



EEG Analysis for Differentiating between Brain Death and Coma in Humans

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ABSTRACT

To have an accuracy and fast diagnosis of brain death is very urgent for patients especially for distinguishing brain death from coma circumstance. Electroencephalogram is a method of invasive recording brain signals with high temporal resolution. So in clinics, EEG is taken as the most reliable method to estimate the brain death state of affairs. The objective of this paper is to find out the statistical rule on brain death and coma detection through EEG signal processing technology analysis on 20 patients' medical data (10 for brain death group, 10 for coma group) and then hope to give aid diagnosis conclusions in clinical practice. First, the independent component analysis (ICA) has been applied to solve artifact removal problem combined with wavelet decomposition method to compute the signal noise ratio (SNR). Moreover, the Fourier transform is calculated to compare the power spectrum of the two groups. In addition, we applied the multi-scale permutation entropy into comparison with complexity of brain death and coma patients' data in different brain inter-rhythms. Finally, the Wilcoxon rank sum has been used to test their statistics significant differences. We proposed our understanding and conclusions on this experiment results. Specially, the real-time brain death and coma patients' distinguishing is discussed based on parallel computational idea such as cloud computing on Hadoop.

Key words

Brain death; Coma; EEG analysis; Signal Complexity, Non-parameter Test.

Academic Discipline And Sub-Disciplines

Computer Science, Data Processing, Signal Processing, Computer Engineering, Neuroscience

SUBJECT CLASSIFICATION

Signal Processing, Statistics, Machine Learning

TYPE (METHOD/APPROACH)

Experimentation, Clinic, Computer Simulation

INTRODUCTION

Brain death is defined as the irreversible loss of all functions of the brain, including the brainstem. The three essential findings in brain death are coma, absence of brainstem reflexes and apnoea [1]-[2]. In clinics, death of brain therefore qualifies as death, as the brain is essential for integrating critical functions of the body. The equivalence of brain death with death is largely, although not universally, accepted [3]-[4]. It is clear that the diagnosis of brain death is very important [2]. Guidelines for determining brain have been proposed for example the apnea test and brainstem function detection [5]. Notably, it is commonly accepted that EEG might serve as an auxiliary and useful tool in the confirmatory tests, for both adults and children [6]-[9].

EEG has been effectively used into diagnosis diseases in clinics and related research area [10]-[12]. It has several nice features forwarding the applications in clinical practice and science research. Non-invasion feature makes it easily accessible and safe to be used in used. Specifically, patients in the deep coma state could be recorded the frontal area of head without big operations, decreasing the risks resulted from movement. High time resolution (milliseconds) feature enables it to catch the real-time dynamic changes of neural activity. Simple and friendly operation steps feature motivates wide-use of EEG in both theory and practice area such as disease diagnosis and classification. EEG can record continuous signals where is much safer than the test on patients' spontaneous breathing with unplugging the ventilator intermittently.

Even though there are such several strong points in EEG application for brain death detection, the reasons for improvement of EEG analysis on brain death diagnosis should be paid attention to are summarized as follows.

1). There are diagnosis mistakes in brain death EEG confirmation. In a Chinese training program [13] on EEG for brain death determination and improvement, all 114 trainees came from 72 3A grade hospitals in which 66 trainees were from department of neurology and 22 ones were from electrophysiology. The total error rate was 9.19% among which the error rate of parameter setting was the highest (11.40%), followed by those of result determination (10.44%), recording techniques (10.25%), environmental requirements (7.46%) and pitfalls (3.68%). We can see that the doctors with professional knowledge of medicine would make mistakes of operations on EEG even if during the period of training

program. In the clinic, the accuracy and in time diagnosis of disease for patients in coma is so urgent that the improvement of interpretation of clinical EEG is so necessary and needs to be highly emphasized.

2). Distinguish from coma and brain death should be confirmed. Patients in coma may or may not progress to brain death and they often show symptoms of absence of movement, and breathing occasionally less brainstem activity, whose clinic performance is similar to brain death. But what is the difference inner mechanism and how come we don't consider a coma to be temporary brain death. We should understand the point in definition of brain death, irreversible loss of functions of the brain, while coma is temporary loss of conscious but still alive [14]-[15].

3). Importance and related works on EEG signal processing need to be applied effectively. Nowadays, there are not only classical EEG signal processing methods but also some newborn algorithms have been proposed by researchers such as the high-order multi-way array analysis, tensor decomposition [16]-[17].

A brain death diagnosis is often made according to some precise criteria following a well-defined procedure [18]. Since the process of brain death determination usually takes a long time and involves certain risks, a practical yet safe method would be desirable for the pre-test of the patient's brain-state status. In our paper, a signal processing method has been put forward in brain death and coma EEG analysis. For preprocessing, the ICA algorithm is used to remove the artifacts and then the wavelet decomposition is applied into second step noise reduction, calculating the SNR factor. For processing, the energy of each group is compared through Fourier transform. And then we calculate the multi-scale permutation entropy in grasping the brain complexity for different inter-rhythms. To estimate the significance difference between the two groups, we employed the Wilcoxon rank sum method into the two not Gaussian distribution datasets. Actually, distinguish of brain death and coma group can be fulfilled in our processing method.

1. Signal preprocessing: Independent component analysis and wavelet decomposition

For EEG signal preprocessing, there is no standard method because of the randomness in noise types from the environment and robustness in subjects' statements. So we applied the ICA algorithm into artifact removal and then a further wavelet decomposition was processed, estimating the SNR (signal noise ration) and MSE (minimum square error) parameters. Here, we chose the data length for 180 seconds.

1.1 Data source

The clinic patients' data were collected from the year 2007 to 2009 including 34 patients (17 brain death, 17 coma) at a third-grade class-A hospital, Shanghai, China. The clinic EEG recorded machine was a portable NeuroScan ESI-64 system (data structure was .cnt file). There were 9 channels placed on the forehead of patients without movement statement. Here, the reference electrodes were located at two ears respectively and an additional channel was taken as ground. Specially, EEG recording channels were Fp1, Fp2, F3, F4, F7, F8 and the corresponding locations were shown as Fig.1. Sampling rate is 1000Hz. The raw EEG data of each group is shown in Fig.2 (10s data example). The experimental procedure was supported by the local ethics committee of the hospital and all collected data were used under access of patients' legal guardians or family. We protected the patients' privacy too.

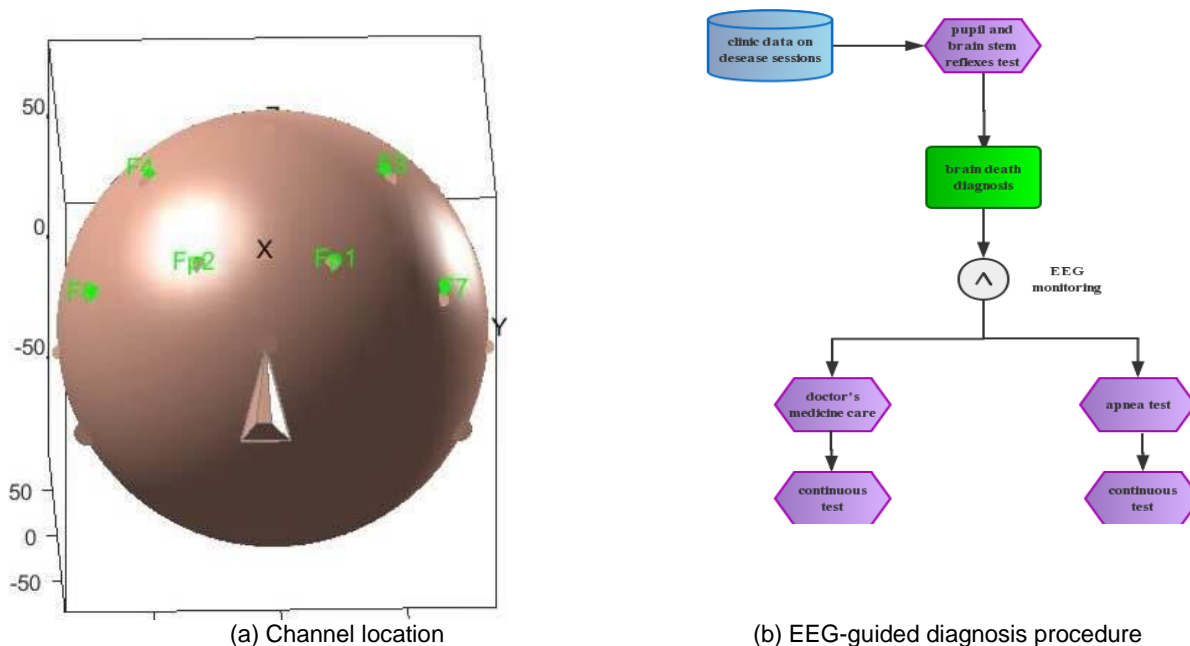


Fig.1 Experiment data source

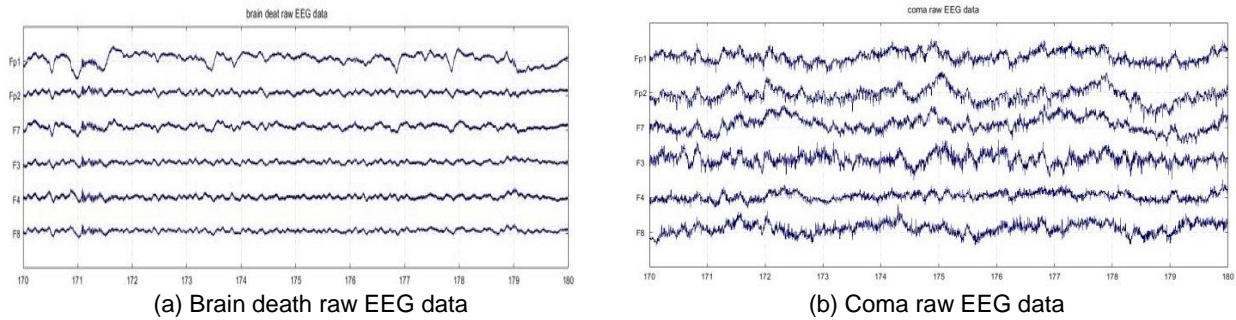


Fig.2 Raw EEG data

1.2 Independent component analysis

ICA, a powerful signal processing tool for blind source separation (BSS), could be used to estimate the physiological brain sources and in fact, has been often used to reveal the source components of EEG signals and has yielded many promising results[19]-[20]. The basic problem of ICA in our current clinic EEG brain signal processing is shown in Fig.3.

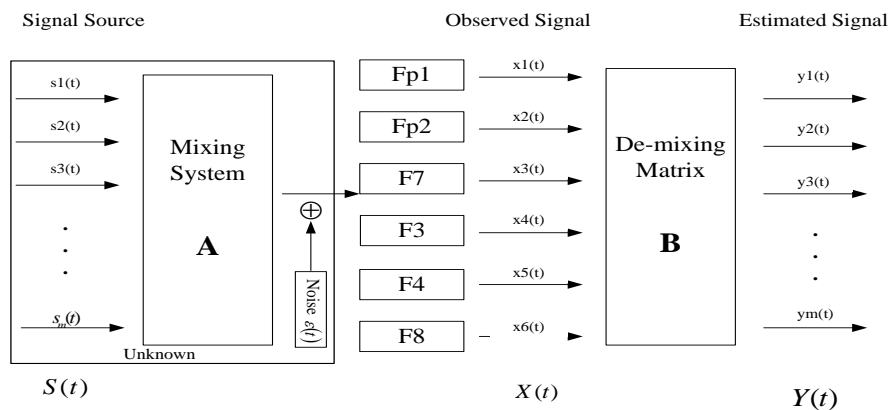


Fig.3 ICA processing flow in clinic brain EEG signal case.

Here we simply made the hypothesis that A is a linear system and channel has no influence on signal which is to say, observed channel number is equal to signal number.

The mixing model can be seen as $X = AS$ and separated model is $Y = BX$. The objective of ICA is to find out the separated matrix B and then the new vector $Y = [y_1(t), \dots, y_n]^T$ should be independent as large as possible. Essentially, ICA is an optimization problem to solve how the separated independent components are approaching to each source signal maximally. We can define the ICA as follows (fig.5 and formula). The basic algorithms in ICA are (MMI) minimum mutual information, info-max and MLE (maximum likelihood estimation).

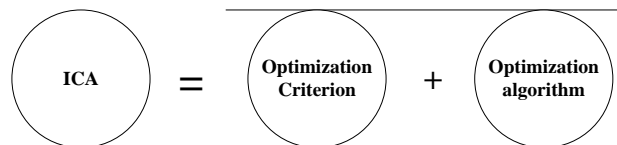


Fig.4 The key of ICA.

1.2.1 MMI

KL divergence is the best test model for statistic independence. Suppose X is one n-dimensional column vector, $p(x)$ is combined probability density functions, $p(x_i)$ is the i th. So if every component is independent among each other and then $P(X) = \prod_{i=1}^N p(x_i)$, the KI solving value is given as formula 1.

$$I(X) = KL[p(x), \prod_{i=1}^M p(x_i)] = \int p(x) \log \left[\frac{p(x)}{\prod_{i=1}^M p(x_i)} \right] dx \quad (1)$$

$I(X) \geq 0$ and only when every component of X is independent from each other, $I(x) = 0$

1.2.2 info-max

Ensuring the minimum of mutual information is a basic step of ICA. Entropy is estimation of the uncertainty information. The combined entropy is defined as formula 2.

$$H(X) = H(x_1, x_2, \dots, x_N) = - \int p(x) \log p(x) dx \quad (2)$$

In the definition of $J(X) = H(X_g) - H(X)$, X_g is a Gaussian distribution random variable with the same variance of X . Clearly, the $J(X)$ could be a good objective function (shown in formula 3).

$$I(X) = J(X) - \sum_{i=1}^n J_i(x_i) + \frac{1}{2} \log \left[\frac{\prod_{i=1}^n c_{ii}}{\det(c)} \right] \quad (3)$$

Here, C is covariance matrix, c_{ii} is the diagonal elements. If the components are irrelevant, the third item in formula 3 will be 0. To get the minimum of mutual information, the $\sum_{i=1}^n J_i(x_i)$ should be maximum. So the objective function could be taken as formula 4.

$$p(X) = \sum_{i=1}^n J_i(x_i) \quad (4)$$

1.2.3 MLE

In EEG signal processing, the only information we could obtain is the observed data X , so the maximum likelihood estimation would be the natural selection method. The log likelihood function is shown in formula 5.

$$L(B) \approx \frac{1}{T} \sum_{i=1}^T \{ \log p_s(B_x(t)) \} + \log |\det B| \quad (5)$$

We calculated the brain mapping components of different groups by ICA, shown in figure 5.

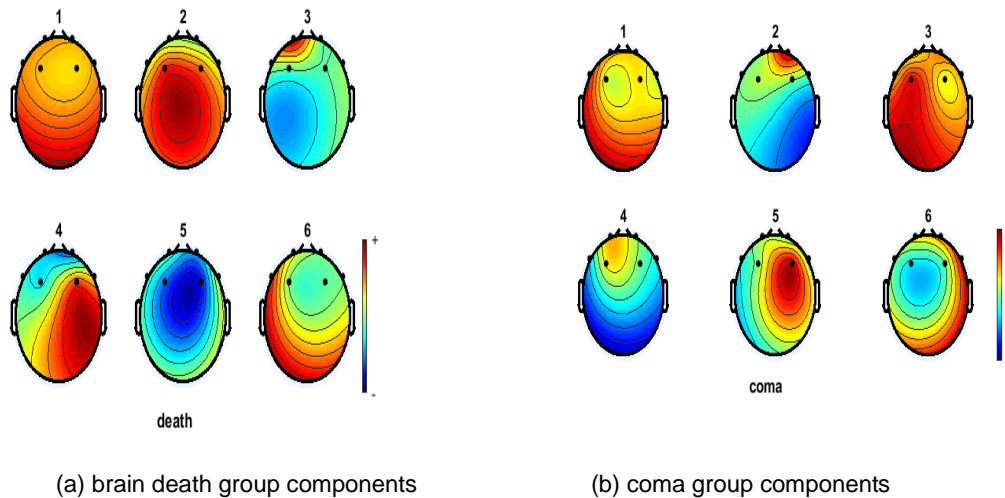


Fig.5 Brian mapping components for the two group data

And then we do the artifact component removal processing. The result of comparison in raw EEG data and artifacts removal data are given in figure 6

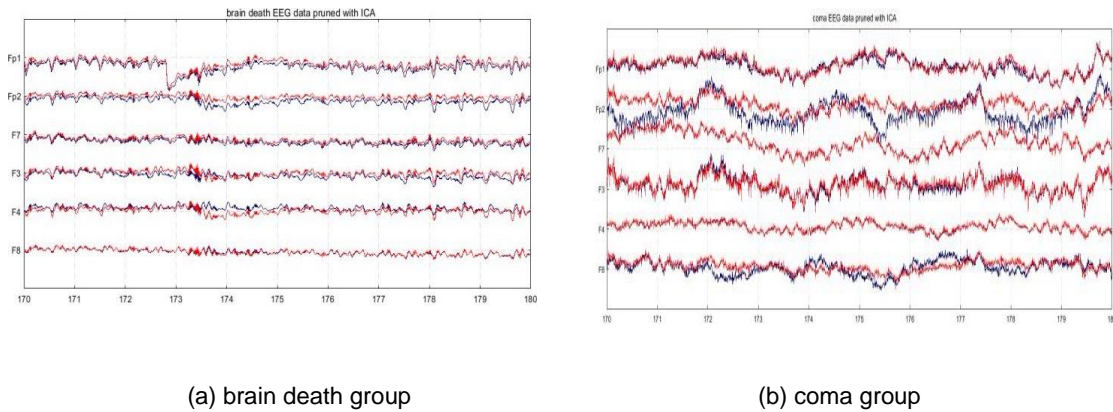


Fig.6 Comparison between raw EEG and denoised data

1.3 Wavelet decomposition

'Wavelet' could analyze the signal combined with time and frequency domains simultaneously. Through wavelet transformation, the signal would be expressed as the linear superposition of wavelet functions clustering. In de-noise processing, wavelet could distinguish the part mutation from noise in signal by the analysis in time-frequency domain. The flow of algorithm application in our case is shown as fig.7.

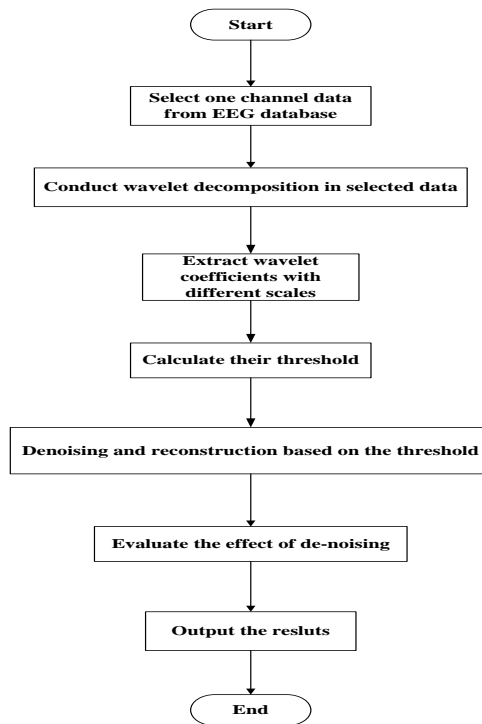


Fig.7 The wavelet algorithm flow in brain-coma EEG processing

Three key steps we should emphasis on are summarized as below.

Step1 Threshold function and value selection

Traditionally, two options for threshold functions including hard threshold ding and soft threshold ding could be

calculated, shown in formula 6. Suppose ω is the wavelet coefficient, $\hat{\omega}_l$ is processed by threshold and l is the threshold value.

$$\hat{\omega}_l = \begin{cases} \omega, & |\omega| \geq l \\ 0, & |\omega| < l \end{cases} \quad (6-1)$$

$$\hat{\omega}_l = \begin{cases} [\text{sgn}(\omega)](|\omega| - l), & |\omega| \geq l \\ 0, & |\omega| < l \end{cases} \quad (6-2)$$

Formula 6-1 is the hard threshold ding in which if the absolute value of wavelet coefficient is greater or equal to the given threshold value, then it remains else define it to 0. Correspondingly, formula 6-2 is the soft threshold ding, greater or equal to the given threshold value and then minus l else setting to 0. Four common value selection methods such as fixed threshold, stein unbiased estimation, heuristic value and minimax threshold value. Here we the unbiased estimation method is applied into threshold value computation.

Setp2 Wavelet function selection

There are several wavelet functions to be selected. Each wavelet function is suitable for special signals. For a definite signal, if the function is not proper, result will be undesirable even missing some useful information. To meet the de-noise need for EEG data, the selection decision should be made through amount of simulation experiments. Based on the related work [21]-[22] the B spline function is suitable for EEG noise reduction because its features are higher smoothness, better frequency, stronger frequency division, smaller frequency band coherence.

Setp3 Evaluation of de-noising result

Here, we use the definition of SNR and MSE to test the result, shown in formula 7. The original data is expressed as eo_i and the estimating signal is taken as el_i . SNR is bigger, MSE is smaller and then the result would be better.

$$SNR = 10 * \log\left(\sum_{i=1}^N \frac{eo_i^2}{(el_i - eo_i)^2}\right) \quad (7-1)$$

$$MSE = \frac{1}{N} \sum_{i=1}^N (el_i - eo_i)^2 \quad (7-2)$$

In this further step of EEG data noise reduction, the SNR and MSE for brain death and coma groups are given as Tab.1 respectively.

Table.1 SNR and MSE for brain death and coma groups

| Brain death | | | | | | |
|-------------|----------|----------|----------|----------|----------|----------|
| Channel | Fp1 | Fp2 | F7 | F3 | F4 | F8 |
| SNR | 160.6767 | 169.0563 | 173.4171 | 170.5558 | 159.0727 | 151.9982 |
| MSE | 0.0015 | 0.0017 | 0.0017 | 0.0813 | 0.0012 | 0.0011 |
| Coma | | | | | | |
| SNR | 133.9567 | 128.7573 | 141.3307 | 155.1837 | 144.2426 | 132.1093 |
| MSE | 0.0036 | 0.0048 | 0.0032 | 0.0169 | 0.0044 | 0.0029 |

2. Signal preprocessing: power spectrum energy, multi-scale permutation entropy

2.1 Fourier transform and analysis

The standard Fourier transform is used to estimate the power spectra energy (formula 8) for each group's data, shown in the fig.8.

(8)

$$E = \lim_{T \rightarrow \infty} \int_{-T/2}^{T/2} |x(t)|^2 dt$$

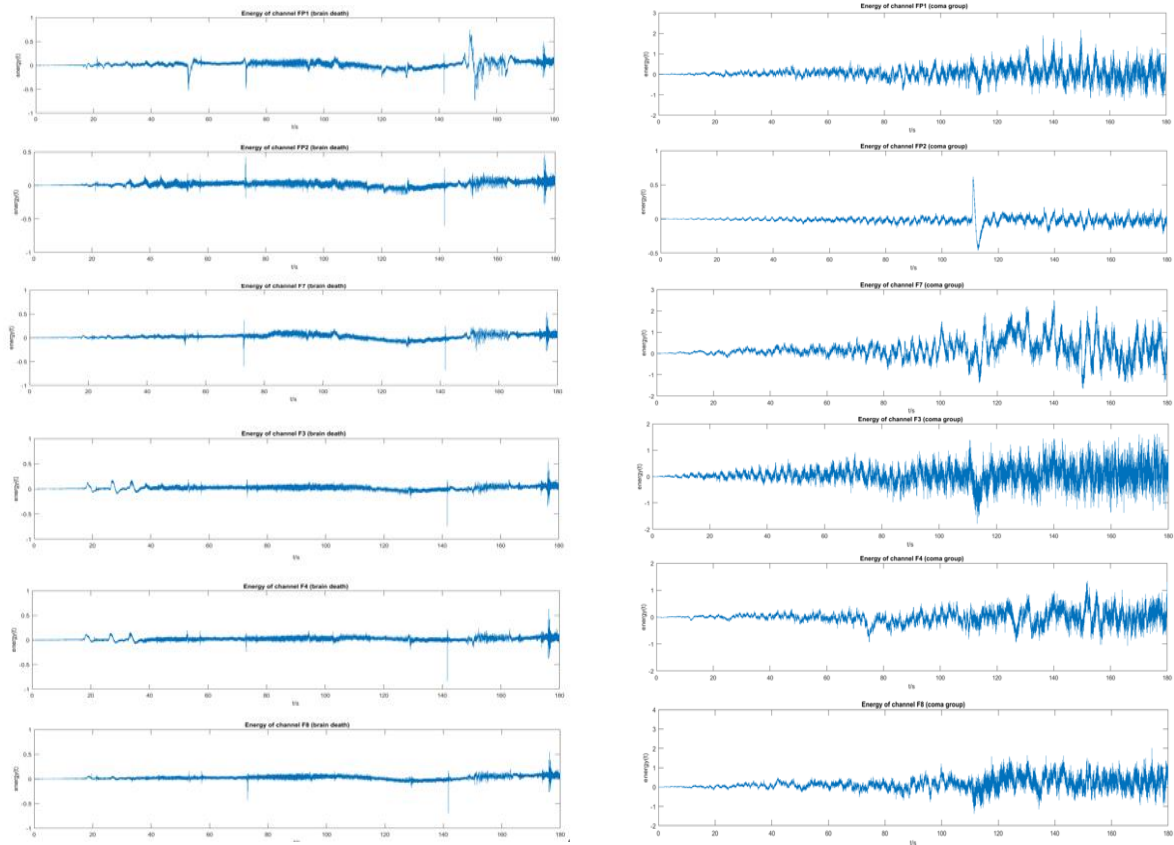


Fig.8 comparison on energy of brain death and coma groups

From the result, it is clear that there is big difference between these groups and the energy amplifier of each channel from coma group is quite bigger than brain death group varying time. After the signal processing for EEG recordings, the patients could be clarify the features of the two categories. Next step, we would do the quantitative analysis to find out more features of distinguishing the brain death and coma groups. The complexity and statistical test have been calculated in turns.

2.2 Multi-scale permutation entropy

Permutation Entropy is a complexity parameter method based on comparison between adjacent values of time series whose performance is similar to other chaotic dynamical systems such as Lyapunov exponent. Unlike some other non-linear monotonic transformation methods, its features include simple, easier to calcite and stronger anti-jamming capability [23]. Multi-scale permutation entropy is a measurement method of finite length time series complexity. Compared with the traditional entropy method with fixed scale factor, multi-scale permutation entropy creates a coarse-grained continuous time series through the coarse graining transformation. And then calculate the data using entropy which fulfil the changing from the single static entropy value to the dynamics entropy sequence [24]. The algorithm flow is given as Fig.8 as well as the key functions in formula 9.

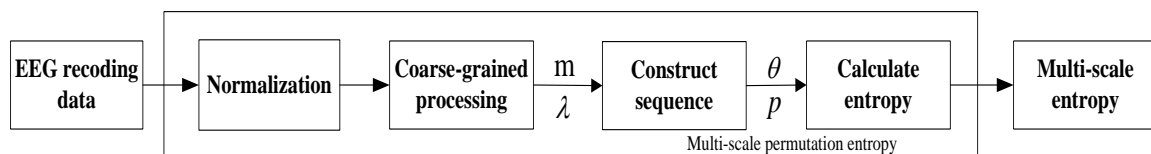


Fig.8 multi-scale permutation entropy algorithm flow

Coarse-grained processing is got by formula 9-1, permutation probability 9-2 and entropy 9-3. Here, the length of original EEG data is L . s is expressed for scale factor, m is the embedding dimension. N corresponds to the number of $m!$ permutation cases on the constructed sequence.

$$X_j^s = \frac{\sum_{i=j*s+1}^j xi, 0 \leq j \leq L/s}{s} \quad (9-1)$$

$$p_j^s = \frac{N_j}{n/s - (m-1)} \quad (9-2)$$

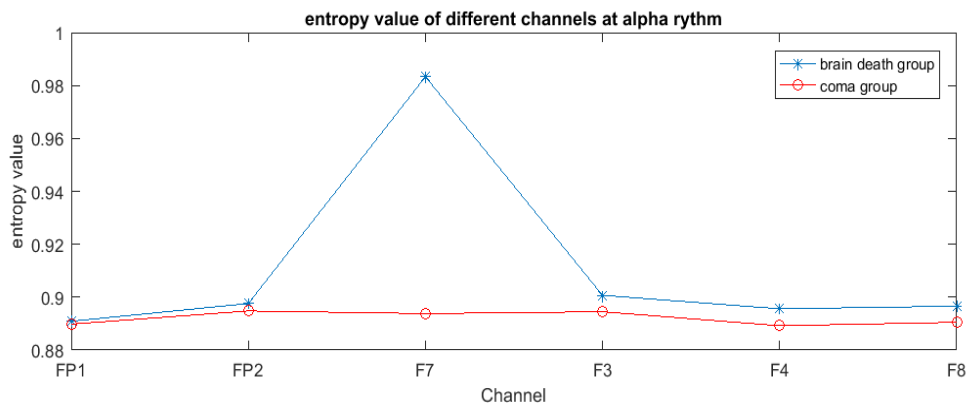
$$E_p^s = \sum_{i=1}^{m!} p_i^s \log p_i^s \quad (9-3)$$

In neuroscience, EEG frequency [25] has been classified into 4 inter-component and the comparison among each other is summarized in Tab.2.

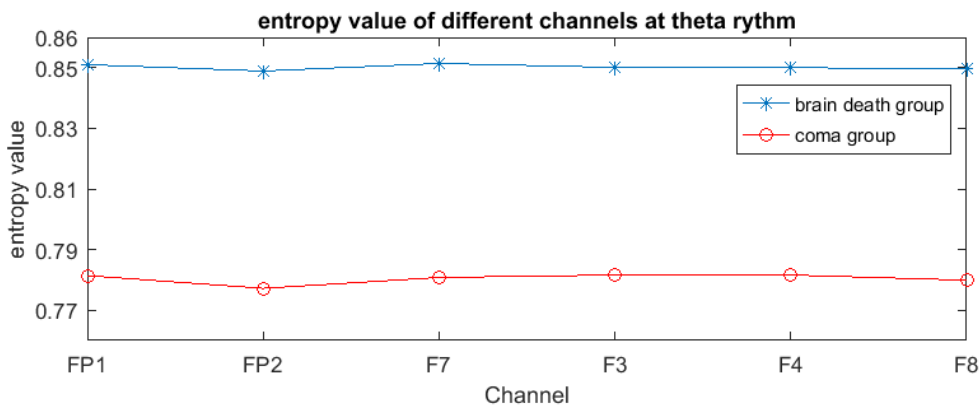
Tab.2 The features of brain inner-rhythms

| Rhythm types | Frequency range | State | Timing |
|--------------|-----------------|--|-------------------------------------|
| Alpha | 7.5-12.5 Hz | Relaxing state, clear, easy to focus task, difficult to feel tired | Need long-term training |
| Beta | 12.5-35 Hz | Nervous state, sensitive to the environment, difficult to focus and easy to feel tired | Occur in clear body state |
| Theta | 3.5-7.5 Hz | Deep relaxing state, much easier to focus on task, full of creativity | Need training to adjust freely |
| Delta | 0.5-3.5 Hz | Sleeping state | Occur under deep state circumstance |

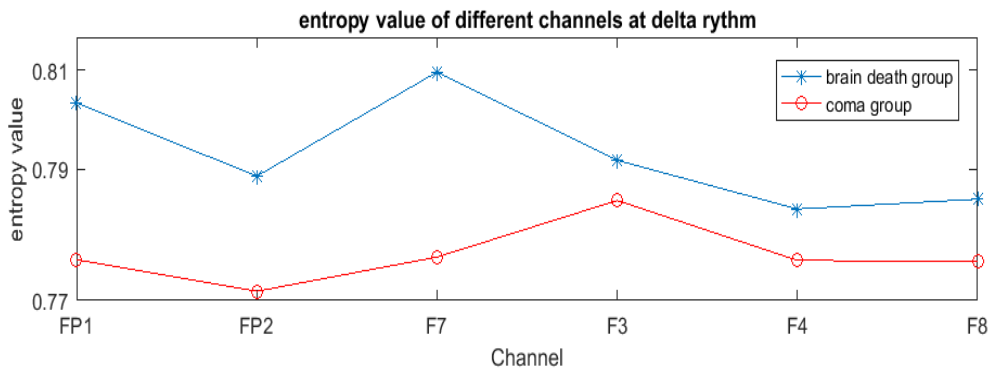
We calculate the multi-scale entropy of EEG data and then reserved the mean entropy value for each channel in different groups. The beta rhythm has much to do with the nervous and very clear brain state, so we escape this component to compare the two clinic patients' groups. The results are given as Fig.9.



(a) Entropy value at alpha rhythm



(b) Entropy value at theta rhythm



(c) Entropy value at delta rhythm

Fig.9 Comparison on brain inner-component for each patients' group EEG data

From the results, the conclusions could be made. On one side, for the entropy value of each channel in different brain rhythms for brain death group patients' EEG data is bigger than the coma group respectively which is accordance with the entropy significance in characterization of the random degree of data. On the other hand, as the rhythm in deeper sleeping state, the difference between each group is bigger which is in line with the clinic hypothesis.

3. Statistical test

To have a quantitative processing on these two groups EEG data samplings, the statistical test could help vary whether the samplings come from the same population. There are two categories of statistical parameters including parameter test and non-parameter test. The confrontation between the two methods are explained in Tab.3.

| Type | Distinctive description | Pros and cons |
|--------------------|--|---|
| Parameter test | Assume the distribution is known, estimate or test the population parameters | Pros: efficiency is high on the known distribution sampling. Cons: the specific and detailed information should be known |
| Non-parameter test | No assumption is needed including the population distribution | Pros: wide application, easy to grasp Cons: if the hypnosis is rejected, the result will be low |

Upon the differences between parameter and non-parameter test, the second one would be a more flexible option. For the EEG data, we have estimated the distribution that they are not normal. Wilcoxon rank sum test is based on the sum of sample data rank. The principle of the test is that arrange in ascending series of observations unified rank with the hypothesis of taking two samples from one sample dataset. If the hypothesis is true and then the rank should be evenly distributed in two samples such even distribution of small, medium and large ranks in the two samples. Else, one sample would have smaller rank value (sum of rank is low) and the other sample may have larger rank value (sum of rank is high).

| Wilcoxon rank sum test procedure | |
|---|--|
| Input: two groups of samples | |
| Method: | |
| 1. make hypothesis; | |
| H0: two samples are from the same population | |
| H1: two samples are from the different population | |
| 2. mix the ranks, set W is the sum of rank, n1 is for one sample amount and n2 is another sample amount. N=n1+n2. | |
| $W_1 + W_2 = \frac{n(n+1)}{2}$ | |
| 3. calculate the sum rank of the smaller group as the test statistical variable T. Suppose the smaller amount sample number is n1 and other number of sample amount is n2, n2-n1 and T value are taken as test binary table. Alpha is significance parameter. | |
| $T = \sqrt{(n1 * n2 * (N + 1)) / 2 * norm(1 - alpha / 2)}$ | |
| 4. get the result based on p value | |
| Output | |
| Mean ranks, sum of ranks and test statistics | |
| End | |

The Wilcoxon rank sum test has been used to estimate the brain death and coma EEG data samples. The results are shown as Tab.4.

Tab.4 Wilcoxon results on different channels

| Channel location | Ranks | | | | | Test statistic | | |
|------------------|--------------|---------------------|--------------------|----------------|--------|----------------|-----------------------|------------------------|
| | Value | Negative ranks | Positive ranks | Ties | Total | Channel | Z | Asymp. Sig. (2-tailed) |
| Fp1 | N | 117748 ^a | 62254 ^b | 0 ^c | 180002 | Fp1 | -89.019 ^e | 0.000 |
| | Mean rank | 46182.00 | 42767.25 | | | | | |
| | Sum of ranks | 2718918942.50 | 1331216058.50 | | | | | |
| Fp2 | N | 133784 ^a | 46218 ^b | 0 ^c | 180002 | Fp2 | -158.813 ^e | 0.012 |
| | Mean rank | 48778.92 | 34065.31 | | | | | |
| | Sum of ranks | 3262919713.50 | 787215287.50 | | | | | |
| F7 | N | 102556 ^a | 77446 ^b | 0 ^c | 180002 | F7 | -36.178 ^e | 0.035 |
| | Mean rank | 47723.77 | 45015.04 | | | | | |
| | Sum of ranks | 2307056192.00 | 1743078809.00 | | | | | |
| F3 | N | 107844 ^a | 72158 ^b | 0 ^c | 180002 | F3 | -70.344 ^e | 0.000 |
| | Mean rank | 47723.77 | 45015.04 | | | | | |
| | Sum of ranks | 2573361071.00 | 1476773930.00 | | | | | |
| F4 | N | 130358 ^a | 49644 ^b | 0 ^c | 180002 | F4 | 145.685 ^e | 0.017 |
| | Mean rank | 48491.08 | 35836.55 | | | | | |
| | Sum of ranks | 3160600101.50 | 889534299.50 | | | | | |
| F8 | N | 118452 ^a | 61550 ^b | 0 ^c | 180002 | F8 | -97.561 ^e | 0.031 |
| | Mean rank | 47031.65 | 41093.05 | | | | | |
| | Sum of ranks | 2785496457.50 | 1264638543.50 | | | | | |

a. coma < brain death
b. coma > brain death
c. coma = brain death
d. Wilcoxon signed ranks test
e. based on positive ranks

From the results, the negative and positive ranks are distributed quite different for each channel on two groups. The p value is less than 0.05, which means the H0 should be rejected. We could confirm that these two samples are from different population and they are independent samples.

4. Conclusion

In our paper, we have do the signal processing including the preprocessing, energy calculation and then the quantitative processing method has been analyzed including complexity measurement and statistical test. All the results show the difference between the brain death and coma EEG data respectively. We could distinguish the two groups through the proposed procedure.

Future work

To improve the speed of brain death diagnosis based on EEG signals and application in the clinics, the real-time calculation should be considered and the cloud computing technology could be applied into the clinics EEG data processing in the era of big data. The parallel platform and cloud computing architecture have been shown in Fig10 – Fig.11.

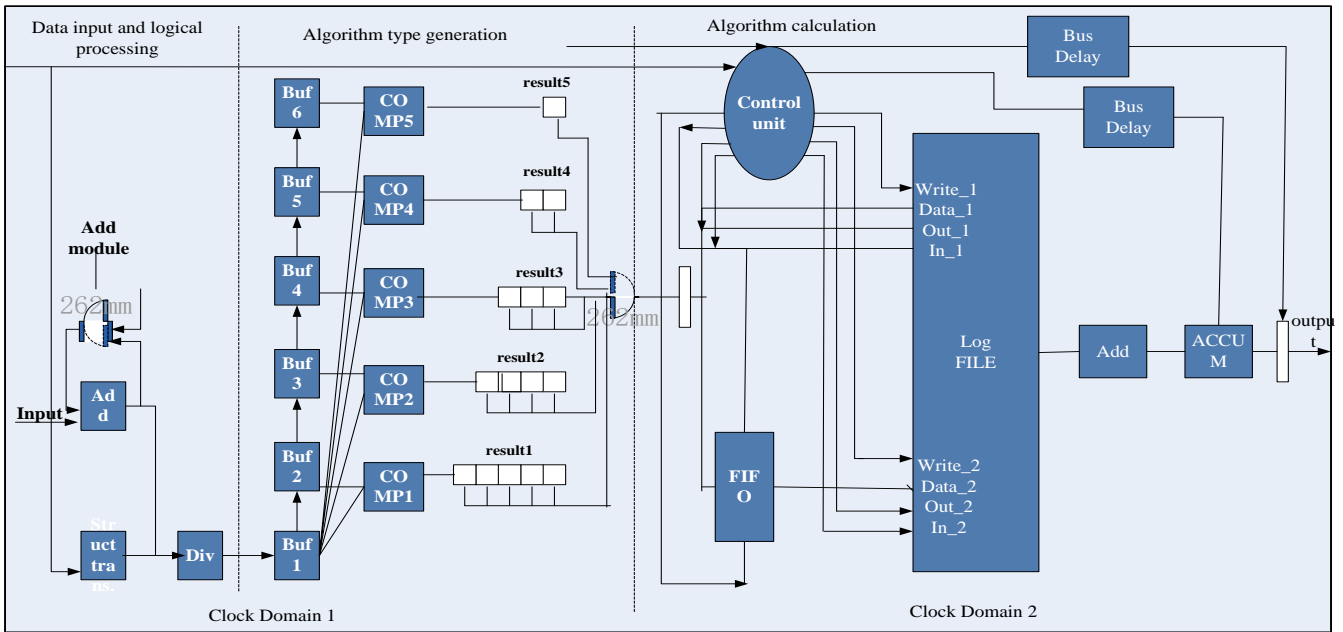


Fig.10 Parallel platform pipe

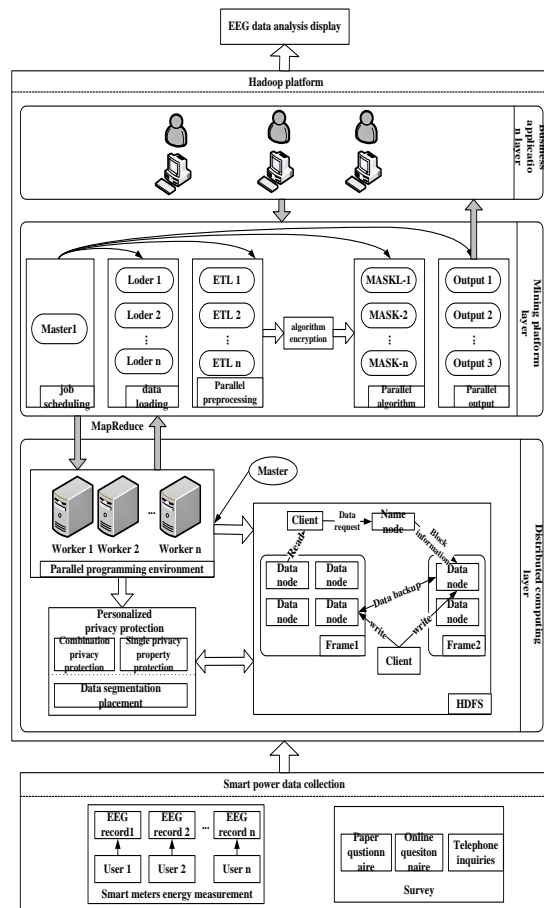


Fig.11 EEG data analysis clouding computing architecture

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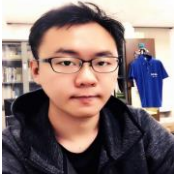
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