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Comparison of neuroimaging modalities for the prediction of conversion from mild cognitive impairment to Alzheimer's dementia

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ABSTRACT

In this study we compared Pittsburgh compound-B (PIB) positron emission tomography (PET) amyloid imaging, fluorodeoxyglucose PET for metabolism, and magnetic resonance imaging (MRI) for structure to predict conversion from amnestic mild cognitive impairment (MCI) to Alzheimer's dementia using data from the Alzheimer's Disease Neuroimaging Initiative cohort. Numeric neuroimaging variables generated by the Alzheimer's Disease Neuroimaging Initiative-funded laboratories for each neuroimaging modality along with apolipoprotein-E genotype (n = 29) were analyzed. Performance of these biomarkers for predicting conversion from MCI to Alzheimer's dementia at 2 years was evaluated in 50 late amnestic MCI subjects, 20 of whom converted. Multivariate modeling found that among individual modalities, MRI had the highest predictive accuracy (67%) which increased by 9% to 76% when combined with PIB-PET, producing the highest accuracy among any biomarker combination. Individually, PIB-PET generated the best sensitivity, and fluorodeoxyglucose PET had the lowest. Among individual brain regions, the temporal cortex was found to be most predictive for MRI and PIB-PET.

1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that is the most common form of dementia, accounting for approximately 60%–80% of cases (Alzheimer's Association, 2012). Mild cognitive impairment (MCI) attributed to AD refers to the symptomatic predementia phase of AD (Albert et al., 2011). Individuals with MCI experience a progressive cognitive decline that is greater than expected for their age and education level. When the cognitive impairment worsens and interferes with activities of daily living, the patient is diagnosed with dementia (Albert et al., 2011). In general, individuals with MCI convert to dementia at a rate of 10%–25% per year, though some will never convert to dementia or might revert to normal cognitive status (Grand et al., 2011).

Because not all MCI is caused by AD, being able to identify phenotypic and endophenotypic characteristics of persons with MCI who will go on to develop dementia would be important prognostic information to allow patients and families to plan and manage treatments including future neuroprotective therapies (Gelosa and Brooks, 2012). "Value of knowing" research suggests that patients and families can benefit from early disclosure of MCI and AD diagnoses (Smith et al., 1998) but there is some question as to patient benefit from knowing the diagnosis (Maguire et al., 1996; Monaghan and Begley, 2004; Pinner, 2000), in part related to level of insight.

AD pathology involves cortical and subcortical atrophy, beta amyloid (Aβ) plaques, and tau neurofibrillary tangles. The 5 most

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[1] 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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commonly studied biomarkers of AD are Aβ plaque positron emission tomography (PET) neuroimaging, cerebrospinal fluid (CSF) $A\beta_{42}$ levels, CSF total (t-tau) and phosphorylated (p-tau) tau levels, fluorodeoxyglucose (FDG) PET, and structural magnetic resonance imaging (MRI), especially of hippocampal volume (Gelosa and Brooks, 2012; Jack et al., 2011). There is a growing literature investigating the use of these biomarkers alone, or in combination, to predict conversion from MCI to dementia.

Pittsburgh compound-B (PIB), a carbon 11-labeled derivative of the thioflavin-T amyloid dye that binds with high affinity to Aβ plaques, is a PET neuroimaging ligand used in clinical research (Klunk et al., 2004; Pike et al., 2007). PIB-positive MCI patients are significantly more likely to convert to Alzheimer's dementia than PIB-negative (Forsberg et al., 2008), in whom higher initial PIB retention levels were associated with faster rates of conversion (Okello et al., 2009). Conversion rates of MCI to dementia were consistently found to be much greater in those who had evidence of positive or high retention on PIB PET: 67% versus 5% in a 20-month study (Villemagne et al., 2011), 38% versus 0% in an average of 21-month follow-up in another study (Wolk et al., 2009), and 50% versus 19% in a 2-year study (Jack et al., 2010b). A low level of CSF $A\beta_{42}$ is a biomarker for plaque formation in the brain. CSF $A\beta_{42}$ levels are inversely correlated with the presence of brain amyloid imaged using PIB (Fagan et al., 2006). In a study by Shaw et al. (2009), $A\beta_{42}$ was the most sensitive CSF biomarker for dementia in the autopsy-confirmed AD cohort ($n = 56$) with a sensitivity for dementia detection (patients accurately identified as converters among all converters) of 96.4% and specificity (patients accurately identified as nonconverters among all nonconverters) of 76.9%.

Increased levels of CSF t-tau and p-tau occur after release from damaged and dying neurons and are constituents of neurofibrillary tangles (Shaw et al., 2009). As with $A\beta_{42}$, CSF levels of t-tau and p-tau are used to predict MCI conversion to Alzheimer's dementia with sensitivities of 69.6% and 67.9%, respectively (Shaw et al., 2009).

FDG-PET measures uptake of labeled glucose which reflects metabolism in brain structures and might be used to distinguish frontotemporal dementia with its anterior functional defects from Alzheimer's dementia with its temporoparietal cortex defects (Albert et al., 2011). Using FDG-PET to predict which patients with MCI would convert to dementia at 18 months, Chételat et al. (2003) found that converters had lower FDG uptake in the right temporoparietal cortex. Drzezga et al. (2005) found that 11 of 13 MCI patients with baseline FDG-PET suggestive for AD converted to dementia by 16 months versus 16 of 17 FDG-PET-negative patients who remained stable at the end of the study.

Whitwell et al. (2007) demonstrated that MRI can detect patterns of cerebral atrophy in patients with MCI and identify early region of interest (ROI) changes associated with dementia. Atrophy of medial temporal structures was noted in MCI 3 years before Alzheimer's dementia was diagnosed. At 1 year before dementia was diagnosed, the extent and magnitude of the atrophy had progressed and spread to the middle temporal gyrus and more posterior temporal regions including the hippocampus, and into the parietal lobe. Dementia had more widespread atrophy especially of medial temporal, frontal, and temporoparietal association cortices. Using Alzheimer's Disease Neuroimaging Initiative (ADNI) data, Risacher et al. (2009) compared MCI converters to Alzheimer's dementia versus MCI-stable patients and found that the degree of neurodegeneration of the medial temporal structures was the best antecedent MRI marker of imminent conversion, with decreased hippocampal volume being the most robust.

Some studies (e.g., Brys et al., 2009; Galluzzi et al., 2010; Jack et al., 2010b; Mattsson et al., 2009; Shaw et al., 2009; Yu et al., 2012) evaluated combinations of biomarkers for their relative or combined predictive value for dementia conversion. Brys et al. (2009) found that adding CSF p-tau to MRI significantly increased overall prediction accuracy of dementia conversion from 74% to 84%. Medial temporal atrophy on MRI scans and abnormal CSF are the single most robust predictors of conversion to Alzheimer's dementia in MCI in which their combination enhances prediction (accuracy of medial temporal atrophy, area under the curve = 0.73, abnormal CSF = 0.74, combination = 0.82) (Galluzzi et al., 2010). Yuan et al. (2009) compared FDG-PET, single-photon emission tomography, and structural MRI to predict conversion to Alzheimer's dementia from MCI ($n = 1112$). For FDG-PET, single-photon emission tomography, and MRI, sensitivity and specificity were 88.8% and 84.9%, 83.8% and 70.4%, and 72.8% and 81.0%, respectively. Yu et al. (2012) compared MRI, FDG-PET, and CSF biomarkers and their combinations to assess which best predicted MCI conversion to Alzheimer's dementia within 2 years. The results indicated that MRI had the best individual predictive power (78% accuracy) but the combination of all 3 biomarkers provided the most accurate prediction (81% accuracy).

In the current study, we compared 3 neuroimaging methods (PIB-PET, FDG-PET, and volumetric MRI) to predict conversion from MCI to Alzheimer's dementia using 2-year follow-up clinical data from the ADNI cohort. We first evaluated each individual biomarker including the ROIs and composite measures from different imaging modalities. Using a variable selection algorithm, we then compared the performance of these biomarkers in a multivariate analysis using all imaging modalities. Finally, we compared individual modalities and their combinations for their prediction performance. To the best of our knowledge, there are no published prediction reports comparing these 3 imaging methods.

2. Methods

2.1. Subjects and design

We analyzed ADNI 1 data available as of August 2011 (http://www.loni.ucla.edu/ADNI). ADNI 1 is a 5-year multisite program funded by a public-private partnership including the National Institute on Aging, Food and Drug Administration, pharmaceutical companies, and nonprofit organizations to investigate the relationship of neuroimaging, biological, clinical, and neuropsychological assessments to disease progression in AD. Recruitment included approximately 800 subjects—200 elderly control subjects, 400 with MCI, and 200 with mild Alzheimer's dementia. Written informed consent was obtained for participation in these studies, approved by the institutional review board at each participating center. Subjects were followed for 2–3 years and assessed every 6–12 months. MCI subjects had Mini-Mental State Examination (MMSE) scores between 24 and 30 (inclusive), a memory complaint, objective memory loss measured according to education-adjusted scores on Wechsler Memory Scale Logical Memory II, a Clinical Dementia Rating of 0.5, absence of significant levels of impairment in other cognitive domains, essentially preserved activities of daily living, and an absence of dementia. Mild AD subjects had MMSE scores between 20 and 26 (inclusive), Clinical Dementia Rating of 0.5 or 1.0, and met National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association criteria for probable AD.

At each visit, subjects were evaluated using cognitive tests including the MMSE (range, 0–30 points), in which lower MMSE scores indicate more cognitive impairment, and the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog); ADAS-Cog 11-item (range, 0–70 points) and ADAS-Cog 13-item (range, 0–85), in which higher scores indicate worse cognitive function. For MCI subjects, the site clinician also assessed whether the subject progressed to Alzheimer's dementia, remained as MCI, or returned