Title:

Caudate Atrophy & Clinical Correlates in
400 Alzheimer's Disease, MCI, & Healthy Elderly Subjects

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Introduction:

Alzheimer's disease (AD) affects 35 million people worldwide (Dartigues, 2009). AD research using MRI has focused on early changes in medial temporal and cortical gray matter. Although caudate atrophy is more typical of motor disorders such as Parkinson's disease (Nakamura et al. 2001), beta-amyloid and tau pathology accumulates in the caudate in AD (Braak and Braak, 1990). Here we mapped 3D patterns of caudate atrophy in a large cohort of AD, mild cognitive impairment (MCI), and matched elderly control subjects. We tested whether caudate atrophy is associated with: (1) clinical scores (MMSE, CDR) and their decline over a 1-year follow-up period; (2) conversion from MCI to AD; (3) immediate and delayed Logical Memory scores from the Wechsler Memory Scale; (4) CSF Aβ, tau, p-tau levels; and (5) age, sex, ApoE genotype, and body mass index. We used cumulative distribution functions and false discovery rate theory (FDR) to rank the relative strengths of these associations.

Methods:

We analyzed T1-weighted structural MRI scans from 400 age- and sex-matched subjects (100 healthy elderly, 200 MCI, and 100 AD) scanned as part of the Alzheimer's Disease Neuroimaging Initiative (http://www.loni.ucla.edu/ADNI; mean age: 75.8+/-6.6 SD). All images were linearly registered to the ICBM-53 standard template (Mazziotta, 2001), prior to automated segmentation. Bilateral caudate nucleus segmentations were generated, for all 400 ADNI subjects, using our recently validated Adaboost algorithm (Morra, 2008). This algorithm identifies structures in images based on thousands of features, as well as prior information on variations in caudate geometry. A machine

learning model is developed that adaptively boosts the weighting of image features that improve segmentation accuracy in a training set of expertly labeled images. 3D parametric models of the automatically generated caudate nuclei were analyzed using the radial distance mapping method (Thompson, 2004). These models were averaged across members of each diagnostic group, to reveal systematic profiles of atrophy in AD and MCI versus healthy elderly controls. Permutation tests and FDR corrections were used to determine the overall significance of associations with clinical and cognitive scores, CSF biomarkers, and other measures. All p-values listed below are corrected for multiple comparisons.

Results:

Compared to the healthy elderly group, caudate volumes were lower in MCI (2.64% left, 4.43% right) and AD (4.74% left, 8.47% right). All clinical tests were associated with bilateral or right caudate atrophy, with generally stronger associations on the right. In statistical maps, caudate atrophy was associated with age, sum-of-boxes CDR, Delayed Logical Memory scores, and body mass index (BMI; greater atrophy in those with higher BMI). Reduced right caudate volume was associated with conversion from MCI to AD, global CDR, Immediate Logical Memory, 1-year decline in MMSE scores, and with CSF tau and p-tau levels. The right caudate was 3.86% larger than left in controls ($p < 0.001$) and 2.13% larger in MCI ($p = 0.01$). This asymmetry was not found in AD. 3D maps of atrophy (**Figure 1**) distinguish AD ($p = 0.064$ left, $p = 0.002$ right) and MCI from healthy controls ($p = 0.037$ left, $p = 0.036$ right). Future conversion from MCI to AD was significantly associated with lower volume in the right caudate on one-year ($p = 0.033$) and two-year ($p = 0.033$) follow-ups. In **Figure 2**, local atrophy was associated with poorer Delayed Logical Memory ($p = 0.019$ left, $p = 0.005$ right), Immediate Logical Memory ($p = 0.004$ right), sobCDR ($p = 0.007$ left, $p < 0.001$ right) and gCDR ($p = 0.013$ right). As shown in **Figure 3**, baseline ($p = 0.001$ right) and 1-year change ($p=0.008$ right) in MMSE scores were associated with right caudate atrophy, as in the volumetric analysis. In **Figure 4**, bilateral atrophy was associated with higher BMI scores in our full sample ($p < 0.001$ left, $p = 0.001$ right) and in the AD group ($p = 0.008$ left, $p = 0.004$ right). CSF Aβ and ApoE effects were not significant after multiple comparisons correction. Caudate atrophy was most strongly correlated (in this order) with: sobCDR, BMI in all subjects, baseline MMSE, BMI in AD, and AD vs. Controls.

Conclusions:

Caudate nucleus atrophy is associated with AD and MCI diagnosis and with poorer performance on standard clinical and cognitive tests, as well as with higher BMI – perhaps reflecting heightened vascular risks for AD. Caudate atrophy is usually regarded as more typical of Parkinsonian dementias, and is somewhat neglected in AD studies. Even so, baseline caudate nucleus anatomy predicted future decline from MCI to AD and future decline in MMSE scores at one- and two-year follow-up intervals. These caudate measures may be useful when combined with other AD biomarkers to identify individuals most likely to decline to AD, and to boost power in drug trials (Hua, 2010; Kohannim, 2010).

References:

1. Braak, H. & Braak, E. (1990), 'Alzheimer's disease: Striatal amyloid deposits and neurofibrillary changes', *Journal of Neuropathology & Experimental Neurology*, vol. 49, no. 3, pp. 215-224.

2. Dartigues, J.F. (2009), 'Alzheimer's disease: a global challenge for the 21st century', *The Lancet Neurology*, vol. 8, no. 12, pp. 1082-1083.

3. Hua, X., et al. (2010), 'Mapping Alzheimer's Disease Progression in 1309 MRI Scans: Power Estimates for Different Inter-Scan Intervals', submitted. Neurobiology of Aging

4. Kohannim, O., et al. (2010), 'Boosting power for clinical trials using classifiers based on multiple biomarkers', submitted.

5. Mazziotta, J., et al. (2001), 'A probabilistic atlas and reference system for the human brain: International Consortium for Brain Mapping (ICBM)', *Philosophical Transactions of the Royal Society B: Biological Science*, vol. 356, no. 1412, pp. 1293-1322.

6. Morra, J., Tu, Z., Apostolova, L.G., Green, A.E., Avedissian, C., Madsen, S.K., Parikshak, N., Hua, X., Toga, A.W., Jack, C.R., Schuff, N., Weiner, M.W., & Thompson, P.M. (2008), 'Validation of a fully automated 3D hippocampal segmentation method using subjects with Alzheimer's disease, mild cognitive impairment, and elderly controls', *NeuroImage*, vol. 43, no. 1, pp. 59-68.

7. Nakamura, T., Ghilardi, M.F., Mentis, M., Dhawan, V., Fukuda, M., Hacking, A., Moeller, J.R., Ghez, C., & Eidelberg, D. (2001), 'Functional networks in motor sequence learning: abnormal topographies in Parkinson's disease', *Human Brain Mapping*, vol. 12, no. 1, pp. 42–60.

8. Thompson, P.M., et al. (2004), 'Mapping Hippocampal and Ventricular Change in Alzheimer's Disease', *NeuroImage*, vol. 22, no. 4, pp. 1754-1766.