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Nonlinear analysis of EEGs of patients with major depression during different emotional states

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ABSTRACT

Background: Although patients with major depressive disorder (MDD) have dysfunctions in cognitive behaviors and the regulation of emotions, the underlying brain dynamics of the pathophysiology are unclear. Therefore, nonlinear techniques can be used to understand the dynamic behavior of the EEG signals of MDD patients.
Methods: To investigate and clarify the dynamics of MDD patients' brains during different emotional states, EEG recordings were analyzed using nonlinear techniques. The purpose of the present study was to assess whether there are different EEG complexities that discriminate between MDD patients and healthy controls during emotional processing. Therefore, nonlinear parameters, such as Katz fractal dimension (KFD), Higuchi fractal dimension (HFD), Shannon entropy (ShEn), Lempel-Ziv complexity (LZC) and Kolmogorov complexity (KC), were computed from the EEG signals of two groups under different experimental states: noise (negative emotional content) and music (positive emotional content) periods.
Results: First, higher complexity values were generated by MDD patients relative to controls. Significant differences were obtained in the frontal and parietal scalp locations using KFD ($p<0.001$), HFD ($p<0.05$), and LZC ($p=0.05$). Second, lower complexities were observed only in the controls when they were subjected to music compared to the resting baseline state in the frontal ($p<0.05$) and parietal ($p=0.005$) regions. In contrast, the LZC and KFD values of patients increased in the music period compared to the resting state in the frontal region ($p<0.05$). Third, the patients' brains had higher complexities when they were exposed to noise stimulus than did the controls' brains. Moreover, MDD patients' negative emotional bias was demonstrated by their higher brain complexities during the noise period than the music stimulus. Additionally, we found that the KFD, HFD and LZC values were more sensitive in discriminating between patients and controls than the ShEn and KC measures, according to the results of ANOVA and ROC calculations.
Conclusion: It can be concluded that the nonlinear analysis may be a useful and discriminative tool in investigating the neuro-dynamic properties of the brain in patients with MDD during emotional stimulation.

1. Introduction

Major depressive disorder (MDD) is a very common psychiatric mood disorder that affects 15–20% of the population [1]. The major signs of MDD are loss of interest, energy and pleasure; a depressed mood; disturbances in sleep; and recurrent suicidal thoughts [2]. Moreover, depressed patients exhibit some symptoms related to cognition, such as low concentration, difficulty in decision making and focusing, according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) diagnostic criteria for MDD [3]. However, the underlying neural activities of these types of functional or cognitive impairments are still under investigation [4].

Therefore, there have been many electroencephalogram (EEG) studies in groups of patients diagnosed with MDD to compare them with healthy controls. Most of these studies have investigated resting state brain activity in MDD patients with the help of conventional linear techniques, such as spectral domain analysis or waveform investigations [5-8]. However, the complex dynamic variations in an EEG time series cannot be discriminated by linear techniques [9]. Moreover, because EEG is a complex and irregular signal with nonlinear behaviors and without a linear relation between cause and effect, a significant number of complexity estimators, such as largest Lyapunov exponents (L1), correlation dimension (D2), mutual information, Shannon entropy (ShEn),

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sample entropy, approximate entropy (ApEn), Lempel-Ziv complexity (LZC), fractal dimension (FD), and Kolmogorov complexity (KC), have been proposed as more appropriate techniques for understanding the underlying dynamics of brain activity with unknown parameters [4]. These estimators are known as nonlinear measures because they reconstruct an attractor from an EEG by characterizing its dynamic behaviors using the dimension of a signal, which gives the degrees of freedom of system, or using entropies that reflect the unpredictability of the signals' dynamics [10].Therefore, over the past 40 years, these measures have been applied to EEG data for characterizing random-appearing series of patterns across time in different physiological states, such as Alzheimer's disease [11-13], dementia [14], epilepsy [15-17], schizophrenia [18-20] and obsessive–compulsive disorder [21].

It must be taken into account that all of these estimators reflect the complexity with different approaches, such as dimensional complexity, regularity and predictability [22,23]. While the D2 and Higuchi FD are related to dimensional complexity, the ApEn is a statistical calculation of regularity of a signal. Some other complexity measures, such as the L1 and entropies, focus on determining the irregularity and predictability of signals. The randomness or degree of irregularity (chaoticness) of finite sequences can be investigated by the LZC and KC. Among all of these complexity estimators, traditional estimators (D2 and L1) are the oldest and have limitations because of their requirement for a noise-free, long and stationary time series [24]. Alternatively, entropy-based complexity estimators calculated in either frequency domain (spectral entropy) or a time series (ShEn, ApEn) have the advantage of anti-noise ability [25]. On the other hand, Katz fractal dimension (KFD), Higuchi's fractal dimension (HFD) and Petrosian FD algorithms simply and quickly estimate the self-similarity of a time interval directly in the time series [26].

Although most of the attention has been paid to analyses of EEGs in MDD patients based on linear techniques [5-8], there have been a small number of studies on nonlinear EEG analysis of patients [4,19,27-29]. To the best of our knowledge, Nandrino et al. [27] conducted the first nonlinear EEG analysis study of MDD patients. They calculated the D2 and found a negative correlation between the symptoms of MDD and its complexity. Li et al. [19] reported that MDD patients exhibited increased LZC values in anterior brain regions when the values were compared with corresponding values in controls. Ahmadlou et al. [28] applied HFD and KFD analyses to both the full band and sub-bands of EEG data in patients with depression and in controls. According to their reports, elevated complexities in patients were particularly observed in the beta and gamma sub-bands of the frontal area in EEG recordings. The same authors proposed a new nonlinear measure called spatiotemporal analysis of relative convergence (STARC) for investigating brain dynamics based on relative EEG convergence in different loci [29]. They found significant STARC differences between male and female MDD patients. Puthankattil and Joseph [30] used signal entropy values to classify the EEG signals of patients with depression and control subjects. In another of their works, the ApEn values of MDD patients and healthy controls were compared [31]. They reported decreased ApEn values, indicating the predictability and regularity of EEG recordings in patients with depression. In another study, Hosseinifard et al. [32] compared the performance of different classification algorithms that used some EEG nonlinear features, such as detrended fluctuation analysis (DFA), HFD, D2, and L1 for discriminating MDD patients from controls. They reported high classification accuracy when the linear discriminant analysis was used with extracted nonlinear features. Similarly, probabilistic neural network-based high classification accuracy in the discrimination of MDD patients and control subjects was obtained by Faust et al. [33]. They used entropy values estimated from the EEG signals of two groups. To compare the depression-detecting ability of linear and nonlinear EEG features, Bachmann et al. [34] calculated the HFD values of EEG signals and found high discrimination accuracy when nonlinear methods were used. To show complex dynamic variations in the EEG signals, computer-aided diagnosis of depression using EEG signals has been proposed for psychiatrists as a tool to confirm their clinical diagnosis [9]. Finally, in a very recent study, Bachmann et al. [4] investigated the LZC values in MDD patients. Their results revealed increased complexities in MDD patients compared to normal controls in all of the investigated brain regions.

Although all of these studies imply that nonlinear methods can be useful for analyzing EEG signals in patients with depression, the reported complexity results are restricted only to the analysis of resting EEG recordings. Complexity approaches have not yet been applied to the EEG signals of MDD patients during emotional processing. It is known that depressed patients have impairments in cognitive functions and the regulation of emotions [35]. However, the underlying factors of the relationship between depression and these impairments are largely unknown. This issue has been investigated in previous studies that explored facial emotion recognitions [35-37]. The processing of emotional stimuli was found to be negatively biased in MDD patients, meaning that patients focus more on negative facial expressions than on neutral or positive expressions and produce more rapid and prominent responses during negative ones [35-38]. These findings are consistent with the results of neuroimaging studies that showed decreased brain activation (in ventral striatum and putamen) to positive stimuli in MDD patients relative to control subjects [39-41]. In MDD patients, attenuated emotional reactivity to positive emotional stimuli is called positive attenuation hypothesis, and increased emotional reactivity to negative emotional stimuli is known as negative potentiation hypothesis [42]. Most of these previous studies investigated emotional processing in MDD patients using neuroimaging findings or self-report evaluations. However, it has been reported that temporal dynamics play an important role in understanding the neural structure of emotional processing [43]. To evaluate the impairments in emotional responses of MDD patients in the present study, which is the first of this kind to our knowledge, EEG data were recorded and analyzed by nonlinear techniques during both rest and different emotional auditory stimulation periods, such as listening to classical Turkish music (CTM) and listening to noise. The primary goals of this research were to determine whether complexity measures, such as ApEn, ShEn, KFD, HFD and KC, can be used to discriminate MDD patients from control subjects and whether the emotional processing in the EEG signals can be measured by complexity differences between patients and controls. The originality of this research was to investigate several complexity and entropy features in the EEG signals, obtained from different brain regions, of MDD patients during different emotional states. We designed a new study protocol to test the hypothesis that MDD patients have differences in brain complexities during different emotional stimulations and show a bias toward negative emotional stimuli. In particular, we hypothesized that patients would have increased brain complexities both at rest and during noise stimulation periods.

2. Methods

2.1. Participants and experimental protocol

The groups in this study were healthy control subjects and MDD patients. There were 15 control subjects, who had no history of any neurological, psychiatric, or psychological disorder or