Integration of structural and functional biomarkers of MRI data toward early diagnosis of Alzheimer's disease

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Introduction: From a number of studies to explore biomarkers of neurodegenerative diseases such as the Alzheimer's disease (AD),abnormalities of volumetric size and neuronal activity were introduced as biomarkers from structural and functional MRI (fMRI) data, respectively [1,2]. For example, the degree of atrophy of the medial temporal lobe including the hippocampus has been proportional to the severity of the AD associated with an episodic memory dysfunction [1]. Also, abnormal hyper- or hypo-activity within affected brain regions has been proposed as one of the potentially useful features from fMRI data to predict a prodromal phase of AD [3]. Despite of these growing evidences, however, the integration of these MRI- and fMRI-driven biomarkers toward early detection of the AD has been limited. In the present study, the symptomatic traits of the AD were identified based on the statistical comparison of the volumetric and neuronal activity information from MRI and fMRI data between case and control groups and were employed as feature vectors of an automated classifier. We hypothesized that the proposed method combining both structural and functional information would increase an accuracy to estimate the severity of a prodromal phase of AD compared to the methods solely based on either MRI or fMRI data.

Method: MRI and fMRI data, acquired using 1.5T GE Signa LX scanner, were obtained from the freely available repository of the fMRI data center (www.fmridc.org, #2-2000-1118W; n = 41; [4]). Among three groups including young healthy subjects (n=14), data from elderly healthy control subjects (HC; n=14) and elderly subjects with a mild cognitive impairment (MCI; n=11, excluding two subject due to a technical difficulty) were adopted.

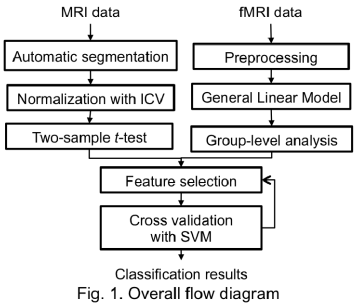

Fig. 1. Overall flow diagram

Fig.1 shows an overall flow diagram illustrating steps including volumetric size and neuronal activity analyses toward an automated identification of the MCI status associated with AD using a support vector machine (SVM) classifier. Firstly, T_1-weighted structural MRI data (TR/TE=9.7/4msec; FA=10°; 1×1×1.25mm^3 voxel-size) were used and 45 brain regions were automatically segmented from the FreeSurfer software (surfer.nmr.mgh.harvard.edu) and the corresponding volumes were divided by an intracranial volume (ICV) to address subject-dependent brain size. A two-sample *t*-test was administered to identify the brain regions whose volumes are significantly different between two groups (*i.e.* HC vs. MCI). The normalized volumes of the identified regions were used as feature vector elements of the MRI data (*i.e.* MRI-based biomarker).

T_2^*-weighted EPI volumes (n=128; fast spin echo; TR/TE=2680/50msec; 3.75×3.75×8 mm^3 voxel-size), acquired during a sensory-motor task, were preprocessed using SPM2 (www.fil.ion.ucl.ac.uk/spm) following steps including slice timing correction, head motion correction, normalization to the Montreal Neurological Institute (MNI) coordinates (3mm isotropic voxel) and spatial smoothing with 8mm isotropic full-width-at-half-maximum Gaussian kernel. Using the preprocessed data, the task-related neuronal activity was estimated from a general linear model (GLM) implemented in SPM2. A group-level analysis via two-sample *t*-test between the HC and MCI groups was adopted and a set of MNI coordinates of activation foci was identified from the substantially different active regions between two groups (p<0.005; minimum of 10 connected voxels). Average *t*-scores of 27 voxels proximal to each of the activation foci were used as feature vector elements of the fMRI data (*i.e.* fMRI-based biomarkers).

During a classification phase, a linear-kernel SVM (LIBSVM; www.csie.ntu.edu.tw/cjlin/libsvm) with a leave-one-out cross validation (CV) scheme was applied to have classification accuracy toward identification of the HC and MCI status. To find the relative importance of the biomarkers identified from MRI and fMRI data analyses, the CV processes were conducted for combination of different number of the available biomarkers.

Results: Fig. 2 shows four brain regions with significantly different volumes between groups from MRI including the bilateral hippocampus and bilateral lateral ventricles (p < 0.05). From the group-level activity from fMRI, the MCI group was showed significantly greater activity than the HC group in eight regions including left caudate ([-15,24,0] in mm; *t*-score = 3.2), left precuneus ([-27,-54,6]; 4.4), right calcarine gyrus ([27,-54,9]; 3.7), right hippocampus ([24,-42,12]; 3.7), right inferior frontal gyrus ([51,33,18]; 4.9), left middle occipital gyrus ([-30,-87,24]; 3.8), right superior occipital gyrus ([24,-78,24]; 4.9), and left inferior frontal gyrus ([-51,24,24]; 3.8). From the CV process using the MRI-based biomarkers, Fig.3a shows boxplots of the average, minimum, and maximum error rates with a minimum error rate of 24.0%. From the CV process using the fMRI-based biomarkers (Fig. 3b), a minimum error rate of 12.0% was achieved when the neuronal activity from six regions such as caudate, precuneus, and bilateral inferior frontal gyri were used as feature vectors. Using both the MRI- and fMRI-based biomarkers (Fig. 3c), a minimum error rate of 8.0% was achieved when five fMRI-based (*i.e.* left caudate, left precuneus, right calcarine gyrus, right hippocampus, and right inferior frontal gyrus) and four MRI-based (*i.e.* bilateral hippocampus and lateral ventricles) biomarkers were adopted as feature vectors.

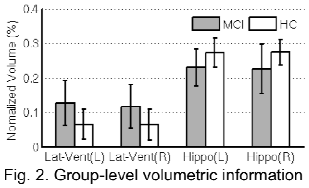

Fig. 2. Group-level volumetric information

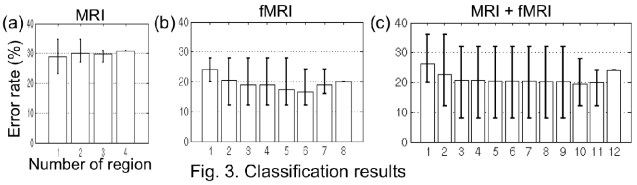

Fig. 3. Classification results

Discussion: A possibility of early detection of the prodromal phase of the AD was presented based on the volumetric analysis from MRI and neuronal activity analysis from fMRI adopting the SVM classifier. The fact that the hippocampus and ventricles were identified as MRI-based biomarkers and the hyperactivity from the MCI subjects in the fronto-limbic region is in good agreement with a previous study [1-4]. As expected, integration of the MRI and fMRI modalities was successfully demonstrated superior performance compared to the adoption of either the MRI or fMRI modality when the corresponding biomarkers were optimally selected. It is our hope that the proposed scheme of integrating the MRI- and fMRI-based biomarkers and subsequent automated classification would provide potentially valuable option to allow early diagnosis of neuropsychiatric conditions associated with both structural and functional abnormalities.

Reference: [1] Dickerson and Sperling, Neuropsychologia. 46, 1624-1635 (2008); [2] Fan et al., Neuroimage.41, 277-285 (2008); [3] Tripolitiet al., J Biomed Inform.43, 307-320 (2010); [4] Buckner et al., J CognNeurosci.Suppl 2, 24-34 (2000) ***Acknowledgement:*** This work was supported by the WCU program (R31-2009-000-10008-0) and Basic Science Research Program (R1005491), National Research Foundation (NRF) grant of Korea.