Automated Hippocampal Segmentation and Mapping Reveals Genetically Accelerated Tissue Loss in 1-year Repeat MRI data from 490 Alzheimer's Disease, MCI, and Control Subjects

J H Morra1, Z Tu1, L G Apostolova1,2, A E Green1,2, C Avedissian1, S K Madsen1, N Parikshak1, A W Toga1, C R Jack3, N Schuff4, M W Weiner4,5, P M Thompson1

[1]Laboratory of Neuro Imaging, UCLA, Los Angeles, CA, United States/[2]Dept. of Neurology, UCLA, Los Angeles, CA, United States/[3]Mayo Clinic College of Medicine, Rochester, MN, United States/[4]Dept. of Radiology, UCSF, San Francisco, CA, United States/[5]Dept. of Medicine and Psychiatry, UCSF, San Francisco, CA, United States

Introduction: We automatically mapped the rates of hippocampal atrophy in 980 MRI scans from 490 subjects scanned twice, one year apart. Our statistical maps revealed the 3D profile of tissue loss rates in Alzheimer's disease, healthy elderly controls, and in subjects with mild cognitive impairment (MCI). We also determined whether loss rates were associated with common variants in the ApoE genotype (2, 3, or 4).

Methods: Our maps were based on baseline and 1-year follow-up scans of 97 AD subjects (49 males/48 females), 245 MCI subjects (160 males/85 females), and 148 healthy control subjects (75 males/73 females). Based on the available data in the ADNI database (in September 2008), we used the largest obtainable sample of subjects who had both baseline and 1-year follow-up scans. All scans were linearly registered to a mean anatomical template. 3D parametric surface-based maps of the hippocampus were automatically created using our recently validated segmentation method [1]. Based on a small training set of manually delineated hippocampi, we used a cascade of AdaBoost algorithms wrapped inside the auto context model (ACM), to optimally segment the entire database. This method agrees with manual raters as well as manual raters agree with each other [1], and takes hours rather than months to apply to 980 images.

Results: First, we performed a volumetric analysis of overall hippocampal volumes (Figure 1). As expected from previous manual segmentation studies of AD or MCI versus healthy controls [2], dynamic hippocampal tissue loss was detected in all 3 diagnostic groups; its 3D profile was mapped here for the first time. Mean hippocampal loss rates increased with worsening diagnosis (AD = 5.59%/year [95% confidence interval, CI: +/-1.44%]; MCI = 3.12%/year [95% CI: +/-0.79%]; healthy controls = 0.66%/year [95% CI: +/-0.96%]). We found a highly significant correlation (Figure 2) between the presence of at least one allele of the ApoE4 genotype and the rate of decrease in hippocampal volume, when all individuals were pooled together. This was somewhat expected, as ApoE4 gene carriers were more likely to have AD. More interestingly, this same correlation was still detected in the healthy normal group, so even cognitively intact individuals carrying ApoE4 have faster hippocampal

loss than non-carriers. In all groups split by diagnosis, ApoE4-carriers lost hippocampal tissue faster than non-carriers, except in the case of the right hippocampus in MCI.

Conclusions: Here we presented the largest hippocampal mapping study to date (using 980 scans from 490 subjects). There were two main findings. First, our results with an automated analysis agreed well with smaller studies using manual or other relatively labor intensive methods. Second, we found that ApoE4 carriers had faster rates of volume loss, both in the full sample of 490, and when only cognitively intact controls were examined. This suggests the value of ApoE genotyping to increase statistical power in clinical trials, and shows that our automated approach can reveal factors that influence brain degeneration in large image databases.

References:

Morra, J (2008), 'Validation of a fully automated 3D hippocampal segmentation method using subjects with Alzheimer's disease mild cognitive impairment, and elderly controls', *NeuroImage*, vol. in press, no. , pp. .

Jack, C (2004), 'Comparison of different MRI brain atrophy rate measures with clinical disease progression in AD', *Neurology*, vol. 62, no. , pp. 591-600.