purpose for which the variables were used (Table 2). For example, if the optimal thresholds of the integral values of R1 and R2 derived from the initial site (73 and 104) were applied to the independent test data from the remaining 6 sites, the sensitivities were 0.73 (proportion of patients/measurement: 96/131) and 0.79 (104/131) and the specificities were 0.63 (proportion of HCs/measurement: 326/514) and 0.63 (324/514) for R1 (positive predictive value (PPV) = 0.37, negative predictive value (NPV) = 0.90) and R2 (PPV = 0.40, NPV = 0.92), respectively.

*Test for differentiation of patients with unipolar MDD from those with BP and SZ*

Using the preliminary data from the initial site, one-way ANOVA performed between the patients with MDD and those with one of the other 2 disorders of interest (BP or SZ) revealed a significant difference in the R1 centroid values [$F(1,53) = 9.54$, $p < 0.01$; $d = 0.96$, 95% CI, (0.25 to 1.62)], but not in the R1 [$F(1,53) = 0.14$, $p = 0.71$] or the R2 [$F(1,53) = 0.05$, $p = 0.83$] integral values.

As the significant R1 centroid value proved to be the most useful variable, we applied it to ROC analysis for the differentiation of patients with unipolar MDD from those with non-MDD disorders. The resulting area under the ROC curve (Az) value was 0.74 [95% CI, (0.61 to 0.87)] and the optimal threshold was 54 [s] from the extreme top left point of the ROC curve (eFig. S4).

To validate the optimal threshold calculated, we applied it to the independent test data of the remaining 6 sites, to differentiate the patients with MDD from those with SZ and BP [Az = 0.81, 95% CI, (0.74 to 0.89); $d = 1.17$, 95% CI, (0.79 to 1.54); optimal threshold = 54 [s], PPV = 0.79, NPV = 0.82; Fig. 4]. Using this threshold (54 [s]), 74.6% of the patients with MDD (proportion of patients/measurement: 41/55) and 85.5% of those with SZ or BP (65/76) were classified correctly [76.9% of BP patients (20/26) and 90.0% of SZ patients (45/50)] (Fig. 5). The ROC curves of MDD v. BP [Az = 0.74, 95% CI, (0.62 to 0.85); $d = 0.81$, 95% CI, (0.32 to 1.29); optimal threshold = 54 [s], PPV = 0.87, NPV = 0.59] and MDD v. SZ [Az = 0.86, 95% CI, (0.78 to 0.93); $d = 1.40$, 95% CI, (0.96 to 1.82); optimal threshold = 54 [s], PPV = 0.89, NPV = 0.78] are shown separately in eFig. S5.

For reference, the test performed for the differentiation between patients with BP and those SZ is shown in Supplementary Material (VII).

*Correlational analysis of demographic and clinical confounding factors*

Correlational analysis showed no significant correlations between any of the significant dependent variables (among the R1 and R2 integral values and the R1 centroid value of NIRS signals) and any of the demographic confounding factors [performance (number of correct words), education years and pre-morbid IQ; $p > 0.05$] for all patients with psychiatric disorders (MDD, BP and SZ).

Regarding clinical confounding factors, a stepwise regression analysis of each significant dependent variable for each disorder revealed that there was no entry clinical variable in the linear regression models, with the exception of the global assessment of functioning (GAF) score (beta = 0.50, $p < 0.01$) for the R2 integral value ($F = 10.73$, $p < 0.01$; $R = 0.50$, $R^2 = 0.25$, adjusted $R^2 = 0.23$) in patients with MDD, and the GAF score (beta = 0.58, $p = 0.01$) for the R2 integral value ($F = 8.43$, $p = 0.01$; $R = 0.59$, $R^2 = 0.35$, adjusted $R^2 = 0.30$) in patients with BP who exhibited depressive symptoms. Thus, only one clinical variable (i.e., GAF score) among all of the medication and clinical variables examined had a significant impact on the R2 integral values for patients with MDD or BP who exhibited depressive symptoms.

**Table 2**
Sensitivities and specificities of the integral values of Region 1 (R1) and Region 2 (R2) signals between healthy controls and all patients with psychiatric disorders, based on the independent data collected from the 6 additional sites.

| Integral value | R1 | | R2 | |
|---|---|---|---|---|
| | Sensitivity | Specificity | Sensitivity | Specificity |
| 160 | 0.95 | 0.27 | 0.90 | 0.39 |
| 150 | 0.93 | 0.30 | 0.89 | 0.43 |
| 140 | 0.92 | 0.34 | 0.88 | 0.47 |
| 130 | 0.90 | 0.37 | 0.87 | 0.52 |
| 120 | 0.88 | 0.42 | 0.85 | 0.57 |
| 110 | 0.85 | 0.46 | 0.82 | 0.61 |
| 100 | 0.82 | 0.50 | 0.78 | 0.64 |
| 90 | 0.78 | 0.54 | 0.76 | 0.68 |
| 80 | 0.74 | 0.61 | 0.73 | 0.73 |
| 70 | 0.72 | 0.65 | 0.64 | 0.76 |
| 60 | 0.66 | 0.71 | 0.57 | 0.78 |
| 50 | 0.57 | 0.75 | 0.52 | 0.81 |
| 40 | 0.47 | 0.80 | 0.43 | 0.86 |
| 30 | 0.38 | 0.84 | 0.33 | 0.89 |

## Discussion

The present multi-site study is the first large-scale, case–control study that demonstrates the utility of NIRS for the differential diagnosis of major psychiatric disorders. The main strengths of this study include the application of a neuroimaging biomarker in clinical practice that allows the clinically useful differential diagnosis of depressive states. The frontal centroid value, which represents the timing of frontal NIRS signal patterns, was a significant variable for differential diagnosis and the optimal threshold derived from the ROC analysis correctly discriminated patients with unipolar MDD (74.6%) from those with non-MDD disorders (85.5%; BP, 76.9% and SZ, 90.0%).

*Single-individual diagnostic classification analyses among various psychiatric disorders*

The present study was not only a case–control study of group comparisons, but also a study specifically designed for examining the practical utility of single-individual diagnostic classification in various psychiatric disorders. Several studies have reported the single-individual diagnostic classification of one psychiatric disorder compared with HCs by applying multivariate statistical methods (e.g.,

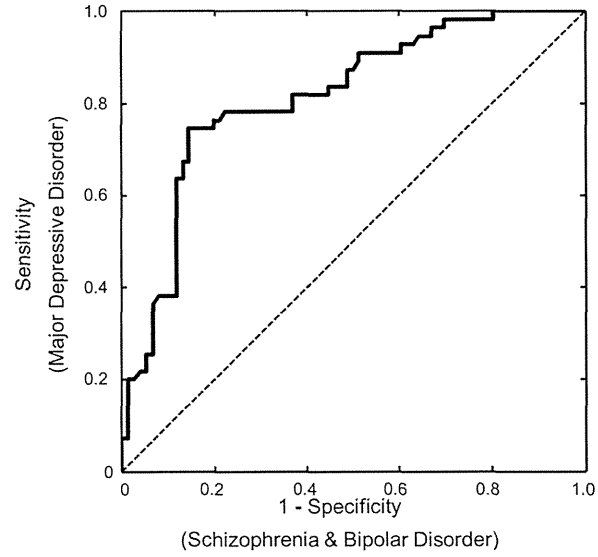


**Fig. 4.** Receiver operating characteristic analysis of the centroid value of Region 1 (R1) near-infrared spectroscopy signal between patients with major depressive disorder and those with either of the other 2 disorders of interest (bipolar disorder and schizophrenia) based on the independent data collected from the 6 additional sites.

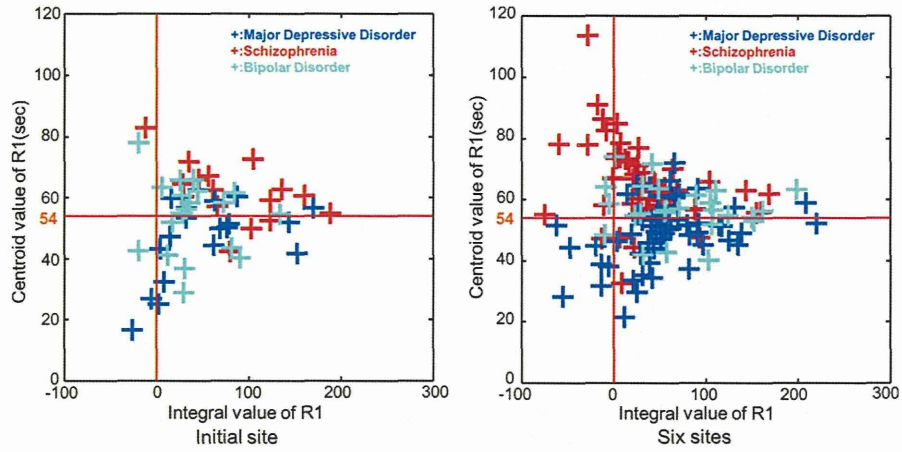


**Fig. 5.** Scatter plots of the centroid and integral values of Region 1 (R1) signal in the patients, both at the initial site (Gunma University) and at the 6 additional sites.

neuroanatomical pattern classification) to structural MRI data (Davatzikos et al., 2005) and NIRS data (Hahn et al., 2013) from SZ and high-risk psychosis samples (Koutsouleris et al., 2009), as well as to functional MRI data from patients with depression (Hahn et al., 2011). These studies were technically sophisticated; however, more research must be performed to test their reproducibility and generalisability in the advanced stage of clinical application, because (1) they were designed for the analysis of one diagnostic classification based on comparison to HCs, and not for differential diagnosis among multiple psychiatric disorders; and (2) they were performed using one relatively small cohort; thus, they must be replicated in another cohort including larger sample groups.

Furthermore, we will discuss briefly our results in comparison with those of other single-individual diagnostic classification studies (Davatzikos et al., 2005; Fu et al., 2008; Hahn et al., 2011; Koutsouleris et al., 2009). We used only a single variable (simple 'centroid value' of NIRS signals) and found that the classification rates (unipolar MDD: 74.6% correct classification; the 2 other disorders: 85.5% correct classification (BP, 76.9%; SZ, 90.0%)) were almost equivalent to the rates reported in the previous MRI studies using multivariate statistical methods (which had 80–90% classification rates in the patient group compared with the HC group).

To determine whether a higher disease classification rate could be achieved by using a multivariate pattern analysis (compared with that obtained using one simple variable), which was used in previous MRI studies, we confirmed the results using the multivariate pattern classification analysis described in Supplementary Material (VIII). The leave-one-out cross-validation method revealed that 4 significant variables, or even one variable (the R1 centroid value), could differentiate patients with unipolar MDD from those with either of the 2 other disorders (non-MDD) with a similar degree of mean accuracy (76.8% (unipolar MDD: 73.0% (54/74), non-MDD: 74.8% (83/111))).

### *Clinical importance and implications*

Another clinically valuable feature of our work is that it aimed to facilitate diagnosis among patients with similar depressive symptoms, which psychiatrists often find to be a difficult task. Most BP patients with depressive symptoms are initially diagnosed with and treated for MDD (Akiskal et al., 1995; Goldberg et al., 2001). Therefore, our findings may help differentiate BP with depressive symptoms from MDD. Depressive symptoms and cognitive deficits are also common early signs of SZ (Hafner et al., 2005). Of particular clinical relevance is the observation that SZ patients with concomitant depression have a greater risk of suicide or an unfavourable disease course (an der Heiden et al., 2005). Therefore, sufficient attention must be given to the diagnosis and treatment of depression in SZ patients.

The results of the present study may draw attention to the heterogeneity observed among MDD patients. Rather than simply being misclassified, approximately 25% of patients with unipolar MDD who were classified by the system as having a non-MDD disorder may have a brain pathophysiology that is biologically different from that of the majority of MDD patients. Evidence suggests that 25–50% of individuals with recurrent major depression (particularly those in atypical early-onset or treatment-refractory subgroups) may in fact have broadly defined BP (Angst, 2007). In this study, 74.6% of the patients with MDD were classified correctly; the remaining 25.4% might include either patients who would progress to a diagnosis of one of the 2 other disorders or patients with a broadly defined BP who were diagnosed with MDD according to the DSM criteria. This explanation might be justified by the finding of a correct classification rate of 75% for patients with MDD. For practical purposes, among patients diagnosed clinically with MDD, the early suspicion of the possibility of a diagnosis of a non-MDD disorder with depression would also provide an opportunity to reduce the hazardous effects of the illness on personal, social and occupational aspects; therefore, our results should be of great clinical importance in practical applications. Thus, a prospective study aimed at elucidating the heterogeneity of unipolar MDD is required.

### *Advantages of the NIRS method*

We used the same NIRS system (a non-invasive, portable and user-friendly device) and the same concise measurement procedure at every site; therefore, inter-site compatibility was not an issue here; however, it may be an obstacle in other neuroimaging multi-site studies. Furthermore, we used a high temporal resolution (0.1 s) in the NIRS system for measuring time-specific characteristics of dynamic prefrontal cortical functions; this enabled analyses that included more detailed time-course comparisons of NIRS signal changes. We created and adopted new variables, such as the 'centroid value', to determine the timing of the haemodynamic response (Fig. 1). The high temporal resolution of NIRS might allow not only the detection of functional abnormalities (e.g., hypofrontality), but also the capture of the specific haemodynamic activation time courses of each psychiatric disorder and aid differential diagnosis.

The practical application of biomarkers requires that they be relatively simple. The simplicity of both the test procedure and the associated data analysis is important not only for the participants, but also for their caretakers and clinicians. Therefore, rather than using complicated multivariate statistical methods, we developed a robust classification algorithm for real-time visual evaluation of patients using the simplest, and lowest number of variables on the basis of a ROC analysis. This was important because we sought to develop a psychiatric practice empowered by the initiative of patients by sharing the 'comprehensively visualised' results that can be easily recognisable by patients and caretakers, rather than results from complicated 'black-box' analyses. In addition, using the condensed VFT (<3 min) developed previously by us, we designed a diagnostic support system in a way that the results are available to clinicians in less than 15 min. The availability of such a 'comprehensively visualised' report to clinicians, patients and their caretakers at a first visit, while laying out a future treatment plan, would likely lead to a paradigm shift to a patient-centred approach in clinical psychiatry.

*Limitations*

The methodological aspects of the present study warrant commentary. First, most of the patients included in the study were taking medications at the time of measurement. To our knowledge, no clear evidence of the effects of medication on NIRS signals has been demonstrated. We found that none of the medications at any dose was significantly correlated with NIRS signals in this study; however, we cannot fully exclude the effects of medication on haemodynamic signals. For confirmation, the application of the algorithm described above (optimal cut-off of the R1 centroid value) to the drug-free patients exclusively, 6 out of 10 patients with MDD patients (60%) and 4 out of 5 patients with SZ (80%) were classified correctly. Second, the size of the sample included in our final analysis was substantially reduced from that initially recruited, because we tried to minimise the confounding factors of age and gender by matching the groups and excluded patients in remission, as well as patients in the manic phase (see Flow diagram). In our confirmatory analysis, we included all non-matched and in-remission patients and found that the results were quite similar, although this analysis had a lower detection power. The optimal threshold of the sample sets before demographical matching was also the same as that calculated originally. These results suggest that the reduction in the total number of study participants after demographical matching did not affect the development of the algorithm [see Supplementary Material (I)]. However, we must consider the possibility that this diagnostic support system is best suited for young and middle-aged patients with moderate or severe symptoms (e.g., aged between 23 and 65 years (mean ± 1.5 SD)). Third, a PCA of haemodynamic response performed to capture a channel cluster led to the identification of 2 cluster regions. Nonetheless, as we thought that pooling many NIRS signals together into only 2 representative regions of interest (R1 (frontopolar and dorsolateral prefrontal regions) and R2 (ventrolateral prefrontal and temporal regions)) might oversimplify the results (see the Discussion of Supplementary Material (II)), we sought to confirm the reliability of the 2 clusters by performing a test–retest analysis in a portion of the samples. We found significant ICCs for both the R1 and R2 integral values and for the R1 centroid value between 2 measurements (see Supplementary Material (IV)). Therefore, we used the two data-derived clusters that reflected a fronto-temporal haemodynamic response during VFT. Fourth, we have controlled some well-known confounders in the analyses. However, the NIRS signal might be affected by the other systemic confounders, such as autonomic function, neuroendocrine function, diet and physical activity. In addition, brain anatomical factors, such as scalp–cortex distance and frontal sinus volume, as well as genetic variants might also be potential confounders. Further studies are required to address the relationship between the NIRS signal and these confounders. If these findings are fully replicated, the development of methods of integrating confounding factors into NIRS signal in the future will be ideal. Fifth, we did not use the exclusion criterion of first-degree relatives with axis I psychiatric disorders for healthy controls. This could give a bias to the data in healthy controls, which means that some of the first-degree relatives of persons with axis I psychiatric disorders might have been included as a healthy control in the present study. However, as the same situations are assumed in real clinical settings, we daringly recruited healthy controls without applying that strict exclusion criterion.

*Conclusions and future implications*

In conclusion, this multi-site study provided evidence that the fronto-temporal NIRS signal may be used as a tool in assisting the diagnosis of major psychiatric disorders with depressive symptoms. Future NIRS research should be performed to study the applicability of this method to (1) the identification of a need for therapy, (2) the assessment of the efficacy of various treatments, (3) the establishment of prognostic predictions that may be clarified by longitudinal follow-up assessments of patients in various clinical stages and (4) the examination of the use of NIRS as a screening tool.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.neuroimage.2013.05.126.

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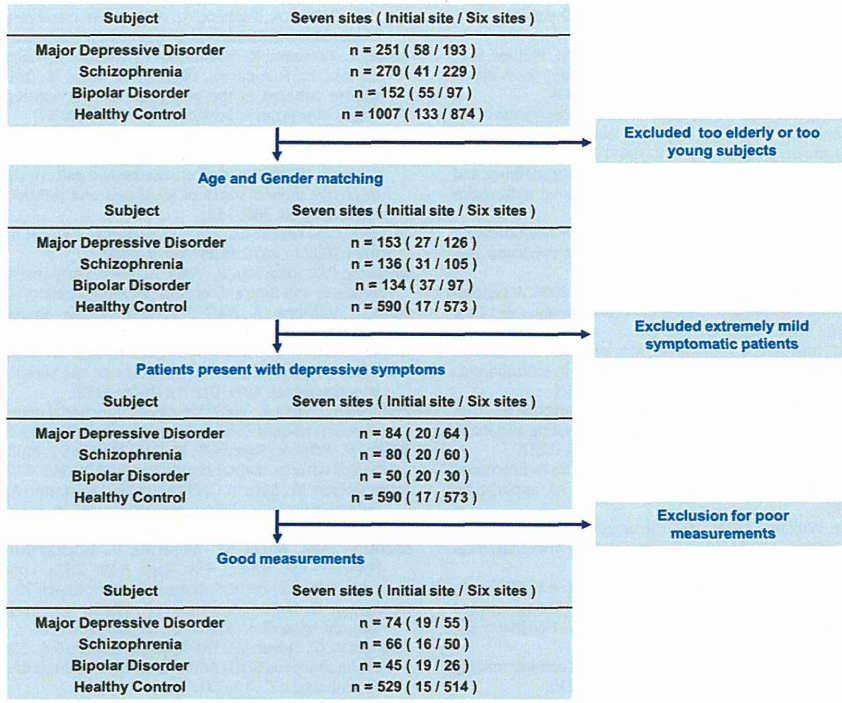


**Flow diagram.** Main analyses were based on matched samples according to the flow diagram.

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## Author contributions

Masato Fukuda designed the experiments and organized the multi-site collaborative study. Ryu Takizawa, Masato Fukuda, Shingo Kawasaki, and Kiyoto Kasai analysed the data and wrote the first draft of the paper. The other contributors performed data acquisition and revised the first draft critically for important intellectual content. All contributors have approved the final version of the manuscript.

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## Conflict of interest

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# Mismatch negativity and P3a/reorienting complex in subjects with schizophrenia or at-risk mental state

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**Introduction:** We measured duration mismatch negativity (dMMN), P3a, and reorienting negativity (RON) in subjects with at-risk mental state (ARMS), patients with first-episode or chronic schizophrenia, and healthy volunteers. The main interest was to determine if these event-related potentials provide a biomarker associated with progression to overt schizophrenia in ARMS subjects.

**Methods:** Nineteen ARMS subjects meeting the criteria of the Comprehensive Assessment of ARMS, 38 patients with schizophrenia (19 first-episode and 19 chronic), and 19 healthy controls participated in the study. dMMN, P3a, and RON were measured with an auditory odd-ball paradigm at baseline.

**Results:** During the follow-up period (2.2 years), 4 out of the 19 ARMS subjects transitioned to schizophrenia (Converters) while 15 did not (non-Converters). dMMN amplitudes of Converters were significantly smaller than those of non-Converters at frontal and central electrodes before onset of illness. dMMN amplitudes of non-Converters did not differ from those of healthy controls, while Converters showed significantly smaller dMMN amplitudes compared to control subjects. RON amplitudes were also reduced at frontal and central electrodes in subjects with schizophrenia, but not ARMS. Converter subjects tended to show smaller RON amplitudes compared to non-Converters.

**Conclusions:** Our data confirm that diminished dMMN amplitudes provide a biomarker, which is present before and after the development of psychosis. In this respect, RON amplitudes may also be useful, as suggested for the first time based on longitudinal observations.

**Keywords: mismatch negativity, reorienting negativity, event-related potentials, prodromal, schizophrenia**

## INTRODUCTION

Schizophrenia is a disorder characterized by positive symptoms (hallucination, delusion, thought disturbance, etc.), negative symptoms (blunted affect, lack of volition, social withdrawal, etc.), and a range of disturbances of cognitive functions (Heinrichs and Zakzanis, 1998; Sumiyoshi et al., 2003; Harvey et al., 2004). In particular, cognitive impairment of schizophrenia is considered to largely determine the outcome of patients, including quality of life and social function (Green, 1996).

Prolonged duration of untreated psychosis (DUP) has been associated with poor long-term outcome, including work function, communication skills, and longer hospitalization (Loebel et al., 1992; Edwards et al., 1999; Malla et al., 2004; Melle et al., 2008; Yamazawa et al., 2008; Chang et al., 2011; Galderisi et al., 2012). On the other hand, shorter DUP has been related with a greater response to antipsychotic drugs in terms of symptoms and quality of life (Perkins et al., 2005). For these reasons, early detection, intervention, and treatment of schizophrenia are needed. In this context, it was reasonable that recent efforts have been directed to subjects with "at-risk mental state (ARMS)" or "ultra-high-risk patients" (McGorry et al., 2009).

The criteria for ARMS require that a young person aged between 14 and 30 years being referred for mental health difficulties met criteria for one or more of the following groups: (i) attenuated psychotic symptoms group (APS): have experienced sub-threshold, attenuated positive psychotic symptoms during the past year; (ii) brief limited intermittent psychotic symptoms group (BLIPS): have experienced episodes of frank psychotic symptoms that have not lasted longer than a week and have spontaneously abated; or (iii) trait and state risk factor group: have a first-degree relative with a psychotic disorder or the identified client has a schizotypal personality disorder, and they have experienced a significant decrease in functioning during the previous year (Yung et al., 1996; Broome et al., 2005).

To promote early diagnosis, objective markers, particularly those based on brain morphology, neurophysiology, and neuropsychology, have been reported to provide useful information (Nakamura et al., 2004; Kawasaki et al., 2007b; Higuchi et al., 2008, 2013b; Takahashi et al., 2011; Takayanagi et al., 2011; Lin et al., 2012). Accordingly, event-related potentials (ERPs) have been suggested to provide a biomarker for cognitive impairment of schizophrenia.

P300 (P3a and P3b) and mismatch negativity (MMN) have been widely used for this purpose. Specifically, patients with schizophrenia have been reported to show smaller P300 amplitudes compared with normal control subjects (Roth et al., 1980; Kawasaki et al., 1997; Bruder et al., 1998). Also, P300 amplitudes have been shown to be reduced in subjects with ARMS (Ozgurdal et al., 2008). On the other hand, P300 is affected by various factors, including medication (Umbricht et al., 1998; Higuchi et al., 2008, 2013a; Sumiyoshi et al., 2009), suggesting the utility as a state marker of psychotic disorders.

Mismatch negativity is another component of ERPs generated in response to occasional variations (e.g., duration, frequency, intensity) of acoustic stimuli, which occurs about 100–200 ms after the onset of deviant stimulation, with peak amplitudes at fronto-central leads (Naatanen et al., 2007, 2012). MMN amplitudes have been suggested to reflect pre-attentive cognitive operations, and decreased in patients with schizophrenia, as indicated by a recent meta-analysis reporting a large effect size (Umbricht and Krljes, 2005). Unlike the case with P300, MMN amplitudes are generally not affected by psychotropic drugs, for example, benzodiazepines (Kasai et al., 2002) and dopamine antagonists (Leung et al., 2007). For these reasons, MMN is considered to provide a trait marker for schizophrenia.

Duration mismatch negativity (dMMN) amplitudes have been shown to be reduced already in the prodromal stage of the illness (Bodatsch et al., 2011; Jahshan et al., 2012; Shaikh et al., 2012; Higuchi et al., 2013b). Furthermore, smaller dMMN amplitudes have been reported in subjects with ARMS who later converted to overt psychosis, compared to those who did not (Shaikh et al., 2012; Higuchi et al., 2013b). Thus, reduced dMMN amplitudes are regarded to predict conversion to schizophrenia in at-risk subjects (Sumiyoshi et al., 2013).

P3a is a positive waveform that appears following MMN, i.e., between 250 and 300 ms after the presentation of stimuli. Its amplitudes are largest at fronto-central electrodes. The P3a component is assumed to reflect a pre-attentive index of deviance detection, and represent the involuntary capture of attention (Friedman et al., 2001).

A negative activity reflecting attentional "re"-orienting follows P3a. This component is referred to as reorienting negativity (RON) (Schroger and Wolff, 1998), which peaks at latencies between 400 and 600 ms, and is centered on fronto-central electrodes (Schroger and Wolff, 1998; Otten et al., 2000; Schroger et al., 2000). The MMN/P3a/RON complex has been shown to provide a neurophysiological index of the cascade of three main processes involved in involuntary attention controls (i.e., automatic change detection, orienting of attention, and reorienting of attention), following deviant stimuli (Berti et al., 2004; Horvath et al., 2008).

Investigations into this series of ERP components should provide further insights into cognitive disturbances in schizophrenia spectrum disorders, which have not been satisfactorily addressed. Specifically, there is little information about the RON in schizophrenia spectrum disorders. Jahshan et al. (2012) measured the amplitudes of MMN, P3a, and RON complex, and found reductions of these parameters in schizophrenia patients. Also, amplitudes of MMN and P3a, but not RON were diminished in individuals at-risk for psychosis. In spite of the above cross-sectional study, further work is needed to test the utility of the ERP complex for predicting progression to schizophrenia in vulnerable individuals.

In this study, we measured dMMN, P3a, and RON amplitudes in subjects with ARMS, first-episode schizophrenia (FES), or chronic phase of the illness. These data were compared with those of normal control subjects. We also attempted to determine if these ERP parameters would predict later progression to schizophrenia in ARMS subjects by means of longitudinal observations. Specifically, preliminary data are provided on the evaluation of RON in relation to transition to overt schizophrenia in vulnerable subjects.

## MATERIALS AND METHODS

### PARTICIPANTS

Diagnosis was made based on the Structured Clinical Interview for DSM-IV (SCID) for schizophrenia and the Comprehensive Assessment of At-Risk Mental State (CAARMS) for ARMS (Yung et al., 2005), by experienced psychiatrists. Most of these subjects were referred from Psychiatric Health and Welfare Center of Toyama (PHWCT), as previously described (Higuchi et al., 2013b). Nineteen ARMS subjects followed at the University of Toyama Hospital participated in this study [male/female = 9/10; mean (SD) age = 19.4 (3.6) years]. Thirty-eight schizophrenia patients also participated in this study. Patients with duration of illness <2 years were defined as FES [$n = 19$; male/female = 9/10; mean (SD) age = 22.8 (5.2) years], while those with duration of illness 2 years or longer were defined as chronic schizophrenia (CS) [$n = 19$; male/female = 9/10; mean (SD) age = 22.9 (3.6) years] (Higuchi et al., 2013b). The patients who allocated "first episode" are defined "single psychotic episode" and "duration of illness is <2 years." CS patients are defined "duration of illness is more than 2 years." Even if patients experienced only one psychotic episode, they allocated to CS group. We recruited normal control subjects from the community by advertisements. They are healthy volunteers [$n = 19$; male/female = 9/10; mean (SD) age = 19.4 (2.5) years] without any personal history of psychiatric illnesses, including schizophrenia or other psychotic disorders. All participants were right-handed. A psychiatric and treatment history was obtained from the subjects, families, and medical records. Subjects with a current history of substance abuse or dependence, seizure, or head injury were excluded from the study. Eligible patients had a complete physical examination and standard laboratory testing was normal. As clinical assessments, the Scale for the Assessment of Positive Symptoms (SAPS) and the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1990) were administered by an experienced psychiatrist. Demographic data at baseline evaluation are shown in **Table 1A**.

At-risk mental state subjects were followed-up at the hospital. Four out of the 19 ARMS subjects transitioned to schizophrenia during the observation period. When DSM-IV criteria were met, e.g., auditory hallucinations persisted or any delusion (for example, disturbance of the self) clearly observed, the subject was regarded to have converted to schizophrenia (Converters; Conv). Subjects who did not develop psychosis were defined as non-converters (Non-C). The average observation period for Non-C subjects was $2.2 \pm 1.5$ years.

**Table 1 | (A) Demographic and clinical data; (B) ERP data.**

| (A) | Healthy controls ($n = 19$) | ARMS ($n = 19$) | First-episode schizophrenia ($n = 19$) | Chronic schizophrenia ($n = 19$) | Group comparison |
|---|---|---|---|---|---|
| Male/female | 9/10 | 9/10 | 9/10 | 9/10 | n.s. |
| Age (years) | 19.4 (2.5) | 19.4 (3.6) | 22.8 (5.2) | 22.9 (3.6) | $F(3,74) = 4.94$, $p = 0.004$ |
| Age of onset (years) | – | – | 22.2 (5.2) | 17.9 (3.9) | $p = 0.007$ |
| Duration of illness (years) | – | – | 0.7 (0.6) | 5.0 (2.3) | – |
| Drug dose[a] | – | 0.1 (0.4) | 1.7 (2.0) | 3.7 (4.2) | $F(2,56) = 8.54$, $p = 0.001$ |
| SAPS | – | 17.3 (7.4) | 27.0 (16.9) | 19.2 (18.0) | $F(2,56) = 2.29$, $p = 0.11$ |
| SANS | – | 60.8 (24.3) | 60.6 (27.2) | 53.3 (22.9) | $F(2,56) = 0.52$, $p = 0.59$ |

| (B) | Healthy controls ($n = 19$) | ARMS ($n = 19$) | First-episode schizophrenia ($n = 19$) | Chronic schizophrenia ($n = 19$) | Analyze of variance (df = 3,75), group effect | |
|---|---|---|---|---|---|---|
| | | | | | *F* | *p* |
| dMMN amplitude (μV) | | | | | | |
| F3 | −6.9 (1.7) | −6.2 (2.0) | −5.0 (1.8) | −4.6 (1.0) | 7.505 | <0.001** |
| F4 | −7.5 (1.4) | −6.5 (2.2) | −5.2 (2.1) | −4.6 (2.0) | 7.767 | <0.001** |
| Fz | −7.4 (1.4) | −6.5 (2.0) | −5.4 (1.9) | −4.8 (1.5) | 8.322 | <0.001** |
| Cz | −6.0 (1.4) | −5.6 (2.1) | −4.8 (1.9) | −3.7 (0.9) | 6.831 | <0.001** |
| Pz | −4.2 (1.4) | −4.5 (4.0) | −3.3 (1.4) | −2.2 (0.9) | 6.240 | 0.001** |
| dMMN latency (ms) | | | | | | |
| F3 | 167.3 (15.1) | 172.1 (17.5) | 173.0 (23.0) | 177.8 (30.7) | 0.702 | 0.55 |
| F4 | 169.1 (15.4) | 175.8 (18.3) | 172.5 (19.7) | 176.6 (24.0) | 0.404 | 0.75 |
| Fz | 172.2 (15.6) | 177.3 (12.6) | 173.0 (19.1) | 176.8 (25.6) | 0.364 | 0.77 |
| Cz | 168.4 (14.8) | 182.3 (18.7) | 174.6 (16.7) | 177.6 (26.2) | 1.675 | 0.18 |
| Pz | 173.0 (15.8) | 188.6 (24.4) | 178.3 (17.4) | 174.8 (30.7) | 1.753 | 0.16 |
| P3a amplitude (μV) | | | | | | |
| F3 | 1.6 (1.8) | 1.1 (1.4) | 1.3 (2.2) | 1.5 (1.3) | 0.277 | 0.84 |
| F4 | 1.4 (2.3) | 1.2 (1.8) | 1.6 (2.1) | 1.4 (1.4) | 0.110 | 0.95 |
| Fz | 2.0 (2.3) | 1.7 (1.5) | 1.7 (2.2) | 1.7 (1.1) | 0.179 | 0.91 |
| Cz | 2.4 (2.4) | 2.1 (1.6) | 2.5 (2.1) | 2.1 (1.4) | 0.209 | 0.89 |
| Pz | 2.0 (2.2) | 1.8 (1.4) | 2.3 (1.8) | 1.8 (1.3) | 0.408 | 0.74 |
| P3a latency (ms) | | | | | | |
| F3 | 255.6 (23.5) | 265.2 (25.0) | 264.2 (28.3) | 262.8 (23.0) | 0.395 | 0.75 |
| F4 | 256.9 (20.2) | 269.7 (28.0) | 262.9 (31.1) | 255.2 (30.8) | 0.755 | 0.52 |
| Fz | 254.6 (21.5) | 268.7 (28.8) | 261.8 (30.9) | 262.3 (22.3) | 0.314 | 0.81 |
| Cz | 255.1 (21.7) | 266.0 (25.9) | 254.8 (28.7) | 262.2 (22.9) | 0.509 | 0.67 |
| Pz | 255.7 (19.8) | 272.2 (27.2) | 254.7 (27.6) | 261.4 (19.7) | 0.359 | 0.78 |
| RON amplitude (μV) | | | | | | |
| F3 | −4.4 (1.7) | −4.1 (1.7) | −3.5 (1.3) | −3.3 (1.3) | 2.320 | 0.08 |
| F4 | −5.2 (1.8) | −4.2 (1.5) | −3.6 (1.7) | −3.4 (1.6) | 4.191 | 0.009** |
| Fz | −5.1 (1.6) | −4.2 (1.8) | −3.9 (1.4) | −3.4 (1.7) | 3.143 | 0.03* |
| Cz | −4.3 (1.9) | −3.8 (2.1) | −3.6 (1.6) | −3.2 (1.6) | 1.143 | 0.33 |
| Pz | −3.1 (1.8) | −2.7 (1.7) | −2.5 (1.5) | −2.6 (1.6) | 0.391 | 0.76 |
| RON latency (ms) | | | | | | |
| F3 | 396.3 (51.8) | 380.7 (49.4) | 395.0 (42.7) | 389.0 (52.6) | 0.395 | 0.75 |
| F4 | 392.7 (53.9) | 404.0 (54.1) | 409.1 (53.1) | 385.4 (53.8) | 0.755 | 0.52 |
| Fz | 396.2 (50.2) | 397.2 (46.8) | 409.3 (40.9) | 397.7 (53.3) | 0.314 | 0.81 |
| Cz | 401.2 (39.0) | 398.3 (44.4) | 412.5 (40.9) | 397.0 (47.4) | 0.509 | 0.67 |
| Pz | 409.5 (48.2) | 401.7 (45.7) | 411.7 (40.7) | 397.4 (58.2) | 0.359 | 0.78 |

*Values represent mean (SD).*

*[a]Risperidone equivalent (mg/day), ARMS, at-risk mental state; SAPS, Scale for the Assessment of Positive Symptoms; SANS, Scale for the Assessment of Negative Symptoms.*

*Values represent mean (SD). ARMS, at-risk mental state.*

**p < 0.05, **p < 0.01.*

### ELECTROENCEPHALOGRAM RECORDING

Electroencephalograms (EEGs) were recorded based on the previous report from our laboratory (Sumiyoshi et al., 2006, 2009; Kawasaki et al., 2007a; Higuchi et al., 2008, 2010, 2013a,b; Itoh et al., 2011).

A 32-channel DC-amplifier (EEG-2100 version 2.22J, Nihon Kohden Corp., Tokyo, Japan) was used. Recordings were performed using an electro cap (Electrocap Inc., Eaton, OH) in a sound-attenuated room. Data were collected with a sampling rate of 500 Hz. EEG data were collected from 29 scalp electrodes (Fp1, Fp2, F3, F4, F7, F8, FC3, FC4, C3, C4, T3, T4, CP3, CP4, TP7, TP8, P3, P4, T5, T6, O1, O2, FPz, Fz, FCz, Cz, CPz, Pz, and Oz according to the extended International 10–20 system). All electrodes were referred to the average amplitude of the ear electrodes (bandwidth = 0.53–120 Hz, 60 Hz notch filter). Electrode impedance was <5 kΩ.

Measurements of dMMN/P3a/RON complex were based on our previous report (Higuchi et al., 2010). One-thousand auditory stimuli were delivered binaurally through headphones with interstimulus intervals 500 ms. Standard/target tones of 50/100 ms duration were randomly presented with the presentation probability of 0.9/0.1. All tones were 60 dB, 1000 Hz, and with a rise–fall time of 10 ms. The subjects were requested to watch silent animation movie (Tom and Jerry) and pay attention to the monitor and ignore the tones.

Averaging of ERP waves and related procedures were performed using Vital Tracer and EPLYZER II software (Kissei Comtec, Co. Ltd., Nagano, Japan). Epochs were 600 ms, including a 100 ms prestimulus baseline. Eye movement artifacts (blinks and eye movements) were manually rejected. MMN waveforms were obtained by subtract standard waveforms from target ones. MMN, P3a, and RON peaks were identified within the 150–250 ms (minus peak), 200–350 ms (plus peak), and 250–500 ms (minus peak) search windows, respectively.

### STATISTICAL METHODS

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) version 20 (SPSS Japan Inc., Tokyo, Japan). We performed comparison of age between four groups (HC, ARMS, FES, and CS) by one-way analysis of variance. Onset age and duration of illness of two schizophrenia groups (first-episode and chronic) were compared by independent *t*-test. Drug dose, SAPS, and SANS score among three groups (ARMS, FES, and CS) were analyzed by one-way ANOVA.

Event-related potential amplitudes and latencies were measured and analyzed at five electrodes; three from frontal lobe (F3, F4, and Fz), and two from midline (Cz and Pz). They are typical electrodes that commonly used on ERP studies. MMN amplitudes are generally largest at frontal electrodes, so we choose three electrodes from frontal lobe. Moreover, grand average waveforms (**Figures 1** and **3**) and scatterplots (**Figures 2** and **4**) were drawn and analyzed by Fz lead as a representative of electrodes because amplitudes ERPs of Fz were largest. Laterality of ERPs was analyzed by F3/F4 comparison as we performed in previous report (Higuchi et al., 2008), but there were no difference in this study (data not shown).

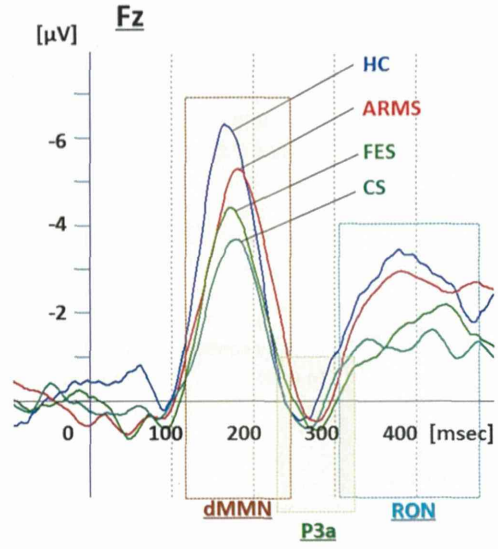


**FIGURE 1 | Duration mismatch negativity (dMMN), P3a, and reorienting negativity (RON) complex waveforms at Fz for all subjects.** Waveforms are presented for healthy controls (HC, blue line), at-risk mental state (ARMS, red line), first-episode schizophrenia (FES, light green line), and chronic schizophrenia (CS, dark green line).

Two-way ANOVA was conducted on amplitudes and latencies of dMMN, P3a, and RON, with "Stage" (HC, ARMS, FES, and CS) and "Lead" (F3, F4, Fz, Cz, and Pz) as fixed factors. Main effects (of Stage and Lead) were described on **Table 1B** (significant differences were seen in all leads of dMMN amplitude and F4/Fz of RON amplitude). The Stage-by-Lead interactions on amplitudes (dMMN, $F = 1.172$, $p = 0.30$; P3a, $F = 0.511$, $p = 0.90$; RON, $F = 1.024$, $p = 0.42$) and latencies (dMMN, $F = 1.254$, $p = 0.246$; P3a, $F = 1.475$, $p = 0.13$; RON, $F = 0.516$, $p = 0.904$) were not significant.

Gender difference between Conv and Non-C were analyzed by Chi-square test. Other factors (age, drug dose, SAPS, SANS, ERP amplitude, and latency) of them were calculated by independent *t*-test. All analyses of variance were corrected by Bonferroni correction.

Correlations of symptoms and ERP amplitudes were performed by Pearson product–moment correlation coefficient. SAPS scores (hallucinations, delusions, bizarre behavior, and positive formal thought disorder) and SANS scores (affective flattening/blunting, alogia, avolition-apathy, anhedonia-asociality, and attention) were used.

Raters were not informed of subjects' profiles and diagnosis.

## RESULTS

### SUBJECTS' PROFILE

Demographic and clinical data of participants are shown in **Tables 1A** and **2**. There was significant group difference in age [$F(3,74) = 4.94$, $p = 0.004$, ANOVA], and Conv subjects were older than Non-C in age ($p = 0.009$, *t*-test). Male/female ratio did not differ between of Conv. and Non-C groups [$\chi^2 = 2.47$, $p = 0.3$, Chi-square test].

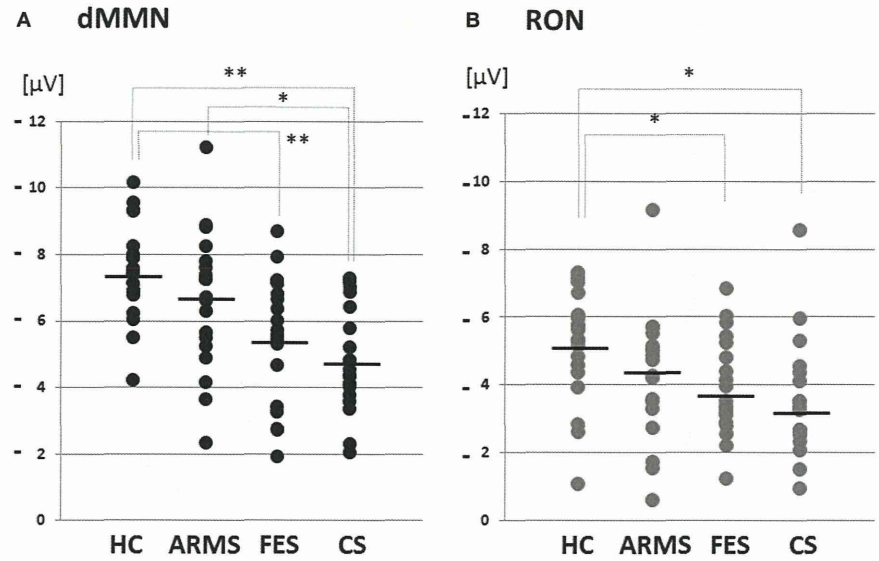


**FIGURE 2 | Distribution of amplitudes of duration mismatch negativity [dMMN; (A)] and reorienting negativity [RON; (B)] at Fz for all subjects**. Data are presented for healthy controls (HC), ARMS, first-episode schizophrenia (FES), and chronic schizophrenia (CS). $*p < 0.05$, $**p < 0.01$.

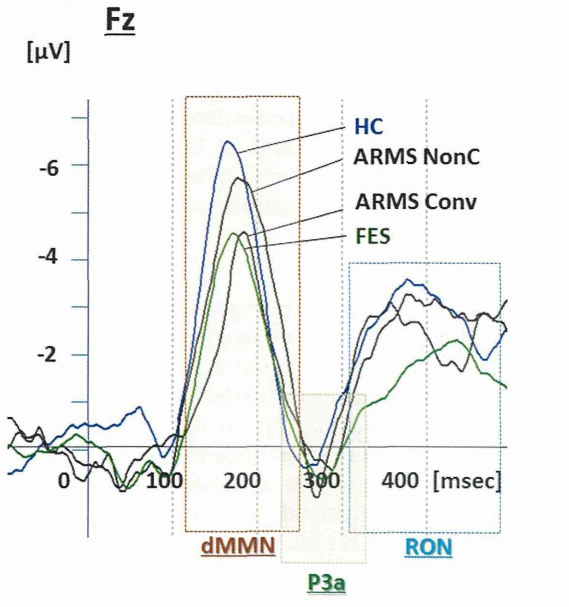


**FIGURE 3 | Duration mismatch negativity (dMMN), P3a, and reorienting negativity (RON) complex waveforms at the Fz lead**. Waveforms are presented for healthy controls (blue line), ARMS Converters (Conv), and non-Converter (Non-C) (black lines), and FES (green line).

Sixteen out of 19 ARMS subjects were not taking any medication, while three were prescribed a small dose of risperidone (1.5 mg/day), aripiprazole (3 mg/day), and sulpiride (150 mg/day), respectively, for acute psychosis episodes (sometimes with strong agitation), based on the criteria of International Early Psychosis Association Writing Group (2005). MMN recordings for these subjects were conducted immediately after medications were started (9, 15, and 27 days). Two out of the three subjects subsequently developed schizophrenia. Thirteen out of 19 FES patients and 15 out of 19 CS patients were taking antipsychotic medications. There were no significant differences among ARMS, FES, and CS groups in SAPS [$F(2,56) = 2.29$, $p = 0.11$, ANOVA] and SANS [$F(2,56) = 0.52$, $p = 0.59$, ANOVA] scores. Conv and Non-C groups did not differ in the SAPS and SANS scores at baseline ($p = 0.08$, 0.24, respectively, $t$-test).

### COMPARISONS OF ERP BETWEEN HEALTHY CONTROLS VS. ARMS VS. SCHIZOPHRENIA

Grand average ERP waveforms in the Fz lead following deviant stimulation are shown in **Figure 1**. Scatterplots of dMMN and RON amplitudes at Fz lead are shown in **Figures 2A,B**, respectively. P3a did not show any statistical differences so we skipped making scatterplot of P3a. ARMS subjects showed relatively smaller dMMN amplitudes at Fz ($-6.5 \pm 2.0\,\mu V$) compared to those of healthy control subjects ($-7.4 \pm 1.4\,\mu V$), which was not statistically significant ($p = 0.13$, $t$-test). On the other hand, FES group showed significantly smaller dMMN amplitudes at Fz ($-5.4 \pm 1.9\,\mu V$) compared to healthy control ($p = 0.001$, $t$-test). Patients with CS showed greater amplitude reductions at Fz ($-4.8 \pm 1.5\,\mu V$) compared to healthy controls ($p = 0.000004$, $t$-test).

At-risk mental state subjects showed relatively smaller RON amplitudes at Fz ($-4.2 \pm 1.8\,\mu V$) than healthy controls ($-5.1 \pm 1.6\,\mu V$), which was not significant ($p = 0.15$, $t$-test). On the other hand, FES group showed significantly smaller RON amplitudes at Fz ($-3.9 \pm 1.4\,\mu V$, $p = 0.02$). Patients with CS also elicited significantly smaller RON amplitudes at Fz ($-3.4 \pm 1.7\,\mu V$) compared to healthy controls ($p = 0.005$, $t$-test).

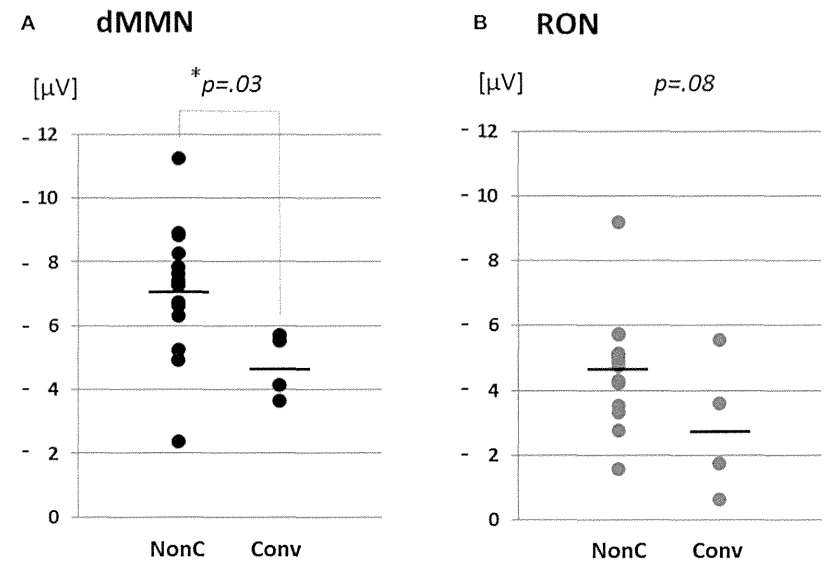


**FIGURE 4 | Distribution of amplitudes of duration mismatch negativity [dMMN; (A)] and reorienting negativity [RON, (B)] at Fz for ARMS.** Data are presented Converters (Conv) and Non-Converter (Non-C). $*p < 0.05$.

Latencies of dMMN, P3a, and RON at any electrodes did not differ among the four groups (see **Table 1B**).

### COMPARISONS BETWEEN CONVERTERS VS. NON-CONVERTERS

Grand average ERP waveforms are shown in **Figure 3**. Scatterplots of dMMN and RON amplitudes at Fz lead are shown in **Figures 4A,B**, respectively. P3a did not show any statistical differences so we skipped making scatterplot of P3a. Waveforms of Conv group were similar to those of FES patients. By contrast, waveforms of Non-C subjects resembled to those of healthy controls. Conv subjects showed significantly smaller dMMN amplitudes at Fz and Cz electrodes compared with Non-C subjects ($p = 0.03$, 0.05 by $t$-test, respectively, **Table 2**). On the other hand, amplitudes of Non-C did not differ from those of HC ($p = 0.51$ at Fz, $t$-test, data not shown) and there was no significant difference in dMMN amplitudes between Conv and FES subjects ($p = 0.44$ at Fz, $t$-test, data not shown). In other electrode of Non-C vs. HC and Conv vs. FES comparisons, differences were smaller and did not reach significance.

Conv subjects tended to show smaller RON amplitudes compared to those of Non-C subjects at Fz and F4 electrodes ($p = 0.08$, $p = 0.08$ by $t$-test, respectively, **Table 2**). Also, HC group showed relatively larger RON amplitudes at Fz lead compared to Conv subjects, which did not reach significant level ($p = 0.08$, $t$-test, data not shown). No significant differences were found at any electrode between FES vs Non-C groups (data not shown).

Latencies of dMMN, P3a, and RON at any electrodes did not differ between Conv and Non-C groups (see **Table 2**).

### RELATIONSHIP BETWEEN SYMPTOMS AND ERPs

We evaluated the correlations between dMMN, P3a, and RON amplitudes and symptoms (SAPS and SANS) in patients (schizophrenia and ARMS, $n = 57$).

Data are shown in **Table 3**. There were significant correlation between attention disorder score (SANS) and dMMN amplitude at Fz and F3 lead ($r = 0.317$; $p = 0.025$, $r = 0.290$, $p = 0.041$, respectively, by Pearson's correlation). Moreover, there were significant correlation between positive formal thought disorder score (SAPS) and RON amplitude at Fz and F3 lead ($r = 0.280$; $p = 0.049$, $r = 0.346$, $p = 0.014$, respectively, by Pearson's correlation). Thus, reduction of ERPs was correlated with severity of some symptoms.

## DISCUSSION

Duration mismatch negativity amplitudes at frontal and central leads were reduced in ARMS subjects who later converted to overt schizophrenia in comparison with non-converters and normal subjects, consistent with previous reports (Bodatsch et al., 2011; Shaikh et al., 2012; Higuchi et al., 2013b). Specifically, the current data from gender matched subjects across groups (**Table 1**) confirmed previous observations in patients with variable demographic backgrounds (Bodatsch et al., 2011; Shaikh et al., 2012; Higuchi et al., 2013b). Importantly, this study is the first to suggest that RON provides a marker for the progression to overt schizophrenia in subjects with ARMS, based on longitudinal observations.

Three out of 4 Conv, 7 out of 15 Non-C, 7 out of 19 FES, 5 out of 19 CS, and 9 out of 19 HC subjects overlapped with subjects in our previous report (Higuchi et al., 2013b). We selected subjects for the current study, according to the following considerations; (1) ARMS subjects with a longer followed-up period, (2) gender-match between HC and schizophrenia patients, (3) younger HC and schizophrenia patients than those used in the previous study. The current one used a longer observation period, and was gender-matched across groups with less variation in age. According to a previous report (Yung et al., 2003), 10–40% of ARMS subjects

**Table 2 | Comparison between converters and non-converters of ARMS subjects.**

| | ARMS ($n=19$) | | Group comparison ($p$) |
|---|---|---|---|
| | Non-C ($n=15$) | Conv ($n=4$) | |
| Male/female | 7/8 | 3/1 | $\chi 2=2.47$, $p=0.3$ |
| Age (years) | 18.3 (2.2) | 23.4 (4.9) | 0.009 |
| Drug dose[a] | 0.1 (0.2) | 0.4 (0.6) | 0.12 |
| SAPS | 15.3 (7.0) | 22.7 (5.8) | 0.08 |
| SANS | 56.9 (26.3) | 73.7 (9.6) | 0.24 |
| dMMN amplitude (μV) | | | |
| F3 | −6.5 (2.1) | −4.9 (0.6) | 0.16 |
| F4 | −7.0 (2.2) | −4.6 (0.9) | 0.06 |
| Fz | −7.0 (2.0) | −4.7 (1.0) | 0.03* |
| Cz | −6.1 (2.1) | −3.7 (0.6) | 0.05* |
| Pz | −3.8 (2.1) | −3.0 (0.4) | 0.48 |
| dMMN latency (ms) | | | |
| F3 | 169.3 (18.5) | 182.5 (8.2) | 0.19 |
| F4 | 174.2 (20.1) | 182.0 (8.1) | 0.47 |
| Fz | 176.2 (13.6) | 181.5 (8.2) | 0.47 |
| Cz | 180.2 (19.7) | 190.0 (13.3) | 0.37 |
| Pz | 186.8 (25.2) | 195.5 (23.2) | 0.54 |
| P3a amplitude (μV) | | | |
| F3 | 1.0 (1.4) | 1.5 (1.1) | 0.60 |
| F4 | 1.2 (2.0) | 1.2 (1.1) | 0.96 |
| Fz | 1.6 (1.5) | 2.0 (1.2) | 0.67 |
| Cz | 1.9 (1.6) | 2.6 (1.4) | 0.47 |
| Pz | 2.0 (1.4) | 0.7 (0.8) | 0.10 |
| P3a latency (ms) | | | |
| F3 | 264.7 (27.9) | 267.0 (27.9) | 0.88 |
| F4 | 270.1 (31.3) | 268.0 (31.3) | 0.90 |
| Fz | 269.1 (32.3) | 267.5 (32.3) | 0.93 |
| Cz | 264.8 (28.8) | 270.5 (28.8) | 0.71 |
| Pz | 268.4 (29.0) | 286.5 (29.0) | 0.26 |
| RON amplitude (μV) | | | |
| F3 | −4.3 (1.7) | −3.1 (1.2) | 0.20 |
| F4 | −4.5 (1.4) | −3.1 (1.0) | 0.08 |
| Fz | −4.6 (1.6) | −2.8 (2.1) | 0.08 |
| Cz | −4.2 (2.1) | −2.5 (1.6) | 0.16 |
| Pz | −2.7 (1.8) | −2.7 (1.1) | 0.97 |
| RON latency (ms) | | | |
| F3 | 388.0 (51.3) | 353.5 (33.4) | 0.22 |
| F4 | 403.6 (51.4) | 405.5 (72.0) | 0.95 |
| Fz | 391.3 (44.8) | 419.5 (53.8) | 0.29 |
| Cz | 399.3 (48.6) | 394.5 (28.4) | 0.85 |
| Pz | 401.8 (51.3) | 401.2 (33.4) | 0.98 |

*Values represent mean (SD).*

*[a]Risperidone equivalent (mg/day).*

*ARMS, at-risk mental state; Non-C., ARMS non-Converters; Conv., ARMS Converters; SAPS, Scale for the Assessment of Positive Symptoms; SANS, Scale for the Assessment of Negative Symptoms.*

**$p < 0.05$.*

later developed schizophrenia, consistent with our observations that 21.0% progressed to the illness.

ARMS subjects as a whole have been reported to demonstrate reduced dMMN amplitudes, but with a lesser degree compared to patients with overt schizophrenia (Bodatsch et al., 2011; Atkinson et al., 2012; Jahshan et al., 2012), consistent with the present results (**Figure 1**). On the other hand, the current data may be partly different from our previous observations indicating the lack of difference in dMMN amplitudes between ARMS subjects as whole and healthy controls (Higuchi et al., 2013b). One of the reasons for this discrepancy may include the difference in age and gender ratio. In fact, as previous reports indicate ERPs amplitudes gradually decrease by age, and male subjects show relatively smaller amplitudes than female because of the difference in skull thickness (Ikezawa et al., 2008; Matsubayashi et al., 2008; Naatanen et al., 2012). Another confounding factor may include the observation periods for follow-up. While our previous report (Higuchi et al., 2013b) employed a relatively short period (mean ± SD = 1.6 ± 0.8 years for non-converters), the present study used a longer period (2.2 ± 1.5 years), similar to those in the literature.

Compared to Non-C, Conv subjects elicited significantly smaller dMMN amplitudes at F4 and Fz leads (**Table 2**). These observations suggest the ability of dMMN amplitudes to differentiate between high-risk individuals who later progress to schizophrenia and those who do not, as has been suggested (Higuchi et al., 2013b; Sumiyoshi et al., 2013).

Little information has been available about the feature of RON in schizophrenia. In this study, RON amplitudes of ARMS subjects as a whole were not different from those of HC subjects, while FES and CS group showed significantly smaller RON amplitudes at Fz and F4 leads compared to the HC group. This finding is consistent with observations by Jahshan et al. (2012). As the results of the current study suggest that RON amplitudes may decrease according to progression of clinical stages of schizophrenia (**Table 1B**; **Figure 1**), they may provide an intermediate phenotype of the illness.

Importantly, RON amplitudes of Conv subjects tended to be smaller than those of Non-C at the Fz and F4 leads (**Figure 4**). The failure to reach statistical significance may be due to the fact that RON waveforms are not stable and smaller compared to dMMN waveforms. Future investigations with a larger number of subjects would be desirable to determine if the combined measurement of RON and dMMN would further facilitate early detection of schizophrenia.

P3a amplitudes were barely detectable in this study (**Figures 1** and **3**). These amplitudes have been reported to be decreased in schizophrenia and ARMS (Friedman et al., 2001; Jahshan et al., 2012; Mondragon-Maya et al., 2013; Nagai et al., 2013). Variations of P3a amplitudes may be large, due, probably, to the difference in measurement.

Limitations of this study include the small sample number, especially in ARMS ($n=19$) and Conv subjects ($n=4$). According to the power analysis, at least 26 patients are needed to obtain adequate effect size (i.e., 0.6). Investigations with a larger number of patients will make the data more satisfactory. Second, significant age difference was seen in the ARMS vs. HC and FES

**Table 3 | ERP amplitudes and symptoms.**

| | SAPS | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Hallucinations | | Delusions | | Bizarre behavior | | Positive formal thought disorder | |
| | *r* | *p* | *r* | *p* | *r* | *p* | *r* | *p* |
| dMMN amplitude (μV) | | | | | | | | |
| F3 | 0.039 | 0.786 | 0.011 | 0.938 | −0.122 | 0.398 | 0.086 | 0.552 |
| F4 | 0.071 | 0.625 | 0.066 | 0.648 | −0.131 | 0.365 | 0.076 | 0.599 |
| Fz | 0.021 | 0.884 | −0.016 | 0.910 | −0.199 | 0.166 | 0.090 | 0.536 |
| Cz | −0.021 | 0.888 | −0.036 | 0.805 | −0.108 | 0.457 | 0.056 | 0.697 |
| Pz | −0.163 | 0.258 | −0.178 | 0.216 | −0.225 | 0.117 | −0.069 | 0.636 |
| P3a amplitude (μV) | | | | | | | | |
| F3 | −0.148 | 0.305 | −0.188 | 0.192 | −0.188 | 0.191 | −0.036 | 0.802 |
| F4 | −0.075 | 0.605 | −0.190 | 0.187 | −0.256 | 0.073 | 0.029 | 0.842 |
| Fz | −0.191 | 0.185 | −0.181 | 0.209 | −0.233 | 0.104 | −0.008 | 0.956 |
| Cz | −0.149 | 0.302 | −0.056 | 0.701 | −0.213 | 0.138 | 0.020 | 0.891 |
| Pz | 0.022 | 0.879 | 0.046 | 0.753 | −0.023 | 0.874 | −0.117 | 0.417 |
| RON amplitude (μV) | | | | | | | | |
| F3 | 0.014 | 0.926 | −0.131 | 0.363 | 0.067 | 0.646 | 0.280 | **0.049*** |
| F4 | 0.087 | 0.549 | −0.092 | 0.523 | −0.158 | 0.274 | 0.244 | 0.087 |
| Fz | −0.024 | 0.869 | −0.109 | 0.450 | −0.265 | 0.063 | 0.346 | **0.014*** |
| Cz | −0.033 | 0.818 | −0.214 | 0.136 | −0.081 | 0.578 | 0.151 | 0.295 |
| Pz | 0.002 | 0.990 | −0.257 | 0.071 | −0.025 | 0.861 | 0.022 | 0.881 |

| | SANS | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Affective flattening | | Alogia | | Avolition-apathy | | Anhedonia-asociality | | Attention | |
| | *r* | *p* | *r* | *p* | *r* | *p* | *r* | *p* | *r* | *p* |
| dMMN amplitude (μV) | | | | | | | | | | |
| F3 | 0.109 | 0.452 | 0.149 | 0.301 | 0.096 | 0.509 | −0.102 | 0.483 | 0.317 | **0.025*** |
| F4 | 0.142 | 0.325 | 0.122 | 0.399 | 0.016 | 0.910 | −0.066 | 0.650 | 0.260 | 0.068 |
| Fz | 0.115 | 0.427 | 0.165 | 0.254 | −0.014 | 0.923 | −0.081 | 0.576 | 0.290 | **0.041*** |
| Cz | 0.060 | 0.680 | 0.147 | 0.307 | 0.117 | 0.420 | 0.050 | 0.730 | 0.262 | 0.066 |
| Pz | −0.041 | 0.778 | 0.066 | 0.650 | 0.122 | 0.400 | −0.063 | 0.666 | −0.007 | 0.963 |
| P3a amplitude (μV) | | | | | | | | | | |
| F3 | −0.029 | 0.843 | −0.034 | 0.815 | 0.037 | 0.796 | −0.037 | 0.796 | 0.130 | 0.368 |
| F4 | 0.021 | 0.883 | 0.021 | 0.885 | 0.003 | 0.984 | −0.102 | 0.480 | 0.148 | 0.306 |
| Fz | −0.043 | 0.767 | 0.032 | 0.823 | −0.032 | 0.827 | −0.090 | 0.533 | 0.101 | 0.487 |
| Cz | −0.066 | 0.649 | −0.029 | 0.843 | 0.012 | 0.934 | −0.010 | 0.943 | 0.112 | 0.441 |
| Pz | 0.063 | 0.662 | −0.027 | 0.852 | 0.108 | 0.454 | −0.046 | 0.753 | 0.032 | 0.827 |
| RON amplitude (μV) | | | | | | | | | | |
| F3 | −0.112 | 0.438 | −0.111 | 0.441 | −0.054 | 0.712 | −0.215 | 0.134 | −0.055 | 0.704 |
| F4 | 0.022 | 0.882 | 0.039 | 0.788 | −0.089 | 0.539 | −0.103 | 0.475 | −0.050 | 0.730 |
| Fz | −0.046 | 0.752 | −0.017 | 0.905 | −0.104 | 0.474 | −0.073 | 0.617 | −0.025 | 0.861 |
| Cz | 0.128 | 0.375 | 0.210 | 0.143 | −0.040 | 0.781 | 0.002 | 0.988 | −0.108 | 0.455 |
| Pz | 0.014 | 0.922 | 0.095 | 0.513 | −0.123 | 0.393 | −0.117 | 0.419 | −0.242 | 0.090 |

*SAPS, Scale for the Assessment of Positive Symptoms; SANS, Scale for the Assessment of Negative Symptoms.*

**$p < 0.05$, $r$ = Pearson product–moment correlation coefficient.*

vs. CS comparisons. Since part of ARMS subjects is regarded as prodromal state of schizophrenia, it is natural that they are mostly younger than schizophrenia patients. Therefore, adjustment of age between FES/CS and ARMS subjects may increase the number of certain type of schizophrenia, e.g., hebephrenic type. Due to an effort to make the FES/CS groups more homogeneous, patients of these groups became somewhat older than the ARMS group. Application of ANCOVA to 19 members may provide over-adjustment. Although MMN amplitudes are reduced gradually by age, the decline is not substantial (−0.056 μV/year in schizophrenia and −0.079 μV/year in healthy control) (Kiang et al., 2009). ARMS/HC subjects are about 2.5 years younger than FES/CS (**Table 1**). According to this formula, about 0.2 μV amplitude reduction may occur between these two. Differences in our data presented (at Fz lead) were 1.1 μV or greater (ARMS vs. FES groups.), which was sufficiently large. Third, some ARMS subjects and most schizophrenia patients were taking antipsychotic drugs, which may be another limitation of the current study. Fourth, in this study, we measured ERPs at baseline, and did not perform follow-up measurements. Therefore, little information is available about longitudinal data of ERPs parameters.

In conclusions, diminished amplitudes in dMMN/RON may provide a biomarker that is present before and after the development of psychosis. Our results should be interpreted with caution before applying to the at-risk population, especially to avoid over-diagnosis. Ideally, the combination with other cognitive modalities, e.g., neuropsychological tests (Higuchi et al., 2013b), brain morphology, and biochemical markers, would enhance the sensitivity and specificity for early diagnosis. These efforts are expected to help improve functional outcome in subjects with schizophrenia and vulnerable individuals as well.

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# 3 精神疾患で認められる所見

これまで鑑別診断および早期介入，予防を目的に，事象関連電位（event-related potential：ERP）を疾患特異的な生物学的マーカーとして用いる試みが多くなされてきた．

本項では代表的なERPであるP300およびミスマッチ陰性電位（mismatch negativity：MMN）を中心に，精神疾患で認められている所見を以下に述べる．なお，P300の下位成分としてP3a（早期成分）とP3b（後期成分）があり，それぞれ異なる性質をもつが，以下P300といえば特に断りのない限りP3bについて述べる．

## P300

多くの精神疾患でP300の異常が報告されている．脳神経疾患（脳血管障害，脳腫瘍，脳炎，神経疾患，てんかんなど）ではP300の発生源と想定されている部位と器質的障害部位とが重なると，異常所見として観察されることが多い．筆者らはヘルペス脳炎で辺縁系の障害をきたした患者において，障害部位の電流密度が減少したことを，LORETA法（low resolution electromagnetic tomography）を用いて示した（**図1**）．LORETAとは脳波マッピングの一つで，ERPの発生源電流密度を3次元的に表示することが可能である．

覚せい剤精神病およびアルコール依存症では，前頭，側頭部のP300振幅のみが減少し，頭頂部の振幅が保たれる．これは同疾患の障害が前頭部に強いことを反映

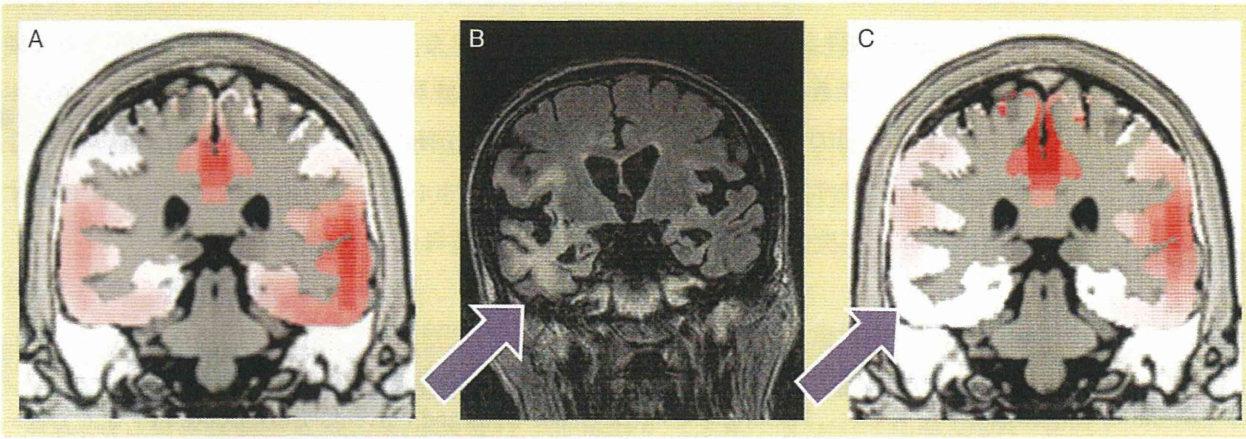


図1　ヘルペス脳炎症例の障害部位の電流密度の減少
A：健常者（47人）より得たP300の発生源電流密度マッピング．電流密度が高い部位を赤で示している．
B：ヘルペス脳炎症例（70歳代，男性）のMRI（FLAIR画像）．
C：症例のP300の発生源電流密度マッピング．特に右側頭葉および辺縁系に障害が強くみられているが，その障害部位に一致して電流密度が低下している．

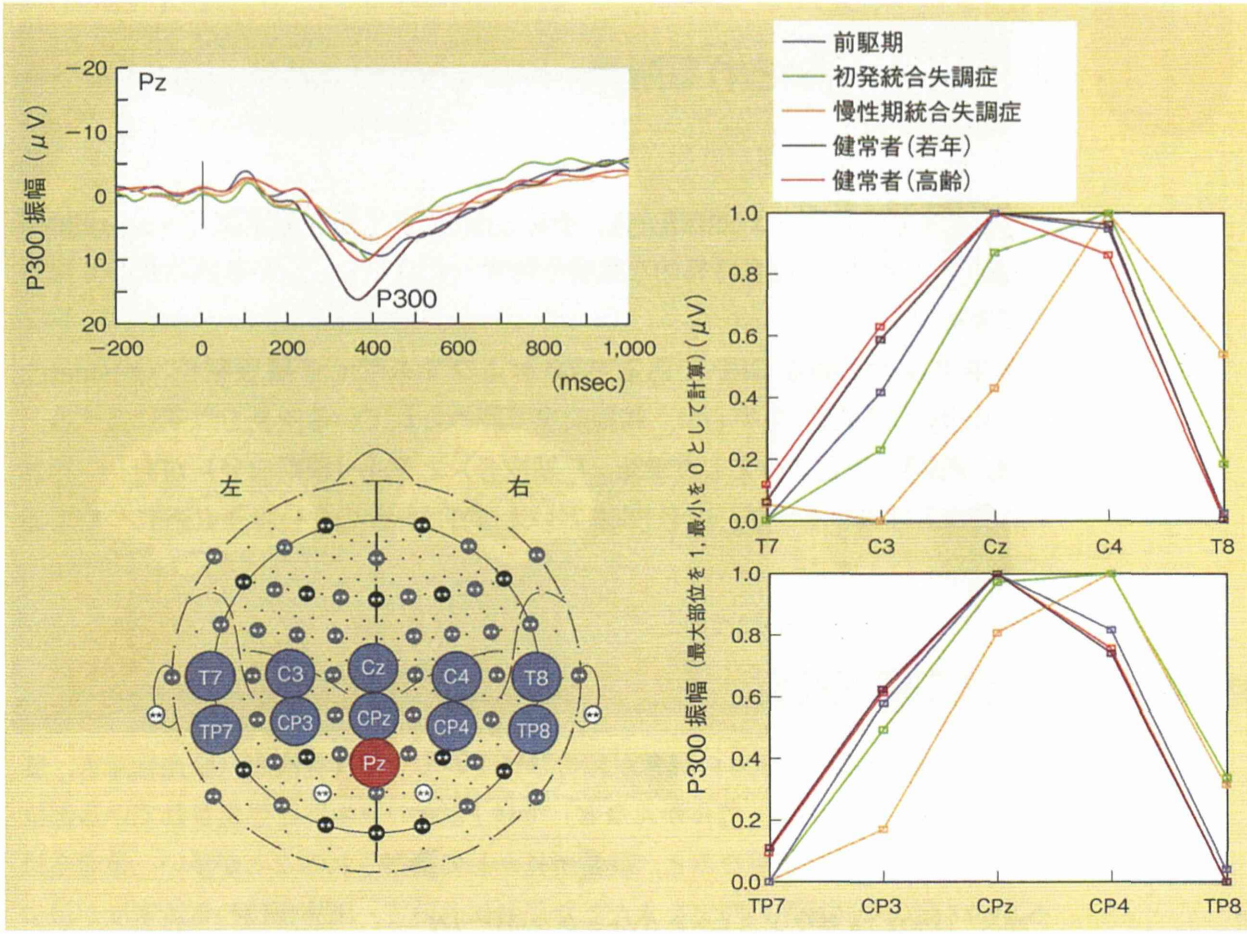


**図 2　統合失調症と健常者の P300 振幅の比較**
両期別の P300 波形（左上）．特に慢性期患者で P300 振幅の低下および潜時の延長がみられる．また，健常者に比較して統合失調症では左側で振幅低下の程度が強く，慢性期ではより顕著となる（右）．
（van der Stelt O, et al. Schizophr Res 2005；77：309-20[3]）

している と考えられる[1]．神経性食思不振症では，神経性大食症に比較して P300 の異常所見がみられることが多く，これは同疾患の認知のゆがみを反映していると考えられる．また，精神遅滞，注意欠陥多動性障害，自閉症スペクトラムなどでも P300 の異常が報告されている．

このように，精神疾患と P300 について数多くの報告がある．本項では，代表的な内因性精神疾患である統合失調症と気分障害，および認知症についてこれまでの知見をまとめた．

## 統合失調症

統合失調症を対象とした ERP のなかでは，P300 が最も多く検討されてきた．統合失調症は若年期の「前駆期状態」と呼ばれる非特異的な精神症状を示す時期を経て「顕在発症」に至り，さらに「慢性期」に移行する．統合失調症では，P300 の振幅低下および潜時の延長が繰り返し報告されてきた．メタ解析によれば，振幅低下の effect size は 0.85 と大きく[2]，罹病期間の短い初発患者よりも慢性期患者で程度が強いとされる．

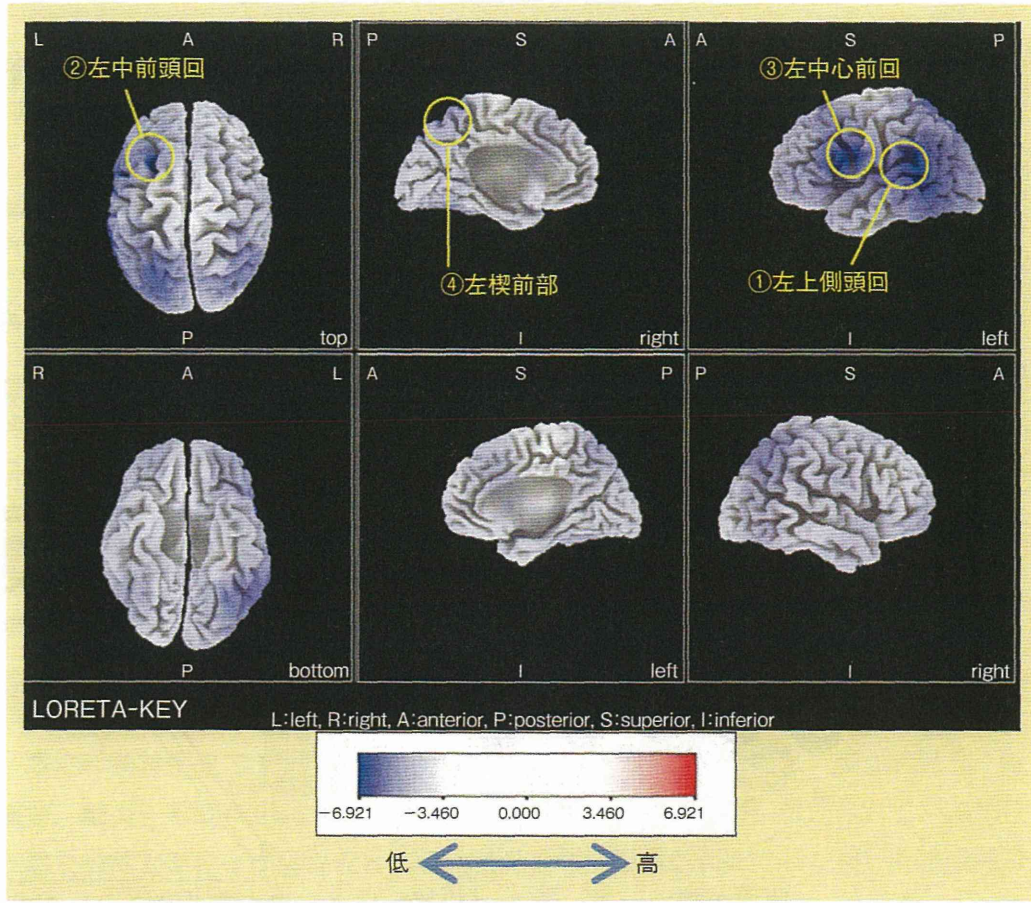


**図3　LORETA 法による P300 の発生源マッピング**

健常者よりも統合失調症で LORETA 値が低い部位が青色で示されている．統合失調症患者は全体的に電流密度が低下しており，特に左上側頭回や前頭前野（中前頭回）などにおいて有意な低下がみられた．

independent *t*-test, $p < 0.001$.

（Higuchi Y, et al. Schizophr Res 2008；101：320-30[4]）

van der Stelt らは，慢性期患者と年齢をマッチさせた健常者との比較を行い，左側の P300 振幅低下の程度が強いことを報告した（**図2**）[3]．また，筆者らは慢性期統合失調症患者の P300 の発生源の局在を前述の LORETA 法を用いて解析した．その結果，左上側頭回，左中前頭回などで電流密度の低下を認め，MRI で測定された構造画像解析による体積減少がみられるとされる部位とほぼ一致した（**図3**）[4]．

最近，統合失調症の前駆期に親和性がある，いわゆるアットリスク精神状態（at-risk mental state：ARMS）を対象に，ERP の検討が行われるようになった．ARMS は，半構造化面接である CAARMS（Comprehensive Assessment of at risk mental state）などにより定義される．この方法を用いると，遺伝的ハイリスクをはじめ微細で持続しない精神病症状や機能低下の兆候を用いて前駆期状態のスクリーニングを行うことができる．研究により，ARMS の P300 振幅にはばらつきがみられる．ARMS は多彩な状態像の患者を包括しており，将来統合失調症を発症するのは約 40 %にすぎないとされる．また，P300 は trait（素因）marker の

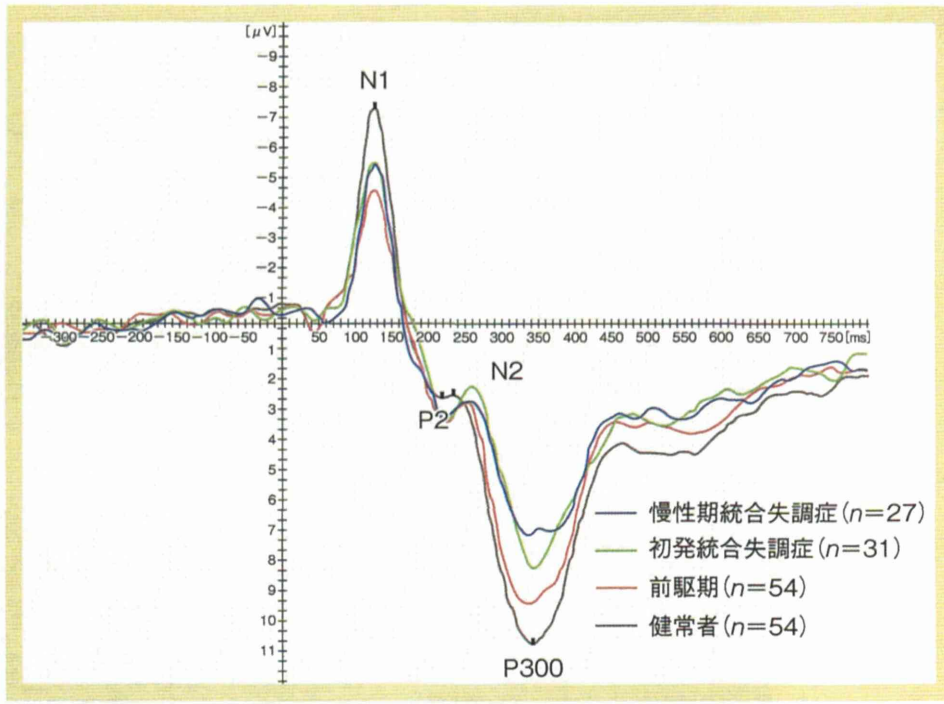


**図4　聴覚性オドボール課題により得られた事象関連電位の波形**
病期の進行に従いP300振幅が減少している．
（Özgürdal S, et al. Schizophr Res 2008；105：272-8[5]）

側面が強い一方，state（状態）によっても変化するといわれる．ARMSのP300についての見解が一致しないのは，これらの理由があると推察される．

Özgürdalらは前駆期を含めた病期の進行に従い，P300振幅が低下することを見出した（**図4**）[5]．さらにFrommannらは，早期ARMSでは左側頭の一部の誘導（TP7）のみで振幅低下をきたすが，後期ARMSでは左側部および正中電極でも差異を認めることを報告している[6]．病期の進行に伴い障害部位が左側頭から正中などの他の部位に拡大していることは，統合失調症の発症メカニズムを考えるうえで興味深い．

## ■気分障害

うつ病患者は健常者と比較してP300振幅が減衰するという報告が多い．潜時については諸説あるが，Karaaslanらは未治療のうつ病患者はP300潜時が延長していることを報告している[7]．それは精神病症状の有無を問わないと述べている．またPapageorgiouらは精神病性うつ病，およびそれと密接な関係があるとされる妄想性人物誤認症候群においてP300を測定し，振幅の低下，潜時の延長がみられることを示した[8]．これらの所見より，うつ病患者はP300潜時が延長するが，精神病症状を伴った場合はP300振幅も影響されるようである．

統合失調症との比較を行った研究もある．Domjánらは，同一施設内で慢性期のI型双極性障害患者と統合失調症患者（罹病期間：各14.4年，13.4年）のERPを比較し，統合失調症患者のみがP300振幅の減少をきたしていることを見出した[9]．

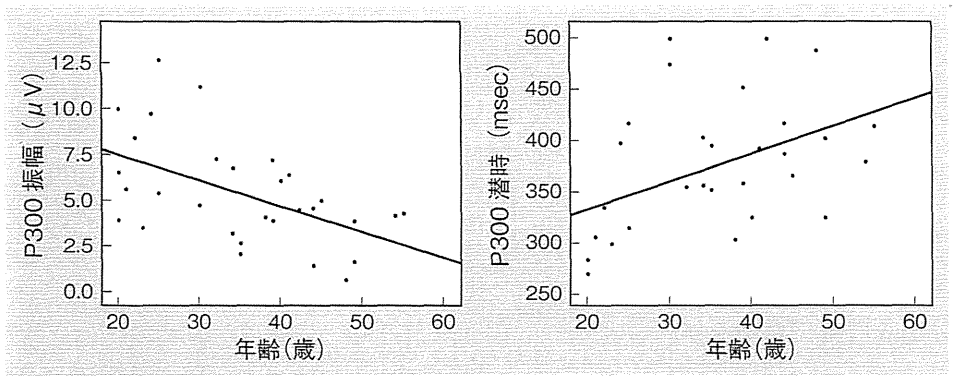


図5　P300の正常加齢による影響
(Juckel G, et al. Neuroimage 2012；60：2027-34[12])

一方，Salisburyらは，同じく慢性期の双極性障害（精神病症状を伴う躁状態）と統合失調症を比較し，ともに振幅が減少しているが双極性障害では潜時の延長がみられないことを報告している．さらに，トポグラフィ解析を用い，双極性障害は前方，統合失調症は後方の障害が強いことを見出した[10]．研究間の結果のばらつきは，後述のような患者の状態や測定条件の不一致によるものかもしれない．

次に，内因性うつ病と神経症性うつ病の比較を行った研究にふれる．斎藤ら[11]は，内因性・神経症性両者で，P300振幅減衰/潜時延長が同程度にみられること，および，内因性うつ病でハミルトンうつ病尺度の得点と強く相関することを報告した．一方，神経症性うつ病のP300所見はばらつきが大きく，症状との相関は見出されなかった．以上は，内因性うつ病の症状は認知過程に強く影響されていること，神経症性うつ病には生物学的な異種性が想定されること，P300が神経症性うつ病のサブタイプを鑑別しうる可能性を示唆するものと思われる．

## ■認知症

まず正常加齢の影響について述べる．P300潜時が加齢によって延長するという見解は一致している．振幅については諸説みられるが，低下することを示した最近の文献がある（図5）[12]．

アルツハイマー型認知症（Alzheimer's disease：AD）におけるP300の診断的有用性については論議が多い．初期のADや高齢者（63歳以上）では，認知症であっても健常者と違いはないとする意見も一部でみられるが，Filipovićらは65歳以下の認知症患者で潜時の延長を報告している（図6）[13]．

また，Gordonらは，認知症とうつ病，統合失調症を比較し，2SD以上潜時の延長を示す割合は，おのおの79％，12％，13％であることを示し，認知症患者のP300の障害が特に強いと述べている[14]．なお，振幅については確立した見解はない．Itoらは，認知機能評価尺度であるGlobal Deterioration Scale得点はP300潜時と有意な正の相関を示す一方，振幅との間には相関はなかったと報告している（図7）[15]．