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Brain connectivity and novel network measures for Alzheimer's disease classification

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ABSTRACT

We compare a variety of different anatomic connectivity measures, including several novel ones, that may help in distinguishing Alzheimer's disease (AD) patients from controls. We studied diffusion-weighted magnetic resonance imaging from 200 subjects scanned as part of the Alzheimer's Disease Neuroimaging Initiative. We first evaluated measures derived from connectivity matrices based on whole-brain tractography; next, we studied additional network measures based on a novel flow-based measure of brain connectivity, computed on a dense 3-dimensional lattice. Based on these 2 kinds of connectivity matrices, we computed a variety of network measures. We evaluated the measures' ability to discriminate disease with a repeated, stratified 10-fold cross-validated classifier, using support vector machines, a supervised learning algorithm. We tested the relative importance of different combinations of features based on the accuracy, sensitivity, specificity, and feature ranking of the classification of 200 people into normal healthy controls and people with early or late mild cognitive impairment or AD.

1. Introduction

Current approaches used to classify Alzheimer's disease (AD) (Klöppel et al., 2008; Kohannim et al., 2010) rely on features such as volumetric measures from anatomic regions in magnetic resonance imaging (MRI) of the brain, cerebrospinal fluid biomarkers, apolipoprotein E genotype, age, sex, body mass index, and, in some cases, clinical and cognitive tests. Here, we attempted to improve our understanding of the best features for AD classification by studying the utility of a variety of brain connectivity measures derived from diffusion-weighted images (DWIs) of the brain. Some of the features we chose came from standard tractography-based maps of fiber connectivity (Rubinov and Sporns, 2010) between brain regions; we supplemented these with more novel features derived from a flow-based connectivity method (Prasad et al., 2013b). We aimed to understand the information contained in the raw connectivity matrices versus network measures derived from them; we used all the resulting features to differentiate diagnostic categories related to AD (e.g., mild cognitive impairment [MCI]). To do this, we employed support vector machines (SVMs), a machine learning algorithm for classification, to learn from training data and then classify a separate test set.

Cui et al. (2012) used SVMs to classify amnestic MCI based on features indexing anatomic atrophy through segmentations of T1-weighted MRI and fraction anisotropy values from diffusion images using tract-based spatial statistics. They ranked the features using Fisher scores and selected the best-performing subset using cross-validation. They achieved an accuracy of 71.09%, sensitivity of 51.96%, and specificity of 78.40% for the classification of amnestic

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[1] Many investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data, but most of them did not participate in the analysis or writing of this report. A complete list of ADNI investigators may be found at http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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MCI. Our method differs in that we use only measures of connectivity from diffusion images for our feature set, and the ranking is computed within a set of features we are interested in evaluating. Laplacian regularized least squares was used to classify AD in Zhang and Shen (2011) where they tried to incorporate structural MRI, PET imaging data, and cerebrospinal fluid biomarker features from MCI into an AD classifier, which achieved a performance of almost 95% accuracy. In our case, we explore classification of both MCI and AD and focus on the information contained in different types of connectivity features. Cortical thickness features from structural MRI were evaluated by Eskildsen et al. (2012) using classification although they focused on conversion from MCI to AD and achieved accuracies ranging from 70% to 76% depending on the time to conversion, in contrast we used classification as a means to understand the information captured in measures of connectivity. The emphasis in the present study is to explore and understand which diffusion-based network measures are predictive of AD in contrast to the goal of optimizing the accuracy of classification in previous studies.

Our results and experiments seek to characterize the information contained in different features used to represent connectivity in the brain. This is related to the problem of feature selection methods (Guyon and Elisseeff, 2003), which rank features in a meaningful way to understand the ones that are important and those that can be discarded because they are redundant or irrelevant. One approach to select the best features (Peng et al., 2005) is to use mutual information to find the most relevant features for a target class. Another popular approach is the least absolute shrinkage and selection operator (Tibshirani, 1996) that uses a linear model and its regression coefficients to choose the best subset of features. De Martino et al. (2008) chose the most informative voxels in functional MR images using a recursive feature elimination approach that repeatedly trains an SVM model to remove features contributing a small amount to the training model. In our technique, we use the accuracy from classification to evaluate different types of brain connectivity features and to understand which ones may have an advantage to classifying MCI or AD. In addition, we used the SVMs to rank the features within the different feature sets to get a better description of what features were driving the classifier.

Our connectivity measure computation, classification framework, and ranking were applied to publicly available structural and diffusion MRI from the Alzheimer's Disease Neuroimaging Initiative (ADNI) (Mueller et al., 2005). We studied neuroimaging data from 200 subjects: 50 normal healthy controls, 38 people with late MCI (LMCI), 74 with early MCI (EMCI), and 38 AD patients.

We extracted measures of connectivity between 68 automatically parcellated regions of interest on the cortex using both fiber and flow connectivity methods and organized the information into connectivity matrices. From these connectivity matrices, we computed a variety of widely used network measures. These features were then fed into a repeated, stratified 10-fold cross-validation design, using SVMs to classify controls versus AD, controls versus EMCI, controls versus LMCI, and EMCI versus LMCI. Our results show a significant difference in the accuracy of various combinations of features that were used to distinguish between the various diagnostic groups.

2. Methods

2.1. Data

Our data were from 200 subjects scanned as part of ADNI-2, a continuation of the ADNI project in which diffusion imaging (among other scans) was added to the standard MRI protocol. The dataset included diffusion MRI data from 50 cognitively normal controls (C), 74 EMCI and 38 LMCI subjects, and 38 people with AD.

Table 1
The demographic details for our age- and sex-matched sample

	All	NC	EMCI	LMCI	AD
N	200	50	74	38	38
Sex	115 M/85 F	23 M/27 F	46 M/28 F	24 M/14 F	22 M/16 F
Age	73.1 ± 7.5	72.4 ± 6.2	72.5 ± 8.0	72.6 ± 5.6	75.8 ± 9.1

The number of subjects (*N*), sex, and age are given for the full sample (all), elderly NCs, EMCI and LMCI subcategories, and AD patients. We carried out 2-sample *t* tests comparing age and sex between all pairs of subcategories and found no significant differences that passed the multiple comparison threshold.
Key: AD, Alzheimer's disease; EMCI, early mild cognitive impairment; F, female; LMCI, late MCI; M, male; NC, normal controls.

Subjects were scanned on 3-T GE Medical Systems scanners, which collected both T1-weighted 3-dimensional anatomic spoiled gradient-echo sequences (256×256 matrix, voxel size $= 1.2 \times 1.0 \times 1.0$ mm^3, inversion time $= 400$ ms, repetition time $= 6.98$ ms, echo time $= 2.85$ ms, and flip angle $= 11°$) and DWIs (256×256 matrix, voxel size $2.7 \times 2.7 \times 2.7$ mm^3, scan time $= 9$ minutes). Per subject, the DWIs consisted of 41 diffusion images with $b = 1000$ seconds/mm^2 and 5 T2-weighted b_0 images. This protocol was chosen after an effort to study trade-offs between spatial and angular resolutions in a tolerable scan time (Jahanshad et al., 2011).

The groups were matched in both age and sex that we confirmed using 2-sample *t* tests and multiple comparison correction. Detailed demographic information for each subgroup of subjects is listed in Table 1.

2.1.1. Image preprocessing

We processed the T1-WIs to parcellate them into 68 cortical regions. We first automatically removed extracerebral tissues from the anatomic images using ROBEX (Iglesias et al., 2011a), a method that learned from manual segmentations of hundreds of healthy young adults. Skull-stripped brains were inhomogeneity corrected using the N3 tool of the Montreal Neurologic Institute (Sled et al., 1998) and aligned to the Colin27 template (Holmes et al., 1998) with the Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB)'s Linear Image Registration Tool (FLIRT) (Jenkinson et al., 2002).

Table 2
List of the 34 regions that are segmented in the cortex by FreeSurfer in each hemisphere, making a total of 64 regions

Cortical regions			
1.	Banks of the superior temporal sulcus	18.	Pars orbitalis
2.	Caudal anterior cingulate	19.	Pars triangularis
3.	Caudal middle frontal	20.	Peri calcarine
4.	Cuneus	21.	Postcentral
5.	Entorhinal	22.	Posterior cingulate
6.	Fusiform	23.	Precentral
7.	Inferior parietal	24.	Precuneus
8.	Inferior temporal	25.	Rostral anterior cingulate
9.	Isthmus of the cingulate	26.	Rostral middle frontal
10.	Lateral occipital	27.	Superior frontal
11.	Lateral orbitofrontal	28.	Superior parietal
12.	Lingual	29.	Superior temporal
13.	Medial orbitofrontal	30.	Supramarginal
14.	Middle temporal	31.	Frontal pole
15.	Parahippocampal	32.	Temporal pole
16.	Paracentral	33.	Transverse temporal
17.	Pars opercularis	34.	Insula

These regions represent the nodes in the connectivity network for both the fiber and flow connectivity methods. In the network, each method calculated the connectivity strength between all pairs of regions. For fiber connectivity, this is computed as the number of tractography fibers that connect the 2 regions and for the flow connectivity it is computed using an approximate maximum-flow algorithm between the regions.