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ABSTRACT

Sleep quantification and automatic scoring of sleep stages via electroencephalogram (EEG) signals has been a challenge for years. It is crucial to investigate the correlation of brain waves by sleep EEG analysis due to the association between rhythmic oscillations of neuronal activity and neocortical synchronization. Multiscale joint permutation entropy (MJPE) had been proven to be capable of measuring the correlation between time series from the view of multiple time scales and thus can be a promising approach to address the challenge. Instead of simulation, we tested the MJPE method on a widely used open dataset of sleep EEG time series from healthy subjects and found that the correlation index obtained by MJPE had the capability of quantifying the brain wave correlations under different sleep stages, reflecting the typical sleep patterns and indicating the weakened correlation with aging. A higher level of correlation was found as the sleep stage advanced. The findings based on the MJPE results were in accordance with previous studies and existing knowledge in sleep medicine. In the second part of the study, we applied MJPE on sleep EEGs from subjects under pathological conditions (sleep apnea and sleep at high altitude). Likewise, the correlation index also properly revealed their sleep architectures, with consistent trends of the correlation through the nights. The effectiveness and practicability of the MJPE method had been verified on sleep EEGs. Therefore, the MJPE method should be encouraged to be widely used for analyzing large-scale sleep EEGs under various pathological conditions to provide insight into the mechanisms of the sleep process and neuron synchronization.

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I. INTRODUCTION

Entropy-based methods derived from information theory have had a wide application on analyzing complex time series in various areas. With the aim of measuring the complexity of time series, permutation entropy (PE) was proposed, which mapped the neighboring values into ordinal patterns. PE has been successfully used in the complexity analysis in the fields of financial markets, traffic systems, and physiology. Time series observed from the complex system in the real world mostly contain multiple channels, while these channels always have relation with each other. Thus, joint permutation entropy (JPE) is developed from PE to investigate the correlation between time series.

It can be gathered from previous studies that the time series in the complex systems show multiscale properties. For example, the study on complexity of biological signals presented the contradictory results for healthy people and patients by entropy-based methods and solved them by taking the factor of scale into...
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II. MULTISCALE JOINT PERMUTATION ENTROPY

The MJPE method quantifies the degree of correlation between two complex time series over a range of scales. Briefly, the method comprises three steps.

A. Construct the coarse-grained dimensional time series

Given two time series \{x_i, t = 1, 2, \ldots, N\} and \{y_j, t = 1, 2, \ldots, N\}, where \(N\) is the equal length of the time series, the coarse-grained dimensional time series \(\{X^s_k\}\) and \(\{Y^s_k\}\) are calculated as

\[
X^s_k = \frac{1}{s} \sum_{t=(k-1)+1}^k x_t, \\
Y^s_k = \frac{1}{s} \sum_{t=(k-1)+1}^k y_t,
\]

where \(s\) denotes the scale factor and \(1 \leq k \leq M = N/s\).

B. Quantify the degree of correlation between each two coarse-grained time series using JPE method

The procedure of JPE can be described as follows:

For scale \(s\), the time-delay embedding representations \(Z_{1,t}^{d,t}\) and \(Z_{2,t}^{d,t}\) for the coarse-grained time series \(\{X^s_t\}\) and \(\{Y^s_t\}\) are defined as

\[
Z_{1,t}^{d,t} = \{X_{i_1}, X_{i_2}, \ldots, X_{i_{l_t-\tau+1}}\}, \quad Z_{2,t}^{d,t} = \{Y_{j_1}, Y_{j_2}, \ldots, Y_{j_{l_t-\tau+1}}\},
\]

where \(l_t = \lfloor \frac{N}{\tau} \rfloor\), \(\tau\) denotes the embedding dimension and \(\tau\) denote the embedding dimension and time delay, respectively. There is one motif that belongs to the \(d!\) possible motifs (representing all unique orderings of \(d\) different numbers) for each of the \(T = M - (d - 1)\) subvectors. Thus, \(Z_{1,t}^{d,t}\) and \(Z_{2,t}^{d,t}\) have the certain motif combination out of \(d! \times d!\) possible distinct motif combinations \(\{(n_{1,t}^{d,t}, n_{2,t}^{d,t})\}\), denoted as \(P(n_{1,t}^{d,t}, n_{2,t}^{d,t})\) denotes the joint probability of \(\{(n_{1,t}^{d,t}, n_{2,t}^{d,t})\}\) appearing in the \(Z_{1,t}^{d,t}\) and \(Z_{2,t}^{d,t}\) and is defined as

\[
p(n_{1,t}^{d,t}, n_{2,t}^{d,t}) = \frac{1}{T}, \quad \text{type}(Z_{1,t}^{d,t}, Z_{2,t}^{d,t}) = \left(\frac{n_{1,t}^{d,t}, n_{2,t}^{d,t}}{T}\right),
\]

where \(\text{type(\cdot)}\) denotes the map from the pattern space to symbol space and \(T\) denotes the cardinality of a set. Then, JPE for scale \(s\) is represented as

\[
JPE(d, \tau) = -\sum_{i,j \in \text{type}(Z_{1,t}^{d,t}, Z_{2,t}^{d,t})} p(n_{i,t}^{d,t}, n_{j,t}^{d,t}) \log p(n_{i,t}^{d,t}, n_{j,t}^{d,t}).
\]

Due to JPE’s range \([0, \ln(d! \times d!)\]), we normalize the JPE value into \([0,1]\) as follows:

\[
0 \leq \frac{JPE(d, \tau)}{\ln(d! \times d!)} \leq 1.
\]

For each scale \(s\), the JPE results of the corresponding coarse-grained time series can be calculated and the JPE values changing with the scale \(s\) denote the MJPE curve. It can be seen that the higher the entropy value, the lower the correlation between time series.
C. Define a correlation index to measure the correlation

It is of great importance to take not only the absolute values of entropy but also the profiles of the MJPE curves into consideration to quantify the overall correlation between time series. Hence, we integrate the entropy values over a preselected range of scales and take the mean value as the correlation index as follows:

\[
MJPE_{1-\text{scale}} = \frac{\sum_{s=1}^{\text{scale}} PE_s(d, \tau)}{\text{scale}}.
\] (5)

In this study, the maximum scale selected is 10, which is determined due to the length of the original time series and frequency components in the coarse-grained EEG time series. We use the quantity \(MJPE_{1-10}\), which denotes the correlation index from scale 1–10, to measure the correlation between two channels of the studied sleep EEG signals. Likewise, the \(MJPE_{1-10}\) value is higher, which means the correlation is lower. For choosing a proper embedding dimension \(d\) in the MJPE method, the constraint \((d! \times d!) \ll N\) must be satisfied in order to obtain reliable statistics. In the PE method, \(d = 3, 4, \ldots, 7\) is recommended to satisfy the constraint \(d! \ll N\). Thus, for the MJPE method, the range for \(d\) should be smaller. Besides, the running time will increase without significantly changing the obtained entropies when \(d\) continues to increase after a certain value. In this paper, we choose \(d\) as 3 and \(\tau\) as 1.

III. TEST OF MJPE INDEX ON NORMAL SLEEP

A. Data collection on the healthy subjects

The sleep recordings used in our study were collected from the Sleep Heart Health Study.\textsuperscript{46–48} Sleep EEG data had a sampling frequency of 125 Hz, while they were manually scored (by 30-s windows for sleep stages) and were reviewed by experienced sleep specialists. In the original database, 301 healthy subjects met the inclusion criterion.\textsuperscript{49,50} However, if there were artifacts in the EEG signals, experienced sleep specialists reviewed and confirmed the removal and then we excluded the sleep data. Hence, we used the EEG signals (channels C3/A2 and C4/A1) of 122 healthy subjects (age 40–82) for our study finally.

Table I presented the percentage of wake, N1, N2, N3, and REM during a whole night. It can be found that the percentage of N1 sleep was very small. Thus, in the following analysis, we combined N1 and N2 stages. For each subject, every 6 successive epochs (3 min) under the same stage were considered as a window and then the EEG signals in the same window were investigated, while inadequate successive data points were ignored.

B. Test results on the sleep EEG from healthy subjects

For 122 healthy subjects, we examined the MJPE method on detecting the change of correlation between EEGs with sleep stages. For each 3 min window under the same sleep stage, the \(MJPE_{1-10}\)
value was calculated. Here, we took a young and an older healthy subject as an example and showed their $MJPE_{1-10}$ values of each 3 min window and the corresponding sleep stages of each window in Figs. 1 and 2, respectively. The $MJPE_{1-10}$ results reflected typical sleep architecture correctly, which can be concluded from the corresponding change of the correlation index with the sleep stage that develops. For a summary of results from 122 healthy subjects, SWS is dominant toward the beginning of the night, REM sleep toward the latter portion of the night, and brief episodes of wakefulness tend to intrude later in the night and usually do not last long. These findings were consistent with the well-recognized sleep architecture and typical sleep patterns. Meanwhile, it can be noted that the $MJPE_{1-10}$ values of the younger subject (Fig. 1) were lower than those of the old subject (Fig. 2), suggesting that the impact of aging on brain wave correlations may be captured by MJPE. Therefore, we further analyzed the correlations between the correlation index $MJPE_{1-10}$ and age in the healthy cohort. We use the mean of $MJPE_{1-10}$ values under the same sleep stage to represent the correlation under
this sleep stage for this subject. The scatter plot (Fig. 3) showed the trend that correlation decreases with aging and Pearson’s correlation coefficients. A significant positive linear correlation between the mean $MJPE_{10}$ value and age indicated that our findings were consistent with the knowledge that the correlation between brain areas becomes lower with age.

Then, for each sleep stage, we averaged the corresponding mean $MJPE_{10}$ values for 122 subjects and showed the mean and standard deviation of mean $MJPE_{10}$ values of different sleep stages for 122 subjects in Fig. 4. The decreasing mean of mean $MJPE_{10}$ values with the deeper sleep stage suggested higher correlation as one’s sleep gets deeper. However, REM sleep showed the descending correlation, which was close to that of N1 and N2. Numerous previous entropy-based studies had demonstrated that with sleep develops from wake to N1, N2, to N3, the entropy of sleep EEG signals showed a gradual decline, but increased during REM sleep indicating that EEG signals tend to be more regular as sleep gets deeper and brain activity gets more synchronized and periodic during NREM sleep. Thus, the decreasing trend of the correlation index between sleep EEGs with deeper sleep was consistent with the previous studies, which revealed the effectiveness of the MJPE method on the sleep EEGs.

The Kruskal-Wallis test was used to analyze the differences of correlation index among different sleep stages. The test results showed that there were significant differences among these different sleep stages. Thus, multiple comparison tests were applied to further study the exact difference between each two sleep stages. It was noteworthy from the multiple comparison test results shown in Fig. 4 that there was a significant difference between each two sleep stages (excluding between N1 and N2, and REM). This method is able to show a significant difference between the wake and REM period, while the importance of this finding remains to be studied further.

IV. RESULTS ON INDIVIDUAL SUBJECTS UNDER PATHOLOGICAL CONDITIONS

A. Data collection on the individual subjects

In this part, we aimed to test the robustness of MJPE on individual subjects under pathological conditions. Sleep-disordered breathing (SDB) is a common sleep disorder, and obstructive sleep apnea (OSA) is the most common type of SDB, characterized by pauses in breathing or periods of shallow breathing during sleep, which cause multiple episodes of hypoxia (low blood oxygen). Both respiratory events and hypoxia disrupt normal sleep. At high altitude, oxygen-restriction often cause hypoxia and will worsen SDB at night. Therefore, sleep quality is significantly altered under such pathological conditions.

Three male subjects underwent attended overnight polysomnography (PSG) at Beijing (two or three days prior to the trip) and the second night after they arrive at Tibet. Sleep studies were performed using the SOMNO V5 (SOMNO medics, Germany). PSG montages are placed according to current American Academy of Sleep Medicine (AASM) recommendations, including standard EEG channels (F4-M1, C4-M1, O2-M1-M2, C3-M2, and O1-M2). PSG studies were manually scored according to AASM recommendations (AASM Manual for the Scoring of Sleep and Associated Events, version 2.3). Apnea-hypopnea index (AHI) and oxygen desaturation index (ODI) are the indicators for the severity of obstructive sleep apnea (OSA), calculated by events per hour during sleep. The higher index indicates more severe pathological conditions. The information for the three cases was listed as follows:

Case 1: 33 years, healthy, BMI 21.1 kg/m$^2$, with no witnessed snoring or detected OSA.

Case 2: 35 years, BMI 25.3 kg/m$^2$, with witnessed snoring for recent few years, characterized by no other symptoms. Diagnostic PSG at Beijing reported an AHI of 28.3/hand ODI of 8.9/h. When exposed to high altitude, his AHI increased to 56.6/h and ODI increased to 49.9/h.

Case 3: 63 years, BMI 26.4 kg/m$^2$, diagnosed with OSA 6 years ago and has been using auto-CPAP (6-15 cm H$_2$O) since then. When exposed to high altitude, his AHI increased from 40.5/h to 70.2/h, ODI increased from 49/h to 131.7/h, and N3 disappeared.

In this study, the EEG channels (C4-M1 and C3-M2) were selected for investigation. Similarly, for these three cases, 3 min EEG data for each sleep stage were extracted from the records and each 3 min EEG record was labeled by its sleep stage: wake, N1, N2, N3, and REM as a window and then apply the MJPE method on these windows of EEG data. For case 2 who has mild sleep apnea, there is no enough length of N1 in Tibet so the correlation index on N1 cannot be obtained. Meanwhile, case 3 is short of deep sleep because of the severe sleep apnea, thus lacking the correlation index on N3 in Beijing and the correlation index on N3 and REM in Tibet.

B. Results on the sleep EEGs from individual subjects

We applied the MJPE method on the sleep EEGs of C3 and C4 for these three cases, respectively. Similarly, we took the average $MJPE_{10}$ of the epochs belonging to the same sleep stage and used
the mean value on behalf of the sleep stage. Figures 5–10 showed the $MJPE_{1-10}$ values of each 3 min window and the corresponding sleep stages of each window of these three cases in Beijing and Tibet. The correlation index is also able to reflect the sleep architecture for these three cases.

For the three cases in Beijing and Tibet, their mean $MJPE_{1-10}$ value and standard error for different windows under the same sleep stage were shown in Figs. 11–16, respectively. From the $MJPE_{1-10}$ results in Figs. 11–16, the same finding that as sleep gets deeper, the $MJPE_{1-10}$ value becomes lower and the correlation gets stronger can be obtained. Thus, the subjects with sleep apnea exhibited a similar trend of the correlation index in different stages of NREM sleep with the healthy subject. Besides, the mean $MJPE_{1-10}$ values increased during REM and all showed higher than those of N2 and N3. However, inconsistency was found in the comparison of the correlation index between REM, wake, and N1 that the correlation index of REM was between that of N1 and N2 for case 1 in Beijing and Tibet, case 3 in Beijing, whereas the correlation index of REM was between
that of wake and N1 for case 2 in Beijing. The reason for the trend of the correlation index during sleep/wake cycle may be that fewer neurons between leads are available for transferring information or that the neurons are more correlated with generated brain waves as sleep gets deeper, while the brain becomes highly active again and additional neurons are available or neurons are less correlated in REM sleep. There were also similar findings on the complexity of sleep EEG signals by entropy-based methods in some previous studies, which may confirm this inconsistency on REM to a certain degree and show the validity of the MJPE method on these sleep EEG data. These alterations in the correlation between EEGs during the sleep/wake cycle indicate that brain activity changes during sleep.

We also utilized the Kruskal-Wallis test to analyze the differences on correlation indices between sleep stages. The Kruskal-Wallis test results showed that there were significant differences among these different sleep stages. Thus, multiple comparison tests were applied to further study the exact difference between each two sleep stages. The multiple comparison test results were also shown in Figs. 11–16 and revealed that for each two sleep stages of case
1 in both Beijing and Tibet and case 3 in Beijing, there was no significant difference between wake and N1, N1 and REM, while the other pairs displayed a significant difference. For case 2 in Beijing, there was no significant difference for wake and N1, N1 and N2, and N1 and REM, while case 2 in Tibet showed a significant difference for all the sleep stage pairs. With regard to case 3 in Tibet, there were only three stages wake, N1 and N2 and the wake stage was significantly different from N1 and N2, while there was no significant difference between N1 and N2. It can be found that it is really difficult to separate wake from N1 and as sleep quality gets worse from cases 1–3, the sleep stage N1 and N2 becomes difficult to differentiate.

V. DISCUSSIONS

There are numerous measures studying the correlation in relevant literature. To better illustrate the advantage of the MJPE method over other methods, we compared the performance of the MJPE method on the sleep EEGs from subjects under pathological conditions with coupling permutation entropy (CPE) and
FIG. 11. The mean $MJPE_{1-10}$ value and standard error for different 3 min windows under the same sleep stage: wake, N1, N2, N3, REM, between C3 and C4, and the significance results obtained by the multiple comparison test for case 1 in Beijing ($\ast$ denotes that there is a significant difference between these two groups).

Transfer entropy (TE). The corresponding CPE and TE results were shown in Figs. 17 and 18, respectively. The CPE result of N1 was higher than that of wake for case 1 in Beijing, while for case 2, the CPE result increased as sleep developed from wake to N2 in Beijing and the CPE results for stages wake, N2, N3, and Rem were close in Tibet. Thus, it can be found that CPE results cannot reflect the sleep architecture for cases 1 and 2 in Beijing and case 2 in Tibet. In terms of TE, the TE results of wake was higher than those of N1, N2, N3, and REM for all three cases in Beijing and Tibet, while the TE results of sleep stages except wake showed close values. Likewise, TE is unable to reveal the typical sleep patterns for these subjects under pathological conditions (sleep apnea and sleep at high altitude). Besides, both CPE and TE results showed bigger standard errors indicating their weaker robustness.

FIG. 12. The mean $MJPE_{1-10}$ value and standard error for different 3 min windows under the same sleep stage: wake, N1, N2, N3, REM, between C3 and C4, and the significance results obtained by the multiple comparison test for case 1 in Tibet ($\ast$ denotes that there is a significant difference between these two groups).

FIG. 13. The mean $MJPE_{1-10}$ value and standard error for different 3 min windows under the same sleep stage: wake, N1, N2, N3, REM, between C3 and C4, and the significance results obtained by the multiple comparison test for case 2 in Beijing ($\ast$ denotes that there is a significant difference between these two groups).

FIG. 14. The mean $MJPE_{1-10}$ value and standard error for different 3 min windows under the same sleep stage: wake, N1, N2, N3, REM, between C3 and C4, and the significance results obtained by the multiple comparison test for case 2 in Tibet ($\ast$ denotes that there is a significant difference between these two groups).
FIG. 15. The mean $\text{MJPE}_{1-10}$ value and standard error for different 3 min windows under the same sleep stage: wake, N1, N2, N3, REM, between C3 and C4, and the significance results obtained by multiple comparison test for case 3 in Beijing (* denotes that there is a significant difference between these two groups).

As a result, it can be concluded by comparison of CPE and TE results on the three cases and MJPE results shown in Sec. IV B that the MJPE method is more applicable to quantify the correlation for these subjects under pathological conditions than these two methods.

Then, we considered the complexity performance for one of the two time series components using the multiscale permutation entropy (MPE). Figure 19 showed the mean MPE1-10 values and standard errors of C3 and C4 for different 3 min windows under the same sleep stage for the three cases in Beijing and Tibet. It can be seen from Fig. 19 that the mean MPE1-10 decreased as the sleep stage advanced, while the mean MPE1-10 increased during REM and all showed higher than those of N2 and N3, which suggested that MPE is able to reflect the typical sleep pattern, with consistent trends of the complexity of EEG time series through the nights.

FIG. 16. The mean $\text{MJPE}_{1-10}$ value and standard error for different 3 min windows under the same sleep stage: wake, N1, N2, N3, REM, between C3 and C4, and the significance results obtained by the multiple comparison test for case 3 in Tibet (* denotes that there is a significant difference between these two groups).

Then, we considered the complexity performance for one of the two time series components using the multiscale permutation entropy (MPE). Figure 19 showed the mean MPE1-10 values and standard errors of C3 and C4 for different 3 min windows under the same sleep stage for the three cases in Beijing and Tibet. It can be seen from Fig. 19 that the mean MPE1-10 decreased as the sleep stage advanced, while the mean MPE1-10 increased during REM and all showed higher than those of N2 and N3, which suggested that MPE is able to reflect the typical sleep pattern, with consistent trends of the complexity of EEG time series through the nights.

FIG. 17. The mean CPE results and standard errors for different 3 min windows under the same sleep stage: wake, N1, N2, N3, and REM for the three cases in Beijing and Tibet.
VI. CONCLUSIONS

The MJPE method was proposed as an effective approach to quantify the correlation between two time series from the ordinal structure at different time scales and had been successfully applied on financial and traffic time series. In this paper, we introduced the MJPE method and defined the correlation index, which can be used in physiological signals such as EEG data. First, the validity and applicability of the MJPE method on sleep EEGs can be demonstrated by MJPE results for the healthy subjects. The MJPE method has the capability of quantifying brain wave correlations under different sleep stages and illustrating the weakened correlation with aging. Compared with other entropy-based approaches, the trend of entropy changing through sleep stages is consistent with previous studies, but significant differences of the correlation index can be found between wake and REM sleep. In the second part, the MJPE method was applied to analyze the correlation between sleep EEGs for three cases: healthy subjects and subjects with mild and severe sleep apnea. The correlation indices also well illustrated the sleep architectures. The same trends of correlation indices in different stages of NREM sleep were found for these cases, which suggest the effectiveness of the MJPE method on sleep EEG under pathological conditions. Results from the Kruskal-Wallis test showed that there were significant differences among these different sleep stage groups for the three cases in Beijing and Tibet, respectively.
Sleep quantification and automatic scoring of sleep stages via the analysis of EEG signals remain a challenge in sleep medicine. There is often association between rhythmic oscillations of neuronal activity and neocortical synchronization during sleep and wakefulness, and the long-range synchrony is usually detected with two or more electrodes placed at some distance apart. At the cellular level, hippocampal activity is partially influenced by and synchronized to the cortical slow oscillation. Each sleep state has significant and specific values to sleep quality and overall health. The identification and quantification of sleep are of great importance. In this study, EEG signals from two channels originating from symmetry brain regions were analyzed by MJPE. The proposed method has shown its validity and applicability on sleep EEGs and is capable to detect the correlation levels between brain areas from the perspective of multiple time scales. The superior quality of the MJPE method on simplicity, sturdiness, and low computational cost ensure its applicability for real-time automatic sleep quantification and bringing in great value to understand the brain activity during sleep. Therefore, the application of the MJPE method on large-scale sleep EEGs under different pathological conditions should be greatly encouraged to provide insight into the mechanisms of sleep process and neuron synchronization.

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