



In-phase matrix profile: A novel method for the detection of major depressive disorder

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ABSTRACT

Background and Objective: Major depressive disorder (MDD) is the leading cause of disability worldwide. Reliable detection of MDD is the basis for early and successful intervention in treating the disorder and preventing disability. We introduce a novel feature extraction method, the in-phase matrix profile (pMP), which is specifically adapted for electroencephalographic (EEG) signals. **Methods:** The pMP characterizes general self-similarity of an EEG signal. The method extracts overlapping one-second-long subsegments from an EEG signal segment, calculates Euclidean distances between all possible subsegment pairs, and subsequently uses the distance values, where subsegments are most in phase, to calculate pMP. The method was applied to the resting-state eyes-closed EEG data of an MDD group and age- and gender-matched healthy controls (66 subjects). Higuchi's fractal dimension (HFD) values were calculated for the same groups for comparison. **Results:** Both pMP and HFD values were higher in MDD. The pMP successfully distinguished MDD and control group in all 30 EEG channels. In contrast, HFD resulted in statistically significant group distinguishability in 13 (43%) channels located mainly in the central region of the head. The highest classification accuracy for pMP was 73% and for HFD 67%. **Conclusion:** The present article shows that pMP outperforms HFD in detecting MDD and is a promising method for future MDD studies. **Significance:** The pMP is a sensitive parameter-free method for detecting MDD that can be used in future studies and is a potential method to reach clinical use for diagnosing MDD.

1. Introduction

Depression is a common disease that, depending on its severity, can strongly affect a person's daily ability to cope and even lead to suicide. Approximately 280 million people worldwide suffer from major depressive disorder (MDD, also referred to as clinical or unipolar depression), which makes it the leading cause of disability in the world [1], and the number has constantly been rising. Preliminary evidence indicates that the recent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which caused the COVID-19 pandemic, has also significantly increased the number of people suffering from MDD [2] and the extent of the full impact of the pandemic on mental health is yet to be seen.

There are different medications and treatment therapies available for MDD. However, many people do not get the help they need, especially in less developed countries [3]. Treatment availability is limited due to several factors, such as the small number of healthcare professionals, misdiagnosis, and the continuing social stigma associated with mental

health problems. At present, MDD diagnosis and treatment monitoring are based on clinical interviews and questionnaires, which depend on the health professionals' experience and the answers given by the examinee. Therefore, the health assessment is based on subjective symptoms, and the conclusions may not be objective. No method, which provides an evaluation based on objective symptoms, is yet in use in clinical practice.

Neuronal activity in the brain is related to all physiological and emotional processes in a human. The brain's bioelectrical signals describe the state of the brain [4], and electroencephalography (EEG) can detect changes in the brain's bioelectric activity. In the case of mental disorders, including MDD, changes in the brain's electric activity occur [5–7], and EEG is a method suitable for detecting bioelectric changes related to mental disorders [7]. The alterations in EEG may appear even before the changes in well-being do, and the EEG features can be the input for an objective tool for assessing the state of the brain. EEG is also appropriate due to its portability and relatively low cost.

The EEG method has long been used to detect various mental

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disorders in research studies [4,7]. Several authors have used different linear EEG methods to detect various brain states/disorders [7–11]. Still, due to the complex nonlinear nature of the EEG signal [12], different nonlinear methods have been engaged to provide more information about mental health. In MDD studies, much attention has been paid to the alpha rhythm, and attempts have been made to find a possible indicator of MDD using only the alpha frequency. Initially, frontal alpha asymmetry [13] was promising, but today it has yielded unreliable results [10,14]. It has also been found that MDD can lower the alpha peak frequency, increase the coefficient of variation [15], and functional connectivity in the alpha frequency band [16].

Nonlinear methods such as fractal dimensions, detrended fluctuation analysis, and correlation dimensions are used to calculate EEG signal complexity measures that have been shown to be indicative of epilepsy [17,18], schizophrenia [19], Alzheimer's [20], and MDD [21–25]. It has been found that the values of features characterizing the complexity of EEG signals are higher in MDD, including fractal dimension estimate called Higuchi's fractal dimension (HFD). HFD is one of the most used nonlinear methods to study MDD and has shown some promising results in distinguishing between MDD and control subjects [9,23,24,26–28]. Although previous research has provided information in which direction EEG features' values in MDD typically change, the distinctiveness of independent groups has been insufficient. The results have not been consistent enough to reach clinical use. Therefore, there is a continuing need to find an even more sensitive method or combination of methods for evaluating the presence or the severity of MDD.

In this paper, we continue this line of research and propose a novel method to characterize the brain's state and help identify MDD. The hypothesis is that a method using a novel approach for considering the temporal complexity of the EEG signal can provide higher sensitivity in the detection of MDD than the previously used methods. We developed the method primarily for resting-state EEG signals, and it describes the complexity of EEG signals via general self-similarity. The proposed in-phase matrix profile (pMP) is a simple-to-use parameter-free method calculated directly in the time domain. The method is based on the Matrix Profile (MP) idea introduced by Yeh et al. [29], which divides a time signal into subsegments and compares the similarity between those subsegments, searching for the best matching subsegments. Unlike in the classic MP, in our method, the length of the subsegments is fixed, and all EEG subsegments that are in phase with each other are used in the calculations of pMP. We compare the proposed novel pMP with the widely used approach based on Higuchi's fractal dimension (HFD) [28].

The remainder of the paper is organized as follows: Section II introduces the classical methods and terminology on which pMP is based and explains the need to modify these methods for resting-state EEG signals. Section III describes the EEG data collection procedure, data preprocessing and explains the calculation procedure of our proposed method according to the preprocessed data. Section IV presents the MDD and control group results for pMP and HFD. Section V explains the nature and limitations of the results obtained and suggests the direction of future research. Finally, Section VI draws the conclusion.

2. Background and related work

2.1. Data mining

As the overall volume of data around us snowballs, different data mining algorithms are evolving in the same way. An essential part of data mining is similarity search, where large amounts of data are searched for patterns or trends in the data set. Popular methods include the distance range query (finds all elements in a data set where the distance from the query to set members is less than a given threshold) and the k-nearest neighbor query (retrieves k elements from a dataset with the lowest distances to query). Those methods have been used in many fields, such as marketing analysis [30], text and document mining [31], and multimedia analysis [32]. The input (query) can be an image,

a word, a sound, a traffic sign, sales data, electricity consumption, etc., and the algorithm searches for a match that meets the specified requirements for that query in a given database.

The EEG signal can be viewed as a large amount of data, and thus data mining algorithms can also be used for EEG signals. Mining EEG signals have been used when working with evoked potentials or looking for a specific pattern, such as blinking [33], exploring the brain's pathways (synchronization likelihood) [34,35], or in sleep studies [36].

2.2. Matrix profile and its limitations in EEG data

In 2016, Yeh et al. [29] presented a new fast similarity search algorithm for data mining, Matrix Profile (MP), which can quickly find from a tremendous amount of data, e.g., electricity consumption over the years, accurate matches where consumption has been most similar or has changed from usual. The advantage of this method is that it is unnecessary to set a threshold below which comparable elements can be considered a match. That allows the MP to be used for time series without fear that some information might go unnoticed due to an unsuitable threshold set. MP is an effective way to find similarities and differences in time signals with a quasi-periodic pattern. The method detects a previously unknown (or known) repeating pattern, a motif, from the time signal. Recently, MP has been used to analyze physiological signals, e.g., electrocardiographic signals (ECG) [37]. In the case of ECG, the motif is a cardiac cycle, and the MP will be able to find anomalies, i.e., a discrepancy from the usual motif pattern, thereby detecting a change in the normal functioning of the heart. The key component for calculating similarity in MP is Mueen's Algorithm for Similarity Search (MASS) [38].

The EEG is inherently a very periodic signal, being a combination of brain waves of different frequencies. In the eyes-closed relaxed state, the most outstanding frequency is the posteriorly dominant alpha rhythm. Thus, on the one hand, there are no repetitive-looking patterns in an average resting-state EEG signal. Still, on the other hand, it can become visibly very periodic with the dominance of the alpha wave. Therefore, EEG differs significantly from quasi-periodic physiological signals, such as an ECG signal, so the MP method described above cannot detect changes in EEG unless the EEG changes considerably over time, such as in epilepsy; there is no such pattern change in EEG for MDD. In the case of resting-state EEG, looking at signals' general self-similarity is more effective, which is what our new method does.

2.3. Definitions and notations

Here we define the principal terms and ideas common in related research and our proposed method. As our method is based on distance profiles, we explain how they can be calculated and the essence of distance profiles.

Segment is a time series $S = s_1, s_2, \dots, s_n$ of length n .

Subsegment set $S_{i,m}$ is a continuous subset of subsegments extracted from S of the length m starting from position i , where $1 \leq i \leq n-m+1$.

$$S_{i,m} = s_{1:m}, s_{2:m+1}, \dots, s_{n-m+1:n}$$

Query q is one specific subsegment from the set $S_{i,m}$ from which the (Euclidean) distances to all subsegments in $S_{i,m}$ are calculated.

Euclidean distance (ED). Both MP and pMP are based on the idea of ED, which in this article shows the distance between two subsegments selected from $S_{i,m}$ in Euclidean space. The smaller the value for ED, the more similar the two subsegments are. By taking any two subsegments from $S_{i,m}$ (query q and a random subsegment s), the Euclidean distance between them can be calculated as in

$$\text{ED}(q, s) = \sqrt{\sum_{j=1}^m (q_j - s_j)^2}. \quad (1)$$

For every ED calculation, the query and the subsegment are first z-normalized. The z-normalization is done as follows: the mean is

subtracted and divided by the standard deviation to get the zero mean and standard deviation of one for each subsegment.

Distance profile (DP). By taking the i -th subsegment from the set $S_{i,m}$ as a query q_i and calculating the distances between q_i and all subsegments in $S_{i,m}$, we get an array of distance values, e.g., the distance profile DP_i corresponding to the i -th subsegment [29] as in

$$DP_i = ED(q_i, s_{1:m}), ED(q_i, s_{2:m+1}), \dots, ED(q_i, s_{n-m+1:n}) \quad (2)$$

As $S_{i,m}$ contains $n-m+1$ subsegments, the same number of DP-s can be calculated. Fig. 1 illustrates graphically how the subsegments are selected between which the ED is calculated and how they form the DP-s.

The DP calculation using the conventional multilevel Euclidean distance calculation (also called the naïve method) described above (2) is computationally expensive. Another way to compute DP-s is like in MP

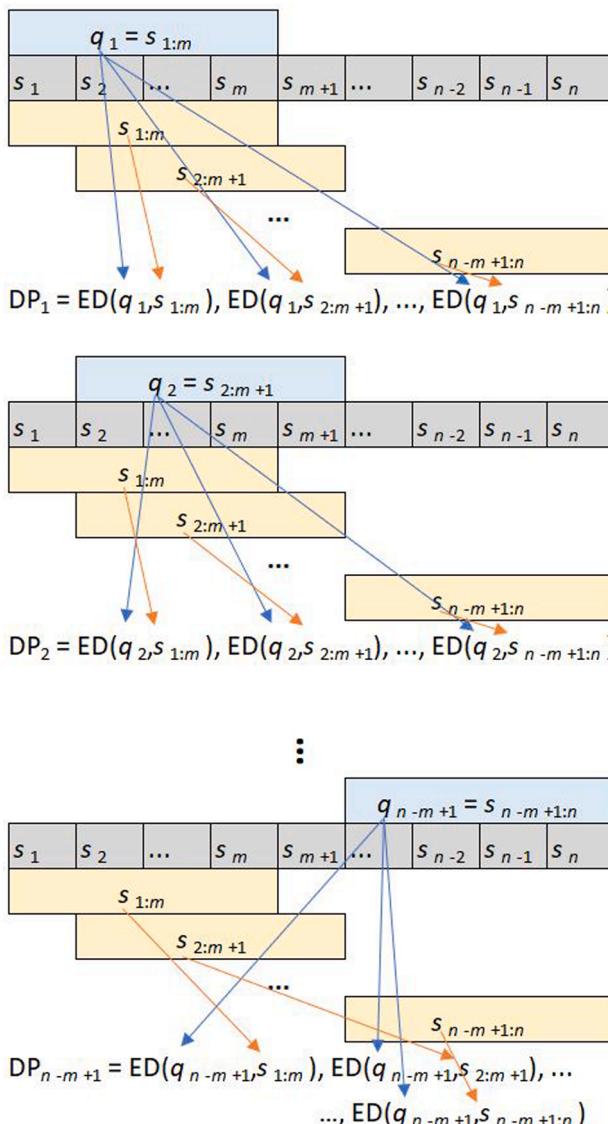


Fig. 1. Extraction and selection of subsegments for calculating distance profiles (DP-s) for an EEG signal segment $S = s_1, s_2, \dots, s_n$. First, $n-m+1$ subsegments ($s_{1:m}, s_{2:m+1}, \dots, s_{n-m+1:n}$) with the length m are extracted from S . Each subsegment is then used as query q , and Euclidean distances (ED-s) are calculated from each q to all subsegments extracted from S . By calculating the distance from a single query to all subsegments, we get the DP corresponding to that particular query. After all possible subsegments have been used as queries, $n-m+1$ DP-s are obtained.

using the MASS algorithm (and other versions, e.g., MASS_V2) [38] to speed up the calculation but still get the same DP-s as using the naïve method. The MASS_V2 uses z-normalized Euclidean distance as a subroutine, exploiting the overlap between subsegments using the fast Fourier transform (FFT) algorithm to calculate dot products to retrieve all distances from a query to all subsegments in $S_{i,m}$ extracted from the time signal S . In that way, it is possible to get a full DP corresponding to one query significantly faster than with the naïve method, which is generally not used for large amounts of data due to time constraints. The code for MASS_V2 is presented in [39].

In the case of classic MP, only the minimum value of each DP is used, excluding trivial matches. The DP minimum value indicates how similar the query and the best matching subsegment from the rest of the segment are. The minimum values from each DP form a sequence called the MP. In our proposed method, we use several values from each DP. In the next chapter, we describe the EEG data on which we applied our proposed method and the specificity of our method.

3. Method

3.1. Subjects

We recorded EEG data from medication-free outpatients diagnosed with MDD and age- and gender-matched healthy controls. Both groups comprised 33 right-handed subjects (12 males and 21 females). The mean age and standard deviation for the control and MDD group were 34.7 ± 15.0 and 34.5 ± 14.9 , respectively, and the age ranged from 18 to 75 years. All MDD group subjects underwent a clinical interview and were diagnosed with MDD by a psychiatrist based on ICD-10 criteria. Healthy controls completed the official Estonian self-report questionnaire (Emotional State Questionnaire – EST-Q) [40] for depressive disorder and anxiety, and the subjects without indication of these mental disorders were selected. The subjects were instructed to abstain from alcohol for 24 h and coffee for two hours before recording.

The study was conducted following the Declaration of Helsinki and was formally approved by the Tallinn Medical Research Ethics Committee. Participation in the study was voluntary, and all subjects signed written informed consent.

3.2. EEG data collection

All the recordings were conducted between 9 am and 12 pm using a Neuroscan Synaps2 acquisition system and a 32-channel Quick-Cap (Compumedics, NC, USA). The Quick-Cap employs electrode positioning according to the extended international 10/20 system. During the recording procedure, participants were lying in a relaxed supine position in a dimly lit laboratory room. Ten minutes of eyes-closed EEG data were acquired in 30 channels and electrooculograms in two channels (vertical and horizontal) to monitor eye movements. To achieve good conductivity between the skin and the electrode, the impedance of EEG electrodes was kept below $10 \text{ k}\Omega$. The EEG data were recorded with a frequency band of 0.3 – 200 Hz at a sampling rate of 1000 Hz.

3.3. EEG data preprocessing

The data were processed using MATLAB software (The Mathworks, Inc.). EEG data were re-referenced using the reference electrode standardization technique (REST) [41]. REST relies on the idea that the EEG recordings are the brain activities generated by the neural current sources, which are attenuated and mixed due to volume conduction. It is a virtual reference that uses an equivalent source model to approximately re-reference EEG signals to a spatial location for a reference point at infinity to achieve roughly zero potential at the reference point, reflecting bioelectrical activity considerably only under the active electrode. Previous studies have shown that the REST reference is

suitable for low-density EEG montage and is a good reference technique for comparing the results across laboratories [42,43].

Parks-McClellan low and high-pass forward-backward filters were applied to the EEG signals to remove baseline fluctuations and high-frequency noise; a frequency bandwidth of 2 to 47 Hz remained for further processing. The calculations did not assume a high sampling rate, therefore, the EEG data were downsampled to 200 Hz. The first 6 min from each recording were used for the following processing and were divided into seventeen 20.48-second (4096 samples) long segments. EEG segments were visually inspected, and segments with muscle, ocular, or other artifacts were manually removed; each subject's first ten clean segments were used for further analysis (Fig. 2).

3.4. In-phase matrix profile

The proposed method, in-phase matrix profile (pMP), is specially adapted for EEG signals and considers the periodicity of alpha waves. The main idea is to calculate Euclidean distances between short sub-segments extracted from an EEG signal segment and to use only those distance values where the subsegments are as well as possible in phase with each other and discard the distances where the subsegments are offset from each other.

First, we calculated DP-s using MASS_V2 for all queries in an EEG segment as in [39]. As DP calculation uses individually z-normalized subsections, it minimizes the effect of EEG electrode impedance variation during the EEG recording. Also, without z-normalization, EEG signal subsegments with higher absolute amplitude would have longer distances between them than lower amplitude signal subsegments even when more similar and z-normalization helps to reduce the chance of obtaining long distances incorrectly due to various amplitude effects. Our study used EEG signal segments of length 20.48 s ($n = 4096$ samples) as shown in Fig. 2 and subsegments of length one second ($m = 200$ samples). The graph in Fig. 3 illustrates one such EEG signal segment (S) and the red part represents the first query (q_1) extracted for DP₁ calculation. The DP of length $n-m+1$ corresponding to the EEG signal segment and the extracted query presented in Fig. 3 is shown in Fig. 4. The DP in Fig. 4 has a sinusoidal appearance. When the query and comparable subsegments are more in phase, the distances are shorter and longer when the query and subsegments are out of phase.

Second, the ED values, where the query was most in phase with the EEG segment, were extracted from DP. Those ED values are seen as negative peaks marked with red circles (p_{neg}) in Fig. 4. As the method aims to find the similarity between EEG subsegments, ED values calculated between out-of-phase subsegments will be left aside.

Third, the median of the extracted ED values DP_{medi} (p_{neg}) was calculated for each DP forming a pMP vector (pMP_{vec}). As we pulled $n-m+1$ different queries from S for the set $S_{i,m}$, we got $n-m+1$ DP-s and consequently a pMP_{vec} with the length of $n-m+1$.

Last, the mean of pMP_{vec} gave us the pMP value for the EEG segment. The calculation for this was as in

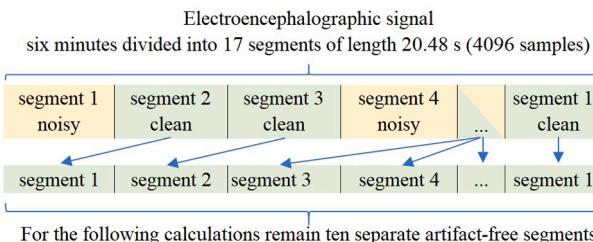


Fig. 2. EEG signal segments used for further calculations. Six minutes of recorded eyes-closed EEG signal was divided into 17 segments of length 20.48 s (4096 samples). After visually inspecting, the segments with muscular, ocular, or other artifacts were discarded. Ten separate clean segments remained for further calculations.

$$\text{pMP} = \overline{\text{pMP}_{\text{vec}}} = \frac{1}{n-m+1} * \sum_{i=1}^{n-m+1} \text{DP}_{\text{medi}}(p_{\text{neg}}), \quad (3)$$

where DP_{medi}(p_{neg}) is the median value of all DP negative peaks p_{neg} for query i .

3.5. Higuchi's fractal dimension

Fractal dimensions are sensitive nonlinear methods to analyze waveform complexity of physiological signals and have been around for decades. Higuchi's fractal dimension [44] is one of the most used fractal dimension estimates considering EEG signals and is calculated in the time domain.

HFD is based on a measure of length (k) of the curve that represents the considered time series, whereas using a segment of k samples as a unit if $L(k)$ scales like $L(k) \sim k^{\text{FD}}$. The curve shows the fractal dimension (FD) and FD measures the complexity of the curve. In this study, the value of FD with a parameter $k_{\text{max}} = 8$ was calculated according to the algorithm described by Higuchi [44].

3.6. Statistics and classification

The present study aimed to examine the capability of the proposed new pMP parameter to differentiate between the MDD and the control group compared to HFD. The pMP and HFD values were calculated for all 30 EEG channels for all 66 subjects. Since we had ten signal segments for each subject's each channel, we used the median pMP and HFD values over these ten segments.

We used the Mann-Whitney U (MWU) test to compare the group differences. MWU test controls the hypothesis that two independent samples come from distributions with equal medians. Due to multiple comparisons, the modified Bonferroni correction was applied to the p values obtained from the MWU test, and the corrected p values p_{Bonf} were calculated as in

$$p_{\text{Bonf}_j} = p_{\text{sorted},j} * (t + 1 - j) \quad (4)$$

where p_{sorted} are the p values obtained from the MWU test sorted in ascending order, t is the total number of tests performed ($t = 30$), and j is the index in descending order $j = t, t-1, t-2, \dots, 1$. Channels up to the first p_{Bonf} value exceeding the significance level $\alpha = 0.05$ were considered statistically significant.

Support vector machine (SVM) with leave-one-out cross-validation was selected as a classifier. The classification accuracy was calculated for pMP and HFD separately using single-channel input.

4. Results

First, in this study, we used a novel pMP method to calculate EEG signals' complexity and examined how pMP distinguished between MDD and control group. Second, this study examined how well HFD differentiated between the two groups. Last, we compared the results obtained with both methods with each other. The group mean values for pMP and HFD in the healthy and MDD groups are presented in Table 1 and Fig. 5.

For both pMP and HFD, the mean values for the MDD group were higher than those for the control group. Both methods resulted in lower values in the occipital area and had higher values on the sides and prefrontal region. The differences in mean values between MDD and control group are shown in the last column of Fig. 5. The dots represent locations of the EEG channels, while extra-large dots represent channels, where the difference between the two groups was statistically significant based on the MWU test after modified Bonferroni correction ($p < 0.05$). The pMP method shows a statistically significant difference between the MDD and control group in all 30 EEG channels. In contrast, a statistically significant difference for HFD between the two groups was revealed in less than half of the channels (43%). Those channels are mainly located

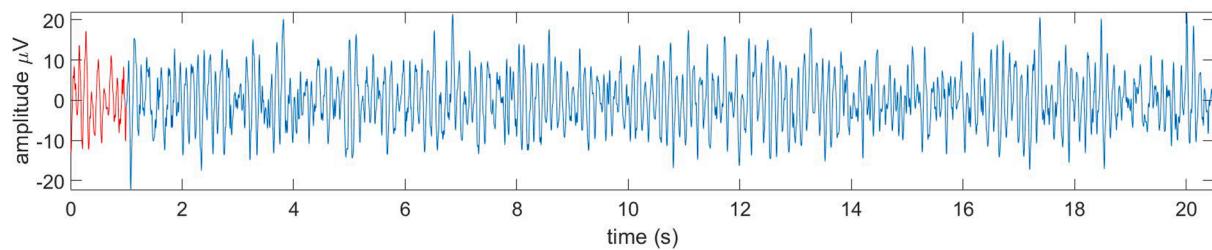


Fig. 3. EEG signal segment in channel FCz with the length of 20.48 s (4096 samples), red part represents the first query q_1 with the length of 1 s (200 samples) extracted from the EEG signal segment.

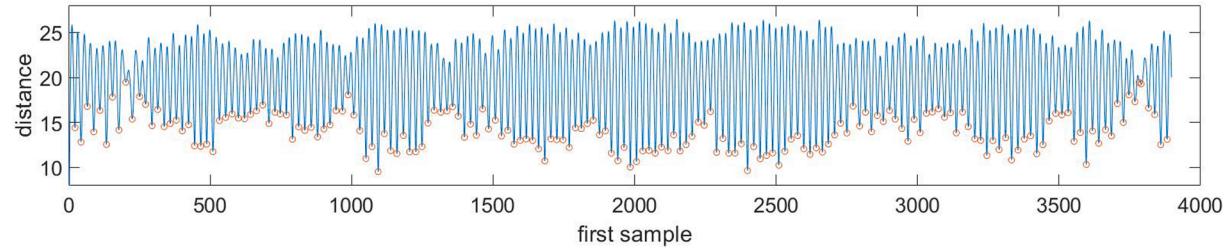


Fig. 4. An example of a Distance Profile (DP) corresponding to an EEG signal segment recorded in channel FCz of length 20.48 s (4096 samples) and a query of length 1 s (200 samples) extracted from the segment. The particular query and the segment are presented in Fig. 3. Red circles correspond to the distances, where the query is most in phase with the segment.

Table 1

The pMP and HFD mean values. Columns represent in-phase matrix profile (pMP) and Higuchi's fractal dimension (HFD) mean values across control and major depressive disorder (MDD) group; p_{Bonf} values are p values obtained from Mann-Whitney U Test with modified Bonferroni correction.

Channel	pMP			HFD		
	Control	MDD	p_{Bonf}	Control	MDD	p_{Bonf}
O2	16.098	17.166	0.039	1.263	1.310	0.047
O1	16.319	17.404	0.039	1.267	1.327	0.055
OZ	16.477	17.322	0.032	1.268	1.325	0.077
PZ	17.051	17.729	0.038	1.278	1.336	0.051
P4	16.929	17.697	0.041	1.280	1.340	0.058
CP4	17.631	18.247	0.031	1.323	1.386	0.030
P8	16.968	17.811	0.038	1.299	1.355	0.034
C4	17.700	18.400	0.013	1.340	1.408	0.009
TP8	18.075	18.636	0.036	1.377	1.438	0.051
T8	18.419	18.852	0.036	1.437	1.509	0.103
P7	17.336	18.291	0.021	1.318	1.388	0.016
P3	16.969	17.889	0.036	1.284	1.352	0.026
CP3	17.552	18.332	0.011	1.321	1.393	0.005
CPZ	17.409	18.212	0.019	1.302	1.373	0.010
CZ	17.496	18.329	0.008	1.325	1.398	0.015
FC4	17.477	18.200	0.036	1.332	1.398	0.052
FT8	18.079	18.624	0.032	1.393	1.457	0.093
TP7	18.274	18.772	0.034	1.400	1.453	0.085
C3	17.614	18.329	0.005	1.337	1.407	0.007
FCZ	17.322	18.150	0.012	1.307	1.376	0.025
FZ	17.123	17.975	0.017	1.291	1.358	0.036
F4	17.447	18.126	0.026	1.339	1.392	0.078
F8	17.950	18.611	0.034	1.384	1.466	0.077
T7	18.379	18.717	0.031	1.444	1.465	0.146
FT7	18.042	18.549	0.032	1.410	1.440	0.158
FC3	17.356	18.172	0.015	1.327	1.393	0.035
F3	17.300	18.093	0.034	1.326	1.393	0.071
FP2	18.064	18.611	0.029	1.429	1.489	0.155
F7	17.925	18.555	0.035	1.392	1.450	0.094
FP1	17.951	18.592	0.033	1.412	1.503	0.099

in the central region of the head (CP4, C4, P3, CP3, CPz, Cz, C3, FCz, Fz, FC3) and a few in the posterior region (O2, P7, P8).

The pMP appears to have greater symmetry in obtained values between the hemispheres, which is best illustrated by the difference

between the MDD and control group in the third column of Fig. 5. In HFD, some asymmetry can be seen between the hemispheres while looking at the topoplot presenting the difference between the MDD and control group. Considering the channel locations indicating the statistically significant differences, the distinctiveness of the groups is somewhat better on the left side of the head. In pMP, the largest difference was observed in the occipital region, while in the case of HFD, the difference was smaller. Although HFD also provided a statistically significant distinction between the control and MDD group in 13 channels in the present study, the pMP result was considerably better, with significant group distinction in every channel.

We used SVM analysis to validate the obtained results. The highest classification accuracy using SVM was 73% in the case of pMP and 67% in the case of HFD.

5. Discussion

The results of the present study, which show higher HFD values for the MDD group compared to the control group, were expected. The results are consistent with previous studies [9,24,26,27], where the reported fractal dimension values were higher in the MDD group compared to the control group. In the present study, the lowest HFD values were in the occipital region regardless of the group. In contrast, HFD values obtained in [9], where the authors presented HFD values in eight channels, showed higher HFD values in the occipital area (O1, O2) and lower values in the prefrontal region (FP1, FP2) with the best MDD and control group distinguishability in parieto-occipital channels. The reason might be that in [9], the Cz channel was used as a reference, while in the current study, we used REST reference. The study by Zapasodi et al. [45] that also used REST reference like in this study, presented lower HFD values in the parieto-occipital area compared to fronto-central and side regions for the healthy control group, which is consistent with our results.

The pMP results have many similarities to those of HFD. Although pMP does not characterize fractality but is still a dimension of complexity, and similarly, the lower values are in the parieto-occipital region. Complexity measures, in general, tend to have higher values in MDD [9,24–27]. Therefore, pMP was also expected to have higher MDD values than the control group.

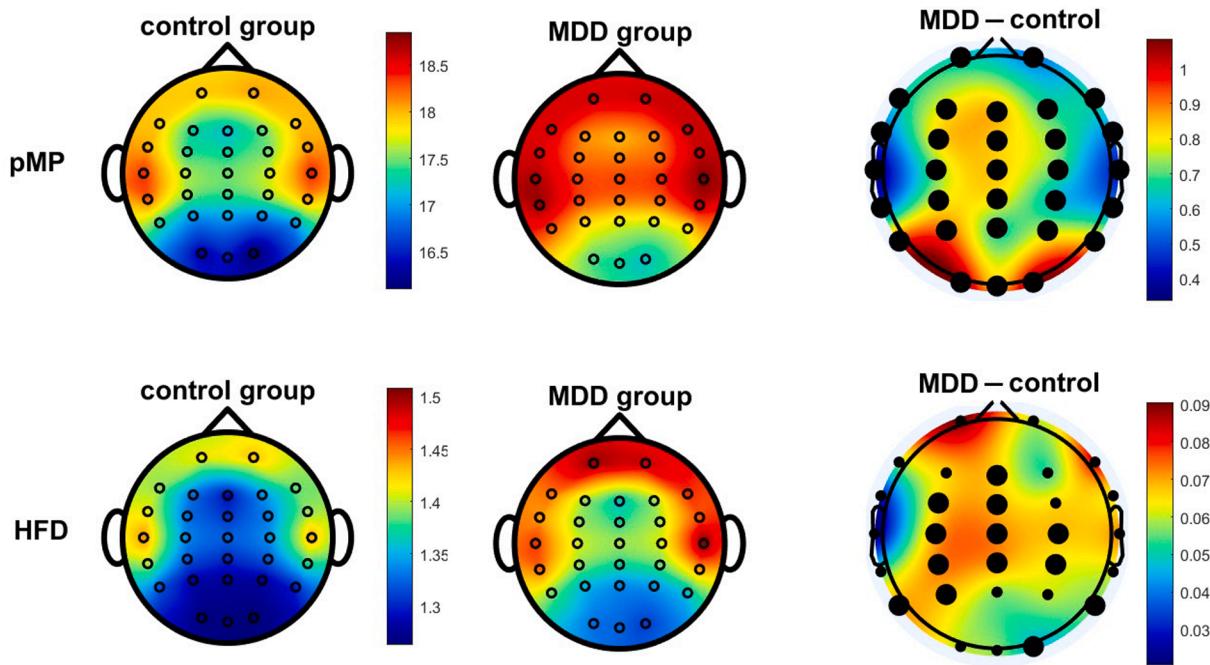


Fig. 5. Control and major depressive disorder (MDD) group mean values for in-phase matrix profile (pMP) in the first row and Higuchi's fractal dimension (HFD) in the second row for 30 EEG channels represented by dots. The MDD and control group differences (MDD – control) are shown in the last column. Extra-large dots represent channels where $p < 0.05$ according to the MWU test with modified Bonferroni correction.

Still, while looking at the pMP values for MDD and control subjects, both have lower values at the occipital region than other regions. The alpha frequency band dominates the occipital region, especially in eyes-closed conditions. This raises the question of whether pMP is strongly influenced by alpha frequencies. Fig. 4 presents a distance profile corresponding to an EEG signal subsegment and a query extracted from the segment for a random subject in the control group for channel FCz. This channel is located in the fronto-central region, so it has a relatively low alpha load. While looking at the negative peaks in Fig. 4, the mean interval between those peaks is 20 samples. Given that the sampling frequency is 200 Hz, this interval, 0.1 s, corresponds to a typical alpha wave duration illustrating that pMP is primarily influenced by the alpha rhythm even in the EEG channel FCz.

Considering that while calculating pMP, each one-second subsegment is individually z-normalized before calculating the ED, the effect of the amplitude of the EEG signal is minimized. Therefore, the pMP value is mainly affected not by the alpha amplitude but by the frequency fluctuations of the alpha frequency. In case the length of the alpha wave changes, the subsegments are no longer so well in phase with each other, resulting in a longer distance between the subsegments, which gives higher values for the DP negative peaks (Fig. 4). Wolff et al. [15] have demonstrated that the alpha peak frequency coefficient of variation is higher for MDD than controls. If the alpha rhythm's frequency variability is higher in the MDD group than in the control group, the higher pMP values for MDD subjects are justified. At the same time, as the most significant results do not appear in occipital channels - channels with the highest load of alpha frequency - other frequencies have a considerable impact, too. Still, the lowest pMP values at the occipital region can be explained by the high load of alpha frequencies, which are seemingly quite consistent in terms of frequency in the occipital region. The alpha frequency alone has been studied extensively in the assessment of MDD, and different levels of associations have been found [14–16], so it is plausible that the alpha frequency contains information about the presence of MDD.

It has been presented previously that the maximum classification accuracy for HFD was 77% when classifying depressive and control subjects in a single EEG channel [46]. At the same time, in the current

study, it was 67%. Apart from different classification method, one has to take into account that in the previous study, the age range of subjects was more narrow and the number of subjects considerably smaller. Considering the results of the current study, pMP indicated somewhat better single-channel accuracy (73%) compared to HFD (67%).

There were some limitations to this study. First, the relatively small number of participants ($n = 66$) does not allow the results to be generalized. In the case of a small group, it is also not appropriate to divide it into subgroups based on gender, age, etc., and analyze the results of narrower groups separately, because there would be too few subjects in each group. Therefore, the method needs to be tested in larger groups. Second, the groups had large age variability. Still, at the same time, the subjects in MDD and control group were age- and gender-matched, which increases the comparability of the groups. However, with age, neurological changes occur in the human brain [47] and thus also changes in the bioelectrical signals measured using EEG. Therefore, it would be important to conduct a similar study to gain better knowledge, dividing the subjects into narrower age groups. It has been found that gender also significantly impacts EEG, and genders should also be analyzed separately [48]. Although the calculation of pMP using the MASS_V2 algorithm is very fast compared to the naïve method, the calculation of pMP is still more computationally intensive compared to HFD and therefore requires more resources. In the present study, we did not investigate the effect of noise on either method. Still, HFD has been shown to be sensitive to noise [49]. Low sensitivity to noise would be a relevant advantage of the measure used to assess MDD. However, as the effect of noise on pMP value and sensitivity has not been studied in the present work, it would be essential to perform a corresponding study. Since pMP values seem to be largely affected by alpha frequency fluctuations, it should be researched if the necessary information for MDD detection is hidden in the alpha frequency band alone. In addition, it could be investigated whether the method can also characterize the severity of MDD.

6. Conclusions

This article introduces a novel EEG-based nonlinear method, in-

phase matrix profile (pMP), for studying MDD. The pMP distinguished the MDD and control group in all 30 EEG channels studied, while HFD distinguished the two groups in 13 channels. As with other complexity measures, pMP values were higher for MDD. The method expresses the complexity of EEG signals and seems to be influenced by EEG alpha frequency. The peculiarity of the method is that it is not significantly affected by the amplitude of the signal.

CRediT authorship contribution statement

Tuuli Uudeberg: Writing – original draft, Methodology, Software, Conceptualization, Formal analysis, Visualization. **Juri Belikov:** Writing – review & editing, Methodology, Supervision. **Laura Päeske:** Writing – review & editing, Investigation, Software. **Hiie Hinrikus:** Writing – review & editing. **Innar Liiv:** Conceptualization. **Maie Bachmann:** Funding acquisition, Writing – review & editing, Supervision, Conceptualization, Investigation, Resources.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The authors do not have permission to share data.

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