

Comparing MRI and CSF Biomarkers in Alzheimer's Disease: Intergroup Discrimination and Predicting Clinical Change

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BACKGROUND AND METHODS

The pathological hallmarks of Alzheimer disease (AD) are the presence of neurofibrillary tangles (NFT) composed of hyperphosphorylated tau and neuritic plaques composed of β -amyloid ($A\beta$) fibrils. Biomarker and imaging indicators of disease that closely reflect the underlying pathology will add great value to clinical assessment as well as to the understanding of underlying mechanisms of AD. In this study we compared two core biochemical and imaging biomarkers, CSF and structural MRI. Two plasma cerebrospinal fluid (CSF) biomarkers in AD have been found to be promising: total tau (t-tau) and $A\beta_{1-42}$. High CSF t-tau protein reflects neuronal and axonal neurodegeneration and $A\beta_{1-42}$ is a major component of amyloid plaques and decrease of $A\beta_{1-42}$ is thought to reflect deposition of soluble $A\beta$ in neuritic plaques. Structural MRI captures disease related structural changes in the brain by measuring brain volume loss, the direct result of loss of neurons, synapses and supporting cellular structures. There is ample evidence supporting that MRI is an approximate in-vivo indicator of neuronal pathology in AD. A technique developed in our lab condenses the degree and location of AD related atrophy on the three dimensional T1-weighted MRI scan into a single number which is called STructural Abnormality iNdex (STAND)-score and correlates well with postmortem NFT Braak stages [1, 2]. In this work, we use STAND-scores as an indicator of the severity or stage of the AD-like pattern of volume loss on structural MRI.

The aims of this work were two-fold in the context of evaluating both the biomarkers: cross-sectional clinical correlations and prediction of future clinical change. In this work, we examine both the aforementioned questions using data from the Alzheimer's disease Neuroimaging Initiative (ADNI) study which consists of large database of normal elderly (CN), amnesic mild cognitive impairment (aMCI) and AD with both MRI and CSF biomarkers.

RESULTS

Cross Sectional Clinical Correlations:

(a) Among all subjects, the correlation between STAND and cognitive scores was stronger than between the CSF and cognitive scores ($p < 0.01$, Choi's test), suggesting STAND is more closely related to cognitive performance than CSF biomarkers. When the subjects were split into groups by clinical diagnosis, there was no significant correlation between the CSF biomarkers and cognitive scores within any of the individual groups. However STAND-score correlated significantly with widely used indices of general cognition - the Clinical Dementia Rating sum of boxes' (CDR-SB) and the Mini Mental State Exam (MMSE) in the aMCI and AD groups suggesting that only structural MRI is closely related to within group variation in cognitive status in aMCI and AD.

(b) Each of the MRI/CSF biomarkers independently contributed ($p < 0.001$) to the prediction of clinical group membership (in univariate models). The model that combined STAND, t-tau and $A\beta_{1-42}$, had better performance than any one disease indicator alone, the contribution of each disease indicator remained significant ($p < 0.001$) and the biggest contributor in the combined model was STAND-scores. Area under ROC (AUROC) and diagnostic

Table 1. MRI and CSF biomarker diagnostic accuracy for AD vs CN

	STAND	t-tau	$A\beta_{1-42}$	t-tau/ $A\beta_{1-42}$
AUROC	0.90	0.80	0.80	0.86
Sensitivity (%)	71	72	90	87
Specificity (%)	95	76	65	75
Accuracy (%)	84	74	77	81

accuracy of AD vs. CN classification based on a threshold value that maximized the accuracy is shown in Table 1.

Prediction of Future Clinical Change:

Average CDR-SB over time by diagnosis for the 25th, 50th, and 75th percentiles of $A\beta_{1-42}$, t-tau and STAND-score at baseline is plotted in Fig. 1. Stratification on $A\beta_{1-42}$ and t-tau was not strongly associated with time to conversion from aMCI to AD. STAND and $\log(t\text{-tau}/A\beta_{1-42})$ were both found to be predictive of future conversion from aMCI to AD with a hazard ratio for an interquartile change (95% CI) of 3.7 (1.7, 7.9) and 2.0 (1.1, 3.4), respectively. The AUROC of STAND (0.70) was found to be higher than AUROC of t-tau/ $A\beta_{1-42}$ (0.58) ($p = 0.05$) in the separation of aMCI subjects who converted within one year follow-up time versus aMCIs who did not.

CONCLUSIONS

Condensing the three-dimensional information from an MRI scan to a single disease relevant number such as STAND-score produces an extremely useful biomarker in disease staging and tracking progression. In this work, we have shown that both CSF and MRI biomarkers independently contribute to intergroup diagnostic discrimination, and intergroup discrimination is improved by combining information from both MRI and CSF. Likewise, both CSF and MRI independently provide predictive information about time to conversion from aMCI to AD. However, MRI provides greater power to effect cross sectional group wise discrimination, better correlation with cognition cross sectionally, and better prediction of future cognitive course in impaired subjects. We therefore conclude that although MRI and CSF provide complimentary information, MRI more closely reflects clinically defined disease stage (degree of cognitive impairment on baseline measures) and intensity (rate of change in cognitive impairment) than the CSF biomarkers tested.

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REFERENCES: [1] Neuroimage 2008; 39: 1186-97. [2] Neuroimage 2008; 42: 559-67.

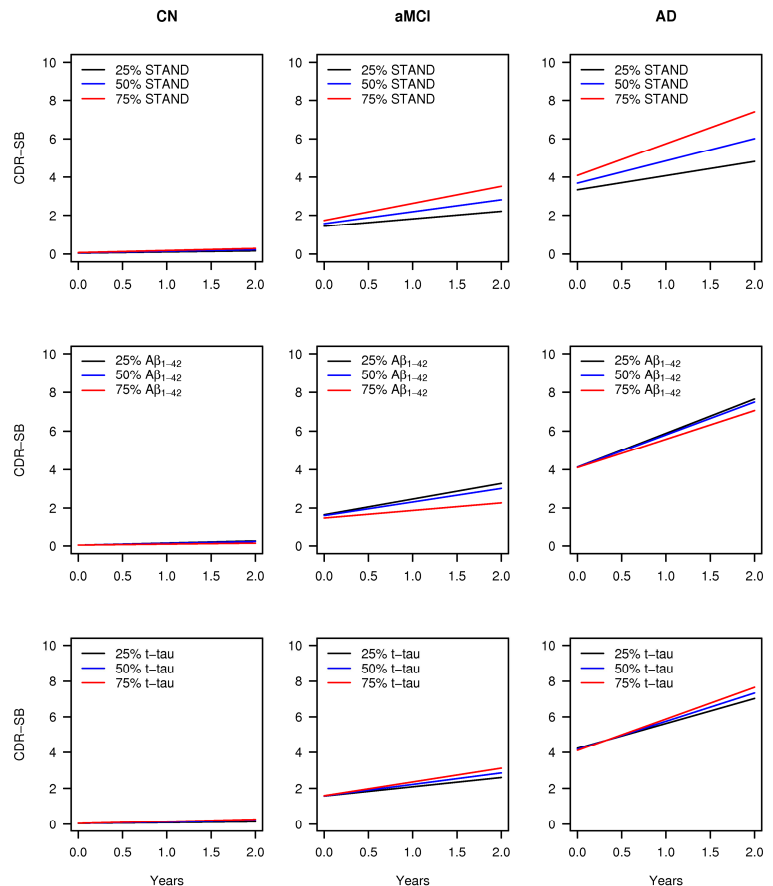


Fig. 1. Average change in CDR-SB over time by diagnosis group and biomarker or imaging measurement. Estimates are from a linear mixed model with time, baseline diagnosis, and the continuous baseline biomarker or imaging measurements (separate models for each predictor) as well as all interactions.