

# Accurate Identification of MCI Patients via Enriched White-Matter Connectivity Network

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**Abstract.** Mild cognitive impairment (MCI), often a prodromal phase of Alzheimer's disease (AD), is frequently considered to be a good target for early diagnosis and therapeutic interventions of AD. Recent emergence of reliable network characterization techniques have made understanding neurological disorders at a whole brain connectivity level possible. Accordingly, we propose a network-based multivariate classification algorithm, using a collection of measures derived from white-matter (WM) connectivity networks, to accurately identify MCI patients from normal controls. An enriched description of WM connections, utilizing six physiological parameters, i.e., fiber penetration count, fractional anisotropy (FA), mean diffusivity (MD), and principal diffusivities ( $\lambda_1$ ,  $\lambda_2$ ,  $\lambda_3$ ), results in six connectivity networks for each subject to account for the connection topology and the biophysical properties of the connections. Upon parcellating the brain into 90 regions-of-interest (ROIs), the average statistics of each ROI in relation to the remaining ROIs are extracted as features for classification. These features are then sieved to select the most discriminant subset of features for building an MCI classifier via support vector machines (SVMs). Cross-validation results indicate better diagnostic power of the proposed enriched WM connection description than simple description with any single physiological parameter.

## 1 Introduction

Mild cognitive impairment (MCI) is commonly defined as subtle but measurable memory disorder - a stage between normal forgetfulness (due to aging) and dementia. Studies suggest that MCI patients tend to progress to probable Alzheimer's disease (AD) at a rate of approximately 10% to 15% per year [7] compared with healthy controls who develop dementia at a rate of 1% to 2% per year [2]. MCI is difficult to diagnose due to the subtlety of cognitive impairments, especially in high functioning individuals.

Models of whole-brain connectivity, which comprise networks of brain regions connected either by anatomical tracts or functional associations, have drawn a

great deal of interest recently due to the increasing reliability of network characterization through neurobiological meaningful and computationally efficient measures [1], [9], [15]. Characterization of the global architecture or topological property of anatomical connectivity patterns in the human brain can provide new and valuable insights into the association between brain functional deficits and the underlying structural disruption related to brain disorders [14].

Brain anatomical circuitry has been experiencing considerable progress recently due to the development of diffusion tensor imaging (DTI), which can delineate white-matter (WM) fiber bundles through characterization of the underlying water molecule diffusion [5]. WM tracts between pairs of brain regions are routinely observed in vivo using diffusion tractography (also called fiber tracking) to model a global connectivity network of macroscopic polysynaptic fiber bundles in the brain [5], [10]. Derived parameters such as fractional anisotropy (FA) and mean diffusivity (MD) are widely used in univariate statistical analyses to localize brain changes related to aging, neurodegenerative and disease [3], [13]. Nevertheless, univariate connectivity based solely on the changes of individual physiological parameter might not be sufficient to accurately differentiate different groups. Hence, an enriched description of WM connections, which is more sensitive to WM microstructural changes, is required to account for the biophysical properties of the connections.

In this study, we propose an effective structural connectivity network-based multivariate classification framework to accurately identify MCI patients from normal aging. The key of our approach involves an enriched description of WM connections via utilizing six physiological parameters, i.e., fiber penetration count (FC), fractional anisotropy (FA), mean diffusivity (MD), and principal diffusivities ( $\lambda_1, \lambda_2, \lambda_3$ ), resulting in six connectivity maps for each subject to account for the connection topology and the biophysical properties of connection. The current study is the first attempt to characterize brain WM integrity using an enriched connectivity description quantified by DTI fiber tractography for the purpose of brain disease identification. Experimental results indicate that the proposed enriched description is more sensitive to WM microstructural changes than simple description with any single physiological parameter, and thus is more conducive to MCI pathology and identification.

## 2 Materials and Methods

### 2.1 Data Acquisition

The present study involved 27 participants (10 MCI patients and 17 socio-demographically matched healthy controls) who were recruited from the Duke-UNC Brain Imaging and Analysis Center, North Carolina, USA. Informed consent was obtained from all participants, and the experimental protocols were approved by the institutional ethics board. Confirmation of diagnosis for all subjects was made by clinical psychiatrists. Characteristics of the participants in this study are shown in Table 1.

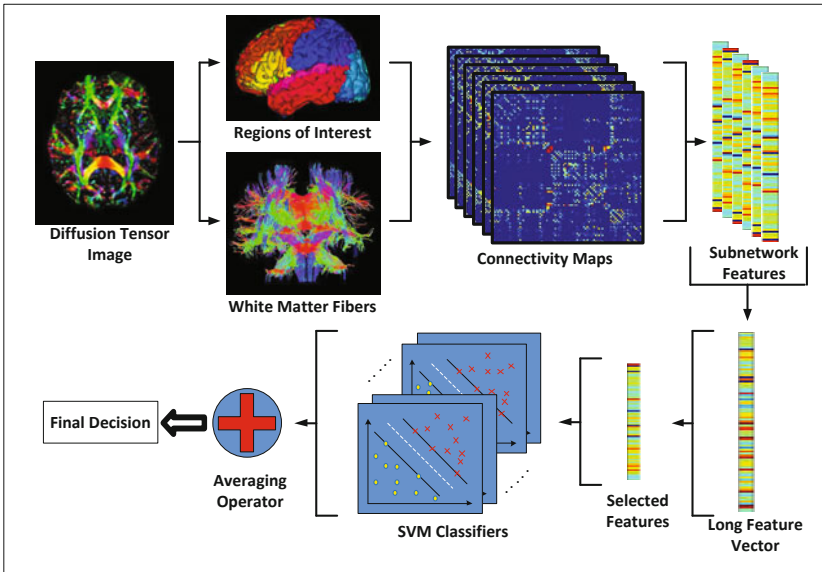
**Table 1.** Demographic information of the participants in this study

Group	MCI	Normal
No. of subjects	10	17
No. of males	5	8
Age (mean $\pm$ SD)	74.2 $\pm$ 8.6	72.1 $\pm$ 8.2
Years of education (mean $\pm$ SD)	17.7 $\pm$ 4.2	16.3 $\pm$ 2.4

Data acquisition was performed using a 3.0 Tesla scanner (GE Signa EXCITE, GE Healthcare). Diffusion-weighted images of each participant were acquired axially parallel to the anterior and posterior commissures (AC-PC) line with 25-direction diffusion-weighted whole-brain volumes using diffusion weighting values,  $b = 1000 \text{ s/mm}^2$ , flip angle =  $90^\circ$ , repetition time (TR) = 17 s and echo time (TE) = 78 ms. The imaging matrix was  $128 \times 128$  with a rectangular FOV of  $256 \times 256 \text{ mm}^2$ , resulting in a voxel dimension of  $2 \times 2 \times 2 \text{ mm}^3$ . A total of 72 contiguous slices were acquired.

## 2.2 Method

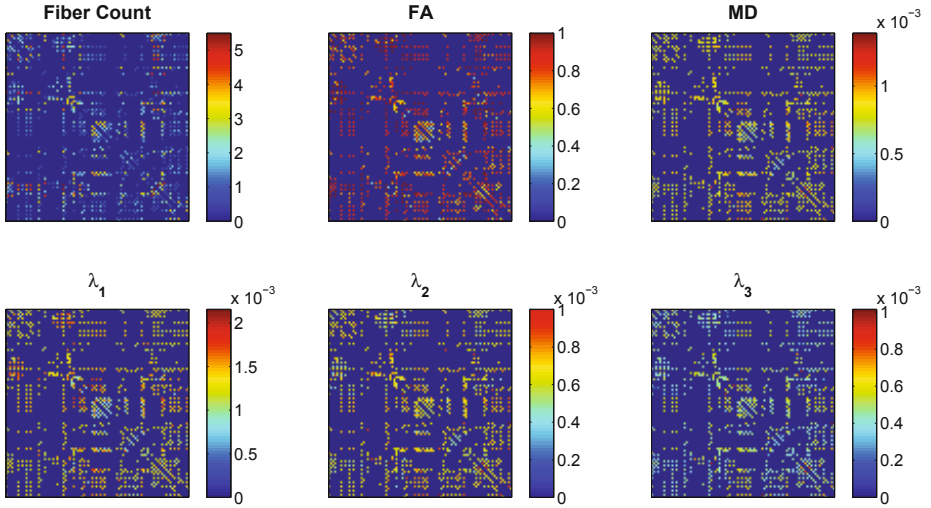
The key of the proposed classification framework involves an *enriched* description of WM connections utilizing six physiological parameters, i.e., fiber penetration count, fractional anisotropy (FA), mean diffusivity (MD), and principal diffusivities ( $\lambda_1, \lambda_2, \lambda_3$ ), resulting in six connectivity networks for each subject. The proposed MCI classification framework is shown graphically in Figure 1.

**Fig. 1.** Classification based on enriched description of WM connections

Each brain image was first parcellated into 90 regions (45 for each hemisphere) by propagating the automated anatomical labeling (AAL) ROIs [16] to each image using a deformable DTI registration algorithm [18]. Whole-brain streamline fiber tractography was then performed on each image using ExploreDTI [11], with minimal seed point FA of 0.45, minimally allowed FA of 0.25, minimal fiber length of 20 mm, and maximal fiber length of 400 mm. The reason for a relatively high FA value allowance was to elucidate the major matured WM fibers during fiber tracking process. During tractography, the number of fibers passing through each pair of regions was counted. Two regions were considered as anatomically connected if fibers passing through their respective mask were present. The existence of WM fibers between a specific pair of regions determines the connection topology of the network.

It is well known that most of the neurological diseases have subtle, spatially, and temporally diffuse pathology, where the brain is damaged in multiple regions, which might be highly interactive with each other, rather than in one single isolated region. In view of this, designing an enriched description of interregional connections, which is more sensitive in conveying the pathological information, is necessary for accurate diagnosis of neurological diseases. The proposed enriched description of WM connections via diffusion tractography is achieved via a collection of physiological parameters which convey rich information related to the topological and biophysical properties of the connection. This is in contrast with simple description using a single physiological parameter which affords only limited information.

The enriched description used in this study consists of six connectivity networks derived based on six commonly used physiological parameters, i.e., fiber penetration count, FA, MD,  $\lambda_1$ ,  $\lambda_2$  and  $\lambda_3$ . These six physiological parameters are the most commonly used measures in DTI analysis which provide the underlying patterns of brain pathologies and thus facilitate to the detection of brain diseases. On top of constructing fiber count based connectivity network, on-fiber FA, MD and principal diffusivities were derived at the same time to form another five connectivity networks. These five connectivity networks shared identical connection topology with the fiber count network, yet conveying different biophysical properties. Notably, each node in these five connectivity networks is the average value of the respective parameter derived from all fibers connecting the region pair. The biophysical information that is conveyed by the proposed enriched description includes: 1) probability of structural connection between two regions (fiber count); 2) the degree of anisotropy (FA); 3) the magnitude of the mean of the total diffusivity (MD); 4) degree of diffusivity along the axonal direction ( $\lambda_1$ ); 5) degree of restriction due to membranes and other effects (diffusivities along two directions which are perpendicular to the axonal direction,  $\lambda_2$  and  $\lambda_3$ ). Undoubtedly, this enriched description provides complex yet subtle characterization of the underlying WM structural patterns, which are pivotal for precise network characterization. An example of the six connectivity networks constructed for one subject is provided in Figure 2.



**Fig. 2.** Connectivity networks of different physiological parameters constructed for a single subject

From each network, the average strength between each ROI and the remaining ROIs is computed as

$$f_i = \frac{\sum_{j:j \neq i \in \zeta} t_{i,j}}{k_i[(k_i - 1)/2]}, \quad (1)$$

where  $k_i$  is the number of ROIs that are connected to  $i$ -th ROI,  $\zeta$  is the subnetwork comprising nodes directly connected to  $i$ -th ROI, and  $t_{i,j}$  is the parameter value between the  $i$ -th ROI and  $j$ -th ROI. Hence, for each network, 90 subnetwork features are extracted to describe the average connection statistics of each ROI with the remaining ROIs. The subnetwork features from all networks of each subject are concatenated to form a long description vector of 540 elements. These elements are first ranked according to their Pearson correlation with respect to the clinical labels, and are then further sieved to select the most discriminant subset of features using the SVM-RFE algorithm [12], [8]. Finally, support vector machines (SVMs) are trained using the selected subset of features. The training process was repeated for all subjects in dataset via leave-one-out cross-validation. Given an unseen testing sample, the final decision was determined by averaging the outcomes from all built SVM classifiers.

### 3 Results

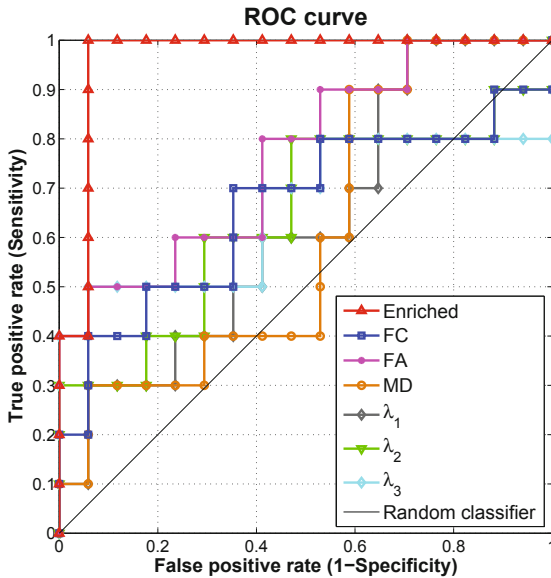
The classification accuracy by the proposed framework (with six parameters) is 92.6%, which is at least a 18.5% increment from that using any single physiological parameter. The classification performance and area under ROC curve

(AUC) of the enriched and simple descriptions are summarized in Table 2. The leave-one-out performance in terms of ROC curve is shown in Figure 3. The AUC of the enriched description is 0.965, which indicates its excellent diagnostic power. We note especially that simple description, in most of the cases, is not able to provide good generalization power as indicated by the much smaller AUC values.

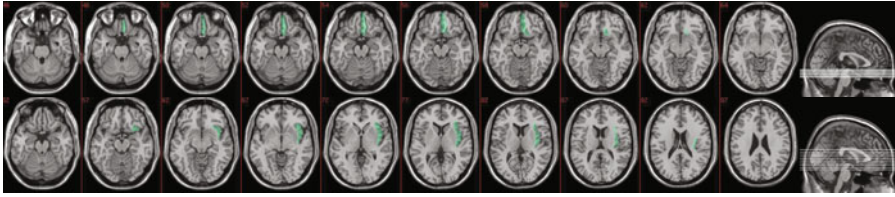
**Table 2.** Classification performance and AUC values for the enriched and simple description approaches

Description Parameter	Accuracy (%)	AUC	Description Parameter	Accuracy (%)	AUC
Enriched	92.59	0.965	$\lambda_1$	62.96	0.629
Fiber count	74.07	0.659	$\lambda_2$	62.96	0.641
FA	74.07	0.765	$\lambda_3$	66.67	0.653
MD	70.37	0.606			

The most discriminant regions that are selected for classification include the rectus gyrus which is located on the orbital portion of the frontal lobe and the insula which is located within the lateral fissure between the temporal lobe and the frontal lobe. The selected most discriminant regions are displayed in Figure 4.



**Fig. 3.** ROC curves for the enriched and simple descriptions



**Fig. 4.** The most discriminant ROIs selected for classification

## 4 Conclusion

The proposed framework, which accounts not only for the connection topology but also the biophysical properties of the connection, is more efficient in delivering relevant and subtle information, particularly for the purpose of classification. It is important to emphasize that the obtained sensitivity/specificity estimates via leave-one-out cross-validation ensures that the predictive power was evaluated on subjects not previously included in the training stage. The brain regions that selected for accurate detection of individuals with MCI include parts of prefrontal and orbitofrontal regions, which have already been reported in previous studies [6], [4]. The promising cross-validation results indicate that the proposed classification framework might provide an alternative and complementary approach to the clinical diagnosis of alterations in brain structure associated with cognitive impairment.

## Acknowledgment

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