Neuroimaging biomarkers track brain degeneration in 676 subjects with Alzheimer's disease, mild cognitive impairment, and healthy controls

Xue Hua[1], Suh Lee[1], Alex D. Leow[1,2], Igor Yanovsky[3], Neelroop Parikshak[1], Yi-Yu Chou[1], April J. Ho[1], Boris Gutman[1], Arthur W. Toga[1], Clifford R. Jack Jr[4], Matt A. Bernstein[4], Eric M. Reiman[5], Danielle J. Harvey[6], John Kornak[7], Norbert Schuff[8], Gene E. Alexander[10], Michael W. Weiner[8,9], Paul M. Thompson[1] and the Alzheimer's Disease Neuroimaging Initiative

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

[2]Resnick Neuropsychiatric Hospital at UCLA, Los Angeles, CA

[3]Jet Propulsion Laboratory, California Institute of Technology, CA, USA

[4]Mayo Clinic, Rochester, MN

[5]Banner Alzheimer's Institute, Dept. Psychiatry, University of Arizona, Phoenix, AZ

[6]Dept. of Public Health Sciences, UC Davis School of Medicine, Davis, CA

[7]Dept. of Radiology and Biomedical Imaging and Dept. of Epidemiology and Biostatistics, and [8]Dept. Radiology, and [9]Dept. Medicine and Psychiatry, UC San Francisco, San Francisco, CA

[10]Dept. Psychology and Evelyn F. McKnight Brain Institute, University of Arizona, Tucson, AZ

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Alzheimer's disease (AD) is a devastating brain disorder that causes enormous personal, social and economic burden; it affects more than 5 million elderly people in the U.S., and over 24 million worldwide. Magnetic resonance imaging (MRI) can measure disease progression, and shows promise for assessing new therapeutic agents and treatment efficacy in clinical trials. In one of the largest MRI studies to date, we used tensor-based morphometry (TBM) to create 3D maps of structural brain atrophy in 676 subjects with AD (N=165; age: 75.6 ± 7.6SD years), mild cognitive impairment (MCI; N=330; 74.8 ± 7.5), and healthy elderly controls (N=181; 75.9 ± 5.1), as part of the Alzheimer's Disease Neuroimaging Initiative (ADNI). Baseline temporal lobe atrophy was correlated with current cognitive performance, future cognitive decline, and conversion from MCI to AD over the following year; it predicted future decline even in healthy

subjects. Over half of the AD and MCI subjects carried the ApoE4 allele, a known risk gene for AD, and they showed greater hippocampal and temporal lobe deficits than age-, gender- and diagnosis-matched non-carriers. ApoE2 gene carriers, around 1/6 of the normal group, showed reduced ventricular expansion versus non-carriers, suggesting a protective effect even in healthy controls.

In 1-year follow-up scans from the same subjects, rates of brain atrophy were correlated with interval changes in the sum-of-boxes clinical dementia rating (CDR-SB), mini-mental state examination (MMSE), and logical memory test scores. Temporal lobe atrophic rates correlated very highly with CSF Tau/Abeta ratio, less so with Abeta(1-42), Tau, pTau/Abeta, pTau in that order; in AD, atrophic rates correlated with pTau and Tau more than Abeta.

Using TBM-derived measures of temporal atrophy, in a statistically pre-defined region of interest within the temporal lobe, only 48 AD and 88 MCI subjects were needed to provide 80% power to detect a 25% reduction in the mean annual rate of change (α=0.05; 2-tailed test). This is a drastic sample size reduction relative to using clinical scores as outcome measures (619 AD/6797 MCI for the ADAS-Cog, and 408 AD/796 MCI for the CDR-SB). As a potential outcome measure, TBM provides high statistical power to track clinically meaningful brain changes, and may save time and costs for large, multi-site neuroimaging studies and clinical trials in AD.

Keywords: Alzheimer's disease, mild cognitive impairment, magnetic resonance imaging, tensor based morphometry, biomarker

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