Discriminant analysis and prediction of aMCI subjects and normal controls using encoding and recognition fMRI tasks

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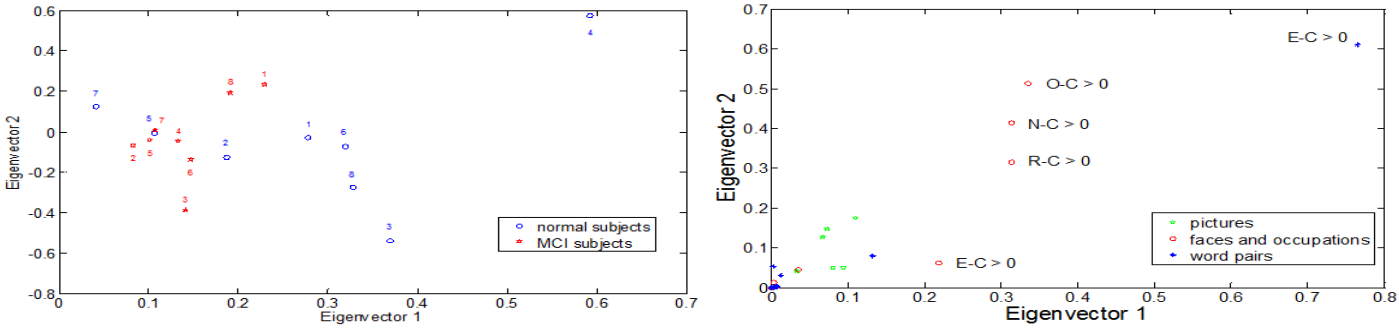
Introduction Alzheimer's disease (AD) is the most common form of dementia in older adults and is characterized by memory loss with pathological changes especially in the medial temporal lobes (MTL). Amnestic mild cognitive impairment (aMCI) is a clinical predictor of AD with an annual conversion rate of 6-25% [1]. Accurate **early** clinical diagnosis of AD is important. With the availability of new sophisticated imaging tools, new possibilities are now visible using fMRI. There have been few studies to characterize memory activation in subregions of the hippocampus for people at risk for AD. In this study we focus on classification and prediction of aMCI subjects and normal controls using three different memory paradigms by studying the activation pattern in specific subregions of the MTL, which are CA1, CA23DG (combining CA2, CA3 and dentate gyrus), Subiculum (SUB), Entorhinal cortex (ERC), Perirhinal cortex (PRC), Fusiform gyrus (FUS), and parahippocampal cortex (PHC).

Methods Comprehensive neuropsychological and clinical tests were administered by trained professionals and neurologists to screen subjects. Modified Hachinski Ischemic Scale (HIS) and the CES-Depression Scale were also used to exclude stroke-related MCI and depression. Eighteen right-handed subjects (ten with aMCI and eight normal controls (NC)) were consented and recruited from the community for participation in this study, which was approved by the institutional review board. Two subjects with aMCI did not qualify for the fMRI study due to incidental imaging abnormalities. Both groups were matched in gender, age and education.

Three memory paradigms involving encoding and recognition tasks were performed. These memory paradigms are referred to as: 1) common outdoor pictures, 2) faces-and-occupations, and 3) unrelated word pairs of objects-and-locations. Each paradigm contained 6 periods of encoding, distraction (control), and recognition (for more information, see ref 1). EPI was performed in a 3.0T GE MRI scanner (8-channel head coil, ASSET=2, TR/TE=2sec/30ms, FA= 70deg, FOV=22cmx22cm, thickness/gap=4mm/1mm, 25 oblique-coronal slices perpendicular to the long axis of the hippocampus, in-plane resolution 96x96, 288 time points). A standard high resolution coplanar T2-weighted structural image was also collected. Activation maps were generated by SPM5 for contrasts Encoding-Control (E-C), Recognition -Control (R-C), Encoding-Recognition (E-R), New-Control (N-C), Old-Control (O-C), New-Old (N-O). Note, each contrast can be positive or negative giving 12 possible contrasts for each paradigm. The subregions of MTL listed above were manually segmented using the high resolution T2 image and number of activated voxels above threshold (p=0.001 uncorrected) were determined for each subregion, contrast and paradigm.

Linear discriminant analysis [3] was used for separation of the aMCI subject group from the normal controls. To limit interpretability of the results, for each of the 36 possible contrasts (3 paradigms x 12 contrasts) we determined the best 3 subregions for separation of the two groups. The corresponding 36 different discriminant functions were then used to transform the original samples to z for each subject yielding a 36x16 transformed feature matrix ***M*** (36 different z values x 16 subjects). Principal component analysis was then carried out on ***M'M*** and ***MM'*** and the dominant two principal components were extracted. To predict the classification of future data based on previous observations, we used the leave-one-out method as cross validation. This method is nearly free of bias for estimating error rates and is the suggested method for small sample sizes. In this procedure, all but one observation are used to compute the classification rule, and this rule is then used to classify the omitted observation. The procedure is then repeated, so that in a sample of size N each observation is classified based on the other N-1 observations.

Results Below is a scatter plot of the values for eigenvector 1 and eigenvector 2 of ***M'M*** where each subject has been identified. It is obvious that all aMCI subjects (see red stars in left Fig) have relatively small values of both eigenvectors whereas most normal controls (except subjects 5 and 7) have a larger first eigenvector. The closeness of subject 5 to the aMCI subjects could mean that this subject may fit aMCI criteria and thus should be reassessed. Next, we show a scatter plot of the two dominant eigenvectors of ***MM'*** and label all 36 different contrasts (right Fig). Note, that all contrasts of the pictures paradigm have very small coefficients of the eigenvectors and are thus inferior to the other paradigms in separating the two groups. Also note that only the contrasts E-C>0, R-C>0, O-C>0, N-C>0 for the face-occupation and E-C>0 for the word pairs paradigms have significant coefficients of the eigenvectors. Since the face-occupation paradigm with the above mentioned contrasts shows significant coefficients, this paradigm is probably the most promising paradigm in separating the groups. This finding is consistent with the notion that recognizing face-occupation pairs requires the hippocampus to associate different types of information [4]. Compared to normal controls, the R-C>0 contrast (recognition activity) leads to less activation in left CA1 and left SUB, and more activation in left PHC (p=0.049) in aMCI. The E-C>0 contrast (encoding activity) leads to less activation in right CA23DG, right CA1, and right FUS in aMCI (p=0.040). Prediction accuracy using the leave-one-out method is at least 75% for both contrasts, which is promising for prediction of aMCI subjects using fMRI patterns using activations in subregions of the MTL.



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