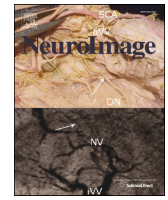
NeuroImage 102 (2014) 294–308

Contents lists available at ScienceDirect

NeuroImage

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



Impact of autocorrelation on functional connectivity

Mohammad R. Arbabshirani [a,b,*], Eswar Damaraju [a], Ronald Phlypo [c], Sergey Plis [a], Elena Allen [a,d,e], Sai Ma [c], Daniel Mathalon [f,g], Adrian Preda [h], Jatin G. Vaidya [i], Tülay Adali [c], Vince D. Calhoun [a,b]

[a] *The Mind Research Network, Albuquerque, NM, USA*
[b] *Department of ECE, University of New Mexico, Albuquerque, NM, USA*
[c] *Department of CSEE, University of Maryland, Baltimore County, MD, USA*
[d] *K. G. Jebsen Cener for Research on Neuropsychiatric Disorders, University of Bergen, Norway*
[e] *Department of Biological and Medical Psychology, University of Bergen, Norway*
[f] *Department of Psychiatry, University of California, San Francisco, CA, USA*
[g] *San Francisco VA Medical Center, San Francisco, CA, USA*
[h] *Department of Psychiatry and Human Behavior, University of California, Irvine, CA, USA*
[i] *Department of Psychiatry, University of Iowa, IA, USA*

A R T I C L E I N F O

Article history:
Accepted 22 July 2014
Available online 27 July 2014

Keywords:
Autocorrelation
Functional connectivity
Independent component analysis
Autoregressive process
Resting-state fMRI

A B S T R A C T

Although the impact of serial correlation (autocorrelation) in residuals of general linear models for fMRI time-series has been studied extensively, the effect of autocorrelation on functional connectivity studies has been largely neglected until recently. Some recent studies based on results from economics have questioned the conventional estimation of functional connectivity and argue that not correcting for autocorrelation in fMRI time-series results in "spurious" correlation coefficients. In this paper, first we assess the effect of autocorrelation on Pearson correlation coefficient through theoretical approximation and simulation. Then we present this effect on real fMRI data. To our knowledge this is the first work comprehensively investigating the effect of autocorrelation on functional connectivity estimates. Our results show that although FC values are altered, even following correction for autocorrelation, results of hypothesis testing on FC values remain very similar to those before correction. In real data we show this is true for main effects and also for group difference testing between healthy controls and schizophrenia patients. We further discuss model order selection in the context of autoregressive processes, effects of frequency filtering and propose a preprocessing pipeline for connectivity studies.

Introduction

Functional connectivity (FC) is defined as correlation (Friston, 2002) or any other measure of statistical dependency among time series of spatially remote brain voxels/regions. FC analysis describes interactions among brain regions during tasks as well as during resting state scans. In recent years, there has been a debate in the neuroimaging community regarding the possible impact of intrinsic autocorrelation in fMRI time-courses on functional connectivity analysis outcome. Some researchers have even questioned the validity of previous connectivity studies by arguing that not correcting for autocorrelation in fMRI time-series may result in spurious high correlation values (Christova et al., 2011; Georgopoulos and Mahan, 2013). These subject-level studies have confirmed that fMRI time-series are autocorrelated through the use of the Durbin–Watson statistic and have suggested to reduce the autocorrelation by using an autoregressive integrated moving average (ARIMA) model which is called prewhitening (Granger and Morris, 1976; Haugh, 1976).

Autocorrelation in fMRI data is assumed to originate from colored physical and physiological noises (Aguirre et al., 1997; Bullmore et al., 2001; Friston et al., 2000; Lenoski et al., 2008; Lund et al., 2006; Purdon and Weisskoff, 1998; Rajapakse et al., 1998; Zarahn et al., 1997). Several methods have been proposed to deal with autocorrelation in the general linear modeling framework (Friston et al., 2000; Gautama and Van Hulle, 2004; Lund et al., 2006; Woolrich et al., 2001). While some studies have suggested that intrinsic fMRI time-series autocorrelation is negligible compared to smoothing induced autocorrelation (Friston et al., 1995), others found it to be a significant confound (Christova et al., 2011; Lenoski et al., 2008; Zarahn et al., 1997).

It should be noted that most of the recent discussions (Christova et al., 2011; Georgopoulos and Mahan, 2013) are based on previous works in economics and econometrics most notably those initiated by Granger. In his seminal paper, "Spurious regression in economics", published in 1974, he strongly warned economists regarding the side-effects of ignoring autocorrelated residuals in a regression model (Granger and Newbold, 1974). While these conclusions are fully valid when dealing with just two autocorrelated time-series, to the best of

* Corresponding author at: The Mind Research Network, 1101 Yale Blvd NE, Albuquerque, NM 87106, USA. Fax: +1 505 272 8002.
E-mail address: marbabshirani@mrn.org (M.R. Arbabshirani).

http://dx.doi.org/10.1016/j.neuroimage.2014.07.045
1053-8119/

our knowledge, no one has investigated the impact of autocorrelation on functional connectivity based on a careful consideration of the specific differences that reign between the two fields.

In neuroimaging, inference is largely related to hypothesis testing and not necessarily focused on the point estimation of the actual correlation value. Most connectivity analyses are performed at the group level. Answers to questions like "Is the connectivity between two brain regions/networks significant?" or "Is there any significant difference in connectivity between two groups/tasks?" are typically of greater interest than estimating the correlation coefficients themselves. While most of economics discussion on this issue consider point estimation, it is not clear to what extent autocorrelation affects group level statistics in functional connectivity studies. Another surprising fact is the lack of explicit calculation of the correlation coefficient of two autocorrelated time-series in the literature, at least to the best of our knowledge. The goal of this study is to investigate the impact of autocorrelation on functional connectivity, defined in this study as the Pearson correlation coefficient between time-series of voxels, regions or networks. To better understand the impact of autocorrelation on Pearson correlation coefficient, first, we theoretically derive an approximation of the bias and variance of correlation coefficient estimator in the presence of autocorrelation in a very simple case with the intent to better understand the process (This is distinct from fMRI time-series simulation, which is outside of the scope of this manuscript). These theoretical results don't necessarily generalize to more complicated models due to the simplifying assumptions of this study. This is followed by simulations in order to validate the theoretical results. Finally, the impact of autocorrelation on real resting-state fMRI time-series is assessed. We also discuss proper preprocessing for connectivity analysis based on these observations. We focus on the resting-state FC given the growing interest in this condition and to avoid the confound that autocorrelation in task-based fMRI heavily depends on the task design.

Theoretical background

Pearson correlation coefficient of two autocorrelated time-series

The most well-known method to model autocorrelation in a time-series is the Box–Jenkins methodology (Box and Jenkins, 1970). In this method, the time-series are observed as outputs of autoregressive integrated moving average (ARIMA) processes. Since calculating the correlation coefficient between two time-series can quickly become highly involved in high ARIMA model orders, we try to assess the impact of autocorrelation in a simple case. Let w and z denote two white bivariate normally distributed time-series. The Pearson correlation coefficient is defined as the covariance between two random processes divided by the product of their standard deviations:

$$\rho_{w,z} = \frac{cov(w,z)}{\sqrt{var(w)var(z)}} \tag{1}$$

$\rho_{w,z}$ measures the normalized linear dependency between w and z. In practice, the correlation coefficient is estimated from a limited sample from random variables w and z:

$$r_{w,z} = \frac{\sum_{i=1}^{N}(w_i-\overline{w})(z_i-\overline{z})}{\sqrt{\sum_{i=1}^{N}(w_i-\overline{w})^2}\sqrt{\sum_{i=1}^{N}(z_i-\overline{z})^2}} \tag{2}$$

where N is the number of samples and $\overline{w}$ and $\overline{z}$ are the empirical mean values of w and z.

Distribution of Pearson correlation coefficient is provided in the Supplementary material. The first two moments of $r_{w,z}$ are:

$$E\left[r_{w,z}\right] \cong \rho_{w,z} - \frac{\rho_{w,z}\left(1-\rho_{w,z}^2\right)}{2N} \tag{3}$$

$$var\left(r_{w,z}\right) \cong \frac{\left(1-\rho_{w,z}^2\right)^2}{N}\left(1+\frac{11\rho_{w,z}^2}{2N}\right). \tag{4}$$

It can be read from Eq. (3) that $r_{w,z}$ is a biased estimator unless $\rho_{w,z}$ is zero.

We assume that w and z are latent random variables only observable through their respective autocorrelated time-series x and y. We are interested in the true correlation coefficient between x and y without the induced effect of autocorrelation. In other words, our interest is the genuine Pearson correlation coefficient between x and y which is the correlation between w and z, $\rho_{w,z}$. However, we observe only x and y, autocorrelated versions of w and z, respectively, and their correlation coefficient, $\rho_{x,y}$. We assume that the time-series are in stationary state. Also, we assume that time-series are de-meaned and de-trended without loss of generality, since the time-series can always be de-meaned and de-trended empirically. Moreover, this is almost always part of the preprocessing of functional connectivity analysis. We denote the sample correlation coefficient between w and z and between x and y with $r_{w,z}$ and $r_{x,y}$ respectively. Sample variances of w, z, x and y are denoted by s_w^2, s_z^2, s_x^2 and s_y^2, respectively. The variables $s_{w,z}$ and $s_{x,y}$ denote sample covariance between (w and z) and (x and y), respectively. We consider simple case of autoregressive process of model order one as an example to understand the impact of autocorrelation of correlation coefficient. Note that, we do not intend to simulate fMRI time-series here because of its complex structure of signal and noise. In order to study the effect of autocorrelation on correlation coefficient, we derive an approximate bias and variance of correlation coefficient estimator, $r_{x,y}$ with respect to autocorrelation coefficients and true empirical correlation coefficient, $r_{w,z}$.

Autoregressive process of order one: AR(1)

An AR(1) process can be written in its recursive form as:

$$x_t = \alpha x_{t-1} + w_t \tag{5}$$

$$y_t = \beta y_{t-1} + z_t \tag{6}$$

where the subscript t denotes the time index in the time-series and α and β are AR(1) coefficients of absolute value less than 1. This condition is necessary for x and y to be stationary. First, we calculate the variance of x and y. Since x and y are demeaned, the first moments of both series are zero. Also, without loss of generality—and for the sake of simplicity—we may assume that initial point in both series is zero. The expected value of the sample variance can be derived and expressed as follows:

$$E\left[s_x^2\right] = E\left[\sum_{i=1}^{N}\frac{x_i^2}{N-1}\right] = \frac{1}{N-1}\left[\frac{N}{1-\alpha^2} - \frac{1-\alpha^{2N}}{\left(1-\alpha^2\right)^2}\right]E\left[s_w^2\right] \tag{7}$$

$$E\left[s_y^2\right] = E\left[\sum_{i=1}^{N}\frac{y_i^2}{N-1}\right] = \frac{1}{N-1}\left[\frac{N}{1-\beta^2} - \frac{1-\beta^{2N}}{\left(1-\beta^2\right)^2}\right]E\left[s_z^2\right]. \tag{8}$$