Model-free analysis of brain fMRI data by recurrence quantification

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We propose a novel model-free univariate strategy for functional magnetic resonance imaging (fMRI) studies based upon recurrence quantification analysis (RQA). RQA is an auto-regressive method, which identifies recurrences in signals without any a priori assumptions. The performance of RQA is compared to that of univariate statistics based on a general linear model (GLM) and probabilistic independent component analysis (P-ICA) for a set of simulated and real fMRI data.

RQA provides an appealing alternative to conventional GLM techniques, due to its exclusive feature of being model-free and of detecting potentially both linear and nonlinear dynamic processes, without requiring signal stationarity. The overall performance of the method compares positively also with P-ICA, another well-known model-free algorithm, which requires prior information to discriminate between different spatio-temporal processes.

For simulated data, RQA is endowed with excellent accuracy for contrast-to-noise ratios greater than 0.2, and has a performance comparable to that of GLM for $t_{SNR} \geq 0.8$. For cerebral fMRI data acquired from a group of healthy subjects performing a finger-tapping task, (i) RQA reveals activations in the primary motor area contra-lateral to the employed hand and in the supplementary motor area, in agreement with the outcome of GLM analysis and (ii) identifies an additional brain region with transient signal changes. Moreover, RQA identifies signal recurrences induced by physiological processes other than BOLD (movement-related or of vascular origin). Finally, RQA is more robust than the GLM with respect to variations in the shape and timing of the underlying neuronal and hemodynamic responses which may vary between brain regions, subjects and tasks.

Keywords: Recurrence quantification analysis; Model-free; fMRI

Introduction

Blood oxygen level-dependent (BOLD) functional magnetic resonance imaging (fMRI) measures changes in the deoxyhemoglobin content which result from neuronal activity. Deoxyhemoglobin induces susceptibility effects that alter the external static magnetic field in both the intra-vascular and extra-vascular compartments. Consequently, changes in deoxy-hemoglobin concentration will affect the effective transverse relaxation time and hence the signal measured at specific volume elements.

A number of procedures may be used to disclose brain areas as active during a specific cognitive task. Model-based univariate strategies are the most commonly employed procedures for fMRI data, given their high sensitivity and computational speed. Linear univariate multiple regressions, through the so-called general linear model framework (GLM; Friston et al., 1995; Worsley and Friston, 1995), provide a good example for this category of methods. Activated brain areas can be revealed by comparing the temporal evolution of the MR signal in each voxel with an external reference model defined by the experimental design. This model represents the expected activation time-course, assuming a known hemodynamic response function (HRF) to a brief stimulus and a linear time invariant system. The overall results are transformed into a visual output, where active volume elements are displayed by the use of a colour scale corresponding to the statistical significance of the fit of the signal time-course in that volume element with the external reference model. Univariate regression analyses are by definition model-dependent; consequently, any conclusion based on the obtained statistics depends on the validity and accuracy of the chosen reference model. In particular, we expect a reduction in sensitivity for the GLM statistics when the underlying hemodynamic response is different from the assumed one (Handwerker et al., 2004).

Multivariate model-free strategies are valid alternatives to the GLM in the absence of any a priori assumptions (e.g. investigation of the brain at rest) and in instances when the model employed fails to predict brain activations, namely when the subject’s response highly deviates from that predicted due to a stochastic neuronal
behaviour, or to an endogenous modulation of neuronal activity, or to a peculiar shape of the hemodynamic response. The lower sensitivity with respect to univariate strategies mainly affects a widespread practice of such strategies: independent component analysis (ICA). ICA transforms the measured time-series into components that are statistically independent from each other (Comon, 1994). ICA can be applied to fMRI data in two different ways, namely spatial ICA (McKeown et al., 1998) and temporal ICA (Biswal and Ulmer, 1999), depending on whether the extracted signal sources are assumed to be independent in their spatial locations rather than in their time profile. Finally, probabilistic ICA (P-ICA) (Beckmann and Smith, 2004) was recently proposed to introduce, as the name suggests, a probabilistic model, performing non-square mixing in the presence of Gaussian noise with improved discrimination between real effects of interest and noise.

In the present paper, we report on a new univariate model-free approach, based upon recurrence quantification analysis (RQA).1 Recurrence analysis is a nonlinear signal processing technique developed from the original idea by Eckmann et al. (1987), that significant periodic structure might be uncovered in physical processes by mathematically embedding the recorded signals into a higher dimensional. By defining a distance threshold in such a space, a bidimensional graphical representation of signal recurrences can be depicted in the form of recurrence plots (RPs) which have proven successful for the quantitative analysis of linear and nonlinear dynamic systems (Eckmann et al., 1987), including respiratory systems, cardiac signals, photo-acoustic emissions and brain activity as determined by electroencephalograms (Webber and Zbilut, 1994; Zbilut and Webber, 1992; Giuliani et al., 1996; Trulla et al., 1996; Zak et al., 1997). In a very recent and comprehensive review (Marwan et al., 2007), the solid theoretical grounds of RPs and RQA have been reassessed, with special emphasis on their ability to deal with dynamical, nonlinear and nonstationary systems. Due to its great flexibility and relatively easy implementation, in the last years RQA has also been used to study the features of some non-dynamic systems, including protein and DNA sequences (Zbilut et al., 1998, 2002; Frontali and Pizzi, 1999). RQA identifies and quantifies recurrent patterns in investigated signals by means of a number of variables (descriptors), as defined in the Appendix, without relying on any assumption or model. To our knowledge, few other univariate data-driven method have been proposed for fMRI data, for example approaches which employ novelty indices (Baumgartner et al., 2000), or fractional Gaussian noise parameters (Maxim et al., 2005). However, Baumgartner and collaborators suggest the use of novelty indices as pre-processing tools to focus precisely on the interesting time-courses prior to any further exploratory or confirmatory approach. The authors validate their approach for simulated data with white noise and they do not show how their method performs when applied to an fMRI study involving tasks. Moreover several novelty indices are based on distributional features of the data, and only some of them make an explicit reference to the dynamical (order-dependent) features of the series. Correspondingly, Maxim and collaborators demonstrate that fractional Gaussian noise provides an accommodating model for fMRI data acquired in the “resting” state, but they do not apply their model for task-related BOLD responses.

The distribution of RQA variables in recurrence plots (see below) may be used to study the dynamics of real and simulated brain activity. We implemented simulations for increasing contrast-to-noise ratios and for different shapes of the hemodynamic response function. We also acquired data in vivo from a group of subjects performing a finger-tapping task. These data sets have been systematically analysed by RQA and the activation maps compared with those resulting from GLM and P-ICA methods. Under most conditions, the qualitative agreement between the three methods was verified, as well as the relatively higher robustness of RQA in the presence of high noise levels. The most interesting result, however, concerns the validation of RQA as an appropriate approach to investigate the BOLD-related activation patterns, regardless of the underlying neural and hemodynamic response, applicable also in the case of group studies. Future and promising RQA applications are foreseeable in the study of: (i) brain activation patterns in response to a cognitive task and (ii) spontaneous brain activity (resting brain, sleep, etc.), where the model- and stimulus-independent features of the method can be fully exploited.

Materials and methods

Data acquisition

Five healthy, right-handed individuals (four females, one male, 22–26 years) volunteered to participate in the study approved by the local ethics authorities, and gave their informed consent as described previously (Bianciardi et al., 2004). Each subject participated at two experimental sessions. A total of 270 BOLD-sensitive image volumes were acquired with a Siemens Vision Magnetom MR system (Siemens Medical Systems, Erlangen, Germany) operating at 1.5 T and equipped for echo-planar imaging. Each volume was subdivided into 11 planes, starting from the vertex and stretching caudally (radio-frequency pulse: 60°; TR: 1000 ms; TE: 60 ms; in-plane resolution: 3×3 mm, matrix 64×64, slice thickness=4 mm and gap between slices=0.4 mm). The 14 initial BOLD images were discarded to remove any possible T1 saturation effects. Visual stimuli were projected indicating onset of the events (finger-tapping) via mirroring to a front projection screen using an LCD video projector located inside the MR room and connected to a PC located outside the MR room. The subjects had to look at the front projection screen on which the visual stimuli were presented. In response to the occurrence of a green dot on the monitor (with a 16 MR scans, ON/OFF cycle), the volunteer was required to push a response button.

Simulations with Gaussian noise

We simulated a whole brain data set of an entire fMRI session, employing the brain mask obtained at point 4) after pre-processing of the fMRI data (see Data analysis, Pre-processing) to define the anatomical borders for the simulated data. For each simulated voxel, we generated time-series \( T(t) \) with 257 time-points \( \{N_{\text{scan}}\} \), with sampling time 1 s consisting of Gaussian noise \( n(t) \) with a defined standard deviation \( \sigma_G \) and mean offset value \( M=2000 \) \( \{n(t) \in \mathbb{N}(M, \sigma_G^2)\} \). In a portion covering 5×8×5 voxels centred at [4–2–52] mm (corresponding to the position of the supplementary motor area, MNI coordinates), we added a simulated BOLD signal \( S(t) \) with standard deviation \( C \) to the noisy time-series.

1 A patent is pending on this method.
The simulated BOLD signal $S(t)$ was calculated by $C \cdot H(t)$, where $H(t)$ is equal to an assumed hemodynamic response function with a standard deviation of $1$. $H(t)$ was generated after convolution of a train of neuronal events (delta functions centred on instants when the stimulus event occurred, $T_{\text{HRF}}$) with an impulse hemodynamic response function ($i_{\text{HRF}}$). In summary:

\[
\begin{align*}
T(t) &= n(t) + C \cdot H(t); \quad \text{for simulated active voxels;} \\
T(t) &= n(t); \quad \text{for simulated resting voxels.}
\end{align*}
\]

A number of simulations of whole brain data sets were performed as follows:

1. **Simulated time-series with different time-course contrast-to-noise ratios ($t_{\text{CNR}}$).**

We define $t_{\text{CNR}} = C / \sigma_G$. We performed these simulations in order to investigate the sensitivity of RQA versus GLM analysis and P-ICA under several experimental conditions. Primarily, we studied variations of the time-course signal-to-noise-ratio, e.g. due to different static magnetic field strengths, voxel size and other acquisition parameters, by changing the noise level $\sigma_G = [200 \ 100 \ 50 \ 25]$ with constant $C = 1\% \cdot M = 20$ ($t_{\text{CNR}} = [0.1 \ 0.2 \ 0.4 \ 0.8]$). We also generated signals with different BOLD-induced contrasts $C = [0.75 \ 1.5 \ 3 \% \ M = 15 \ 30]$ and constant $\sigma_G = [100 \ (t_{\text{CNR}} = [0.15 \ 0.3])$, in order to simulate different BOLD responses (e.g., age, gender differences). $S(t)$ was generated using an $i_{\text{HRF}}$ equal to the default hemodynamic response function employed in SPM2 [for a detailed description see Data analysis, General Linear Model (GLM)], and $T_{\text{HRF}}$ equal to a stick function of unitary maximum amplitude. In Fig. 2A, we show an example of a simulated single-voxel time-series for each case.

2. **Simulations of modulated neuronal and hemodynamic responses by means of different generated time-series signals $S(t)$**.

In this case, we studied the performance of different analytical approaches when the neuronal response is endogenously modulated, e.g., during neuronal habituation (see Fig. 2B: 16-s blocks of stimulus events were multiplied by a trapezoidal function $= 1 - 0.03:0.55$, and convolved with a SPM2-standard $i_{\text{HRF}}$) or when the $i_{\text{HRF}}$ kernel employed for simulating the BOLD response is altered (see Fig. 2C: different onsets: 1 s and 3 s; shape: response-to-undershoot delay $= 5$ s/10 s; response-to-undershoot dispersion $= 3$ s/1 s; undershoot-to-overshoot ratio $= 1:5$, onset $= 2$ s, kernel length 32 s, while the onset of the neuronal event, $T_{\text{HRF}}$ was kept fixed). In each case, the obtained $H(t)$ was normalised to a unitary standard deviation before adding noise components. For these simulated data, we scaled contrast and noise levels as follows: $\sigma_G = 100$, $C = 1\% \cdot M = 20$; $t_{\text{CNR}} = 0.2$.

**Simulations with auto-correlated noise**

Given that temporal auto-correlation is present in real fMRI data, we included temporal auto-correlation in the noise model and generated time-series for different time-course contrast-to-noise ratio.

The synthetic auto-correlated noise was generated according to an auto-regressive model of order 3, AR(3). The optimal model order may vary depending on tissue type, magnetic field strength, MR acquisition sampling rate and respiratory and heart rates (Purdon and Weisskoff, 1998). Penny et al. (2003) showed that a model order equal to 3 was sufficient to describe auto-correlation in all brain voxels, with auto-correlation of cerebrospinal fluid being of higher model order than that of grey or white matter (real data set, field strength $2 \ T$ and $TR = 2 \ s$). Given our higher (double) sampling rate, we hence prudentially chose this model as a good approximation to the true correlations.

We first estimated plausible AR parameters from real data and then generated synthetic correlated noise. In particular, from residual terms of 145 fMRI time-series in active voxels (as found with GLM analysis) on one investigated subject, we estimated the AR(3) model using the Yule–Walker method. We computed the average across voxels of the estimated parameters ($\phi_i > i = 1:3$, respectively, equal to $[0.23 \ 0.05 \ 0.13]$) as well as their standard deviation $\sigma_\phi$, equal to about 0.07 for each parameter. In each voxel of the simulated brain we hence simulated noise according to an AR(3) model with parameters ($i = 1:3$) generated according to a random distribution $N(\phi_i, \sigma_\phi)$.

The standard deviation of the white noise input to the AR model was varied as $\sigma_G$ in simulation with only Gaussian noise (see above). In particular, we repeated simulation varying the noise level $\sigma_G = [200 \ 100 \ 50 \ 25]$ with constant $C = 1\% \cdot M = 20$ ($t_{\text{CNR}} = [0.1 \ 0.2 \ 0.4 \ 0.8]$). The resulting noise level of the AR(3) auto-correlated noise $\sigma_{AR}$ was respectively $[213.0 \ 106.5 \ 53.2 \ 26.6]$.

**Data analysis**

Simulated and experimental data were first pre-processed and then analysed by means of the general linear model, probabilistic independent component analysis, and recurrence quantification analysis. Finally, in the case of simulations, we compared the three investigated procedures by means of receiver operating characteristic (ROC) curves.

**Pre-processing**

For each collected MR voxel time-series, we performed the following pre-processing steps:

1. correction for involuntary motion during MR scanning;
2. brain normalisation to MNI (Montreal Neurological Institute) coordinates;
3. application of a spatial smoothing filter for each brain 3D volume by convolution with an isotropic Gaussian kernel (FWHM = 8 mm for our data), in order to increase the MR signal-to-noise-ratio;
4. masking of non-brain voxels;
5. voxel-wise removal of low frequency temporal noise (e.g. static magnetic field drift and other aliased effects) by offset and linear trend removal;

\[^2\] $t_{\text{CNR}}$ values are given prior to spatial smoothing in order to have general reference values to compare with $t_{\text{CNR}}$ computed on real raw data, independently of the smoothing applied. Indeed, in the literature $t_{\text{CNR}}$ or $t_{\text{SNR}}$ values are given usually for unsmoothed data (Triantafyllou et al., 2005); nevertheless, $t_{\text{CNR}}$ after smoothing can be calculated directly from $t_{\text{CNR}}$ before smoothing (Triantafyllou et al., 2006), given the fraction increase $V$ in the voxel volume due to smoothing and the constant $\lambda$ describing the physiological contributions to image noise. In particular, for uncorrelated physiological noise, smoothing will increase $t_{\text{CNR}}$ with a factor equal to $\sqrt{V}$; for correlated physiological noise, this increase will be mitigated depending on the degree of correlation, $V$, $\lambda$ and image SNR.
(6) temporal pre-whitening, in order to correct for correlated observations. For the simulated data set with Gaussian noise we only performed steps (3) and (5). In P-ICA the temporal pre-whitening procedure is an automatic step before the analysis and hence step (6) was also performed. Nevertheless, this additional step should not favour P-ICA with respect to the other two employed analysis procedures, since in case of Gaussian noise temporal pre-whitening strategies do not affect the outcome of the analysis. For simulated data with auto-correlated noise we performed steps (3), (5) and (6) during all the considered analysis strategies. We carried out steps (1) to (3) through SPM2 (Statistical Parametric Mapping, Wellcome Department of Imaging Neuroscience, London, UK, http://www.fil.ion.ucl.ac.uk/spm/spm2.html), steps (4) and (5) on Matlab 6.5. Step (6) was performed concurrently with data analysis. Each analysis tool (SPM2 for GLM analysis, MELODIC for P-ICA and a Matlab custom routine for RQA) employs a different pre-whitening strategy; a common feature between the different whitening procedures is their implementation as an iterative cycle comprising preliminary data analysis, estimation of the residuals or of non-activated voxels, pre-whitening and again data analysis. The details of each pre-whitening strategy and their differences are explained below within the description of each different analysis strategy and of the employed tool.

**General Linear Model (GLM)**

Univariate regression analysis and the more sophisticated General Linear Model framework applied to the analysis of fMRI data are described in detail in Friston et al. (1995) and Worsley and Friston (1995). In summary, the fMRI data, \( y \) are fitted to a reference model \( H \) for each voxel. \( H \) is obtained after convolution of a train of stimulus events (delta functions centred on instants when the event occurred, \( T_{\text{on}}-T_{\text{off}} \)) with a kernel assumed to represent the hemodynamic impulse–response function \( h_{\text{HRF}} \). The shape of the \( h_{\text{HRF}} \) can be arbitrarily chosen but is usually set to a linear combination of a positive (response) and negative (undershoot) gamma function occurring around 5 and 15 s, respectively, after the neural event. The output of the GLM analysis consists of a \( \beta \)-value, which is proportional to the effect size (activation amplitude), and of a \( t \)-value, by which the statistical significance of the activation can be quantitatively assessed.

The GLM framework as implemented in SPM2 (Statistical Parametric Mapping, Wellcome Dept. of Imaging Neuroscience, London, UK, http://www.fil.ion.ucl.ac.uk/spm/spm2.html) was used to analyse experimental and simulated data. The task-related function \( H \) was obtained by convolving the stimulus events with the standard \( h_{\text{HRF}} \) [response (undershoot) delay: 6 s (16 s), dispersions for response and undershoot: 1 s; undershoot-to-overshoot ratio: 6; onset: 0 s and kernel length: 32 s]. The six roto- translational parameters defined based on the motion-correction procedure (first pre-processing step) were used as covariates of no interest.

SPM2 temporal whitening filter is generated from the noise covariance matrix, estimated by expectation maximization assuming a first-order autoregressive model plus white noise (Friston et al., 2002a,b). This approach is also based on an iterative procedure, with hyper-parameters defining the covariance matrix that depend on the variance of the parameter estimates and vice versa. The covariance matrix and the filtering are globally estimated on the whole-brain data set, considering a pooled matrix of residuals.

**Probabilistic independent component analysis (P-ICA)**

ICA (independent component analysis) decomposes the 4D fMRI data into spatial and temporal components. It can pick out different activation and artefactual components without any model being specified. Thus, the output is a new 4D data set (each volume being a separate spatial component) and a separate set of time-courses (temporal components). In addition, probabilistic ICA converts spatial maps to Z-statistics maps based on the estimated standard error of the residual noise. Our analysis was carried out by means of MELODIC (multivariate exploratory linear decomposition into independent components) Version 2.00, part of FSL (FMrib’s Software Library, www.fmrib.ox.ac.uk/fsl, release 3.3), for the estimation of a probabilistic independent component analysis model (Beckmann and Smith, 2004). Normalisation of the voxel-wise variance was applied to the input data according to the standard pre-processing routine in MELODIC. Pre-processed data were spatially whitened (de-correlated) and projected into a \( N_{\text{IC}} \)-dimensional subspace by the probabilistic principal component analysis algorithm, where the number of dimensions \( N_{\text{IC}} \) was estimated using the Laplace approximation to the Bayesian evidence of the model order. The spatially whitened observations were decomposed into a set of time-courses and spatial maps by optimising for non-Gaussian spatial source distributions using a fixed-point iteration technique. The estimated component maps were normalized by the standard deviation of the residual noise and thresholded by fitting a Gaussian mixture model to the histogram of intensity values (alternative hypothesis test at \( p\geq0.5 \)). Data were also temporally pre-whitened to account for serial correlations. In P-ICA, data are temporally pre-whitened with respect to the noise covariance, estimated from residuals at each voxel location. In P-ICA, a temporal whitening filter that closely matches the auto-correlation function of the noise is applied and yields the so-called best linear unbiased estimate (Bullmore et al., 1996; Locascio et al., 1997; Purdon and Weisskoff, 1998; Woolrich et al., 2001). Since a signal model in P-ICA is not pre-specified, iteratively residuals and the mixing matrix are estimated. In particular, the noise covariance matrix is estimated according to a two-step iterative process based on estimation of the mixing matrix, auto-correlation estimation of the residuals, and tapering with a Tukey window (Woolrich et al., 2001). At the end of this iterative cycle, the whitening filter can be computer by the use of the Cholesky decomposition of the estimated noise covariance matrix. Both the covariance matrix and the filtering are determined on a voxel-by-voxel basis, as opposed to SPM2 implementation. Since P-ICA exploratory approach allows modelling of various sources of variability, e.g., temporally consistent physiological noise, as part of the signal already in the formulated model, the noise model itself can actually be quite simplistic.

Discrimination between task-related and task-unrelated IC components, was achieved by cross-correlating each IC component with the reference model \( H \) employed for GLM analysis in SPM2. Task-related IC components were identified for statistical testing at a Bonferroni-corrected statistical threshold of \( p<0.001 \).

**Recurrent quantification analysis (RQA)**

The first and fundamental step of the method (see also the Appendix) lies in the projection of a time-series of \( N_{\text{scans}} \) points into an \( m \)-dimensional space \( (m>2, m=\text{embedding dimension}) \) by means of an embedding procedure. The procedure includes: (i)
inserting \( m \) copies of the time-series into the \( m \) columns of a \( N \times m \) matrix, called embedding matrix (EM), and (ii) shifting each column from the previous one by a fixed lag (each shift between adjacent columns being equal to the time delay \( \Lambda, N = N_{\text{columns}} - \Lambda \cdot (m - 1) \)). As a consequence, subsequent rows of the EM correspond to subsequent and overlapping windows of length \( m \) along the original series. The choice of the embedding dimension copes with the need of having a window large enough to keep track of significant interactions, without excluding too many points from the analysis: \( \Lambda \cdot (m - 1) \) of the initial (or final) points of the series, in fact, cannot be considered in the EM matrix as a consequence of the embedding shift.

In the following step, an intermediate, square \( N \times N \) matrix is constructed, where each \( i \), \( j \) element is a similarity index between the \( i \)th and \( j \)th rows of the EM. In this work, we used as an index the Euclidean distance in the \( m \)-dimensional space between the couple of points corresponding to the \( i \)th and \( j \)th rows of the embedding matrix. The square matrix is easily transformed into a recurrence plot (RP) of identical size by defining as a recurrence any index the Euclidean distance in the matrix not exceeding a given threshold \( \varepsilon \) (sometimes also called “radius”); the corresponding dots in the RP are darkened and the others left blank (examples of 2D RP plots for two fMRI time-series are shown in Fig. 1, see below).

While a formal definition of the whole procedure is provided in the Appendix, here it is worth stressing that: (i) RPs make it possible to visualize in 2D higher dimensional correlations in the time-series, (ii) at difference with standard spectral FFT methods, RPs can be safely used to study rather short and even nonstationary series; and (iii) it is straightforward to characterize each RP through some quantitative descriptors of its graphical features (Zbilut and Webber, 1992; Webber et al., 1994; Giuliani et al., 1996; Marwan et al., 2002).

In particular, single recurrent points are counted by the RR (recurrence rate) descriptor, namely the fraction of darkened points in the whole RP. Four descriptors deal with diagonal stretches of points: DET (determinism, percentage of recurrent points forming lines parallel to the main diagonal), ENTR (a Shannon entropy calculated over the distribution of deterministic line lengths), LMAX (maxline, length of the longest deterministic line), and \( L < \) (mean diagonal line, average length of diagonal lines).

Also vertical stretches of points are considered by LAM (laminarity, percentage of recurrent points forming vertical lines) and TT (trap time, average length of vertical lines). Finally, TREND describes the non-uniform distribution of recurrences in the RP, in terms of decreasing density of points towards the edges (see the Appendix).

In the present paper, we analysed simulated and experimental data by means of Recurrence Plot Toolbox 5.8 (R22.4, http://www.agnl.d.uni-potsdam.de/~marwan/toolbox/) developed by Norbert Marwan (Marwan and Kurths, 2002) and running in a Matlab environment. For each voxel, we computed a RP plot (embedding=4; radius \( \varepsilon=1.2 \) times signal standard deviation) and calculated the values of determinism (DET), since it is a quite sensitive and robust descriptor among the RQA parameters. The embedding was set to 4, which corresponds to a good compromise between sensitivity and specificity, favoured by higher and lower embedding, respectively. Finally, the radius was set equal to 1.2 and corresponded to the highest accuracy as determined by the ROC curves (see below) for the detection of activation in simulated data, with respect to radius values ranging between 0.5 and 1.7 (results not shown).

Prior to RQA, we applied pre-whitening to correct for noise correlation. In RQA, we cannot estimate a covariance matrix from residuals, since without any explicit model for the underlying signal we cannot disentangle residuals from signals in the observed data. For this reason, in order to pre-whiten data before RQA, we could adopt at least three strategies: (1) assuming an a priori noise model (like 1/f or autoregressive noise models) and estimating a covariance noise matrix in non-activated voxels, as defined based on a preliminary RQA analysis, then reconstruct a whitening filter and again apply RQA on whitened observations (an iterative cycle as in P-ICA and SPM2); (2) perform additional measurements during the task session, like monitoring of head motion, of respiratory and cardiac rates to prospectively (Lee et al., 1996) or retrospectively (Glover et al., 2000; Lund et al., 2006; Birn et al., 2006) correct for signal fluctuations induced by these processes; and (3) acquire a resting state data-set on the same subjects, and exploiting spatial noise coherence of noise sources, thus implementing a local whitening filter (De Zwart et al., 2007). Strategy nos. (2) and (3) would probably be the best option for pre-whitening prior to RQA, since they perform very well and they do not need any signal model. However, in the lack of additional measurements performed on the same subjects, we pre-whitened our data according to strategy no. (1), which is sensitive to the actual noise level in inactive regions, given an assumed noise structure. In particular, we adopted the same pre-whitening strategy of SPM2 (based on expectation maximization assuming a first-order autoregressive model plus white noise), computing the pre-whitening filter on a pool of 300 inactive voxels (semi-automatic procedure).

In Fig. 1, we show recurrence plots for two fMRI time-series from a volunteer performing the motor task, selected according to a GLM analysis. The first voxel, located in the left pre-central gyrus, BA6 showed significant (\( p<0.05 \), corrected for family-wise errors; \( Z\text{-value}=8.96 \)) activation while the second voxel in the left inferior parietal lobule, BA2, was judged not significant (\( Z\text{-value}=-0.37 \)). The calculated RQA parameters are reported in Table 1. A higher fraction of recurrent points forming diagonal and vertical segments is present in the RP of time-series A) than in the RP of time-series B). This is also reflected by the higher value of RQA parameters, namely recurrence, determinism and laminarity for time-series A) as compared to B).

**ROC curves**

For simulated data, we also computed ROC curves, i.e. true positives (TPs) versus false positives (FPs) for different threshold-values (\( Z \)-values for GLM and P-ICA, determinism values for RQA). We employed ROC curves to measure the accuracy of each performed test and to define an optimised threshold value for RQA.

In order to count TPs and FPs, we subdivided each simulated data set into three regions: the first one (A) consisted of 200 voxels in which we simulated activity signals; the second one (B) was the ensemble of 282 voxels, which are first neighbours to the boundaries of region A, and which may be partially activated due to spatial smoothing; the third region (C) consisted of the remaining (excluding regions A and B) 9752 brain voxels (without any BOLD simulated activation). On the basis of this segmentation and for a given threshold, we defined TPs and FPs as the number of activated voxels pertaining respectively to regions A and C, divided by the size of the considered region (200 and 9752). For P-ICA, if activation was split into more than one task-related IC component.
Fig. 1. Single-voxel magnetic resonance signals from a human brain and their recurrence plots. Time-series (A and B) pertain to an active and inactive brain region, respectively, as established by GLM analysis (p < 0.05, corrected for family-wise error). Below each signal the corresponding un-thresholded recurrence plot (embedding dimension $m=4$, delay $\Lambda=1$) is reported.
quantification analysis under different conditions, we simulated Simulated data with Gaussian noise Results

population mean activation. For RQA, we implemented a level GLM parameter estimates, to establish the significance of the

If 0.7

In Fig. 3 (left), we compare results for different procedures (z-statistic for GLM and P-ICA, determinism values for RQA) applied to analyse simulated data with increasing $\text{t}_{\text{CNR}}$ values, either induced by variations of the time-course signal-to-noise ratio or by different BOLD contrasts. GLM z-statistics (Fig. 3A) and the values of determinism obtained via RQA (Fig. 3C) increase with time-course contrast-to-noise ratio ($t_{\text{CNR}}$). For GLM, we obtained mean $z$-values ($\pm$S.D.) = [6.0 7.2 8.0 8.7 9.0 10] ± [1.4 1.0 0.6 0.4 0.4 0.3] and for RQA mean determinism values ($\pm$S.D.) = [0.841 0.854 0.872 0.909 0.932 0.973] ± [0.015 0.016 0.021 0.027 0.026 0.007], respectively for $t_{\text{CNR}}$ = [0.1 0.15 0.2 0.3 0.4 0.8]). We remark that in this case simulated BOLD signals have exactly the same shape and timing as the reference model employed in the GLM design matrix (i.e., a choice which favours GLM analysis). In this context, by definition GLM $t$-values increase proportionally with the simulated BOLD signal amplitude and with the inverse of the noise standard deviation. On the contrary, since RQA is model-free, changes in determinism purely reflect the interplay between the noise and the underlying signal in the time-series, for a given signal shape and ordering. Finally, P-ICA $z$-values (Fig. 3B) do not increase monotonically with $t_{\text{CNR}}$. This result is unexpected since P-ICA $z$-scores, in contrast to raw IC estimates, depend on the amount of variability explained by the entire decomposition at each voxel location (Beckmann and Smith, 2004). Nevertheless, our finding can be explained considering that one simulated signal source was split into several “component maps” (i.e., a high number of $z$-scores equal to 0, as visible in Fig. 3B for $t_{\text{CNR}}$ = 0.1 and $t_{\text{CNR}}$ = 0.4).

In Fig. 3 (right), given a constant $t_{\text{CNR}}$ ($=0.2$), we show the results of different analyses for data with endogenously modulated neuronal responses and $t_{\text{HRF}}$ values other than the one used for the reference function. As expected from it being a model based analysis, GLM sensitivity decreases when the model is incorrectly specified. In this case, the sensitivity of GLM statistics (Fig. 3A) is significantly lower with respect to GLM $z$-values obtained for the standard neuronal and hemodynamic response functions – however only for $t_{\text{HRF}}$ with onset delays greater than 1 s and whenever changes in the global shape of the $t_{\text{HRF}}$ occur, in agreement with previous findings (Handwerker et al., 2004). Statistical results obtained by means of P-ICA (Fig. 3B) and RQA (Fig. 3C) are independent of both neuronal and hemodynamic changes and are hence more robust in this respect than GLM analysis. Nevertheless, comparing ROC curves (results not shown) obtained for simulated signals with $t_{\text{CNR}}$ = 0.2 and with different neuronal and hemodynamic response functions, GLM analysis
is still more accurate than RQA and (to a much lesser extent) than P-ICA, even if the GLM model is incorrectly specified. This result depends on the much higher sensitivity of GLM analysis (employing the correct model) with respect to RQA for $t_{\text{CNR}} = 0.2$ (see Fig. 4C). Nevertheless, given the same accuracy for both GLM analysis (employing the correct model) and RQA, e.g. for a higher value of $t_{\text{CNR}}$, we expect that this situation would reverse in favor of RQA.

![Fig. 2. Simulated signals used in this work. (A) Examples of single-voxel time-series (at position $[4 \sim 4.52]$ mm) with increasing $t_{\text{CNR}}$ (BOLD contrast $C=[20 \ 15 \ 20 \ 30 \ 20]$ and noise level $\sigma_G=[200 \ 100 \ 100 \ 50 \ 25]$, respectively). (B) Commonly assumed neuronal response and endogenously modulated (e.g. habituation within blocks of stimulation) neuronal response. (C) Different iHRFs employed for simulations. We added simulated signals ($C=20$) with functions shown in panels B and C to noisy time-series with $\sigma_G=100$.](image1)

![Fig. 3. GLM, P-ICA and RQA analysis of simulated signals. The box plots refer to the 200 voxels in which BOLD activation was simulated by signals depicted in Fig. 2. Panels A and B contain $z$-values for GLM and all significantly activated P-ICA components, respectively; panel C contains the determinism values obtained from the RQA of simulated data with different $t_{\text{CNR}}$ (left) and for several neuronal and hemodynamic responses (right). For details see the text and Fig. 2.](image2)
Fig. 4 contains the ROC curves for GLM, P-ICA and RQA for thresholds ranging between $-4$ and $+13$ for GLM $z$-values, $-4$ and $25$ for P-ICA $z$-values, and between $0.5$ and $0.99$ for RQA determinism values. GLM is the most accurate method, since it is model-based and simulated signals were generated according to the same reference model as the one employed in the analysis. P-ICA always behaves excellently, if significant active components are appropriately chosen by the use of a priori assumptions regarding the underlying hemodynamic response function; however, its accuracy does not increase monotonically with $t_{\text{CNR}}$, deviating (decreasing) for $t_{\text{CNR}}=0.4$, probably due to the splitting of signal sources into several “component maps”. RQA fails for $t_{\text{CNR}}=0.1$, and has a fair accuracy for $t_{\text{CNR}}=0.15$, while is an excellent test for $t_{\text{CNR}} \geq 0.2$ (including all types of simulated signals with different neuronal and hemodynamic responses, not shown), with a performance comparable to that of P-ICA for $t_{\text{CNR}} > 0.4$. Moreover, for $t_{\text{CNR}} = 0.8$, RQA performs comparably to the GLM approach.

As for RQA, the determinism threshold for which we obtained FPs $\leq 2\%$ (for all $t_{\text{CNR}}$ values) and TPs $\geq 95\%$ ($t_{\text{CNR}} \geq 0.3$) was equal to $0.867$. This corresponds to the $97.5$th percentile of the distribution of determinism calculated after shuffling of the very same data-set. Hence, we employed the $97.5$th percentile ($p < 0.025$) also to threshold experimental data (see below).

Simulated data with auto-correlated noise

In Fig. 5, we show the ROC curves for GLM, P-ICA and RQA applied to simulated data ($t_{\text{CNR}} = [0.1 0.2 0.4 0.8]$) with auto-correlated noise, after pre-whitening, with respect to data with Gaussian noise (the latter are also shown in Fig. 4). All the employed analyses (except for $t_{\text{CNR}} = 0.1$ and $0.8$ with P-ICA) are less accurate in the former than in the latter case, indicating that residual noise auto-correlation is still present after pre-whitening. This result can be explained considering that SPM2 and RQA pre-whitening filters model only first-order auto-correlation and that the noise order generated in simulated data was equal to 3. The degree of accuracy loss depends on the $t_{\text{CNR}}$ (the effect being very small for high $t_{\text{CNR}}$) and on the analysis procedure: in particular for $t_{\text{CNR}} = [0.1 0.2 0.4 0.8]$ the % variation in accuracy between simulated data with correlated versus Gaussian noise for GLM, P-ICA and RQA was equal respectively to $[−1.0610 −0.0260 −0.0410 −0.0718]$, $[+6.7753 −2.0981 −0.1925 +0.0005]$ and $[−2.3018 −10.3304 −1.4010 −0.0001]$. In conclusion, even though noise auto-correlation is generally an issue in fMRI not completely solved, for $t_{\text{CNR}}$ greater and equal than $0.8$ for all the analysis procedures noise auto-correlation does not impact the outcome of the analysis.

Experimental data

We analysed fMRI data acquired during the performance of a motor task (finger-tapping) by means of GLM analysis, P-ICA and RQA. For a transverse brain slice located at $z=56$ mm (MNI coordinates), we show results of these analyses for subject N. 1, session 2, and for the whole group of subjects.

Single-subject results

By means of GLM analysis, the left post-central gyrus extending to the left pre-central gyrus (237 voxels) and supplementary motor area (24 voxels) were identified as active based on the assumed model $H$. In particular, in Fig. 6 we show the estimated effect size ($A$) and the statistically significant task-related activation ($B$, red–yellow) of the above described areas ($p < 0.05$ corrected for family-wise errors), obtained by means of GLM analysis. In Fig. 6B (blue–cyan/green–white), we also show voxels with residual movement-related deactivation/activation.
With regard to P-ICA, the optimal number of components was equal to 145. IC maps relative to all ICs covered a large part of the brain, from parietal to frontal areas. Only three IC components (Ns. 7, 58, 82) out of 145 were task-related ($p_{<}0.001$, Bonferroni-corrected).

IC map n. 7 covered the left post-central gyrus (Fig. 6C), left pre-central gyrus (Fig. 6C), supplementary motor area (Fig. 6C), and right pre-central gyrus (Fig. 6C).

Left middle–frontal gyrus (Fig. 6D), pre-central gyrus (Fig. 6D) and few voxels in left post-central gyrus (Fig. 6D) and in the right inferior parietal gyrus were active in IC map n. 58.

Finally, IC map n. 82 showed activation in the left precentral gyrus, in left supplementary motor area extending to middle cingulum and in few voxels of right middle frontal and right pre-central gyri (no voxels survived for slice $z=56$ mm).

As for RQA, maps of determinism values are shown in Fig. 6E for plane $z=56$ mm.

In determinism maps, left pre-central gyrus (Fig. 6F), left post-central gyrus and left supplementary motor area (SMA was significantly active in slice $z=52$ mm, not shown) were significantly active, in agreement with GLM results. Except for small changes in the position of some activated regions (e.g. supplementary motor area right versus left), the same areas were found in other RQA parameter maps (recurrence, laminarity). Moreover, with respect to GLM analysis, by means of RQA we found additional activation in left and right superior and middle–frontal gyri (BA4, at $p_{<}0.003$, permutation test), which both showed task-related deactivation in the GLM analysis (Fig. 7B, green). In addition, a few voxels in the left and right superior parietal lobules and the superior frontal gyrus (BA8) showed significant recurrent patterns, with signal recurrence probably linked to movement-related deactivations (results not shown, visible in the average group map of movement-related effects but not significant at $p_{<}0.01$ uncorrected for multiple comparisons).

Finally, a cluster in the right superior frontal gyrus (BA6) was identified as significantly active in the RQA, but not in the GLM analysis. Signals extracted from this region (results not shown) showed a positive transient response in the time-window 3–8 s after the stimulus block onset followed by a negative response (8–20 s) and a final return to baseline. Interestingly, this region was previously (Bianciardi et al., 2004) detected by the use of GLM for the same group of subjects performing a motor tapping task according to different event-related designs (as opposed to the anterior cingulum (BA24, a region with a vessel visible in fMR images), and in the right inferior frontal gyrus (BA44 and 48).

**Group analysis results**

We analysed 10 activation patterns from 5 different subjects (see Data acquisition) at the population level based on the GLM and RQA. In Figs. 7A, C we show, respectively, the group average map of GLM $\beta$-values and RQA determinism values. In the left pre-central, left post-central and supplementary motor areas, both GLM (Fig. 7B) and RQA (Fig. 7D) detected significant activations at the population level (for RQA, SMA was significantly active in slice $z=50–54$ mm, not shown in Fig. 7B). Moreover, the RQA activation pattern also comprised the precuneus (Fig. 7D) and the right pre-central gyrus (BA4, at $p_{<}0.003$, permutation test), which both showed task-related deactivations in the GLM analysis (Fig. 7B, green). In addition, a few voxels in the left and right superior parietal lobules and the superior frontal gyrus (BA8) showed significant recurrent patterns, with signal recurrence probably linked to movement-related deactivations (results not shown, visible in the average group map of movement-related effects but not significant at $p_{<}0.01$ uncorrected for multiple comparisons).

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**Fig. 5. ROC curves of simulated signals with auto-correlated noise for the three methods used in this work.** Panels A–C refer to GLM analysis, P-ICA, and RQA, respectively, of simulated data with different $ICNR$ ($ICNR=[0.1 0.2 0.4 0.8]$). We show the performance of the three analysis procedures for data with auto-correlated (magenta) versus Gaussian (black) noise. For simulations with auto-correlated noise, signals were added to noise generated according to an autoregressive model of order 3 and pre-whitening procedures were applied prior to further analysis. X and Y axes refer to false positives (FPs) and true positives (TPs). In each panel, the inset is a zoomed view of the ROC curve. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
significant task-related (red related deactivation/activation (blue T1 image (plane
through GLM, and of the determinism calculated through RQA, respectively.
features of signals and does not rely on any a priori assumption
RQA and other already assessed approaches, both model-dependent
RQA is an auto-regressive approach which describes several
Desirable features of RQA
RQA, GLM and P-ICA: a global comparison
the spatio-temporal coherence of measurements to detect brain active areas. This is not the case for RQA, since it is an auto-regressive approach. Indeed, for each single voxel, RQA seeks signal auto-correlation and regularity over time in the embedding space, without any spatial or temporal constraints.
We evaluated the performance of RQA for the detection of functionally active brain areas during the execution of an established task, for both simulated and experimental data. We investigated this issue by ROC curves obtained by systematic comparison of the three methods over simulated signals under different regimes (Figs. 4 and 5). It is worth recalling that ROC curves are able to evaluate an analytical method performance: (a) in its dependence upon various working parameters or experimental conditions (for example, $\text{IC}_{\text{CNR}}$ ratios), or (b) as compared to other concurrent methods. The only prerequisite is the availability of a truly reliable reference method (gold standard). As for the simulation results considered in Figs. 4 and 5, the gold standard is obviously not necessary; in the case of experimental results,

### Discussion

The aim of the present study was to check the hypothesis that RQA is a valid approach for fMRI data analysis. This task was achieved by the examination of similarities and differences between RQA and other already assessed approaches, both model-dependent (GLM) and data-driven (P-ICA).

### Desirable features of RQA

RQA is an auto-regressive approach which describes several features of signals and does not rely on any a priori assumption regarding the underlying signal. Among other auto-regressive procedures such as ARIMA (Pankratz, 1983), RQA has many desirable features concerning the possible interpretation of the numerical descriptors provided by the analysis in a wider (mechanistic) perspective than that associated with mere classification purposes. First, the typical RQA descriptors such as recurrence, determinism, entropy, laminarity, etc., provide a rich and flexible set of tools helpful to both classification and mechanistic assessments. For instance, for the fMRI data, we demonstrated that RQA parameters quantitatively measure both BOLD-related effects and physiological processes of other origins (head movement, flow effects, etc.). Second, RQA is simple and compact, since it identifies descriptors with intuitive and, in certain circumstances, physically sound meaning. Moreover, RQA gives a global and unique description even for massive amounts of data, such as those produced by fMRI. Third, for fMRI, the selection of RQA working parameters (embedding, radius) is unique for all brain voxels, and RQA results from different voxels can be compared quantitatively. Finally, the most desirable RQA feature is that it does not require the stationarity of the studied signals: this freedom from the stationary character of the signal stems from the fact the recurrences correspond to the repetition of very short (the length being equal to the embedding dimension) portions of the studied signal at different instants of time. RQA packages are readily available as free-ware (http://homepages.luc.edu/~cwebber; http://www.agnld.uni-potsdam.de/~marwan/toolbox/).

![Image](image-url)
RQA (permutation test at 500 series of regressors such as a canonical responses, an option in GLM analysis is to model the signal with a shapes and temporal changes of the hemodynamic and neuronal excellent accuracy for contrast-to-noise ratios at least in the mid- GLM is the method with greater sensitivity and specificity with i.e., the first two elements in a Taylor approximation. Nevertheless, decreases (Fig. 3, right panels), while RQA and P-ICA are more hemodynamic response shape and timing, GLM sensitivity failure or departures from GLM assumptions of the neuronal and  

The choice of a neurocognitive application does not favour RQA with respect to the commonly employed model-based procedures (like GLM). Indeed, the latter approaches employ reference functions which have been refined during many years of experimental fMRI and which may capture the greatest part of experimental data, we briefly discuss the influence of noise auto-correlation on the analyses outcome, also with respect to our simulation employing auto-correlated noise (see Fig. 5). Auto-correlated noise affects the outcome of RQA. Indeed, auto-correlation is a measure of how well a signal matches a time-shifted version of itself, as a function of the amount of time shift. Auto-correlation is hence a global feature of a time-series. RQA is based on a measure of the distance between signal segments and hence it is a local measurement of groups of signal samples, both close and far away one to each other (i.e. it is a measure of the auto-correlation of the signal at all the possible time scales). For this reason, if a signal is auto-correlated, even though RQA does not measure directly auto-correlation, auto-correlation is a signal feature to which RQA is sensitive. For instance, if a signals has a 1-lag auto-correlation (which is found typically in fMRI in vivo null data due to subject motion, fluctuation in physiology, etc., Penny et al., 2003), with respect to white noise we expect to have more recurrent point on diagonal lines adjacent to the main diagonal, with the remaining part of an RQ plot (reflecting distances between segments greater than 1 time-point) unaffected by it. Nevertheless, for correlated noise, pre-whitening strategies are usually employed and, we expect that if the filtering procedure is good enough, nor results of GLM analysis nor of RQA (nor of P-ICA) should change for simulated data with “coloured” noise with respect to using Gaussian noise without pre-whitening. In the presence of correlated noise, with respect to white noise as shown previously, the comparison of the three analysis procedures shifts towards the comparison of the whitening procedure adopted by each software. In our simulations we showed that, for all the analysis procedures, signals are affected by residual noise auto-correlation even after pre-whitening (see Fig. 5); however, the effect decreases drastically for high for tCNR with no significant effects on accuracy for tCNR ≥ 0.8. With regard to the choice of a pre-whitening strategy before analyzing real data with RQA, probably the best option is to adopt a nuisance variable regression (Lund et al., 2006), comprising different sources of noise auto-correlation (movement, respiratory and cardiac effects, spontaneous BOLD fluctuations), given that additional measurements of these processes are becoming a common practice in fMRI. From the above discussed simulations results, we expect to observe different activation patterns when analysing single-subject and group experimental fMRI data via GLM analysis or RQA. The number and location of active voxels may indeed change depending on tCNR for this data set (GLM being favoured for
low $t_{\text{CNR}}$ values) and on the agreement between the assumed and the actual neuronal and hemodynamic responses (RQA being more robust in this respect). Moreover, RQA projects different underlying processes onto a unique spatial description: for this reason, additional activation patterns visible in RQA maps with respect to GLM activation may disclose both BOLD responses which do not conform to a priori hypothesis and non-BOLD physiological processes. These hypotheses were experimentally verified. We applied RQA and GLM to analyse experimental fMRI data, generated from different volume elements of the brain and acquired from a group of subjects performing a motor task. The aim of this work was to produce via RQA a spatial picture of the time-dependent changes in the system, and to pick up the active areas without too strict a priori assumptions. At the subject (Fig. 6) and at the group level (Fig. 7), regions common to both RQA and GLM analysis comprised left motor and pre-motor areas, in agreement with the task performed. With RQA variables, we detected additional activations in many voxels pertaining to frontal, parietal, occipital areas and also in the ipsi-lateral motor cortex with respect to the hand employed for tapping. As explained above, these areas were either true BOLD activation with signal features deviating from GLM assumptions, or areas where processes not directly linked with the stimulus-driven BOLD effect occurred. To discriminate between those circumstances we tested separately different hypothesis. For instance, we explicitly modelled the estimated rotational and translation movement parameters in our GLM: for subject N. 1, we verified that residual movement-related signal changes were present in the same fronto-parietal areas detected through RQA and hence that processes of non BOLD origin may produce the detected significant recurrences in RQA. With regard to group activation, significant recurrent patterns in precuneus and right pre-central gyrus identified by RQA could be explained by inspection of BOLD task-related deactivations. Interestingly, RQA also detected transient signals concurrent with blocks of tapping in right superior frontal gyrus (BA6) at the group level, confirming its robustness with respect to BOLD responses which do not conform to a priori hypothesis (as also demonstrated in simulations). Valuably, due to its features, RQA may also be a valuable approach to disclose inter-individual differences in executing tasks needing high level cognitive processing, an issue which may be worth investigating in the future.

**RQA vs. P-ICA in neurocognitive studies**

In the present study, we also compared the performance of RQA with respect to another approach, P-ICA, which can avoid the need for a priori assumptions. RQA projects different underlying processes on a single spatial description, while P-ICA identifies several components which should reflect each a distinct physiological process. Thus RQA of experimental fMRI data may result in capturing areas with atypical BOLD signals, as well as activations generated by different processes like endogenous responses (but also movement artefacts, as discussed above). On the contrary, by means of P-ICA, a huge number of independent components is generated (>100 for our simulated and experimental data) and unless components are discriminated a posteriori with respect to the task or to any other measured physiological process (like cardiac and respiratory processes, vessel flow, etc.) it is difficult to localise any underlying cerebral process. Once again, P-ICA needs prior information, while RQA is completely model-free. In this context, it is hence surprising that for high time-course contrast-to-noise ratio RQA performance in terms of accuracy is comparable to that of P-ICA.

**Relevance of $t_{\text{CNR}}$ for RQA**

Since high $t_{\text{CNR}}$ seems to be a crucial factor for RQA accuracy, we remark that temporal contrast to noise ratio equal to 0.8 is representative of performance on real fMRI data. In our simulation, it was obtained considering a percentage signal change $dS/S$ of 1% and a noise standard deviation $\sigma_n$ equal to 25. The latter, for a signal offset value $M=2000$ employed to simulate our data, corresponds to a temporal signal-to-noise ratio ($t_{\text{CNR}}=M/\sigma_n$) of 80. Percentage signal changes of 1% are common in fMRI and $dS/S$ up to a few percent can be measured (Gati et al., 1997) depending on brain region/tissue vascular content, task parameters, voxel size, echo-time, field strength etc. Moreover, with commercial volume head coils and 3 T scanners, $t_{\text{CNR}}$ of 80 (before smoothing) can be reached (Triantafylou et al., 2005) and with higher field strengths (Triantafylou et al., 2005) and/or with the use of phased array coils (Bodurka et al., 2007) $t_{\text{CNR}}$ is even higher. As an example in the GLM framework, $t$-values (assuming the highest number of degrees of freedom, i.e. Gaussian noise, no temporal filters applied and only one regressor in the design matrix $X$) can be predicted multiplying $t_{\text{CNR}}$ with the square root of the number of time-points and also with design efficiency (DE). Here we define $DE=1/(\sqrt{X^2})/N$; for block designs with duty cycle=0.5, DE is one of the highest achievable and is equal to 1/4. Hence for $t_{\text{CNR}}=0.8$, $N=257$ and a block design with balanced ON and OFF periods we expect a $t$-value equal to about 9.1, which indeed is representative of a real fMRI measurement. Moreover, in GLM analysis, given an established $t_{\text{CNR}}$ level, the number of measurements can be adjusted to achieve statistical significance for an effect (Murphy et al., 2007).

**RQA applied to investigate neurocognitive processes vs. spontaneous activity**

Considering neurocognitive applications and the different approaches to data analysis of RQA, P-ICA and GLM, distinct pictures of the underlying cerebral physiological changes can be obtained depending on the employed approach. We expect that the theoretical differences elucidated above will be even more crucial for studies which do not employ any stimulation, i.e., the investigation of spontaneous activity (e.g. resting brain rhythms, sleep, epilepsy, drug effects, etc.). For those applications, model-based approaches, like GLM analysis, can generally not be used, since no model is available. Moreover, model-free approaches, like P-ICA, which were only recently introduced in fMRI to investigate unpredictable cerebral activity (De Luca et al., 2006), are spatially multivariate, looking for spatially coherent signal changes. In this respect, RQA has a more general validity, searching for spontaneous signal ordering over time at each voxel location, even in absence of a spatially coherent activation. For this reason, we expect that many interesting issues concerning spontaneous brain activity, which require unsupervised analysis methods, may most benefit from the use of RQA.

**Conclusions**

In the present work, RQA was applied to analyse the spatial distribution of RQA variables generated from time varying signals that have spatial contiguity, i.e., fMRI signals collected from a
plurality of area or volume elements, of the human brain. We demonstrated that recurrence quantification analysis (RQA) is successful for the quantitative analysis of cerebral fMRI data. With respect to conventional GLM techniques, in fact, RQA has the exclusive feature of being model-free and of detecting potentially both linear and non-linear dynamic processes, without requiring stationarity of the signal under investigation.

Instead of exploring the performance of RQA to identify active brain areas in absence of any stimulation (a field which we aim to investigate in the near future), we started validating RQA parameters closely related to the level of recurrent signal variations in the voxel. This overcomes the main weak point of the traditional analysis, related to the level of recurrent signal variations in the voxel. In the present work, we employed periodic block design; nevertheless, considering its distinctive features, the use of RQA for event-related protocols may be even more interesting.

Our main conclusions can be summarized as follows:

- MR signals produced by contiguous volume elements (voxels) in the human brain are described by RQA parameters closely related to the level of recurrent signal variations in the voxel. This overcomes the main weak point of the traditional analysis, namely the arbitrary selection of an external reference in order to discriminate between active and non-active areas.
- RQA activation patterns are characterized by a higher level of complexity with respect to GLM statistical parametric maps.
- Even direct comparison with another well-known model-free analytical tool, (P)ICA, resorts positive to the RQA approach particularly for high time-course contrast-to-noise ratios, and in general for its independence from the operator’s choices.

Appendix A. Recurrence quantification procedure

Assuming that a time-series represents the trajectory of a dynamical system in a higher dimension phase space, such phase space can be reconstructed from the time-series by an embedding procedure and a time delay:

\[ \bar{x}(i) = (x(i), x(i+\Lambda), \ldots, x(i+(m-1)\Lambda)) \]  

(A.1)

where \( x(i) \) is the time-series \( i=1, \ldots, N_{\text{scans}} \) for fMRI data and \( \bar{x}(i) \) is the result of its deconvolution into an \( m \)-dimensional embedding space, being \( \Lambda \) the time delay. The number of points (states) \( i \) considered in the phase space trajectory are \( N = N_{\text{scans}} - (m-1) \) (hence for \( \bar{x}(i) \), \( i \) only varies between 1 and \( N \)).

The recurrence of state \( \bar{x}(i) \) can be visualized by projection into a 2D subspace, a recurrence plot, RP (Eckmann et al., 1987). In such a space, two points along the trajectory \( (\bar{x}(i), \bar{x}(j)) \) are said to recur if the distance between them \( (R_{ij}) \) is lower than a given threshold, \( \varepsilon \) (also called radius). This can be mathematically expressed as:

\[ R_{ij} = \Theta (\varepsilon - \| \bar{x}(i) - \bar{x}(j) \|) \]  

(A.2)

where the bimodal Heaviside function, \( \Theta \), only allows the presence of black/white dots in the plot.

A number of small scale structures can be easily identified and quantified in the RPs, according to the following definitions:

- determinism \( (\text{DET}) = \frac{\sum_{i,j=1}^{N} P(i)}{\sum_{j=1}^{N} R_{ij}} \) = percentage of recurrent points which form diagonal lines of minimal length \( = l_{\text{min}} \) being \( P(i) \) the histograms of the lengths of the diagonal lines;
- laminarity \( (\text{LAM}) = \frac{\sum_{i=1}^{N} vP(v)}{\sum_{v=1}^{v_{\text{min}}} P(v)} \) = percentage of recurrent points which form vertical lines having at least the length of \( v_{\text{min}} \) \( P(v) \) is the frequency distribution of the lengths of the vertical lines;
- trapping time \( (\text{TT}) = \frac{\sum_{i=1}^{N} vP(v)}{\sum_{v=1}^{v_{\text{min}}} P(v)} \) = average length of vertical lines;
- entropy \( (\text{ENTR}) = -\sum_{i=1}^{N} p(l) \ln p(l) \) = Shannon entropy of the distribution of the diagonal line lengths, with \( p(l) = \frac{P(l)}{\sum_{l=l_{\text{min}}}^{N} P(l)} \);
- trend \( (\text{TREND}) = -\frac{\sum_{i=1}^{N} [i - (N/2)](\text{RR}_i - \text{RR}_1)}{\sum_{i=1}^{N} [i - N/2]^2} \) = paling of the RP towards its edges;
- longest deterministic line \( (\text{LMAX}) = \max \{|l_i; i = 1, \ldots, N_i|\} \);
- mean diagonal line \( <L> = \frac{\sum_{i=1}^{N} l_{\text{min}} l_{\text{max}} P(i)}{\sum_{l=l_{\text{min}}}^{N} P(l)} \).

All the above analytical definitions of the RQA descriptors have been incorporated into the software tools available free of charge on the following web sites:

- http://homepages.luc.edu/~cwebber/
- http://www.agnld.uni-potsdam.de/~marwan/toolbox/

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