



## High-dimensional morphometry

## Single time point high-dimensional morphometry in Alzheimer's disease: group statistics on longitudinally acquired data



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## ABSTRACT

Quantitative assessment of medial temporal lobe atrophy has been proposed as a biomarker for Alzheimer's disease (AD) diagnostic and prognostic in mild cognitive impairment (MCI) due to AD. We present the first results of our high-dimensional morphometry technique, tracking tissue composition, and atrophy changes on T1-weighted magnetic resonance imaging at various time points. We selected 187 control subjects, 17 control subjects having progressed to MCI and/or AD, 178 subjects with stable MCI, 165 subjects with MCI having progressed to AD, and 147 AD subjects from the Alzheimer's Disease Neuroimaging Initiative study. Results show statistically significant differences between almost every diagnostic and time point comparison pairs (0–12, 12–24, and 24–36 months), including controls having progressed to either MCI or AD and trajectory dynamics that demonstrate the algorithm's ability at tracking specific pathology-related neurodegeneration.

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## 1. Introduction

## 1.1. High-dimensional morphometry in Alzheimer's disease

The relationship between magnetic resonance imaging (MRI) measures and pathophysiological changes in Alzheimer's disease (AD) has been well researched. MRI-pathologic studies have confirmed that MRI tracks brain atrophy due to neuronal loss (Csernansky et al., 2004; Jack et al., 2002) at the global, regional, and local level (Chetelat and Baron, 2003; Fox and Schott, 2004) up to 10 years before disease onset (Tondelli et al., 2012). Global measures have included longitudinal volumetric analyses and calculated atrophy rates for the whole brain (Chan et al., 2003; Chen et al., 2004; Ezekiel et al., 2004; Fox and Freeborough, 1997; Fox and Schott, 2004; Fox et al., 1999; Jack et al., 2005), global gray matter

concentrations differences (Chetelat et al., 2005; Fan et al., 2008; Ishii et al., 2005; Karas et al., 2003, 2004; Kloppel et al., 2008; Shiino et al., 2006), and cortical thinning (Lerch et al., 2005, 2008; Singh et al., 2006; Thompson et al., 2004). Regional measurements have included medial temporal lobe atrophy estimates (Frisoni et al., 1996; Korf et al., 2004; Visser et al., 1999), including our own (Duchesne and Mouiha, 2011; Duchesne et al., 2008, 2010, 2012) and enlargement of the temporal horn in the lateral ventricle (Frisoni et al., 2002; Rossi et al., 2004). Local measurements have principally revolved around manual or semiautomated volumetry of the hippocampus, the entorhinal cortex, and the temporal neocortex (de Toledo-Morrell et al., 2004; Du et al., 2001; Grundman et al., 2002; Korf et al., 2004; Pennanen et al., 2004). Hippocampal atrophy as measured on MRI has been correlated with confirmatory pathologic findings (Ashburner et al., 2003; Csernansky et al., 2004). In those subjects with mild cognitive impairment (MCI) progressing to probable AD, measurable hippocampus and entorhinal cortex atrophy have some predictive value (Coimbra et al., 2006; Herholz, 2003; Jagust et al., 2006; Klunk et al., 2004; Nordberg, 2004; Weiner et al., 2005).

Based on the available evidence, medial temporal lobe atrophy assessment has therefore been proposed as a biomarker for the diagnosis of AD (McKhann et al., 2011) and the establishment of AD as a putative cause for MCI (Albert et al., 2011). Volumetric measurement of specific structures, in particular the hippocampus, is

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<sup>1</sup> Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database ([adni.loni.ucla.edu](http://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](http://adni.loni.ucla.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf).

the technique most commonly used for quantitative evaluation (Boccardi et al., 2011). However, the accuracy and predictive ability of hippocampus volumetric assessment, even longitudinally, is almost equal to advanced neuropsychological testing (Ewers et al., 2012). It is therefore useful to confirm an established clinical impression, rather than inform physicians regarding future disease progression, especially in the presymptomatic period. One reason for this limitation stems from the simple fact that volumetric evaluation does not capture many aspects of neurodegeneration, such as experienced in AD and evidenced in neuropathologic findings (Braak and Braak, 1996). Techniques that can quantitatively estimate tissue change multifactorially, or that do so over larger areas, up to and including the whole brain, should therefore have a wider predictive range as related to the dynamic disease process. This was exemplified on the one hand by the work done by Liu et al. (2010), where the highest accuracy was reached with 24 different regional cortical volumes and 34 cortical thicknesses, and on the other hand by the nonlocal patch technique of Coupe et al. (2012), centered on the hippocampus but able to exploit subtle tissue changes, which reached equally high sensitivity and specificity.

To this end, *over the last decade* a number of techniques have attempted to characterize mono- or multimodal image information and embed machine learning principles to both characterize and discriminate subject populations (Ortu et al., 2012). There is increasing evidence that this family of algorithms allows for better discrimination of AD and prediction of conversion in MCI from a number of reports (Cuingnet et al., 2011; Fan et al., 2008; Jhoo et al., 2010; Kloppel et al., 2008; Koikkalainen et al., 2011; López et al., 2011; Misra et al., 2009; Vemuri et al., 2008; Westman et al., 2011; Zhang et al., 2011). Notable works include Davatzikos et al. (2008) who reported a high degree of accuracy in prediction using a high-dimensional image analysis and pattern classification technique; Fan et al. (2008) who extended this work to combine MRI and positron emission tomography analysis to yield very high predictive accuracy in 30 MCI subjects with area under curve of 0.98; and Hua et al. (2009) who used tensor-based morphometry-derived summary statistics to show that sample sizes can be greatly reduced compared with clinical metrics. In other works, Wolz et al. (2011) have compared and combined multiple metrics (tensor-based morphometry, hippocampal segmentation, cortical thickness measures, and manifold learning) and showed that the combination of multiple measures, across larger regions of the brain, reaches high sensitivity, and specificity. Yet, the new class of approach proposed by Coupe et al. (2012), relying on information extracted using nonlocal patches on a well-targeted area (the hippocampus), shows that characterization of tissue changes can be equally effective to track neurodegeneration.

We have developed and presented such a machine learning-based technique (Duchesne et al., 2008, 2010), using a high-dimensional morphometry to extract both composition and deformation tissue characteristics related to the pathology within a large volume of interest (e.g., medial temporal lobe). Tissue composition is estimated via an intensity proxy a gray matter fuzzy map, whereas tissue deformation is measured via a spatial proxy the Jacobian of nonlinear deformation fields (see Section 2.5). Those measures are combined to provide an index related to disease progression, the disease evaluation factor (DEF) (Duchesne and Mouiha, 2011). Such changes in tissue composition have been reported via voxel-based morphometry (Ferreira et al., 2011) and contrast studies (Salat et al., 2011), whereas volumetry (Chetelat and Baron, 2003) and tensor-based morphometry (Hua et al., 2008, 2009) reports have shown pathology-related tissue deformations in specific brain areas. By incorporating both spatial and intensity features, we are able to capture different properties of the advancing pathologic process and predict future clinical status for an individual subject. Although we have applied this

methodology in earlier work to the single-time point, single-scanner discrimination of probable AD from age-matched healthy controls (Duchesne et al., 2008, 2010), as well as the prediction of amnesic MCI progression to clinically probable AD (Duchesne et al., 2008, 2010), the characteristics of our metric and its ability at tracking group differences related to future conversion in a large multicentric longitudinal setting remained to be studied.

## 1.2. Study objectives

The main objective of the presented study is to estimate DEF progression in time for the different clinical populations in the Alzheimer's Disease Neuroimaging Initiative (ADNI) (data used in the preparation of this article were obtained from the ADNI database ([adni.loni.ucla.edu/](http://adni.loni.ucla.edu/)). The ADNI was launched in 2003 by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, the Food and Drug Administration, private pharmaceutical companies, and nonprofit 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, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment 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 coinvestigators from a broad range of academic institutions and private corporations, and subjects have been recruited from over 50 sites across the United States and Canada. The initial goal of ADNI was to recruit 800 adults, aged 55–90 years, to participate in the research, approximately 200 cognitively normal older individuals to be followed for 3 years, 400 people with MCI to be followed for 3 years, and 200 people with early AD to be followed for 2 years." For up-to-date information, see [www.adni-info.org/](http://www.adni-info.org/)) data set. In this manuscript, we report the first results of our high-dimensional metric on longitudinally acquired data for control subjects (CTRL), control subjects having progressed to either MCI or AD (pCTRL), stable MCI subjects (sMCI), MCI having progressed to AD (pMCI) and AD subjects.

Specifically, we wanted to (1) report longitudinal statistics for the DEF metric over a 36-month time frame for these clinical groups, including power calculations; and (2) test the following 3 hypotheses:

- The DEF would track age-related structural decline in a group of CTRL subjects over time.
- The DEF would track neuropathologic structural decline in groups of pCTRL, pMCI, and AD subjects over time.
- The difference between age-related and neuropathologic decline would be statistically significant at the group level throughout the disease time course.

Our aim was to verify the ability of the proposed method in tracking the atrophy progression in the different clinical groups of the ADNI data set and report meaningful severity progressions across the groups, especially concerning control and MCI subjects which will convert in future to pathologic stages.

## 2. Methods

### 2.1. Ethics

Each participant from the ADNI cohort was formally evaluated using eligibility criteria that were described in detail elsewhere

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