NeuroImage 134 (2016) 658–670

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

A multivariate nonlinear mixed effects model for longitudinal image analysis: Application to amyloid imaging

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ARTICLE INFO

Article history:
Received 24 November 2015
Revised 4 March 2016
Accepted 1 April 2016
Available online 16 April 2016

Keywords:
Longitudinal image analysis
Progression score
Amyloid imaging

ABSTRACT

It is important to characterize the temporal trajectories of disease-related biomarkers in order to monitor progression and identify potential points of intervention. These are especially important for neurodegenerative diseases, as therapeutic intervention is most likely to be effective in the preclinical disease stages prior to significant neuronal damage. Neuroimaging allows for the measurement of structural, functional, and metabolic integrity of the brain at the level of voxels, whose volumes are on the order of mm^3. These voxelwise measurements provide a rich collection of disease indicators. Longitudinal neuroimaging studies enable the analysis of changes in these voxelwise measures. However, commonly used longitudinal analysis approaches, such as linear mixed effects models, do not account for the fact that individuals enter a study at various disease stages and progress at different rates, and generally consider each voxelwise measure independently. We propose a multivariate nonlinear mixed effects model for estimating the trajectories of voxelwise neuroimaging biomarkers from longitudinal data that accounts for such differences across individuals. The method involves the prediction of a progression score for each visit based on a collective analysis of voxelwise biomarker data within an expectation–maximization framework that efficiently handles large amounts of measurements and variable number of visits per individual, and accounts for spatial correlations among voxels. This score allows individuals with similar progressions to be aligned and analyzed together, which enables the construction of a trajectory of brain changes as a function of an underlying progression or disease stage. We apply our method to studying cortical β-amyloid deposition, a hallmark of preclinical Alzheimer's disease, as measured using positron emission tomography. Results on 104 individuals with a total of 300 visits suggest that precuneus is the earliest cortical region to accumulate amyloid, closely followed by the cingulate and frontal cortices, then by the lateral parietal cortex. The extracted progression scores reveal a pattern similar to mean cortical distribution volume ratio (DVR), an index of global brain amyloid levels. The proposed method can be applied to other types of longitudinal imaging data, including metabolism, blood flow, tau, and structural imaging-derived measures, to extract individualized summary scores indicating disease progression and to provide voxelwise trajectories that can be compared between brain regions.

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1. Introduction

It is important to characterize the temporal trajectories of disease-related biomarkers in order to monitor progression and to identify potential points of intervention. Such a characterization is especially important for neurodegenerative diseases, as therapeutic intervention is most likely to be effective in the preclinical disease stages prior to significant neuronal damage. For example, in Alzheimer's disease, brain changes evident in structural, functional, and metabolic imaging may occur more than a decade before the onset of cognitive symptoms (Bateman et al., 2012), with cortical amyloid-β (Aβ) accumulation being one of the earliest changes (Jack et al., 2013; Sperling et al., 2014a; Villemagne et al., 2013). Such brain changes can be measured using neuroimaging techniques and can be tracked over time at the individual level via longitudinal studies.

Given the focus on preventing and delaying the onset of incurable neurodegenerative diseases, the emphasis of clinical trials has shifted to studying clinically normal individuals with positive biomarkers, for example those exhibiting brain amyloid in the case of AD, in order to identify early intervention opportunities in the preclinical stages of

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http://dx.doi.org/10.1016/j.neuroimage.2016.04.001
1053-8119/Published by Elsevier Inc.

disease (Sperling et al., 2014b). It is important to determine the temporal trajectories of hypothesized biomarkers in the early disease stages in order to better understand their associations with disease progression. Current neuroimaging methods allow for the characterization of the brain at the mm^3 level, generating hundreds of thousands of measurements that can be used as potential biomarkers of neurodegenerative diseases. Understanding the temporal trajectories of these voxelwise measurements can provide clues into disease mechanisms by identifying the earliest and fastest changing brain regions.

Changes in voxelwise neuroimaging measurements over time are commonly studied using linear mixed effects models (Bernal-Rusiel et al., 2012, 2013; Ziegler et al., 2015). Univariate linear mixed effects models use time or age to characterize changes in a single imaging measure. However, time or age may not be the appropriate metric for measuring disease progression due to variability across individuals. While covariates can be included in linear mixed effects models to account for this variability, choosing the correct set of covariates is difficult and covariates generally have a more complicated association with disease progression than the assumed linear relationship of linear mixed effects models. Instead, this variability can be accounted for by aligning individuals in time based on their longitudinal biomarker profiles within a multivariate framework. This is the premise of the Disease Progression Score method, which has been applied to studying changes in cognitive and biological markers related to Alzheimer's disease (Jedynak et al., 2012, 2014; Bilgel et al., 2014). It is assumed that there is an underlying progression score (PS) for each subject visit that is an affine transform of the subject's age, and given this PS, it is possible to place biomarker measurements across a group of subjects onto a common timeline. The affine transformation of age removes across-subject variability in baseline biomarker measures as well as in their rates of longitudinal progression. Each biomarker is associated with a parametric trajectory as a function of PS, whose parameters are estimated along with the PS for each subject. This allows one to "stitch" data across subjects to obtain temporal biomarker trajectories that fit an underlying model (Fig. 1).

Previous approaches have used certain cognitive measures, such as ADAS-Cog (Caroli and Frisoni, 2010; Yang et al., 2011), MMSE (Doody et al., 2010) or CDR-SB (Delor et al., 2013) as a surrogate for disease progression to delineate the trajectories of other AD-related cognitive measurements. These methods operate with the assumption that disease progression is reflected by a single cognitive measurement rather than a profile of multiple measurements, and therefore are inherently limited in their characterization of disease evolution. Younes et al. (2014) fitted a piecewise linear model to longitudinal data assuming that each biomarker becomes abnormal a certain number of years before clinical diagnosis, and this duration was estimated for each biomarker to yield longitudinal trajectories as a function of time to diagnosis. A quantile regression approach was employed by Schmidt-Richberg et al. (2015) to align a sample of cognitively normals and mild cognitively impaired (MCI) with a sample of MCI and AD, and then to estimate biomarker trajectories. These approaches assume that all individuals are on a path to disease and require knowledge of clinical diagnosis. Therefore, they are not suitable for studying the earliest changes in individuals who have not converted to a clinical diagnosis. Donohue et al. (2014) applied a self-modeling regression model within a multivariate framework to characterize the longitudinal trajectories of a set of cognitive, CSF, and neuroimaging-based biomarkers. This approach allows for across-subject variability only in the age of onset, not in progression speed. Models incorporating fixed effects as well as individual-level random effects have been proposed to study ADAS-Cog (Ito et al., 2011; Schiratti et al., 2015b) and regional cortical atrophy (Schiratti et al. 2015b), and Schulam et al. (2015) used a spline model that incorporates longitudinal clustering and modeling of individual-level effects to study trajectories of scleroderma markers. These mixed effects models take into consideration each measure separately rather than using them within a unifying framework. Others have used event-based probabilistic frameworks to determine the ordering of changes in longitudinal biomarker measures as well as the appropriate thresholds for separating normal from abnormal measures (Fonteijn et al., 2012; Young et al., 2014). These methods characterize longitudinal biomarker trajectories in a discrete framework rather than a continuous one. Schiratti et al. (2015a) proposed an extension to their earlier approach to model multiple measures together. Biomarker trajectories are assumed to be identical except for a shift along the disease timeline, and this assumption prevents hypothesis testing regarding rate of change across biomarkers. Furthermore, biomarkers are assumed to be conditionally independent given the subject-level random effects, but this assumption is not realistic when biomarkers are voxel-based neuroimaging measurements.

Here, we adapt the disease progression score principle to studying longitudinal neuroimaging data by making substantial innovations to the progression score model and parameter estimation procedure. First, voxelwise imaging measures constitute the biomarkers in the model, and are analyzed together in a multivariate framework. Studying progression at the voxel level rather than using region of interest (ROI)-based measures allows for the discovery of patterns that may not be

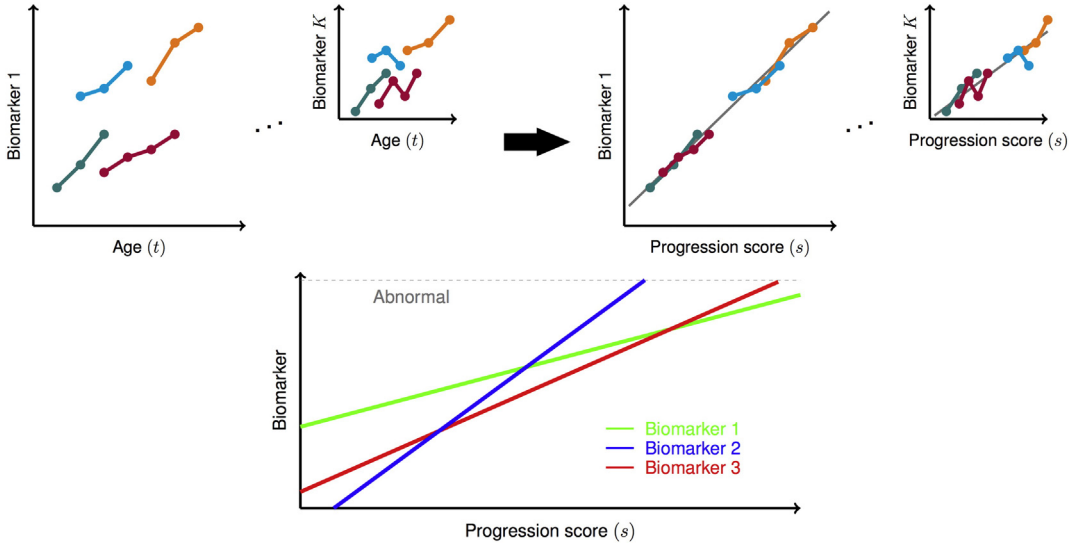

Fig. 1. Illustration of the biomarker alignment concept in the progression score model. The biomarkers we consider in this work are PET measures of cerebral amyloid across a total of $K \approx 30{,}000$ voxels. Top: Progression score (PS) aligns longitudinal measures better than age, and allows for the estimation of a trajectory for each biomarker/voxel (in gray). Bottom: Estimated biomarker trajectories can be compared on the common PS scale.