MRI shape analysis predicts progression from mild cognitive impairment to Alzheimer's disease

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INTRODUCTION: The pharmaceutical industry is on the verge of a breakthrough in the treatment of Alzheimer's disease (AD). As in most diseases, early treatment of patients, before they have too much irreversible degeneration of brain tissue, is likely to be more effective than later treatment. However, it is currently almost impossible to test drugs in patients with early Alzheimer's disease (AD), due to the difficulties of making this diagnosis. Only about 10-15% of patients with symptoms of mild cognitive impairment (MCI) suggestive of possible early AD will actually develop the disease per year. This poses two major challenges for drug development: i) the near term conversion rate is too low to allow for reasonably sized clinical trials, and ii) it is unlikely that regulators would approve a drug for a population of patients, most of whom don't get the disease. To overcome these challenges, we have developed a method to predict progression from MCI to AD using automated analysis of intensity and shape from baseline MRI data. This procedure was validated on data from a single site (Duchesne, ICAD 2005a,b; Duchesne, Neurobiol Aging. 2008) and gave 81% predictive accuracy for conversion 2.5y later on average. Our goal is to evaluate this procedure on multi-site data.

METHODS: ***Subjects and Image Acquisition***: Baseline MRI data from 200 of the 400 MCI subjects participating in the Alzheimer's Disease Neuroimaging Initiative (ADNI) were used in this study. T1-weighted MRI data acquired with a 3D MPRAGE (or equivalent) protocol from 1.5T and 3.0T magnets from 42 study sites were included in this subset. All data was subjected to preprocessing that included correction for intensity non-uniformity (Sled, TMI, 1998;17:87-97), registration to the Talairach-like MNI stereotaxic space (Collins, J Comput Assist Tomog, 1994;18:192-205) and resampling onto a $1mm^3$ grid. The data was split into *training* (n=100) and *test* (n=100) sets. By 12 months, follow-up data was available for 163 of the 200 subjects, where 36 of these (22% of follow-up) converted to AD (the remained stable or reverted to normal). By 24 months, follow-up data was available for 136 subjects of the 200 original MCI subjects, where 58 subjects (42.3% of follow-up) had converted to AD and 69 remained stable or reverted to normal. Our goal was to predict which subjects would convert to AD using only the baseline MRI data.

Processing: Two types of processing were applied to extract features from the data. *First*: A population-specific anatomical average model (i.e., an MCI model) was constructed using the MRI data from the *training* subset, using a Minimal Deformation Template (MDT) method similar to (Grabner *et al.* MICCAI 9 (Pt 2) 2006;58-66) with non-linear registration. Shape information was extracted from the (4mm step) deformation field that non-linearly mapped the MDT MCI model to each subject via the Jacobian determinant of the local deformation vectors. Only Jacobian values within a brain-mask were input into a principal component analysis. We found that 22 principal components (PC) explained 90% variability in the MCI Jacobian data. Four of the 22 eigenvalues were found to be discriminatory in linear discriminant analysis (LDA) to identify converters and non-converters. *Second:* The hippocampi (HC) of each volume was automatically segmented using a technique based on non-linear registration to a template library, followed by label fusion (Collins, HBM 2009; Collins, ICAD 2009). In short, MRI for each subject was linearly registered to an AD model, resampled and compared (using mutual information) to the MRIs of a library of 40 prelabeled volumes already registered in this space. The N (=6) most similar scans, as defined by mutual information, were used as models in the ANIMAL algorithm (Collins, Human Brain Mapping, 1995) to segment the HC. The N segmentations were then combined using a voting scheme to obtain a consistent labeling of the HC on the subject's MRI. The HC volume was used as an additional feature for classification.

RESULTS: The MDT MCI model was warped onto each of the baseline MRI volumes of the *test* set to estimate a deformation field and a corresponding Jacobian volume. These volumes were projected onto the 22 PCs identified earlier and the 22 eigenvalues were stored in a feature vector for each subject in the *test* set. When using the LDA classifier built on the training data, we were able predict progression to AD in the independent *test* set with 65% accuracy at 12 months and 64% accuracy at 24 months using only the Jacobian features in the classifier. Adding baseline HC volume (from the automatic fusion segmentation procedure) increases the accuracy to 73% at 12 months and 69% at 24 months. Specifying prior probabilities (i.e., expected 15%/year conversion) increases prediction accuracy even further at 12 months to 78.5%.

DISCUSSION: Alzheimer's currently affects approximately 25 million people in North America and will quadruple in prevalence by 2050 due to aging of the population. The social and financial costs are enormous. The tools we will develop will make it feasible to perform drug trials in patients with MCI, who in fact, have prodromal Alzheimer's disease and will progress to develop AD. Looking forward, these tools also will make it possible to select patients in the clinic for early treatment.

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