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Machine-learning-based diagnosis of schizophrenia using combined sensor-level and source-level EEG features

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ABSTRACT

Recently, an increasing number of researchers have endeavored to develop practical tools for diagnosing patients with schizophrenia using machine learning techniques applied to EEG biomarkers. Although a number of studies showed that source-level EEG features can potentially be applied to the differential diagnosis of schizophrenia, most studies have used only sensor-level EEG features such as ERP peak amplitude and power spectrum for machine learning-based diagnosis of schizophrenia. In this study, we used both sensor-level and source-level features extracted from EEG signals recorded during an auditory oddball task for the classification of patients with schizophrenia and healthy controls. EEG signals were recorded from 34 patients with schizophrenia and 34 healthy controls while each subject was asked to attend to oddball tones. Our results demonstrated higher classification accuracy when source-level features were used together with sensor-level features, compared to when only sensor-level features were used. In addition, the selected sensor-level features were mostly found in the frontal area, and the selected source-level features were mostly extracted from the temporal area, which coincide well with the well-known pathological region of cognitive processing in patients with schizophrenia. Our results suggest that our approach would be a promising tool for the computer-aided diagnosis of schizophrenia.

1. Introduction

1.1. Diagnosis of schizophrenia

Schizophrenia is diagnosed primarily using diagnostic criteria from the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), by asking patients a series of questions to elicit information such as duration of illness and clinical symptoms (American Psychiatric Association, 2013). The clinical symptom severity of schizophrenia is measured using clinical scales such as the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1988). Various diagnostic tools can help psychiatrists and clinical psychologists diagnose schizophrenia, but traditional clinical diagnoses might be sometimes inaccurate because schizophrenia patients sometimes intentionally hide their symptoms, and even experts sometimes have difficulty differentiating schizophrenia from other mental illnesses due to similar symptoms (Lindstrom et al., 1994; McGorry et al., 1995; Norman et al., 1996). Thus, many researchers have sought to develop objective, quantitative biomarkers that can enhance the overall accuracy of diagnosis with the aid of neuroimaging technologies. Among a variety of neuroimaging modalities, electroencephalography (EEG) is regarded as one of the most useful, thanks to its high temporal resolution and low cost. Many studies report disrupted cerebral information processing in schizophrenia, in the context of altered event-related potential (ERP) waveforms (Odonnell et al., 1995; Ozgurdal et al., 2008; Turetsky et al., 1998; Wang et al., 2003), disrupted functional connectivity patterns (Lynall et al., 2010; Winterer et al., 2003), and reduced source activity (Kawasaki et al., 2007; Kim et al., 2014; Pae et al., 2003; Wang et al., 2010).

1.2. Machine-learning-based diagnosis of schizophrenia

Recently, an increasing number of researchers have attempted to differentiate patients with schizophrenia from healthy controls using machine learning (ML) methods with EEG biomarkers. Some of these studies used sensor-level biomarkers, such as ERP amplitude and latency, as features for classification (Neuhaus et al., 2013; Neuhaus et al., 2011). For example, Neuhaus et al. (2011) sought to identify schizophrenia using amplitudes/latencies of N100 and P300 that were evoked using visual and auditory oddball paradigms, respectively, and they reported a fairly high classification accuracy of 72.4%. Later, the same group (Neuhaus et al., 2013) reported improved classification accuracy

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of 79.0% using ERP components that were evoked in a visual target-locked paradigm. Previous studies including the ones described above used only sensor-level features such as ERP peak amplitudes and latencies extracted from raw EEG signals. However, these sensor-level features have an inherent limitation in that the signals can be distorted and smeared due to volume conduction (Nolte et al., 2004; Nunez et al., 1997; van den Broek et al., 1998), and thus potentially lose important information regarding underlying cortical activity. In fact, some EEG-based brain-computer interface (BCI) studies that classified different brain activity patterns during mental imagery tasks have reported increased classification accuracy using source-level features rather than sensor-level features (Ahn et al., 2012; Kamousi et al., 2007; Qin et al., 2004). However, these source-level features have not been widely applied to clinical applications, and have especially never been applied to machine-learning based diagnosis of schizophrenia.

1.3. Purpose of this study

In this study, we used both sensor-level features and source-level features for the differentiation of schizophrenia patients and healthy controls. We hypothesized that simultaneous use of both sensor-level and source-level features would enhance classification accuracy. To test this hypothesis, we used EEG data recorded while participants were performing an auditory oddball task, of which the results were known to be relatively consistent through a series of previous studies. The P300 amplitude evoked by the auditory oddball paradigm is significantly decreased in schizophrenia patients compared to healthy controls, and source activity is also reduced in patients with schizophrenia. In the present study, we compared classification accuracies for three different cases: ML with sensor-level features only, ML with source-level features only, and ML with combined two-level features.

2. Methods

2.1. Participants

Thirty-four patients with schizophrenia (20 males and 14 females) and 34 healthy controls (14 males and 20 females) were recruited for this study from the Psychiatry Department of Inje University Ilsan Paik Hospital. Patients who had diseases of the central nervous system, medical histories of alcohol and drug abuse, experience with electrical therapy, mental retardation, or head injuries with loss of consciousness were excluded from the study by initial screening interviews. The patients were diagnosed based on the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV), Axis I Psychiatric Disorders. Their clinical symptoms were also measured using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1988). Healthy controls were recruited from the local community through local newspaper ads and posters. After an initial screening using the same criteria, control subjects were interviewed using the Structured Clinical Interview for DSM-IV Axis II Disorders (Allen, 1998). All subjects provided written informed consent, and the study protocol was approved by the Institutional Review Board of Inje University Ilsan Paik Hospital. Table 1 presents demographic data for patients and healthy controls.

2.2. EEG acquisition and pre-processing

The stimuli used for the auditory oddball paradigm were composed of target tones with 1500 Hz tone frequency and standard tones with 1000 Hz tone frequency. The duration of each stimulus was set to 100 ms, and rising and falling times were set to 10 ms. Four-hundred pure tone stimuli consisting of 15% target tones and 85% standard tones were presented in random order with an inter-stimulus interval (ISI) of 1500 ms. The participants were required to press a response button when target tones were presented.

Scalp EEG data were recorded using a NeuroScan SynAmps2 amplifier (Compumedics USA, El Paso, TX, USA) from 62 Ag/AgCl scalp electrodes (FP1, FPZ, FP2, AF3, AF4, F7, F5, F3, F1, FZ, F2, F4, F6, F8, FT7, FC5, FC3, FC1, FCZ, FC2, FC4, FC6, FT8, T7, C5, C3, C1, CZ, C2, C4, C6, T8, TP7, CP5, CP3, CP1, CPZ, CP2, CP4, CP6, TP8, P7, P5, P3, P1, PZ, P2, P4, P6, P8, PO7, PO5, PO3, POZ, PO4, PO6, PO8, CB1, O1, OZ, O2, and CB2) evenly arranged in a head cap according to a modified 10–20 electrode system. The ground electrode was placed on the forehead and the reference electrodes were attached at both mastoids. The vertical electrooculogram (VEOG) channels were located above and below the right eye and the horizontal electrooculogram (HEOG) channels were placed on the outer canthus of each eye. EEG data were recorded with a 0.1–100-Hz band-pass filter at a sampling rate of 1000 Hz, with 60 Hz noise removed using a notch filter.

2.3. Sensor-level feature set

The EEG data were processed using Scan 4.3 software (Compumedics USA, El Paso, TX, USA). First, eye blinking artifacts were removed using established mathematical procedures (Semlitsch et al., 1986), and other gross artifacts were rejected by visual inspection. After artifact rejection, the data were band-pass filtered at 1 to 30 Hz and epoched from 100 ms before the target stimulus onset to 900 ms after the target stimulus onset. The epochs were rejected if they contained significant physiological artifacts (amplitude exceeding ± 75 μV) at any site over all electrodes. Artifact-free epochs were averaged across trials and electrodes for ERP analysis. Among the 60 trials of target condition, the numbers of remaining epochs after artifact rejection were 53.09 ± 9.89 for normal controls and 47.59 ± 13.86 for patients with schizophrenia (no significant difference between two groups). P300 peak amplitude and latency were computed across all electrodes, when P300 was defined as a maximum between 250 and 500 ms post-stimulus (Bharath et al., 2000; Hopfinger and Maxwell, 2005; Lazzaro et al., 1997). In total, 124 sensor-level features (P300 amplitude and latency of 62 electrodes) were used as candidate sensor-level features.

Table 1
Demographic data of patients with schizophrenia and healthy controls.

	Schizophrenia patients	Healthy controls	*p*
Cases (*N*)	34	34	
Gender (male/female)	14/20	20/14	0.225
Age (years)	33.91 ± 13.30	34.74 ± 13.16	0.798
Education	13.59 ± 9.06	13.97 ± 13.10	0.827
Illness duration (months)	51.88 ± 68.64		
Dosage of antipsychotics (chlorpromazine equivalents, mg)	511.10 ± 398.22		
Positive and Negative Syndrome Scale (PANSS)			
Positive score	20.70 ± 7.00		
Negative score	19.03 ± 6.45		
General score	42.67 ± 11.00		
Total score	82.36 ± 21.49		

2.4. Source-level feature set

To extract source-level features, the data were first bandpass filtered at 1 to 55 Hz. EEG cortical sources were estimated using minimum norm estimation (MNE) implemented in the eConnectome Matlab toolbox (He et al., 2011). A three-layer boundary element method (BEM) model constructed from the MNI-152 standard template was used to compute the leadfield matrix. Cortical current density values at 7850 cortical vertices were evaluated for every time point of each epoch. To minimize potential loss of information contained in raw data, segmented raw EEG data were used instead of averaged ERP data. After estimating the cortical current density distribution at every time point, 314 dipole sources were extracted as evenly as possible from the original cortical surface model. We first selected dipoles by simply skipping a constant number in the original vertices, and then manually adjusted locations of some vertices when distributions of vertices at certain areas were too dense or too sparse. Each of the 314 time-series signals were averaged over time from 0 to 500 ms after the target stimulus onset. In total, 314 averaged cortical current density values were used as candidate source-level features.

2.5. Feature selection and classification

To discriminate schizophrenia patients from healthy controls, three different feature sets were tested: (1) the sensor-level feature set (124 features), (2) the source-level feature set (314 features), and (3) the combined feature set (124 + 314 = 438 features). To select features for classification, we compared Fisher's scores for each candidate feature, which is one of the most widely used feature selection methods in many previous pattern classification studies. The number of features ranged from 1 to 20 (Lal et al., 2004; Li et al., 2009). The classification accuracy was evaluated using leave-one-out cross-validation (LOOCV) with support vector machine (SVM) classifier (Schlögl et al., 2005; Weston, 1999), for each feature set. Fig. 1 illustrates the overall analysis procedures adopted in this study.

3. Results

3.1. Maximum and average classification accuracy

The number of features varied from one to 20, for each of which the classification accuracy was evaluated. Table 2 summarizes the classification accuracies for three different feature sets with respect to the number of features used for the classification. This table also includes information on the ratio of sensor-level features to source-level features in the features selected from the combined feature set. A maximum classification accuracy of 88.24% was reported for the combined-level feature set, which was higher than those for the sensor-level feature set (80.88%) and source-level feature set (85.29%). The classification accuracies averaged over different numbers of features were reported to be 78.24%, 72.72%, and 71.40%, for the combined feature set, sensor-level feature set, and source-level feature set, respectively. Statistical analysis using analysis of variance (ANOVA) showed significant differences among the three different cases ($p = 0.003$), and the following post-hoc analysis revealed that the combined feature set yielded significantly enhanced classification accuracy compared to both the sensor-level features (Bonferroni corrected $p = 0.027$) and the source-level features (Bonferroni corrected $p = 0.004$) (note: all datasets passed the normality test, see Fig. 2 for the distribution). The maximum accuracy for the source-level feature set was higher than that for the sensor-level feature set, whereas the average accuracy for the source-level feature set was slightly lower than that for the sensor-level feature set. This result originated from the high dependence of the source-level features on the number of features. Contrary to the source-level feature set, the combined feature set resulted in stable and reliable classification accuracies that were less dependent on the number of features than the source-level feature set. It is noteworthy that even the minimum accuracy was higher than 70% when two levels of features were used simultaneously. Interestingly, the average ratio of sensor-level

Table 2
Classification accuracies (unit: %) for three different feature sets: sensor-level, source-level, and combined feature sets. The last column shows the ratio of sensor-level features and source-level features included in the selected combined feature set. Bold letters represent the maximum accuracy of each feature set.

Number of features	Accuracy			Sensor feature/ source feature
	Sensor level	Source level	Combined	
1	75.00	69.12	79.41	0/100
2	67.65	79.41	76.47	0/100
3	72.06	80.88	76.47	0/100
4	77.94	**85.29**	72.06	25.0/75.0
5	69.12	77.94	82.35	20.0/80.0
6	79.41	83.82	72.06	16.7/83.3
7	79.41	63.24	86.76	28.6/71.4
8	76.47	67.65	83.82	37.5/62.5
9	63.24	67.65	80.88	44.4/55.6
10	**80.88**	79.41	80.88	50.0/50.0
11	69.12	69.12	79.41	45.5/54.5
12	76.47	66.18	80.88	50.0/50.0
13	67.65	82.35	77.94	58.3/41.7
14	73.53	72.06	75.00	57.1/42.9
15	72.06	58.82	**88.24**	53.3/46.7
16	64.71	66.18	76.47	56.3/43.7
17	70.59	73.53	72.06	58.8/41.2
18	72.06	61.76	70.59	61.1/38.9
19	72.06	67.65	82.35	63.2/36.8
20	75.00	55.88	70.59	65.0/35.0
Average ± s.d.	72.72 ± 4.92	71.40 ± 8.58	78.24 ± 5.19	50.5/49.5

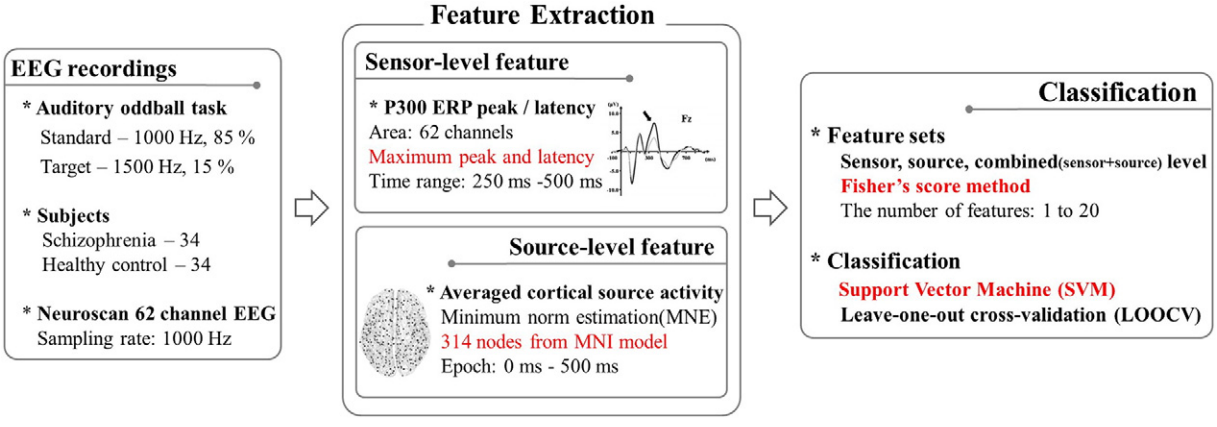

Fig. 1. The procedure for machine-learning-based classification of schizophrenia.

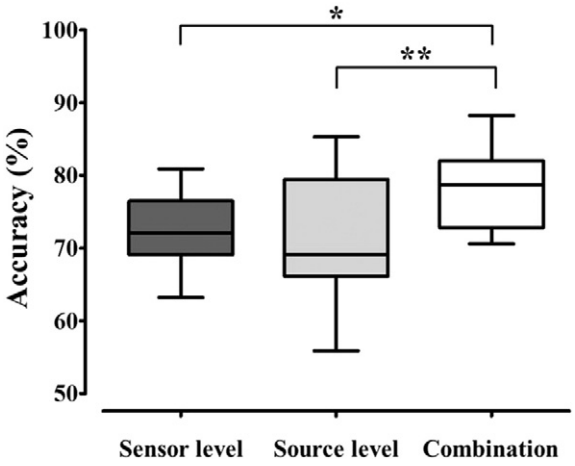

Fig. 2. Classification accuracies for three different feature sets. * $p < 0.05$, ** $p < 0.01$.

features to source-level features in the combined feature set was nearly equal to one, demonstrating that sensor-level and source-level features harmoniously contributed to overall classification accuracy.

3.2. Spatial distribution of selected features

The maximum classification accuracy of 88.24% was achieved when 15 features were selected from the combined-level feature set. We investigated the spatial distribution of each of the selected features. We found that eight sensor-level features and seven source-level features were consistently selected in most cross-validation iteration. The spatial locations of eight sensor-level features and seven source-level features are depicted in Fig. 3. The sensor-level features were mainly distributed around the frontal area (AF4, F1, Fz, F2, F3, F8, FC6, FT8), where the P300 amplitudes in these electrodes were significantly decreased in patients with schizophrenia compared to the healthy controls ($p < 0.01$, *t*-test; Fig. 4). The selected source-level features were distributed mainly in the left temporal area, and the values for cortical current density were also decreased in schizophrenia patients compared to healthy controls (not significant in statistical tests). Note that P300 latency features were not selected in any cases listed in Table 2.

4. Discussion

In this study, we demonstrated that simultaneous use of sensor-level and source-level feature sets could improve overall classification accuracy in the machine-learning-based diagnosis of schizophrenia. A maximum classification accuracy of 88.24% was obtained when the combined feature set was used, whereas the highest classification accuracies were 80.88% and 85.29% for sensor-level and source-level feature sets, respectively. The average classification accuracy of the combined feature set (78.24%) was also much higher than either the sensor-level feature set (72.72%) or the source-level feature set (71.40%). By investigating 15 features selected from the combined feature set, we also found that eight sensor-level features were located in the frontal area and seven source-level features were distributed in the left temporal cortex.

4.1. Use of source-level features for classification

EEG has been regarded as the most appropriate neuroimaging modality for investigating fast changes in brain activity due to its superior temporal resolution over other imaging modalities. Although a large number of researchers have used EEG to investigate neural correlates underlying various mental disorders and to develop neurophysiological biomarkers to diagnose them, EEG has some intrinsic limitations. First, sensor-level EEG signals might not reflect brain activities right below the recording electrodes due to the low spatial resolution originating from volume conduction (Nolte et al., 2004; Nunez et al., 1997; van den Broek et al., 1998). Second, EEG data might have poor signal-to-noise ratios (SNR) as they can be severely contaminated by various noises and artifacts (Lange and Inbar, 1996; Lemm et al., 2006). Based on the belief that EEG source imaging might have benefits on these issues, some previous EEG-based BCI studies investigated whether the use of source-level features could enhance classification accuracy and BCI performance.

Some EEG-based BCI studies showed that the use of source-level features or the use of both source-level and sensor-level features could significantly increase the BCI classification accuracy compared to when only sensor-level features are used (Ahn et al., 2012; Kamousi et al., 2007; Qin et al., 2004). Qin et al. (2004) and Kamousi et al. (2007) reported that the source-level EEG signals are effective features for classifying left- and right-hand motor imagery tasks because they are free from the volume conduction effect. Ahn et al. (2012) also demonstrated that using combined features could improve classification accuracy because source-level features provide additional information. However, to the best of our knowledge, source-level features have not been applied to the classification of psychiatric disorders. Our results indicate that the simultaneous use of sensor-level and source-level features enhances the performance of machine-learning-based diagnose of schizophrenia, coinciding well with the results of previous BCI studies.

4.2. Selected sensor-level and source-level features

It is well-known that cognitive function in schizophrenia patients is declined compared to healthy controls (Keefe et al., 2005; Kuperberg and Heckers, 2000), which has been demonstrated by many studies using various cognitive tasks (Egan et al., 1994; Karlsgodt et al., 2008; Pakarinen et al., 2007). Among the experimental paradigms, the auditory

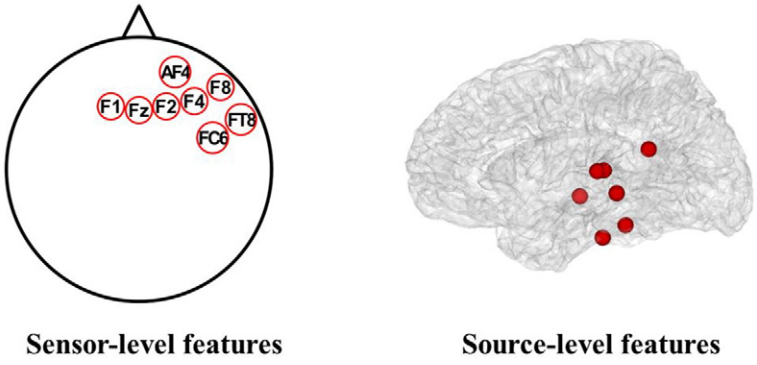

Fig. 3. The spatial distributions of sensor-level and source-level features selected from the combined feature set when the classification accuracy was at a maximum: (left) sensor-level features, (right). source-level features.

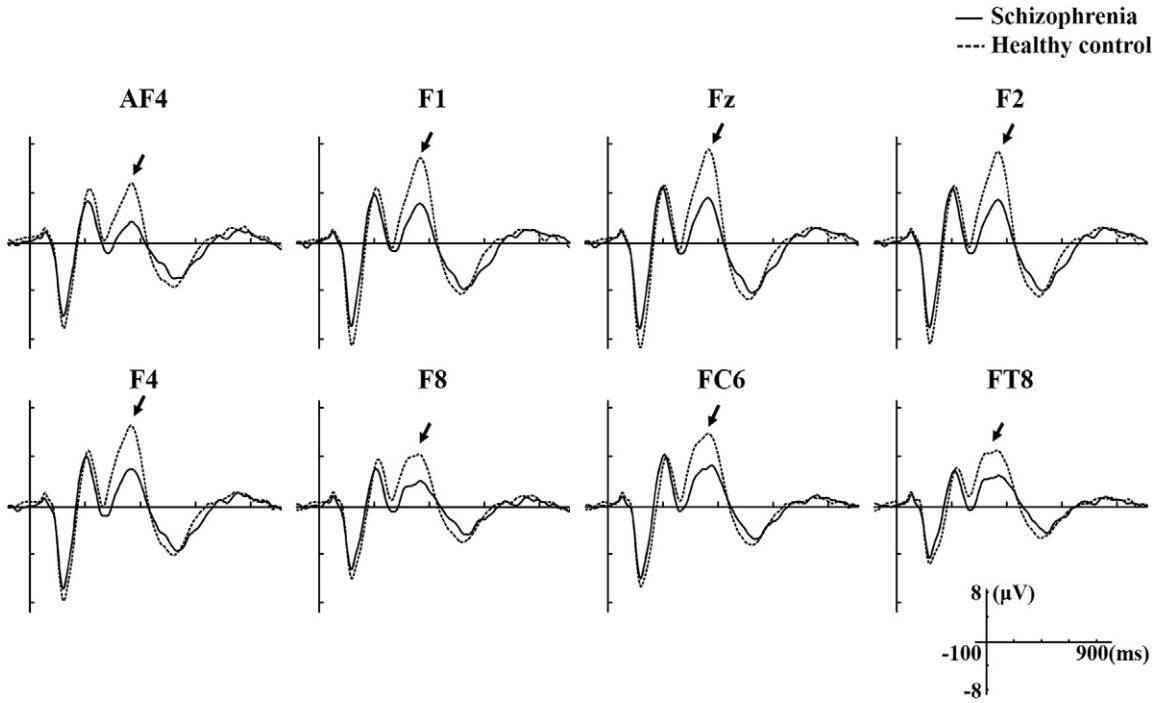

Fig. 4. The P300 waveforms at eight selected sensor-level features shown in Fig. 3. The P300 amplitudes were significantly decreased in schizophrenia patients compared to healthy controls at all electrodes ($p < 0.05$). Blue arrows indicate P300 peaks on ERP waveform.

oddball task is most frequently used for evaluating cognitive decline in patients with mental disorders because this task not only consistently shows good performance in evaluating cognitive decline, but also is relatively easy and time-efficient (Polich et al., 1986; Polich and Kok, 1995).

Many studies that use auditory oddball tasks to measure cognitive decline in schizophrenia report altered event-related potential (ERP) waveforms and reduced source activity at specific cortical regions in schizophrenia. Previous studies reported disrupted characteristics of P300 such as reduced P300 amplitudes and prolonged latency in schizophrenia compared to healthy controls (Doege et al., 2009; Mathalon et al., 2000). Mathalon et al. (2000) and Doege et al. (2009) found reduced P300 amplitude in the frontal area, which is now known as a trait marker of schizophrenia. Some recent studies investigated brain areas reflecting cognitive deficits in schizophrenia using EEG source imaging (Kawasaki et al., 2007; Kim et al., 2014). Kawasaki et al. (2007) found that the source activities in schizophrenia patients were significantly decreased compared to those in healthy controls, especially in the superior temporal gyrus, medial frontal area and temporo-parietal junction. Kim et al. (2014) reported altered P300 source activation in middle temporal and precuneus, and also presented negative relationships between source activation and symptom scores.

In the present study, we assessed the spatial distribution of sensor-level and source-level features extracted from the combined feature set when maximum classification accuracy was achieved. Among these 15 features, eight features were selected from among the sensor-level features and seven features were selected from among the source-level features. All selected sensor-level features were located in the frontal area, when the P300 amplitudes at the selected locations were significantly reduced in schizophrenia patients compared to healthy controls. This result agrees with previous auditory oddball task studies that reported reduced P300 amplitude in the frontal area (Doege et al., 2009; Mathalon et al., 2000). The frontal P300 amplitudes are negatively correlated with cognitive function in patients with schizophrenia, and reduced P300 amplitude generally indicates deficits in cognitive function (Kim et al., 2003). Moreover, some studies have suggested that the reduced frontal P300 amplitudes in schizophrenia are more tightly associated with positive symptoms such as hallucination (Higashima et al., 2003; Mathalon et al., 2000).

On the other hand, all seven features selected from the source-level feature set were spatially distributed in the left temporal area, when the source activity was also decreased in patients with schizophrenia compared to healthy controls. This result coincides with those of previous EEG source imaging studies that reported reduced cortical source activity around the left temporal area in patients with schizophrenia (Kim et al., 2014; Mathalon et al., 2000; Pae et al., 2003; Turetsky et al., 1998). Dysfunction of the left temporal area is known to indicate declined cognitive functions in patients with schizophrenia. Some studies have demonstrated that reduced source activity in the left temporal region is negatively correlated with negative symptoms of schizophrenia (Kawasaki et al., 2007; Kim et al., 2014). In summary, the features selected from both sensor-level and source-level feature sets reflected well-known electrophysiological dysfunction in schizophrenia, which might contribute to the high classification accuracy of our approach.

4.3. Limitations

There are some limitations in the present study. First, all of the patients were on medication, and thus we could not control for possible confounding effects of antipsychotic drugs. Second, we did not use individual head models for EEG source imaging, as the individual MRI data were not available. Nevertheless, our results demonstrate that the use of source-level features together with sensor-level features could significantly improve classification accuracy, and thus is a promising approach for the computer-aided diagnosis of schizophrenia. In future studies, we will apply our approach to other mental disorders such as Alzheimer's disease, depression, and anxiety disorder. In addition, we will further investigate the possibility of other types of features such as high gamma activities, functional connectivity and graph theoretical indices in the machine-learning-based diagnosis of schizophrenia.

Conflict of interest

All the authors declare that they have no conflicts of interest.

Contributors

Miseon Shim designed the study and wrote the manuscript. Han-Jeong Hwang developed the machine learning program used for the analysis. Do-Won Kim processed EEG data. Seung-Hwan Lee designed the study and wrote the protocol. Chang-Hwan Im supervised the study process and manuscript writing. All authors contributed to and have approved the final manuscript.

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