Structural and Functional Markers of Conversion to Alzheimer's Disease

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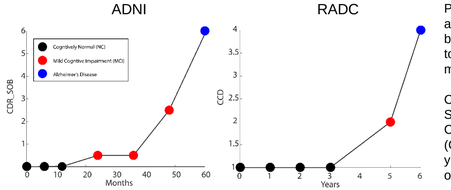
Objective

To develop a neuroimaging based biomarker to distinguish patients with Mild Cognitive Impairment (MCI), who go on to develop Alzheimer's disease (MCI converters or MCIc) from those who do not (MCI stables or MCIs).

Background

Only a small proportion (6.8-8.1%, [1]) of patients with Mild Cognitive Impairment (MCI) go on to develop Alzheimer's disease (AD).



Progression of a sample ADNI and RADC subjects from being a normal control to MCI to AD over a period of several months.

Clinical Dementia Rating - Sum of Boxes for ADNI and Clinical Cognitive Diagnosis (CCD) for RADC resp., on the y axis, quantify the magnitude of dementia.

Here we use structural and functional features extracted from sMRI and resting fMRI scans respectively, of MCI subjects. We train a Support Vector Machine (SVM) classifier to predict whether the subject will progress to AD or not.

References

[1] Mitchell, Alex J., and Mojtaba Shiri-Feshki. "Rate of progression of mild cognitive impairment to dementia–meta-analysis of 41 robust inception cohort studies." *Acta Psychiatrica Scandinavica* 119.4 (2009): 252-265.
[2] Petersen, Ronald Carl, et al. "Alzheimer's disease neuroimaging initiative (ADNI): clinical characterization." *Neurology* 74.3 (2010): 201-209.
[3] De Jager, Philip L., Hyun-Sik Yang, and David A. Bennett. "Deconstructing and targeting the genomic architecture of human neurodegeneration." *Nature neuroscience* 21.10 (2018): 1310.
[4] Shirer, W. R., et al. "Decoding subject-driven cognitive states with whole-brain connectivity patterns." *Cerebral cortex* 22.1 (2012): 158-165.
[5] Son, Seong-Jin, Jonghoon Kim, and Hyunjin Park. "Structural and functional connectional fingerprints in mild cognitive impairment and Alzheimer's disease patients." *PloS one* 12.3 (2017): e0173426.
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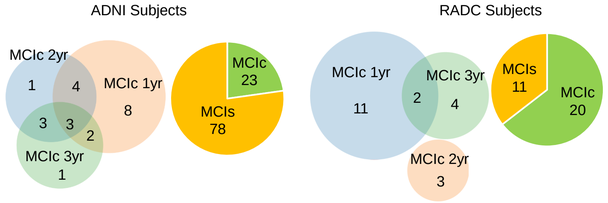
Methods

a) Subject Details

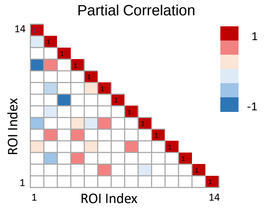
Resting state 3T fMRI scans for MCI subjects (n= 132) were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database ([2], MCIc n=23, MCIs n=78) and the Rush Alzheimer's Disease Center (RADC) database ([3], MCIc n=20, MCIs n=11).

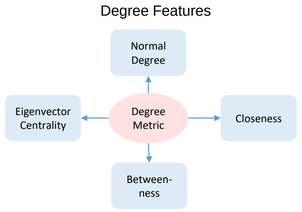


b) Processing Pipeline

A standard pipeline was used to preprocess the scans, and parcellate the brain into 14 network ROIs (regions of interest) (Shirer et al, [4]).

We calculated various measures of functional connectivity among these regions, including those based on zero-lag partial correlations (PC), lagged correlations (AR), and a graph-based metric of connectivity degree [5].

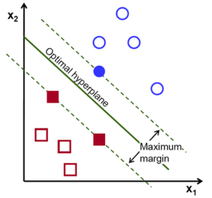


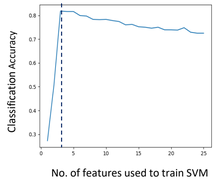


Structural MRI (sMRI) features, including surface area, cortical thickness, and Hippocampal volume were extracted with FreeSurfer to complement these functional features.

c) Recursive Feature Elimination based on SVM:

We trained an SVM classifier, using these features, to predict whether an MCI subject will convert to AD or not. Recursive Feature Elimination (RFE) was used to obtain highest accuracy, while retaining the minimal number of features [6].





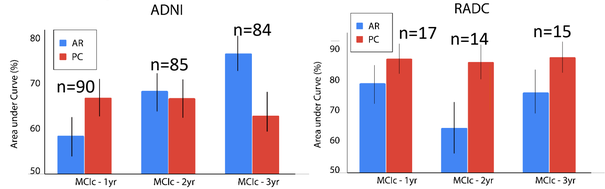
Left: Representative 2-D example of an SVM Classifier

Right: Representative graph of the RFE algorithm selecting optimal features for maximizing SVM accuracy

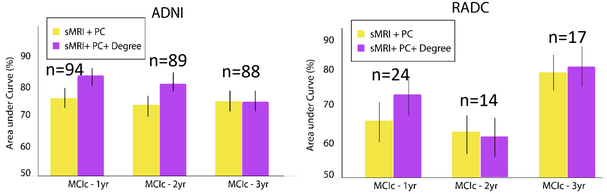
MCIc - 1yr : Scan was acquired less than 1 year prior to conversion
MCIc - 2yr : Scan was acquired between 1 to 2 years prior to conversion
MCIc - 3yr : Scan was acquired more than 2 years prior to conversion

Results

Among the functional connectivity metrics, zero-lag (partial) correlation (PC) significantly outperformed lagged correlation features (AR) in terms of classification accuracy.



sMRI features invariably improved the classification accuracies. A combination of sMRI, PC and degree metrics resulted in the maximum Area Under the Curve (AUC accuracy) for both the ADNI and RADC data



Inferences

SVM-RFE combining structural and functional features permitted predicting which MCI subjects would convert to AD, with an accuracies up to 85%

The results pave the way for predicting the onset of AD before the manifestation of dementia symptoms.

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