps. EEG was acquired at a digitization rate of 512 Hz and stored in a DC-100-Hz bandpass. Blink and eye movements were monitored via electrodes placed on the outside of the left and right eyes and above and below the left eye. EEG data were processed offline using the Brain Vision Analyzer package (Brain Products, Gilching, Germany), and the average values of the left and right mastoid processes were used as references offline. Epochs were clipped starting 100 ms before and ending 900 ms after stimulus onset. Blink and eye movement artifacts were corrected by the Gratton, Coles, and Donchin method 26). Epochs containing EMG or other activities greater than ±100 μV were removed before additive averaging. Averages were calculated separately for the target and standard stimuli separately after baseline correction with values 100 ms before the stimulus. P300 and N200 were calculated from the response to the target stimulus, and N1 and P1 were calculated from the response to the standard stimulus. The amplitude and latency of the P300 peak were identified as the most positive data points between 350 and 650 ms, and N200 as the most negative data point between 190 and 380 ms post-stimulus. The P1 peak was identified as the most positive data point between 60 and 200 ms, and N1 as the most negative data point between 75 and 260 ms after stimulus onset. The choice of time windows was guided by the previous study 41) and was determined by careful visual inspection of the individual ERP average and grand average data. These peaks were measured at the electrode sites where they were maximal (P300: Cz, Pz; N200: Fz, Cz; P1: PO3/PO4, O1/O2; N1: P7/P8, PO7/PO8).

The minimum number of trials for subjects to be included in the analysis was 75% (target stimuli: 27 trials, standard stimuli: 108 trials). All subjects met this criterion. The mean number of target and standard stimuli used to construct individual means was not significantly different between groups at the baseline or follow-up ($t<1.41$, $P>0.16$), involving approximately 35 and 139 trials, respectively.

4. Statistical analysis

Independent t-tests were used to evaluate between-group differences in sex, age, handedness, measurement interval, years of education, parental

socioeconomic index, estimated premorbid IQ, IQ at examination, and GAF (Table 1). ERPs were analyzed using repeated measures analysis of variance with Group (HC or CHR) as the between-subjects factor and electrode and time (baseline or follow-up) as within-subjects factors.

5. Correlation analysis

Because we previously found a correlation between the visual P300 amplitude and SOPS-positive symptom scores 40), the correlation between the P300 amplitude and SOPS-positive symptom scores at Pz of CHR at the baseline and follow-up was examined separately using Spearman's ρ.

6. Results

1) Demographic and neuropsychological variables

There were no significant differences in sex, age, handedness, years of education, parental socioeconomic index, estimated premorbid IQ, or IQ at examination between the two groups. CHR had significantly lower GAF scores than HC, both at the baseline and follow-up (Table 1). The measurement interval was also significantly shorter in CHR, due to the relatively long measurement interval (30 months) of one of the HC patients. Note that the statistical results reported below would have been the same if this HC subject had been excluded.

Since the counts of target stimuli were more than 90% accurate in both groups at both time-points and did not differ between groups ($t<0.15$, $P>0.38$), it is unlikely that the following results were influenced by epochs containing misidentified targets. The CHR SOPS-positive symptom score improved over time ($t=2.4$, $P=0.03$), but the SOPS-negative symptom score did not ($t=1.5$, $P=0.15$).

2) ERP variables

Figure 1 shows the grand averages of visual ERPs in each group. Values for each component are summarized in Table 2.

3) Peak amplitude and latency of P300

There was a main effect of Group, $F(1, 45)=6.43$, $P=0.02$, $\eta 2=0.13$, suggesting that the P300 amplitude was smaller for CHR than for HC at both time-points.

There was a main effect of time on the P300 amplitude, $F(1, 45)=7.08$, $P=0.01$, $\eta 2=0.14$, reflecting a trend toward a decreasing P300 amplitude over time in both groups. Other interactions were not significant ($Fs<0.90$, $Ps>0.35$).

The P300 peak latency was slower in CHR at both time-points, $F(1, 45) = 5.70$, $P = 0.02$, $\eta 2 = 0.11$. No other significant main effects or interactions were found ($Fs<1.62$, $Ps>0.21$).

4) N200 peak amplitude and latency

The N200 amplitude did not differ

between groups, F (1, 45) =0.18, P = 0.67. There was no significant interaction (Fs<3.43, Ps>0.07).

The N200 latency was significantly shorter in the central than frontal region in both groups [F (1, 45) =38.77, P<0.001], but there was no difference between groups [F (1, 45) =0.30, P=0.59]. No other significant main effects or interactions were found (Fs<3.58, Ps>0.07).

5) P1 peak amplitude and latency

The P1 amplitude and latency did not differ between groups (Fs<2.17, Ps<0.15). No significant interaction was observed (Fs<2.39, Ps>0.13).

6) N1 peak amplitude and latency

The N1 amplitude and latency did not differ between groups (Fs<2.56, P<0.12). No significant interaction was observed (Fs<0.94, Ps>0.42).

7) Correlation between P300 and clinical variables at each time-point

There was a significant negative correlation between the P300 peak amplitude and SOPS-positive symptom score at the baseline (ρ=-0.73, P<0.001, Figure 2, upper panel). The P300 amplitude change score (baseline-follow-up) was negatively correlated with the SOPS-positive symptom score change score (baseline-follow-up), but this did not reach significance (ρ=-0.46, P=0.07). In an exploratory analysis, we examined the correlation between the P300 value and SPAN total score, but found no significant correlation (-0.12<ρ<0.11, 0.62<P<0.66).

There was no significant correlation between P300 values and chlorpromazine equivalents at any time-point, whether calculated for all CHR cases (-0.28<ρ<0.12, 0.15<P<0.79) or only for drug-treated subjects (-0.08<ρ<0.03, 0.87<P<0.98).

II. Discussion

We longitudinally investigated the P300 ERP component of the visual oddball task in CHR and HC, and examined the correlation between P300 and symptoms in CHR. The P300 amplitude was smaller and P300 latency was prolonged at both time-points in CHR compared with HC. Unlike our previous study, in which patients with first-episode schizophrenia showed a progressive decrease in the P300 amplitude over time, there was no progressive change in CHR compared with HC.

The question of whether the onset of psychosis can be predicted has received considerable attention in studies focusing on CHR. Among several neurophysiological measures, mismatch negativity (MMN) has been the most studied, and abnormalities of MMN have been reported in CHR 2)5)13)29)31)45)50)51), and MMN, especially in response to duration deviation, is considered one of the

predictors of conversion. 6). P300 has been reported to be impaired in CHR, mostly to auditory stimuli 9)21)44)59), but also to visual stimuli 35). For example, Fusar-Poli et al. longitudinally evaluated auditory P300 28 months after the baseline, and reported that the P300 amplitude was consistently reduced in CHR, but no difference was found between the baseline and follow-up 23). van Tricht, M.J. et al. reported that the P300 amplitude in response to an auditory oddball task was already reduced in CHR, and that the group of subjects who later converted to psychosis had smaller amplitudes than the group of subjects who did not convert 60). Although no progressive decrease was observed longitudinally in these samples, van Tricht et al. reported that auditory P300 can be used to predict conversion to psychosis and the time to conversion, suggesting its potential role as a baseline predictive biomarker 23)61). To our knowledge, no studies have investigated visual P300 as a predictor of conversion, and the present study did not include persons with onset, so further investigation is needed to determine whether a reduction in visual P300 distinguishes those who convert to psychosis from those who do not.

In our previous study, the SPAN total score was decreased in patients with first-episode schizophrenia, and the visual P300 amplitude was positively correlated with the score 41).

In the present study, CHR subjects did not show a decrease in the SPAN total score, so the lack of a significant correlation is not surprising. On the other hand, a decrease in the P300 amplitude was correlated with symptom severity as assessed by the SOPS-positive symptom scale, even if symptoms had improved at follow-up. Furthermore, P300 change scores were negatively correlated with positive symptom change scores at the trend level.

In this study, the P300 amplitude decreased over time in both groups, but latency did not change. This may reflect the normal development of visual P300, as reported by Stige, S. et al. 55), in which visual P300 amplitude decreases with age but latency does not change. When subject age and the measurement interval were added as covariates, the results were similar, but only the main effect of time was not significant. Thus, the trend-level correlation between changes in the P300 amplitude and SOPS-positive symptoms over time may reflect a complex and indirect relationship between developmental changes and positive symptoms, suggesting that clinically improved subjects exhibited smaller decreases in the P300 amplitude over time.

In CHR, P300 latency was

significantly prolonged at both time-points and did not change significantly over time. Diffusion tensor imaging studies reported smaller fractional anisotropy (FA) values at CHR 4)32)33)49). Furthermore, Domen, P. et al. showed that the whole-brain mean FA values of siblings of schizophrenic patients were significantly decreased throughout the 3-year follow-up period 15). Begré, S. et al. reported that FA values correlated with P300 latency in patients with schizophrenia 3). Therefore, the delayed P300 latency in the present study suggests that pathophysiological changes that may manifest as white matter damage slow neuronal processing and are already present in CHR, but not progressing, at least during the observation period of the present study. Lee, S.Y. et al. reported that visual P300 latency is normal in CHR 35), but given that this is the only previous study that investigated visual P300 in CHR, it remains unclear whether P300 latency is prolonged in CHR.

Regarding the early component, one study reported impaired N100 suppression in the auditory double-click paradigm 10), and another reported reduced N100 amplitude to sinusoidal sounds in CHR, while others reported normal N100 in the auditory oddball task 9)60). It should be noted that in the latter study sample, the N100 amplitude decreased in CHR throughout the transition to psychosis 61). To our knowledge, no studies have investigated the initial component of visual stimuli in CHR other than our previous study. In the present study, no abnormalities were found either at the baseline or follow-up. Although a reduced P1 amplitude was consistently reported in schizophrenia in studies using stimuli specific to the magnocellular pathway (low contrast and spatial frequency) 16)20), it was not found in studies using stimuli biased toward the parvocellular pathway (high contrast and spatial frequency) or simple visual stimuli oddball task (low contrast and spatial frequency) 12)58). In order to selectively focus on P1 in CHR, it is essential to select tasks that are processed via the magnocellular pathway. Evidence for whether P1 is abnormal in CHR is lacking because there have been no neurophysiological studies focusing on this early visual component.

Visual N200 is considered an index of stimulus classification 53)54) and has been reported to be decreased in schizophrenic patients almost independently of P300 11)18)19)47)62). Although N200 in this study was not significantly different between CHR and HC, given that no other reports have examined visual N200 in CHR, it is too early to draw a firm conclusion

that N200 is normal in this subject group.

As summarized in Table 2, the amplitude and latency of each component are highly correlated between the baseline and follow-up for each group, reinforcing the reliability of our data. However, the latencies of some of the initial components (P1 at PO4 and O2 for HC, P1 at O1 and N1 at PO8 for CHR) did not correlate between the two time-points. This may be due to the susceptibility of these small, early components to artifacts. Although the use of averages near the peak or within the time window may provide some test-retest reliability, the peak amplitude values were employed for comparability with previous studies.

In summary, the present study showed a sustained decrease in the visual P300 amplitude and prolonged latency throughout a one-year follow-up period in CHR who did not convert to psychosis. The decrease in amplitude was more pronounced at both time-points in subjects with more positive symptoms. However, although there is evidence that P300 is sensitive to the progression of schizophrenia, the question of whether abnormalities in visual P300 can be used to detect subjects who subsequently develop psychosis is unclear, since there were no subjects in this sample who developed psychosis. Visual P300 is a potential biomarker of prodromal symptoms. However, at this stage, it is unclear whether this ERP component is an indicator of neurocognitive deficits present in clinically high-risk individuals with or without psychosis, or whether visual P300 abnormalities are predictive of the development of schizophrenia. The question of visual P300 as a biological marker of the development of psychosis requires future studies that include those who develop psychotic symptoms. On the other hand, it is becoming increasingly clear that the clinical symptoms exhibited by individuals at high risk of psychosis constitute an attenuated psychosis syndrome, even if they do not evolve into psychosis, and are now recognized as a formal psychiatric disorder. Thus, P300 in response to visual stimuli may be an important indicator of the pathophysiological changes underlying this clinical condition.

Conclusion

The present study 43) analyzed data from the visual oddball task in a high-risk group based on EEG data accumulated by the Boston CIDAR Study, which was conducted to evaluate the onset and progression of schizophrenia from multiple perspectives and longitudinally. As is well-known, about 20 to 30% of patients

in at-risk mental state and ultra high-risk groups will develop schizophrenia or other psychiatric disorders within 3 years, and there is a need for an indicator to predict the onset of psychiatric disorders at the stage of being judged as high risk. Event-related potentials, which can be obtained by electroencephalography, are one of the few objective indicators of psychiatric disorders and are expected to be utilized in the future. Among them, it has been reported that P300 can be used to predict a shorter time to the onset of psychosis in the presence of abnormalities and a future alleviation of symptoms in the absence of abnormalities, regardless of whether auditory or visual stimuli are used 27)28). For MMN, it has also been reported that the smaller the amplitude, the shorter the time to onset 22)45). As described in this paper, no participant in the present data set (fortunately) developed schizophrenia during the observation period. This may be due in part to the short observation period, but it is also possible that participation in such a large-scale study and extensive follow-up, including by psychologists, may have prevented the onset of schizophrenia.

In any case, among patients with schizophrenia, of which the prevalence is said to be 1% of the population, only a small percentage can be considered a high-risk group in advance, and the majority of cases develop without any prodromal symptoms being a problem. Since P300 and MMN can be measured easily, it may be interesting to follow-up the progress in a large group of teenagers, regardless of the presence or absence of prodromal symptoms.

There are no conflicts of interest to disclose in connection with this paper.

References

1) Annett, M.: A classification of hand preference by association analysis. Br J Psychol, 61 (3); 303-321, 1970

2) Atkinson, R. J., Michie, P. T., Schall, U.: Duration mismatch negativity and P3a in first-episode psychosis and individuals at ultra-high risk of psychosis. Biol Psychiatry, 71 (2); 98-104, 2012

3) Begré, S., Kleinlogel, H., Kiefer, C., et al.: White matter anisotropy related to electrophysiology of first episode schizophrenia during NoGo inhibition. Neurobiol Dis, 30 (2); 270-280, 2008

4) Bloemen, O. J. N., de Koning, M. B., Schmitz, N., et al.: White-matter markers for psychosis in a prospective ultra-high-risk cohort. Psychol Med, 40 (8); 1297-1304, 2010

5) Bodatsch, M., Ruhrmann, S., Wagner,

M., et al.: Prediction of psychosis by mismatch negativity. Biol Psychiatry, 69 (10); 959-966, 2011
6) Bodatsch, M., Brockhaus-Dumke, A., Klosterkötter, J., et al.: Forecasting psychosis by event-related potentials-systematic review and specific meta-analysis. Biol Psychiatry, 77 (11); 951-958, 2015
7) Boston CIDAR Study. (https://bricweb.bidmc.harvard.edu/bostoncidar) (参照 2021-08-31)
8) Bramon, E., Rabe-Hesketh, S., Sham, P., et al.: Meta-analysis of the P300 and P50 waveforms in schizophrenia. Schizophr Res, 70 (2-3); 315-329, 2004
9) Bramon, E., Shaikh, M., Broome, M., et al.: Abnormal P300 in people with high risk of developing psychosis. Neuroimage, 41 (2); 553-560, 2008
10) Brockhaus-Dumke, A., Schultze-Lutter, F., Mueller, R., et al.: Sensory gating in schizophrenia: P50 and N100 gating in antipsychotic-free subjects at risk, first-episode, and chronic patients. Biol Psychiatry, 64 (5); 376-384, 2008
11) Bruder, G., Kayser, J., Tenke, C., et al.: The time course of visuospatial processing deficits in schizophrenia: an event-related brain potential study. J Abnorm Psychol, 107 (3); 399-411, 1998
12) Butler, P. D., Martinez, A., Foxe, J. J., et al.: Subcortical visual dysfunction in schizophrenia drives secondary cortical impairments. Brain, 130 (Pt 2); 417-430, 2007
13) Carrión, R. E., Cornblatt, B. A., McLaughlin, D., et al.: Contributions of early cortical processing and reading ability to functional status in individuals at clinical high risk for psychosis. Schizophr Res, 164 (1-3); 1-7, 2015
14) del Re, E. C., Spencer, K. M., Oribe, N., et al.: Clinical high risk and first episode schizophrenia: auditory event-related potentials. Psychiatry Res, 231 (2); 126-133, 2015
15) Domen, P., Peeters, S., Michielse, S., et al.: Differential time course of microstructural white matter in patients with psychotic disorder and individuals at risk: a 3-year follow-up study. Schizophr Bull, 43 (1); 160-170, 2017
16) Doniger, G. M., Foxe, J. J., Murray, M. M., et al.: Impaired visual object recognition and dorsal/ventral stream interaction in schizophrenia. Arch Gen Psychiatry, 59 (11); 1011-1020, 2002
17) Duncan, C. C.: Event-related brain potentials: a window on information processing in schizophrenia. Schizophr Bull, 14 (2); 199-203, 1988
18) Egan, M. F., Duncan, C. C., Suddath, R. L., et al.: Event-related potential abnormalities correlate with structural brain alterations and clinical features in patients with chronic schizophrenia. Schizophr Res, 11 (3); 259-271, 1994
19) Ford, J. M., White, P. M., Csernansky, J. G., et al.: ERPs in

schizophrenia: effects of antipsychotic medication. Biol Psychiatry, 36 (3); 153-170, 1994
20) Foxe, J. J., Doniger, G. M., Javitt, D. C.: Early visual processing deficits in schizophrenia: impaired P1 generation revealed by high-density electrical mapping. Neuroreport, 12 (17); 3815-3820, 2001
21) Frommann, I., Brinkmeyer, J., Ruhrmann, S., et al.: Auditory P300 in individuals clinically at risk for psychosis. Int J Psychophysiol, 70 (3); 192-205, 2008
22) Fryer, S. L., Roach, B. J., Hamilton, H. K., et al.: Deficits in auditory predictive coding in individuals with the psychosis risk syndrome: prediction of conversion to psychosis. J Abnorm Psychol, 129 (6); 599-611, 2020
23) Fusar-Poli, P., Crossley, N., Woolley, J., et al.: Gray matter alterations related to P300 abnormalities in subjects at high risk for psychosis: longitudinal MRI-EEG study. Neuroimage, 55 (1); 320-328, 2011
24) Fusar-Poli, P., Borgwardt, S., Bechdolf, A., et al.: The psychosis high-risk state: a comprehensive state-of-the-art review. JAMA Psychiatry, 70 (1); 107-120, 2013
25) Fusar-Poli, P., Carpenter, W. T., Woods, S. W., et al.: Attenuated psychosis syndrome: ready for DSM-5.1? Annu Rev Clin Psychol, 10; 155-192, 2014
26) Gratton, G., Coles, M. G., Donchin, E.: A new method for off-line removal of ocular artifact. Electroencephalogr Clin Neurophysiol, 55 (4); 468-484, 1983
27) Hamilton, H. K., Roach, B. J., Bachman, P. M., et al.: Association between P300 responses to auditory oddball stimuli and clinical outcomes in the psychosis risk syndrome. JAMA Psychiatry, 76 (11); 1187-1197, 2019
28) Hamilton, H. K., Woods, S. W., Roach, B. J., et al.: Auditory and visual oddball stimulus processing deficits in schizophrenia and the psychosis risk syndrome: forecasting psychosis risk with P300. Schizophr Bull, 45 (5); 1068-1080, 2019
29) Higuchi, Y., Sumiyoshi, T., Seo, T., et al.: Mismatch negativity and cognitive performance for the prediction of psychosis in subjects with at-risk mental state. PLoS One, 8 (1); e54080, 2013
30) Hollingshead, A. B.: Two Factor Index of Social Position. Yale University Press, New Haven, 1957
31) Hsieh, M. H., Shan, J. C., Huang, W. L., et al.: Auditory event-related potential of subjects with suspected pre-psychotic state and first-episode psychosis. Schizophr Res, 140 (1-3); 243-249, 2012
32) Karlsgodt, K. H., Niendam, T. A., Bearden, C. E., et al.: White matter integrity and prediction of social and role functioning in subjects at ultra-

high risk for psychosis. Biol Psychiatry, 66 (6); 562-569, 2009
33) Katagiri, N., Pantelis, C., Nemoto, T., et al.: A longitudinal study investigating sub-threshold symptoms and white matter changes in individuals with an 'at risk mental state' (ARMS). Schizophr Res, 162 (1-3); 7-13, 2015
34) Kim, M., Lee, T. Y., Lee, S., et al.: Auditory P300 as a predictor of short-term prognosis in subjects at clinical high risk for psychosis. Schizophr Res, 165 (2-3); 138-144, 2015
35) Lee, S. Y., Namkoong, K., Cho, H. H., et al.: Reduced visual P300 amplitudes in individuals at ultra-high risk for psychosis and first-episode schizophrenia. Neurosci Lett, 486 (3); 156-160, 2010
36) Mathalon, D. H., Ford, J. M., Pfefferbaum, A.: Trait and state aspects of P300 amplitude reduction in schizophrenia: a retrospective longitudinal study. Biol Psychiatry, 47 (5); 434-449, 2000
37) Miller, T. J., McGlashan, T. H., Woods, S. W., et al.: Symptom assessment in schizophrenic prodromal states. Psychiatr Q, 70 (4); 273-287, 1999
38) Nieman, D. H., Ruhrmann, S., Dragt, S., et al.: Psychosis prediction: stratification of risk estimation with information-processing and premorbid functioning variables. Schizophr Bull, 40 (6); 1482-1490, 2014
39) Novak, G. P., Ritter, W., Vaughan, H. G. Jr., et al.: Differentiation of negative event-related potentials in an auditory discrimination task. Electroencephalogr Clin Neurophysiol, 75 (4); 255-275, 1990
40) Oribe, N., Hirano, Y., Kanba, S., et al.: Early and late stages of visual processing in individuals in prodromal state and first episode schizophrenia: an ERP study. Schizophr Res, 146 (1-3); 95-102, 2013
41) Oribe, N., Hirano, Y., Kanba, S., et al.: Progressive reduction of visual P300 amplitude in patients with first-episode schizophrenia: an ERP study. Schizophr Bull, 41 (2); 460-470, 2015
42) Oribe, N., Hirano, Y., De lRe, E., et al.: Progressive reduction of auditory evoked gamma in first episode schizophrenia but not clinical high risk individuals. Schizophr Res, 208; 145-152, 2019
43) Oribe, N., Hirano, Y., Del Re, E., et al.: Longitudinal evaluation of visual P300 amplitude in clinical high-risk subjects: an event-related potential study. Psychiatry Clin Neurosci, 74 (10); 527-534, 2020
44) Ozgürdal, S., Gudlowski, Y., Witthaus, H., et al.: Reduction of auditory event-related P300 amplitude in subjects with at-risk mental state for schizophrenia. Schizophr Res, 105 (1-3); 272-278, 2008

45) Perez, V. B., Woods, S. W., Roach, B. J., et al.: Automatic auditory processing deficits in schizophrenia and clinical high-risk patients: forecasting psychosis risk with mismatch negativity. Biol Psychiatry, 75 (6); 459-469, 2014
46) Polich, J.: Updating P300: an integrative theory of P3a and P3b. Clin Neurophysiol, 118 (10); 2128-2148, 2007
47) Potts, G. F., O'Donnell, B. F., Hirayasu, Y., et al.: Disruption of neural systems of visual attention in schizophrenia. Arch Gen Psychiatry, 59 (5); 418-424, 2002
48) Ritter, W., Simson, R., Vaughan, H. G. Jr., et al.: A brain event related to the making of a sensory discrimination. Science, 203 (4387); 1358-1361, 1979
49) Saito, J., Hori, M., Nemoto, T., et al.: Longitudinal study examining abnormal white matter integrity using a tract-specific analysis in individuals with a high risk for psychosis. Psychiatry Clin Neurosci, 71 (8); 530-541, 2017
50) Shaikh, M., Valmaggia, L., Broome, M. R., et al.: Reduced mismatch negativity predates the onset of psychosis. Schizophr Res, 134 (1); 42-48, 2012
51) Shin, K. S., Kim, J. S., Kang, D. H., et al.: Pre-attentive auditory processing in ultra-high-risk for schizophrenia with magnetoencephalography. Biol Psychiatry, 65 (12); 1071-1078, 2009
52) Simson, R., Vaughn, H. G. Jr., Ritter, W.: The scalp topography of potentials in auditory and visual discrimination tasks. Electroencephalogr Clin Neurophysiol, 42 (4); 528-535, 1977
53) Soltani, M., Knight, R. T.: Neural origins of the P300. Crit Rev Neurobiol, 14 (3-4); 199-224, 2000
54) Sponheim, S. R., McGuire, K. A., Stanwyck, J. J.: Neural anomalies during sustained attention in first-degree biological relatives of schizophrenia patients. Biol Psychiatry, 60 (3); 242-252, 2006
55) Stige, S., Fjell, A. M., Smith, L., et al.: The development of visual P3a and P3b. Dev Neuropsychol, 32 (1); 563-584, 200
56) Stoll, A. L.: The Psychopharmacology Reference Card. McLean Hospital, Belmont, 2001
57) Takahashi, T., Suzuki, M.: Brain morphologic changes in early stages of psychosis: implications for clinical application and early intervention. Psychiatry Clin Neurosci, 72 (8); 556-571, 2018
58) van der Stelt, O., Frye, J., Lieberman, J. A., et al.: Impaired P3 generation reflects high-level and progressive neurocognitive dysfunction in schizophrenia. Arch Gen Psychiatry, 61 (3); 237-248, 2004
59) vanderStelt, O., Lieberman, J. A., Belger, A.: Auditory P300 in high-risk, recent-onset and chronic schizophrenia. Schizophr Res, 77 (2-3); 309-320, 2005

60) van Tricht, M. J., Nieman, D. H., Koelman, J. H. T. M., et al.: Reduced parietal P300 amplitude is associated with an increased risk for a first psychotic episode. Biol Psychiatry, 68 (7); 642-648, 2010
61) vanTricht, M. J., Nieman, D. H., Koelman, J. H. T. M., et al.: Auditory ERP components before and after transition to a first psychotic episode. Biol Psychol, 87 (3); 350-357, 2011
62) Vohs, J. L., Hetrick, W. P., Kieffaber, P. D., et al.: Visual event-related potentials in schizotypal personality disorder and schizophrenia. J Abnorm Psychol, 117 (1); 119-131, 2008
63) Wechsler, D.: Wechsler Abbreviated Scale of Intelligence. 1999
64) Wilkinson, G. S., Robertson, G. J.: WRAT 4: Wide Range Achievement Test, 4th ed: professional manual. Psychological Assessment Resources, Lutz, p.494, 2006
65) Woods, S. W.: Chlorpromazine equivalent doses for the newer atypical antipsychotics. J Clin Psychiatry, 64 (6); 663-667, 2003

表 1　背景情報

		HC	CHR	統計		
				t or χ^2	df	*P*
性別（男/女）		15/13	13/6	1.04	1	0.31
ベースライン時年齢（歳）		20.0±3.8	21.0±4.1	−0.96	45	0.35
フォローアップ時年齢（歳）		21.0±3.8	22.1±4.1	−0.94	45	0.35
測定間隔（月）		12.5±3.8	10.6±2.2	4.03	45	0.05*
利き手[a]		1.1±3.1	1.1±2.9	−0.37	45	0.97
教育年数		13.6±2.6	13.1±2.1	0.64	45	0.52
親の社会経済指標[b]		1.7±0.90	2.1±0.9	−1.44	45	0.16
検査時 IQ[c]		117.8±23.0	116.3±13.4	0.25	45	0.81
推定病前 IQ[d]		116.3±16.7	111.2±16.4	1.05	45	0.3
GAF	ベースライン	83.4±8.5	49.1±9.8	12.78	45	<0.001**
	フォローアップ	83.2±9.1	54.5±10.0	9.78	42	<0.001**
SOPS 陽性症状尺度	ベースライン		12.5±4.5			
	フォローアップ		9.2±6.0			
SOPS 陰性症状尺度	ベースライン		12.8±7.6			
	フォローアップ		11.2±7.9			
Spatial Span subtest of the Wechsler Memory Scale	ベースライン	12.5±3.0	11.2±2.7	1.47	41	0.15
	フォローアップ	12.3±2.6	11.0±3.0	1.56	41	0.12
薬剤量（クロルプロマジン換算：mg）	ベースライン		80.7±106.9			
	フォローアップ		84.1±123.1			

特に示していなければ平均±標準偏差で表す．
HC：健常対照群，CHR：ハイリスク群，GAF：Global Assessment of Functioning，SOPS：Scale of Prodromal Symptoms
[a]Annett Handedness Questionnaire に基づく．
[b]Hollingshead method に基づく．点数が高いほど社会的地位が低いことを示す．
[c]Wechsler Abbreviated Scale of Intelligence の Vocabulary and Block Design サブテストより推定．
[d]Wide Range Achievement Test-4（WRAT-4）Reading サブテストより推定．
*測定間隔は CHR が有意に短い．
**GAF はいずれの測定時にも CHR で有意に低い．
（文献 43 より和訳して引用）

Table 1 Background information

Unless otherwise indicated, data are expressed as mean ± standard deviation.
HC: Healthy control group, CHR: High-risk group, GAF: Global Assessment of Functioning, SOPS: Scale of Prodromal Symptoms
a Based on the Annett Handedness Questionnaire.
b Based on the Hollingshead method. Higher scores indicate lower social status.
c Estimated from the Vocabulary and Block Design subtest of the Wechsler Abbreviated Scale of Intelligence.

d Estimated from the Reading subtest of the Wide Range Achievement Test-4 (WRAT-4).

*CHR show a significantly shorter measurement interval.

**GAF was significantly lower in CHR on both occasions.

(Adapted from ref. 43)

表 2　各所における P300/N200/P1/N1 の平均振幅と潜時

		HC		再テスト信頼性		CHR		再テスト信頼性	
振幅		ベースライン	フォローアップ	ピアソンの相関	級内相関係数	ベースライン	フォローアップ	ピアソンの相関	級内相関係数
P300	Pz	19.7±6.5	18.2±6.5	r=0.72, P<0.001	r=0.84, P<0.001	16.1±6.7	13.1±5.6	r=0.41, P=0.07	r=0.58, P=0.04
	Cz	17.4±6.8	16.1±6.1	r=0.48, P=0.01	r=0.65, P=0.004	14.6±6.0	11.6±4.9	r=0.49, P=0.03	r=0.65, P=0.01
N200	Fz	−3.4±4.7	−2.6±4.9	r=0.53, P=0.003	r=0.70, P=0.001	−2.3±4.5	−4.1±5.2	r=0.56, P=0.01	r=0.71, P=0.006
	Cz	−0.4±4.2	−0.9±4.4	r=0.33, P=0.08	r=0.50, P=0.04	−0.8±4.5	−2.1±4.0	r=0.67, P=0.002	r=0.8, P=0.001
P1	PO3	4.2±2.8	3.5±2.6	r=0.65, P<0.001	r=0.79, P<0.001	2.4±2.0	3.1±2.9	r=0.29, P=0.22	r=0.43, P=0.12
	PO4	4.0±3.0	3.5±2.2	r=0.49, P=0.008	r=0.63, P=0.005	2.8±1.8	3.3±2.7	r=0.36, P=0.12	r=0.50, P=0.07
	O1	5.0±3.3	4.0±2.5	r=0.65, P<0.001	r=0.77, P<0.001	3.5±2.4	3.8±2.7	r=0.55, P=0.01	r=0.71, P=0.006
	O2	4.2±3.0	3.4±2.2	r=0.55, P=0.002	r=0.69, P=0.002	3.0±1.8	2.7±2.4	r=0.40, P=0.08	r=0.56, P=0.05
N1	P7	−2.0±1.7	−2.0±1.9	r=0.63, P<0.001	r=0.77, P<0.001	−1.7±2.6	−1.3±2.4	r=0.61, P=0.005	r=0.76, P=0.002
	P8	−3.2±2.7	−2.6±2.4	r=0.65, P<0.001	r=0.79, P<0.001	−1.8±2.0	−1.6±2.8	r=0.74, P<0.001	r=0.82, P<0.001
	PO7	−2.6±2.2	−2.2±2.6	r=0.64, P<0.001	r=0.78, P<0.001	−2.2±3.4	−1.6±3.1	r=0.72, P=0.001	r=0.83, P<0.001
	PO8	−3.5±3.3	−3.0±3.2	r=0.67, P<0.001	r=0.81, P<0.001	−2.2±3.3	−2.0±2.7	r=0.75, P<0.001	r=0.85, P<0.001
潜時		ベースライン	フォローアップ	ピアソンの相関	級内相関係数	ベースライン	フォローアップ	ピアソンの相関	級内相関係数
P300	Pz	424.6±33.4	424.3±33.2	r=0.50, P=0.006	r=0.67, P=0.003	442.3±29.2	440.8±32.3	r=0.41, P=0.08	r=0.58, P=0.04
	Cz	420.5±30.4	423.1±25.9	r=0.49, P=0.008	r=0.65, P=0.004	438.4±30.9	442.5±29.2	r=0.42, P=0.07	r=0.59, P=0.03
N200	Fz	317.3±31.4	318.8±27.3	r=0.66, P<0.001	r=0.80, P<0.001	321.1±38.8	316.3±30.9	r=0.59, P=0.008	r=0.73, P=0.004
	Cz	301.0±29.3	297.6±28.9	r=0.37, P=0.05	r=0.54, P=0.03	305.7±44.3	309.3±30.7	r=0.61, P=0.005	r=0.73, P=0.004
P1	PO3	143.6±24.6	139.6±25.9	r=0.30, P=0.11	r=0.47, P=0.06	129.9±22.2	137.7±27.3	r=0.51, P=0.03	r=0.67, P=0.01
	PO4	141.0±20.7	134.0±22.4	r=0.10, P=0.61	r=0.18, P=0.30	132.0±22.9	136.8±27.5	r=0.72, P=0.001	r=0.82, P<0.001
	O1	141.3±21.9	139.0±24.1	r=0.32, P=0.09	r=0.49, P=0.05	133.5±23.1	132.7±32.8	r=0.17, P=0.47	r=0.28, P=0.24
	O2	133.9±25.5	132.7±23.7	r=0.22, P=0.25	r=0.36, P=0.12	133.1±21.0	135.5±25.2	r=0.39, P=0.10	r=0.55, P=0.05
N1	P7	171.5±40.0	169.1±43.5	r=0.46, P=0.01	r=0.63, P=0.007	178.5±17.0	181.2±11.0	r=0.64, P=0.003	r=0.74, P=0.003
	P8	171.7±32.8	171.5±32.0	r=0.54, P=0.003	r=0.70, P=0.001	179.7±15.2	177.0±24.8	r=0.34, P=0.15	r=0.47, P=0.09
	PO7	163.8±36.7	164.9±45.8	r=0.41, P=0.03	r=0.57, P=0.02	180.3±17.5	178.1±13.2	r=0.46, P=0.04	r=0.62, P=0.03
	PO8	163.8±34.1	168.5±33.9	r=0.59, P=0.001	r=0.75, P<0.001	181.1±16.2	177.6±24.4	r=0.22, P=0.4	r=0.34, P=0.20

平均±標準偏差で表す.
HC：健常対照群, CHR：ハイリスク群
(文献 43 より和訳して引用)

Table 2 Mean amplitude and latency of P300/N200/P1/N1 at various locations

Expressed as mean ± standard deviation.

HC: Healthy control group, CHR: High-risk group.

(Adapted from ref. 43)

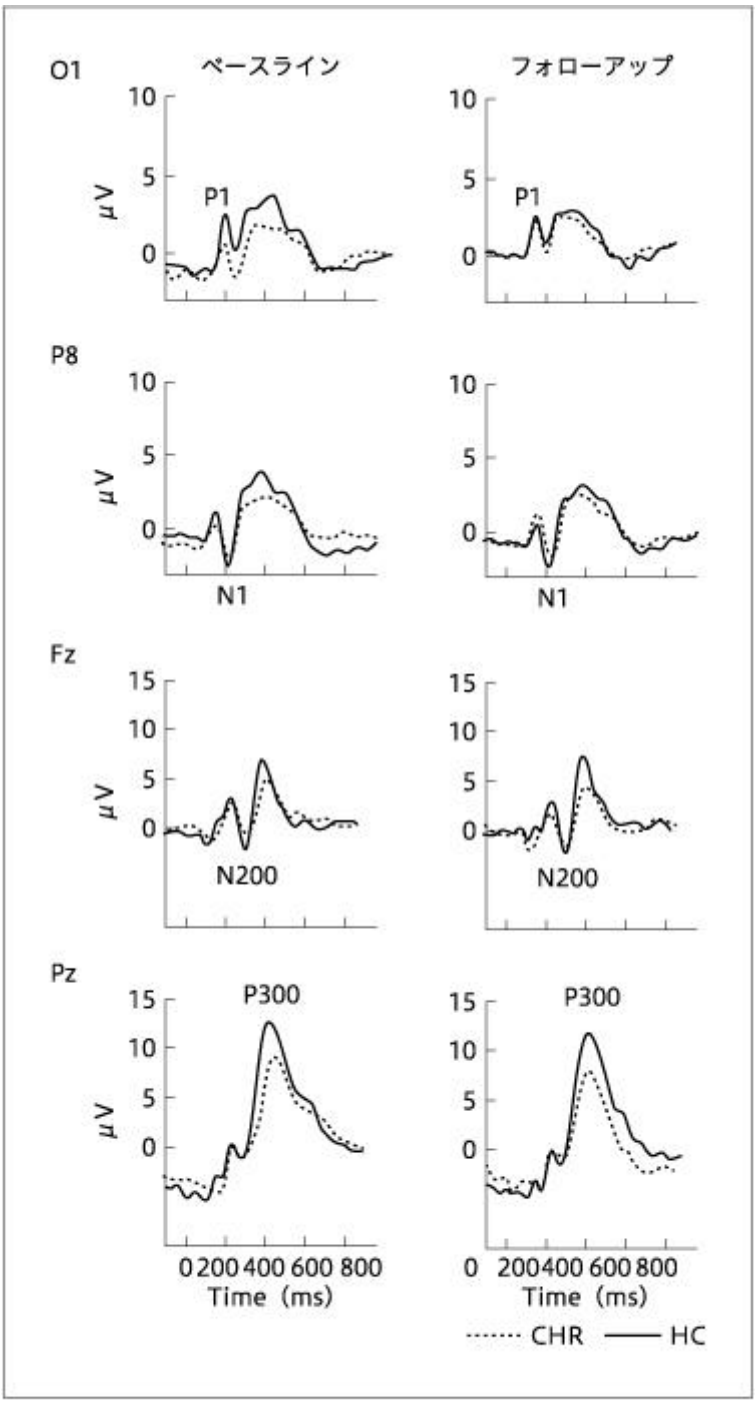

図 1　視覚刺激に対する事象関連電位
P1 は O1，N1 は P8，N200 は Fz，P300 は Pz で測定．
（文献 43 より和訳して引用）

Figure 1 Event-related potentials to visual stimuli
P1 is measured with O1, N1 with P8, N200 with Fz, and P300 with Pz.
(Adapted from ref. 43)

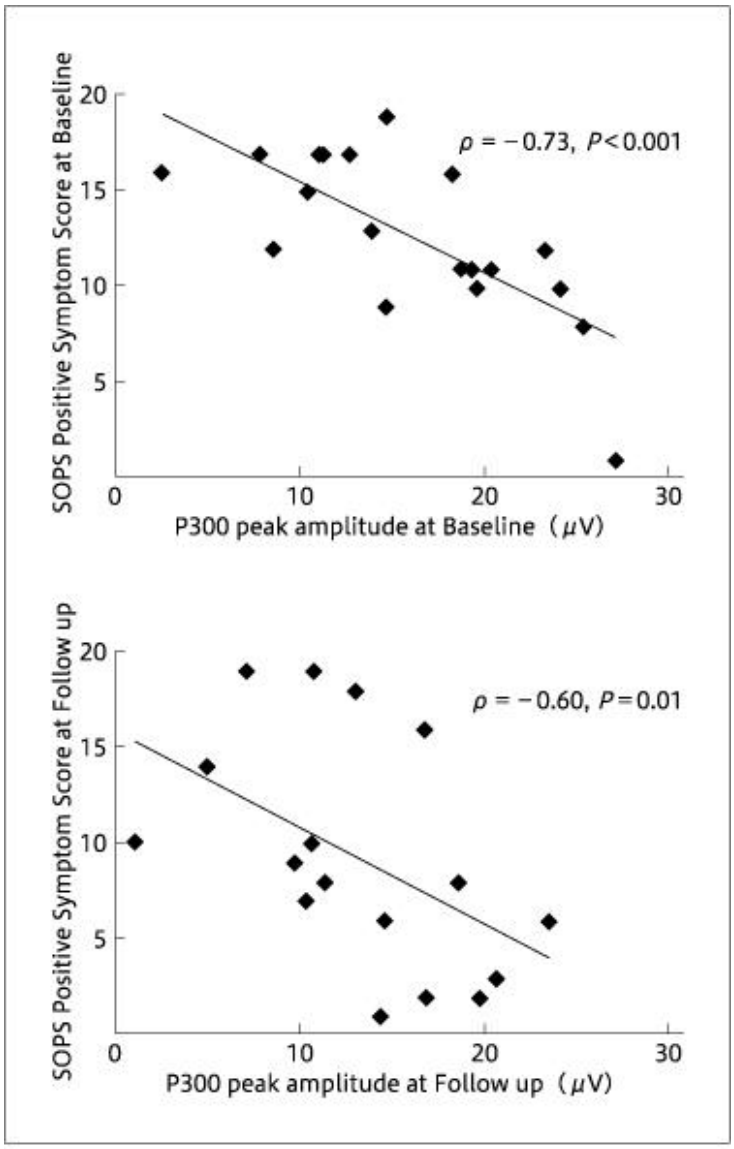

図 2　ベースライン時の P300 ピーク振幅と SOPS 陽性症状の散布図（上段），フォローアップ時の P300 ピーク振幅と SOPS 陽性症状の散布図（下段）

Pz における P300 ピーク振幅は，ベースライン時およびフォローアップ時の SOPS 陽性症状スコアと負の相関がみられた．
（文献 43 より引用）

Figure 2 Scatter plots of P300 peak amplitude and SOPS-positive symptoms at baseline (upper panel) and P300 peak amplitude and SOPS-positive symptoms at follow-up (lower panel).

P300 peak amplitude at Pz was negatively correlated with SOPS-positive symptom scores at baseline and follow-up.

(Adapted from ref. 43)