Published in final edited form as:

Proc IEEE Int Symp Biomed Imaging. 2010 April ; 2010: 241–244. doi:10.1109/ISBI.2010.5490368.

VENTRICULAR MAPS IN 804 SUBJECTS CORRELATE WITH COGNITIVE DECLINE, CSF PATHOLOGY, AND IMMINENT ALZHEIMER'S DISEASE

Yi-Yu Chou¹, Natasha Leporé¹, Sarah K. Madsen¹, Priya Saharan¹, Xue Hua¹, Clifford R. Jack², Leslie M. Shaw³, John Q. Trojanowski³, Michael W. Weiner⁴, Arthur W. Toga¹, Paul M. Thompson¹, and the Alzheimer's Disease Neuroimaging Initiative (ADNI)

¹Laboratory of Neuro Imaging, Dept. Neurology, UCLA School of Medicine, Los Angeles, CA

²Mayo Clinic, Rochester, MN

³Dept. Pathology and Laboratory Medicine, and Institute on Aging, University of Pennsylvania School of Medicine, Philadelphia, PA

⁴Depts. Radiology, Medicine & Psychiatry, UC San Francisco and VA Medical Center, San Francisco, CA

Abstract

There is an urgent need for neuroimaging biomarkers of Alzheimer's disease (AD) that correlate with cognitive decline, and with accepted measures of pathology detectable in cerebrospinal fluid (CSF). Ideal biomarkers should also be able to predict future decline, and should be computable automatically from hundreds to thousands of images without user intervention. Here we used our multi-atlas fluid image alignment method (MAFIA [1]), 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. Surface-based correlation maps were assessed using a cumulative distribution function method to rank influential covariates according to their effect sizes. The resulting approach is highly automated, and boosts the power of fluid image registration by integrating multiple independent registrations to reduce segmentation errors.

Index Terms

ADNI; lateral ventricles; MRI

1. INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia. Over time, the disease gradually erodes a person's memory and ability to carry out daily activities, and can lead to changes in personality and behavior. Cognitive assessments are notoriously variable over time, and there is increasing evidence that neuroimaging may provide accurate, reproducible measures of brain atrophy, that correlate with the underlying pathology, and with declining cognition. Recent studies found that tensor-based morphometry of brain MRI required 5–10

times fewer subjects than standard clinical measures to detect slowing of AD and MCI progression, at both 1.5 and 3T [2][3].

There is great interest in determining which MRI-based measures link best with standard cognitive assessments [4] and which measures can optimally predict future clinical decline, often defined as conversion to AD over a specific follow-up interval [5]. Ventricular measures have been proposed as a useful biomarker of disease progression as they show a relatively high effect size in distinguishing disease from normality. Here we used a high-throughput method, known as *multi-atlas fluid image alignment* (MAFIA [1]), to create detailed surface-based maps of ventricular anatomy in 804 subjects, comparing groups of AD and MCI subjects to controls. This work is related to ongoing efforts by other groups on ventricular surface segmentation [6], surface parameterization [7], surface-based statistics [8], and merging multiple segmentations to reduce anatomical labeling error [9].

Our goal was to determine, and rank, the clinical and pathological correlates of ventricular expansion, using detailed maps rather than simple volumetric summaries. By using maps of voxel-based correlations, we were able to create cumulative distribution function (CDF) plots to rank correlates by effect size. We also investigated, at a pointwise level, 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 Score (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 (pTau_{181p}), beta amyloid (A β ₁₋₄₂), Tau/A β ₁₋₄₂ and the pTau_{181p}/A β ₁₋₄₂ ratio.

2. MATERIALS AND METHODS

2.1. Subjects

804 baseline MRI scans, from 184 AD patients (age: 76.1 ± 7.6 SD years), 391 amnesic MCI subjects (75.0 ± 7.3 years), and 229 healthy elderly controls (76.0 ± 5.0 years), were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset (<http://www.loni.ucla.edu/ADNI/>). All subjects underwent thorough clinical and cognitive assessment at the time of scan acquisition; scores are summarized in Table 1. Several biomarkers obtained from the CSF were also included for assessing correlations, including A β ₁₋₄₂, Tau, pTau_{181p}, Tau/A β ₁₋₄₂, and pTau_{181p}/A β ₁₋₄₂. To adjust for global differences in brain position and scale, we spatially normalized all images to the ICBM-53 average brain template with a 9-parameter linear transformation using the Minctracc algorithm [10]. Aligned images were resampled in an isotropic space of 220^3 voxels with a final voxel size of 1 mm³. To equalize image intensities across subjects, registered scans were histogram-matched.

2.2. Automated Lateral Ventricle Segmentation and Shape Modeling

Lateral ventricular volumes were automatically estimated for all scans using a “multi-atlas” technique we recently validated [1,11]. Briefly, a small subgroup of 6 images (2 AD, 2 MCI and 2 normal) were randomly chosen and the lateral ventricles were manually traced in

contiguous coronal brain sections, following previously described criteria with established inter- and intra-rater reliability [12]. Lateral ventricular surface models were converted to parametric meshes (we refer to these labeled images as ‘atlases’) [13]. We fluidly registered each atlas and the embedded mesh models to all other subjects, treating the deforming image as a Navier-Stokes viscous fluid (as pioneered by Christensen et al. [14], and Gramkow [15]), guaranteeing a diffeomorphic mapping. Fluid transforms were applied to the manually traced ventricular boundary using tri-linear interpolation, generating a propagated contour on the unlabeled images. Sets of points representing tissue boundaries were re-sampled and made spatially uniform by stretching a regular rectangular grid (100×150 surface points) over each surface. This scheme creates parametric surfaces and matches homologous points from the ventricular surfaces across subjects. For each surface model, a medial curve was defined as the 3D curve traced out by the centroid of the ventricular boundary. The local radial size was defined as the radial distance between a boundary point and its associated medial curve. This allows statistical comparisons of local surface geometry at equivalent 3D surface locations across subjects for subsequent shape and thickness analysis.

By integrating multiple propagated labels, random digitization errors from each hand-traced segmentation are significantly reduced. The resulting average model is also robust to inaccuracies in individual registrations that may occur when non-global minima of the intensity-based cost function are reached. This improves the power to detect disease effects by combining multiple segmentations for each scan [1,11].

2.3. Ventricular Statistical Maps and Analysis

Surface contractions and expansions were statistically compared between groups at equivalent locations using Student's t -tests (2-tailed), and were correlated with different clinical characteristics. P -values describing the uncorrected significance of these statistics were plotted onto the average surface model, as a color-coded map. To correct for multiple comparisons, overall permutation-based significance values were assigned to the maps by comparing the supra-threshold area of the statistical map (with uncorrected p -values below 0.01) to the null distribution of this supra-threshold area, estimated using 10000 random permutations of the data [16].

To rank which clinical measures and CSF biomarkers were most strongly linked with ventricular morphology, we created cumulative distribution function (CDF) plots of the resulting uncorrected p -values (as in a conventional false discovery rate analysis). The x -value at which the CDF plot intersects the $y = 20x$ line represents the highest statistical threshold that can be applied to the data, for which at most 5% false positives are expected in the map. The use of the $y=20x$ line is related to the fact that significance is declared when the volume of suprathreshold statistics is more than 20 times that expected under the null hypothesis. If there is no such intersection point (other than the origin), there is no evidence to reject the null hypothesis. Our empirical CDFs of p -values are the flip of the more common FDR PP plot; steeper CDFs show stronger effect sizes.

3. RESULTS

3.1 Correlating Ventricular Morphology with Clinical Scores and CSF Biomarkers

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, shown in Figure 1a, suggest widespread progressive expansion of ventricular spaces in AD compared to controls ($p=0.0001/0.0001$ (left/right)), and a more restricted pattern of expansion in MCI ($p=0.0017/0.0039$ (left/right)).

Our results in Figure 1b indicate that all clinical measures including lower MMSE ($p=0.0002/0.0001$ (left/right)), higher Global CDR ($p=0.0001/0.0001$ (left/right)), higher sum-of-boxes CDR ($p=0.0001/0.0001$ (left/right)), higher Geriatric Depression Scores ($p=0.0052$ (left)) and lower delayed logical memory scores ($p=0.0004/0.0004$ (left/right)) were significantly associated with lateral ventricular expansion. For CSF biomarkers (Figure 2c), correlations were significant between ventricular expansion and lower $A\beta_{1-42}$ protein levels in the pooled data (entire sample of all AD, MCI and normal subjects; $p=0.0147/0.0031$ (left/right)). Ventricular expansion was also correlated with higher Tau and Tau/ $A\beta_{1-42}$ within the AD group ($p=0.0459$ (left) and 0.0499 (left), respectively).

Cumulative distribution curves (Figure 1d) 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, and 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%, and are regarded, by convention, as significant after multiple comparisons correction. This approach ranks the effect sizes of different covariates of interest: FDR was controlled when showing 97% of the surface for MMSE, 98% for the sum-of-boxes CDR score, 97% for the global CDR score, 36% for the Geriatric Depression Score, 95% for delayed logical memory scores, and 54% for $A\beta_{1-42}$ but only 6% for Tau, and 8% for Tau within the AD group.

3.2 Predicting Future Cognitive Decline

One goal of ADNI is to determine which brain imaging measures predict future clinical decline, primarily for “enrichment”, a statistical strategy that empowers drug trials by selecting as candidates those at highest estimated risk of imminent cognitive decline. Figure 1c 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 ($p=0.0016/0.0011$ (left/right)), global CDR ($p=0.0268/0.0023$ (left/right) and sum-of-boxes CDR scores ($p=0.0028/0.0008$ (left/right)). All these p -values are were corrected for multiple comparisons by permutation.

4. DISCUSSION

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 $A\beta_{1-42}$ 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 higher Tau level and Tau/A β ₁₋₄₂ ratio within the AD group showed comparable but slightly lower 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.

These ventricular maps can be rapidly computed from large databases. They satisfy criteria for being valid biomarkers of the disease, as they correlate with current cognitive performance and future cognitive decline, and with accepted biochemical markers of the underlying pathology. Future studies will compare the power of these measures with TBM measures and with hippocampal segmentations. It would also be of interest to combine them with genetic and cognitive data to improve their predictive validity.

REFERENCES

1. Chou YY, et al. *NeuroImage*. 2008; 40(2):615–630. [PubMed: 18222096]
2. Hua X, et al. *NeuroImage*. 2009 Dec; 48(4):668–681. [PubMed: 19615450]
3. Ho A, et al. *Human Brain Mapping*. 2009 Sep 24. [Epub].
4. Jack CR, et al. *Neurology*. 2004; 62:591–600. [PubMed: 14981176]
5. Fleisher A, et al. *Neurology*. 2008; 70:191–199. [PubMed: 18195264]
6. Carmichael OT, et al. *Alzheimer Dis Assoc Disord*. 2007 Jan-Mar;21(1):14–24. [PubMed: 17334268]
7. Wang, Y., et al. *Int. Symposium on Biomedical Imaging (ISBI2009)*. Boston, MA: 2009.
8. Ferrarini L, et al. *NeuroImage*. 2006; (32):1060–1069.
9. Wolz R, et al. *NeuroImage*. 2009 [Epub ahead of print].
10. Collins DL, et al. *J. Comput. Assist. Tomogr*. 1994; 18:192–205. [PubMed: 8126267]
11. Chou YY, et al. *NeuroImage*. 2009; 46(2):394–410. [PubMed: 19236926]
12. Narr KL, et al. *Biol. Psychiatry*. 2001; 50:84–97. [PubMed: 11526999]
13. Thompson PM, et al. *NeuroImage*. 1996; 3:19–34. [PubMed: 9345472]
14. Christensen G, et al. *IEEE Trans Image Process*. 1996; 5:1435–1447. [PubMed: 18290061]
15. Gramkow, C., et al. *Master's Thesis. IMM-Dan. Tech. Univ*; 1996.
16. Thompson PM, et al. *J. Neurosci*. 2003; 23:994–1005. [PubMed: 12574429]

Fig.1.

Significance maps for correlations between local ventricular enlargement and (a) diagnosis and cognitive scores, (b) CSF biomarkers, (c) subsequent cognitive decline over the following year. (d) Cumulative Distribution Functions (CDFs) of significance maps associating ventricular enlargement with clinical measures and CSF biomarkers. Red values (*right*) show the percentage of the maps with significant correlations, when a threshold is applied to control the false discovery rate at 5%.

Table 1

Demographic and clinical scores [mean (SD)] for all covariates examined.

	Normal	MCI	AD
N	229	391	184
Male/Female	118/111	255/136	93/91
Age (years)	75.99 (5.03)	74.96 (7.28)	76.05 (7.61)
Volume (L/R)	29830(6235)/ 27307(5603)	31971(7085)/ 29091(6513)	34322(6602)/ 32018(6549)
MMSE	29.11(1.00)	26.99(1.77)	23.2(2.0)
Global CDR	0 (0)	0.50 (0.03)	0.74(0.25)
Sum-of-boxes CDR	0.03 (0.12)	1.60 (0.87)	4.33(1.60)
Geriatric Depression Score	0.83 (1.15)	1.57 (1.37)	1.65 (1.44)
Delayed Logical Memory	12.98 (3.59)	3.76 (2.69)	1.22 (1.84)
MMSE Change	0 (1.36)	-0.68 (2.59)	-2.44 (4.14)
Global CDR Change	0.01 (0.20)	0.03 (0.20)	0.23 (0.54)
Sum of Boxes CDR Change	-0.08 (0.98)	0.69 (1.28)	1.41 (2.55)
Geriatric Depression Change	0.21(1.21)	0.42 (1.76)	0.12 (1.85)
Delayed Logical Memory Change	0.35(3.68)	0.54(3.47)	-0.29 (2.50)
Tau	69.66 (31.31)	104.09 (61.24)	118.96 (52.02)
Aβ₁₋₄₂	206.27 (54.07)	161.63 (52.89)	143.55 (40.49)
pTau_{181p}	25.05 (14.72)	35.71 (18.11)	41.19(19.34)
Tau/Aβ₁₋₄₂	0.39 (0.27)	0.76 (0.60)	0.89 (0.44)
pTau_{181p}/Aβ₁₋₄₂	0.14 (0.13)	0.26 (0.18)	0.32 (0.18)