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Classification of Bipolar Disorder and Schizophrenia Using Steady-State Visual Evoked Potential Based Features

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ABSTRACT The accurate discrimination between bipolar disorder (BD) and schizophrenic patients is crucial because of the considerable overlap between their clinical signs and symptoms (e.g., hallucination and delusion). Recently, electroencephalograms (EEGs) measured in the resting state have been vastly analyzed as a means for classifying the BD and schizophrenic patients, but EEGs evoked by external audio/visual stimuli have been rarely investigated, despite their high signal-to-noise ratio (SNR). In this study, in order to investigate whether EEGs evoked by external stimuli can be used for classifying the BD and schizophrenic patients, we used a visual stimulus modulated at a specific frequency to induce steady-state visual evoked potential (SSVEP). In the experiment, a photic stimulation modulated at 16 Hz was presented to two groups of the schizophrenic and BD patients for 95 s, during which the EEG data were recorded. Statistical measures of SSVEPs (mean, skewness, and kurtosis) described in SNR units were extracted as features to characterize and classify the variations of brain activity patterns in the two groups. Two brain areas, O1 and Fz, showed a statistically significant difference between the two groups for SNR mean and kurtosis, respectively. Among five applied classifiers, *k*-nearest neighbor provided the highest classification accuracy of 91.30% with the best feature set selected by Fisher score. An acceptable accuracy for binary classification (>70%) was retained until analysis time was reduced up to 10 s using a support vector machine classifier, and 20 s for other classifiers. Our results demonstrate the potential applicability of the proposed SSVEP-based classification approach with relatively short single-trial EEG signals.

INDEX TERMS Bipolar disorder, diagnosis of psychiatric diseases, electroencephalography (EEG), schizophrenia, steady-state visual evoked potential (SSVEP).

I. INTRODUCTION

Bipolar disorder (BD) and schizophrenia are psychiatric disorders that share several signs and symptoms, such as hallucination and delusion [1], [2]. It is still a big challenge for psychiatrists to differentiate between them in the first interviewing session [3] using qualitative criteria, such as those found in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-V) [4] and the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) [5]. The manic phase is a common episode that occurs in both BD and schizophrenic patients. When a psychotic patient within this episode is referred to a psychiatrist, accurate diagnosis becomes highly challenging using ICD-10 or DSM-V because these conventional diagnostic criteria are qualitative and there is no physiological measurement carried out in this crucial diagnosis.

To overcome this drawback, researchers have attempted to characterize electroencephalograms (EEGs) and features of scalp EEGs were widely used to classify the two psychiatric disorders. For example, in [6], EEG data were recorded from 18 patients with BD type I in eyes-closed resting state and

18 patients with schizophrenia. Absolute spectral powers and coherence features were extracted from their EEGs to differentiate the two groups. The results showed higher coherence values at six pairs of electrodes on the right hemisphere of the brain of schizophrenic patients compared with those of patients with BD type I. Although they implied discriminative observations on the EEG features of schizophrenic and BD patients, direct classification using the EEG features between them was not performed.

In our previous work [7], we introduced a framework to classify BD from schizophrenic group by analyzing their EEG data measured in eyes-closed resting state. To classify BD and schizophrenic group, diverse types of features, e.g., phase-locking value [8], robust synchronization [9], and synchronization likelihood [10], were extracted from the recorded EEG signals. Afterwards, a suitable subset of discriminative features was selected from the pool of features by a proposed greedy-overall-relevancy feature selection method. Finally, by applying the selected features to the modified nearest neighbor classifier, a 92.45% classification accuracy was obtained. We also achieved an increased classification accuracy of up to 98.95% using a novel covariance weighting method in the Riemannian space of the covariance matrices [11]–[13].

Although several studies have been conducted to differentiate psychiatric diseases by analyzing EEGs recorded in the resting state, recording EEGs in the resting state for a long time increases the risk of contamination caused by additive noises, such as electrooculogram (EOG) and electromyogram (EMG). Furthermore, some previous studies [14], [15] emphasized the importance of EEGs that are evoked by auditory or visual stimuli because of the two following reasons: i) with evoked potentials, the possibility of removing additive noises by taking an average over synchronous events becomes considerably higher than spontaneous EEGs measured in the resting state; ii) evoked potentials are generated in the visual and auditory networks of the brain, and any abnormal characteristics can reveal deficiencies in those pathways due to the psychiatric disease. Therefore, this potential can be used to identify relevant psychiatric diseases. Moreover, psychiatric patients do not generally want to participate in experiments requiring long EEG recording. Thus, it is demanded to introduce a novel classification framework that can decrease required EEG recording time while preserving its diagnosing accuracy.

In this study, we investigated the separability of BD and schizophrenic patients by analyzing their steady-state visual evoked potentials (SSVEPs). An SSVEP is a frequency and phase-locked EEG response to a temporally modulated visual stimulus (e.g., a light flicker) [16]. Thus, an increased spectral power at a stimulation frequency is generally observed around the occipital areas a few seconds (> 2 s) after repetitively presenting a visual stimulus, together with its harmonic components [16]. The advantage of SSVEP is its higher signal-to-noise ratio (SNR), compared with resting state EEGs. Analyzing SSVEP has repeatedly provided high classification accuracy for communication purposes for patients with neurodegenerative diseases, e.g., $> 90\%$ for multi-class brain-computer interfaces [17]–[20]. In addition, SSVEP has been used to characterize neuronal substrates. For example, it was shown that visual processing abnormalities are associated with impairments in cognitive functions [21], which affects the SSVEP waveform in schizophrenic patients [22]–[25]. Moreover, the discrimination of schizophrenic patients from control subjects by comparing the SNR of their SSVEPs was investigated from the statistical point of view [21]. They demonstrated that SNR was reduced in schizophrenic patients in response to visual stimuli with low luminance contrast and low spatial frequency, compared to the control group. Besides the previous studies showing visual dysfunction in schizophrenic patients [21]–[25], another study demonstrated that BD patients also have significantly different neural activities in their visual systems as compared with healthy subjects [26]. Furthermore, one study directly compared neuronal activities evoked by visual stimuli between healthy subjects and patients with BD and schizophrenia. It was demonstrated in [27] that patients with BD have relatively intact visual function compared to those with schizophrenia, showing significantly different amplitude and latency between the two patient groups. Thus, it is expected that the two groups of patients would show different SSVEP responses because SSVEP is also a neural response modulated by the involvement of visual processing, thereby it can be used as useful features in automatically classifying the two groups.

Despite active research using SSVEP, to the best of our knowledge, no SSVEP-based study aimed at distinguishing between BD and schizophrenia has ever been conducted. In this study, we introduce a simple SSVEP-based classification framework, containing relevant feature extraction, feature selection, and classification. Our contributions in this paper are briefly listed below:

i) Characterizing the difference of SSVEP responses between BD and schizophrenia patients.

ii) Choosing proper features and a classifier for classifying BD from schizophrenia patients.

iii) Investigating the effect of recording length on classification accuracy [17]–[19].

The rest of this paper is organized as follows. Materials and methods are explained in Section II. Experimental results and their corresponding discussions are found in Sections III and IV, respectively, and followed by the conclusion in Section V.

II. MATERIALS AND METHODS

A. PATIENTS

Twenty-six patients with schizophrenic and twenty-seven patients with BD participated in this study. These patients were selected from the pool of the Pediatric Neurology Outpatient Clinics of Hafez hospital in Shiraz, Iran. We acquired the ethical approval for our study from the

TABLE 1. Demographic characteristics of the patients with bipolar disorder (BD) and schizophrenia (SZ).

	BD	SZ	*p*-value
Number of patients	23	23	-
Gender (male/female)	14/9	8/15	0.139
Age (years)	18.57 ± 3.52	20.39 ± 4.26	0.107
Years since onset	2.73 ± 2.17	4.76 ± 3.71	0.073
Family history	7 (30.4%)	6 (26.14%)	1.000
Anguish or depression background	16 (60.9%)	13 (56.5%)	1.000
Headache background	13 (56.5%)	7 (30.4%)	0.137
Tension background	5 (21.7%)	1 (4.3%)	0.189

Values are mean ± standard deviation in age and years since onset, whereas values are given as the number of subjects with percent in family history, anguish or depression, headache, and tension background. The *p*-values are obtained using Wilcoxon rank sum test for age and years since onset, and chi-squared test for gender, family history, anguish or depression background, headache background, and tension background.

Institutional Review Board Committee of Hafez Hospital. The exclusion criteria included a past or current history of substance dependence, clinically estimated mental retardation, significant neurological disorder such as epilepsy, or history of head injury causing a loss of consciousness for at least 1 h. The patients were diagnosed using the Structured Clinical Interview for DSM-V [4].

To ensure the labeling procedure that assigns all patients to either BD or schizophrenia, we did not ask the patients who referred to the psychiatrists for the first time, instead, we selected patients who had positive responses to their prescribed drugs. This is because there is no guarantee that the labeling of the patient performed by the psychiatrist in the first interview session is accurate, considering that there is a high overlap between the clinical signs manifested by BD and schizophrenic patients. A total of 26 patients with schizophrenia and 27 patients with BD originally participated in the measurements. However, one of the schizophrenic patients had to be excluded from further analysis because of technical problems in the EEG recording, resulting in unusable EEG data. Moreover, the two oldest patients with schizophrenia and four youngest patients with BD were also excluded in order to match the two groups based on age from the statistical point of view, thereby enhancing the confidence in our analysis results. In total, 23 patients with schizophrenia and 23 patients with BD were included for the analysis. Table 1 summarizes the demographic characteristics of all patients who participated in this study. The *p*-values were obtained using Wilcoxon rank sum test for age and years since onset, and the chi-squared test was used for gender, family history, anguish or depression background, headache background, and tension background. No demographic factors showed any statistically significant difference between the two groups ($p > 0.05$).

B. EEG RECORDING PROCEDURE

The patients were individually evaluated in the Clinical Neurophysiology Laboratory at the Medical School of the University of Shiraz. They were seated in a reclined chair in an electrically shielded and sound-attenuated room. The scalp EEG data were recorded using a Scan LT system (Compumedics, Inc.) from 21 Ag/AgCl scalp electrodes (Fp1, Fp2, F3, F4, F7, F8, Fz, C3, C4, Cz, T3, T4, T5, T6, P3, P4, Pz, O1, O2, A1, and A2) according to the international 10–20 system. The average value between A1 and A2 was used as the reference. The ground electrode was located on the left cheek, which was used by the recording software to reject the power line noise. The EEG data were recorded at a sampling rate of 250 Hz with an online bandpass of 0.01 – 40 Hz (40 dB decay rate of the side lobe).

For SSVEP recordings, a photic stimulator (Compumedics, Inc.) containing light diodes (15×5 cm in size and 17×4 white diode array) was placed at a view of approximately 45°. The distance between the stimulator and patients was about 50 cm. The stimulus frequency was selected as 16 Hz because this frequency generally exhibits higher SNR than other frequencies do [28]. In addition, this frequency is outside of the alpha band (8 – 13 Hz), which generally shows many false positives due to relatively strong spontaneous alpha power [29], [30]. The EEG data were recorded for each patient during the photic stimulation that was presented for a relatively long period of time (107 ± 18 s) to obtain high SNR of SSVEPs [23]. We selected a fixed time range of 95 s from the stimulus onset time for the analysis to ensure the same amount of data for all patients. However, we used only 37.5 s of data from only one particular patient with schizophrenia because of technical problems during the measurement. The amount of data of this patient was smaller than those of the

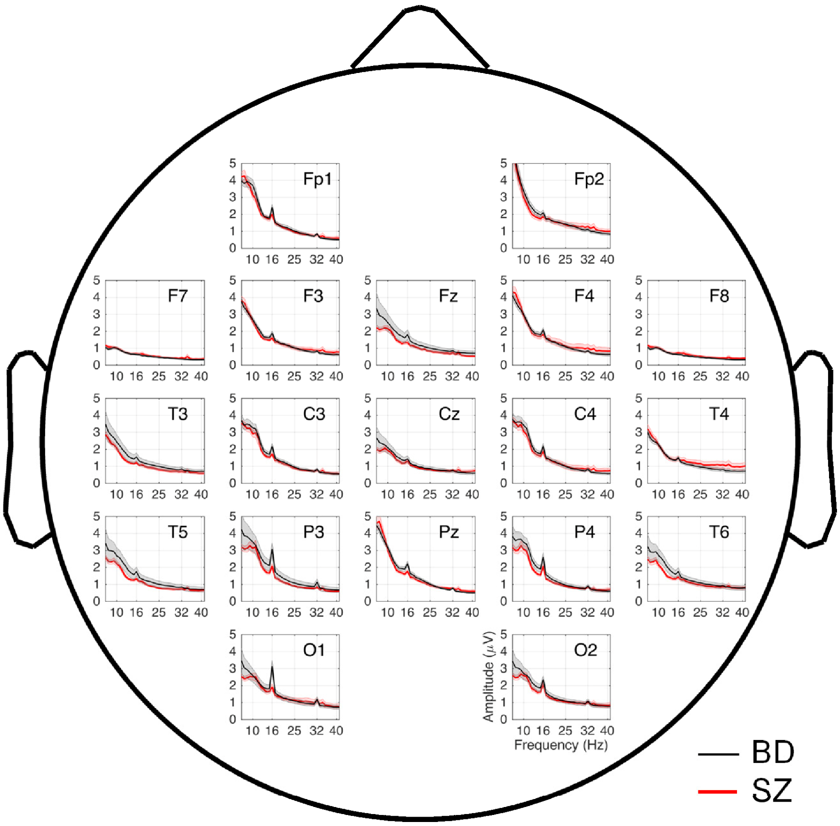

FIGURE 1. Mean power spectral densities evoked by 16 Hz visual stimulation for each group. The shaded regions indicate the standard errors for bipolar disorder (BD) and schizophrenia (SZ). Black line: BD; red line: SZ.

others, but all analysis methods, which will be presented in the following sections, were identically applied.

C. FEATURE EXTRACTION

To better detect the SSVEP peaks, we used SSVEP SNR, which is calculated by dividing the SSVEP amplitude at the stimulus frequency ($f = 16$ Hz) by the sum of SSVEP amplitudes over neighboring frequencies [26]:

$$SNR = \frac{nX(f)}{\sum_{k=1}^{n/2} [X(f+k) + X(f-k)]}, \tag{1}$$

where f is the stimulus frequency, $X(f)$ is the amplitude at f Hz, and n is the number of neighboring frequency points. In fact, the employed SNR measures the ratio of SSVEP amplitude at the stimulus frequency over the mean of SSVEP amplitudes at adjacent frequencies. In our analysis, we considered f at 16 and 32 Hz because the second harmonic of SSVEP response is also informative [17], [29]. With further consideration, we will see that the stimulus frequency and its second harmonic are both visible around the occipital areas (see Fig. 1 in advance). We empirically set the parameter $n = 6$, because no consensus has been reached at finding an optimum value for n. In previous literature, n has different values ranging from 6 to 16 [17], [30]–[32].

The SSVEP amplitude, $X(f)$, was calculated by taking a fast Fourier transform from successive windowed signals with 50% overlap, where each window had a length of one second. This approach was identically applied to the schizophrenia patient with only 37.5 s of EEG data. In this study, the mean, skewness, and kurtosis of the SNR values of SSVEPs at 16 and 32 Hz were proposed as suitable features for classifying BD patients from schizophrenic ones. The skewness is the third order statistics of a signal which measures the asymmetry of a distribution. The kurtosis is the fourth order statistics of a signal, measuring the flatness or sharpness of the signal distribution. The total number of the features was 114, since 6 features (the mean, skewness, and kurtosis of SNR values of SSVEPs at 16 and 32 Hz) were extracted for each channel (19 electrodes were used).

D. FEATURE SELECTION

The feature selection is an essential stage for classification problems when the input dimension is high compared to the number of trials. At this stage, an excessive number of irrelevant features are removed, thereby both avoiding the overfitting and decreasing the computational complexity. To reduce the dimensionality and select subsets of relevant features, we used the Fisher score [35] as a feature selection criterion, which has been widely used in pattern

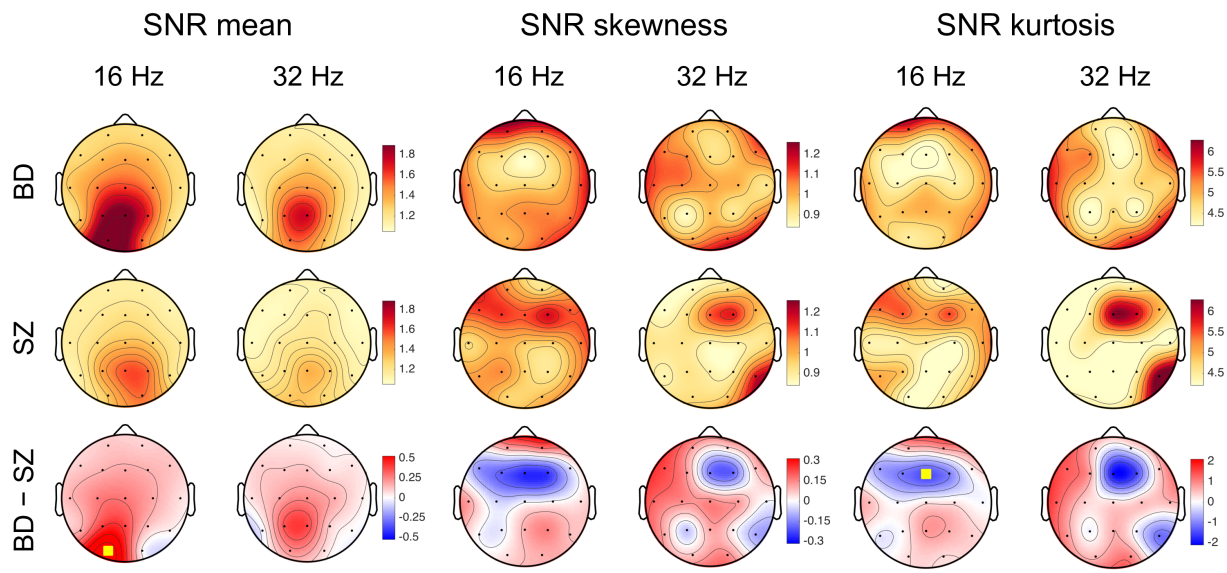

FIGURE 2. Mean topographic maps for the mean, skewness, and kurtosis of SSVEP-SNRs at 16 and 32 Hz for each group (BD: bipolar disorder; SZ: schizophrenia). The difference between BD and SZ are shown in the third row. Yellow squares denote statistically significant channels (two-sample t-test; $p < 0.01$, Bonferroni correction): O1 in SNR mean at 16 Hz and Fz in SNR kurtosis at 16 Hz. Note the different range of the color bars.

classification [36]–[41]. The Fisher score is defined as:

$$(\text{Fisher score})_k = \frac{|m_i - m_j|^2}{s_i^2 + s_j^2}, \qquad (2)$$

where k is the index of the k-th feature, m represents a mean, s^2 represents a variance, and the subscripts i and j denote two different classes (BD and schizophrenia in this study). A higher Fisher score means that the distance between the mean values of the two classes is larger than the lower Fisher scores, whereas the variance within each class is smaller than lower Fisher scores, thus ensuring better discrimination between two classes.

After computing the Fisher score for each feature, the top N features with the highest Fisher scores were selected for classification, whereas the other features were discarded. In this study, we evaluated the classification performance for different values of N, ranging from 1 to 10 in order to observe the effect of the number of features.

E. CLASSIFICATION

The classification of schizophrenic and BD patients was carried out using the following five classifiers that are widely used in classification problems [42]–[43]: linear discriminant analysis (LDA), quadratic discriminant analysis (QDA), support vector machine (SVM) with a second order polynomial kernel, k-nearest neighbors (KNN), and logistic regression analysis (LRA) based on binary logistic model. The classification accuracy was evaluated using the leave-one-out cross-validation (LOOCV). In LOOCV, the feature vectors of patients are split into a training and test set. All selected features of one patient are considered as the test set, and the rest of the features belonging to the other patients are considered as the training set. This loop is repeated until the set of features of each patient was used as a test set once. The classification accuracy was calculated by dividing the number of correctly classified trials by the number of total trials. The above procedure was performed using the MATLAB R2012b (MathWorks). Classifiers used in the procedure were applied using the PRTools (available from http://37steps.com/software/), which is a MATLAB toolbox for pattern recognition. The main idea of the KNN classifier is to find the K nearest neighbors to a test sample according to the Euclidean distance in the feature space, and the test sample is then assigned to a class based on whichever had the shorter distance. The number of the nearest neighbors for the KNN classifier was selected by optimizing the leave-one-out error on selected features.

III. RESULTS

The mean power spectral densities of SSVEP segments over the two groups within the range of 1 to 40 Hz for each channel are depicted in Fig. 1. The plots are arranged according to the international 10–20 system, and EEG channel labels are shown in the top right of each plot. Large SSVEP peaks are found in the brains of both BD and schizophrenic patients at the stimulus frequency of 16 Hz in their parietal and occipital areas. Although the amplitude is relatively small, SSVEP peaks can be also observed at 32 Hz, the second harmonic frequency of 16 Hz. The SSVEP amplitudes for BD are generally larger than those for schizophrenic patients. Specifically, a large amplitude difference can be visually observed in O1 at 16 Hz.

Topographic maps for the mean, skewness, and kurtosis of SSVEP-SNRs at 16 and 32 Hz are shown in Fig. 2, which were obtained by averaging all patient data for each group.

The configuration of EEG electrodes in topographic maps is same as Fig. 1. Similar to the amplitude values shown in Fig. 1, the SNR mean values at 16 Hz in the BD group are generally larger than those in the schizophrenic group. A significantly smaller SNR mean in the schizophrenic group compared with that of the BD group is observed specifically at O1 at 16 Hz, which agrees with the result exhibited in Fig. 1 (yellow square, two-sample t-test, Bonferroni corrected $p < 0.01$). Even though a similar topographical pattern is observed for the second harmonic component (32 Hz), there is no case showing statistical difference between the two groups. Note that the number of channels (19) was used for Bonferroni correction ($0.01/19 \approx 0.0005$). The SNR skewness and kurtosis show similar spatial distribution in each patient group. The SNR skewness and kurtosis in occipital channels are not as large as the SNR mean. At 16 Hz, SNR skewness and kurtosis in fronto-central areas for BD patients are smaller than those in schizophrenic patients. Morever, SNR kurtosis at Fz provides a statistically significant value between the two groups (yellow square, two-sample t-test, Bonferroni corrected $p < 0.01$). At 32 Hz, SNR skewness and kurtosis of BD patients are smaller than those of schizophrenic patients in frontal and temporal areas. For both the skewness and kurtosis of SNR at 32 Hz, a statistically significant difference is not observed.

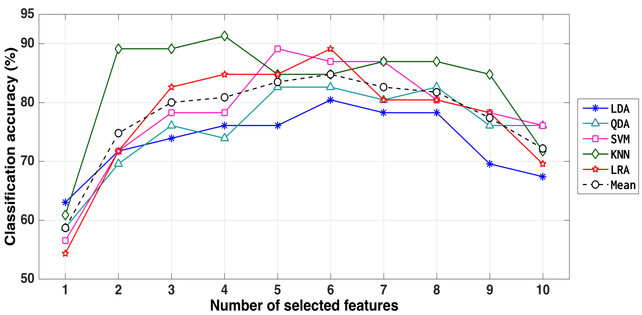

FIGURE 3. Classification accuracies (%) of five different classification algorithms with respect to the number of selected features (LDA: linear discriminant analysis; QDA: quadratic discriminant analysis; SVM: support vector machine; KNN: *k*-nearest neighbors; LRA: logistic regression analysis). Mean classification accuracies are denoted by 'Mean' for each number of features in the figure. Leave-one-out cross-validation was applied to compute classification accuracy. Note that the range of classification accuracy is between 50 and 95%. The maximum accuracy (91.30%) is found for KNN when four features are used. Classification accuracy was estimated using 95 s EEG data from stimulus onset for all patients, except one patient with schizophrenia for whom 37. 5 s data were used due to technical problems during the measurement. The mean classification accuracy of the five classifiers is statistically higher when using 5 and 6 features than using only 1 feature (Friedman test, Bonferroni corrected $p < 0.01$).

Figure 3 presents the classification accuracies evaluated through the LOOCV for the five classification algorithms with respect to the number of features selected by the Fisher score. As mentioned, the number of selected features varied from 1 to 10 to see the effect of the number of features. The mean classification accuracies of the five classifiers are plotted with a black dashed line for different numbers of selected features in Fig. 3. The classification accuracy continuously increases until the number of selected features is six on the average, and it decreases after that, showing the curse of dimensionality phenomenon. The maximum mean accuracy of 84.78% over the five classifiers is achieved when six features are selected. In line with this result, classification performance is statistically higher when using five or six features than using one feature (Friedmann test, Bonferroni corrected $p < 0.01$). For KNN, the maximum classification accuracy of 91.30% is achieved when four features are selected, and LRA also showed a comparable accuracy of 89.13 % when six feature are used. The classification accuracies of over 80% are achieved for all classifiers when suitable numbers of features are used (6 features for LDA; 5–8 features for QDA; 5–7 features for SVM; 2–9 features for KNN; 3–8 features for LRA). For the KNN classifier, classification accuracies obtained are greater than or at least equal to approximately 85%, except when the numbers of features are 1 and 10. The performance of KNN is significantly higher than that of LDA and QDA, and SVM also showed statistically higher performance compared with LDA (Friedman test, Bonferroni corrected $p < 0.01$).

Table 2 summarizes the features selected by the Fisher score sorted in descending order. The most commonly selected features by LOOCV were SNR mean at O1 and SNR kurtosis at Fz, both at 16 Hz. This result coincided with the statistical results shown in Fig. 2. The highest mean classification accuracy was obtained for the following eight features: SNR mean at O1, Pz and P3, SNR kurtosis at Fz, SNR skewness at Fz at 16 Hz; SNR mean at F3, Cz and C4 at 32 Hz. Note that skewness was also selected as a useful feature even though there was no channel showing a statistically significant difference between the skewness of the two groups (Fig. 2). This means that the skewness feature can provide additional discriminative information, together with the mean and kurtosis features showing a statistical difference between the two groups.

To evaluate the effect of the length of analysis time on the classification accuracy, a classification performance is assessed by continuously reducing the analysis time length by 10 s using the same analysis framework. As described in Section 2, only 37.5 s of data were available for one patient with schizophrenia. These data were used although a time length of more than 37.5 s was required for this patient. Fig. 4 represents changes in the mean classification accuracies of five classifiers and their averages with respect to different time lengths. The highest classification accuracies are illustrated with the best features for each classifier. The results for 95 s are also included in Fig. 4. A monotonic increase trend in the classification accuracy for the five classifiers is found by increasing the time length. An acceptable classification accuracy for a binary classification (>70% as described in [42]) was obtained when the time length was 10 s by using SVM, while it was 20 s by using all classifiers, except QDA (69.56 %). A mean accuracy of over 80% was obtained when the time length was 70 s. LRA shows statistically higher classification performance than the other

TABLE 2. Ten most selected features by the Fisher score in the leave-one-out cross-validation for ten different number of selected features.

Number of selected features									
1	2	3	4	5	6	7	8	9	10
O1 16 m (83.6%)	**Fz 16 k** (50%)	**O1 16 m** (33.3%)	**O1 16 m** (25%)	**O1 16 m** (20%)	**O1 16 m** (16.7%)	**O1 16 m** (14.3%)	**O1 16 m** (12.5%)	**O1 16 m** (11.1%)	**O1 16 m** (10%)
Fz 16 k (17.4%)	**O1 16 m** (48.9%)	**Fz 16 k** (33.3%)	**Fz 16 k** (25%)	**Fz 16 k** (20%)	**Fz 16 k** (16.7%)	**Fz 16 k** (14.3%)	Fz 16 s (12.5%)	Fz 16 s (11.1%)	Fz 16 s (10%)
-	Fz 16 s (1.1%)	F3 32 m (28.3%)	F3 32 m (24.5%)	F3 32 m (20%)	F3 32 m (16.7%)	F3 32 m (14.3%)	**Fz 16 k** (12.5%)	**Fz 16 k** (11.1%)	**Fz 16 k** (10%)
-	-	Fz 16 s (3.6%)	Fz 16 s (12%)	C4 32 m (16.1%)	C4 32 m (15.2%)	Fz 16 s (14 %)	F3 32 m (12.5%)	F3 32 m (11.1%)	F3 32 m (10%)
-	-	P3 16 m (0.7%)	C4 32 m (11.4%)	Fz 16 s (13.5%)	Fz 16 s (13.4%)	C4 32 m (14%)	C4 32 m (12.5%)	C3 32 m (11.1%)	C3 32 m (10%)
-	-	Pz 16 m (0.7%)	Pz 16 m (1.1%)	C3 32 m (6.1%)	C3 32 m (10.9%)	C3 32 m (12.4%)	C3 32 m (12%)	C4 32 m (11.1%)	C4 32 m (10%)
-	-	-	P3 16 m (0.5%)	P3 16 m (1.7%)	Cz 32 m (5.4%)	Cz 32 m (9.6%)	P3 16 m (9.8%)	P3 16 m (10.4%)	Cz 32 m (9.7%)
-	-	-	Cz 32 m (0.5%)	Cz 32 m (1.3%)	P3 16 m (2.9%)	P3 16 m (4%)	Cz 32 m (9.8%)	Cz 32 m (10.4%)	P3 16 m (9.3%)
-	-	-	-	Pz 16 m (0.9%)	Pz 16 m (1.1%)	Pz 16 m (0.9%)	Pz 16 m (1.6%)	P3 32 m (5%)	P3 32 m (6.7%)
-	-	-	-	F8 32 m (0.4%)	Fz 16 m (0.4%)	Cz 16 m (0.6%)	P3 32 m (1.4%)	F4 16 s (1.9%)	Pz 16 m (4.1%)

Each column is sorted in descending order, and each entry represents channel label, stimulus frequency (16: 16 Hz; 32: 32 Hz), statistical measures of SSVEP-SNR values (m: SNR mean; s: SNR skewness; k: SNR kurtosis), and percentage in total (rounded to 1 digit after the decimal point). The two features denoted by bold font (O1 16 m and Fz 16 k) are the most important (selected) features for classification.

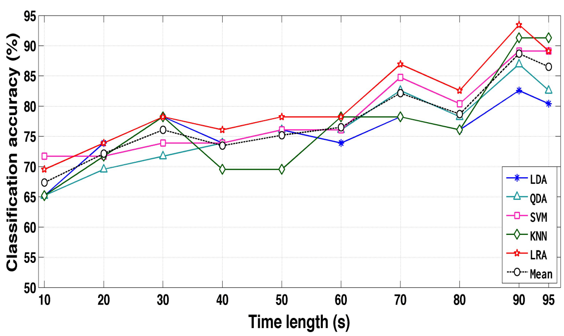

FIGURE 4. Classification accuracies (%) of five different classification algorithms with respect to different time lengths. The maximum classification accuracies of each classification algorithm are shown after considering the different numbers of features varying from 1 to 10 for each analysis time length, and thus the number of features used for classification varies between the classification algorithms as well as different analysis time lengths. 'Mean' represents the mean classification accuracies of each classification algorithm. Note that the range of classification accuracy is between 50 and 95%. The mean classification accuracy of the five classifiers is statistically higher when using 90 s data length than 10 s and 95 s data length than 10 and 20 s, respectively (Friedman test, Bonferroni corrected $p < 0.01$).

classifiers, indicating that LRA would be the best choice with a small amount of EEG data (Friedman test, Bonferroni corrected $p < 0.01$). Classification performance is statistically higher when using 90 s data length than 10 s and 95 s data length than 10 and 20 s, respectively (Friedman test, Bonferroni corrected $p < 0.01$).

IV. DISCUSSION

In the present study, we demonstrated that discriminating between BD and schizophrenia with a high accuracy can be possible by using our proposed simple SSVEP-based classification framework. A maximum classification accuracy of 91.30% was obtained when the number of features selected by the Fisher score is four with KNN. We also showed that a reasonable accuracy for a binary classification (> 70% as described in [42]) can be obtained with only 10 s of EEG data with a proper classifier (SVM in this study), demonstrating the potential clinical use of our SSVEP-based framework to quantitatively classify different psychiatric disorders (BD vs. schizophrenia) with a relatively small amount of EEG data.

The reason for using the SSVEP is that it has been known to have high SNR [16] and is less susceptible to artifacts produced by EOG [45] and EMG noises [46]. Therefore, we can obtain SSVEP peaks in the frequency domain without any complicated preprocessing steps for noise reduction and artifact correction, as shown in [17]–[20]. On the other hand, for the analysis of resting state EEG [6], [7], we generally need manual editing and additional algorithms (e.g., independent component analysis) for noise reduction and artifact correction.

Another advantage of the high SSVEP-SNR is that it can reduce EEG recording time and the number of electrodes, which are extremely important for clinical use. Thanks to the high SSVEP-SNR, a relatively small amount of data can be used to quantitatively discriminate between schizophrenic and BD patients with an acceptable classification performance, as demonstrated in this study; only 10 s of EEG data were required for the SVM classifier to obtain reasonable accuracy for two class classification (>70%).

The classification accuracy obtained in this study is considerably precise compared to those of previous research findings, which used 180 s of recording in the resting state [7]. Even though we used 21 electrodes that cover the international 10–20 system, only three or four electrodes (or features) (e.g., Fz, O1, and F3) can be used to achieve a reasonable classification accuracy according to the feature selection result listed in Table 2. However, because characteristics of features generally change if data length used to extract features varies, proper features would change depending on the length of analysis time. We confirmed this effect when investigating the effect of the length of analysis time, where four mostly selected features were fixed for classification (O1 16 m, Fz 16 k, Fz 16 s, and F3 32 m). As a result, similar to Fig. 4 showing classification accuracies obtained using the best features for each analysis data length, classification accuracies increased as analysis time length increased, but they more fluctuated and showed lower performance in general, compared to those shown in Fig. 4. (detailed results are not shown here). Also, note that only two channels showed a statistically significant difference between BD and schizophrenic patients (O1 for SNR mean and Fz for SNR kurtosis). However, this does not mean that only the two channels can be fully used for classifying the two groups, but that they contain the most discriminative information. The required time and number of electrodes for EEG recording are crucial for clinical use, especially for impatient psychiatric patients because they cannot concentrate on the experiment and keep stayed for a long time in general. Thus, it is expected that our proposed analysis framework using SSVEP might be practically introduced for clinical use in view of its relatively short EEG recording time using only a few number of electrodes.

Deviations in SSVEP responses, such as reduced spectral power in the alpha or beta frequency bands, have been reported in schizophrenic patients, compared to healthy control subjects [22]–[25], which have been shown in thalamus, frontal and occipital regions [28], [47]. A similar observation was also revealed in this study, though we compared schizophrenia with BD. In the topographic maps of the SNR mean (Fig. 2), larger SNR values were mainly observed over the occipital lobe in both BD and schizophrenic patients, but overall SNR mean values in the schizophrenic group are lower than those in the BD group at 16 Hz.

Mean powers of SSVEP-SNRs have been used in previous studies to distinguish schizophrenic patients from other psychiatric disorders or normal subjects [22]–[25]. In the present study, skewness and kurtosis, as higher order statistics of SSVEP-SNRs, were also used as novel features to classify the two psychiatric diseases. Note that the classification accuracy of up to 91.30%, which was obtained using the three features (mean, skewness, and kurtosis), was significantly higher than that obtained by using only the mean features: a maximum mean classification accuracy of 75.65% is achieved when the number of features selected by the Fisher score is three, and a maximum classification accuracy of 80.43% is obtained when the number of selected features is 10 with SVM (not shown here in detail).

There are several evidences on the improper connections between the cerebral hemispheres in schizophrenic patients, leading to deteriorate the normal EEG patterns [48]–[51]. In this study, the skewness and kurtosis of SSVEP-SNR were used to precisely measure the effect of schizophrenia on the shape of SSVEP in terms of non-Gaussianity and the amount of sharpness/flatness. Because the distribution of SSVEP-SNR captures data variability, these statistical indexes demonstrate both the variability of SSVEP-SNR during a long trial recording and the disease-related difference in the response of their visual processing systems. The achieved results implied higher skewness and kurtosis in the fronto-parietal areas in schizophrenic patients compared to those of BD ones. This result implies a potential deficit in the visual processing path of schizophrenic patients, leading to the generation of unstable VEP patterns.

In our previous study [26], we used a visual evoked potential (VEP) paradigm similar to our SSVEP one for quantitatively discriminating between patients with BD and attention deficit hyperactivity disorder (ADHD). Because of the significantly different neural responses to the VEP paradigm between BD and ADHD patients, we could discriminate between BD and ADHD patient groups with a high accuracy of up to 92.85 %. As our proposed SSVEP approach is also based on the fact that different psychiatric disorders present different neural characteristics during visual processing, it is expected that our proposed approach could similarly be applied to the discrimination between BD and ADHD patients. In this sense, our SSVEP approach could be extended to classify any type of psychiatric disorders if they manifest the different degrees of visual function. In particular, to increase diagnostic accuracy, our quantitative diagnostic method could be incorporated in the first stage of disease identification using traditional qualitative methods, such as ICD-10 or DSM-V.

In the present study, we used five different classifiers to get as high classification accuracy as possible. The performance of KNN was statistically higher than that of LDA and QDA, and SVM also showed statistically higher performance than LDA (Fig. 3). Moreover, LRA showed statistically higher classification performance than the other classifiers when investigating the impact of the length of analysis time (Fig. 4). However, it is hard to provide a proper reason why a particular classifier shows better performance than others because classification accuracies of different classifiers highly depend on given datasets. For example, although KNN showed the highest classification accuracy (91.3 %), the classification accuracy of KNN also varied depending on the number of selected features and time length. Thus, a classifier showing higher performance might change if some experimental variables change, such as number of samples, type of psychiatric disorders employed in the experiment, and so on. Unfortunately, to the best of our knowledge, only the way to find the best classifier for given dataset is to undergo trial and error with different classifiers. For our SSVEP dataset, KNN, SVM, and LRA showed higher classification performance than other classifiers in general.

V. CONCLUSION AND FUTURE WORKS

In this research, we proposed an SSVEP-based framework for the classification of BD and schizophrenic patients. In addition, because possible deficits in the interhemispheric interaction of the brain of schizophrenic patients would affect visual pathways, skewness and kurtosis of SSVEP SNRs were suggested as new classification features in order to detect the deterioration. Using high SNR of SSVEP amplitude, we do not need to apply a heavy preprocessing, making this method computationally inexpensive. Moreover, short recording times with a relatively small number of electrodes for SSVEP in this framework is an advantage over other methods requiring long recording time with more number of electrodes (e.g., at least 19 for the international 10-20 system) in the resting state. Therefore, our proposed classification framework can be easily incorporated into routine clinical practice (e.g., in the first interviewing session) as an assistant diagnostic tool with conventional qualitative criteria, such as DSM-V and ICD-10 for a more accurately discrimination between BD and schizophrenia.

The present study had a few shortcomings that can be compensated in future studies. One limitation is that we cannot control the possible confounding effects of antipsychotic drugs taken by the patients. Second, we used only one frequency (16 Hz) for modulating a visual stimulus in testing our framework. Because it has been well-documented that SSVEPs can be induced between 1 and 100 Hz [52] and there are subject-specific frequencies that yield higher SNR SSVEPs [31], various frequencies can be considered not only to investigate different neuronal substrates in terms of the modulation frequency, but also to increase diagnostic accuracy.

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