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INVESTIGATION INTO INDICES OF AGING AND SCHIZOPHRENIA USING THE PHOTIC DRIVING RESPONSE

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Abstract. *In the current study, we quantitatively evaluated aging and schizophrenia using statistical indices reflecting enhancement and suppression at arbitrary frequencies using photic stimulation (PS). This index corresponds to the Z-score, which reflects the distance between two amplitude distributions at an arbitrary frequency at rest and during PS. We measured EEGs from three groups: 50 healthy subjects aged between 20-30, 30 healthy subjects aged 60 and over, and 31 schizophrenia patients aged 60 and over. We obtained frequency characteristics of Z-scores in each group. Prominent characteristics of fundamental and harmonic components that were sensitive to schizophrenia disease and aging were observed at 6, 7 and 10 Hz PS. We then defined two indices to evaluate schizophrenia symptoms and aging: the average of Z-scores at fundamental and all harmonic frequencies except the harmonics in alpha band and gamma band over 30 Hz (Index A), and the subtraction value of the minimum Z-score in alpha band from the average of the Z-scores in gamma band (Index B). The results revealed a significant difference between the older healthy group and the schizophrenia group in Index A, and between the younger and older groups in Index B.*

Keywords: Photic driving response, Aging, Schizophrenia, Z-scores

1. **Introduction.** The photic driving response is a routine part of electroencephalography (EEG) examinations, and is commonly used for detecting epilepsy. Routine EEG data are not typically reassessed if no disease is detected in inspection by a medical doctor. As such, a large amount of EEG data is stored but not analyzed. In the current study, we describe an index to aid diagnosis by extracting characteristic patterns within EEG signals. The photic stimulus (PS) response consists of elicited rhythmic activity. In the frequency domain, the response includes the fundamental component for which the frequency is equivalent to the stimulus frequency (f_0), and the harmonic component, for which the frequencies are nf_0 ($n \geq 2$). In the current study, we analyzed a large number of healthy subjects between 20 and 30 years of age, subjects aged 60 years and over, and schizophrenia patients (aged 60 years and over), to develop indices of the effects of aging and schizophrenia based on EEG data. Previous studies of the relationship between EEG and aging have revealed that the alpha frequency decreases with age [1]. Lindsley

reported on the occipital alpha rhythm in healthy children, analyzing the frequency and amplitude of the EEG signal [2]. However, previous reports have revealed little variation in peak frequency with aging, suggesting that it does not provide a sensitive measure of the effects of aging in the brain. Numerous studies have been conducted to measure and analyze photic driving responses [3-6]. Few studies have examined the relationship between photic driving responses and biological aging in humans. Celesia et al. reported that the latencies of the first major negative and first major positive deflection of the visual evoked response were significantly delayed ($p < 0.001$) with advancing age. In addition, the critical frequency photic driving response, which is defined as the highest frequency of photic driving response expressed in flashes per second, exhibited an inverse correlation with age, decreasing in older subjects [7]. However, the study focused solely on its amplitude/latency and critical frequency, and did not examine the frequency components of the photic driving response. Liu et al. investigated changes in task-related brain oscillations and corticocortical connections in patients with mild cognitive impairment (MCI) and those with normal aging using cross-mutual information (CMI) analysis. During EEG measurement, however, subjects performed the auditory oddball paradigm [8]. In addition, Martin et al. reported that spindle density, amplitude, and duration were higher in young subjects than in middle-aged and elderly subjects [9]. Vallesi measured the go/nogo-P3 event-related potential (ERP) and reported that the parietal go-P3 latency was delayed with aging, while the central nogo-P3 was more pronounced in older adults than in younger controls. The amplitude of this component was negatively correlated with go reaction times [10].

Several previous studies examined the photic driving response or steady state visual evoked potential (SSVEP) in schizophrenia patients [11,12]. Jin et al. reported that patients with schizophrenia exhibit lower EEG responses to photic stimulation in the alpha frequency [13]. In addition, Krishnan et al. reported that SSVEP signal power at beta and gamma frequencies of stimulation were reduced in schizophrenia [14]. Ramakrishnan et al. reported that increasing density of K-complexes is related to enhanced problem solving performance in schizophrenia [15]. The differences in the spatiotemporal dynamics of cortical oscillation across brain regions of patients with schizophrenia and normal subjects during the auditory oddball task using magnetoencephalography (MEG) and EEG were studied by Fujimoto et al. They concluded that desynchronization (ERD) and synchronization (ERS) measured by time-frequency analyses using MEG are useful for clarifying data processing dysfunction in schizophrenia [16].

Aging and disease type are considered to be the most important factors affecting EEG results. Previous reports have typically only examined the relationship between EEG findings and a single factor such as aging or a specific disease type, using a simple index such as frequency power. However, using the currently proposed method, two factors can be evaluated in two dimensions. In a previous study, we proposed a method for analyzing the photic driving response and EEG data at eye opening and closure using Z-scores [17,18]. Compared with simpler indices, such as the ratio of averaged amplitude at rest and during PS, our proposed method can provide a stable assessment of enhancement and suppression by PS. Importantly, even if the ratio mentioned above is small and unclear in higher-order harmonics, this method can be used to obtain prominent peaks. In the current manuscript, we report the frequency characteristics of Z-scores between healthy and psychiatric disease groups. However, the ages of the patients in the sample varied widely, and patients suffered from various psychiatric diseases. As such, the present study sought to test a large sample, specifically examining the effects of aging and schizophrenia. In addition, we propose new quantitative indices for evaluating both aging and schizophrenia, and examine their validity.

2. **Methods.** Multichannel EEG was recorded using a Nihon Kohden polygraph (EEG-1100) with a 0.3 s time constant, a 60 Hz high cut filter, and a 97.5 nV quantization level. EEG signals digitized at a sampling frequency of 200 Hz were recorded from 19 electrodes placed according to the international 10/20 system with monopolar derivation from bilateral reference electrodes attached to the corresponding earlobes. We used five electrodes, (P_3, P_4, P_z, O_1, O_2), at which the photic driving response is prominent.

An experimental cycle involving a block without PS (at rest) for 10 s followed by a block with PS for 10 s was repeated. The photic pulse stimuli had the following parameters: the brightness of the flash stimulus was 30,000 cd/m^2, the light intensity was 4.0 lx/s, the pulse width was 2 ms, and the equipment was placed 30 cm in front of the subjects. All data reported in this study were recorded from participants at Utsunomiya Hospital after obtaining informed consent and ethics committee approval of the hospital. We measured EEG in response to stimulation at 3, 6, 7, 10, 14 and 18 Hz during routine examination of the subjects included in three groups, as shown in Table 1. A cycle involving a 10-s period without PS (at rest) followed by a 10-s period with PS was repeated in ascending order of increasing PS frequency.

We introduced an indicator for measuring the distance between two amplitude distributions at rest and during PS to evaluate enhancement and suppression by PS. The analysis method is described in detail in our previous paper [17]. Briefly, we defined each section as a block of activity while the participant was either 'at rest' or 'during PS', as shown in Figure 1. Each window shows the shortest block of data for analysis, referred to hereafter as the 'analysis window'. One sample amplitude value was calculated from each analysis

TABLE 1. Age and the number of data

	age	number of data
healthy subjects between 20 and 30 years old	23.2 ± 1.85	50
healthy subjects 60 years and over	69.6 ± 7.63	30
schizophrenia patients 60 years and over	72.9 ± 8.68	31

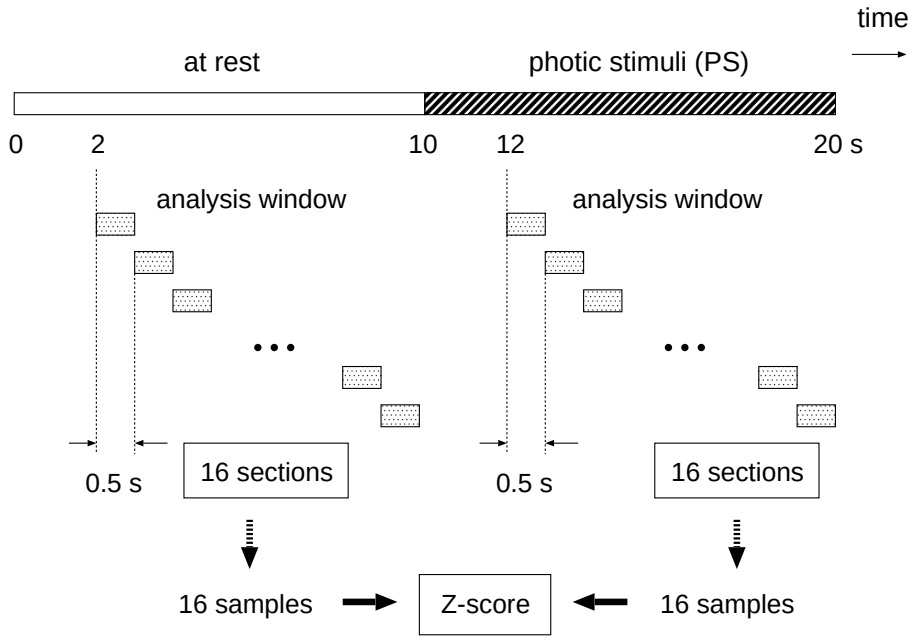


FIGURE 1. Flowchart of the method for obtaining Z-score

window. These values were used to obtain Z-scores as an indicator, as described below. In each period, the first 2 s of data were discarded to avoid the effects of the orienting response, and off-response stimuli. The comparison was thus performed with the remaining 8 s of data in each block. The photic driving response is not constant over a 10-second period. Rather, the amplitude of all frequency components varies within a short time. For this reason, we divided the EEG waveform into a large number of short segments. We set the window size to cover 100 points in 0.5 seconds, providing a frequency resolution of 0.5 Hz. Using this window with no overlap, we obtained 16 samples from 16 sections, to construct a distribution of Z-scores for each analysis frequency. Each PS frequency was then constructed.

We used a discrete Fourier transform to calculate frequency components. Using this method, it is possible to calculate frequency components at integral multiples of the fundamental frequency (i.e., 2 Hz in this study). However, it is not possible to obtain frequency components with a resolution less than 2 Hz. Therefore, we estimated uncalculated frequency components using the approximation method [19]. The amplitude spectrum was obtained between 0 and 40 Hz, at a resolution of 0.5 Hz. The frequency spectrum can be obtained with the following equation by a trapezoidal integral approximation of the continuous Fourier transform, $X(f) = \int_{-\infty}^{\infty} x(t)e^{-j2\pi ft}dt$.

$$X_N^*(f) = \Delta t \sum_{k=0}^{N-1} x(k\Delta t)e^{-j2\pi fk\Delta t} \tag{1}$$

where N is the number of sample points in the analysis window. The amplitude spectrum can then be calculated easily from the real and imaginary parts of $X_N^*(f)$. We introduced the Z-scores in Mann-Whitney U-tests as an indicator for measuring the distance between two amplitude distributions at rest and during PS. This test is based on the non-parametric Wilcoxon rank-sum test for assessing whether two sample sets of observations come from the same distribution. However, the Z-scores are only used for measuring the distance between two distributions, not for statistical testing. This method has the advantage that the influence on Z-scores of extremely large or small amplitudes in a local section can be diminished. In addition, more stable frequency characteristics in Z-scores can be obtained, because the method uses the rank according to the amplitude rather than an original amplitude.

We defined the rank-sum of two groups consisting of amplitudes at rest and during PS as: R_1 and R_2 (R_1 is ahead of R_2) after arranging data in descending rank order for amplitude. We denoted the sample numbers as N_1 and N_2, set here to 16 between two sections. U-statistics for the above two distributions are expressed as:

$$U_1 = R_1 - \frac{N_1(N_1+1)}{2} \tag{2}$$

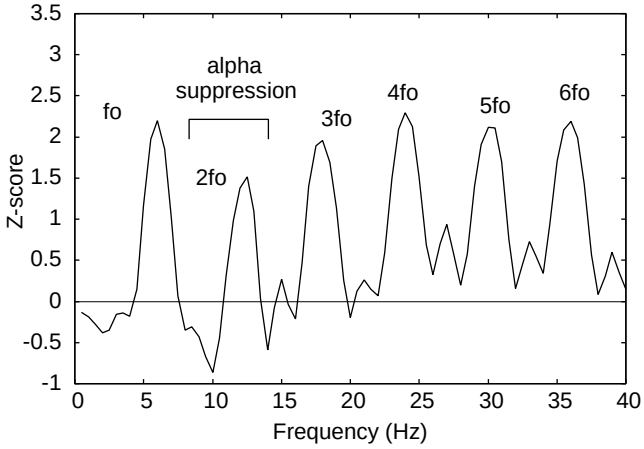
$$U_2 = R_2 - \frac{N_2(N_2+1)}{2} = N_1N_2 + \frac{N_1(N_1+1)}{2} - R_1 \tag{3}$$

The latter equation of Equation (3) is derived from the relation, $U_1 + U_2 = N_1N_2$. For large samples, the normal distribution approximation can be applied. Finally, the Z-score is calculated by the following equation.

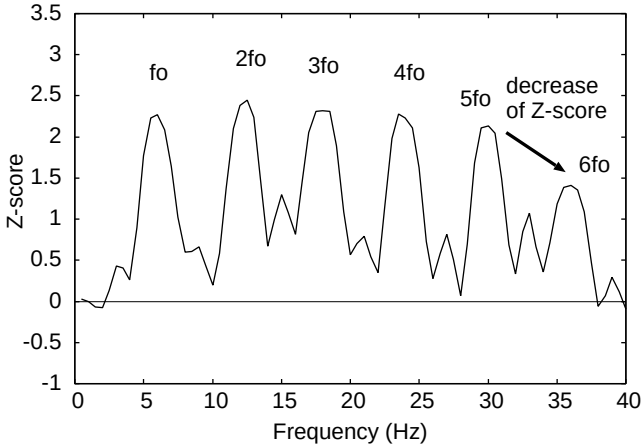
$$Z = \frac{N_1 \cdot N_2/2 - U_2}{\sqrt{N_1 \cdot N_2(N_1+N_2+1)/12}} \tag{4}$$

Positive and negative values in the above Z-scores indicate that EEGs are enhanced and suppressed by PS, respectively.

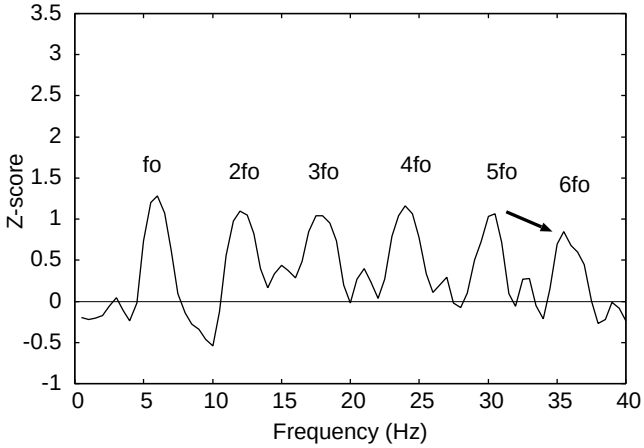
3. **Results.** We evaluated frequency characteristics less than 40 Hz using Z-scores. Here we show the results for responses at 6, 7 and 10 Hz PS, because lower frequency stimulation involves a large number of harmonic components. The 3 Hz stimulation condition is not reported here, because the condition did not elicit prominent effects in our analysis. Figure 2 shows the averaged Z-scores elicited by 6 Hz PS at five electrodes, as described in



(a) Healthy subjects aged between 20 and 30 years ($N = 50$)



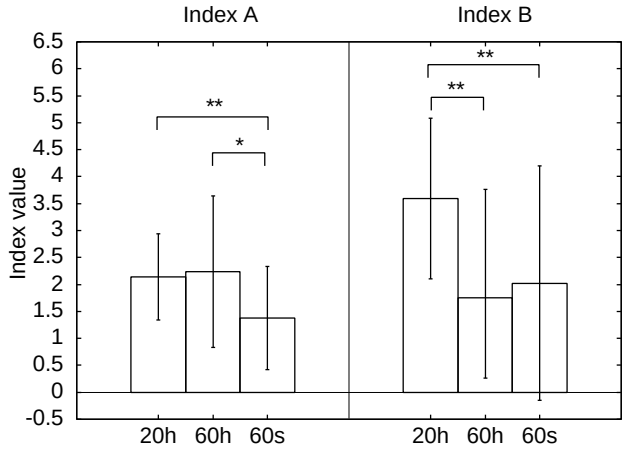
(b) Healthy subjects aged 60 years and over ($N = 30$)



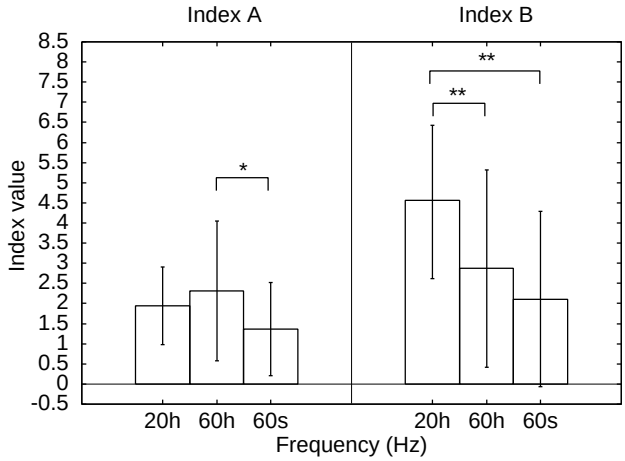
(c) Schizophrenia patients aged 60 years and over ($N = 31$)

FIGURE 2. Averaged frequency characteristics of Z-scores in response to 6 Hz PS

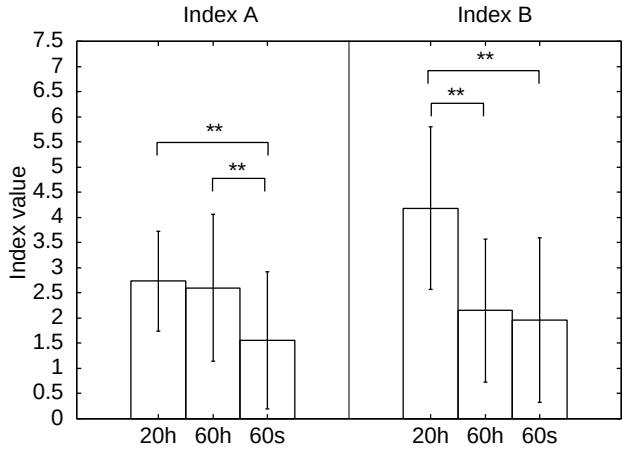
the 'Methods' section for healthy subjects between 20 and 30 years old (a), healthy subjects aged 60 and over (b) and schizophrenia patients aged 60 and over (c), respectively. The results revealed prominent peaks at fundamental and harmonic frequencies, as shown



(a) 6 Hz PS



(b) 7 Hz PS



(c) 10 Hz PS

FIGURE 3. Values of two indices (Index A and Index B). (*: $p < 0.05$, **: $p < 0.01$) (20h: healthy subjects aged between 20 and 30 years, 60h: healthy subjects aged 60 years and over, 60s: schizophrenia patients aged 60 years and over)

in Figure 2. Figure 2(a) shows the average of the younger healthy subject group, revealing that Z-scores were small in the second harmonic frequency range corresponding to the alpha frequency band. Z-scores exhibited high positive values at the fundamental and harmonic frequency, except $2f_0$, and EEG frequency components which were substantially enhanced by PS at these frequencies. On average, the older healthy subject group did not show the above-mentioned suppression around the second harmonic frequency, but exhibited decreased Z-scores above 30 Hz corresponding to the gamma frequency band, as shown in Figure 2(b). Schizophrenia patients aged 60 years and over exhibited weak enhancement in response to PS over the entire frequency range, and small decreases of Z-score could be seen at the harmonic frequency over 30 Hz. Similar frequency characteristics were also obtained with 7 Hz and 10 Hz PS.

In the current study, we hypothesized that schizophrenia is associated with decreased Z-scores at fundamental and harmonic frequencies in the whole range, and that aging changes the degree of this decrease in both the alpha frequency band and the harmonic frequencies in the gamma band. We used the following indices to test this assumption.

Index A: averaged value calculated from Z-scores at fundamental and harmonic frequencies except the alpha and gamma frequency bands.

Index B: value subtracted minimum Z-score in alpha frequency band from averaged Z-score at harmonic frequencies in gamma frequency band.

Index A reflects the Z-scores at fundamental and harmonic frequencies without enhancement or suppression at the alpha and gamma frequencies. Index B reflects the difference in Z-scores between two values at alpha and gamma frequencies, which becomes smaller in older subjects and patients because of a lack of suppression in the alpha frequency band and a decrease of Z-scores of the harmonic frequency in the gamma band. Here, the frequency at which the alpha wave was most suppressed is defined as the minimum Z-score exhibiting maximum suppression in the alpha band (8∼13 Hz). In the 6 Hz PS condition, Index A can be calculated as the average of Z-scores at 6, 18, 24, 30 Hz. Index B can also be calculated by subtracting the minimum Z-score in the alpha band from Z-scores at 36 Hz.

We then calculated these indices for the healthy subjects and schizophrenia patients, and performed Tamhane's multiple comparisons among three groups (healthy subjects aged between 20 and 30 years, healthy subjects aged 60 years and over, and schizophrenia patients aged 60 years and over). The results in 6, 7 and 10 Hz PS are shown in Figure 3. The results revealed a significant difference between both healthy subject groups and schizophrenia patients in Index A except between healthy subjects aged between 20 and 30 years and schizophrenia patients aged 60 years and over at 7 Hz PS. In contrast, Index B revealed an age-related difference.

4. **Discussion.** The results revealed the frequency characteristics of Z-scores in response to 6 Hz among three groups: healthy subjects over 60, healthy subjects aged between 20 and 30 years, and schizophrenia patients over 60, as shown in Figure 2. Three frequency characteristics were also observed in response to 7 Hz and 10 Hz PS. Here we focus on the results in response to 6 Hz PS, because 6 Hz PS is the lowest stimulus frequency among the three listed above, and is a frequency at which many harmonic components appear.

In the younger healthy subjects, prominent peaks were observed at fundamental and all harmonic frequencies, except the second harmonic frequency (12 Hz, $2f_0$). These results indicate that alpha suppression by PS causes a decrease in Z-scores because the second harmonic is included in the alpha frequency band. The central frequency of alpha components in the group aged between 20 and 30 years was close to the second harmonic frequency, and Z-scores at $2f_0$ were susceptible to alpha suppression. However, we found

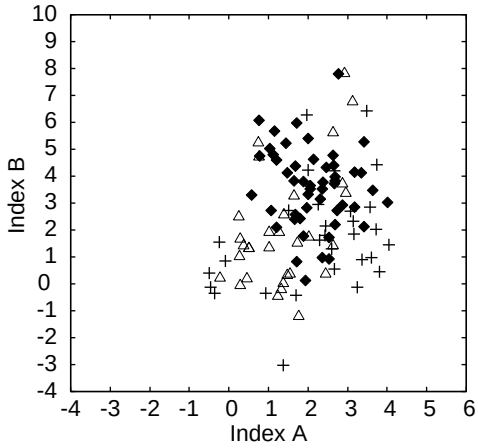
that enhancement by PS was greater than alpha suppression, reflected in the positive value of the Z-scores. Alpha suppression was not observed in the older healthy subjects group. It has been well established that alpha peak frequency decreases with age [1]. Accordingly, if the alpha peak is far away from the second harmonic frequency, then the effects of suppression at the second harmonic frequency would be expected to be weakened. In contrast, in the gamma frequency band, decreased Z-scores would be expected.

In the schizophrenia group, Z-scores at fundamental and all harmonic frequencies were small compared with the healthy groups. Moreover, no alpha suppression was observed, but a decrease in Z-scores in the gamma band was found in the older healthy group. Many studies have reported a relationship between gamma oscillation in EEG and either schizophrenia or aging [11,12]. Krishnan et al. reported SSVEPs in schizophrenia at seven different stimulation frequencies (4, 8, 17, 20, 23, 30 and 40 Hz) [14]. According to their results, both healthy subjects and patients exhibited an inverse relationship between the power and frequency of stimulation. Schizophrenia patients exhibited reduced signal power compared with healthy control subjects in the beta and gamma frequencies of stimulation. Our current results in the gamma frequency are in accordance with these previous findings. Werkle-Bergner et al. recorded EEG during a simple choice-reaction task requiring discrimination of squares and circles of different sizes [20]. Although this previous study differed from the current experiment in the use of a discrimination task, the researchers reported that older adults exhibited smaller increments in evoked gamma power with increasing stimulus size compared with younger adults.

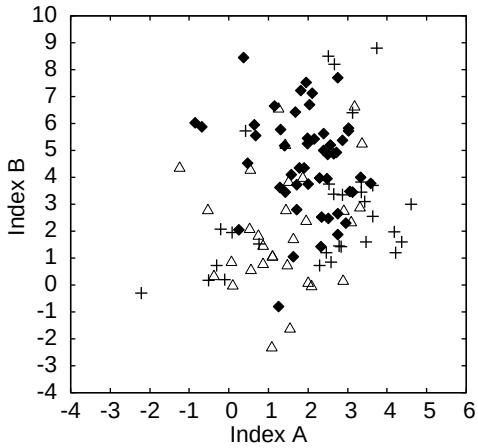
In the current study, we performed statistical analysis using two novel indices. For all PS frequencies (6 Hz, 7 Hz and 10 Hz) except between healthy subjects aged between 20 and 30 years and schizophrenia patients aged 60 years and over at 7 Hz PS, healthy participants (both the older and younger groups), and schizophrenia patients exhibited a significant difference in Index A. Index B revealed a significant difference between the younger subjects and both the older healthy subjects and the patient group. These results revealed that Index A and Index B exhibited higher values for healthy and younger subjects, respectively. Overall, our findings indicate that these indices may be useful for evaluating schizophrenia and aging.

Additionally, we plotted the intraindividual data on a 2-D graph with these two axes to examine the ability of our method to provide indices of schizophrenia and aging, as shown in Figure 4. The results revealed three clusters corresponding to the three groups, although there was variability in each sample and extreme outliers in each cluster. These samples contributed to the large standard deviation shown in Figure 3 though the results still revealed a significant difference between the average values. From the results, it appears that younger healthy subjects, older healthy subjects and elderly schizophrenia patients were concentrated in the upper right, lower right, and lower left regions of the graph, respectively. Although we examined a relatively small number of young schizophrenia patients in the current study, these samples appeared to locate in the upper left region of the graph with small Index A values and large Index B values.

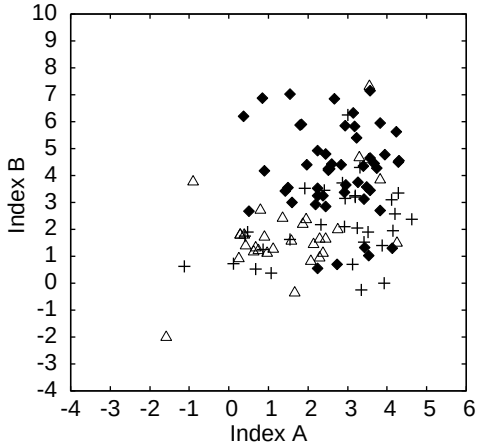
To test the advantages of our method, we compared the current results with the conventional method using the ratio of averaged amplitude during PS and at rest, which is commonly used as an indicator for comparing two subject's states. Figure 5 shows the averaged amplitude ratio in 20-30 year old subjects in the 6 Hz PS condition. The results revealed that the detection of the ratio was unstable, particularly in the higher order harmonics, such as $5f_0$ and $6f_0$. In contrast, the Z-scores in the current method (see Figure 2) revealed recognizable peaks at the fundamental and harmonic frequencies. EEG signals are highly variable over time, meaning that amplitudes at some frequencies exhibit extremely low or high local values, in conventional measurement methods. Therefore, the



(a) 6 Hz PS



(b) 7 Hz PS



(c) 10 Hz PS

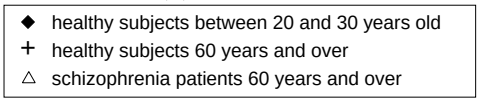


FIGURE 4. The scatter plot of two indices, Index A and Index B

averaged amplitude ratio is affected by local values. Using the current method, we propose that amplitude variation by these outliers does not have a large effect on Z-score, because the method is based on the rank order used in the Mann-Whitney U-test rather than the

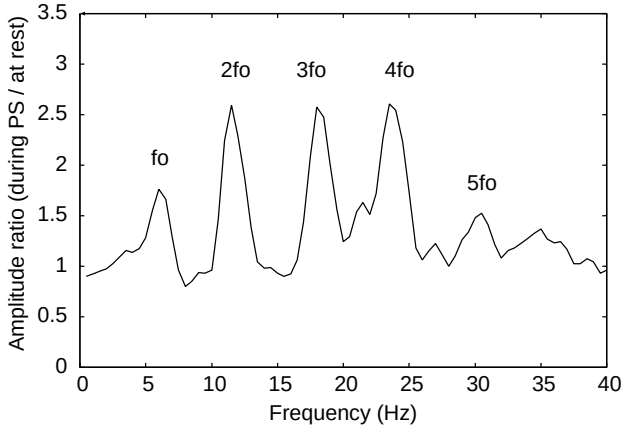


FIGURE 5. Amplitude ratio calculated by dividing the amplitude during PS by that at rest (PS 6 Hz)

TABLE 2. Maximum classification accuracies by the best threshold setting for each index. (Index A: Classification accuracy between younger and older healthy subjects. Index B: Classification accuracy between healthy subjects and schizophrenia patients.)

	Index A (%)	Index B (%)
6 Hz PS	78.8	72.1
7 Hz PS	76.3	77.0
10 Hz PS	78.8	73.8

original amplitude value. We propose that this is why the Z-scores in our method can be used to detect all fundamental and harmonic peaks stably. In summary, the current method can detect small differences between two signals, by considering the variability in EEG signals in short time analysis windows even when frequency amplitude spectrums are similar. Therefore, the ability to detect small differences between two signals with similar amplitude spectrum values may have applications for examining non-biological as well as biological signals. If the currently proposed indices are used for screening, our analysis may be helpful for medical assessment and earlier detection of diseases.

Finally, to test the performance of our method, we calculated the classification accuracy between younger and older healthy subjects, and between older healthy subjects and older patients with schizophrenia using an optimal threshold. The results revealed that both Index A and Index B exhibited performance of around 75%. Below, we report the values to demonstrate the effectiveness and efficiency of our results.

5. **Conclusions.** In the current study, we investigated a novel method for indexing frequency characteristics in the photic driving response for three groups (younger healthy subjects, older healthy subjects and older schizophrenia patients) in Z-scores, by evaluating enhancement and suppression by photic stimuli.

Here, we reported the results for 6, 7 and 10 Hz PS, which exhibited prominent responses in the fundamental and harmonic components that were sensitive to schizophrenia and aging. For schizophrenia patients, Z-scores over the frequency range under 40 Hz exhibited small values. In addition, no suppression in the alpha band or decreased Z-scores in the gamma band were observed in older subjects and patients.

We then defined two indices for evaluating schizophrenia and aging. Index A reflects average Z-scores at the fundamental and all harmonic frequencies, except the harmonics in the alpha and gamma bands over 30 Hz. Index B was defined as the subtraction of the minimum Z-score in the alpha band from the average of the Z-scores in the gamma band.

The results revealed a significant difference between both healthy groups and the schizophrenia group in Index A, except between healthy subjects aged between 20 and 30 years and schizophrenia patients aged 60 years and over at 7 Hz PS, and between the younger group and the two older groups in Index B. As such, these indices may provide useful criteria for evaluating the effects of schizophrenia and aging. Moreover, this method could be used to remove age-related bias in EEG evaluation.

In future research, we plan to investigate advanced indices that are more sensitive to disease and aging, which can be tested with other psychiatric disorders and a wider age range.

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