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Imaging proteomics for diagnosis, monitoring and prediction of Alzheimer's disease

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ABSTRACT

Proteomic and imaging markers have been widely studied as potential biomarkers for diagnosis, monitoring and prognosis of Alzheimer's disease. In this study, we used Alzheimer Disease Neuroimaging Initiative dataset and performed parallel independent component analysis on cross sectional and longitudinal proteomic and imaging data in order to identify the best proteomic model for diagnosis, monitoring and prediction of Alzheimer disease (AD).

We used plasma proteins measurement and imaging data from AD and healthy controls (HC) at the baseline and 1 year follow-up. Group comparisons at baseline and changes over 1 year were calculated for proteomic and imaging data. The results were fed into parallel independent component analysis in order to identify proteins that were associated with structural brain changes cross sectionally and longitudinally. Regression model was used to find the best model that can discriminate AD from HC, monitor AD and to predict MCI converters from non-converters.

We showed that five proteins are associated with structural brain changes in the brain. These proteins could discriminate AD from HC with 57% specificity and 89% sensitivity. Four proteins whose change over 1 year were associated with brain structural changes could discriminate AD from HC with sensitivity of 93%, and specificity of 92%. This model predicted MCI conversion to AD in 2 years with 94% accuracy. This model has the highest accuracy in prediction of MCI conversion to AD within the ADNI-1 dataset. This study shows that combination of selected plasma protein levels and MR imaging is a useful method in identifying potential biomarker.

Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disorder. Emerging diagnostic techniques using multiple imaging modalities have contributed tremendously to our knowledge of the disease in recent years (Perrin et al., 2009), but AD's pathophysiology still remains largely elusive. Emerging disease-modifying strategies for AD necessitate accurate biomarkers for early diagnosis, monitoring and prognosis more than ever before. Magnetic resonance imaging (MRI) measures have been shown to predict conversion of mild cognitive impairment (MCI) to AD (deToledo-Morrell et al., 2004; Jack et al., 1999; Risacher et al., 2010; Whitwell et al., 2008) and cognitive decline in elderly people (Mungas et al., 2002; Rusinek et al., 2003). Similarly proteomic indices have been shown to have diagnostic value in AD (Britschgi and Wyss-Coray, 2009; Hye et al., 2006; Ray et al., 2007) and predict MCI conversion to AD (Ray et al., 2007). There are potential advantages of proteomics over imaging as biomarkers in AD. For example, a recent study on familial AD estimated that changes in Aβ amyloid and tau protein levels may occur 5 years before brain atrophy is detectable in MRI (Bateman, 2012). A group of investigators recently used multivariate approach for analyzing proteomic profile in Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset and found that apoE, B-type natriuretic peptide, C-reactive protein, and pancreatic polypeptide are significantly different between MCI and AD group (Hu et al., 2012). They also showed that CSF Aβ42 levels and t-tau/Aβ42 ratios correlated with the number of apoE4 alleles, plasma levels of B-type natriuretic peptide and pancreatic polypeptide (Hu et al., 2012).

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[2] Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.ucla.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.ucla.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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However it is not clear if any of these proteins are associated with changes in the brain, as they did not use any imaging data in their analysis.

Combining imaging markers with proteomics (i.e. imaging proteomics) provides an opportunity to identify proteins that are specifically associated with changes in the brain (Mattay et al., 2008; Meyer-Lindenberg and Weinberger, 2006). In addition, this approach may provide further mechanistic insights into pathophysiological mechanisms of AD, which in turn could serve as new targets for therapeutic strategies (Britschgi and Wyss-Coray, 2009).

Data mining in a large dataset with many different variables is prone to the problem of over fitting, and is all the more challenging due to the within-modality correlations with mass univariate techniques (Pearlson, 2009). Simply reducing the number of features considered does not necessarily address the problem, as the relationship between variables may also provide crucial information; for example, the discovery of metabolic syndrome X (Eckel et al., 2005) was based on a set of closely correlated physiological variables.

Parallel independent component analysis (PICA) greatly diminishes this methodological problem (Liu et al., 2008). PICA is an unsupervised multivariate algorithm to extract independent within-modality patterns with strongest between-modality connections when more than one modality is available. The intermodal associations between resulting components are then further identified and quantified. These components can be later compared on a component-wise basis between experimental groups. PICA has been applied widely in neurosciences research such as assessing relationships between electroencephalography (EEG), structural and functional MRI (fMRI), with single-nucleotide polymorphism (SNP) array (Jagannathan et al., 2010; Liu et al., 2009a, b), EEG with fMRI (Wu et al., 2010) and positron emission tomography (PET) with structural MRI (Tosun et al., 2011). Here, we used PICA to explore the relationship between structural MRI data and proteomics in ADNI dataset. The goal was to determine proteins that were associated with brain structural changes and therefore could have potential value as biomarkers for diagnosis and monitoring AD as well as predicting MCI conversion to AD.

Methods

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative database (adni.loni.ucla.edu). The ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies and non-profit organizations, as a $60 million, 5-year public–private partnership. The primary goal of ADNI has been to test whether serial MRI, positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians to develop new treatments and monitor their effectiveness, as well as lessen the time and cost of clinical trials. The principal investigator of this initiative is Michael W. Weiner, MD, VA Medical Center and University of California—San Francisco. ADNI is the result of efforts of many co-investigators from a broad range of academic institutions and private corporations, and subjects have been recruited from over 50 sites across the U.S. and Canada. The initial goal of ADNI was to recruit 800 subjects, but ADNI has been followed by ADNI-GO and ADNI-2. To date these three protocols have recruited over 1500 adults, ages 55 to 90, to participate in the research, consisting of cognitively normal older individuals, people with early or late MCI, and people with early AD. The follow up duration of each group is specified in the protocols for ADNI-1, ADNI-2 and ADNI-GO. Subjects originally recruited for ADNI-1 and ADNI-GO had the option to be followed in ADNI-2. For up-to-date information, see www.adni-info.org. Here, we used ADNI-1 and ADNI Plasma QC Multiplex Data.

Subjects

The eligibility criteria for the inclusion of participants are described at: http://adni.loni.ucla.edu/wp-content/uploads/2010/09/ADNI_GeneralProceduresManual.pdf. Subjects are divided into the following groups:

Healthy controls (HC): Mini-Mental State Examination (MMSE) scores between 24 and 30, clinical dementia rating (CDR) of 0, non-depressed and non-MCI.
MCI subjects: MMSE scores between 24 and 30, with memory complaint, objective memory loss measured by education adjusted scores on Wechsler Memory Scale Logical Memory II, a CDR of 0.5, no significant levels of impairment in other cognitive domains, and preserved activities of daily living.
Mild AD subjects: MMSE scores between 20 and 26, CDR of 0.5–1.0, meeting NINCDS/ADRDA criteria for probable AD (McKhann et al., 1984).

In this study, we chose AD and HC subjects from ADNI database who had baseline and 12-month-follow-up plasma proteins measurement and had pre-processed quality checked structural MRI data. For the MCI patients, only those who had baseline plasma proteins levels and had been followed up for at least two years were selected ($n = 300$), of whom 110 subjects converted to AD during the follow up period.

Targeted multiplex proteomics

Procedure of plasma protein data collection and measurement is explained in detail elsewhere (http://adni.loni.ucla.edu/wp-content/uploads/2010/11/BC_Plasma_Proteomics_Data_Primer.pdf). In brief, plasma proteins were measured in a subset of EDTA plasma samples (obtained in the morning following an overnight fast) at baseline and 1 year follow up, using a 190 analyte multiplex immunoassay panel. The panel, referred to as the human discovery map, was developed on the Luminex xMAP platform by rules-based medicine (RBM) to contain proteins previously reported in the literature to be altered as a result of cancer, cardiovascular disease, metabolic disorders, and inflammation. In addition, RBM partnered with Satoris (Inc., California, USA) to include plasma proteins previously reported to change in patients with Alzheimer's disease (Ray et al., 2007). Assays have been qualified based on the least detectable dose, precision, cross-reactivity, dilutional linearity, and spike recovery. Results of analyses on 148 analytes, which passed quality control, were used in this study.

MRI acquisition and preprocessing

High-resolution T1-weighted MRI scans were acquired on 1.5 Tesla MRI scanners from Siemens, General Electric Healthcare, and Philips Medical Systems with the standard ADNI MRI protocol (Jack et al., 2008). Each subject was scanned with a sagittal 3D MP-RAGE sequence, with acquisition parameters: inversion time (TI)/repetition time (TR): 1000/2400 ms; flip angle: 8°; 24 cm field of view; $192 \times 192 \times 166$ acquisition matrix, and a voxel size of $1.25 \times 1.25 \times 1.2$ mm^3. In plane, zero-filled reconstruction yielded a 256×256 matrix for a reconstructed voxel size of $0.94 \times 0.94 \times 1.20$ mm^3, later reconstructed to 1 mm isotropic voxels. The scan quality was evaluated by the ADNI MRI quality control center at the Mayo Clinic following standardized criteria. Images were calibrated with phantom-based geometric corrections to ensure consistency among scans acquired at different sites. Image corrections were applied using a processing pipeline at the Mayo Clinic, consisting of: (1) correction of geometric distortion due to gradient non-linearity (Jovicich et al., 2006), i.e., "gradwarp", (2) "B1 correction"