Multiple Connection Pattern Combination From Single-Mode Data for Mild Cognitive Impairment Identification

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Mild cognitive impairment (MCI) is generally considered to be a key indicator for predicting the early progression of Alzheimer’s disease (AD). Currently, the brain connection (BC) estimated by fMRI data has been validated to be an effective diagnostic biomarker for MCI. Existing studies mainly focused on the single connection pattern for the neuro-disease diagnosis. Thus, such approaches are commonly insufficient to reveal the underlying changes between groups of MCI patients and normal controls (NCs), thereby limiting their performance. In this context, the information associated with multiple patterns (e.g., functional connectivity or effective connectivity) from single-mode data are considered for the MCI diagnosis. In this paper, we provide a novel multiple connection pattern combination (MCPC) approach to combine different patterns based on the kernel combination trick to identify MCI from NCs. In particular, sixty-three MCI cases and sixty-four NC cases from the ADNI dataset are conducted for the validation of the proposed MCPC method. The proposed method achieves 87.40% classification accuracy and significantly outperforms methods that use a single pattern.

Keywords: functional connectivity, effective connectivity, multiview, multimodal, mild cognitive impairment

INTRODUCTION

As the most concerning neurodegenerative disease, Alzheimer’s disease (AD) comes to be the most common causes of dementia (Gaugler et al., 2016). In particular, AD can seriously interfere with patient’s daily lives, and eventually lead to deaths. Thus, a natural ambition is to delay the progression of AD during its early stages via pharmacological and behavioural interventions. In particular, mild cognitive impairment (MCI) is often considered an early indicator of potential progression to AD (Wee et al., 2012). Nearly 10–15% of patients with MCI progress to AD per year (Misra et al., 2009). Therefore, the accurate diagnosis of MCI has attracted considerable attention.

Recently, functional magnetic resonance imaging (fMRI) comes to a popular technique to reveal brain activities and patterns for the MCI diagnosis (Kevin et al., 2008). However, due to the random and asynchronous spontaneous brain activity between the subject and the scanner, it is still a challenge to identify MCI patients and normal controls (NC) based on fMRI alone. In contrast, the connectome-based methods provide a new stable biomarker which potentially helps us to understand brain information (Stam, 2014). Specifically, several studies have illustrated that several neurological diseases, such as AD (Chen et al., 2016), MCI (Gao et al., 2020), autism...
spectrum disorder (Li et al., 2017), and Parkinson’s disease (Abós et al., 2017) are highly related to the functional brain connections.

Notably, the exiting works are highly dependent on the estimated networks or connections. Thus, several efforts have been devoted to estimating the ideal network by incorporating additional biological priors into BCs to improve the discriminative ability of the networks, e.g., sparsity (Lee et al., 2011), scale-free priors (Li et al., 2017), modularity (Qiao et al., 2016; Li et al., 2020c; Li et al., 2020a), and group sparsity (Liang et al., 2018; Zhang et al., 2019). Moreover, the data noisy prior (Li et al., 2019) and domain knowledge prior (Li et al., 2020d) can also be adopted. However, these approaches may still be insufficient to identify MCI from NCs, since they focus only on a single connection pattern, which fails in combining the information from the multiple connections for neurological disorder diagnosis.

In this paper, we provide a simple yet valuable approach, i.e., multiple connection pattern combination (MCPC), which combines the information from multiple connection patterns to achieve a better diagnostic performance of neurological disorders. In particular, a multi-kernel support vector machine (MK-SVM) trick is employed as a naive attempt to combine the multiple connection patterns for the MCI diagnosis. Further, an MCI identification task is explored to verify the performance of the proposed MCPC method. The highlights of this paper are as follows.

1) To our best knowledge, MCPC is the first attempt that combines the multiple connection patterns to identify MCI from NCs. The experimental results also confirm that the proposed MCPC scheme significantly outperforms single-pattern methods.

2) We identify hubs and consensus connections based on the proposed multiple connection patterns. Analyses of graph theory attributes and critical functional connectivity are performed to discriminate individuals with MCI from NCs and identify the pathological mechanism of MCI.

### MATERIALS AND METHODS

#### Data Preparation

The publicly available neuroimaging data from the Alzheimer’s disease Neuroimaging Initiative (ADNI)\(^1\) database (Jack et al., 2010) is adopted. Notably, 127 participants, including sixty-three MCIs and 64 NCs were included in this experiment. The SPM8 toolbox\(^2\) is used to pre-process the fMRI data according to a commonly adopted pipeline for fMRI. Finally, the pre-processed BOLD time series signals were partitioned into 116 ROIs, based on the Automated Anatomical Labeling (AAL) atlas.

#### Construction of Multiple Brain Connection

We adopted the commonly-used BC estimation model to discover the connection patterns, including Pearson’s correlation (PC), sparse representation (SR) and Granger causality mapping (GCM). Let \(X \in R^{T \times N}\) the BOLD signal matrix, where \(T\) is the volume length and \(N\) is the ROI number. Denote \(x_i \in R^T\) the fMRI time series derived from the \(i\)th ROI \(i = 1, \cdots, N\). Then, the details of these methods are given as follows.

#### Pearson’s Correlation

Pearson’s correlation (PC) is among the most simplicity and intuitiveness scheme for the BC estimation. The edge weights of the PC-based BC \(W = (W_{ij}) \in R^{N \times N}\) is in the following:

\[
W_{ij} = \frac{(x_i - \bar{x}_i)(x_j - \bar{x}_j)}{\sqrt{(x_i - \bar{x}_i)^2(x_j - \bar{x}_j)^2}}
\]  

(1)

where \(x_i - \bar{x}_i\) is a centralized counterpart of \(x_i\).

#### Partial Correlation With Sparse Representation

Due to the cofounding effect caused by the PC-based method, the partial correlation method involves regressing complex factors from other ROIs that naturally come into being (Huang et al., 2010). Inspired by the sparsity nature of the brain connection, one popular solution is to incorporate an additional \(l_1\)-norm constraint, resulting in a sparse representation (SR)-based BC estimation scheme, as follows.

\[
\min_w \sum_{i=1}^n \|x_i - \sum_{j \neq i} W_{ij} x_j\|^2 + \lambda \sum_{j \neq i} |W_{ij}|
\]  

(2)

where \(\lambda\) is the hyper-parameter for controlling the balance of sparsity and partial correlation.

#### Granger Causality Mapping

Granger causality mapping (GCM) models the effective connectivity, i.e., causality relations among nodes, which connection is thereby nonsymmetric (Goebel et al., 2003). Specifically, given two-time \(x[n]\) and \(y[n]\), the Granger causality mapping process from \(x[n]\) to \(y[n]\) is defined as follows:

\[
F_{x,y} = \ln\left(\frac{\sum \xi_{ij}}{\sum \eta_{ij}}\right)
\]  

(3)

where \(\xi_{ij}\) and \(\eta_{ij}\) are the residuals of the restricted and unrestricted regression models, respectively, and \(\Sigma\) indicates the variance.

#### Combination of Multiple Connection Patterns

The simplest way to combine the information for multiple connection patterns is to concatenate all of the data directly. However, this approach is quite inappropriate in cases with high-dimension curves and small samples. To achieve this, this paper provided Multiple Connection Pattern Combination (MCPC), which is given in Figure 1. Specifically, an MK-SVM model is adopted to combine multiple information. Notably, this is the first attempt, which combines the information from different connectomes derived from single-mode data. Here, the primal
The problem of MK-SVM is given as follows: (Rakotomamonjy et al., 2007)

\[
\min_w \frac{1}{2} \sum_{m=1}^{M} \beta_m \|u^m\|^2 + C \sum_{i=1}^{n} \xi_i
\]

s.t. \( y_i \left( \sum_{m=1}^{M} \beta_m (w^m)^T \phi_m(x_i^m) + b \right) \geq 1 - \xi_i \)

\( \xi_i \geq 0, i = 1, \ldots, n \)

where \( n \) is the number of training samples and \( M \) is the number of connection patterns, \( y_i \in \{1, -1\} \) representing the label of the patients or healthy controls from the \( i \)th sample. \( \phi_m \) represents the mapping function, \( w^m \) represents the hyperplane in the Represent Hilbert Kernel Space (RHKS) and \( \beta_m \) denotes the combined weight of the \( m \)th connection pattern.

Then, the dual form of the MK-SVM can be expressed as:

\[
\max_{\alpha} \sum_{i=1}^{n} \alpha_i - \frac{1}{2} \sum_{i,j=1}^{n} \alpha_i \alpha_j y_i y_j \sum_{m=1}^{M} \beta_m k^m(x_i^m, x_j^m)
\]

s.t. \( \sum_{i=1}^{n} \alpha_i = 0 \)

\( 0 \leq \alpha_i \leq C, i = 1, \ldots, n \)

where \( k^m(x_i^m, x_j^m) = \phi_m(x_i^m)^T \phi_m(x_j^m) \) \( \beta_m \) is learned based on Alain’s method (Rakotomamonjy et al., 2007). Additionally, we utilized the commonly-used linear kernel as a naive attempt due to its simplicity. The predictive level based on the MK-SVM can be formulated as follows:

\[
f(x_1, x_2, \ldots, x_M) = \text{sign} \left( \sum_{i=1}^{n} y_i \alpha_i \sum_{m=1}^{M} \beta_m k^m(x_i^m, x) + b \right)
\]
Accuracy $= \frac{TP + TN}{TP + FP + TN + FN}$ (7)

Sensitivity $= \frac{TP}{TP + FN}$ (8)

Specificity $= \frac{TN}{TN + FP}$ (9)

Here, TP (TruePositive) is the number of the positive subjects that are correctly classified in the ASD identification task. Similarly, TN (TrueNegative), FP (FalsePositive) and FN (FalseNegative) are the numbers of their corresponding subjects, respectively.

The classification results based on single connection patterns are given in Table 1, which results are achieved by a single linear kernel SVM classifier. In addition, the results based on combining the partial connection patterns (e.g., PC + SR, PC + GCM and SR + GCM) are also reported. The ROC curve is given in Figure 4.

From these results in Table 1 and Figure 4, we can easily observe that the performance of MCPC achieves much better results than that of the single-kernel SVM. The results indicate the rationality of the proposed MCPC. To investigate the significance of model performance improvement, differences between various AUCs were compared by using a Delong test (Delong et al., 1988), the proposed MCPC methods are significantly superior to results of the single pattern, e.g., PC, SR, GCM under 95% confidence interval with $p$-value equals to 0.0251, 0.041 and 0.005, respectively. The superior performance illustrated that the proposed MCPC approach can significantly improve the classification performance with only single modal data. In addition, although the MCPC only use single-mode data, it can still significantly improve the accuracy of the MCI diagnosis.

**Distribution of Hubs**

The hub nodes (the top 5% degree of brain nodes) of the MCI and NC groups based on three different BC network estimation methods are obtained. As shown in Tables 2-5, the
distribution of hub nodes of the networks estimated by the PC, SR and GCM methods are similar. Most hubs are mainly distributed in the parietal lobes, temporal, and frontal, which correspond to the default mode network (DMN) and frontoparietal task control (FTC) network. Furthermore, the results suggest that hub nodes in the NC group are mainly located in the DMN. In comparison, the distribution of hub nodes in patients with MCI covers a relatively wide range of brain connection distributions, such as the frontoparietal task control network and visual network, in addition to the DMN.

**Consensus Connections**

In this study, the nested cross-validation scheme was adopted to evaluate the performance of the proposed MCPC. In particular, the selected connections in each validation loop might vary due to the validation resampling. Thus, we record the consensus connections and regard them as the most discriminative features for differentiating individuals with MCI from NCs (Li et al., 2020b). The consensus connections based on different...
connection pattern methods are shown in Figure 5. In addition, the degrees of consensus connection for different patterns are given in Tables 6-8. As shown in Tables 6-8, among the three BC estimation methods, the brain connection based on the PC method exhibits the maximum number of consensus connections. It is worth noting that the consensus connections with significant differences between MCI individuals and NCs are associated with multiple brain regions: the frontal lobe, occipital lobe, cingulate gyrus, hippocampus, and thalamus. Moreover,

DISCUSSION
Classification With Different Network Estimation Methods
From the classification results in Table 1, the SR method exhibited the highest accuracy compared to the PC and GCM methods. Although the PC method obtained more consensus connections, GCM considered more graph theory information with directions, SR achieves the best results in the single-pattern methods. These results indicated that the SR approach can
The Distribution of Discriminative Features
The hub nodes of the consensus connections obtained from the three different BC estimation methods (PC, SR and GCM) are given in Tables 6-8. It can be significantly found that the most discriminative brain regions and functional connections between the MCI and NC groups were mainly distributed in the temporal, frontal and parietal lobes, which correspond to the DMN, FTC, VN, and AN. Previous studies have verified that these subnetworks correspond to various cognitive functions, such as attention, execution, and spatial positioning (Rolle et al., 2017; Bi et al., 2018). Our results suggest that patients with MCI may have altered subnetworks and corresponding cognitive functions. In particular, the DMN exhibited the most significant discriminative ability, which was consistent with previous studies of brain connections involving MCI and NC groups (Gao et al., 2020). In fact, the DMN has always been regarded as the key role for cognitive function (Anticevic et al., 2012; Liu et al., 2019). In addition, we found abnormalities in the subcortical network involving the thalamus, putamen, and amygdala in MCI. In recent years, several studies have indicated that the individuals in the early stages of AD, including subjective cognitive decline and MCI, exhibit abnormalities in subcortaneous nuclei, e.g., basal forebrain, basal ganglia, and thalamus (Fernández-Cabello et al., 2020; Xu et al., 2021). In a follow-up study, we intend to use a more detailed brain atlas than that used in this study to further explore subcortical nuclei in the early stage of AD.

CONCLUSION
In this paper, we attempt to improve the performance of MCI identification by single-mode data by generating multi-view information. Specifically, we utilized the information associated with multiple brain connection patterns, which are derived from the fMRI data. The MKSVM is selected to identify the MCI from the NCs as a naive attempt, which successfully combines the information from the multiple brain connection patterns. The experimental results reveal that the MCPC strategy can significantly improve the diagnosis performance than the single pattern. Further analysis of the hub nodes and consensus connections among brain connections emphasize the importance of the DMN in the pathological mechanism associated with the early stage of AD.

DATA AVAILABILITY STATEMENT
The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding authors.

AUTHORS CONTRIBUTIONS
XX and WL drafted the initial manuscript. LP and XG collected and pre-processed the functional MRI data. ZW and XX designed experiments and analyzed the final results. XG and PJW revised the manuscript.

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REFERENCES

Abós, A., Baggio, H. C., Segura, B., García-Díaz, A. I., Compta, Y., Martí, M. J., et al. (2017). Discriminating Cognitive Status in Parkinson’s Disease through Functional Connectomics and Machine Learning. Sci. Rep. 7 (1), 1–13. doi:10.1038/srep45347
Anticevic, A., Cole, M. W., Murray, J. D., Corlett, P. R., Wang, X.-J., and Krystal, J. H. (2012). The Role of Default Network Deactivation in Cognition and Disease. Trends Cognitive Sciences 16, 584–592. doi:10.1016/j.tics.2012.10.008
Bi, X.-A., Sun, Q., Zhao, J., Xu, Q., and Wang, L. (2018). Non-linear ICA Analysis of Resting-State fMRI in Mild Cognitive Impairment. Front. Neurosci. 12, 413. doi:10.3389/fnins.2018.00413

Chen, G., Shu, H., Chen, G., Ward, B. D., Antuono, P. G., Zhang, Z., et al. (2016). Staging Alzheimer’s Disease Risk by Sequencing Brain Function and Structure, Cerebrospinal Fluid, and Cognition Biomarkers. J. Natl. Cancer Inst. 108, 193–204. doi:10.1093/jnci/djv108

Delong, E. R., Delong, D. M., and Clarke-Pearson, D. L. (1988). Comparing the Areas under Two or More Correlated Receiver Operating Characteristic Curves: a Nonparametric Approach. Biometrics 44, 837–845. doi:10.2307/2531595

Fernández-Cabello, S., Kronbichler, M., VAN Dijk, K. R. A., Goodman, J. A., Spreng, R. N., Schmitz, T. W., et al. (2020). Basal Forebrain Volume Reliably Predicts the Cortical Spread of Alzheimer’s Degeneration. Brain 153, 2302–2317. doi:10.1093/brain/awaa102
Liang, X., Vaughan, D. N., Connelly, A., and Calamante, F. (2018). A Novel Group-Learning Approach to Improve the Accuracy of Functional Brain Network Estimation for Mild Cognitive Impairment Classification. *Front. Neurosci.*, 14, 165. doi:10.3389/fnins.2020.00165

Huang, S., Li, J., Sun, L., Ye, J., Fleisher, A., Wu, T., et al. (2010). Learning Brain Connectivity of Alzheimer’s Disease by Sparse Inverse Covariance Estimation. *Neuroimage* 50, 935–949. doi:10.1016/j.neuroimage.2009.12.120

Hyekyoung Lee, H., Dong Soo Lee, D. S., Hyejin Kang, H., Boong-Nyun Kim, B. N., Huang, S., Li, J., Sun, L., Ye, J., Fleisher, A., Wu, T., et al. (2010). Learning Brain Connectivity of Alzheimer’s Disease by Sparse Inverse Covariance Estimation. *Neuroimage* 50, 935–949. doi:10.1016/j.neuroimage.2009.12.120

Wee, C.-Y., Yap, P.-T., Zhang, D., Denny, K., Brown, J. N., Potter, G. G., et al. (2012). Identification of MCI Individuals Using Structural and Functional Connectivity Networks. *Neuroimage* 59, 2045–2056. doi:10.1016/j.neuroimage.2011.10.015

Xu, X., Li, W., Tao, M., Xie, Z., Gao, X., Yue, L., et al. (2020b). Effective and Accurate Diagnosis of Subjective Cognitive Decline Based on Functional Connectivity and Graph Theory View. *Front. Neurosci.* 14, 577887. doi:10.3389/fnins.2020.577887

Zhang, Y., Zhang, H., Chen, X., Liu, M., Zhu, X., Lee, S.-W., et al. (2019). Strength and Directionality of Brain Connectivity in Multiple Kernel Learning. Proceedings of the 24th international conference on Machine learning, 20 June 2007, 775–782. doi:10.1145/1273496.1273594

Rolfe, C. E., Anguera, J. A., Skinner, S. N., Vrytek, B., and Gazzaley, A. (2017). Enhancing Spatial Attention and Working Memory in Younger and Older Adults. *J. Cogn. Neurosci.* 29, 1483–1497. doi:10.3389/fnagi.2021.001159

Stam, C. J. (2014). Modern Network Science of Neurological Disorders. *Nat. Rev. Neurosci.* 15, 683–695. doi:10.1038/nrn3801

Wang, T., Li, W., Li, H., Xu, B., Zhang, M., et al. (2021). Morphological, Structural, and Functional Networks Highlight the Role of the Cortical-Subcortical Circuit in Individuals with Subjective Cognitive Decline. *Front. Aging Neurosci.* 13, 339. doi:10.3389/fnagi.2021.688113

Zhang, Y., Zhang, H., Chen, X., Liu, M., Zhu, X., Lee, S.-W., et al. (2019). Strength and Similarity Guided Group-Level Brain Functional Network Construction for MCI Diagnosis. *Pattern Recognition* 88, 421–430. doi:10.1016/j.pr.2018.12.001

Zhou, Z., Chen, X., Zhang, Y., Hu, D., Qiao, L., Yu, R., et al. (2020). A Toolbox for Brain Network Construction and Classification (BrainNetClass). *Hum. Brain Mapp.* 41, 2808-2826. 10.1002/hbm.24979.

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