Assessing interactions of linear and nonlinear neuronal sources using MEG beamformers: a proof of concept

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Abstract


Methods: Two periodic sources were simulated and the effects of transient source correlation on the spatial and temporal performance of the MEG beamformer were examined. Subsequently, the interdependencies of the reconstructed sources were investigated using coherence and phase synchronization analysis based on Mutual Information. Finally, two interacting nonlinear systems served as neuronal sources and their phase interdependencies were studied under realistic measurement conditions.

Results: Both the spatial and the temporal beamformer source reconstructions were accurate as long as the transient source correlation did not exceed 30–40 percent of the duration of beamformer analysis. In addition, the interdependencies of periodic sources were preserved by the beamformer and phase synchronization of interacting nonlinear sources could be detected.

Conclusions: MEG beamformer methods in conjunction with analysis of source interdependencies could provide accurate spatial and temporal descriptions of interactions between linear and nonlinear neuronal sources.

Significance: The proposed methods can be used for the study of interactions between neuronal sources.

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Keywords: MEG; Beamformer; Coherence; Mutual information; Phase synchronization; Nonlinear oscillators

1. Introduction

One of the most active areas of research in contemporary neuroscience deals with the issue of functional connectivity and neural integration. At the microscopic level progressively more evidence has accumulated for distributed and transient cell assembly coding (Engel and Singer, 2001; Roelfsema et al., 1997; Sakurai, 1996, 1998, 1999; Singer, 1999, 2001) with the possibility of partially overlapping cell assemblies contributing to different processes simultaneously at different frequencies (Sakurai, 1996, 1998, 1999) or even encoding information by manipulating the timing of their peak responses rather than the level of their mean activity (Engel and Singer, 2001; Roelfsema et al., 1997; Singer, 1999, 2001). In particular, the latter phenomenon was proposed as a universal binding mechanism applicable to all levels of description of cortical networks and is referred to as

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the synchronization hypothesis in the neurophysiological literature (Engel and Singer, 2001; Roelfsema et al., 1997; Singer, 1999, 2001; Varela et al., 2001; von Stein et al., 2000). At the macroscopic level of large-scale cortical networks, signals of interest such as the Electroencephalogram (EEG) and Magnetoencephalogram (MEG) are of an oscillatory nature and thus the phenomenon relevant to the coordination of the timing of the network’s responses is phase synchronization (Varela et al., 2001). Certainly, there is considerable experimental evidence in support of synchronization subserving large-scale integration in the form of transient and task-specific interactions between brain areas during various perceptual and cognitive tasks. This has been mostly demonstrated by coherence or phase synchrony analysis of scalp EEG recordings (Robinson et al., 1999; Saranthein et al., 1998; Tallon-Baudry and Bertrand, 1999, review in Varela et al., 2001). A second dynamical approach to functional connectivity (Friston, 2000b; Kelso, 1995) considers the changes in dynamic emergence and disruption of synchronous and asynchronous (Friston, 2000a) coupling between brain regions as the substrates of the neural code. In this model the brain evolves through a succession of global states determined by its coordination dynamics (Bressler and Kelso, 2001). From this perspective, the brain is in a metastable regime due to the interplay of forces mediating functional integration on one hand and functional segregation of inputs on the other (Bressler and Kelso, 2001; Friston, 2000b; Kelso, 1995), where abrupt state transitions seem to be functionally significant (Bressler and Kelso, 2001; Kelso, 1995; Friston, 1997, 2000c). In fact, such transient, mostly nonlinear, interdependencies between brain areas have been demonstrated only recently in scalp EEG (Breakspear and Terry, 2002a,b) and MEG sensor recordings (Stam et al., 2003). Interestingly, nonlinear interdependence was more pronounced in MEG sensor data as compared to EEG scalp recordings (Stam et al., 2003). Nevertheless, virtually all of the results at the macroscopic level described above were obtained by analysis of EEG/MEG sensor level data and therefore hindered by dispersion of the source signal in sensor space. This is particularly problematic when interdependencies are to be investigated (Lachaux et al., 1999; Nunez et al., 1997, 1999).

Ideally, in order to study neuronal interactions one has to go beyond the sensor level: first neuronal sources have to be identified and then their temporal activity has to be estimated before possible interdependencies can be investigated. In order to do this it is necessary to produce a solution to this inverse problem through the use of an appropriate assumption set. In this paper we use a variation of a nonlinear minimum variance beamformer (Robinson and Vrba, 1999) based on the assumption that no two distinct neuronal sources are perfectly linearly related (VanVeen et al., 1997). Throughout this paper the terms correlation and coherence will be used to denote such strictly linear relationships between time series.

It has recently been demonstrated that MEG beamformers identified frequency specific and spatially selective task related changes in neuronal spectral power, which were spatially coincident with BOLD (Blood Oxygen Level Dependent)-fMRI responses for the same task (Barnes et al., 2003; Singh et al., 2002). Similarly, Hall et al. (2005) have recently shown that beamformer estimates of human visual cortical gamma band activity concur spatially, temporally and functionally with local field potential recordings and BOLD-fMRI in the primate. This empirical evidence gives some initial confidence in the assumptions behind the beamformer. Most importantly, the temporal resolution of the MEG recordings is preserved in such reconstructions and the time series of specific regions of interest, usually referred to as ‘virtual electrodes’, can be examined. Since MEG beamformer techniques have been shown to provide reliable estimates both of the spatial location and the time courses of activity of neuronal sources, a natural question would be whether these methods are suitable for the study of neuronal interactions. A pioneering technique of imaging coherent brain sources using MEG beamformer methods was introduced recently (Gross et al., 2001). Nonetheless, there is a potential pitfall in this approach, namely that the MEG beamformer methodology is based on the underlying assumption that no distinct neuronal sources are perfectly linearly related (Robinson and Vrba, 1999; Sekihara et al., 2002; VanVeen et al., 1997). In fact, both deterioration of the ‘virtual electrode’ signal intensity and temporal distortion in the presence of high, long-lasting, source correlations have been reported in the literature (Sekihara et al., 2002). One mitigating factor is that we typically use beamformer analysis over relatively long time periods (s). From an information-theoretical point of view, such long-term cortico-cortical correlations are not efficient in the healthy brain (Friston, 2000a) because context-dependent information transfer is necessarily more transitory. Furthermore, empirical studies show that neuronal synchrony seems to be a very transient phenomenon (see Singer, 1999; Varela et al., 2001 for a review).

### Table 1

<table>
<thead>
<tr>
<th>Simulated cortical sources</th>
<th>Coordinates of simulated sources (mm)</th>
<th>Coordinates of estimated source location (mm) and associated peak T-values as in Eq. (2), calculated over a bandwidth of 0–80 Hz using the contrast time windows T_{active} (0.0–0.87 s) and T_{passive} (–0.5–0.0 s). Note the close correspondence between the coordinates of the simulated sources and the coordinates of the estimated source locations given the 5 mm grid.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Source 1</td>
<td>[2.5, 2]</td>
<td>[2.5, 2]</td>
</tr>
<tr>
<td>Source 2</td>
<td>[–1.8,4,3,0.34]</td>
<td>[–2.4,5,0.5]</td>
</tr>
</tbody>
</table>

T denotes the pseudo-t-values as in Eq. (2), calculated over a bandwidth of 0–80 Hz using the contrast time windows T_{active} (0.0–0.87 s) and T_{passive} (–0.5–0.0 s). Note the close correspondence between the coordinates of the simulated sources and the coordinates of the estimated source locations given the 5 mm grid.

1 Commonly referred to as phase transitions in dynamical systems theory.
In Section 1 of this paper we describe a simulation study and examine the effects of transient source correlation on the spatial and temporal performance of the MEG beamformer. In Section 2 we show that for a typical time window of beamformer analysis the interdependencies of the simulated sources are preserved. In Section 3 we simulate two interacting nonlinear oscillating systems representing neuronal sources and show that the MEG beamformer method in conjunction with a phase synchronization detection method based on Mutual Information are suitable for characterizing the phase interdependencies of these systems.

2. Methods

2.1. Simulation of transiently correlated sources

Two distant dipolar neuronal sources were simulated over 100 epochs (see Table 1 for coordinates). The time courses of the simulated dipoles consisted of uncorrelated (one predominantly at 20 Hz, the other at 40 Hz) and correlated signal segments (predominantly at 20 Hz, see Fig. 1, the top panel shows the two time courses superimposed). Both sources were of 2 nAm peak amplitude with additive Gaussian ($\sigma = 1$ nAm) white noise. The correlation coefficient between the two correlated signal segments was $r = 0.666 (P < 0.01, N = 687)$. 

Fig. 1. Parameterisation of transient source correlation: The time courses of the simulated sources consisted of a segment of white noise in both simulated dipoles (time: $-0.55 - 0.0$ s), then a segment of noisy different frequency oscillations (20 and 40 Hz dipole 1 and 2, respectively; time: $0.0 - 0.55$ s) and finally a segment of noisy 20 Hz oscillations in both dipoles (time: $0.55 - 1.1$ s). The progressive shift of the covariance time window by 10% of its length across the data allowed for a parameterisation of the relative duration of the correlated source activity with respect to the length of the covariance time window. The bottom two panels show the time courses of the two simulated sources and the top panel shows their superimposed time courses.

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Fig. 2. Localization of the transiently correlated sources by the beamformer. The beamformer was formulated over a covariance time window that contained transient correlated source activity over 23% of the total duration. The image shows the SPM of the pseudo-t measure as in Eq. (2) over a bandwidth of 0–80 Hz using the contrast time windows $T_{active}$ (+0.0–0.87 s) and $T_{passive}$ (−0.5–−0.0 s), see Fig. 1.
Forward solutions of the induced magnetic field in the sensor space, the lead field, were calculated using a single sphere model (Sarvas, 1987) and 3rd order gradiometer configuration (151 channel OMEGA MEG system, CTF Systems Inc., Canada). Sensor white noise at 10fTesla/Hz over a 0–80 Hz bandwidth was added to the signals.

### 2.2. Adaptive beamformer techniques

Adaptive beamformer techniques are spatial filtering methods for localizing sources of brain electrical activity from EEG/MEG sensor recordings. As the details of these techniques are beyond the scope of this paper, we will only concentrate on some essential qualitative characteristics of the beamformer techniques. Detailed and formal descriptions of the method can be found in (Barnes and Hillebrand, 2003; Hillebrand et al., 2005; Robinson and Vrba, 1999; Sekihara et al., 2002; VanVeen et al., 1997) and experimental imaging applications in (Hillebrand et al., 2005; Singh et al., 2002, 2003). MEG data is collected over a number of epochs, each containing a stimulus or task window and a rest period. Some time and frequency range within each epoch is used to define a covariance time window \( T_{\text{cov}} \). The choice of covariance window ultimately determines the spatial filter properties of the beamformer (Barnes and Hillebrand, 2003). For each possible source a weight vector or spatial filter is calculated. The output of the beamformer techniques are beyond the scope of this paper, we will only concentrate on some essential qualitative characteristics of the beamformer techniques. Detailed and formal descriptions of the method can be found in (Barnes and Hillebrand, 2003). For each possible source a weight vector or spatial filter is calculated. The output of this spatial filter, when applied to the MEG data, gives an estimate of the electrical activity, \( \gamma(t) \), termed the virtual electrode output, given by

\[
\gamma(t) = (L_0^T C^{-1} L_0)^{-1} L_0^T C^{-1} m(t) = W_0^T m(t),
\]

where \( m(t) \) is a column vector of N MEG channels at a single time instant \( t \), \( W_0^T \) is a weight vector for the source \( \theta \), \( L_0 \) is the lead field vector for source \( \theta \) and \( C \) is the data covariance matrix computed over time window \( T_{\text{cov}} \).

A contrast window consisting of a pair of time (or time-frequency) segments, say \( T_{\text{active}} \) and \( T_{\text{passive}} \), can be defined, and for each voxel in a pre-defined source space, a statistical parameter can be computed from measures of spectral power change across all pairs of contrast windows. We used the standard pseudo-t measure from the CTF SAM software, given by

\[
T_\theta = \frac{p_{\text{active}}^\theta - p_{\text{passive}}^\theta}{\sqrt{\frac{1}{N_{\text{active}}} + \frac{1}{N_{\text{passive}}}}},
\]

where \( \theta \) is the lead field vector for source \( \theta \). Edges of the beamformer space, weighted sensitivity maps, were calculated using a single sphere model (Sarvas, 1987) and 3rd order gradiometer configuration (151 channel OMEGA MEG system, CTF Systems Inc., Canada). Sensor white noise at 10fTesla/Hz over a 0–80 Hz bandwidth was added to the signals.

A volumetric Statistical Parametric Map (SPM) can subsequently be obtained by estimating this index of change in neuronal activity (Eq. 2) for each voxel in the source space sequentially (using a grid of 5 mm in this study).

The sources were first spatially localized by the beamformer formulation using an approximately 1.4 s long covariance time window, which in this case contained transient correlated source activity amounting up to 23% of its total length. The following contrast time windows were used for the localization of the sources (see Fig. 1): \( T_{\text{active}} \) (0.0–0.87 s) and \( T_{\text{passive}} \) (0.5–0.0 s). The spatial location of the two sources was estimated from the two largest peak values of the SPM in the 0–80 Hz-frequency range (see Fig. 2 and Table 1).

Since the covariance window completely determines the spatial filter (Eq. (1)), an easy way to parameterize the effect of transiently correlated source activity is to introduce a segment of bivariate data containing correlated source activity and then just move the covariance window across the data allowing for increasingly longer correlated segments. The next step was therefore, to estimate the time series of electrical activity in the two voxels while varying the relative duration of correlated source activity with respect to the total duration of the covariance time window \( T_{\text{cov}} \). For this purpose the beamformer was formulated over a 0.6 s long moving covariance time window. \( T_{\text{cov}} \) was progressively shifted by 10% of its length across the data towards the segment containing correlated source activity and thus allowed for a parameterisation of correlated source activity with respect to the duration of the covariance time window (see Fig. 1).

Note that each of the covariance time windows represents a new beamformer spatial filter because a new set of beamformer weights is determined. The time series of the two voxels at the same location was then computed for each new set of weights.

### 2.3. Measures of temporal performance of the beamformer

Two summary measures were computed for the quantification of the beamformer estimates as a function of the relative duration of correlated source activity:

1. A reliability measure corresponding simply to the mean correlation coefficient between the simulated time series and its beamformer estimate (the virtual electrode time series) across 100 epochs.

\[
r = \frac{1}{N_{\text{epochs}}} \sum_{j=1}^{N_{\text{epochs}}} \left( \frac{p \sum_{i=1}^{p} \hat{e}_{ij} \hat{s}_{ij} - \sum_{i=1}^{p} \hat{e}_{ij} \sum_{i=1}^{p} \hat{s}_{ij}}{\sqrt{\left[ p \sum_{i=1}^{p} (\hat{e}_{ij})^2 \right]^2 \left[ p \sum_{i=1}^{p} (\hat{s}_{ij})^2 \right]^2}} \right)
\]

where \( \hat{e}_{ij} \) is an index for data points, \( i=1\ldots p, p \) the total number of data points in each epoch of data, \( j \) is an index for epochs of data, \( j=1\ldots N_{\text{epochs}}, \) and \( N_{\text{epochs}} \) is the total number of epochs of the dataset,
sim_{ij}\) is the simulated time series and \(\text{est}_{ij}\) is the estimated time series of the virtual electrode. Here \(\text{est}_{ij}\) is given by the virtual electrode output at the SPM maximum (see Eq. (1)).

2. A pointwise relative error measure between the simulated time series and its beamformer estimate. We used the relative difference measure (RDM- see Meijs et al., 1989).

\[
\text{RDM} = \frac{1}{N_{epochs}} \sum_{j=1}^{N_{epochs}} \frac{\sqrt{\sum_{i=1}^{p}(\text{est}_{ij} - \text{sim}_{ij})^2}}{\sqrt{\sum_{i=1}^{p}(\text{sim}_{ij})^2}}
\]

(4)

The symbols and indices are the same as in Eq. (3). The mean correlation coefficient and the RDM were computed separately for each source.

Because the SAM software used here does not supply orientation values for the reconstructed sources, a 180-degree phase ambiguity may exist especially when comparing multiple beamformer runs. As a consequence, the beamformer may ‘flip’ its sign from one run to the next. In order to avoid this problem, we calculated the correlation coefficient between the simulated data and the reconstructed virtual electrode time series for each beamformer run and in case of a negative coefficient, thus when the beamformer had indeed flipped its orientation by 180 degrees, we ‘flipped’ back the virtual electrode time series by multiplying it by \(-1\). This ensured that the virtual electrode data and simulated data were ‘in phase’ as opposed to ‘antiphase’ and thus enabled us to compute (pointwise) errors for the temporal performance of the beamformer and compare them across beamformer runs.

2.4. Reconstruction accuracy of source interactions

When the reconstruction of the time series of true sources is imperfect, this can have a larger, supralinear, effect on measures of source interactions, since these measures are based on a pair of such reconstructed time series. Since the temporal performance of the beamformer is likely to deteriorate in the presence of long-lasting correlations, it would be useful to know the degree of deterioration in measures of signal interdependency as a function of the relative duration of correlated source activity. In order to parameterize this effect, relative difference measures (RDM_interaction, see below), were computed for 3 relevant measures of signal interdependency for beamformer reconstructions corresponding to different durations of source correlations. Details of the measures of signal interdependency (i.e. coherence and synchronization indices) employed are provided in the following section; however, the RDM measures for the interactions were generally defined as follows

\[
\text{RDM}_\text{interaction} = \frac{1}{N_{epochs}} \sum_{j=1}^{N_{epochs}} \frac{\sqrt{\text{Mreconstr}_{ij} - \text{Mtrue}_{ij})^2}}{\sqrt{\text{Mtrue}_{ij})^2}}
\]

(5)

with \(j\) and \(N_{epochs}\) defined as above, \(\text{Mtrue}_{ij}\) is the true measure of signal interdependency (as calculated between the simulated signals) and \(\text{Mreconstr}_{ij}\) is the reconstructed measure of signal interdependency (as calculated for the virtual electrode outputs of the beamformer). We used 3 signal interdependency measures here, the coherence function, defined as the average value over a broad frequency band (0–80 Hz), the synchronization index at 20 Hz (based on narrow band filtered data, here a 10 Hz wide bandpass filter centred at 20 Hz was used) and the synchronization index between source1 and 2 at 20 and 40 Hz, respectively (the data was bandpass filtered using a 10 Hz wide filter centred at 20 and 40 Hz, respectively).

2.5. Measures of signal interdependency

All of the following measures discussed were applied to the virtual electrode time series.

2.5.1. Coherence estimation

Coherence as a function of frequency \((\tilde{\gamma}^2_{a,b}(f))\) is estimated as the magnitude-squared cross spectrum divided by the power spectra of both time series, that is

\[
\tilde{\gamma}^2_{a,b}(f) = \frac{|\tilde{G}_{a,b}(f)|^2}{\tilde{G}_a(f)\tilde{G}_b(f)}
\]

(6)

where \(\tilde{G}_{a,b}(f)\) is the cross-spectral density functions of time series recorded in virtual electrodes a and b and \(\tilde{G}_a(f), \tilde{G}_b(f)\) are the auto spectra of the time series in virtual electrodes a and b, respectively.

Coherence is an indirect measure of phase concentration: it evaluates the strictly linear relationships between a pair of signals at a given frequency. If coherence \(\sim 1\) this indicates a perfect linear relationship, if coherence \(\sim 0\), then no linear relationship can be assumed for the signals in question.

2.5.2. Phase synchronization analysis

This section comprises a brief review of the broader topic of phase synchrony. Recently two methods for detection of phase synchrony in brain signals were proposed independently (Lachaux et al., 1999; Tass et al., 1998, for a comparison see Van Quyen et al., 2001). The first one is based on convolution with Morlet wavelets, whereas the second one involves narrow band filtering and utilizes the analytic signal concept (Gabor, 1946) and thus the Hilbert transform, in order to obtain uniquely defined estimates of the instantaneous phase and instantaneous
amplitude. In Tass et al., 1998, the variable of interest is the univariate instantaneous phase difference of paired signals and a synchronization index (SI) is proposed on the basis of either Shannon Entropy or conditional probability. In this study we adopted a very similar approach but we treated the bivariate instantaneous cyclic phases (the instantaneous phases of the signals were wrapped in the interval [0 2π], that is φ_k mod 2π and φ_l mod 2π) of paired signals as the variables of interest and calculated a phase synchrony index based on Mutual Information (MI). A similar method was proposed for detecting phase locking from experimental data but it was not applied specifically to brain signals (Palus, 1997).

The Shannon Entropy of a given univariate probability of a distribution of the phase angle in a given time series can be easily estimated using histogram based methods (Van Quyen et al., 2001) according to:

\[ H(φ_k) = - \sum_{k=1}^{N_{bims}} p(φ_k) \ln p(φ_k) \] (7)

where \( N_{bims} \) is the number of bins in the histogram and \( p(φ_k) \) is the relative frequency of the phase in the \( k \)th bin. The number of bins was determined as the cubic root of the number of data points in the distribution. The binned distribution was then evenly spaced between its maximum and minimum.

The joint entropy can be estimated analogously as

\[ H(φ_k, φ_l) = - \sum_{k=1}^{N_{bims}} \sum_{l=1}^{M_{bims}} p(φ_k, φ_l) \ln p(φ_k, φ_l) \] (8)

where \( N_{bims} = M_{bims} \) are the number of bins in the univariate phase distributions \( φ_k, φ_l \), respectively, and \( P(φ_k, φ_l) \) is the relative joint frequency of finding the phase \( φ_k \) and phase \( φ_l \) in the \( k \)th and \( l \)th bin, respectively.

Mutual information (MI) between the instantaneous phases of two signals is then:

\[ MI(φ_k, φ_l) = H(φ_k) + H(φ_l) - H(φ_k, φ_l) \] (9)

We used a histogram-based method to assess Mutual Information. With this method the maximal MI is a function of the number of chosen histogram bins. The MI measures we present here have been normalized by the maximal possible MI.

Explicitly

\[ SI = \frac{MI}{MI_{max}}, \quad SI \in [0, 1] \] (10)

where \( MI \) is the observed Mutual Information and \( MI_{max} = \ln(N_{bims}) \).

In this way we obtain a synchronization index, SI, between 0 and 1, where SI = 0 represents no synchronization and SI = 1 represents perfect synchronization.

An important feature of the synchronization index based on MI is that it can identify interdependence between phase at different frequencies and thus \( n:m \) phase locking\(^2\) according to

\[ |nφ_k - mφ_l| \leq c \] (11)

where \( φ_k, φ_l \) are the instantaneous phases of the two frequency signals, \( c \) is a constant and \( n, m \) are integers defining the frequency ratio of the signals. If the analysis is done across the entire combination space in terms of all possible cross frequency interactions, \( n \) and \( m \) can be explicitly set to the mean frequency of the frequency range on which the analysis is being conducted. Explicitly, if two signals of interest are narrow band filtered at two different frequency ranges, say range_1 = \( f_1 \) to \( f_2 \) for signal 1 and range_2 = \( f_3 \) to \( f_4 \) for signal 2 and \( φ_k \) and \( φ_l \) are the instantaneous phases of the narrow band filtered signals 1 and 2, respectively, then Eq. (11) can be used in the following way:

\[ \left| \frac{f_3 + f_4}{2} φ_k - \frac{f_1 + f_2}{2} φ_l \right| \leq c \] (12)

That is, \( n = (f_3 + f_4)/2 \) and \( m = (f_1 + f_2)/2 \).

The products \( nφ_k \) and \( mφ_l \) are then substituted in place of the instantaneous phase angle values \( φ_k \) and \( φ_l \) in Eqs. (7)–(10) and then the cross frequency, high-order synchronization index SI is computed for every possible frequency combination.

2.5.3. Assessment of event-related changes in measures of signal interdependency

In most experimental cases it is useful to assess an (event-related) modulation in some signal quantity during the experimental condition (‘active state’) with respect to some baseline (‘passive state’) rather than just the raw values. Although the distinction between ‘active’ and ‘passive’ states is clearly an oversimplification, since there are no true ‘passive’ brain states, we used this distinction for simplicity, while we would practically expand this terminology to denote a more general distinction between different brain states, defined as states that are subject to differential experimental manipulation. In our study the white noise signals segment was chosen as baseline. The epoch-wise differences of ‘active state’ and ‘passive state’ in coherence and in the phase synchronization index based on MI described above were then subjected to non-parametric permutation testing, implicit in which was a correction for multiple comparisons. The ‘event-related’ differences were then thresholded at a given significance level (in this paper alpha = 0.01 unless otherwise stated) and only significant results are displayed.

2.5.4. Simulation of interacting nonlinear oscillators

Phase synchronization is essentially a nonlinear phenomenon defined as the adjustment of the rhythms of two or
more self-sustained oscillating systems due to weak interaction (Pikovsky et al., 2001). Self-sustained oscillators are systems that have their own independent and autonomous oscillatory activity. In other words, in order to study synchronization, one has to measure systems whose parameters and nature of coupling are known. We accomplish this by simulating two coupled Rössler systems (identical to those in Tass et al., 1998) as active neuronal sources at distinct locations using the same spatial coordinates as in the simulation study above. The main point in this particular part of the study implementing the Rössler oscillators as neuronal sources was not to parameterize the effect of the correlation between them, but test if interactions between nonlinear systems could be identified under realistic measurement conditions.

The Rössler systems are defined by a system of 6 ordinary differential equations:

\[
\begin{align*}
\dot{x}_{1,2} &= -\omega_1 \psi_{1,2} - z_{1,2} + \xi_{1,2} + \varepsilon(x_{2,1} - x_{1,2}), \\
\dot{\psi}_{1,2} &= \omega_2 x_{1,2} + 0.15 \psi_{1,2}, \\
\dot{z}_{1,2} &= 0.2 + z_{1,2}(x_{1,2} - 10)
\end{align*}
\]

where the parameters \(\omega_1 = 1.015\), \(\omega_2 = 0.7\), \(\omega_1\) represent the natural frequencies of the two systems and govern their initial frequency mismatch \((\delta\omega = |\omega_1 - \omega_2|)\); \(\varepsilon\) is the parameter governing the coupling strength of the two systems and \(\xi_{1,2}\) are two Gaussian delta correlated noise processes.

The integration of the above systems was realized in MATLAB using the Runge-Kutta technique. The step of integration was set to \(2\pi/1000\). We varied the coupling strength \(\varepsilon\) and obtained phase synchronization indices based on MI for two levels of coupling, namely \(\varepsilon = 0.0\) or ‘no coupling’ corresponding to autonomous oscillation and \(\varepsilon = 0.17\) or ‘moderate coupling’. From a dynamical systems point of view, this constellation corresponds to a linear, symmetrical, bi-directional coupling of two non-identical nonlinear systems.

The solutions of the \(x_{1,2}\) oscillatory variables of the Rössler systems were then resampled at 1250 Hz for a total duration of 1 s and their forward solutions were computed over 100 epochs. Sensor white noise at 10 Tesla/Hz over a 0–80 Hz bandwidth was added to the signals. Subsequently we applied the same methods described above in order to obtain the beamformer reconstruction of the spatial location and the time series of the Rössler systems.

Additionally, in order to study the spectral and temporal dynamics of the Rössler systems as reconstructed in the virtual electrode time series, multiresolution time-frequency analysis was performed using Morlet wavelets. Then the average spectral power across epochs was plotted for both virtual electrode time series.

Although the Rössler systems do not directly relate to ‘brain-like’ models, we chose to implement them because they possess the essential and universal features and mechanisms of coordination of oscillatory behavior (Pikovsky et al., 2001). Two of the basic features shared by interacting Rössler systems and interacting neuronal networks are that both show nonlinear and nonstationary oscillatory time courses and their interactions near equilibrium (after initial transients have died off) are specified by a two-opponent gradient interplay. Specifically, both neural and abstract (model) oscillators express characteristic frequencies forcing them to autonomous oscillation on one hand and bi-directional coupling of their instantaneous activities obliging them to cooperation and integration on the other.

3. Results

3.1. Spatiotemporal performance of the beamformer in the presence of correlated source activity

The results of the simulation of transiently correlated sources are summarized in Table 1 and Figs. 2 and 3. Fig. 2 shows the results of the spatial localization of the sources and coordinates are given in Table 1. As is evident, although the sources were highly correlated over 23% of the duration of the covariance window, the localization errors are negligible (given the 5 mm grid spacing). Fig. 3 shows a qualitative description of the temporal performance of the beamformer in the presence of correlated source activity. Examples of the reconstructed time series, the ‘virtual electrode’ (shown in blue) are plotted together with normalised source strength.
the simulated time series (shown in red) for low, medium and very high correlation levels (from top to bottom). It is evident that the beamformer can tolerate duration of transient correlations as high as 30% of the covariance window over 100 epochs. Nevertheless the effects of temporal distortion demonstrated for long-term, high correlations in Sekihara et al., 2002 are also evident in the bottom panel. At high durations of source correlation, here 90% of the covariance time window, the temporal resolution of the beamformer deteriorates and the reconstructed source intensity is clearly reduced. These results are quantified in Figs. 4 and 5 by means of reliability and relative error plots. In Fig. 4 the reliability measure of the temporal performance of the beamformer is displayed. It is quite evident that the reliability of the beamformer estimates, that is the correlation between simulated data and the beamformer estimates, drops monotonically with the relative duration of the source correlation with respect to the covariance window but it is nevertheless quite reasonable for beamformer formulations including less than 40% correlated activity in the covariance window. Fig. 5 shows the Relative Difference Measure (RDM) as a function of relative duration of the source correlation. This plot is consistent with the reliability plot since for durations of source correlations higher than 40% of the covariance window, there is a steep increase of the RDM.

3.2. Reconstruction accuracy of simulated source interactions

Fig. 6 demonstrates the results of the relative different measures of the interaction metrics, that is the interaction

Fig. 4. Reliability measure (see Section 2, Eq. (3)) of the beamformer as a function of the relative duration of correlated source activity with respect to the length of the covariance time window and the mean correlation coefficient between the simulated sources (the mean is taken across 100 epochs). Note the monotonic decrease of the reliability measure with increasing durations of correlated source activity. The reliability measure is nevertheless reasonable for beamformer formulations including less than 40% correlated activity in the covariance window.

Fig. 5. Relative Difference Measure (see Section 2- RDM, Eq. (4)) as a function of the relative duration of transient source correlation with respect to the total duration of the covariance time window and the mean correlation coefficient between the simulated sources. Note the monotonic increase of the RDM measure with increasing durations of correlated source activity. The RDM measure is relatively low for beamformer formulations including less than 40% correlated activity in the covariance window.

errors, as a function of the relative duration of source correlation. Essentially two of the 3 measures, the relative difference measures for coherence and the synchronization index at 20 and 40 Hz (see methods) show similar behaviour, they increase almost monotonically with
increasing durations of source correlation. Source correlations that extend over 40% of the time window of beamformer analysis are associated with higher errors in the measures of source interactions. However the errors are relatively small for shorter durations of source correlation. The error measure for the synchronization index (SI) at 20 Hz is originally high, it decreases for moderate durations of source correlations and then increases again for longer durations. The initial high values are possibly due to the fact that the sources are not synchronized at 20 Hz to begin with, so the absolute values of the SI are very small. Hence small errors in the reconstructed time series will cause large errors in the SI. Eventually, as larger portions of the signal become synchronized the error seems to be reasonably sized and then with increasing source correlation the errors are similar to the 20 and 40 Hz case.

3.3. Reconstruction of signal interdependencies by the beamformer

Since both the spatial localization and the temporal reconstruction of the simulated sources were very good for moderate durations of transient source correlation the next step is to explicitly raise the question whether source interdependencies are preserved in the beamformer estimates. For this purpose the beamformer was formulated over a time window, which contained a transient source correlation for 20% of the covariance time window. The time series of the sources were reconstructed and then coherence and phase analysis was performed on the particular segment of data containing correlated, noisy 20 Hz oscillations. The coherence analysis quantifies the increase of the linear relationship between the two simulated sources at 20 Hz. The phase synchrony analysis also correctly identifies the increase of the 1:1 phase interdependence between the two sources.

3.4. Reconstruction of interacting Rössler systems and their interdependence

Fig. 9 illustrates the results for the simulation of two Rössler systems serving as neuronal sources. For clarity of illustration of the effects of coupling on the amplitudes and phases of the Rössler systems, the original time series (the direct solutions of the integration) are shown here and not the reconstructed virtual electrode time series. Essentially, the reconstructed time series exhibit the same spectral and phase changes in the transition from ‘no-coupling’ to the ‘moderate-coupling’ as the original solutions except for the presence of additional strong simulated white noise that was projected from the sensors. Nonetheless the time-frequency and phase analysis described below concerns the reconstructed virtual electrode time series.

Fig. 8 shows the results of phase synchrony analysis for a segment of simulated data that contains 20 and 40 Hz oscillations in source 1 and 2, respectively (Fig. 1, time: 0.0–0.55 s) with respect to white noise data serving as a baseline (Fig. 1, time: −0.5–0.0 s). Since the simulated sources are periodic and stationary, a 1:2 stable relationship exists between their phases. The analysis of the virtual electrode time series accurately reconstructs this relationship suggesting that nonlinear high order phase interdependencies can be detected in the estimated time series.
and thus no coupling between the systems and 0.0–0.5 s corresponds to moderate coupling between the systems. Note the marked overall decrease in power in the coupled case with respect to the autonomous case. In the case of moderate coupling between the systems the only noticeable spectral peak lies at approximately 30–32 Hz in both systems and corresponds to a ‘compromise’ frequency lying somewhere in between the frequencies of the two systems in the autonomous case.

Fig. 9C shows the results of the phase synchrony analysis of the two virtual electrode time series corresponding to the two Rössler systems. The ‘no coupling’ time during which the systems oscillate autonomously (−0.5–0.0 s) served as baseline. The phase synchrony index increases significantly between the two systems at 28–35 Hz in the coupled case indicating phase and frequency locking of the two systems at these frequencies. Additionally the phase synchrony index decreases between the 30–35 Hz oscillations in the first virtual electrode and the 25–30 Hz oscillations in the second virtual electrode, which corresponds to the main frequencies of oscillation in the uncoupled case as evident in Fig. 9B. These results portray the transition to synchronization in the form of adjustment of both the phases and the frequencies of the coupled systems. The transition to synchronization in this case is not smooth as it is reflected in the concurrent considerable spectral power drop observed in the time frequency plots. Coupling of the systems forces them to adjustment of their rhythms. However, due to the great initial frequency
detuning of the two systems this ultimately leads to an additional dissipation of energy. This spectral power drop bears striking phenomenological resemblance to an event related decrease in the spectral power of ongoing brain rhythms as recorded by EEG/MEG, known as ERD (Event Related Desynchronization, Pfurtscheller and Lopes da Silva, 1999).

4. Discussion

In this paper we have shown that MEG beamformers can accurately reconstruct the spatial location and the time series of simulated neuronal sources that exhibited a transient correlation. In our simulation study the reconstruction of the time series was not affected if the duration of the transient correlation in source activity did not exceed 30–40 percent of the total duration of the covariance time window, that is the period over which the beamformer weights are computed. At longer durations, effects of temporal distortion and signal cancellation were observed, a finding which is consistent with previous literature (Gross et al., 2001; Sekihara et al., 2002; VanVeen et al., 1997). This would suggest that if the beamformer is formulated using covariance time windows that are long relative to the duration of any transient linear phase synchrony index decreases between the 30–35 Hz oscillations in the first virtual electrode and the 25–30 Hz oscillations in the second virtual electrode, which correspond to the main frequency of oscillation in the uncoupled case as evident in the spectrograms. These results portray the transition to synchronization in the form of adjustment of both the phases and the frequencies of the coupled systems.
(and zero phase lagged) interactions, it could provide us with accurate estimates of both the spatial and temporal aspects of neuronal source activity. The trade off is that the longer the covariance window, the smaller the portion of stimulus related activity relative to baseline state, and hence a decrease in overall SNR resulting in a loss of spatial resolution (Gross et al., 2001; VanVeen et al., 1997).

In our simulations we have shown that even source coherence, corresponding to correlation in the frequency domain, is preserved and can be assessed using the beamformer methodology. In addition, a method for detecting phase synchronization in the time series of neuronal sources was introduced. The method is based on Mutual Information and is a modification of previously proposed methods (Pikovsky et al., 2000; Tass et al., 1998; Van Quyen et al., 2001). It allows for detecting and quantifying both simple and high order n:m phase locking and returns a synchronization index that can be assessed statistically by non-parametric permutation testing. Using the beamformer methods in conjunction with this approach, both frequency and high order $n:m$ phase locking between simulated periodic, oscillatory sources could be correctly quantified. Our approach to the detection of phase synchronization of neuronal sources is comparable to a method proposed recently in Tass et al., 2003. The main difference of the two methods lies in the algorithm for the reconstruction of neuronal sources from MEG sensor data: our approach is based on adaptive beamformer techniques, whereas in Tass et al., 2003, Magnetic Field Topography (Ioannides et al., 1990) is utilized for the estimation of cerebral current source density from sensor data.

Current thinking in theoretical neuroscience considers brain function to be the product of a large assembly of coupled nonlinear dynamical subcomponents exhibiting transient and inherently metastable dynamics (Bressler and Kelso, 2001; Friston, 1997, 2000a–c; Kelso, 1995). Recent fascinating developments in nonlinear science have provided a more specific framework for understanding coordination phenomena and especially synchronization in weakly coupled nonlinear oscillating systems (Pikovsky et al., 1999, 2000, 2001; Rosenblum et al., 1996), stressing the significance along with the universality and scale invariance of phase synchronization in the coordination of oscillatory activity. As a first step towards investigating coordination phenomena of brain sources, in this study we simulated two coupled nonlinear Rössler oscillators, reconstructed their activity using beamformer methods and looked at their phase interdependencies. By doing so we wanted to test whether the interactions of such nonlinear systems serving as neuronal sources can be detected by the beamformer methods in conjunction with the phase synchronization analysis described above. The prediction was that by increasing the coupling of the systems, phase synchronization\(^3\) would occur, which would result in an increase of the MI based synchronization index. By introducing a large initial frequency mismatch between the systems, and thus making the synchronization transition less smooth (Pikovsky et al., 2001), we were aiming to imitate conditions that are more likely to occur in real mesoscopic and macroscopic cortical network interactions. Macroscopic cortical networks can oscillate at quite distinct frequencies (Pfurtscheller and Lopes da Silva, 1999) and might even exhibit nonlinear high-order, cross-frequency ($n:m$) synchronization (Schack et al., 2002). Another important prediction was that although the phases of the two systems may be bounded and interdependent, the amplitudes might still be chaotic in time and not strongly interdependent, especially since the systems were expected to undergo a ‘rough’ synchronization transition. In our simulation study, with just two coupled nonlinear oscillating brain sources, we replicated these predictions for phase synchronization of chaotic oscillators reported previously in a totally different context (Pikovsky et al., 1999, 2000, 2001; Rosenblum et al., 1996). These interactions of nonlinear oscillating systems could be identified by a combination of the beamformer methods and our phase synchrony analysis based on Mutual Information.

Recently, it has become increasingly clear that phase synchronization is not by far the only relevant or quantifiable nonlinear coordination phenomenon in the brain. One major conceptual problem is that phase synchronization is a phenomenon which can be observed between so called ‘phase coherent’ oscillators, that is oscillators that exhibit more or less a singular approximate periodicity, so that phase can be clearly defined (Boccaletti et al., 2002). The Rössler attractors display such a phase coherent behavior but this not typical for healthy brain signals, which tend to exhibit multiple and sometimes interrelated periodicities. The phase synchronization approach is strictly speaking only valid if applied to narrow-band filtered signals, which in the optimal case will be centered on one of the present system periodicities. Of course several problems arise, which are related to the choice of filtering parameters and the possibility of partial destruction of otherwise present nonlinear structure, which might involve more than one periodicity. Several authors have stressed the importance of generalized synchronization (first described by Rulkov et al., 1995) as a putative mode of interaction in the brain and

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\(^3\) Phase synchronization in chaotic systems: The phases of the systems are bounded for some region of the system parameters and strongly interdependent, whereas the amplitudes may remain chaotic in time and independent. Complete Synchronization in chaotic systems: both phase and amplitudes are bounded and the systems follow an identical trajectory in state space. For an exhaustive discussion see Pikovsky et al., 1999; Pikovsky et al., 2001.
have proposed methods for quantification of this phenomenon (Breakspear and Terry, 2002b; David et al., 2004; Quian Quiroga et al., 2002; Stam and van Dijk, 2002; Stam et al., 2003). Generalized synchronization refers to a more general class of nonlinear interdependence between dynamical systems, in which trajectories in one system can be directly mapped to a second system by means of a deterministic functional relationship. Various methods have been developed to quantify this phenomenon; most of them involve time-delay embedding algorithms with the reconstruction of a multidimensional state space. The majority of these methods take advantage of the fact that the local structure, the relationships between neighboring data points in state space, will be functionally related in two interacting systems, if such a direct mapping function exists. The main benefit of these methods over the ones quantifying phase synchronization is a conceptual one. These methods do not require an arbitrary partitioning of the signal in to frequency bands and can therefore quantify a broader range of coordination phenomena, especially metastable and nonstatic nonlinear phenomena, which cannot be captured by phase synchronization based metrics. These phenomena arise through transient and weak coupling and seem to be very important from a theoretical point of view (Friston, 1997, 2000c). In fact, a study testing the performance of several interdependence measures, found generalized synchronization metrics to be more sensitive than phase synchronization metrics, especially when the coupling was weak (David et al., 2004). Nevertheless both kinds of metrics seem to be qualitatively equivalent in realistic measurement conditions (Quian Quiroga et al., 2002) and seem to be comparable in terms of their ability to capture nonlinear components in a certain interaction (David et al., 2004).

The disadvantages of the generalized synchronization based methods is that they require long computation times, they are sensitive to noise and to nonstationarity of the data, they involve several parameters for the time-delay reconstruction and most importantly, their computation requires a large number of data samples which limits their effective temporal resolution. Methods quantifying phase synchronization on the contrary can potentially offer very good temporal resolution, which can be of great importance considering the transient nature of real brain interactions.

In summary, we have presented a general framework for the identification of macroscopic interactions across active brain regions. MEG beamformer methods in conjunction with phase synchronization analysis based on Mutual Information provide accurate spatial and temporal descriptions of the simulated interactions between linear and nonlinear neuronal sources. The practical utility of these methods will be established through applications to experimental neuroimaging data.

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