ABSTRACT

Electroencephalogram (EEG): It is used to diagnose, monitor, and manage neurophysiological disorders related to epilepsy and sleep disorders. The definition of sleep and wakefulness in polysomnography is also made with the EEG technique. The relationship between depression and sleep disturbances has been examined in many epidemiological and clinical studies. Clinical observations and studies suggest that the changes in sleep structure in depression are sensitive, even specific. This study aims to research the structural differences in sleep EEGs of healthy subjects and subjects with depressive disorder between their non-rapid eye movement (NREM), non-rapid eye movement (N2), and rapid eye movement (REM) stages by using the Itakura Distance Measure. In comparison between the N2 and REM epochs of the healthy subjects, the distance is short. In the comparison between N2 and REM epochs of depressed subjects with each other and healthy subjects, the distance has been found to be large. The study indicates that the sleep EEG of the patients differs in the N2 stage as much as it does in REM.

INTRODUCTION

Sleep is a physiologic, periodic resting state of the body in which the eyes are closed and sensations are diminished. Rather than an inactive phase of the body, sleep is a dynamic process and has many functions that help to sustain homeostasis and reconstruct the body and the central nervous system. Sleep is the primary function of the brain and plays an essential role in an individual's performance, learning ability, and physical movement.

Humans spend around one-third of their lives sleeping, and conditions such as insomnia and obstructive sleep apnea are frequent and can severely affect physical health. 50–70 million people suffer from sleep disorders in the United States. In addition, more than 90% of patients with depressive disorders suffer from sleep disorders. Sleep apnea is estimated to be common in 2–4% of adults and 1–3% of children. Approximately 33% of the world's population suffers from insomnia symptoms [1].

Changes in EEG may carry important clinical information. Accurate detection and characterization of such EEGs can be valuable for the clinical assessment of the neurological condition. The scoring of sleep is an important step in the investigation of sleep structure, the classification of diseases, and the selection of appropriate treatment applications.

There are four sleep stages: one for rapid eye movement (REM) sleep and three for non-REM (NREM) sleep. These stages are determined based on an analysis of brain activity during sleep, which shows distinct patterns that characterize each stage. The classification of sleep stages was updated in 2007 by the American Academy of Sleep Medicine (AASM). Before that, most experts referred to five sleep stages, but today, the AASM’s definitions of the four stages represent the consensus understanding of the sleep cycle [1].

The human body goes through two stages of sleep: (1) rapid eye movement (REM) sleep and (2) non-rapid eye movement (NREM) sleep; This sleep is further divided into three stages, N1-N3. Sleep quality and the time spent in each sleep stage may vary due to depression, aging, traumatic brain injuries, medications.

N1 (Stage 1), light sleep (5%): This is the lightest stage of sleep and begins with more than 50% of alpha waves being replaced by low-amplitude mixed waves.

N2 (Stage 2), Deeper Sleep (45%): This stage is characterized by the presence of sleep spindles, K-complexes, or both. Stage 2 sleep lasts approximately 25 minutes in the first cycle and becomes longer with each successive cycle, eventually accounting for approximately 45% of total sleep.

N3 (Stage 3), Deepest Non-REM Sleep (25%): This is considered the deepest stage of sleep and is characterized by signals with much lower frequencies and higher amplitudes, known as delta waves. This stage is the most difficult to wake up from.

REM (25%): REM is associated with dreaming and is not considered a restful sleep phase. Although the EEG resembles that of an awake person, the skeletal muscles are atonic and inactive, except for the respiratory muscles of the eyes and diaphragm, which remain active. This phase usually begins 90 minutes after falling asleep, and each REM cycle extends throughout the night. The first period usually lasts 10 minutes, and the last period lasts about an hour. REM is when dreaming occurs [2].

Depression is a common mood disorder that might cause a persistent feeling of sadness, a loss of interest, and impairments of memory and concentration. Depressed patients normally experience cognitive impairment and suffer long and severe emotional depression. In severe cases, some patients will experience paranoia and illusions. As a result, diagnosing depression in its early curable stages is critical and may save a patient’s life [3].

The symptoms of depression appear mostly as behavioral ones. Normally, the help of psychiatrists or counselors is sought for diagnosis and treatment. Identification of depression in its early stages is crucial to preventing it from reaching a severe and irreversible state. The electroencephalogram (EEG) may be used as a tool for making an objective diagnosis of depression [4].

EEG is widely used in brain function studies. Recently, many studies [5, 7, 8] have demonstrated the relationship between depression and EEG. Many studies [7, 9, 10, 11, 12, 14] showed asymmetries in the EEG of depressed patients over the frontal cortex. Moreover, the EEG showed significant differences between healthy subjects and depressed patients in many research studies [6, 14, 15, 16].

Research on the human brain is being carried out intensively to understand the mechanisms underlying depression. The most commonly used diagnosis of depression is a scale-based interview with a psychologist or psychiatrist. Current depression detection methods are labor intensive and results depend on the doctor’s experience. As a result, many patients with depression are not accurately diagnosed and do not receive optimal treatment. Therefore, finding appropriate and effective methods for detecting depression is an important research topic. With the latest advances in technology, the use of physiological data for the diagnosis of mental disorders opens a new avenue for an objective and accurate tool for detecting depression. Among all kinds of physiological data, electroencephalogram (EEG) reflects emotional human brain activity in real time [3].

In Article 4, recent studies on computer-aided diagnosis (CAD) of depression using EEG signals are presented. Chaos theory and nonlinear dynamical methods are used to extract the bispectrum, power spectrum, phase entropies, wavelet energy and entropy, correlation dimension, fractal dimension, largest Lyapunov entropy, and approximate entropy [4].

Ahmadlou et al. [17] investigated EEGs obtained from patients with major depressive disorder using wavelet-chaos methodology.
Puthankattil et al. [18] extracted relative wavelet energy parameters from the discrete wavelet transform (DWT) coefficients and used ANN to classify the EEG signal into normal and depressed classes. Ahmadiou et al. [19] presented a novel nonlinear method for the analysis of brain dynamics.

Faust et al. [20] present a depression diagnosis support system using entropies extracted from the wavelet packet decomposition coefficients of the EEG signal.

Bachmann et al. [21] compared the linear and nonlinear methods for depression detection based on EEG signals. Even though a number of papers have been published using nonlinear methods, there are other nonlinear methods [21–46] that are worth exploring for the EEG-based diagnosis of depression.

Sleep disturbances are common in depression. It has been estimated that more than 90% of patients with major depressive disorder have concurrent sleep problems [47–49]. Sleep problems may manifest as insomnia, hypersomnia, early morning awakenings, frightening dreams, or excessive sleepiness in the daytime in depressive patients [50]. Soehner et al. have found that the presence of insomnia is associated with more severe depression [51]. It has been observed that chronic sleep disturbances are associated with the recurrence of depressive episodes and suicide [52–53]. In polysomnographic examinations, it is observed that more time is needed to fall asleep, there is a shortened REM latency and a longer duration of the first REM period, there is less slow-wave sleep, and there is increased wakefulness during sleep in depressive patients [54–55]. Armitage et al. [56] have reported that there was a difference in terms of wave amounts of fast and slow frequencies between the sleep EEGs of depressed and healthy subjects [54]. Röschke reported that there were differences in theta and beta activity during an NREM sleep period [57].

Figure 1 shows sample normal (a) and depression (b) EEG data.

A number of studies have used autoregressive (AR) models to detect changes in the EEG signal [58–60]. Based on the AR model parameters, Itakura distance has been used for automatic sleep stage classification effectively [58]. The Itakura distance measure used for such quantification requires the same order for the AR models in all EEG segments. In their pilot study, Estrada et al. investigated EEG and EOG signals acquired from 10 sleep apnea patients undergoing overnight polysomnography and used the Itakura distance to classify sleep stages [58].

To our knowledge, no previous study has investigated the structural differences of sleep EEGs with the Itakura Distance between depressive patients and healthy subjects. In this preliminary study, we aimed to clarify more specific points in EEG signals by comparing signals between depressive patients and healthy subjects. To do this, EEG signals from every different sleep stage are isolated and compared with each other. This study aims to research the structural differences between healthy subjects and subjects with depressive disorder by using the Itakura Distance Measure.

**MATERIALS AND METHODS**

**A- Subjects:** The study group consists of two male subjects (H1 and H2) (ages 23–24) with major depressive disorder and two male subjects (D1 and D2) (ages 23) without any psychiatric complaints or findings who were under polysomnographic examination in the Sleep Research Center of Gülhane Training and Research Hospital Department of Psychiatry. The subjects were not on any medication. In sleep records, a polysomnographer named Somnostar Alpha is used. The polysomnographer uses a 0.5–35 Hz filter and takes samples at 200 Hz (low-Hz

**Figure 1.** Sample normal and depression EEG data.
The EEG record obtained from the polysomnographer is evaluated using Matlab software (The Mathworks, Massachusetts, USA).

B- Polysomnographic examination: In polysomnographic records, two EEGs (C3 and A2, C4 and A1), two EOGs (left and right), two EMGs (mental or submental and tibial muscular), and an ECG are used. EEG records were evaluated and scored by a psychiatrist. The first night is regarded as adaptation night. Each polysomnographic examination is scored in epochs lasting 30 seconds, which consist of 6000 spots. The Itakura distance was calculated by using the epoch corresponding to the first N1 of H1 and the epoch corresponding to the first N1 of H2. Later, the calculation of the Itakura distance was done by comparing the second corresponding N1 epoch of H1 with the second N1 epoch of H2. The calculated Itakura distances were graphed and interpreted visually. This idea was used separately for all other phases, and the Itakura distances were calculated for each phase and presented in a graphic form. Epochs with artifacts were not evaluated. The C3-A2 record taken on the second night is used for sleep EEG data.

C- Statistical method: In parametric modeling, a mathematical model is fitted to a sampled signal in order to study a time series. The AR modeling technique can be formulated either in the frequency domain as a spectral matching problem or in the time domain as a linear prediction problem. The code written in MATLAB was developed to calculate the Itakura distance by the researchers in the study.

Statistical Analysis
There are two methods to quantify the differences between the two waveforms. The first of these is a spectral distance measure, which measures the difference between the power spectra of two waveforms. The second method is called the Itakura distance measure, which measures the distance between the AR parameter vectors of the two waveforms. This method has been successfully applied in speech processing applications to measure the distance between two speech utterances modeled as AR processes [61]. A more extensive account of these and other distance measures can be found in [62].

Itakura distance measure
Let the AR model of a segment of baseline EEG be given by:

\[ x(t) = a_0 x(t - 1) + a_1 x(t - 2) + \ldots + a_p x(t - p) + e(t) \]  \hspace{1cm} (1)

and that of a segment of EEG during the experiment be given by:

\[ y(t) = b_0 y(t - 1) + b_1 y(t - 2) + \ldots + b_p y(t - p) + v(t) \]  \hspace{1cm} (2)

Here, we assume that the optimal order for both segments of EEG is p. Let the optimal AR parameter vector in each case be given by, \( \alpha = (1, a_1, \ldots, a_p) \) and \( \beta = (1, b_1, \ldots, b_p) \), respectively. The Itakura distance measure to test how far \( \beta \) is from optimality if it is used to model \( x(t) \) is defined as,

\[ d_i(\alpha, \beta) = \log \frac{\beta^T R_x \beta}{\alpha^T R_x \alpha} \]  \hspace{1cm} (3)

[61] where \( R_x \) is the autocorrelation matrix of \( x(t) \) at given by:

\[ R_x = \begin{bmatrix} r_x(0) & r_x(1) & \ldots & r_x(p) \\ r_x(1) & r_x(0) & \ldots & r_x(p - 1) \\ \vdots & \vdots & \ddots & \vdots \\ r_x(p) & r_x(p - 1) & \ldots & r_x(0) \end{bmatrix} \]  \hspace{1cm} (4)

The individual elements of the above matrix denote the autocorrelation of \( x(t) \) at different lags, and they can be estimated as follows:

\[ r_x(k) = \frac{1}{N} \sum_{n=1}^{N-k} x(n)x(n + k), \quad k = 0, 1, 2, \ldots, p \]  \hspace{1cm} (5)

Similarly, the AR parameter vector \( \alpha \) can be tested to see how well models \( y(t) \) by defining another Itakura distance measure given by

\[ d_i(\beta, \alpha) = \log \frac{\alpha^T R_y \alpha}{\beta^T R_y \beta} \]  \hspace{1cm} (6)

A symmetric distance measure can then be defined by combining the above two distance measures as follows:

\[ d_i(\alpha, \beta) = \frac{1}{2} \left[ d_i(\alpha, \beta) + d_i(\beta, \alpha) \right] \]  \hspace{1cm} (7)

[61-63].

In this study, each sleep EEG epoch was modeled with the AR(4) model, and the parameters were estimated based on that (optimal AR model order determination using the Akaike Information Criterion (AIC)).

The parameters in the AR model were considered to be the parameters that changed over time and were estimated by the Kalman filter. Using a time-varying autoregressive model, we take advantage of the fact that the EEG signals are not always the same. The time-varying coefficient of the AR model is estimated using the Kalman filter (see Appendix).

Two healthy subjects and two subjects with depression have been studied. Each epoch is compared with the same-numbered epoch of the other patient. Using the Itakura Distance Measure, it is determined whether there is a structural difference between epochs or not. Itakura
Distance Measure uses AR (4), which is one of the time-series models, and the autocorrelations in each epoch.

According to this distance measure, the comparison of REM epochs for H1 and H2 is shown in Figure 2.

The comparison of the N2 epochs of H1 and H2 is shown in Figure 3.

The comparison of REM epochs for D1 and H1 is shown in Figure 4.

Figure 2. The comparison between the REM epochs of subjects H1 and H2.

Figure 3. The comparison between period 2 epochs of the healthy subjects H1 and H2.

Figure 4. The comparison between the REM epochs of subject number one with depressive disorder and the healthy subject number one.

Figure 5. The comparison between period 2 epochs of subject number one with depressive disorder and the healthy subject number one.

The comparison of the N2 epochs of D1 and H1 is shown in Figure 5.

The comparison of the N2 epochs of D1 and H2 is shown in Figure 6.

The comparison of N2 epochs in D1 and D2 is shown in Figure 7.
RESULTS AND DISCUSSION

The current study found that the distance was short when the N2 and REM epochs of the healthy subjects were compared, respectively (Figure 2 and Figure 3). This result shows that these two wave models are structurally similar to each other. The distance has been found to be large when the N2 and REM stages of depressive subjects are compared with those of healthy subjects (Figures 4 and Figures 5). This result shows that the EEG signals of the subjects in the two groups are structurally different from each other. It is known that sleep disturbances are common in depression patients. It is accepted that approximately 5% of the total sleep time is N1, 50% is N2, and 20% is N3 and N4 sleep. The remaining 25% is REM sleep. Since N2 and REM stages comprise 65–80% of total sleep, they provide important clues in understanding the quality of sleep.

The findings obtained in our study are compatible with the literature. Polysomnographic studies in sleep studies have shown that depressed patients require more time to fall asleep, have a shorter REM latency and a longer first REM period, increased REM intensity in sleep, decreased slow-wave sleep, and increased wakefulness during sleep [54][55]. Armitage et al. [56] found a difference in the amount of waves of fast and slow frequencies between the sleep EEGs of depressed and healthy subjects [54]. Röschke reported differences in theta and beta activity during a NREM sleep period [57].

Patients with depression show characteristic sleep-EEG changes [72], including:

(i) Impaired sleep continuity
(ii) Disinhibition of REM sleep: shortened REM latency or sleep-onset REM periods
(iii) Changes in non-REM sleep (decreased stage N2)

CONCLUSION

The study indicates that the sleep EEGs of the depressed patients differ in N2 and REM stages from those of healthy subjects with the use of the Itakura Distance Measure. This method may be used as an indicator to assist psychiatrists in sleep research and clinical diagnosis. By combining this information with clinical findings, it may be easier for the psychiatrist to make a diagnosis based on objective numerical data.

The major limitation of this study is its small sample size. Further studies with larger sample sizes may reveal structural differences more accurately. This can be an important resource for researchers and psychiatrists evaluating patients in the clinical setting in terms of making objective decisions based on quantitative data.

AUTHORSHIP CONTRIBUTIONS

Authors equally contributed to this work.

DATA AVAILABILITY STATEMENT

The authors confirm that the data that supports the findings of this study are available within the article. Raw data that support the finding of this study are available from the corresponding author, upon reasonable request.

CONFLICT OF INTEREST

The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.
ETHICS

There are no ethical issues with the publication of this manuscript.

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Appendix

Let \( y \) be the one-channel EEG signal. We suppose that an AR can describe the EEG. The AR model has found many applications in EEG analysis, although EEG is a non-stationary signal [64]–[68]. The AR model is given as:

\[
y(t) = b_1 y(t-1) + b_2 y(t-2) + \ldots + b_p y(t-p) + v(t)
\]

where \( p \) is the order of the model. Since the EEG is a non-stationary signal, we let the AR parameter vary with time.

\[
y(t) = b_{1t} y(t-1) + b_{2t} y(t-2) + \ldots + b_{pt} y(t-p) + v(t)
\]

or in vector notation

\[
y(t) = \varphi(t) \theta(t) + v(t)
\]

where \( \varphi(t) = [y(t-1), y(t-2), \ldots, y(t-p)]^T \) is a px1 vector and \( \theta(t) = [b_{1t}, b_{2t}, \ldots, b_{pt}]^T \). The vector \( \theta(t) \) contains the AR parameters and varies in time:

\[
\theta(t) = \theta(t-1) + w(t)
\]

where \( w(t) \) is Gaussian noise with zero mean and covariance \( R_1(t) \). This describes an AR model for the EEG signal with a time-varying coefficient in state-space form. To estimate those coefficients, we use the KF. Consider the dynamical linear model given as:

\[
y(t) = \varphi(t)^T \theta(t) + v(t)
\]

\[
\hat{\theta}(t) = \hat{\theta}(t-1) + w(t)
\]

where \( \hat{\theta}(t) \) is a px1 state vector at time \( t \), \( y(t) \) is an observation at time \( t \), and \( w(t) \) and \( v(t) \) are the states and observation noise which are assumed white and Gaussian, respectively. The KF is given with the following equations:

\[
K(t) = [P(t|t-1) \varphi(t)] [\varphi(t)^T P(t|t-1) \varphi(t) + R_1(t)]^{-1} (A3)
\]

\[
P(t|t-1) = P(t-1|t-1) + R_1(t) (A4)
\]

\[
e(t) = y(t) - \tilde{y}(t) (A5)
\]

\[
\tilde{y}(t) = \varphi(t)^T \hat{\theta}(t|t-1) (A6)
\]

\[
\hat{\theta}(t) = \hat{\theta}(t|t-1) + K(t)e(t) (A7)
\]

\[
P(t|t) = P(t|t-1) - K(t) \varphi(t)^T P(t|t-1) (A8)
\]

where \( K(t) \) Kalman gain [69-71].