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OBM Neurobiology

Original Research

Dynamic Functional Connectivity Fading Analysis and Classification of Alzheimer's Disease, Mild Cognitive Impairment and Normal Control Subjects based on Resting-State fMRI Data

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Academic Editors: Golam Sharoar and Ricardo C. Araneda

Special Issue: Alzheimer's Disease Research

OBM Neurobiology
2020, volume 4, issue 2
doi:10.21926/obm.neurobiol.2002059

Received: September 29, 2019
Accepted: May 17, 2020
Published: June 01, 2020

Abstract

In this paper, motivated by the fading effect in wireless communications, where severe channel fading is related to information loss during the transmission, we evaluate and analyze the fading effect in time-varying functional connectivity of AD, MCI and NC subjects based on the resting-state fMRI data, and then apply that for AD, MCI, NC classification. We show that in some critical brain regions, compared with NC subjects, AD subjects suffer more severe and long lasting fading in the functional connectivity level; in other words, AD subjects show selective loss in the amount of information successfully exchanged between the brain regions. On the other hand, MCI subjects experience less severe and shorter fading in functional connectivity level in general, and the connectivity level of MCI may be tangled together with that of either NC or AD. The underlying neurobiological basis for the possible

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information loss during the transmission process in AD is that the most vulnerable neurons in AD are the association neurons with long projections that formulate the communication channels or links between the brain regions, and these vulnerable neurons often suffer from loss of dendrites that leads to a significant impairment of synaptic transmission. We also show that, compared with static network connectivity pattern analysis that extracts only the region-level spatial variability, dynamic network connectivity pattern analysis, which exploits both the temporal and spatial variability in functional connectivity, can achieve much higher accuracy in the classification of AD, MCI and NC. When the AD, MCI and NC subjects are all mixed together, the prediction accuracy of time-varying connectivity based classification is 90.9%, 75.0% and 80.0% for NC, MCI and AD, respectively. Our result is consistent with existing results on dynamic functional connectivity analysis for AD and MCI.

Keywords
Dynamic functional connectivity; fading effect; Alzheimer's disease; resting-State fMRI

1. Introduction

Alzheimer's Disease (AD) is the most common form of dementia, and causes problems with memory, thinking and behavior. It is a degenerative brain disorder, characterized by progressive deterioration of nerve cells, eventually leading to cell death. Mild Cognitive Impairment (MCI) is a condition in which people show a slight, but noticeable and measurable decline in cognitive capabilities, beyond what is considered normal for their age. MCI is a transitional stage of dementia between normal control NC and AD [1]. Accurate distinction of AD and MCI from normal control (NC) subjects is critical for early diagnosis and treatment of brain disorders.

Studies on AD and MCI have largely relied on functional magnetic resonance imaging (fMRI) [2-4], which is a non-invasive diagnosis method that maps brain activities to metabolic changes (such as the blood-oxygen-level dependent (BOLD) contrast) in cerebral blood flow. For AD and MCI subjects, the BOLD time series are generally obtained under resting-state fMRI, as the difficulty to obtain subjects cooperation could influence task-related fMRI results. The corresponding connectivity is therefore often referred to as intrinsic functional connectivity [3, 5].

It has long been observed that the abnormal brain functions in AD and MCI are closely related to the weakening or loss of functional connectivity across the regions in the default mode network (DMN), consisting of the posterior cingulate, inferior parietal, inferolateral temporal, anterior cingulate, prefrontal, and hippocampal regions [6-16]. The neurobiological basis here is that among the most vulnerable neurons in AD are the large pyramidal neurons, particularly the association neurons with long projections in these regions [17]. At the same time, decreased cross-connectivity within the DMN is often accompanied by increased connectivity between certain regions, such as the left and right hippocampi, and also the regions in the attentional fronto-parietal and salience networks, and this was considered to reflect the compensatory mechanisms of the brain [15, 18].

In literature, functional connectivity is often defined as the pair-wise correlation of BOLD time series between different brain regions [5, 19]. Over the last two decades, the measurement of the

functional connectivity has evolved from the traditional static approaches to the more contemporary dynamic approaches [20-25]. The "static" approaches assume that functional connectivity is time-invariant, or say, temporal stationary throughout the recording period in resting-state fMRI [26], and actually use the entire BOLD time series to calculate the average connectivity between the regions. On the other hand, the "dynamic" approaches admit that the brain (even in the resting-state) is never static but have fluctuations, and hence examine the time-variant patterns in the functional connectivity between two brain regions [27, 28]. One commonly used method is to apply a sliding window to paired BOLD time series and calculate the correlation within each window period, so as to elucidate the dynamic characteristics of brain connectivity [29].

Brain analysis based on dynamic functional connectivity have proved to be very fruitful in identifying differences during age-related brain development and psychopathology [5, 22, 27], and in associating the dynamic changes of brain network connectivity with brain diseases [28, 30-32]. Dynamic functional connectivity analysis was also applied to the field of neurodegenerative disorders, especially AD. In [33], a sliding window analysis approach was used to demonstrate the non-stationary nature of the brain's modular organization and to construct dynamic graphical representations of brain connectivity. It was found that differences in connectivity observed in AD and normal control can be explained by differences in the dwell time in DMN sub-network configurations. In [34], the evolution of dynamic functional connectivity disruptions was investigated across the AD spectrum. It was observed that oscillatory patterns in dynamic functional connectivity are progressively altered over the AD continuum, and there is a smaller set of functional configurations in the brain of AD subjects. A subsequent study in [35] further demonstrated a statistical significant progressive loss of wholebrain metastability in AD subjects due to the degenerative cognitive impairment. Moreover, dynamic functional connectivity has also been used to develop non-invasive diagnostic biomarkers in the early stages of AD, and it was found that comparing with its static counterpart, dynamic functional connectivity based analysis can result in higher accuracy in the classification of AD, MCI and NC subjects [36-38]. Recently, in [29], both temporal and spatial variability of dynamic functional connectivity networks were extracted, and integrated to develop automated biomarkers for the classification of early and late MCI patients by using manifold regularized multi-task feature learning and multi-kernel learning techniques. The authors reported significant improvement in classification performance in comparison with static functional connectivity based methods, and dynamic functional connectivity methods that exploit only the temporal variability or spatial variability of the network. A nice review on the application of dynamic functional connectivity analysis for the assessment of some of the most common neurodegenerative conditions (such as the Alzheimer's disease, Parkinson's disease, dementia with Lewy bodies etc.) was provided in [39].

In this paper, we propose to analyze the fading effect in the time-varying functional connectivity of AD, MCI and NC based on resting-state fMRI data. The idea of fading analysis comes from channel modeling and characterization in wireless communications [40]. In communications, fading effect describes how the signal power is attenuated when the signal travels from the transmitter to the receiver, or say, from the source to the destination. When the received signal power is lower than a certain threshold, the transmitted information cannot be recovered or extracted from the received signal, we say that the signal experiences severe fading. In general, severe channel fading leads to information loss in the transmission, and the duration of each

fading corresponds quantitatively to the actual number of bits (which denotes the amount of the information) that are lost during a particular fading.

Here, using Pearson correlation as a measure for the functional connectivity, we partition the observed fMRI signal time series recorded at each brain region into successive blocks, and calculate the Pearson correlation among the time synchronized blocks corresponding to related region pairs. The successive blocks can either be chosen to overlap with other or to be non-overlapping. In this way, instead of a single Pearson correlation value, we obtain a Pearson correlation vector which exhibits how the functional connectivity between brain regions is changing with time. Our analysis indicates that in some critical brain regions, compared with NC subjects, AD patients suffer more severe and long lasting fading in the functional connectivity level, in other words, AD patients show selective loss in the amount of information successfully exchanged between the brain regions. On the other hand, MCI subjects experience less severe and shorter fading in functional connectivity level in general, and the connectivity level of MCI may be tangled together with that of either NC or AD.

To illustrate the physical meaning of the fading effect in Pearson correlation, we revisit its relationship with mutual information, which characterizes the information successfully transmitted between the brain regions. In general, the Pearson correlation represents the linear dependence between two brain regions, while the mutual information characterizes both linear and non-linear dependence between them. However, closed-form relationship between Pearson correlation and mutual information can be derived under certain conditions, and the fading in Pearson correlation is directly related to lower mutual information.

We further use the Pearson correlation vectors obtained from selected region pairs to generate feature vectors, and apply them to perform classification of AD, MCI and NC subjects. First, we use a regularized linear discriminant analysis (LDA) to reduce the dimension of the feature vector space, by mapping it to a subspace where the difference among AD, MCI and NC is maximized. Regularization techniques are exploited here to reduce the noise effect due to limited data size. Second, using the projected vectors, we construct the decision tree and carry out the classification using the multi-class AdaBoost classifier. Using LDA and AdaBoost for AD, MCI and NC classification, we conduct both network-level time-invariant connectivity pattern analysis (which uses only single Pearson correlation values), and network-level time-varying connectivity pattern analysis (which use the Pearson correlation vectors). By network-level connectivity pattern analysis [41], we mean that instead of looking at the functional connectivity between different pairs separately, we jointly examine the spatial variability in functional connectivity between all the brain region pairs in a selected brain subnetwork, so as to obtain more accurate classification among AD, MCI and NC.

Our numerical results based on experimental fMRI data indicate that: the time-varying connectivity analysis delivers much more accurate results, and can achieve a prediction accuracy of 90.9%, 75% and 80% for NC, MCI and AD, respectively. At the same time, compared with the identification of NC subjects and AD patients, it is generally more difficult for the classifier to identify the MCI patients, and the classification accuracy for MCI subjects is much lower than that for AD and NC. The underlying argument is that MCI is a transitional stage of dementia between NC and AD, and hence MCI subjects generally share some similar characteristics in functional brain connectivity with AD or NC subjects.

The rest of paper is organized as follows: in section II, we present the fading effect analysis of

time-varying functional connectivity for AD, MCI and NC; in section III, we perform the classification of AD, MCI and NC based on network-level time-varying connectivity pattern analysis. We conclude and also discuss some open problems in section IV. Moreover, in the supplementary material, we provide detailed information on fMRI data acquisition, pre-processing, region of interest (ROI) generation, regularized LDA, basic tree construction and the multi-class Adaboost classifier.

The study was approved by the Michigan State University Institutional Review Board. All subjects or their legal representatives provided written informed consent.

2. Fading Analysis of Dynamic Functional Connectivity for AD, MCI and NC

In this section, we will first introduce the concept of fading, then explore the fading effects in dynamic functional connectivity for AD, MCI and NC by examining the Pearson correlation among critical brain regions. We will further explain the physical meaning of the fading in Pearson correlation by illustrating the relationship between Pearson correlation and mutual information.

2.1 What is Fading?

The concept of fading comes from channel modeling and characterization in wireless communications [40]. Fading is the variation in the attenuation of a signal when it is transmitted through a channel. In communication systems, fading is often caused by multipath propagation, where the received signal is the superposition of the scaled/attenuated and delayed version of the original signal. As the signal travels a different path from the transmitter to the receiver, it experiences different propagation effect, resulting in selective fading in both the time domain and frequency domain. A typical Rayleigh fading [40] channel is illustrated in Figure 1. As can be seen, the power of the received signal drops below -100 dB from time to time. At some instants, the power even drops below -120dB. This significant variation in the received signal power is referred to as fading. In communication systems, when the received signal power is below a certain threshold, then the signal can no longer be recovered. In other words, severe channel fading leads to information loss in the transmission. At the same time, the duration of severe fading is corresponding quantitatively to the amount of information that is lost during a particular fading. The actual amount of the information lost is determined by the fading duration, fading depth, transmission speed (also known as data rate), and error recovering capability of the system.

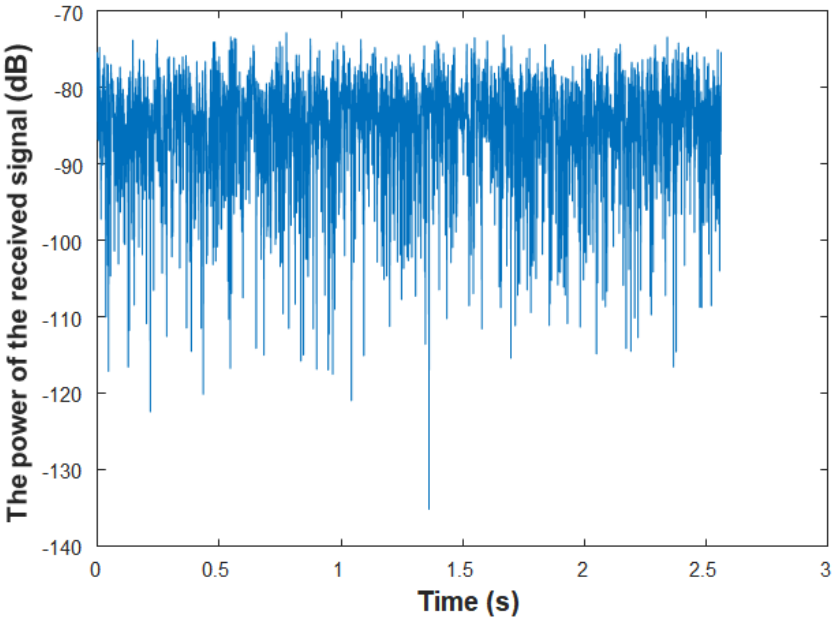

Figure 1 Fading effect in wireless Communications**.**

2.2 Fading Effect in Time-Varying Pearson Correlation

In this paper, we will explore the fading effect in dynamic functional connectivity for AD, MCI and NC. The time-varying functional connectivity will be calculated using the sliding window method.

Let $\boldsymbol{X} = [x_1, x_2, \cdots, x_N]$ and $\boldsymbol{Y} = [y_1, y_2, \cdots, y_N]$ represent the observed brain signals at two brain regions. The corresponding Pearson correlation is defined as:

$$p = \frac{< \boldsymbol{X} - \mu_x, \boldsymbol{Y} - \mu_y >}{\| \boldsymbol{X} \|_2 \cdot \| \boldsymbol{Y} \|_2}, \qquad (1)$$

where μ_x, μ_y denote the mean of X and Y, respectively; and $\|\cdot\|_2$ denotes the Euclidean norm. Now we select a sliding time window of length L, and let the time difference between two successive windows be J. For n = 1, define $\boldsymbol{X}_1 = [x_1, x_2, \cdots, x_L]$, $\boldsymbol{Y}_1 = [y_1, y_2, \cdots, y_L]$. For n > 1, $\mathbf{X}_n = [x_{(n-1)J+1}, x_{(n-1)J+2}, \cdots, x_{(n-1)J+L}]$, $\mathbf{Y}_n = [y_{(n-1)J+1}, y_{(n-1)J+2}, \cdots, y_{(n-1)J+L}]$. Given a time-series of length N, the total number of windows will be $N_p = \frac{N-L}{J} + 1$. For n = 1,⋯ ,N_p, let $p(n)$ be the Pearson correlation across $\boldsymbol{X}_n$ and $\boldsymbol{Y}_n$. That is, we now get a Pearson correlation vector (rather than a fixed value only) to characterize the time-varying functional connectivity.

Using this method, we evaluate the time-varying functional connectivity for AD, MCI and NC based on resting-state fMRI data used in [19]. Ten (10) patients with mild-to-moderate probable AD, 11 MCI patients, and 12 age- and education- matched healthy NC subjects were recruited to participate in the study, which was approved by the Michigan State University Institutional Review Board. All subjects or their legal representatives provided written informed consent. All subjects were carefully screened to exclude those with a history of stroke, brain tumors, aneurysms, brain surgery, serious head injury, or other significant neurological disease, as well as those with uncontrolled diabetes, hypertension, and hypothyroidism. All subjects were also screened for MR-incompatible metallic implants. NC subjects were community-dwelling older adults recruited from the Greater Lansing area in Michigan. The AD and MCI patients were recruited through the

Memory Disorders Clinic in the Department of Neurology at Michigan State University and were diagnosed using standard criteria by a practicing neurologist (NINCDS-ADRDA criteria for clinically probable AD and Petersen criteria for MCI). Details on fMRI data acquisition and pre-processing are provided in the supplementary material.

The paper by Zhu *et al* [19] specifically demonstrated that the functional connection between the hippocampus and the isthmus of the cingulate gyrus was reduced in AD, in comparison with that of the normal subjects. Following [19], we explore the time-varying functional connectivity of the isthmus of the cingulate gyrus with the hippocampus, the superior frontal gyrus, as well as that of the posterior cingulate cortex and the superior frontal gyrus. All the regions used here were identified based on the FreeSurfer segmentation. The results are obtained by averaging the corresponding Pearson Correlation vector within each subject group, and are shown in Figure 2, respectively. Here we chose $L = 80$ and $J = 1$.

It can be observed that compared with NC subjects, AD patients suffer severe and long lasting fading in functional connectivity level; MCI subjects tend to experience less severe fading in general, however, the functional connectivity performance of MCI may be tangled together with that of either NC or AD. In some brain regions, such as the left and right hippocampi, and the right isthmus of the cingulate gyrus and left hippocampus, AD patients showed higher functional connectivity level than MCI subjects. As we mentioned earlier, this reflects the compensatory mechanism of the brain. The region-level spatial variability in the connectivity pattern explains why we cannot just conduct AD, MCI and NC classification based on the connectivity analysis of a particular brain region pair, but need to explore the network-level connectivity pattern analysis that takes the connectivity of all the regions in a selected subnetwork into consideration simultaneously.

From Figure 2, it can also be observed that compared with the connectivity between other regions, stronger functional connectivity exists between the left and right isthmi of the cingulate gyrus, and the left and right hippocampi for all subjects, indicating that *the hippocampi and the isthmi of the cingulate gyrus play particularly significant roles in cognitive activities*. In certain brain regions, such as the left and right isthmi of the cingulate gyrus, the left posterior cingulate cortex and the left superior frontal gyrus, for example, AD patients started with a relatively high functional connectivity level, but were not able to maintain it along the time. This may be caused by decreased and unstable energy supply [17].

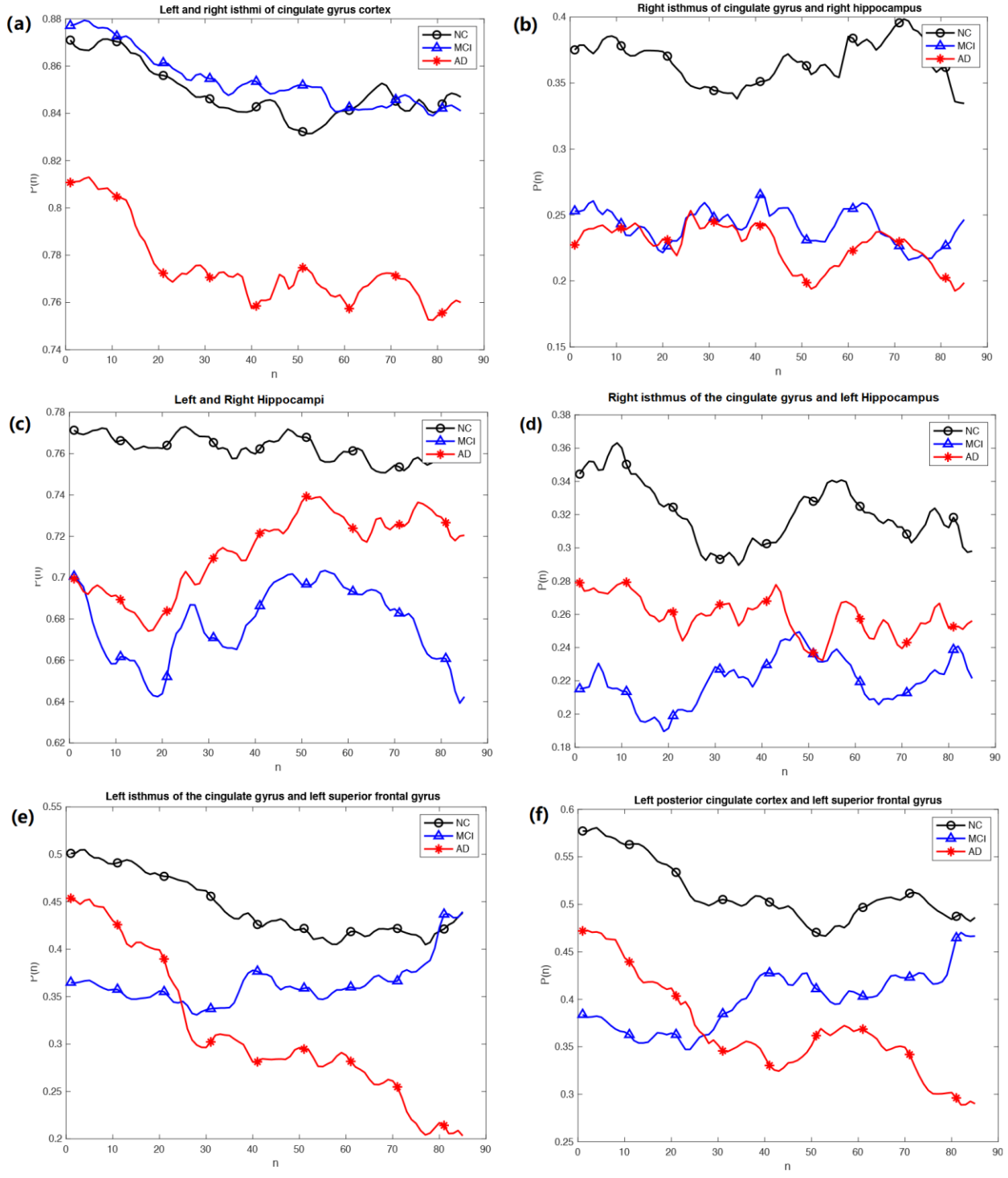

Figure 2 Fading effect in the functional connectivity of AD, MCI and NC, in terms of Pearson Correlation: (a) Between the left and right isthmi of the cingulate gyrus; (b) Between the right isthmus of the cingulate gyrus and the right hippocampus; (c) Between the left and right hippocampi; (d) Between the right isthmus of the cingulate gyrus and the left hippocampus; (e) Between the left isthmus of the cingulate gyrus and the left superior frontal gyrus; (f) Between the left posterior cingulate cortex and the left superior frontal gyrus.

2.3 An Explanation from the Information Theory Perspective

The physical meaning of the fading effect in Pearson correlation can be better understood through its relationship with mutual information. Let X be a random variable with sample space Ω_x, and $P_X(x)$ the probability that $X = x$. Then, the entropy of X is defined as

$$H(X) = -\sum_{x\in\Omega_x} P_X(x) log P_X(x) \qquad (2)$$

If we consider X as an information source that emits messages from Ω_x, then the physical meaning of $H(X)$ is the average uncertainty or information per message of the source X before it is observed.

Let X and Y represent the observed brain signals at two different brain regions, then the mutual information between X and Y is defined as

$$I(X,Y) = H(X) - H(X|Y), \qquad (3)$$

where $H(X|Y)$ is the conditional entropy. Let Ω_y be the sample space of Y, $P_Y(y) = Pr\{Y = y\}$, and $P_{X|Y}(x|y) = Pr\{X = x|Y = y\}$, then

$$\begin{aligned} H(X|Y) &= -\sum_{y\in\Omega_y} P_Y(y) \sum_{x\in\Omega_x} P_{X|Y}(x|y) log P_{X|Y}(x|y) \qquad (4)\\ &= -\sum_{x\in\Omega_x}\sum_{y\in\Omega_y} P_{X,Y}(x,y) log\left[\frac{P_{X,Y}(x,y)}{P_Y(y)}\right] \qquad (5)\end{aligned}$$

where $P_{X,Y}(x,y) = Pr\{X = x, Y = y\}$ is the joint probability. The physical meaning of $H(X|Y)$ is the average uncertainty or information left in X per message after Y is observed. This implies that

The mutual information $I(X, Y)$ = the total uncertainty in X − the uncertainty left in X after Y is observed.

That is, the physical meaning of the mutual information is "the average uncertainty removed about X per message after Y is observed." For this reason, the mutual information $I(X, Y)$ is also explained as the information which is successfully transmitted or passed (per message on average) through the channel between X and Y. It can be shown that

$$\begin{aligned} I(X,Y) &= I(Y,X) \qquad (6)\\ &= H(X) + H(Y) - H(X,Y), \qquad (7)\end{aligned}$$

where $H(X,Y)$ is the joint entropy of X and Y defined as

$$H(X,Y) = -\sum_{x\in\Omega_x}\sum_{y\in\Omega_y} P_{X,Y}(x,y) log P_{X,Y}(x,y) \qquad (8)$$

In general, the Pearson correlation represents the linear dependence between two brain regions, while the mutual information characterizes both linear and non-linear dependence between them. However, closed-form relationship between Pearson correlation and mutual information can be derived under certain conditions. More specifically, when X and Y follow normal distributions and their joint distribution is bivariate normal, that is $X \sim \mathcal{N}(\mu_x, \sigma_x^2)$, $Y \sim \mathcal{N}(\mu_y, \sigma_y^2)$ and

$$\binom{X}{Y} \sim \mathcal{N}\left(\binom{\mu_x}{\mu_y}, \quad \Sigma\right), \qquad \Sigma = \begin{pmatrix} \sigma_x^2 & \rho\sigma_x\sigma_y \\ \rho\sigma_x\sigma_y & \sigma_y^2 \end{pmatrix}$$

then it can be proved that [42]

$$I(X,Y) = -\frac{1}{2} log(1-\rho^2), \tag{9}$$

where ρ is the ensemble average representation of Pearson correlation coefficient between X and Y. In fact,

$$H(X) = \frac{1}{2} log(2\pi e\sigma_x^2); H(Y) = \frac{1}{2} log(2\pi e\sigma_y^2); \tag{10}$$

$$\begin{aligned} H(X,Y) &= \frac{1}{2} log[(2\pi e)^2|\Sigma|] \\ &= \frac{1}{2} log[(2\pi e)^2(1-\rho^2)\sigma_x^2\,\sigma_y^2] \end{aligned} \tag{11}$$

Equation (9) then follows from equations (7), (10) and (11).

Note that each fMRI voxel can represent a million or so brain cells. Based on the central limit theorem, the underlying distribution of the BOLD signal is generally modelled as Gaussian. The mutual information corresponding to the time-varying Pearson correlation is illustrated in Figure 3. Our results indicate that compared with NC subjects, in general, AD patients have a much lower amount of successfully transmitted information among these brain regions, and MCI subjects tend to experience less severe decrease in mutual information.

We would like to explore this phenomenon from two aspects. First, is there information transmission among the brain regions during the resting-state? The answer is yes. In literature, it has been observed that the brain's operations are mainly intrinsic, involving the acquisition and maintenance of information for interpreting, responding to and predicting environmental demands [43, 46]. In [46], the author compared the intrinsic activity with the activity evoked by tasks and found that: the brain's on-going *intrinsic (i.e., resting state) activity* is substantially and consistently larger than the task activity and consistently so for all levels of analysis. It has also been reported that the brain's intrinsic activity is spontaneous, and exhibits a surprising level of spatial and temporal organization across the whole brain [47, 48]. The observed spatial coherence of the intrinsic activity across the brain demonstrates the existence of functional connectivity as expressed in the maps of resting state coherence, and the intrinsic functional connectivity analyses also demonstrate the existence of large-scale brain functional connectivity networks [48]. In other words, existing work on intrinsic activity demonstrated that for the normal functioning of brain, there are intrinsic information exchanges among the brain regions even during the resting-state.

We would like to emphasize here that the results shown in Figures 2 and 3 reflect the averaged functional connectivity level within each group, either AD, or MCI, or NC. While we have no control over the intrinsic functional connectivity level, from the numerical results obtained from the NC group, it is reasonable to say that for normal brain functioning, the intrinsic functional connectivity level needs to be maintained above a certain threshold, which may vary with the significance of the brain region pair in the network, and may also vary from individual to individual.

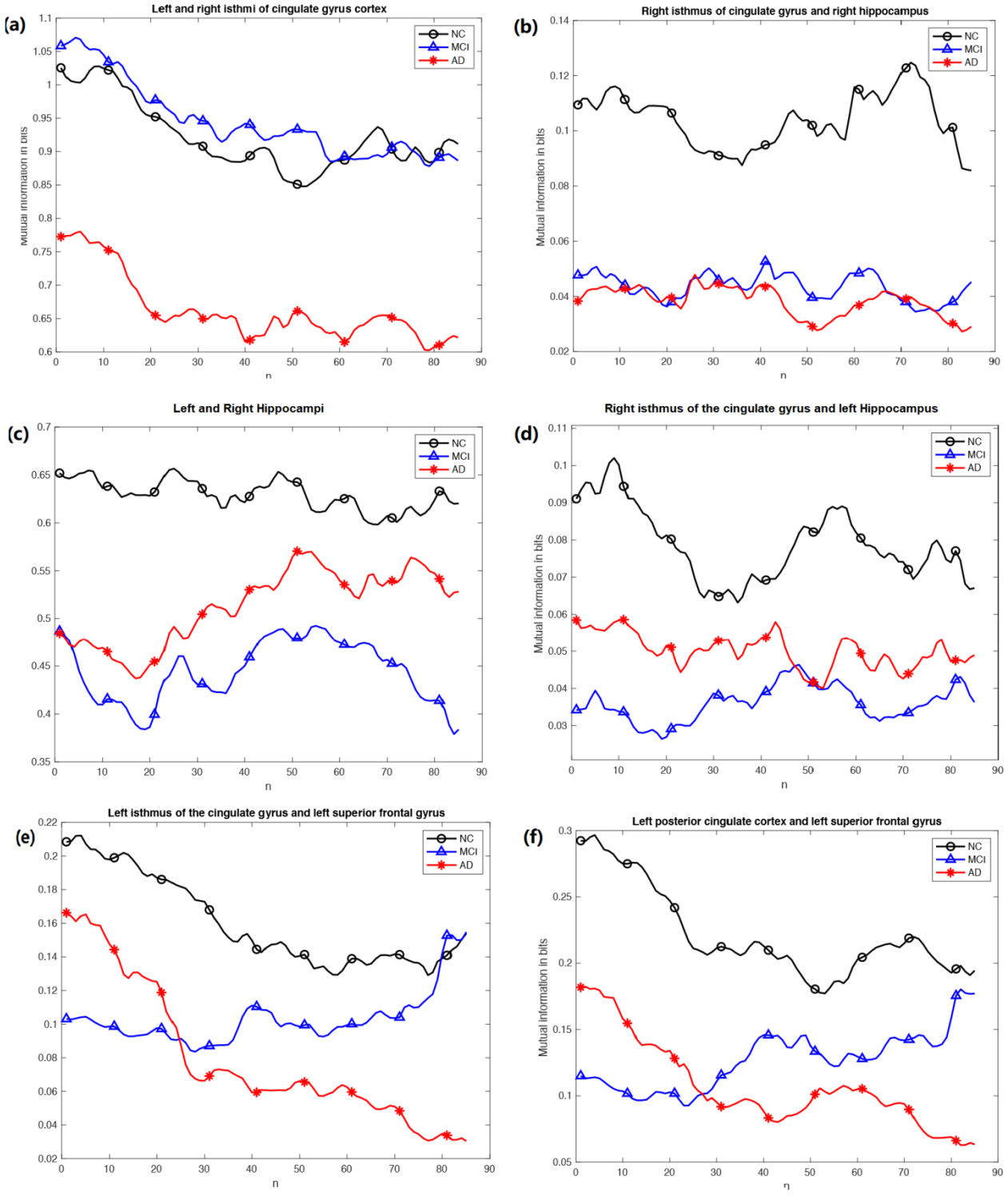

Figure 3 Fading effect in the functional connectivity of AD, MCI and NC, in terms of mutual information: (a) Between the left and right isthmi of the cingulate gyrus; (b) Between the right isthmus of the cingulate gyrus and the right hippocampus; (c) Between the left and right hippocampi; (d) Between the right isthmus of the cingulate gyrus and the left hippocampus; (e) Between the left isthmus of the cingulate gyrus and the left superior frontal gyrus; (f) Between the left posterior cingulate cortex and the left superior frontal gyrus.

Second, whether channel fading could be a cause for the decrease in the successful information exchanges in AD? To find the answer to this question, we need to take a more careful look at the neurobiological basis for the weakening of functional connectivity in AD. In [17, 49, 50], it was reported that the most vulnerable neurons in AD are the large pyramidal neurons, particularly the association neurons with long projections that formulate the communication channels or links between the brain regions. It was also reported that in AD, neurons vulnerable to injury or cell death are characterized by significant decreases in the expression of genes related to mitochondrial metabolism and energy production [17]. Moreover, vulnerable neurons often suffer loss of dendrites that leads to a significant impairment of synaptic transmission, but the cells may still survive for a time in this altered state [51, 53]. These evidences indicate that AD patients suffer selective channel fading in certain brain regions, leading to the loss in functional connectivity or successful information transmission among these regions.

Last but not least, from the numerical results, strong information exchange (i.e. higher intrinsic functional connectivity level) can be observed between the left and right isthmi of the cingulate gyrus, and the left and right hippocampi for all subjects. This may be an indication that these regions play more significant roles in the brain network. This also explains that why in the simulations (as shown in Section III), the feature vectors constructed based on the functional connectivity among the left and right isthmi of the cingulate gyrus, and the left and right hippocampi result in the highest accuracy for AD, MCI and NC classification.

3. Classification of AD, MCI and NC based on Network-Level Time-Varying Connectivity Pattern Analysis

In this section, we conduct the classification of AD, MCI and NC based on the time-varying functional connectivity characterized using the Pearson correlation vector. Instead of considering just one pair of regions, we will formulate a region-of-interest (ROI) subnetwork and perform network level connectivity pattern analysis. After the feature vectors are generated, they will be processed using a regularized LDA for dimension reduction, and then be fed into the multi-class AdaBoost classifier for classification of AD, MCI and NC.

ROI Sub-Network Formulation: The default mode network (DMN) is one of the well-studied networks at the resting state [48]. Previous resting-state fMRI studies have demonstrated that the DMN is affected by AD [19, 54-56]. Both hippocampus and ICC are part of the DMN, and can be well defined anatomically through the FreeSurfer software [56], even in brains with abnormal anatomy [19]. Recall that the paper by Zhu *et al* [19] specifically demonstrated that the functional connection between hippocampus and ICC was reduced in AD. Motivated by the observations above, in this paper, we select the right and left hippocampi and ICCs (4 regions) as our ROI sub-network.

Network-Level Time-Varing Connectivity Pattern Analysis: Our network level time-varying connectivity pattern analysis is carried out following the procedure below.

First, we calculate the Pearson correlation vectors between all possible pairs of the ROIs within the group to formulate the feature vectors. Assuming the length of the Pearson correlation vector be N_p. As we now have 4 regions in the ROI sub-network, so 6 Pearson Correlation vectors can be calculated, each corresponds to a pair of ROIs. For each subject j, we can then obtain a d–dimensional ($d = 6N_p$) vector $\mathbf{x}_j$, by stacking all of the Pearson correlation vectors, with each

vector corresponding to a pair of ROIs. When we have *n* subjects, we get the feature vector set $\{\mathbf{x}_1,\cdots,\mathbf{x}_n\}$.

Second, using a regularized LDA (please refer to the supplementary material), we map $\{\mathbf{x}_1,\cdots,\mathbf{x}_n\}$ to a one-dimensional subspace or axis, where the differences among AD, MCI and NC subjects are maximized, and denote the projected vectors as $\{y_1,\cdots,y_n\}$. Here regularized LDA is used to reduce the noise effect (caused by both biological variability and measurement errors) in the size-limited data set.

Finally, we construct the decision trees based on $\{y_1,\cdots,y_n\}$ and carry out the classification using the multi-class AdaBoost classifier. Please note that detailed information on decision tree construction and multi-class classification using AdaBoost is provided in the supplementary material.

Next, we evaluate the performance of the proposed network-level time-varying connectivity analysis in the classification AD, MCI and NC, and also compare that with the results in [41], where time-invariant connectivity analysis was used, that is, only the Pearson correlation value, rather than the Pearson vector, was used to characterize the functional connectivity between ROI pairs.

The performance of the classifier is evaluated using the Leave-One-Out (LOO) cross-validation. As was pointed out in [57], comparing with other method, LOO might have a higher estimate error. However, in our study, as the size of data sample is small, splitting the data into two sets based on a threshold would generate a biased testing set which contains only a few subjects for each category. That is why LOO is chosen to evaluate the performance of the classifiers in this case. As described earlier, the ROIs used are the hippocampus and ICC from both hemispheres of the brain.

In our simulation, for the calculation of the Pearson correlation vector, the length of the sliding window was chosen as $L = 40$ and the time difference between two successive sliding windows was chosen as $J = 20$. For $n = 1,\cdots,N_p$, let $\mathrm{p} = [p(1),p(2),\cdots,p(N_p)]$ be the correlation vector we obtained. We define $\widetilde{\boldsymbol{p}} = [p_{avg}, p_{min}, p_{max}]$, where p_{avg}, p_{min}, p_{max} denote the mean, minimum value and maximum value of $\boldsymbol{p}$. We then use $\widetilde{\boldsymbol{p}}$ to construct the feature vector instead of using $\boldsymbol{p}$ directly. This design generates $6 \times 3 = 18$ features for each subject (Table 1 and Table 2).

Note that in [41], we compared the performance of regularized LDA, combined with different classifiers, including Bayesian, AdaBoost, L2 penalty and radial basis function (RBF) kernel. It was found that regularized LDA, together with the AdaBoost classifier, delivered the best performance. Therefore, here we apply regularized LDA and AdaBoost for AD, MCI and NC classification to performance both static connectivity analysis (which uses only single Pearson correlation values) and dynamic connectivity analysis (which use the Pearson correlation vectors). It can be seen that the dynamic connectivity analysis delivers much more accurate results, and can achieve a prediction accuracy of 90.9%, 75.0, and 80.0% for NC, MCI and AD, respectively. Also, as expected, compared with NC subjects and AD patients, MCI patients is generally more difficult to be identified, and the classification accuracy for MCI patients is much lower than that for AD and NC subjects. This is because that MCI is a transitional stage of dementia between NC and AD, and hence MCI patients generally share some similar characteristics in functional brain connectivity with AD patients or NC subjects. As a result, the classification algorithm is prone to mis-recognize MCI subjects as AD or NC subjects.

Table 1 Regularized LDA with AdaBoost: Static connectivity analysis.

	Predicted Class			Recall
Actual Class		NC	MCI	AD	
	NC	10	2	0	83.3%
	MCI	2	7	2	63.6%
	AD	1	1	8	80.0%
Precision		76.9%	70.0%	80.0%	

Table 2 Regularized LDA with AdaBoost: Dynamic connectivity analysis.

	Predicted Class			Recall
Actual Class		NC	MCI	AD	
	NC	10	1	1	83.3%
	MCI	1	9	1	81.8%
	AD	0	2	8	80.0%
Precision		90.9%	75.0%	80.0%	

4. Conclusions and Discussions

In this paper, first, we evaluated the possible fading effect in time-varying functional connectivity of AD, MCI and NC subjects based on the resting-state fMRI data. We revisited the relationship of Pearson correlation and mutual information (which quantifies the successful information exchange between the brain regions), and provided an explanation on the physical meaning of Pearson correlation from an information theoretic perspective. Second, relying on network-level time-varying functional connectivity pattern analysis, we performed AD, MCI and NC classification using machine learning tools, including regularized LDA and multi-class AdaBoost classifier. It was observed that, compared with static network connectivity pattern analysis that extracts only the region-level spatial variability, dynamic network connectivity pattern analysis, which exploits both the temporal and spatial variability in functional connectivity, can achieve much higher accuracy in the classification of AD, MCI and NC. Overall, our results are largely consistent with existing results in dynamic functional connectivity analysis for AD, MCI and NC. More specifically, we would like to share the following observations and discussions.

a) *Selective loss in intrinsic functional connectivity and possible channel fading in AD:* In this research, it was observed that compared with NC subjects, AD patients suffer much more severe and long lasting fading in the intrinsic functional connectivity level (either measured by Pearson correlation or the mutual information) especially in the DMN. MCI subjects tend to experience less severe fading in functional connectivity than AD patients in general, however, the functional connectivity performance of MCI may be tangled together with that of either NC or AD. This explains why it is more difficult to distinguish MCI from NC and AD. In certain brain regions, such as the left and right isthmi of the cingulate gyrus, the left posterior cingulate cortex and the left superior frontal gyrus, for example, AD patients started with a relatively high functional connectivity level, but were not able to maintain it along the time.

The underlying neurobiological basis is that the most vulnerable neurons in AD are the large

pyramidal neurons, particularly the association neurons with long projections that formulate the communication channels or links between the brain regions. The vulnerable neurons are characterized by significant decreases in the expression of genes related to mitochondrial metabolism and energy production, and often suffer from loss of dendrites that leads to a significant impairment of synaptic transmission. This implies that very likely, AD patients suffer selective channel fading in certain brain regions, which leads to the loss in intrinsic functional connectivity or successful information transmission among these regions.

In some brain regions, such as the left and right hippocampi, and the right isthmus of the cingulate gyrus and left hippocampus, AD patients showed higher functional connectivity level than MCI subjects. This reflects the compensatory mechanism of the brain, and is also consistent with existing results. Moreover, strong information exchange (i.e. higher intrinsic functional connectivity level) were observed between the left and right isthmi of the cingulate gyrus, and the left and right hippocampi for all subjects. This reflects the significance of these regions and the corresponding links in the brain network.

b) *Network-level dynamic connectivity pattern analysis and classification of AD, MCI and NC:* The network-level dynamic connectivity pattern analysis used here exploited the dynamic function connectivity among all the region pairs in a selected subnet work. This can be regarded as a method that extracts both the temporal variability and the region-level spatial variability in functional connectivity. As expected, it delivers better performance in AD, MCI and NC classification than its static counterpart that exploits only the region-level spatial variability. In the numerical analysis, we explored different sets of ROIs, it was observed that the sub-network consisting of the left and right isthmi of the cingulate gyrus and the left and right hippocampi achieved the highest accuracy in classification. One possible reason is that, as we mentioned earlier, these regions tend to have stronger functional connectivity comparing with other brain regions, as shown in Section II.

We would like to point out that our analysis was based on a modest data size, hence one of the contributions of the paper was that we introduced a new regularized LDA approach, aiming to achieve more accurate statistical estimation based on a limited sample size. The proposed framework here can be applied to other classification problems as well, especially those under limited sample size.

c) *Limitations and future work:* Following our discussions in Section II.C, from the information theoretic perspective, the progressive connectivity weakening in AD may be because that the channels or the links between the brain regions experience more severe fading as time goes on. In addition to qualitative description, it would be desirable if we can achieve more quantitative characterization on the channel fading, so as to develop new biomarkers to distinguish AD and MCI from NC. More specifically, if we can evaluate the channel coherence time (i.e. the time duration over which the channel is considered to be invariant) and channel coherence bandwidth (i.e. the frequency range over which the channel magnitude spectrum is considered to be flat), and relate channel coherence time and bandwidth to the dwell-time in brain subnetwork configuration and loss in functional connectivity, respectively, we may get a better understanding of brain functions and the progression of AD.

Moreover, circuits in different brain regions form a dynamic communication network, and connectivity between the brain regions generates our minds. Normal brain functions rely on both the normal functioning of each related brain region and successful information exchange or

sufficient connections between them. Therefore, in addition to connectivity, we also need to investigate the neuronal activity in individual brain regions. That is, to get better understanding about AD, we should examine the information processing, storage and transceiving capabilities of each individual brain region as well. It would also be very interesting to explore the time-varying functional connectivity between brain regions for MCI or early AD patients under simple cognitive tasks. This would make it possible for us to further quantize the dynamic information exchange between brain regions, so as to identify early stage AD more accurately and hence assist timely diagnosis and treatment.

Supplementary Material

The supplementary material provided detailed information on (i) fMRI data acquisition, pre-processing and ROI generation; (ii) Regularized LDA; (iii) Basic tree construction and the multi-class Adaboost classifier. These processes/algorithms have been used to generate our numerical results. The following additional materials are downloaded at the page of this paper.

1. Supplementary Material, S1: fMRI Data Acquisition, Pre-Processing and ROI Generation.
2. Supplementary Material, S2: Regularized Linear Discriminant Analysis.
3. Supplementary Material, S3: Decision-Tree Construction and the Multi-Class AdaBoost Classifier.

Author Contributions

Tongtong Li initiated the idea of fading effect analysis in time-varying functional connectivity and its application in AD, MCI and NC classification. Yuan Liang, Yu Zheng and Brighty Renli helped with the numerical analysis. Tongtong Li wrote the paper. David C. Zhu and Yu Fang edited the paper and helped with result explanation. David C. Zhu is the owner of the fMRI data.

Competing Interests

The authors have declared that no competing interests exist.

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