



High-dimensional morphometry

Disentangling normal aging from Alzheimer's disease in structural magnetic resonance images



Marco Lorenzi^{a,*}, Xavier Pennec^a, Giovanni B. Frisoni^{b,c}, Nicholas Ayache^a, for the Alzheimer's Disease Neuroimaging Initiative[†]

^aAsclepius Research Project, INRIA Sophia Antipolis, Sophia Antipolis, France

^bIRCCS Fatebenefratelli, Brescia, Italy

^cMemory Clinic, University Hospitals and University of Geneva, Geneva, Switzerland

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ABSTRACT

The morphology observed in the brains of patients affected by Alzheimer's disease (AD) is a combination of different biological processes, such as normal aging and the pathological matter loss specific to AD. The ability to differentiate between these biological factors is fundamental to reliably evaluate pathological AD-related structural changes, especially in the earliest phase of the disease, at prodromal and preclinical stages. Here we propose a method based on non-linear image registration to estimate and analyze from observed brain morphologies the relative contributions from aging and pathology. In particular, we first define a longitudinal model of the brain's normal aging process from serial T1-weight magnetic resonance imaging scans of 65 healthy participants. The longitudinal model is then used as a reference for the cross-sectional analysis. Given a new brain image, we then estimate its anatomical age relative to the aging model; this is defined as a *morphological age shift* with respect to the average age of the healthy population at baseline. Finally, we define the *specific morphological process* as the remainder of the observed anatomy after the removal of the estimated normal aging process. Experimental results from 105 healthy participants, 110 subjects with mild cognitive impairment (MCI), 86 with MCI converted to AD, and 134 AD patients provide a novel description of the anatomical changes observed across the AD time span: normal aging, normal aging at risk, conversion to MCI, and the latest stages of AD. More advanced AD stages are associated with an increased morphological age shift in the brain and with strong disease-specific morphological changes affecting mainly ventricles, temporal poles, the entorhinal cortex, and hippocampi. Our model shows that AD is characterized by localized disease-specific brain changes as well as by an accelerated global aging process. This method may thus represent a more precise instrument to identify potential clinical outcomes in clinical trials for disease modifying drugs.

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1. Introduction

The objective of computational anatomy when applied to neurodegenerative diseases, such as Alzheimer's disease (AD), is to understand the pathological changes affecting brain morphology (Frisoni et al., 2010; Schill et al., 2002). However, the morphology

of the brain affected by AD is not completely related to the disease, especially in asymptomatic and prodromal stages, because the brain structure is also the result of patient phenotype and clinical history. In a brain affected by AD, we can identify 2 major processes contributing to morphological changes: normal aging and AD pathology itself.

- *Age-related anatomical changes.* It is known that aging is related to progressive impairment of neural mechanisms (Burke and Barnes, 2006), to chemical alterations in the brain, and to changes in cognition and behaviour (Hof and Mobbs, 1984). It has been observed that morphological changes in the aging brain are heterogeneous and primarily lead to gray matter loss in frontal, temporal, and parietal areas (Long et al., 2012; Sowell et al., 2003).

* Corresponding author at: INRIA Sophia Antipolis, Asclepius Research Project, Sophia Antipolis, France. Tel.: +33 4 92 38 76 60; fax: +33 4 92 38 76 69.

E-mail address: marco.lorenzi@inria.fr (M. Lorenzi).

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- **Disease-related anatomical changes.** AD is a neurodegenerative disease characterized by the cooccurrence of different phenomena. It starts with the deposition of amyloid plaques and tau proteins in neurofibrillary tangles, which is followed by the development of function brain loss, and finally by widespread structural atrophy (Jack et al., 2010). The typical pattern of brain tissue loss seen in AD mirrors tau deposition (Thompson et al., 2003) and involves primarily hippocampi, the entorhinal cortex, the posterior cingulate, and secondarily the temporal, parietal, and frontal cortices (Frisoni et al., 2010). Aging is the primary risk-factor in AD and leads to patterns of structural loss overlapping the pathological ones. However, the magnitude of brain atrophy caused by AD is generally striking compared with normal aging. As claimed in previous studies, AD is more likely to be a pathological state concurrent to aging, identified by specific biochemical and structural hallmarks (Barnes, 2011; Nelson et al., 2011).

Being able to separately model healthy aging and AD would allow us to describe a given anatomy as being composed of distinct and concurrent factors. Such a decomposition would be extremely interesting not only to improve the understanding of the disease but also for clinical purposes, such as for early diagnosis and for the development of drugs targeting the atrophy specific to the pathology. It is important to notice that, although brought on completely different biological mechanisms, aging and AD often map to common areas, and the correct identification of the respective contributions can be difficult, especially in morphometric studies. Moreover, it is plausible that these phenomena are not completely independent and may overlap to create a positive “feedback” process. Thus, the onset of pathological changes may lead to accelerated global aging in the long term (Fjell et al., 2012), and vice versa.

A reliable estimate of the aging component is also important for modeling the evolution of the disease and for subsequent statistical analysis. When comparing the longitudinal observations from different clinical groups, at different aging stages, it is crucial to correctly position the observations on the time axis. This is not straightforward because the disease appears at different ages and chronologically older brains may have greater structural integrity than younger ones affected by the pathology. Therefore, it might be of practical interest to compute an index of age shift “relative” to a reference anatomical model.

The idea of modeling the time course of AD with respect to clinical and demographic factors was proposed in previous statistical studies (Ito et al., 2012; Samtani et al., 2012; Yang et al., 2011). However, these works were limited to scalar observations such as clinical scores and demographics and thus do not provide an explicit model which relates structural changes in the entire brain to the disease and aging. Moreover, the disease progression was identified by clinical measures and was not therefore explicitly associated with a temporal time course.

Although imaging-based surrogate measures of aging have been provided by different methodological studies (Davatzikos et al., 2009; Franke et al., 2010; Konukoglu et al., 2013), the idea of separately investigating aging and residual morphological changes has not been proposed before.

The objective of this work is to introduce a framework to identify and disentangle the brain anatomical changes related to normal aging from those related to other biological processes, such as AD. In particular, our framework is based on the hypothesis that relates the development of AD to the abnormal accumulation of beta-amyloid (A β) peptide in the brain (Jack et al., 2010). We thus define “normal aging” as the morphological brain evolution which is not caused by A β . This evolution is modeled by nonlinear

registration and is used as a reference to characterize observed anatomy as a contribution from normal morphological aging (normal aging process) plus a specific morphological process that encodes the subject’s specific variability such as pathological traits. We test our framework on healthy participants positive to the cerebrospinal fluid (CSF) A β 42 marker, in participants affected by mild cognitive impairment (MCI) and in AD patients.

The method is based on diffeomorphic nonlinear registration and is detailed in Section 2. In Section 3, we show that such a framework provides a meaningful and accurate description of anatomical brain changes across the stages of AD, characterized by increased morphological aging plus specific and local atrophy features.

2. Methods

The proposed method relies on specific modeling assumptions which are summarized here:

- The model of normal aging is derived from imaging data by applying a registration-based protocol detailed in Section 2.1. In particular, we assume that normal aging can be modeled through nonlinear registration as a smooth and continuous process that can be extrapolated backward and forward in time beyond the observed imaging follow-up time. Moreover, we assume that normal aging is a constant process in time, that does not accelerate nor decelerate with respect to the biological age of the elderly population. We show in Sections 3.4. and 3.5. that these simple assumptions lead to plausible experimental results compared with imaging and clinical data, and that the proposed model is a generalization of the classical linear mixed-effect (LME) modeling of univariate data used in longitudinal studies (Fitzmaurice et al., 2011).
- We define the *specific morphological process* as the remainder of the observed anatomy modulo the normal aging process. Thus, the specific morphological process encodes the morphological traits that cannot be described by the model of normal aging. In this study we aim to show that this specific process provides valuable information for discriminating pathological traits specific to AD across the whole disease time span (Section 3.6).

The framework was developed in the following way. We want to model the anatomy represented by a magnetic resonance image, I_k , acquired for a given subject k . For this purpose we describe the anatomical changes with respect to a reference anatomical template, T , through nonlinear image registration. This work is based on diffeomorphic registration parameterized by stationary velocity fields (SVFs) (Lorenzi et al., 2013). The nonlinear registration setting estimates one-to-one smooth deformations that spatially align the anatomies represented by pairs of images. These deformations are completely identified voxel-wise by tangent velocities in the deformation space (Arsigny et al., 2006).

As illustrated in Fig. 1, we parameterize the subject-to-template deformation ϕ_k by the flow of a SVF w_k , which is denoted $\phi_k = \exp(w_k)$. In this framework the observed anatomical changes are entirely encoded in the SVF w_k .

Because the space of SVFs is a linear vector space (contrarily to the space of deformations that it generates), we assume that w_k can be decomposed into the algebraic sum of the normal deformation parameter w_{age}^k plus a specific deformation parameter w_{specific}^k (Fig. 2).

The proposed framework analyzes these different components by processing the observed anatomy in different modeling steps as described in the following sections.

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