

Differential Diagnosis of Neurodegenerative Dementias using Structural MRI

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INTRODUCTION

The three common neurodegenerative disorders associated with dementia in the elderly are: Alzheimer disease (AD), Frontotemporal lobar degeneration (FTLD), Lewy body disease (LBD). Presently, there can be considerable uncertainty in the clinical diagnosis of these syndromes antemortem because of clinical heterogeneity, subtle symptoms early in the disease process, and the frequent occurrence of mixed dementias. Much of the imaging literature devoted to developing methods to improve diagnosis in dementia has been devoted to the task of differentiating a single specific dementing disorder from healthy elderly controls. Relatively little effort has been directed at differentiating among different dementing disorders.

We have developed a system that can detect disease specific atrophy patterns on structural MRI and then labels the pattern a "STructural Abnormality INdex" or STAND-Map. To train the diagnostic algorithm, we used antemortem MRI scans of demented subjects who came to autopsy and were found to have pathologically confirmed "pure" neurodegenerative dementias. Our rationale is that if each neurodegenerative disorder is examined independently in pathologically confirmed "pure" dementia cases (which are a part of our database), they will be associated with a unique pattern of atrophy in their STAND-Map specific to the dementia disease process. STAND-Maps representing "pure" dementia disorders can then be used as reference templates to differentially diagnose specific syndromes in new incoming patients.

MATERIALS AND METHODS

Subjects: Pathologically confirmed subjects with only a single dementia pathology and 3D T1-weighted structural MRI scan at the time of clinical diagnosis of dementia were identified. Numbers of subjects in each dementia pathology group were AD (44), LBD (18), FTLD (28). Note, all FTLD subjects had pathologically confirmed diagnoses, but we also restricted ourselves to FTLD subjects with the most common clinical sub-type – the behavioral or frontal variant. A group of 25 pathology confirmed CN (Path-CN) was identified in order to visualize the disease specific topographic pattern of neurodegeneration in each dementia (see Fig 1).

Steps of the differential diagnosis system:

1) **Computation of STAND-Maps:** All structural T1-weighted MRI images were segmented into gray matter (GM), white matter (WM) and CSF. The GM of each patient was parcellated by normalizing an in-house modified AAL atlas with 118 regions-of-interest (ROI) to the patient's MRI scan. GM density in each ROI was scaled by the total intracranial volume to adjust for head size differences. Age adjusted Z-scores were computed using MRI scans from cognitively normal (CN) subjects. For each individual scan, STAND-Map represents age and gender adjusted Z-scores of regional GM volume.

2) **STAND-Maps specific to each dementia disease process:** STAND-Maps of all the pathologically confirmed subjects were computed. Regions of neurodegeneration in each pathology in comparison to Path-CN are shown in Fig. 1.

3) **Classifiers separating each dementia from the other two dementia groups:** Each independent dementia disease process is illustrated on one of the three axes in Fig. 2(a) diverging at the origin. We can construct classifiers that detect each dementia independently by separating it from the other two e.g. if the z-axis represents the AD related disease process, then the solid plane defines the classifier that differentially detects only AD (by separating it from LBD and FTLD). We used linear support vector machine (SVM) classifiers with feature reduction using SVM-RFE to accomplish this. We used leave-one out cross-validation to optimize the classifier parameters and to compute the area under the ROC (AUROC) for each classifier.

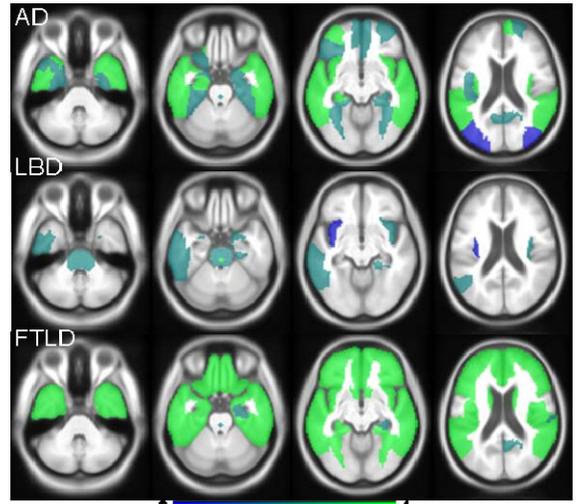


Fig 1. Regions of neurodegeneration in each dementia pathology when compared to Path-CN. Colorbar represents the t-statistic ($p < 0.01$).

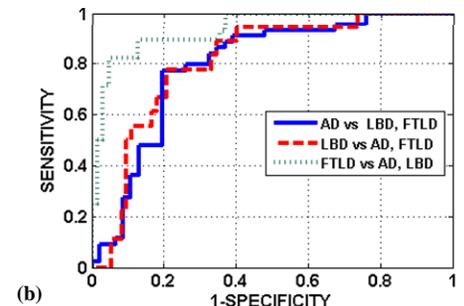
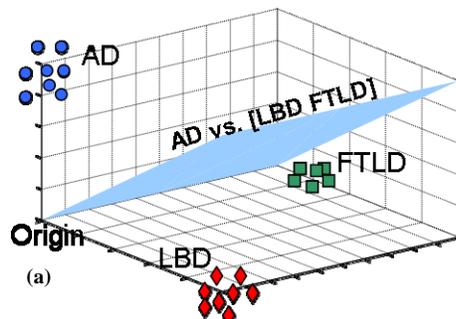


Fig 2. (a) Illustration of the proposed pathology based dementia syndrome detection system. (b) ROC-curves of the three different classifiers.

RESULTS: STAND-Maps for each dementia disorder when compared to CN in pathologically confirmed cases mirror the known anatomic distribution of pathological neurodegeneration in the literature for AD, LBD and FTLD (Fig. 1). AUROC for discriminating AD, LBD and FTLD was 0.79, 0.81 and 0.94 respectively and ROCs are shown in Fig 2(b).

CONCLUSIONS: STAND-Map of each dementia syndrome in pathologically confirmed cases is unique and may be very useful for the differential diagnosis of new incoming subjects. The proposed framework establishes a direct relationship between a structural abnormality biomarker (MRI) and the "gold standard" of pathology. This information is then incorporated to provide differential diagnosis in new incoming patients with dementia. This system can also be used to determine the relative contribution of several different disease processes underlying the clinical presentation of dementia in an individual subject.

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