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On the directionality of cortical interactions studied by structural analysis of electrophysiological recordings

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Abstract. To investigate the directionality of neural interactions as assessed by electrophysiology, we adapted methods of structural analysis from the field of econometrics. In particular, within the framework of autoregressive modelling of the data, we considered quantitative measures of linear relationship between multiple time series adopting the Wiener-Granger concept of causality. The techniques were evaluated with local field potential measurements from the cat visual system. Here, several issues had to be addressed. First, out of several statistical tests of the stationarity of local field potentials considered, those based on the Kolmogorov-Smirnov and on the reverse arrangement statistics proved to be most powerful. The application of those tests to the experimental data showed that the large part of the local field potentials can be considered stationary on a time scale of 1 s. Second, out of the several investigated methods for the determination of an optimal order of the autoregressive model, the Akaike Information Criterion had the most suitable properties. The identified order of the model, across different repetitions of the trials, was consistently 5–8. Third, although the individual segments of field potentials used for the analysis were relatively short, the methods of structural analysis applied produced reliable results, confirming findings of simulations of data with similar properties. Furthermore the features of the estimated models were consistent among trials, so that the analysis of average measures of interaction appears to be a viable approach to investigate the relationship between the recording sites. In summary, the statistical methods considered have proved to be suitable for the study of the directionality of neuronal interactions.

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1 Introduction

The investigation of brain activity by means of electrophysiological recordings is one of the major gateways to the understanding of the functioning of the brain. In this respect the analysis of the interactions and the cooperativity between groups of neurons is traditionally carried out by reporting measures of association such as correlations or coherences among recording sites. A question which is left unresolved by those types of analysis is the one concerning the directionality of information flow. The relevance of establishing which set of neurons is influencing which in a given behavioural condition derives, for example, from the current debate about the role of bottom-up or top-down processing of information in the brain. In the visual system, the hierarchical organization of the various areas and the high degree of reciprocity of the connections are recognized architectural principles (Felleman and Van Essen 1991). From the functional point of view, however, the system has been mainly considered to operate essentially in a feed-forward manner. This view has been challenged by several experiments clearly pointing to the functional relevance of the existing anatomical connections from hierarchically higher visual areas to lower ones. Top-down interactions could tune the activity of lower areas, providing them with information about context or expectations, notions that are supposedly extracted in higher regions. The present study has to be viewed in the light of the current efforts to move from a pure phenomenological description of the electrophysiological measurements to a mechanistic understanding of the brain processes.

As opposed to the neurosciences, the concepts of directional relationship, causality and feedback have a solid tradition in the field of econometrics, where they constitute the so-called structural analysis of time series. The causality notion adopted in the present work is commonly referred to as Wiener-Granger causality, and is probably the best established approach. The idea behind the definition is to study how informative a set of variables is for the prediction of a second set, and under appropriate constraints, to interpret predictability in

terms of causality. There have been a few applications of directional dependence measures in physiology. The first traces date back to the work of W. Gersch (see, for example, Gersch 1972, 1987), who studied the localization of an epileptic focus using electroencephalogram (EEG) recordings. Another report dealt with the regulation of circulatory parameters by the autonomous nervous system (Baselli et al. 1988). In this work, we present methods used to determine the direction of linear relationships in temporal systems and we describe the application of those principles to local field potentials recorded in behaving cats, focusing on the problems that have to be addressed with this specific class of data. We emphasize the application of the methods to real world data from behaving animals, as opposed to synthetic data from simulations.

1.1 Overview of the present work

The investigation of the directionality of neural interactions can take advantage of measures of Granger-causality in the multiple simultaneous recordings obtained from the experiments. These causality definitions have a very natural interpretation within the framework of multivariate autoregressive models (vector autoregressions or VAR) of the data. Interrelationships between individual variables are examined considering both time and frequency domain properties of the VAR model describing the process.

The structure of the present work is as follows. In the methodological section, after a brief description of the source of the experimental data, we describe a few aspects of the VAR modelling technique. Next, causality is introduced from a rather general point of view, and, moving to the domain of practical application, tests and measures that we will apply to the experimental data are presented. Then follows a discussion of some spectral properties of the models and of the causality measures. In the results section, we first describe the steps that were undertaken to attack problems of the practical implementation of the outlined methods. We start by discussing the issue of the stationarity of the recordings, then move to the questions of identification, estimation and validation of the model. In particular, the statistical procedures to be applied to the data were chosen based on simulation studies from a set of proposals from the literature. An example of causality analysis is presented at the end of the section. In the discussion, we point out some general aspects that have to be considered in the interpretation of the results.

2 Methods

2.1 Origin of the experimental data

The set of data we analyzed consisted in recordings from 48 experimental trials (called segments) in which a trained cat performed a visuomotor behavioural task (Chiang et al. 1997). The trial started when the cat was looking at a video screen. After a short variable period (around 500 ms), a first stimulus was presented on the monitor. The stimulus, a dark rectangle, moved from left to right and the cat had to track it visually. Upon appearance of a second visual stimulus, after a time randomly distributed at 500–2000 ms, the cat had to make a behavioural decision: a cartoon mouse (the GO stimulus) indicated that it had to press a lever in front of it. In NO-GO trials a little rectangle had to be tracked visually. Under both conditions, the cat was rewarded with food upon correct performance.

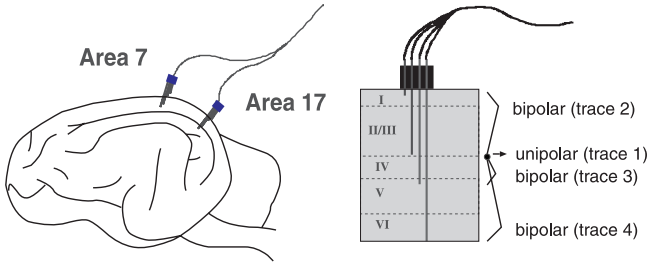

Fig. 1. Position of the two groups of electrodes in the cortex (*left*) and of the four single electrodes of each group in the different layers of the grey matter (*right*)

The trials lasted for about 6 s over which intracortical local field potentials were recorded. Potentials were collected with low impedance platinum/iridium electrodes with 100–200 kΩ at 1 kHz. A total of eight electrodes placed at different depths in the cortical grey matter were used. Four of the electrodes were in area 17, which belongs to the primary visual areas, the remaining four in area 7, which is part of the dorsal visual pathway and situated higher up in the hierarchy of visual areas. The position of the electrodes in the brain and in the cortical layers, together with the combinations of electrodes used to obtain the recordings are illustrated in Fig. 1. Data were analogically bandpass filtered at 0.5–100 Hz; moreover an analogical notch filter was applied to eliminate line frequency artefacts.

2.2 Causal interaction within the framework of autoregressive models

2.2.1 Autoregressive model of a stationary stochastic process

Vector autoregressions (VAR, cf. Lütkepohl 1993 or Hamilton 1994) belong to the simplest modelling techniques for multiple stationary time series. In relation to our efforts to investigate relations between brain regions, the major appeal of such methods is that they provide a concise description of the temporal interrelationships between multiple recording sites. The success of autoregressive techniques in a number of research fields resides in their generality and in the availability of a well developed statistical theory regarding estimation and inference questions. This is often not the case for other more sophisticated techniques, such as nonlinear models. VAR models have been applied in various

circumstances with success to electrophysiological data, in particular EEG measurements (see e.g. Gersch 1970, 1972; Franaszczuk et al. 1985; Lopes da Silva and Mars 1987). For an n-dimensional process $\{\mathbf{y}_t, t \in \mathbb{Z}\}$ an autoregressive model of order p, VAR(p), is defined by the following linear difference equation:

$$\mathbf{y}_t = \mathbf{c} + \mathbf{A}_1\mathbf{y}_{t-1} + \cdots + \mathbf{A}_p\mathbf{y}_{t-p} + \boldsymbol{\epsilon}_t \ . \tag{1}$$

$$\boldsymbol{\epsilon}_t \text{ is white noise } E[\boldsymbol{\epsilon}_t] = 0, \quad E[\boldsymbol{\epsilon}_t\boldsymbol{\epsilon}_\tau'] = \begin{cases} \boldsymbol{\Omega} & \text{for } t = \tau \\ 0 & \text{otherwise} \end{cases},$$

$\mathbf{c}$ is a $n \times 1$ vector of constants and the p $n \times n$ matrices $\mathbf{A}_i$ are the coefficients of the model. The elements of the noise time series $\{\boldsymbol{\epsilon}_t\}$ are called the innovations of the process. The prime ($'$) denotes transposition of the matrix. $\boldsymbol{\Omega}$, the noise covariance matrix, is a $n \times n$ symmetric, positive definite matrix.

A VAR(p) process is covariance-stationary if the solutions of the equations

$$\det(\mathbf{I}_n - \mathbf{A}_1 z - \mathbf{A}_2 z^2 - \cdots - \mathbf{A}_p z^p) = 0$$

lie outside the unit circle. The expression on the left-hand side where $\mathbf{I}_n$ denotes the n-dimensional identity matrix, is called the *reverse characteristic polynomial* of the VAR(p) process. For a stationary process with $\boldsymbol{\mu} = E[\mathbf{y}_t]$ we can define the jth autocovariance matrix as

$$\Gamma_j = E[(\mathbf{y}_t - \boldsymbol{\mu})(\mathbf{y}_{t-j} - \boldsymbol{\mu})'] \ .$$

Γ_0 is the covariance matrix of the process. From the definition it follows directly that $\Gamma_{-j} = \Gamma_j'$.

Various commonly used methods of estimation of the model are based on the so called Yule-Walker equations. Assuming that the process is stationary with mean $\boldsymbol{\mu}$, (1) can be written in mean-adjusted form as $\mathbf{y}_t - \boldsymbol{\mu} = \mathbf{A}_1(\mathbf{y}_{t-1} - \boldsymbol{\mu}) + \cdots + \mathbf{A}_p(\mathbf{y}_{t-p} - \boldsymbol{\mu}) + \boldsymbol{\epsilon}_t$. Postmultiplying both sides of the equation by $(\mathbf{y}_{t-j} - \boldsymbol{\mu})'$ and taking expectations gives the Yule-Walker equations

$$\Gamma_0 = \mathbf{A}_1\Gamma_1' + \cdots + \mathbf{A}_p\Gamma_p' + \boldsymbol{\Omega}$$

$$\Gamma_j = \mathbf{A}_1\Gamma_{j-1} + \cdots + \mathbf{A}_p\Gamma_{j-p} \qquad \text{for } j > 0$$

The set of equations for $j = 1, 2, \ldots, p$ can be put together in a system:

$$[\Gamma_1, \ldots, \Gamma_p] = [\mathbf{A}_1, \ldots, \mathbf{A}_p] \begin{bmatrix} \Gamma_0 & \cdots & \Gamma_{p-1} \\ \vdots & \ddots & \vdots \\ \Gamma_{-p+1} & \cdots & \Gamma_0 \end{bmatrix} = \mathbf{A}\Gamma$$

and the matrix $\mathbf{A}$ of the model coefficients can be obtained by solving the system of linear equations. The fact that the matrix Γ is symmetric (and positive semidefinite) permits the use of efficient numerical algorithms for the calculation of the inverse, that, for instance, make use of the Cholesky factorization of the matrix. An interesting recursive algorithm for successively increasing the order of the model has been proposed by Whittle (1983).

Once a satisfying model has been selected it is possible to analyze its properties in the time and in the frequency domain, and to address the question of the mutual influences of the different channels.

2.2.2 Structural analysis using VAR models

A possibility to study the direction of information flow between multiple recording sites is offered by the so-called structural analysis of time series. In this context, a fundamental conceptual and practical tool is the Granger-causality notion that was developed in the 1960s and 1970s mainly due to the contribution of Clive J.W. Granger (1963, 1969, 1980). Due to the influence of earlier proposals by Wiener, those concepts are also referred to as Wiener-Granger causality. The definition is based on intuitive properties of temporal system, such as that "the past and present may cause the future, but the future cannot cause the past" (Granger 1980). Considering two (possibly multivariate) time series $\mathbf{X} = \{x_t\}$ and $\mathbf{Y} = \{y_t\}$, causality is expressed in terms of predictability: if the time series $\mathbf{X}$ causes the time series $\mathbf{Y}$, then knowledge of the past of $\mathbf{X}$ and $\mathbf{Y}$ should improve a prediction of the present value of $\mathbf{Y}$ compared to the knowledge of the past of $\mathbf{Y}$ alone. The definition maintains that there is no external source of temporal dependence between the two considered systems; in other words one has to be confident that the domain of relevant information for the temporal relations of the variables of interest can be restricted to the past of the same variables.

Granger causality can be formalized as follows. Suppose that $\boldsymbol{\Omega}_t$ is the information set containing all information in the universe up to period t. The quality of forecast is measured in terms of the mean squared error (MSE) of the prediction. Let $\mathrm{MSE}_y(h \mid \boldsymbol{\Omega}_t)$ denote the MSE based on $\boldsymbol{\Omega}_t$ of the optimal (in the MSE sense) h-step predictor of the process $\mathbf{Y}$ at origin t. $\mathbf{X}$ is said to Granger cause $\mathbf{Y}$ if

$$\mathrm{MSE}_y(h \mid \boldsymbol{\Omega}_t) \neq \mathrm{MSE}_y(h \mid \boldsymbol{\Omega}_t \setminus \{x_s \mid s \leq t\})$$

for at least one $h = 1, 2, \ldots$

If current x is useful in forecasting current y, then instantaneous causality between $\mathbf{X}$ and $\mathbf{Y}$ is said to be present:

$$\mathrm{MSE}_y(1 \mid \Omega_t \cup \{x_{t+1}\}) \neq \mathrm{MSE}_y(1 \mid \Omega_t) \ .$$

The latter definition (at least for stationary time series with a VAR representation) is symmetric, i.e. if $\mathbf{X}$ causes $\mathbf{Y}$ instantaneously, then there is also instantaneous causality from $\mathbf{Y}$ to $\mathbf{X}$. Instantaneous causality will arise, for instance, if true causation exists but data are collected insufficiently frequently to detect it. Common input is another possible source of instantaneous interactions. Only extra knowledge about the physical system generating the time series helps determine the direction of causality in this case.

Causal relations and various other aspects of the relationships between variables constituting a multivariate

stochastic process can be conveniently analyzed in the context of a VAR model. The conditions for non-causality can be, for instance, expressed as a set of zero constraints for the coefficients of the VAR model (Granger, 1980; Lütkepohl 1993). A number of tests have been developed based on these properties. Other causality tests exploit alternative representations of a VAR and are, in general, based on the normality of the estimators of the parameters of interest. This condition is usually satisfied only asymptotically and there is limited knowledge about the behaviour of the estimators for samples of finite length. Monte Carlo studies are therefore useful to ascertain the applicability of the methods of interest in a given practical situation.

In the context of causality analysis J. Geweke (1982) proposed a measure of linear dependence (or information) between two blocks of variables **X** and **Y** constituting a multivariate jointly stationary process $\mathbf{Z} = \{[x_t, y_t]'\}$. In the following, we assume that **X** and **Y** are k- and l-dimensional processes, respectively, and **Z** $k + l = n$ dimensional. The measure can be expressed as the sum of three components related to the linear relationship from **X** to **Y**, to the relationship in the opposite direction and to instantaneous causal dependence between the two variables. Moreover, the fact that a decomposition by frequency of Geweke's measure has been proposed, makes it very appealing for applications in electrophysiology. Define with $\mathrm{var}(X \mid \Omega)$ the MSE of the best linear forecast of a time series **X** based on the information set Ω. If we denote with X^- the past of **X**, with X^+ the past and present of **X**, and with X the whole time series, we have that

$$F_{X,Y} = \log\left\{\frac{\det[\mathrm{var}(X \mid X^-)]}{\det[\mathrm{var}(X \mid X^-, Y)]}\right\}$$

$$= \log\left\{\frac{\det[\mathrm{var}(Y \mid Y^-)]}{\det[\mathrm{var}(Y \mid Y^-, X)]}\right\}$$

represents a measure of linear dependence (or information) between the two time series. It can be decomposed in a measure of instantaneous linear feedback $F_{X\cdot Y}$ and two directional measures $F_{X\to Y}$ and $F_{Y\to X}$.

$$F_{X,Y} = F_{X\to Y} + F_{X\cdot Y} + F_{Y\to X}$$

with

$$F_{Y\to X} = \log\left\{\frac{\det[\mathrm{var}(X \mid X^-)]}{\det[\mathrm{var}(X \mid X^-, Y^-)]}\right\}$$

$$F_{X\to Y} = \log\left\{\frac{\det[\mathrm{var}(Y \mid Y^-)]}{\det[\mathrm{var}(Y \mid Y^-, X^-)]}\right\}$$

$$F_{X\cdot Y} = \log\left\{\frac{\det[\mathrm{var}(X \mid X^-, Y^-)]}{\det[\mathrm{var}(X \mid X^-, Y^+)]}\right\} \quad .$$

Under the assumption that the disturbances are Gaussian, $F_{X,Y}$ results from a population analog of likelihood-ratio statistic to test the hypothesis that the two time series are not mutually informative. In that case, the denominator is expected to be equal to the numerator, and the statistics to have asymptotical χ^2 distributions. More specifically, for a sample of size T, under the null hypothesis that the respective values vanish, the distribution of $TF_{X\cdot Y}$ will be $\chi^2(kl)$, that of $TF_{Y\to X}$ and $TF_{Y\to X}$ $\chi^2(pkl)$.

In practical terms, for two time series **X** and **Y** that can be modeled as VAR processes, the causality measures can be computed from the estimated covariance matrices of the innovations. For instance $\mathrm{var}(X \mid X^-, Y^+)$ can be obtained from the variance-covariance matrix $\mathrm{var}(\epsilon_t)$ of a suitable autoregressive model of the form $\mathbf{x}_t = \sum_{k=1}^{p} \mathbf{A}_k \mathbf{x}_{t-k} + \sum_{j=0}^{p} \mathbf{B}_j \mathbf{y}_{t-j} + \epsilon_t$.

2.2.3 Spectral properties of the autoregressive models

The population spectrum of a k-dimensional process **X** with absolutely summable autocovariances $\{\Gamma_j\}_{j=-\infty}^{\infty}$ can be defined as

$$\mathbf{s}_{\mathbf{x}}(\lambda) = \sum_{j=-\infty}^{\infty} \Gamma_j e^{-i\lambda j} \quad .$$

The $k \times k$ spectral matrix $\mathbf{s}_{\mathbf{x}}$ has as jth diagonal element the power spectral density of the jth univariate processes. The off-diagonal elements represent the cross-spectra of the respective univariate processes. Assuming that **X** can be represented by the VAR(p) $\mathbf{x}_t = \sum_{k=1}^{p} \mathbf{A}_{1_k} \mathbf{x}_{t-k} + \epsilon_{1t}$ with $\mathrm{var}(\epsilon_{1t}) = \Sigma_1$, we have the following expression for the population spectrum of the process: $\mathbf{s}_{\mathbf{x}} = (\mathbf{I}_k - \mathbf{A}_{1_1} e^{-i\lambda} - \mathbf{A}_{1_2} e^{-2i\lambda} - \cdots - \mathbf{A}_{1_p} e^{-pi\lambda})^{-1}$ $\Sigma_1 (\mathbf{I}_k - \mathbf{A}'_{1_1} e^{i\lambda} - \mathbf{A}'_{1_2} e^{2i\lambda} - \cdots - \mathbf{A}'_{1_p} e^{pi\lambda})^{-1}$.

Certain aspects of the intrinsic relations between variables can be explored by the analysis of multiple and partial coherences, as exposed in detail, e.g. by Franaszczuk et al. (1985) and Gersch (1972). A decomposition by frequency of the measures of linear feedback $F_{Y\to X}$ and $F_{X\to Y}$ has been proposed by Geweke (1982). Subject to some practically weak and verifiable conditions (the invertibility of some operators) there exist non-negative functions $f_{Y\to X}(\lambda)$ and $f_{X\to Y}(\lambda)$ such that

$$F_{Y\to X} = \frac{1}{2\pi} \int_{-\pi}^{\pi} f_{Y\to X}(\lambda) \mathrm{d}\lambda \qquad \text{and}$$

$$F_{X\to Y} = \frac{1}{2\pi} \int_{-\pi}^{\pi} f_{X\to Y}(\lambda) \mathrm{d}\lambda \quad .$$

The definitions, taking $f_{Y\to X}(\lambda)$ as an example, can be justified as follows. Defining the polynomial lag operator $A(L) = A_0 - \sum_{k=1}^{p} A_k L^k$ with $L^j x_t = x_{t-j}$, we have the following representation of the projection of $[x_t, y_t]^T$ on its past

$$\begin{bmatrix} A_2(L) & B_2(L) \\ D_2(L) & C_2(L) \end{bmatrix} \begin{bmatrix} x_t \\ y_t \end{bmatrix} = \begin{bmatrix} \epsilon_{x2t} \\ \epsilon_{y2t} \end{bmatrix} \quad ,$$

$$\mathrm{var} \begin{bmatrix} \epsilon_{x2t} \\ \epsilon_{y2t} \end{bmatrix} = \begin{bmatrix} \Sigma_{x2} & W \\ W' & \Sigma_{y2} \end{bmatrix} \quad .$$

In this case, $A_2(0) = \mathbf{I}_k$ $C_2(0) = \mathbf{I}_l$ $B_2(0) = 0$, $D_2(0) = 0$. If the system is premultiplied by

$$\begin{bmatrix} \mathbf{I}_l & 0 \\ -W'\Sigma_{x2}^{-1} & \mathbf{I}_k \end{bmatrix}$$

we obtain

$$\begin{bmatrix} A_2(L) & B_2(L) \\ D_3(L) & C_3(L) \end{bmatrix} \begin{bmatrix} x_t \\ y_t \end{bmatrix} = \begin{bmatrix} \epsilon_{x2t} \\ \epsilon_{y3t} \end{bmatrix} ,$$

where the disturbances ϵ_{x2t} and ϵ_{y3t} are uncorrelated by construction. Inversion of the operator leads to the so-called *moving average* representation of the process:

$$\begin{bmatrix} A^2(L) & B^2(L) \\ D^3(L) & C^3(L) \end{bmatrix} \begin{bmatrix} \epsilon_{x2t} \\ \epsilon_{y3t} \end{bmatrix} = \begin{bmatrix} x_t \\ y_t \end{bmatrix} .$$

From the latter representation of X, if we define $\mathrm{var}(\epsilon_{y3t}) = \Sigma_{y3}$, the spectral matrix $\mathbf{s_x}$ can be decomposed additively in

$$\mathbf{s_x}(\lambda) = \tilde{A^2}(\lambda)\Sigma_{x2}\tilde{A^2}(\lambda)' + \tilde{B^2}(\lambda)\Sigma_{y3}\tilde{B^2}(\lambda)' .$$

Here $\tilde{A^2}(\lambda)$ and $\tilde{B^2}(\lambda)$ denote the Fourier transforms of the operators A^2 and B^2 and with the prime ($'$) we indicate transposition and conjugation of the matrix. The first term of the sum is the part of the power spectrum of X contributed by the past of X when it is regressed on both the past of X and the past of Y. The spectral decomposition of $F_{Y\to X}$ is then defined as

$$f_{Y\to X}(\lambda) = \log\left\{ \frac{\det[\mathbf{s_x}(\lambda)]}{\det[\tilde{A^2}(\lambda)\Sigma_{x2}\tilde{A^2}(\lambda)']} \right\} .$$

The proposed spectral decomposition represents then the limiting value of a likelihood ratio statistic for the hypothesis that the variation in Y at frequency λ is attributable completely to ϵ_{x2t}.

The analysis of the causality measure in the spectral domain is a very useful tool to determine the contribution of different frequencies to the detected causality links. This is of particular interest to neurophysiologists because of the solid tradition of investigating the biological basis of processes eliciting activity in specific frequency bands. The decomposition of the feedback measured does not require numerical techniques other than those used for the estimation of the autoregressive model.

The quantification of the precision of the spectral estimates is difficult to obtain, in particular for small samples, as the asymptotic approximations could be unreliable. As suggested by Geweke (1984), we calculated a bootstrap correction for bias of the spectral decomposition as well as approximate bootstrap confidence intervals. In contrast to Geweke's proposal, in which a parametric distribution of the residual for the generation of the bootstrap samples was used, we resampled from the computed residuals of the autoregression (Efron and Tibshirani 1993). As for the spectral measures, the confidence bounds are non-negative functions of frequency, so they cannot be directly used for hypothesis testing.

3 Application and evaluation of the analysis techniques

3.1 Stationarity of local field potentials

The statistical stationarity of the data, i.e. the time invariance of the mechanism generating them, is a requirement for the modelling techniques we intend to employ. It is therefore necessary that the considered data reasonably satisfy stationarity criteria before attempting to apply such methods.

The problem of the assessment of stationarity is a difficult one. This because stationarity is a property of the stochastic process under study, and, in the practical situation, one has available only a single realization of it. Various statistical procedures for the detection of nonstationary time series have been proposed in the literature. Since each of them relies on a number of assumptions about the process, none has gained general acceptance. In this work we considered four statistical tests that have been previously applied to electroencephalographic data and we studied their performance with simulated data.

The tests we evaluated initially were the Kolmogorov-Smirnov (KS) test on the amplitudes of the process (McEwen and Anderson 1975), the same test applied on the spectra (McEwen and Anderson 1975), the reverse arrangement test and the run test applied on mean square values of subsegments of the signal (Bendat and Piersol 1986; Blinowska and Malinowski 1991). The KS test on the periodogram was unreliable with our data and the run test had a very low power in simulations, so they were discarded. We further evaluated the remaining two tests for their power for the detection of nonstationarities of the same kind, but in general more subtle, than those illustrated in Fig. 2. The choice of the type of nonstationarity we introduced (sudden changes in the parameters of an autoregressive process) is motivated by our observation of the recordings and is in line with other experimental investigations (Abeles et al. 1995). Other sorts of nonstationarity, such as transient spikes, which also occur in the data, were not considered here. For the KS test and the RA test, the power was of 50% and 56%, respectively, for a level of 5%. The combination of the two criteria at the 5% level gave a power of 66%. Figure 2 shows the principles of the analysis with a simulated nonstationary trace and two typical experimental time series. In conclusion, based on simulations, we selected the KS test on the amplitudes and the reverse arrangement test (Bendat and Piersol 1986) as statistical procedures suitable to identify nonstationarities in our set of data.

With these results in mind we could then perform the analysis of experimental data. Since our electrophysiological signals were lowpass filtered, downsampling was necessary to reduce the statistical dependence

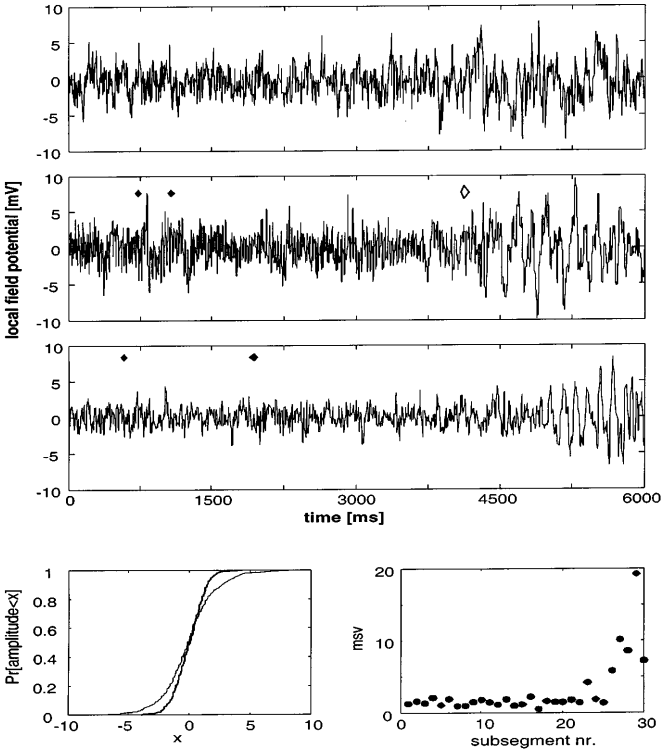

Fig. 2. In the upper trace an example of simulated nonstationary time series (abrupt change of 10% in the autoregressive parameters at $t = 3800$ ms) is shown. The middle and lower traces are examples of nonstationarities related to sudden changes in regime of the experimental recordings. In the plots the *filled diamonds* indicate the presentation of a visual stimulus, the *open ones* a movement of the cat. A typical observation is that activity dominated by the low frequencies appears abruptly near the end of the trial, usually when the cat is no longer attending to the monitor. The nonstationarities in the simulations were generally slightly less pronounced than those in the real data. For the data of the lower trace, the left bottom panel shows the amplitudes in the first (*dashed line*) and second (*solid*) half of the trial plotted in a cumulative way. The mean square values in 30 adjacent subsegments of the recording period are displayed in the right bottom panel

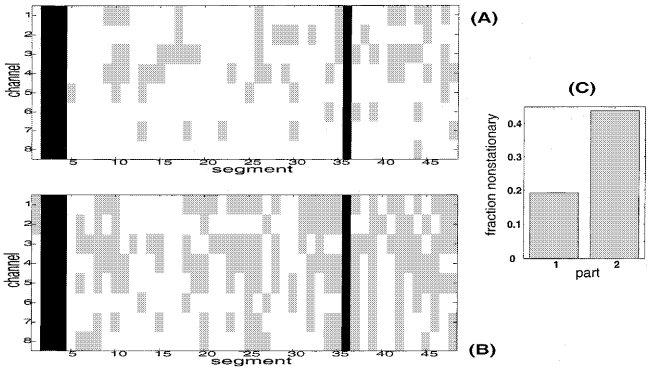

Fig. 3A–C. Stationarity of the recordings from 8 electrodes in 48 segments. The first (**A**) and the second (**B**) half of the traces considered separately. In *black* are indicated the recordings with clear artifacts that were not considered for the analysis. *Grey squares* denote recording considered nonstationary by the combination of the KS test on the amplitudes and a RA test, both at the 5% level. Clearly the number of nonstationary recordings is much higher in the second half of the experiments. This relates to the fact that the cat often started eating and moving heavily near the end of the trial and this causes abrupt changes in the local fields. In the first half of the trial, with the cat generally looking at the screen, the data were very often stationary. There is a certain difference between the two examined areas, the electrodes located in area 17 (1–4) producing more often nonstationary signals compared to those in area 7. Furthermore, the nonstationarities are often grouped in vertical bands, indicating that the change in the structure of the process during an experiments could be revealed at many of the locations of measurement. **C** Fraction of nonstationary segments in the first and second part of the trials

of nearby measurements of the potentials, which affects the efficacy of the tests employed (in particular of the KS test). We found, again using synthetic data, that a sampling frequency of 250 Hz (slightly above the Nyquist rate, in agreement with McEwen and Anderson, 1975) ensured good properties of the tests. The analysis of a test set of experiments evidenced that long recordings (about 5–6 s) are clearly more often nonstationary than short ones (1–2 s). The nonstationary segments were mainly associated with movements of the cat and changes in its attentional state (see Fig. 3). In contrast, if the animal was still and attending to the stimuli presented on the screen (from our point of view the interesting part of the experiment), the local field potentials could be very often qualified as stationary on a time scale of 1–2 s. The methods used proved to be suitable to detect nonstationary data and give us confidence that a large fraction of the recordings that we intend to submit to structural analysis can be considered stationary.

3.2 Practical VAR modelling

As for all statistical fitting procedures, modelling with a VAR process consists of an identification and estimation step (e.g. the determination of the order p, the estimation of the coefficients) and a validation step. For each, several approaches can be applied, so, in a given practical situation, one has to identify those most advantageous.

We tested some of the proposed algorithms for the estimation of the coefficients of the model, such as the ordinary least-squares (OLS) solution of the autoregressive equations, the direct method as well as the recursive Whittle algorithm for the solution of the Yule-Walker equations and numerical maximum likelihood estimation. All the considered methods performed well with synthetic data with the OLS and the Whittle algorithm being slightly superior to the others. Also with our experimental data the latter two techniques were practically equivalent from the point of view of the results. Considerations based on the computational demand speak in favour of Whittle's method for the application to large data sets.

There are subtle problems with the selection of an appropriate order of the model. The basic compromise is between good fit and good prediction: as one estimates models with a growing number of parameters, the fit to the data will improve in parallel with an increase in the variance; from a certain point on, the model might then produce poorer predictions. The problem can be very

serious when, as very often in neurophysiology, one is tempted to incorporate as many channels as possible in the model to obtain a good coverage of the dynamics. Thus, a very popular strategy for the order selection is based on the concept that the prediction error should be minimal for the optimal model. Since, in structural problems, we are interested in comparing the quality of prediction under different conditions, we adopted this approach in our applications.

In practical work the use of the Akaike Information Criterion (AIC) (Akaike 1974) is very popular. For an observation of length T of a Gaussian VAR it is defined by

$$\mathrm{AIC}_p = \log(\det(\hat{\Omega})) + 2n_{\mathrm{est}}/T \ .$$

The determinant of the estimated covariance matrix of the innovations, $\det(\hat{\Omega})$, is the term that decreases with increasing order of the model. The second term represents the penalty assigned to large models: the number of freely estimated parameters n_{est} in an n-dimensional VAR(p) model is equal to $n^2 \times p$. Other criteria used in practical work are the Bayesian Information Criterion (BIC) and the Hannan-Quinn Criterion (HQC). Compared to AIC, those two criteria have the advantage to estimate the order consistently. The only difference of those criteria with AIC is the weight assigned to the number of freely estimated parameters: $\log(T)n_{\mathrm{est}}/T$ for BIC and $2\log(\log(T))n_{\mathrm{est}}/T$ for HQC. For $T \geq 16$ it turns out that $\mathrm{BIC} \leq \mathrm{HQC} \leq \mathrm{AIC}$ (Lütkepohl 1993, p. 133).

We were also interested in the ability of those methods to identify the correct order of VAR processes with known properties. The three criteria performed very well in the order identification of simulated VARs of various dimensions and orders (n and p ranging over 1–8), provided that the time series were sufficiently long. To get an impression of the results with samples of the size we deal with in the experiments, we performed simulations of stationary Gaussian VAR processes of 200 time steps. The coefficients used were similar to those observed in the experimental models. In a series of 200 simulations of a VAR(5) AIC, HQC and BIC correctly detected the order in respectively 100%, 91% and 98% of the cases for a three-dimensional process, and in 99%, 86% and 19% of the cases for a four-dimensional process. The correct order of a VAR(8) was found in 97%, 48% and 1% of the cases ($n = 3$), and in 98%, 41% and 0% of the cases ($n = 4$). The wrong results were in all cases underestimates, so the problem of overestimation described for AIC did not appear here. For the reasons exposed, we performed the identification of the model of the experimental data using Akaike's criterion.

The inspection of the AIC curves (AIC_p versus p) from a set of experimental data, examples of which are shown in Fig. 4, reveals several aspects. The curves have very similar basic properties, with a fast initial decline and a flat minimum. Minima are consistently confined at 5–8 and lie most frequently at 6 or 7. The curves are very flat in that region, so the differences between the values at a given order are rather small. For the cases we present in the following, we decided to fit models of order 7 to the data. Considering AIC, orders of 5 or 6 could also have been acceptable, but two reasons motivated our choice. First, the fact that the residuals of models of order 7 resembled much better white noise than, e.g order-5 residuals. A related second aspect is our interest in the spectral properties of the data. Since the complexity of the spectra estimated with autoregressive methods increases with the order of the model, our choice permits the maintenence of a reasonable resolution in the frequency domain.

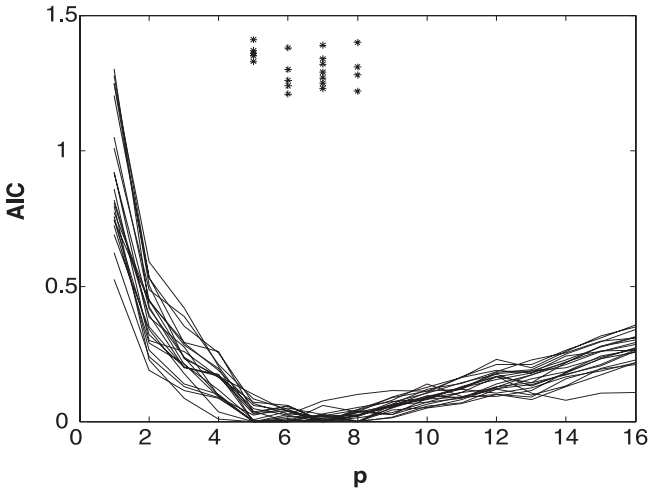

Fig. 4. Values of AIC as a function of the order of the model for 20 examples of three-dimensional time series (two channels from area 17, one from area 7) of 200 points. Data were bandpass filtered at 2–100 Hz. Estimation of the model was performed with the Whittle algorithm (see text). The curves are shifted by subtracting the respective minimal value so that they have a minimum of zero. The asterisks indicate the order at which the minima were located

Once a model has been estimated, it is important to consider statistical properties of the residuals

$$\hat{\epsilon}_t = (y_t - \bar{y}) - \sum_{i=1}^{p} \mathbf{A}_i (y_{t-i} - \bar{y}), \quad t = 1, \ldots, T$$

such as their correlation structure and their distribution. The electrical brain activity contains different amounts of power in distinct frequency bands, and one might wonder how well these spectral properties are described by the autoregression. The whiteness of the residuals (or, in our case, the absence of significant time-lagged correlation) is an indication in this sense. In fact, the fitting procedure can be viewed as the reconstruction of a linear filter transforming the observed process into a white noise time series. It is therefore necessary to verify the white noise assumption for the residuals, to confirm that the temporal relationships between the variables are actually captured by the model.

The whiteness was assessed by means of a Portmanteu test (Lütkepohl 1993) and by examining auto and crosscovariances of the univariate residuals. For data we considered stationary, the residuals of our models were almost always free of relevant correlations.

Many of the statistical procedures described earlier assume the gaussianity of the process as a starting point. Normality of the process is required for instance for most methods used to set up forecast intervals of a VAR. Furthermore, it ensures that the estimation of the coefficients by least-squares or by related methods have suitable properties, for instance consistency or asymptotical equivalence with maximum-likelihood estimation. The asymptotical normality of the coefficients requires weaker conditions (see, for example, Lütkepohl, 1993, p.82). In turn, these properties are important for the statistical tests addressing the structural features of the model. For stationary VAR, the normality of the process is equivalent to the normality of the white noise process ϵ_t generating it. The analysis of the normality of the residuals was performed by inspection of the normal plots and by a Kolmogorov-Smirnov test considering the univariate time series from the multivariate model. The classical test for multivariate normality (like those evaluating third and fourth moments of the distribution) require a much larger number of observations than we have available to produce meaningful results. The processes had a normal distribution in approximately 80% of the cases that we considered stationary. The exceptions were cases with slightly longer tailed distributions. The inspection of the traces indicated that those were probably due to very short spike-like potentials, i.e. undetected brief nonstationarities.

Having our specific physiological questions and our set of recordings in mind, we confined our attention to multivariate time series of dimensions of 2–6 and of a length of 200–400 points (corresponding to approximately 1–2 s). The principles of estimation, identification and model checking exposed above would apply independently on the size of the model. However, as the number of parameters to be estimated grows quadratically with the dimensions of the time series, high dimensional models require very long recordings to be properly characterized. With our set of data, modelling of the multichannel local field potentials with stationary VAR processes could be performed with success in a large fraction of cases.

3.3 Considerations on averaging over different trials

One of the major practical problems we have to face relates to the length of the time series and the typical "behavioural times" of the animal, which are, under natural conditions, very brief. In our experimental situation, we can assume that the typical period of the trials when the cat is attending to the monitor and awaiting the appearance of the behaviourally relevant stimulus will be of a few seconds. This quite short length, that we consider an upper bound for the period during which we can hope to observe stationary activity, constrains the quality of the estimation of the model and of the inference on the structure of interactions. Causality measures computed from single trials will therefore be relatively noisy estimates of the true values. Given the availability of repetitions of the experiment it is tempting to make statements about the average relationships between the recording sites in a given behavioural situation. Averaging measures over different repetitions could be of help. Of course, this solution is only reasonable if the data show sufficient regularity, as expressed, for example, in the stability of the models over different trials. We will present evidence in this sense in the next paragraph.

3.4 Causality in a test data set

In the following we present examples of structural analysis methods applied to a test set of experimental recordings. We initially investigated the stability of individual models over the different trials, to see whether an average structure would emerge. As a first step, we considered bivariate experimental time series. The analysis of the coefficients of a VAR(7) model revealed a marked constancy over different trials. Figure 5 displays, for a particular combination and experimental condition, the confidence interval for the coefficients obtained in several repetitions of an experiment. The stability was highest for the large values on the diagonal of the first few coefficient matrices and was related to the relative stability of the autospectra. Although off-diagonal elements were usually smaller than diagonal ones, they were often significantly different from zero. The opposite could be asserted for time series with similar univariate properties but no inter-relationship (Fig. 6); we take this as a sort of control case to check

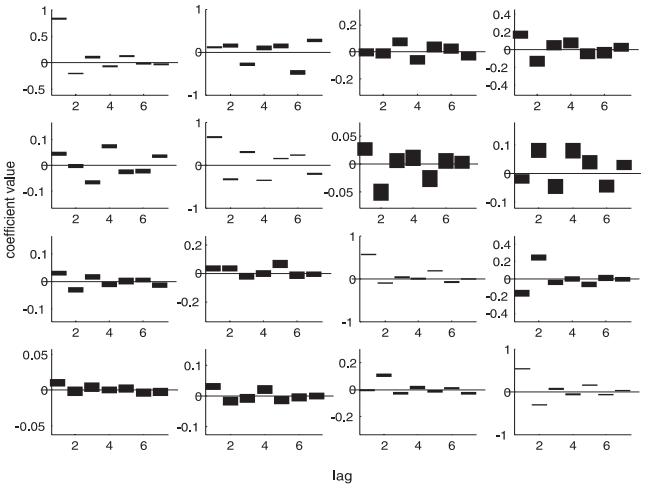

Fig. 5. Stability of the coefficients of a four-dimensional VAR(7) model of two bipolar recording form each area, estimated in 48 trials (recordings of 1 s at the beginning of the trial). The 16 plots represent the entries of the 4×4 coefficient matrices. For each plot, the seven bars indicate the 95% confidence intervals (bases on a *t*-distribution) for the coefficients of the seven matrices of the model. It is clear that the diagonal elements of the coefficient matrices are larger and more stable than the off-diagonal ones, in particular for the matrices with low indices. This is a consistent observation across all combinations of electrodes and positions of the analysis window. This is related to the fact that the autospectra have rather constant features in different trials

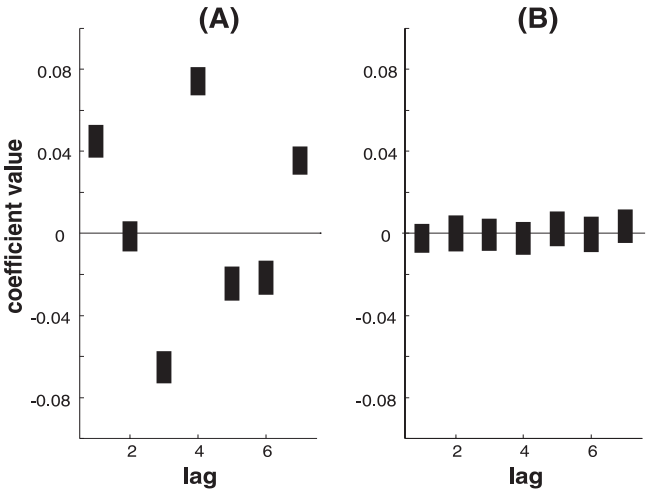

Fig. 6. **A** Stability of an off-diagonal element of the model coefficients matrices of Fig. 5. Six of the coefficient are significantly different from zero over the 48 repetitions of the experiment. This fact can be interpreted as the presence, on average of Granger causality within area 17, as measured with the considered electrodes. The picture could change by the introduction of different recording sites. **B** As a control, we plot the corresponding coefficients from a set of experimental time series with supposedly no causal relationship. Here, the time series is constituted of the same combination of the channels from area 17 but from randomly chosen and different segments. Since there is no evoked potential locked with the beginning of the time series we assume that there is also no causality between recordings from different trials. As expected, the coefficients are not significantly different from 0

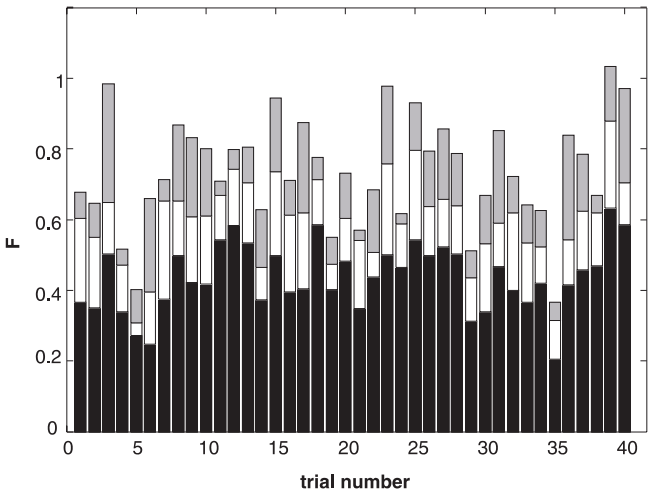

Fig. 7. Example of intra-areal interaction with a marked asymmetry which is detectable with the methods described. The three bipolar recordings from area 17 were considered here. Linear dependence from channels two and three grouped (supragranular and granular layers) versus channel four (granular and infragranular) is displayed. Due to the presence of nonstationarities, some of the segments are not considered for the analysis. *Black bars* quantify the causality from the second group to the first; *white bars* refer to the opposite direction and *grey bars* indicate the amount of instantaneous dependence

for a bias in the estimation of the model. Off-diagonal coefficients model the effect of a given channel on a different one, so their values can be interpreted in the light of Granger's causality definition. In this sense, the fact that those coefficients are often significantly different from zero (more often for the first lags) is an indication that bidirectional feedback exists in the system. Very similar results to those of the bivariate model discussed are obtained with models of higher dimensional data. If measurements from different areas are considered, it turns out that coefficients relating recordings from one and the same area are, in general, slightly larger and more stable than coefficients reflecting interareal interactions. This is an indication of stronger coupling within than between cortical areas (see Fig. 5).

Considering individual trials, we also performed statistical tests to determine the direction of Granger causality and to detect instantaneous causality between the channels of the multivariate process. We implemented classical procedures for testing constraints on the coefficients of a linear regression based on the Wald statistic or on likelihood ratio statistics (described, for example, in Lütkepohl 1993 or in Geweke et al. 1983). The first remark to address concerns the fact that those tests have only asymptotical validity and, in some cases, they perform relatively poorly with small samples. In agreement with the literature (Geweke et al. 1983), the test based on the Wald statistic seemed to have the most favorable small sample properties. A few hundred data points were sufficient to detect causality reliably in four-dimensional VAR(7) processes that had statistical properties derived from the models of experimental time series. This was true for models with dimensions up to six, in the case of data corresponding to one second of recording. Six channels were excessive for recordings of 1 s.

Next, we applied Geweke's measures to the experimental data. If used to conduct a test of causality, the Wald statistic has probably slightly better properties than the likelihood-ratio test from the Geweke's measures; nevertheless, there is an advantage of having a quantitative value decomposable in the three described components. Using such measures, in fact, the results of repetitions of trials can be analyzed and the average behaviour of the cat can be judged more conveniently than using the binary result (or the p-values) of testing procedures on the individual trials. Examples of preliminary results of the causality analysis with Geweke's measures, together with an example of spectral decomposition of the measures are presented in Figs. 8 and 9. There, we show the dependence measure for three-dimensional models of the bipolar channels in area 17, which show a marked directional component, and four-dimensional models from both areas with slight differences in the feedback measures dependent on the behavioural context. The frequency decomposition shown reveals the presence of peaks that deserve a careful analysis. These results would be difficult to obtain with more traditional methods such as those based on correlations and coherences. The findings of this exploratory evaluation might be interesting from the physiological point of view and encourage us to continue our study in more depth and with larger data sets.

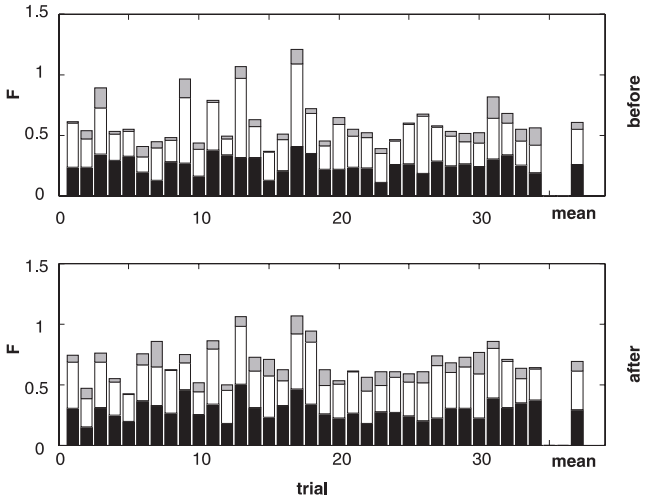

Fig. 8. Example of a comparison between the signals before (*upper row*) and after (*lower row*) the first visual event (the preparatory one) in 34 trials. A pair of bidimensional measurements were considered for this analysis: channels 2 and 4 from area 17 and channels 6 and 8 from area 7. The channels pairs correspond to recordings from the supragranular layers (channels 2 and 6) and from granular an infragranular layers (4 and 8). From the before-event and the after-event conditions, there is a slight increase in the dependence in both directions ($p < 0.05$, Wilcoxon signed rank test). It can also be noted that, in this example, the coupling in the bottom-up direction is stronger than the top-down one ($p < 0.05$ after the event)

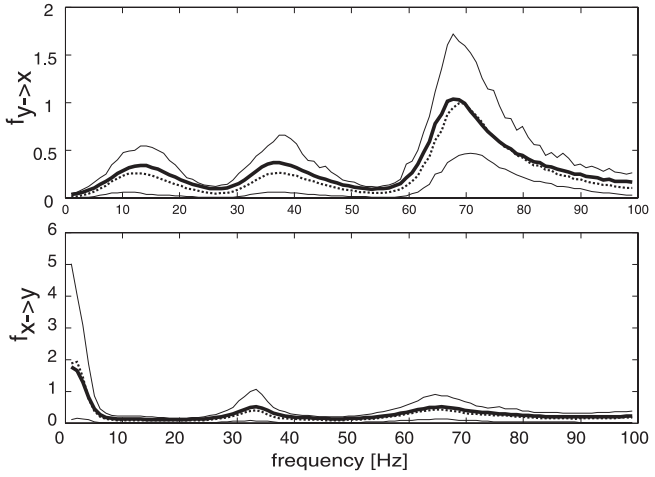

Fig. 9. Example of the spectral decomposition of the causality measures. Model of channels 2 and 3 (area 17) and 5 and 6 (area 7), subdivided in two blocks according to the area. The *thick line* represents the values of the decomposition of the dependence measure, *central dotted line* indicates the values with a bootstrap correction for bias, the *thin external lines* delimit approximate 95% bootstrap confidence levels for the latter function, obtained with 200 repetitions. From the data it is apparent that the contributions to the linear dependence come in prevalence from the high frequencies of the γ band. Further evidence for the consistency of the patterns of feedback in the frequency domain can be obtained from the analysis of the full set of recordings available. The major peaks in the traces shown here are consistently present throughout the different experiments

4 Discussion

4.1 Why stationary and linear models?

The analysis of the interaction among brain structures presented in this paper was performed using linear models of stationary time series. Above, the validity of the assumption of stationary data was investigated. Here we would like to discuss alternative modelling approaches, such as techniques for nonstationary and/or nonlinear processes.

The types of nonstationarities we typically encounter in our data are transients or rapid and radical changes in the spectral properties of the data. The most common models of nonstationary time series such as ARIMA or GARCH (Hamilton 1994), are not suited to describe such phenomena. Modelling the data as processes with changes in regime may be an attractive alternative to the stationary models used here. Autoregressive models with time-varying coefficients, based on the time-dependent Kalman filter or other techniques, have been described (see c.f. Hamilton 1994). Some of these have also been applied to biomedical signals (Mainardi et al. 1997) and electrophysiological recordings (Gersch 1987). However, various methodological questions are still unresolved. Moreover, in the present context, such an approach has specific drawbacks. First, the number of free parameters to be fitted is generally larger and, therefore, the methods require measurements of lengths which are usually not available. Second, such general models do not exploit characteristic features of the experimental design. In our case, short episodes of approximately stationary conditions are separated by externally triggered events, such as the presentation of a stimulus. Therefore, under the assumption of piecewise stationarity, each episode can be modeled separately. This keeps the number of additional parameters to a minimum and the resulting comparisons are statistically more powerful.

Linearity is the second important property of the models used here. It has to be noted that, for data generated by a Gaussian process (which seems to be often the case for our measurements) linear predictors are optimal, meaning that they are superior to any other predictor in the MSE sense. Nonlinear dynamical models, such as those based on neural networks, are very interesting modelling tools. For some nonlinear and non-Gaussian problems methods have been developed that outperform traditional modelling techniques (Ungar 1995). Their most serious drawback in the present context is that there is no general theory that allows the causality measures of our interest to be estimated. Together with the fact that structural analysis has been mostly developed for autoregressive time series, the reasons exposed justify our choice to model the data as stationary VAR processes.

4.2 Causality analysis: a note of caution

Interesting considerations on the appropriate interpretation of causality measures have been proposed by Granger (1980). From both the conceptual and the practical point of view, the most delicate issue concerns

the assumption of the completeness of the information set we use to make statements about causality in our system. True Granger causality can only be assessed if the information set, consisting in our case of the past and present of the modeled time series, contains all possible relevant information for the problem. In this sense, it is a clear advantage to be able to attack the problem from the multivariate point of view, by modelling multiple channels at one time. In fact, as repeatedly pointed out in the literature (Franaszczuk et al. 1985; Gersch 1987), multiple pairwise comparisons of association measures can be very misleading. Hence, there is no way to be absolute certain about the size of the information set relevant for a given structural problem. As long as those issues are unresolved, the interpretation of the causality measures as expressing direct and exclusive relationships, will have to be considered to a certain extent speculative.

In such a complex and highly interconnected system as the brain, the problem of missing information is obvious. It is already an enormous effort to enumerate all the structures influencing the activity in a given area. Moreover, considering the huge number of neurons contributing to the activity in any small brain region, the problem might seem intractable. However, we do not want to advocate a fatalistic view. To the contrary, if the experimental paradigm, the cortical areas to record from and the type of signal measured are chosen with sufficient care, we can expect the proposed methods to give meaningful and interpretable results. The measurement of a spatially averaged signal, such as the bipolar local field potential, is a first step in this direction, since it reduces the complexity of the signal enormously, while maintaining the specificity of the responses to a large degree. It is also clear that only precise and extensive knowledge of the system studied, can make the design of appropriate experiments easier. Imaging studies could be performed to identify brain regions specifically involved in a given task. This kind of data could then guide the experimenter in the selection of the areas from which to record electrophysiologically. Finally, structural analysis findings may be interpreted in the light specific knowledge about the anatomical substrate of the interactions identified. It has to be noted that the exposed conceptual difficulties are by no means specific to the methods we apply here. The problem of missing information will equally affect all other conceivable methods addressing the same basic question, such as the study of cross correlations or coherences. It will primarily remain a matter of expertise and care in the design of the experiments to be able to give sensible interpretations to the results of structural analysis.

Another aspect intrinsic in the practical implementation of the concept of causality is the appearance of instantaneous interactions. For certain combinations of recording chosen for the analysis, the fraction of total causality attributed to instantaneous relationships may be substantial. This is often the case when we consider bipolar recordings from electrodes close to one another (e.g. sampling from supragranular versus granular layers, i.e. trace 2 versus trace 3, see Fig. 1). As we have mentioned previously, the direction of instantaneous causality cannot be determined using structural analysis, unless one can impose extra constraints to the physical system. Possible reasons for the appearance of instantaneous interactions are a too-low sampling rate or a source of common input. Our primary interest is the investigation of the relationship between areas. For the interareal dependence measures presented in the examples, the fraction causality regarded as instantaneous tends to be minimal compared to the directional components. We can take this as an indication that the mentioned issue is not relevant here and that our sampling rate is adequate.

4.3 Conclusion

In summary, we believe that structural analysis is an appropriate framework to address the question of the directionality of cortical interactions. If interpreted with sufficient caution, the results of the analysis can offer valuable insights into brain functioning that would be very difficult to obtain using other methods. Future work will focus on the detailed analysis of a larger set of experiments which are in progress. Only more extensive experience with those methods will reveal whether they will become a useful complement to more traditional techniques in the future.

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