NeuroImage xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

NeuroImage

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

Estimating anatomical trajectories with Bayesian mixed-effects modeling

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ARTICLE INFO

Article history:
Received 24 September 2014
Accepted 30 June 2015
Available online xxxx

Keywords:
Brain morphology
Lifespan brain aging
Dementia
Longitudinal analysis
Multi-level models
Bayesian inference

ABSTRACT

We introduce a mass-univariate framework for the analysis of whole-brain structural trajectories using longitudinal Voxel-Based Morphometry data and Bayesian inference. Our approach to developmental and aging longitudinal studies characterizes heterogeneous structural growth/decline between and within groups. In particular, we propose a probabilistic generative model that parameterizes individual and ensemble average changes in brain structure using linear mixed-effects models of age and subject-specific covariates. Model inversion uses Expectation Maximization (EM), while voxelwise (empirical) priors on the size of individual differences are estimated from the data. Bayesian inference on individual and group trajectories is realized using Posterior Probability Maps (PPM). In addition to parameter inference, the framework affords comparisons of models with varying combinations of model order for fixed and random effects using model evidence. We validate the model in simulations and real MRI data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) project. We further demonstrate how subject specific characteristics contribute to individual differences in longitudinal volume changes in healthy subjects, Mild Cognitive Impairment (MCI), and Alzheimer's Disease (AD).

Introduction

Magnetic Resonance Imaging (MRI) and computational morphometry have become important tools for *in-vivo* analysis of changes in healthy and pathological brain development and aging (Frisoni et al., 2010; Fjell and Walhovd, 2010). One of the most exciting research questions is the nature of variability in aging brain structure (Raz et al., 2005, 2010; Raz and Rodrigue, 2006) and function (Pudas et al., 2013; Grady, 2012) observed across individuals. Most aging studies apply cross-sectional designs, providing estimates of population average, age-related, differences via pooling within cohorts (Ziegler et al., 2012a). However, exploring the large heterogeneity of true within-subject brain changes necessarily requires repeated measures and longitudinal designs (Raz and Lindenberger, 2011).

Longitudinal assessments offer significant advantages over cross-sectional studies (for an introduction see e.g. Fitzmaurice et al., 2008). A longitudinal study is more powerful for a fixed number of subjects. It permits separation of within- and between-subject variability, and helps to ameliorate confounds. Another important advantage is that in addition to providing estimates of population average brain changes it enables a characterization of systematic differences in longitudinal trajectories among individuals. This allows researchers to identify adverse as well as protective factors that may influence healthy and pathological changes in brain anatomy and function over time (see e.g. Taki et al., 2013; Thambisetty et al., 2012; Smith et al., 2010; Debette et al., 2011; den Heijer et al., 2012). Moreover, individual subjects' trajectories are promising biomarkers for early stage diagnosis (Chetelat and Baron, 2003), tracking of disease progression (Fonteijn et al., 2012; Jedynak et al., 2012; Sabuncu et al., 2014; Donohue et al., 2014; Young et al., 2014) and monitoring of potential treatments (Douaud et al., 2013).

Crucially, longitudinal MR-based morphometry is prone to artifacts due to scanner inhomogeneities, registration inconsistency, and subtle scanner-positioning or hydration-related deformations of the brains (Schnaudigel et al., 2010; Littmann et al., 2006; Kempton et al., 2009). Sophisticated within-subject registration pipelines have been introduced recently to parameterize structural changes in an unbiased fashion (Ashburner and Ridgway, 2013; Leung et al., 2012; Lorenzi and Pennec, 2013; Holland et al., 2011; Reuter et al., 2010, 2012).

An essential difference between longitudinal and cross-sectional analysis lies in the modeling assumptions about each individual. With a single observation per subject one has to assume the process of

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[1] Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (www.loni.usc.eduwww.loni.usc.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.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

http://dx.doi.org/10.1016/j.neuroimage.2015.06.094
1053-8119/

interest is identical across subjects (using fixed-effects assumptions). In contrast, longitudinal designs allow one to parameterize individual variations in the process by including random effects (or random coefficients). Modeling repeated measurements of behavior is well established in psychology and psychometry (for review see McArdle, 2009). In the last decade, there has been a growing interest in applications of mixed-effects models in the context of neuroimaging of development (Shaw et al., 2006, 2008; Raznahan et al., 2011a,b, 2014; Schumann et al., 2010) and aging neuroscience (Lerch et al., 2005; Lau et al., 2008; Carmichael et al., 2010). More articles focus specifically on methods for analysis of longitudinal MRI (Resnick et al., 2000; Chan et al., 2003; Frost et al., 2004; Bernal-Rusiel et al., 2012) and voxel-wise or vertex-wise longitudinal modeling (Guillaume et al., 2014; Li et al., 2013; Skup et al., 2012; Chen et al., 2013; Bernal-Rusiel et al., 2013).

Bayesian inference has been successfully applied to functional brain scans in multiple domains, ranging from general linear models, group analysis, spatial models, analysis of connectivity, to model comparisons (for extensive review see Woolrich, 2012). Bayesian inference typically exploits hierarchical observation models that take into account different levels of observations (e.g. scans and subjects), allows for the inclusion of biologically informed prior-beliefs about parameters, and affords comparisons among competing (nested or non-nested) models. Bayesian treatment of whole-brain neuroimaging data might also increase the sensitivity by finessing the problem of multiple comparison (Friston and Penny, 2003; Schwartzman et al., 2009). In contrast to classical inference, it also enables the assessment of evidence in favor of the null hypothesis; i.e., no aging-related change or preservation of structural integrity. These issues speak to a Bayesian framework for modeling structural change trajectories. However, there are currently only a few existing studies that consider longitudinal structural MRI (Schmid et al., 2009; Chen et al., 2012).

Here, we propose a generic modeling framework for longitudinal morphometric brain changes in development and aging studies. After diffeomorphic registration on the within-subject (Ashburner and Ridgway, 2013) and between-subject (Ashburner and Friston, 2011) level, we build a generative linear mixed-effects model of repeated observations. The model inversion flexibly accommodates unbalanced and sparse designs with potentially different numbers of follow up scans per subject. Using Expectation Maximization (EM) we obtain voxelwise individual and group level change parameters and compute Posterior Probability Maps (PPM) (Friston and Penny, 2003) for inference about regionally specific effects. In other words, we focus on making regionally specific inferences about longitudinal changes in anatomy, that properly account for both within and between subject variability in neurodevelopmental trajectories.

We validate the model using simulated data and a large MRI sample from the ADNI cohort. We then demonstrate a parametric analysis of subject specific covariates and explore the model space to optimize explanations of individual trajectory differences.

Methods

In this section, we introduce a generative model of local structural trajectories using random and fixed effects; i.e., a mixed effect, hierarchical or multilevel model. We describe the Bayesian formulation, the implicit (empirical) prior covariance components and their estimation using expectation maximization (EM). We extend this framework to modeling of trajectories over multiple groups and review the use of probabilistic parameter maps (PPM) for inference on model parameters. We conclude this section with a treatment of Bayesian model selection of ensemble trajectory models.

A generative model of local structural trajectories

The model for age-related changes of local brain structure (per voxel or region) is based upon the following generative model, which comprises a likelihood and prior. The model is an application of the Bayesian linear hierarchical observation framework introduced by Friston et al. (2002a) (for application in the context of fMRI see also Friston et al., 2002b).

We here consider the special case of a two level model, one for individual structural trajectories and a second level for an ensemble of trajectories, denoted by ε. The first level likelihood model is based on the assumption that the trajectory of underlying volumetric changes is sampled from subject-specific functions of age or time

$$y_{ij} = g\left(t_{ij}, \boldsymbol{\theta}_i^{(1)}\right) + \epsilon_{ij}^{(1)} \tag{1}$$

where the measurement y_{ij} is the j-th of m_i observations (e.g. of gray matter density at a single voxel) obtained from the i-th of N subjects at age t_{ij}, and $\epsilon_{ij}^{(1)}$ denotes an i.i.d. Gaussian measurement error with variance σ^2. In what follows we use time centered t_{ij} in order to develop trajectories around the reference age, i.e. t_r, which typically is chosen as the mean age of the sample. Individual differences of trajectories are thus encoded by subject-specific change parameters $\boldsymbol{\theta}_i^{(1)}$ resulting in an ensemble of age-related trajectories $\varepsilon = \{g(t, \boldsymbol{\theta}_i^{(1)})\}_{i=1}^{N}$ for a sample of individuals. In particular, we parameterize the function describing the trajectory using a D degree polynomial expansion of age

$$g\left(t, \boldsymbol{\theta}_i^{(1)}\right) = \sum_{d=1}^{D+1} \theta_{di}^{(1)} t^{d-1} \tag{2}$$

with coefficients $\boldsymbol{\theta}_i^{(1)} = [\theta_{1,i}^{(1)}, \ldots, \theta_{D+1,i}^{(1)}]^T$. For example, for $D = 2$ we have 3 coefficients per subject, encoding the intercept, slope and quadratic terms. We can easily write these linear models using compact matrix notation with individual design matrices and change parameters as $\mathbf{g}_i = \mathbf{X}_i^{(1)}\boldsymbol{\theta}_i^{(1)}$. Then, the model for all subjects follows

$$\begin{bmatrix} \mathbf{y}_1 \\ \mathbf{y}_2 \\ \vdots \\ \mathbf{y}_N \end{bmatrix} = \begin{bmatrix} \mathbf{X}_1^{(1)} & & & \\ & \mathbf{X}_2^{(1)} & & \\ & & \ddots & \\ & & & \mathbf{X}_N^{(1)} \end{bmatrix} \begin{bmatrix} \boldsymbol{\theta}_1^{(1)} \\ \boldsymbol{\theta}_2^{(1)} \\ \vdots \\ \boldsymbol{\theta}_N^{(1)} \end{bmatrix} + \boldsymbol{\epsilon}^{(1)} \tag{3}$$

$$\mathbf{y} = \mathbf{X}^{(1)}\boldsymbol{\theta}^{(1)} + \boldsymbol{\epsilon}^{(1)} \tag{4}$$

with subject i-th observations $\mathbf{y}_i = [y_{i1}, y_{i2}, \ldots, y_{im_i}]^T$, $M = \sum m_i$ concatenated observations y, first level design matrix $\mathbf{X}^{(1)}$, concatenated change parameters $\boldsymbol{\theta}^{(1)}$, and first level Gaussian errors $\boldsymbol{\epsilon}^{(1)}$. Vectorizing observations y_{ij} in 'person-scan' format, i.e. the successive scans are grouped by subjects (all from subject 1, all from subject 2, etc.), is a natural way to arrange longitudinal data with missing scans and varying number of follow ups. This additionally simplifies the structure of the first level design matrix, which then takes a block-diagonal form. Note, that this first level model explicitly accommodates unbalanced designs, i.e. $\mathbf{X}_i^{(1)} \neq \mathbf{X}_j^{(1)}$, with varying ages and numbers of scans per subject.

The sample change parameters of the trajectory functions are determined by (primarily non-age-dependent) subject specific effects. Note that these second level regressors can be chosen to model covariates of interest, e.g. IQ scores, genetic markers, or symptom severity, as well as purely confounding variables, e.g. global brain parameters. These measures are summarized in a centered $N \times R$ between-subject covariates matrix $\mathbf{Z}$ with entries z_{ir}. For example, in the results section below, we use a genetic risk score as a covariate of interest and test to see how this predicts first level parameters. Now, we adopt the following linear second level model

$$\begin{bmatrix} \boldsymbol{\theta}_1^{(1)} \\ \boldsymbol{\theta}_2^{(1)} \\ \vdots \\ \boldsymbol{\theta}_N^{(1)} \end{bmatrix} = \begin{bmatrix} \mathbf{I} & z_{11}\mathbf{I} & & z_{1R}\mathbf{I} \\ \mathbf{I} & z_{21}\mathbf{I} & & z_{2R}\mathbf{I} \\ \vdots & & \ddots & \vdots \\ \mathbf{I} & z_{N1}\mathbf{I} & & z_{NR}\mathbf{I} \end{bmatrix} \begin{bmatrix} \boldsymbol{\theta}_1^{(2)} \\ \boldsymbol{\theta}_2^{(2)} \\ \vdots \\ \boldsymbol{\theta}_{R+1}^{(2)} \end{bmatrix} + \boldsymbol{\epsilon}^{(2)} \tag{5}$$

Please cite this article as: Ziegler, G., et al., Estimating anatomical trajectories with Bayesian mixed-effects modeling, NeuroImage (2015), http://dx.doi.org/10.1016/j.neuroimage.2015.06.094