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Multivariate dynamical modelling of structural change during development

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ABSTRACT

Here we introduce a multivariate framework for characterising longitudinal changes in structural MRI using dynamical systems. The general approach enables modelling changes of states in multiple imaging biomarkers typically observed during brain development, plasticity, ageing and degeneration, e.g. regional gray matter volume of multiple regions of interest (ROIs). Structural brain states follow intrinsic dynamics according to a linear system with additional inputs accounting for potential driving forces of brain development. In particular, the inputs to the system are specified to account for known or latent developmental growth/decline factors, e.g. due to effects of growth hormones, puberty, or sudden behavioural changes etc. Because effects of developmental factors might be region-specific, the sensitivity of each ROI to contributions of each factor is explicitly modelled. In addition to the external effects of developmental factors on regional change, the framework enables modelling and inference about directed (potentially reciprocal) interactions between brain regions, due to competition for space, or structural connectivity, and suchlike. This approach accounts for repeated measures in typical MRI studies of development and aging. Model inversion and posterior distributions are obtained using earlier established variational methods enabling Bayesian evidence-based comparisons between various models of structural change. Using this approach we demonstrate dynamic cortical changes during brain maturation between 6 and 22 years of age using a large openly available longitudinal paediatric dataset with 637 scans from 289 individuals. In particular, we model volumetric changes in 26 bilateral ROIs, which cover large portions of cortical and subcortical gray matter. We account for (1) puberty-related effects on gray matter regions; (2) effects of an early transient growth process with additional time-lag parameter; (3) sexual dimorphism by modelling parameter differences between boys and girls. There is evidence that the regional pattern of sensitivity to dynamic hidden growth factors in late childhood is similar across genders and shows a consistent anterior-posterior gradient with strongest impact to prefrontal cortex (PFC) brain changes. Finally, we demonstrate the potential of the framework to explore the coupling of structural changes across *a priori* defined subnetworks using an example of previously established resting state functional connectivity.

1. Introduction

The human brain undergoes profound structural changes during development and aging. Magnetic resonance imaging (MRI) has become an invaluable tool to measure these brain changes *in vivo*. There is an increasing number of advanced longitudinal neuroimaging projects that focus on the specific patterns of change during brain maturation and development (for review see Mills and Tamnes, 2014). Several aspects of brain anatomy have been reported to undergo curvilinear changes with different markers progressing differently during development (Giedd et al., 1999; Lenroot et al., 2007; Raznahan et al., 2011; Mills et al., 2016). Recent studies indicate that cortical gray matter volume exhibits its highest volume during mid-to-late childhood, and decreases across the second decade (Tamnes et al., 2013; Aubert-Broche et al., 2013; Wierenga et al., 2014; Mills et al., 2016). There is also longitudinal evidence for gender differences in the shapes of developmental trajectories, with peak sizes 1 to 2 years earlier in females (Lenroot et al., 2007), although these differences are

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reduced when overall cranial volume is taken into account in the statistical model (Mills et al., 2016). Converging findings from cross-sectional and longitudinal studies in late childhood and adolescence also suggest that puberty-related physiological and hormonal changes induce brain changes in specific networks (Blakemore et al., 2010).

The primary goal of the current study was to develop a novel modelling framework rather than clarifying phenotype-specific questions about brain trajectories of regional gray matter volumes. One limitation of most previous studies on structural development is that mass-univariate techniques like general linear models (GLM) or linear-mixed models (LME) (Bernal-Rusiel et al., 2012; Ziegler et al., 2015) are applied. That often involves whole brain explorative analysis in order to identify local structural correlates of age or time, which survive a correction for multiple comparisons. The analysis of region-specific effects is often followed by a *post hoc* discussion and integration of observed results across multiple brain regions, which involves potential anatomical, physiological and neurological causal factors. In this context, terms such as 'states', 'processes' and 'trajectories' are used rather informally in the literature.

Here we introduce the characterisation of structural imaging data using multivariate differential equation models. This general approach will allow us to study the structural changes underlying brain development, plasticity, ageing and degeneration from a dynamical systems perspective. In our approach 'states' and 'trajectories' then take on a precise meaning endowed by the formal specification of a dynamical system with input factors. Our framework avoids serious limitations of univariate models, e.g. multiple testing, by providing a multivariate model for a whole set of brain regions under Bayesian inference. With regard to structural dynamics, states, x, would correspond to a vector of structural indices (e.g. gray matter volumes) in a set of brain regions at a single time point. The system then responds to inputs, u, a vector of values at a single time point comprising for example levels of hormones, growth factors or proteins. The change in state is then given by

$$\frac{dx}{dt} = f(x, u, a) \tag{1}$$

where $f(x, u, a)$ describes a dynamical process governed by parameters a. These parameters define, for example, the time constants of interactions among states. Most generally the states may only be observable through a noisy observation function $y = g(x, w) + e$. This overall description corresponds to the multiple-input-multiple-output (MIMO) system described previously (Friston et al., 2003; Friston, 2002).

In the study of development, hormonal or growth factor variables u would perturb states leading to periods of maximal growth. Such models are readily able, for example, to describe the logistic, multiple-logistic and other patterns of growth observed in biology (Thompson and Growth, 1945; Murray, 2002). Additionally, interactions among state variables might account for regional patterns of volumetric change arising from synaptic growth and pruning. This would add value to current univariate perspectives on structural changes (reviewed in Mills and Tamnes 2014), by adding a multivariate and dynamic perspective. It also relates to the recently proposed notion of 'maturational coupling', i.e. exploring similarities of changes across brain regions (Raznahan et al., 2011), but in principle should additionally enable quantification of joint underlying processes. Our proposal shares the ambitions of the Dynamical Bayesian Network (DBN) approach for studying inter-regional dependencies in structural brain imaging (Chen et al., 2012). The DBN approach operates in discrete time and models discrete observations (e.g. stable/atrophy), whereas the MIMO approach operates in continuous time and models continuous observations (e.g. gray matter volumes).

The DBN and MIMO frameworks share the benefits of a nonlinear dynamical systems perspective, thus going beyond linear-mixed effects models. However, being based on differential equations, the MIMO approach is closer to standard approaches in systems biology and neuroscience (Dayan and Abbott, 2001; Deco et al., 2008; Ingalls, 2013). Indeed, the work in this paper uses the same model estimation and inference algorithm ('Variational Laplace' (Friston et al., 2007)) that is incorporated in the Dynamic Causal Modelling (DCM) framework for making inferences about changes in brain connectivity from fMRI (Friston et al., 2003) or M/EEG data (Daunizeau et al., 2009).

In what follows, we describe sample specifics, details about longitudinal MR image processing, and the specification of system inputs. Then we introduce the specifics of the proposed model, briefly revisiting the procedures for inference. In the later sections of the paper we aim to demonstrate the construct validity of a dynamical systems approach in the context of brain maturation using a large sample of healthy children and adolescents. We present model estimates and examples for evidence-based model comparison using the empirical data. We hypothesise that intrinsic regional dynamics in development can be described using a multivariate linear dynamical system. According to previous findings we also expect substantial contributions of a puberty-related factor and a growth factor to the regional gray matter dynamics. Finally, using our novel approach we study an example of inter-regional connectivity and whether structural changes during development do reflect functional networks previously observed in resting state fMRI (Smith et al., 2009).

2. Methods

2.1. Sample

For the purpose of validation with real data, we used a subsample of the NIH Pediatric MRI Data Repository created by the NIH MRI Study of Normal Brain Development (Evans and Group, 2006). This project focuses on brain development in healthy typically developing infants, children and adolescents from a demographically balanced population based sampling. The data was acquired in multiple pediatric centers and included a variety of MR-based sequences and protocols (https://nihpd.crbs.ucsd.edu). A major part of the project aims at exploring the general course of normal brain development. Notably, the screening procedures excluded subjects with a family history of inherited neurological disorders or a lifetime history of Axis I psychiatric disorders, abnormalities during perinatal development, birth complications, physical growth problems, neurological or specific psychiatric disorders. A detailed description of the full sample acquisition and exclusion criteria can be found in Evans and Group (2006).

Image processing started with a sample from release 5 of the NIH MRI study objective 1 of the children and adolescents. The sample downloaded from the NIH repository included 770 scans of 401 subjects scanned at ages 4.8–21.9 years with zero, one or two annual follow-up scans per subject. A detailed overview of the acquisition protocols of the NIH MRI Study of Normal Brain Development can be found here (http://pediatricmri.nih.gov/nihpd/info/protocols.html) and in Evans and Group (2006). The available sample included data from both primary protocols and fallback protocols with either 1 mm or 3 mm slice thickness, respectively. We observed variations in raw data slice resolution influencing the quality of the image preprocessing results and discarded further 32 scans due to any serious artifacts in image segmentation, registration, or nonlinear normalization. After MR preprocessing we quality checked the image data (for details see Section 2.3). Indications for lower data quality, higher frequency of usage of the fallback (rather than the standard) protocols, and much sparser density of sampling at the lower age range resulted in discarding children younger than six years. We further focussed on a longitudinal sample for validation of our dynamical systems model, i.e. we included only subjects having follow-up measurements. The analyzed sample consisted of 289 children and adolescents (151 females, 135 males) with ages 6–21.9 years (M=12.47, SD=3.88 years) with in total 637 scans (338 from females and 299 obtained