NeuroImage 125 (2016) 791–802

Contents lists available at ScienceDirect

NeuroImage

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

State space modeling of time-varying contemporaneous and lagged relations in connectivity maps

Peter C.M. Molenaar [a,b,*], Adriene M. Beltz [a], Kathleen M. Gates [c], Stephen J. Wilson [b]

[a] Department of Human Development and Family Studies, The Pennsylvania State University, University Park, PA 16802, USA
[b] Department of Psychology, The Pennsylvania State University, University Park, PA 16802, USA
[c] Department of Psychology, University of North Carolina, Chapel Hill, NC 27559, USA

ARTICLE INFO

Article history:
Received 25 August 2015
Accepted 31 October 2015
Available online 4 November 2015

Keywords:
Cigarette smoking
Functional connectivity
Neural networks
Stationarity
Time-varying
Verbal working memory

ABSTRACT

Most connectivity mapping techniques for neuroimaging data assume stationarity (i.e., network parameters are constant across time), but this assumption does not always hold true. The authors provide a description of a new approach for simultaneously detecting time-varying (or dynamic) contemporaneous *and* lagged relations in brain connectivity maps. Specifically, they use a novel raw data likelihood estimation technique (involving a second-order extended Kalman filter/smoother embedded in a nonlinear optimizer) to determine the variances of the random walks associated with state space model parameters and their autoregressive components. The authors illustrate their approach with simulated and blood oxygen level-dependent functional magnetic resonance imaging data from 30 daily cigarette smokers performing a verbal working memory task, focusing on seven regions of interest (ROIs). Twelve participants had dynamic directed functional connectivity maps: Eleven had one or more time-varying contemporaneous ROI state loadings, and one had a time-varying autoregressive parameter. Compared to smokers without dynamic maps, smokers with dynamic maps performed the task with greater accuracy. Thus, accurate detection of dynamic brain processes is meaningfully related to behavior in a clinical sample.

Introduction

Background and study motivation

Advances in connectivity mapping of functional neuroimaging data have significantly increased science and society's understanding of the brain (Behrens and Sporns, 2012; Smith, 2012). Many of these advances concern data-driven connectivity analyses (Gates and Molenaar, 2012; Smith et al., 2011). One type of connectivity analysis is directed functional connectivity mapping, which aims to reveal the direction of relations between brain regions of interest (ROIs) based on statistical dependencies in the neural signal (Friston et al., 2013). It has been accomplished by means of several analysis techniques, particularly structural equation modeling (SEM) involving only contemporaneous directed connections, and vector autoregressive modeling (VAR) involving only lagged directed connections. Estimates of both contemporaneous and lagged directed connections can be obtained with structural VARs (Chen et al., 2011; Smith et al., 2012), and (extended) unified structural equation modeling (euSEM, cf. Gates et al., 2010, 2011; Kim et al., 2007). In order to streamline computation and aid interpretation, these analysis techniques often assume stationarity, implying that connectivity parameters are constant across the neuroimaging time series, but emerging evidence suggests that this assumption is not always an appropriate one (reviewed in Hutchison et al., 2013).

Researchers have generally used one of two approaches for detecting time-varying relations in connectivity maps. First, sliding windows show time-varying, or dynamic, relations in these maps. In general, they determine change in connectivity indices between ROIs across equally-spaced sections – or windows – of the time series (for a description, see Franke et al., 2008). The indices of interest are usually derived from a correlation analysis, but parameters from other analyses (e.g., time-frequency and independent components) have also been used (Chang and Glover, 2010; Kiviniemi et al., 2011). This work shows that time-varying relations are present in resting state and task-related functional connectivity maps, and that some of the variation is systematic (e.g., as determined by clustering algorithms) within and between individuals (Allen et al., 2014; Betzel et al., 2012; Chang and Glover, 2010; Chang et al., 2013; Handwerker et al., 2012; Jones et al., 2012; Kiviniemi et al., 2011; Rack-Gomer and Liu, 2012; Sakoğlu et al., 2010; Tagliazucchi et al., 2012; Thompson et al., 2013).

Second, time-varying (structural) VARs and state space models with time-varying parameters enable model-based approaches to dynamic connectivity mapping. In general, they determine time-varying connectivity parameters (including Granger causality indices) between ROIs

* Corresponding author at: Department of Human Development and Family Studies, The Pennsylvania State University, University Park, PA 16802, USA.
E-mail address: pxm21@psu.edu (P.C.M. Molenaar).

http://dx.doi.org/10.1016/j.neuroimage.2015.10.088
1053-8119/Published by Elsevier Inc.

using sophisticated estimation techniques. Models for blood oxygen level-dependent (BOLD) functional magnetic resonance imaging (fMRI) data have primarily been estimated with recursive least squares (for a description, see Möller et al., 2001). State space models with time-varying parameters have been considered in, for instance, Milde et al. (2010) and Havlicek et al. (2011), while Primiceri (2005) presents a general discussion of time-varying structural VARs. Because of their direct relevance to the present model, these approaches will be further discussed below (see Model specification section). Models for electroencephalography (EEG) and magnetoencephalography (MEG) data have also been estimated with Kalman filters and smoothers (for a description, see Bar-Shalom and Fortmann, 1988), which provide more noise suppression than sliding windows and more stable estimates than recursive least squares (Milde et al., 2010; Vedel-Larsen et al., 2010). Importantly, work using time-varying VARs has similarly found that dynamic relations are present in task-related effective connectivity maps (Hemmelmann et al., 2009; Hu et al., 2012; Milde et al., 2010; Wacker et al., 2011).

Sliding windows and time-varying VARs indicate that the stationarity assumption does not hold for data-driven connectivity mapping, but these approaches have limitations. Sliding window approaches provide a coarse, piecemeal estimate of dynamic relations, with findings varying based on window length; for example, the signal-to-noise ratio is lower in short versus long windows (discussed in Hutchison et al., 2013). So far, time-varying VARs have only been used to estimate lagged dynamic relations using fixed (i.e., not freely estimated) variances for both invariant and time-varying parameters, while only the latter should have nonzero variances. Moreover, it is unclear whether Kalman filters similar to those that have been applied to EEG and MEG data are appropriate for BOLD data, for which dynamic contemporaneous relations are of greatest relevance due to the comparatively low temporal resolution of the BOLD signal (Beltz and Molenaar, 2015; Smith et al., 2011). Thus, questions remain concerning the presence of time-varying relations in data-driven connectivity maps. Do time-varying relations exist when contemporaneous *and* lagged connection parameters are estimated within the same model? This is a key question because both parameter types must be calculated within the same model in order to ensure accurate magnitude and direction of ROI relations (Gates et al., 2010; Kim et al., 2007). Furthermore, can *arbitrary* (i.e., freely estimated, without information about which relations are dynamic and how they vary in time) contemporaneous and lagged time-varying connection parameters in BOLD fMRI data be estimated with an optimized second-order extended Kalman filtering/smoothing approach? This is a key question because current Kalman filtering approaches do not freely estimate the variances of time-varying parameters (Havlicek et al., 2011), requiring that all relations be estimated as dynamic (e.g., Milde et al., 2010). This may bias results if both constant and dynamic relations are present in the time series.

It is important to address these methodological limitations because converging evidence suggests that dynamic relations in functional neuroimaging data reflect meaningful neural processes. Time-varying functional relations have been found with multiple neuroimaging modalities, including fMRI, EEG, and MEG in human beings and local field potential recordings in cats, suggesting that they are not a mere methodological byproduct of one signal type in human beings (e.g., Betzel et al., 2012; Chang and Glover, 2010; de Pasquale et al., 2010; Hemmelmann et al., 2009; Milde et al., 2010; Popa et al., 2009). In fact, recent work has demonstrated correspondence between dynamic brain relations measured by BOLD fMRI and EEG (e.g., Chang et al., 2013; Tagliazucchi et al., 2012). Moreover, time-varying relations have been linked to experimental conditions (e.g., caffeine intake), behavior (e.g., vigilance during an attention task), and disease states (e.g., Alzheimer's disease and schizophrenia), suggesting that they are validly reflecting brain-based processes (Jones et al., 2012; Rack-Gomer and Liu, 2012; Sakoğlu et al., 2010; Thompson et al., 2013). Finally, time-varying analysis approaches have the potential to increase understanding of systematic temporal changes in brain connectivity that were previously detected, but not necessarily interpreted in terms of neural network stationarity. For example, past work on the neural underpinnings of olfactory habituation implemented unique task paradigms in order to overcome the systematic decreases in brain activity that correspond to repeated presentations of an odorant (e.g., Karunanayaka et al., 2014), but advances in time-varying analyses would permit explicit modeling of such habituation effects.

Current study

The goal of the current study was to validate exploratory state space models (SSMs) in simulated data and then to estimate the models for BOLD fMRI data, allowing for explicit modeling of both contemporaneous and lagged time-varying connection parameters without a priori information about which parameters are dynamic. SSMs, of which VARs are a special case (that do not include measurement models), also allow for dimension reduction based on principled statistical methods. Last but not least, to the best of our knowledge for the first time in neuroimaging an optimal raw data maximum likelihood method (for Gaussian series) or quasi-maximum likelihood method (for non-Gaussian series) was used, consisting of a second-order extended Kalman filter/smoother (sEKFS) embedded within a nonlinear optimizer. The sEKFS can be conceived of as acting as E-step and the nonlinear optimizer as M-step in a nonstandard EM-algorithm. This is an extension of our previous work (Beltz and Molenaar, 2015; Gates et al., 2010; Gates and Molenaar, 2012; Gates et al., 2011) regarding innovative connectivity and grouping procedures for BOLD fMRI data, procedures that are among the best in the field (as tested in Gates and Molenaar, 2012; Smith et al., 2011).

To accomplish our goal, we utilized BOLD fMRI data from nicotine-deprived cigarette smokers performing a verbal working memory task. These data are ideal for this methodological investigation because the nature of the sample and specificity of the task facilitated the interpretation of dynamic relations, when they were found. For instance, past work has shown differences between the brain activity of smokers and non-smokers during verbal working memory tasks, and the differences were modulated by nicotine deprivation (Sutherland et al., 2011; Xu et al., 2006).

Methods

Participants

Participants were 30 cigarette users (22 men, 8 women), aged 19 to 45 years; they were randomly selected from a sample of 118 individuals, who participated in one of two fMRI studies on smoking cue reactivity (Wilson et al., 2012, 2013). For both studies, participants had to report smoking an average of 15 to 40 cigarettes per day for the past 24 months, be right-handed, and pass an MRI safety screening.

Procedures

The testing procedures and task are outlined here and described in detail elsewhere (Nichols et al., 2014; Wilson et al., 2012, 2013). Eligible participants (as determined with a phone interview) came to the lab for a baseline session that included questionnaire and psychological task completion. Participants were cigarette-deprived for 12 h before the neuroimaging session, as confirmed with carbon monoxide (CO) levels. During this session, they provided structural MRI data and fMRI data during multiple tasks, including the verbal working memory task.

Measures

Baseline assessment

During the baseline assessment, basic demographic information and information regarding smoking patterns were assessed with standard