Ranking the Clinical and Pathological Correlates of Ventricular Expansion Mapped in 804 Alzheimer's

Abstract No:

2507

Authors:

YIYU CHOU[1], Natasha Lepore[2], Priyanka Saharan[1], Sarah Madsen[1], Xue Hua[1], Clifford Jack Jr.[3], Leslie Shaw[4], John Trojanowski[4], Michael Weiner[5], Arthur Toga[1], Paul Thompson[1]

Institutions:

[1]Laboratory of Neuro Imaging, Dept. of Neurology, UCLA School of Medicine, Los Angeles, CA, [2]University of Southern California, Los Angeles, CA, [3]Mayo Clinic College of Medicine, Rochester, MN, [4]University of Pennsylvania, Philadelphia, PA, [5]UC San Francisco, San Francisco, CA

Introduction:

Alzheimer's Disease (AD) is a dementing illness characterized by progressive neuronal degeneration and cognitive decline. There is an urgent need for neuroimaging biomarkers of AD that correlate with cognitive decline, and with accepted measures of pathology detectable in cerebrospinal fluid. Here we used our multi-atlas fluid image alignment method, to automatically segment parametric 3D surface models of the lateral ventricles in brain MRI scans from 184 AD, 391 MCI, and 229 healthy elderly controls. Radial expansion of the ventricles, computed pointwise, was correlated with measures of (1) clinical decline, (2) pathology from CSF, and (3) future deterioration. The ultimate goal of this work is to determine, and rank, the clinical and pathological correlates of ventricular expansion, using detailed maps rather than simple volumetric summaries. By using maps of pointwise correlations, we were able to create cumulative distribution function plots to rank correlates by effect size.

Methods:

804 subjects were scanned as part of the Alzheimer's Disease Neuroimaging Initiative (http://www.loni.ucla.edu/ADNI/), including 184 AD patients (age: 76.1 ± 7.6SD years), 391 amnestic MCI subjects (75.0 ± 7.3 years), and 229 healthy elderly controls (76.0 ± 5.0 years). 3D T1-weighted images were spatially normalized to the ICBM-53 average brain template with a 9-parameter rigid-body transformation. We then applied our automated segmentation approach ("Multi-Atlas Fluid Image Alignment" [1]) to create detailed surface-based maps of ventricular anatomy. Local ventricular shape differences and radial expansions were visualized using surface-based statistical maps. P-values describing the significance of group differences produced a color-coded map showing how regional ventricular expansion correlated with baseline measures and future (1-year) changes in scores on the Mini-Mental State Exam (MMSE), global and sum-of-boxes Clinical Dementia Rating (CDR), Geriatric Depression Scores (i.e., more severe depression) and the delayed logical memory test, as well as biomarkers of AD pathology including CSF levels of tau protein (Tau), 181-phosphorylated tau protein (pTau181p), beta amyloid (ABeta 1-42), Tau/ABeta 1 -42 and the pTau181p/ABeta 1-42 ratio.

Results:

At each surface point, correlations were assessed for each group between the radial distances and several clinical measures and biomarkers obtained from CSF at baseline. The resulting statistical maps (Figure 1) show widespread expansion of ventricular spaces in AD versus controls, and a more restricted pattern of expansion in MCI. All clinical measures including lower MMSE, higher Global CDR, higher sum-of-boxes CDR, higher Geriatric Depression Scores and lower delayed logical memory scores were significantly associated with lateral ventricular expansion. For CSF biomarkers (Figure 2), correlations were significant between ventricular expansion and lower ABeta 1-42 protein, higher Tau levels in the pooled data (entire sample of all AD, MCI and normal subjects), and within the AD group.

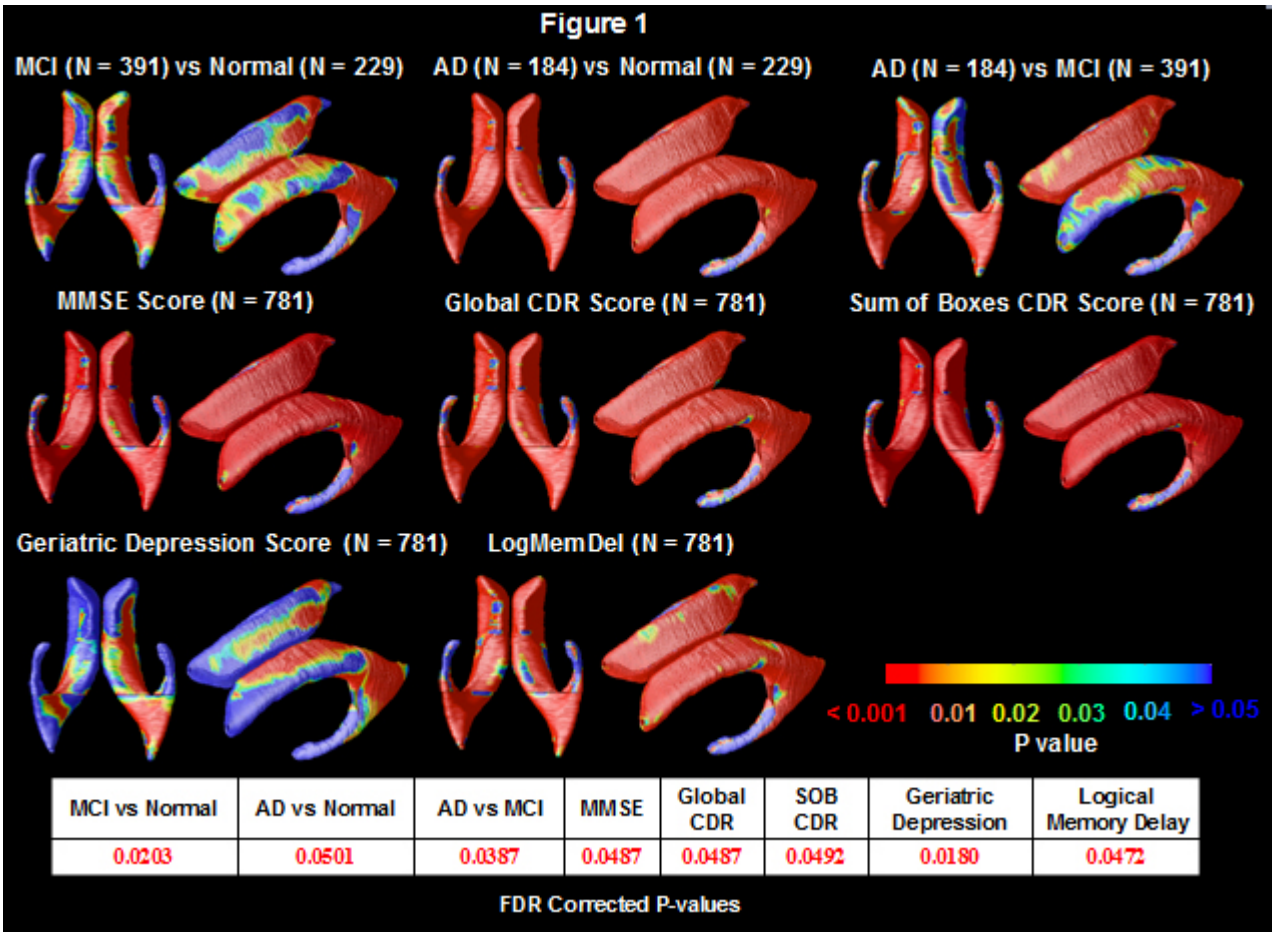
Figure 3 reveals regions where ventricular expansion at baseline correlated with subsequent clinical changes over 1 year; maps were significant overall, after correcting for multiple comparisons, for

predicting future changes in MMSE, global CDR and sum-of-boxes CDR scores.

Cumulative distribution curves (Figure 4) show relative effect sizes for associations between ventricular expansion and different pathological markers and clinical scores. Curves that rise more sharply at the origin denote statistical maps with greater effect sizes. Those curves that intersect the line y=20x at points other than the origin, pass the conventional criterion for controlling the false discovery rate (FDR) at an expected rate of 5%. These are regarded, by convention, as significant after multiple comparisons correction. This approach ranks the effect sizes of different covariates of interest.

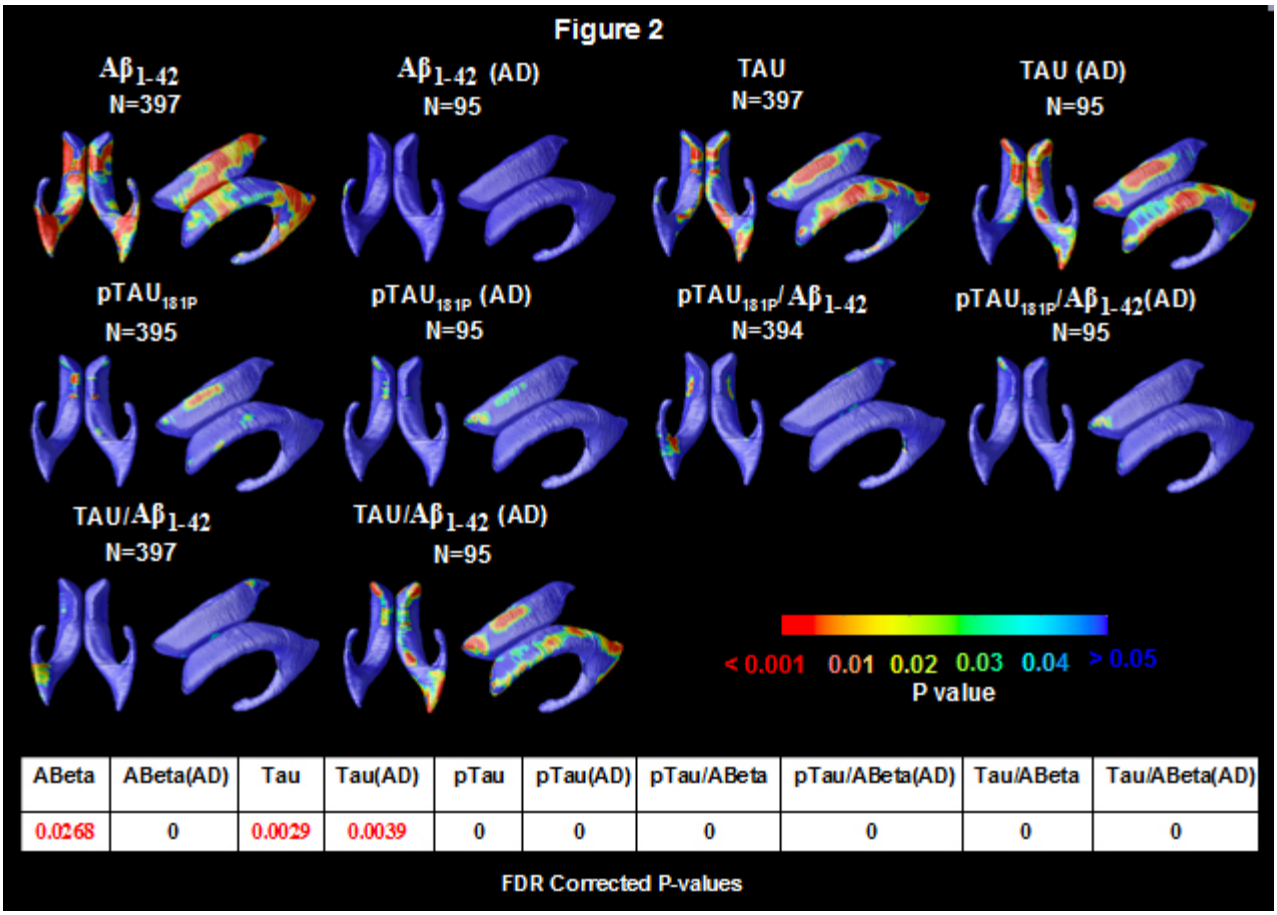
Conclusions:

The clinical scores most highly correlated with lateral ventricular expansion were MMSE, global CDR, sum-of-boxes CDR scores, Geriatric Depression scores, and delayed logical memory. Lower ABeta 1-42 protein level was the CSF biomarker most highly correlated with ventricular expansion when all subjects were combined, showing that MRI-derived measures of atrophy are good indices of the underlying pathology. Other CSF biomarkers including increased Tau level in pooled data and within the AD group also showed comparable effect sizes. Ventricular expansions were also linked with future decline in MMSE, and changes in global CDR and sum-of-boxes CDR scores over the following 1-year follow-up interval.



MCI vs Normal	AD vs Normal	AD vs MCI	MMSE	Global CDR	SOB CDR	Geriatric Depression	Logical Memory Delay
0.0203	0.0501	0.0387	0.0487	0.0487	0.0492	0.0180	0.0472

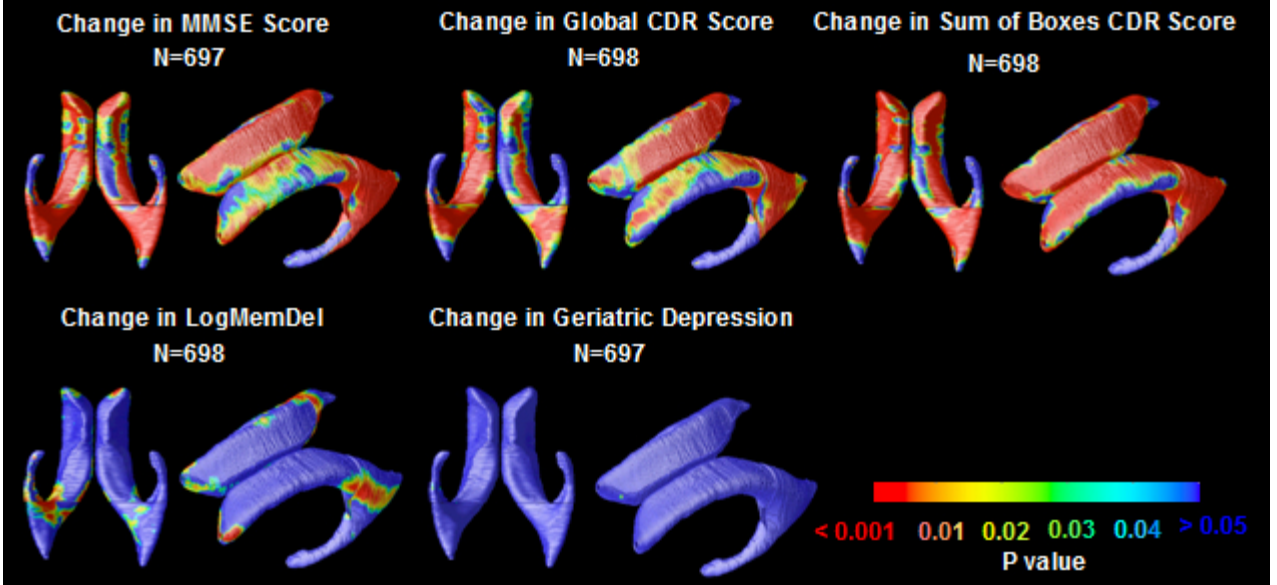
Figure 2



ABeta	ABeta(AD)	Tau	Tau(AD)	pTau	pTau(AD)	pTau/ABeta	pTau/ABeta(AD)	Tau/ABeta	Tau/ABeta(AD)
0.0268	0	0.0029	0.0039	0	0	0	0	0	0

FDR Corrected P-values

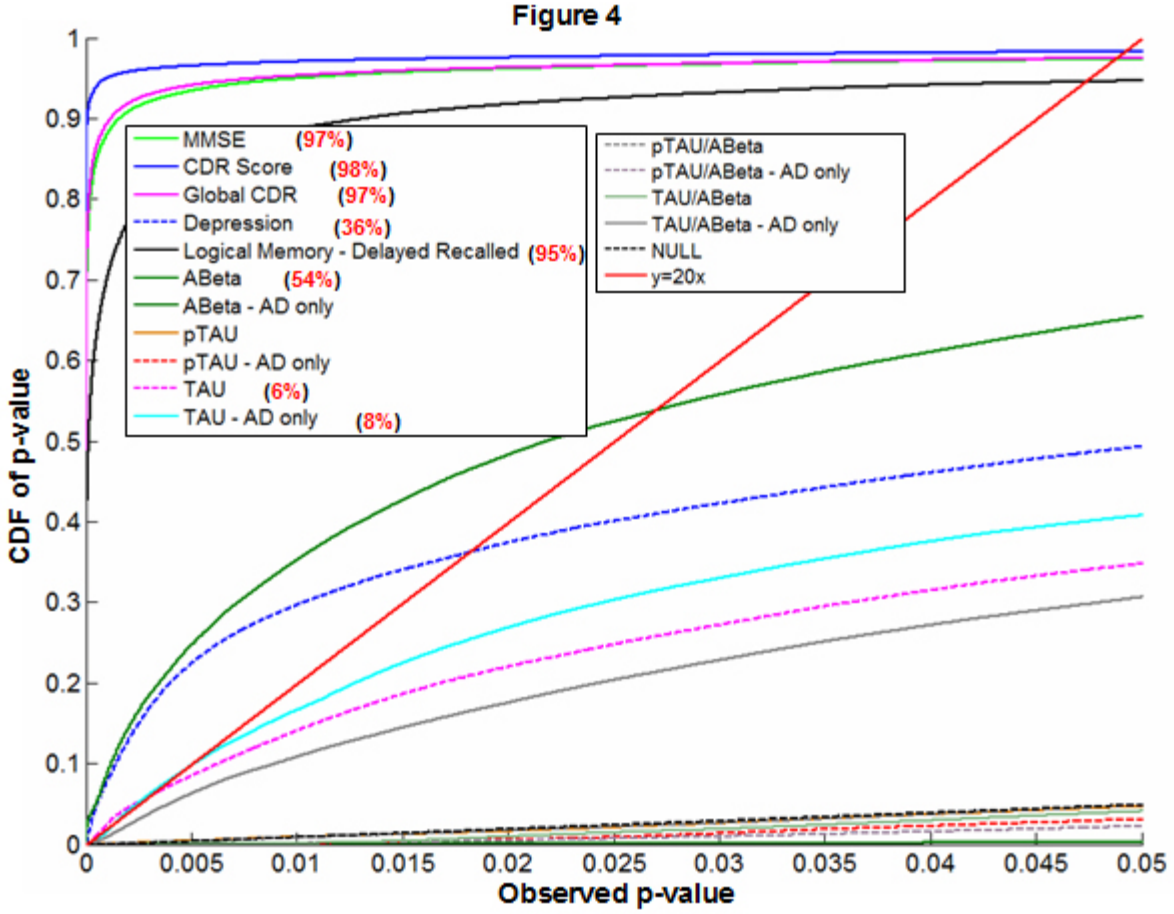
Figure 3



Change in MMSE	Change in Global CDR	Change in SOB CDR	Change in Logical Memory Delay	Change in Geriatric Depression
0.0416	0.0333	0.0410	0	0

FDR Corrected P-values

Figure 4



References:

CHOU, YY. (2008), 'Automated Ventricular Mapping with Multi-Atlas Fluid Image Alignment Reveals Genetic Effects in Alzheimer's Disease', *NeuroImage*, vol. 40, no. 2, pp. 615-630.

Categories

- Alzheimer and Dementia (Disorders of the Nervous System)
- Anatomical MRI (Imaging Techniques and Contrast Mechanism)
- Anatomical Studies (Neuroanatomy)