LETTER

Functional Connectivity and Small-World Networks in Prion Disease

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SUMMARY We characterized prion disease by comparing brain functional connectivity network (BFCN), which were constructed by 16-ch scalp-recorded electroencephalograms (EEGs). The connectivity between each pair of nodes (electrodes) were computed by synchronization likelihood (SL). The BFCN was applied to graph theory to discriminate prion disease patients from healthy elderlies and dementia groups.

key words: *dementia, prion disease, EEG, brain functional connectivity network, graph theory*

1. Introduction

Prion disease develops when normal prion proteins change into transmissible abnormal ones and the converted proteins accumulate in the brain [1]. It is specified as an intractable disease in Japan [2]. Mortality and incidence rates were remarkable in elderly people [3]. Prion disease causes rapid cognitive decline, movement disorders, and visual deficit [4]. Patients of this disease will be in danger of increasing in aging and die within a year [5]. Therefore, early diagnosis is very important.

Early diagnosis of prion diseases is a challenging problem. Diagnosis of prion disease are made by many kinds of biomarkers [6]. However, clinical diagnosis is not always accurate and is increasingly misdiagnosed [5], [7].

In this study, brain functional connectivity network (BFCN) was proposed as a new biomarker. BFCN is the brain network constructed by electroencephalograms (EEGs) and has been suggested as one of the most promising tools to offer new insight into the structural and functional organization of brain, with a potential also for clinical implications [8]. BFCN could be expressed by graph structure based on graph theory. There are many reports about brain functional connectivity in many kinds of brain disease [8]–[16], and some of them indicated a small-world network [8], [9], [11]–[13]. The reports about functional connectivity in prion disease has been conducted in recent years [15], [16], but they did not examine small-world network.

We constructed BFCNs in healthy elderlies, dementia groups, and prion disease patients. BFCNs were applied to the indices of graphs. Then, we attempted to discriminate prion disease patients from healthy elderlies and dementia groups by comparing them of BFCNs based on local and global connectivities.

2. Materials and Methods

2.1 EEG Measurement

The study protocol including all EEG data analyses, was approved by Research Ethics Committee, Faculty of Medicine, Teikyo University. The subjects consist of 10 healthy elderlies, 33 dementias and 3 prion disease patients. EEG measurements were through a Nihon Kohden EEG-1224 for the subjects. The device was equipped with 16 Ag/AgCl electrodes (a Nihon Kohden H503A) were attached at Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T3, T4, T5, and T6 based on the International 10-20 System. In addition, reference electrodes, A1 and A2, were attached at earlobes and potential difference were measured between them and each electrode. The sampling rate was set to be 500 Hz. The filter setting was high pass filter (= 120 Hz). All the subjects were instructed to lie on their back in the resting state with eye closed for 5 minutes at least. All EEG data was deleted 2 minutes from the starting time and after 1 minute were used for the data analysis as stable EEG data. All EEG data was passed through band pass filter and separated into six frequency bands: delta (0.5–4 Hz), theta (4–8 Hz), lower alpha (8–10 Hz), upper alpha (10–13 Hz), beta (13–30 Hz), gamma (30–45 Hz).

2.2 Synchronization Likelihood (SL)

After the EEG measurement, the synchronization likelihood (SL) was calculated. SL is a method based on the concept of generalized synchronization and detects nonlinear and linear dependencies between two signals [17]. Figure 1 shows an outline of calculation of SL at reference time i. In channels A and B, proximity between reference vectors ($X_{A,i}$ and $X_{B,i}$) and state vectors are calculated by critical distance ($r_{A,i}$ and $r_{B,i}$). State vectors that are closer than critical distance are called "recurrence", which are represented in white in

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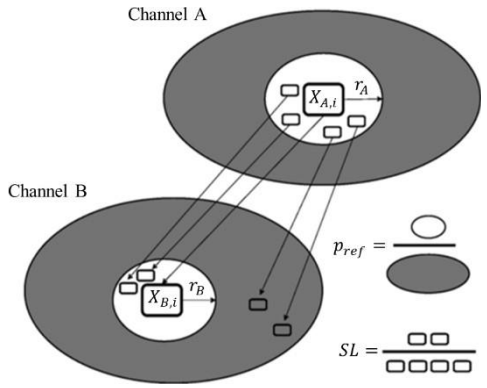

Fig. 1 An outline of calculation of SL. Reproduced from T. Montez et al. (2006) with permission.

Fig. 1. Whereas state vectors that are not closer than critical distance are represented in gray in Fig. 1. SL value is the number of simultaneous recurrences in channels A and B divided by the total number of recurrences within channels. In Fig. 1, SL value is $2/4 = 0.5$. In order to obtain a SL time series, reference time i increases with 16 ms increment. Finally, SL value is the average of SL time series.

In this study, SL values of ${}_{16}C_2 = 120$ pairs of electrodes were calculated because EEGs were measured at 16 electrodes. The result of calculating the SL values for all pairs of electrodes is substituted a square 16×16 matrix (the number of EEG channels). Each entry $N_{i,j}$ contains the SL values between channels i and j ($N_{i,j} = N_{j,i}$). We defined this matrix as a "synchronization matrix".

2.3 Graph Theory

16×16 synchronization matrices were applied to graph theory. BFCNs constructed for each group were divided into some un-overlapping modules by the optimization of quality function called "modularity" [19], [20]. In this study, modularity is based on eigenvalue decomposition of modularity matrices constructed by the number of edges at a node and of the entire network.

16×16 synchronization matrices were converted to binary matrices to compute clustering coefficient and characteristic path length. A binary graph is a network with elements 1 if a pair of nodes are connected or 0 if it is not connected. Clustering coefficient is the index how densely networks are connected. Clustering coefficient is also an index of local structure, and has been interpreted as a measure of resilience to random error (if node i is lost, its neighbors remain still connected) [13]. Characteristic path length is the average shortest path length any two nodes of the graph. Characteristic path length is a global characteristic; it indicates how well integrated a graph is, and how easy it is to transport information or other entities in the network [13]. Small-world networks consist of the high clustering coefficient and the short characteristic path length [13].

Synchronization matrices can be converted to graphs by considering degree, which is the average number of edges per nodes. In this way, graphs in the three groups are guaranteed to have the same number of edges so that any remaining differences in clustering coefficient and characteristic path length between the groups reflect differences in graph organization [9]. We conducted one-way analysis of variance (one-way ANOVA) to examine these differences. Statistical significance was defined for p-value < 0.05.

3. Results

3.1 Brain Functional Connectivity Network Construction

BFCNs were constructed by synchronization likelihood and modularity. Edges are based on the SL values. BFCNs in dementia groups and prion disease patients were constructed by normalized SL values [10]. For each electrode pair, averages of SL values in the healthy elderlies were calculated, and averages of SL values in dementia groups and prion disease patients were divided by them. In this study, BFCNs were binary. Edges of BFCNs in dementia groups and prion disease patients were connected when averages of SL values in dementia groups and prion disease patients divided by them in healthy elderlies were higher than 1. Nodes are based on the modularity.

Figure 2 shows BFCNs for six frequency bands in dementia groups, and prion disease patients. The nodes in the same module shows high functional connectivity from modularity. The SL value between Fp1-Fp2 was lower for all frequency bands in dementia groups and for delta, theta, and gamma in prion disease patients than in healthy elderlies.

3.2 Clustering Coefficient and Characteristic Path Length

Clustering coefficient C and characteristic path length L were computed as a function of degree K for all frequency bands. For clustering coefficient, significant differences among three groups were illustrated for all frequency bands. The most significant difference was illustrated for $K = 5.75$ (p-value $= 1.56 \times 10^{-6}$) for lower alpha (Fig. 3 (a)). On the other hand, for characteristic path length, significant differences among three groups were illustrated for upper alpha, beta, delta, and gamma. The most significant difference was illustrated for $K = 7.375$ (p-value $= 6.49 \times 10^{-5}$) for upper alpha (Fig. 3 (b)).

4. Discussion

The frontal cortex helps mediate the working memory that is used for temporary storage and manipulation of information and involved in many higher cognitive functions [21]. Therefore, the cognitive dysfunction is associated with functions of the frontal cortex [22]. For BFCNs, Frontal cortex region contains Fp1 and Fp2. In this study, suppose BFCNs having lower SL value between Fp1 and Fp2 have a low functional connectivity in frontal cortex region. For all frequency bands in dementia groups, and delta, theta, and gamma in prion disease patients indicate low functional

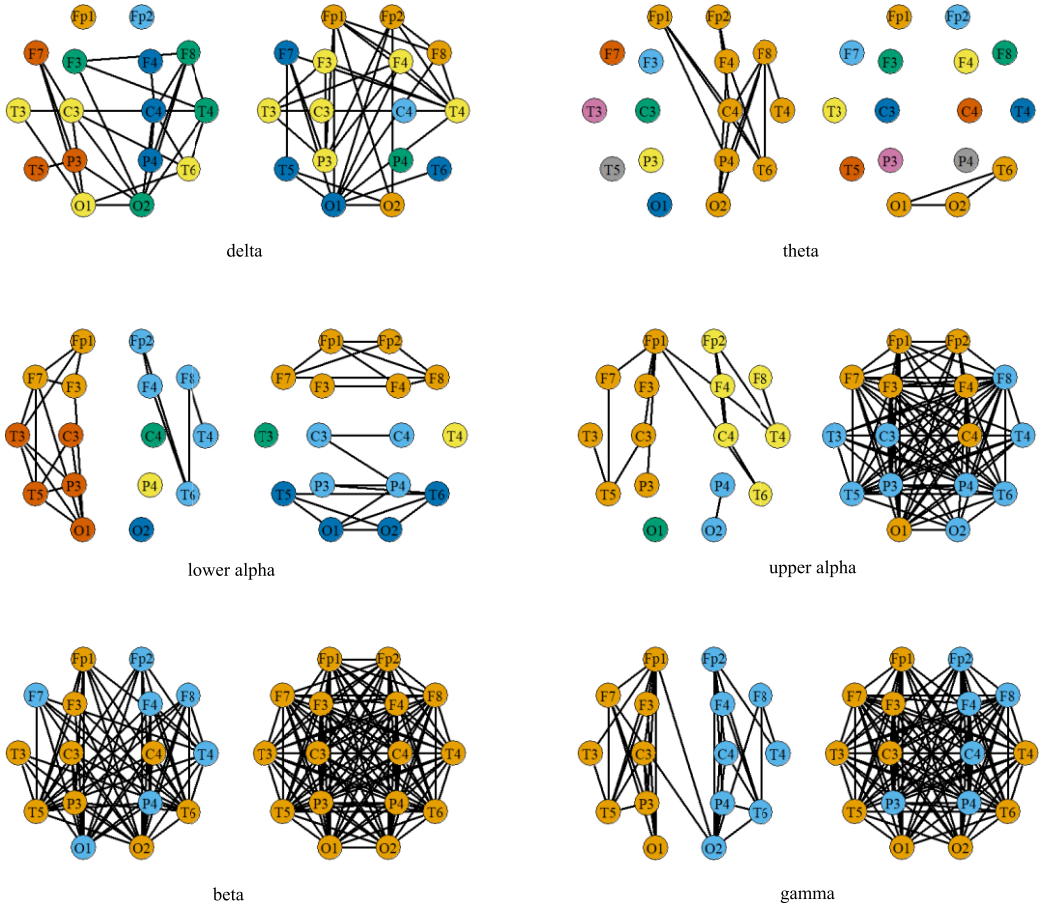

Fig. 2 Non-overlapping community in BFCNs. Left is dementia groups, and right is prion disease patients for each frequency band.

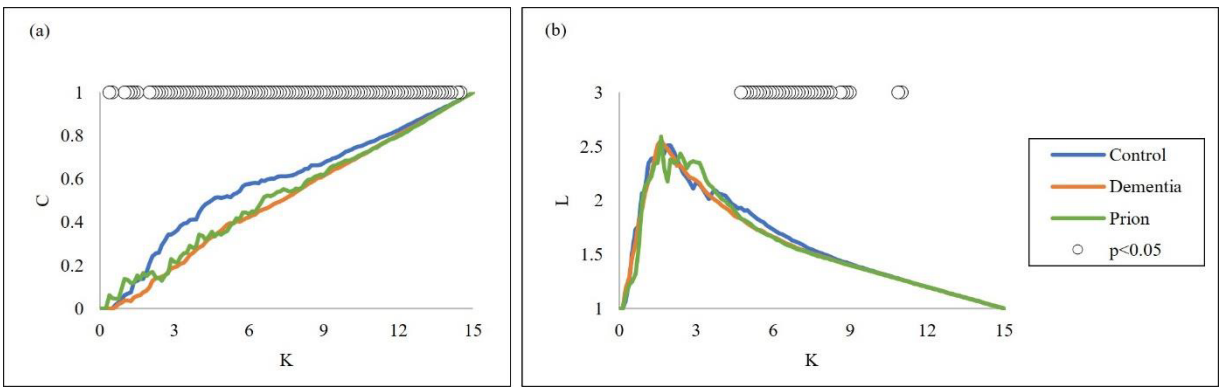

Fig. 3 Clustering coefficient C and characteristic path length L as a function of degree K. (a) is for lower alpha, and (b) is for upper alpha. Blue lines represent healthy elderlies, orange ones represent dementia groups, and green ones represent prion disease patients. Open circles depict where the difference among three groups is significant (one-way ANOVA, $p < 0.05$).

connectivity in frontal cortex region.

BFCNs are organized into small-world networks, and reflect the cognitive function [23]. In this study, clustering coefficient and characteristic path length were computed as a function of degree. For all frequency bands, significant differences among three groups were illustrated for clustering coefficient or characteristic path length. Stam *et al.* [9] showed a loss of small-world network characteristics in Alzheimer's disease for beta only. Our results will provide the possibility of changes of small-world network characteristics in dementia for all frequency bands. In addition, Freeze *et al.* [15] and Paoletti *et al.* [16] showed brain

networks in prion disease, but they did not indicate about a small-world network. Our results will provide it in prion disease.

5. Conclusion

Lower connectivity in frontal cortex region and variation of small-world networks reflect cognitive dysfunction and change in dementia and prion disease. Former tendency was indicated for all frequency bands in dementia groups and for three frequency bands in prion disease patients by construction of BFCNs. The latter tendency was indicated for all frequency bands by computation of clustering coefficient and characteristic path length. A purpose of this study was to discriminate prion disease patients from healthy elderlies and dementia groups. These results indicated the possibility of discrimination prion disease from dementia groups and healthy elderlies. Future study should reduce the number bias of individuals in the three groups and analyze in the same way as in this study.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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