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The personalized Alzheimer's disease cortical thickness index predicts likely pathology and clinical progression in mild cognitive impairment

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Abstract

Introduction: An Alzheimer's disease (AD) biomarker adjusted for age-related brain changes should improve specificity for AD-related pathological burden.

Methods: We calculated a brain-age-adjusted "personalized AD cortical thickness index" (pADi) in mild cognitive impairment patients from Alzheimer's Disease Neuroimaging Initiative. We performed receiver operating characteristic analysis for discrimination between patients with and without cerebrospinal fluid evidence of AD and logistic regression in an independent sample to determine if a dichotomized pADi predicted conversion to AD dementia.

Results: Receiver operating characteristic area under the curve was 0.69 and 0.72 in the two samples. Three empirical methods identified the same cut-point for pADi in the discovery sample. In the validation sample, 83% of pADi + mild cognitive impairment patients were cerebrospinal fluid AD biomarker positive. pADi + mild cognitive impairment patients (n = 63, 38%) were more likely to progress to AD dementia after 1 (odds ratio = 2.9) and 3 (odds ratio = 2.6) years.

Discussion: The pADi is a personalized, magnetic resonance imaging–derived AD biomarker that predicts progression to dementia.

Keywords: AD index; AD signature; Alzheimer's disease; Cortical thickness; Mild cognitive impairment

1. Background

Positron emission tomography (PET) and cerebrospinal fluid (CSF) biomarkers are the gold standard for identifying individuals with molecular evidence of Alzheimer's disease (AD) neuropathology, but these procedures are invasive (CSF), expensive (PET), and only accessible in specialized centers (PET) [1,2]. Magnetic resonance imaging (MRI), on the other hand, is noninvasive, less expensive, and more readily available than PET but less specific than amyloid PET or CSF to AD-related neurodegeneration. Although the magnitude of hippocampal atrophy in patients scanned in vivo and followed to autopsy correlates with the burden of neurofibrillary tangle pathology [3], hippocampal atrophy can also be seen in patients with a variety of neurodegenerative and other pathologies [4–6]. Spatial patterns of regional

[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/wpcontent/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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brain atrophy measured by MRI may be sensitive to the typical localization of different types of neurodegenerative conditions, providing increased specificity [7]. For example, temporoparietal atrophy is strongly associated with the localization and magnitude of neurofibrillary tangles in AD [8,9], and in vivo tau PET investigations show a close correspondence between regional atrophy and tau PET signal [10–12]. However, the specificity of different cortical patterns of atrophy for AD pathology has received limited investigation [13].

Regional atrophy also shows clear relationships to the clinical characteristics of patients with neurodegenerative diseases [7,14,15]. Cortical thickness is a biologically meaningful measure interpretable with an MRI scan in an individual person that is highly reliable within and across scanner manufacturers, sequences, and field strengths [16]. We previously showed that nine regions of interest (ROIs) cortical thickness AD signature measure is a valid reflection of AD continuum severity and is reliable across multiple samples including those scanned at different field strengths [17]. Moreover, we have shown that it is associated with memory performance, cognitive decline, and progression to dementia [17–25], is a better predictor of progression from mild cognitive impairment (MCI) to AD compared to entorhinal [18] or hippocampal volume [24], and is closely associated with AD-like CSF characteristics [22].

One challenge associated with MRI-based biomarkers of neurodegenerative disease is that aging itself is associated with regional brain atrophy; we have shown that areas of prominent age-related cortical atrophy include regions partially overlapping with the AD signature [23,26–28]. Indeed, reducing the influence of age-related atrophy by adjusting the AD signature for these cortical changes resulted in increased correlation with CSF tau and amyloid β (Aβ) and better prediction than molecular markers of progression from MCI to dementia in 1 year [24].

Importantly, the cortical age-adjusted AD signature in our previous study was calculated as a residual from a group-level analysis. Therefore, while this study demonstrated the validity of a cortical age-adjusted AD signature MRI biomarker, the approach may not be generalizable to individual patients, potentially limiting its clinical applications. The goal of the present study was to calculate a cortical age-adjusted AD signature marker based on individual rather than group-level data and to identify a cut-point that could be used to classify individuals as high or low risk of likely harboring AD pathology based on CSF Aβ and tau. We chose to use a ratio of aging-signature cortical thickness to AD-signature cortical thickness because a ratio is more likely to be applicable across differences in scanners, sequences, or processing pipelines, and because this ratio can be interpreted as increasing likelihood of AD pathology with higher values.

With these motivations and this background in mind, we undertook this study hypothesizing that the "personalized AD cortical thickness index" (pADi) would discriminate patients with MCI who have molecular evidence of AD from MCI patients who likely do not have AD and that discrimination would be better than the AD signature alone (i.e., not adjusted for age-related cortical atrophy) or the aging signature. This would support the predictive pathological validity of this biomarker. We further hypothesized that a pADi cut-point derived from this MRI measure based on molecular biomarkers would predict progression from MCI to dementia with effect sizes similar to CSF biomarkers themselves, potentially supporting the use of this quantitative MRI measure probabilistically as a less expensive and invasive corollary of amyloid PET or CSF. This would support the predictive clinical validity of this biomarker.

2. Methods

The data and methods for biomarker (MRI, CSF) processing reported below are similar to those previously described in Dickerson and Wolk [24]. In addition, we provide a detailed analysis plan to test our hypotheses about an individualized MRI-derived, cortical age-adjusted AD biomarker, the pADi.

2.1. Participants

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 as public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial MRI, PET, other biological markers and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD.

For the current analysis, we selected individuals with a baseline diagnosis of MCI who had baseline CSF and MRI data available. Detailed diagnostic, inclusion, and exclusion criteria are described on the ADNI website (http://www.adni-info.org/). Methods for clinically characterizing patients as MCI or dementia have been described previously [29]; biomarkers were not used to facilitate the clinical diagnoses. "Conversion to AD Dementia" was defined as an ADNI diagnosis of AD dementia at follow-up assessments in patients who were initially classified as MCI at baseline.

2.2. Standard protocol approvals, registrations, and patient consents

Each participant gave written informed consent in accordance with institutional Human Subjects Research Committee guidelines.

2.3. MRI and analysis

We performed this analysis with a discovery sample and a validation sample. The discovery sample consisted of 149 MRI scans collected on a 3T scanner. One hundred ten of