Time delay and partial coherence analyses to identify cortical connectivities

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Abstract Recently it has been demonstrated by Albo that partial coherence analysis is sensitive to signal to noise ratio (SNR) and that it will always identify the signal with the highest SNR among the three signals as the main (driving) influence. We propose to use time delay analysis in parallel to partial coherence analysis to identify the connectivities between the multivariate time series. Both are applied to a theoretical model (used by Albo) to analyse the connections introduced in the model. Time delay analysis identifies the connections correctly. We also apply these analyses to the electroencephalogram (EEG) and electromyogram (EMG) of essential tremor patients and EEG of normal subjects while bimanually tapping their index fingers. Biologically plausible cortico-muscular and cortico-cortical connections are identified by these methods.

1 Introduction

Coherence measures the degree of linear association (in frequency domain) between the two signals (Amjad et al. 1997; Halliday et al. 1995). The common influence of the third signal on the correlation between two signals is addressed by partial coherence analysis (Lopes et al. 1980; Turbes and Schneider 1989; Halliday et al. 1995; Sherman et al. 1997; Mima et al. 2000a; Timmermann et al. 2003; Kubota et al. 2003; Raethjen et al. 2004). Understanding the role of more than one signal in the correlation between two signals has led to the graphical model (Dahlhaus 2000; Rosenberg et al. 1998). If the partial coherence between two signals is zero (is below the pre-defined confidence limit), it is usually concluded that the presumed signal whose contributions are removed by partial coherence, is responsible for the correlations (coherence) between the two signals. Alternatively, the conclusion that the presumed signal has caused the other two signals has been drawn (Gersch and Goddard 1970). This idea has been used by Gersch to identify the source of the epileptic foci (Gersch and Goddard 1970). But the concept of attributing the causal (driver) nature to a signal when it abolishes the coherence between the two signals upon partial coherence analysis, is questioned in the recent past (Albo et al. 2004). It has been demonstrated by (Albo et al. 2004) using an AR2 model as source signal and two of its time delayed versions as response signals that partial coherence analysis can yield spurious results. In this model, the source signal namely the AR2 process is contaminated with the highest amount of noise. In one of the time delayed versions of AR2, a slightly less amount of noise is added. Yet another time delayed version of AR2 is left out as noise free. This is labeled as Case I in (Albo et al. 2004). Upon partial coherence analysis, they found that the signal with the highest signal to noise ratio (SNR) which, in their case, is the last version stated above, was incorrectly identified as driver signal. They provide further evidences for skepticism of partial coherence technique by analysing the neuronal data (theta rhythms) recorded from different centers of the limbic system of the rat. At the end they propose to use Granger causality analysis (Bernasconi and König 1999; Liang et al. 1998; Baccala and Sameshima 2001; Kamiński et al. 2001) to identify the causal relation between the different neuronal signals.

From the above discussion it is clear that a zero value of partial coherence between three signals need not necessarily imply that the connection between the two signals are established only through the third signal. Even if the results of partial coherence are correct, from a zero value of partial coherence, one cannot understand the nature (direction) of interaction between the signals.
Time delay between the signals allows to identify the direction of the information flows. By analysing the time delay between the signals, we can verify the results of the partial coherence and also we can understand the nature of the interaction between the signals. Though from the delay analysis we can understand the nature of information flow, it will be difficult to judge whether or not the connection between two centers is direct or indirect. In the foregoing discussion we ascribe the direction of information flow between centers based on delay analysis and/or partial coherence analysis. In an ideal situation both analyses should yield the same results. Since the results of the partial coherence analysis are susceptible to SNR of the signals, in an experimental setting, it will be very difficult to rely on the results of one of the analyses alone. In this study we use delay analysis in parallel to the partial coherence analysis. In this study we only consider the correlations between three signals. In parallel we estimate the delay between the three distinguishable pairs. Based on the results of these analyses, we establish the connection and direction (from delay analysis) between the three signals considered. Many physiological questions are related only to processes happening in a particular frequency band and hence the natural selection will be frequency specific methods. We use the maximizing coherence method to identify the delay between the two signals at a given frequency (Carter 1987; Govindan et al. 2005; Raethjen et al. 2005). Due to the time delay between the two signals there will be (time) misalignment between them. Because of this misalignment the coherence estimated between the two signals will be slightly reduced. In order to compensate for this reduction in the coherence and thereby to estimate the time delay, we artificially shift the time series by a time lag. Coherence in a selected frequency band is estimated as a function of lag. Coherence will increase as a function of lag and reach a maximum value at the time lag equal to the time delay between the two signals.

First, we perform time delay and partial coherence analyses for the model used in (Albo et al. 2004) to identify the connections (used) between the different variables of the model. We find that the time delay analysis unambiguously identifies the direction of interaction between different variables of the model. Using these techniques we analyse the electroencephalogram (EEG) and electromyogram (EMG) of essential tremor (ET) patients, to understand the direction of interaction between different variables of the model. Using these techniques we analyse the electroencephalogram (EEG) and electromyogram (EMG) of essential tremor (ET) patients. To understand the flow of the movement related information. In one of these examples (all cortical areas show comparable SNR), both analyses yield conforming results while in the other example again the results of delay analysis differ from the partial coherence analysis.

2 Materials and Methods

2.1 Data acquisition

Details of spectral analysis of ET can be found in (Raethjen et al. 2005). This study was approved by the local ethics committee and all the subjects gave informed consent. In a dimly lit room, subjects are asked to sit on a comfortable chair in a slightly supine position with both hands held against gravity (for normal subjects the hands are kept in a comfortable position to execute rhythmic bimanual movement of the index fingers) while the forearms are supported. EEG is recorded with 64-channel EEG system (Neuroscan) with standard electrode position (Klem et al. 1999). Surface EMG is recorded bipolarly from EMG electrodes attached to wrist extensors and flexors of both arms. In the case of normal subjects during the bimanual finger tapping the EMG electrodes are positioned on the index extensors and flexors muscles of the forearm. EEG and EMG data are sampled at a rate of 1000 Hz. EEG and EMG are band pass filtered on line between 0.01 to 200 Hz and 30-200 Hz, respectively. Data are stored in a computer and are analysed offline. Each recording lasted for 1-4 minutes. Artefacts like eye blinks, base-line shift, etc., are discarded by visual inspection. Further, EMG signals are full wave rectified (magnitude of the deviations from mean value) and EEG is made reference free by constructing second (spatial) derivative, Laplacian (Hjorth 1991; Hjorth 1975).

2.2 Methods

Let \(x(t), y(t)\) and \(z(t)\) be the three simultaneously measured signals of length \(N\). Let the sampling frequency be \(s\) Hz. Following (Halliday et al. 1995), we calculate coherence and partial coherence as follows: We divide the signals in to \(M\) disjoint time segments of length \(L\), such that \(N = LM\). We calculate, power spectra \(S_{xx}, S_{yy}, S_{zz}\) and cross-spectra \(S_{xy}, S_{xz}, S_{yz}\) in each of the disjoint windows. Finally, we average these quantities across all the segments to get the estimate of the same. We estimate coherence between the signals \(x(t)\) and \(y(t)\) as follows:

\[
C_{xy}(\omega) = \frac{|S_{xy}(\omega)|^2}{S_{xx}(\omega)S_{yy}(\omega)}
\]

Similarly, we estimate the partial coherence between the three signals \(x(t), y(t)\) and \(z(t)\) as follows:

\[
C_{xyz}(\omega) = \frac{|CY_{xy}(\omega) - CY_{xz}(\omega)CY_{yz}(\omega)|^2}{(1-C_{xx}(\omega))(1-C_{yy}(\omega))}
\]
where $C_{y_j}(\omega)$ is a complex valued function whose magnitude is called coherency (Halliday et al. 1995) between the two signals $i$ and $j$. The over-cap indicates the estimate of that quantity. In the following discussions, for the sake of convenience, we use these quantities without over-cap. The confidence limit for coherence at 100% $\alpha = 1 - (1 - \alpha)^{1/(M-1)}$. Similarly the confidence limit for partial coherence at 100% $\alpha = 1 - (1 - \alpha)^{1/(M-2)}$ (Brillinger 1981; Halliday et al. 1995). In our calculations we have set $\alpha = .99$. Any value of coherence above the confidence limit is considered to show significant correlation between the time series and the value of coherence below this confidence limit indicates lack of correlation between the two time series. For the interpretation of partial coherence we refer to Sect. 11. In the above spectral estimations, we choose a segment length of $L = 1s$ which results in a frequency resolution of 1 Hz for the estimated spectral quantities. However, one can choose different segment lengths to have a good compromise between sensitivity and reliability of the estimated quantities.

We extend the coherence analysis to estimate the time delay between the two signals $x(t)$ and $y(t)$. Analogous to cross-correlation, if there is a time delay $\tau$ between the two signals, the value of coherence will be slightly reduced. In order to compensate for this reduction in the coherence due to $\tau$, we shift one of the time series $y(t)$ (assuming $x(t)$ is the time delayed version of $y(t)$), by a constant time lag $\tau$. We discard the extra $\tau$ points (in sample units) in $y(t)$ to have the same length for both time series. We estimate the coherence $C(\tau)_{\omega_0}$ in a selected frequency band $\omega_0$ as a function of $\tau$. The value of $C(\tau)_{\omega_0}$ will increase as a function of $\tau$ and reach a maximum value when $\tau = \delta$. This procedure is repeated for the other time series $y(t)$ to estimate the time delay from $x(t)$ to $y(t)$. This idea of estimating the time delay by maximising the coherence has been successfully applied to acoustic signals (Carter 1987). A similar idea using phase synchronisation, has been employed to estimate the time delay between and among different meteorological variables (Rybski et al. 2003). Since coherence measure is sensitive to the length of the data, we discard the points corresponding to maximum $\tau$ from both time series, and consider only the length of the time series which is integer multiple of the segment length $L$. In this way $C(\tau)_{\omega_0}$ estimated at different values of $\tau$ will have the same confidence limit. This ensures that the maximum value of the coherence is reached only because of the time delay and not because of the different lengths of the data used in the estimation of the $C(\tau)_{\omega_0}$.

We have used the confidence limit (see above) to assess the significance of $C(\tau)_{\omega_0}$. For the theoretical model which is AR2 and its time delayed variants, one can obtain the error-bar of the delay from standard deviations of the delays estimated for several realisations of the AR2 process. In order to get the error-bars of the estimated delay (variability of the delay) for the biological data, we use surrogate analysis (Kantz and Schreiber 1997). We synthesise surrogate data for this purpose by exploiting one of the basic assumptions of spectral analysis: that the data in disjoint segments are independent (Halliday et al. 1995). We shuffle the disjoint segments of the time series from which the original spectrum is estimated. This is done only for one of the time series from which time delayed information is assumed to flow to another time series. Then, we repeat this procedure for the other time series. Thus, in this type of surrogate the original spectrum of both the time series is preserved but only the cross spectrum will be different. We prepare 19 different surrogates for each of our analyses and calculate the time delay coherence function $C(\tau)_{\omega_0}$ for each of the realisations. We make a null hypothesis that $C(\tau)_{\omega_0}$ calculated for the original time series $x(t)$ and $y(t)$ is due to spurious correlations. We estimate the significance of the difference $S(\tau)$ between $C(\tau)_{\omega_0}$ and $C(\tau)_{\omega_0}^{\text{surr}}$ as $S(\tau) = |C(\tau)_{\omega_0} - < C(\tau)_{\omega_0}^{\text{surr}} >|/\sigma[C(\tau)_{\omega_0}^{\text{surr}}]$, where $< . . >$ indicates the average over all the surrogates and $\sigma[.]$ represents the standard deviation between different realisations. If $S(\tau) > 2$ then we reject the null hypothesis that $C(\tau)_{\omega_0}$ is due to spurious correlation (Kantz and Schreiber 1997; Theiler et al. 1992). Though we compute $S(\tau)$ for all values of $\tau$ at which $C(\tau)_{\omega_0}^{\text{surr}}$ and $C(\tau)_{\omega_0}$ are estimated, for simplicity we report here only $S(\tau = \delta)$. When the null hypothesis is rejected, we calculate the error-bars of the delay as follows: We subtract $C(\tau)_{\omega_0}^{\text{surr}}$ from $C(\tau)_{\omega_0}$ and estimate delay for each surrogate subtracted realisation. We report the mean value of these delays as the delay between the two time series and their standard deviation as the error-bar of the delay. For the sake of clarity, we plot

$$C'(\tau)_{\omega_0} = [C(\tau)_{\omega_0} - < C(\tau)_{\omega_0}^{\text{surr}} >] - [C(\omega_0) - < C(\omega_0)_{\omega_0}^{\text{surr}} >].$$

Note that $C(\omega_0)$ is the value of the coherence at $\tau = 0$ and $< C(\omega_0)_{\omega_0}^{\text{surr}} >$ is the average of all the surrogates at $\tau = 0$. By this definition, $C'(\tau)_{\omega_0}$ will pass through a zero value at $\tau = 0$ and reach a maximum value at $\tau = \delta$. Based on the above arguments we calculate the delay between the two time series as

$$\delta = \max_{\tau} C'(\tau)_{\omega_0}.$$

The preference of this method over other conventional methods of delay estimation is discussed in (Govindan et al. 2005). It has been shown by Carter (Carter 1987) that the uncertainty in the estimation of coherence due to the time delay between the two time series is proportional to $1/L$ (where $L$ is the FFT length used in the estimation of the spectral quantities). In order to favor the estimation of the time delay, we increase the uncertainty in the coherence estimation by decreasing $L$ (which in turn results in the poorer frequency resolution of the spectral estimates). Sometimes, decreasing
the frequency resolution may result in the loss of coherence (as the spectral quantities are poorly estimated) which should be checked before proceeding to the delay analysis. In the foregoing analysis, we have used a frequency resolution of 5 Hz for the theoretical model and a frequency resolution of 2 Hz for the biological systems.

As this method relies on the bias (due to delay) in the (coherence) estimator, results obtained might be sensitive to the other factors causing the bias in the coherence estimate. In addition to delay, the other two dominant factors which can affect coherence estimator are the FFT length \( L \) (see above) and the SNR of the signals. As discussed above the \( FFT \) length is coupled to the delay (Carter 1987) in causing the bias in the coherence estimate. By properly choosing this value (usually in the range of \( 1/5 \) sec to \( 1/2 \) sec) one can minimise the effect due to this bias. The bias caused by SNR cannot be addressed directly. However, the error-bars of the delay estimate to some extent can reflect the effect of SNR on the delay estimate. Further, length of the dataset can cause bias in the coherence. For a given system, the number of points for the time shifted coherence is kept the same (for all pair combinations, see above) to avoid this bias. Since all the time shifted coherence analysis is done for the same number of points (see above) it will not affect the final results.

3 Application to Model system

In this section we test our hypothesis that delay can serve as a measure to identify the direction of interaction, in a group of three coherent signals and can overcome the methodological pitfalls inherent to partial coherence analysis (Albo et al. 2004). We choose to use the model used in (Albo et al. 2004) which is an AR2 process (source) and its time delayed versions as response signals. AR2 processes have been used to model biological processes (Honerkamp 1994; Timmer et al. 1998a; Timmer et al. 1998b). The model is given by:

\[
X_1(t) = X_0(t - \delta_1) + \eta_1(t) \\
X_2(t) = X_0(t) + \eta_2(t) \\
X_3(t) = X_0(t - \delta_2) + \eta_3(t),
\]

where \( X_0(t) = 0.8X_0(t - 1) - 0.5X_0(t - 2) + \eta_0(t) \) is a AR2 process. \( \eta_i(t) \) are Gaussian white noise processes with zero mean and unit variance. We assume 1000 Hz as sampling frequency. We set \( \delta_1 = 3 \) ms, \( \delta_2 = 5 \) ms, \( var(\eta_1(t)) = 0.04, var(\eta_2(t)) = 0.06 \) and \( var(\eta_3(t)) = 0.0 \). In this model, there is a delayed flow of information from \( X_2(t) \) to \( X_1(t) \) and \( X_3(t) \) with a delay of 3 and 5 ms, respectively. Also there is delayed information flow from \( X_1(t) \) to \( X_3(t) \) with a delay of 2 ms. By construction of the model, \( X_2(t) \) is the mediator as it is solely responsible for the existence of (establishing the connection between) \( X_1(t) \) and \( X_3(t) \).

Results of the delay, coherence and partial coherence analyses for this model are given in Fig. 1. Figures 1(b,c,f) show a significant coherence between the three time series. Figures 1(d,g,h) display partial coherence between the time series \( X \) and \( Y \) accounting for the common influence of the third time series \( Z \) and is indicated by \( X - Y/Z \).

**Figure 1 will appear here.**

In Fig. 1d the partial coherence between \( X_1(t) \) and \( X_2(t) \) accounting for the common influence of \( X_3(t) \) is insignificant seemingly indicating that the connection between \( X_1(t) \) and \( X_2(t) \) is mainly established through \( X_3(t) \). In Fig. 1(g,h) there is a decrease in the (partial) coherence (compared to their coherence shown in Fig. 1(c,f), respectively) when the influence of the third signal is removed. One may conclude that the third signal in Fig. 1(g,h) also shares some of its signal with the other two variables but is not solely responsible for the correlation between these two. Thus, the partial coherence analysis already indicates that all signals are interconnected but \( X_3(t) \) with the highest SNR is identified as the main influence (mediator) to establish the connection between the other variables within this network. The direction of interaction introduced in the model is shown in Fig. 1j. The connections identified by partial coherence analysis are shown in Fig. 1k.

Now, we consider the results of the delay analysis shown in Fig. 1(a,e,i). In Fig. 1a there is a delay of \( 3 \pm 0.35 \) ms from \( X_2(t) \) to \( X_1(t) \) and the significance of deviation from the surrogates is \( S(\delta) = 69.3 \). In Fig. 1e there is a delay of \( 2 \pm 0.28 \) ms from \( X_1(t) \) to \( X_3(t) \) and the significance of deviation from the surrogates is \( S(\delta) = 102.87 \). In Fig. 1i there is delay of \( 5 \pm 0.47 \) ms from \( X_2(t) \) to \( X_3(t) \) and the significance of deviation from the surrogates is \( S(\delta) = 91.24 \). In all these cases, \( S(\delta) \) is greater than 2 standard deviations indicating that the correlations in \( C(\tau_{\omega0}) \) are not spurious. From delay analysis, it is clear that there is flow of information from \( X_2(t) \) to \( X_1(t) \) and \( X_3(t) \) with a delay of 3 and 5 ms, respectively. The fact that \( X_1(t) \) and \( X_2(t) \) both project to \( X_3(t) \) but no information flows from \( X_3(t) \) to \( X_1(t) \) or \( X_2(t) \) clearly rules out that \( X_3(t) \) is the main influence as suggested by the partial coherence analysis. Conclusion based on the delay analysis is shown in Fig. 11.

We also have repeated the analysis for slightly higher intensity of noise to check the robustness of the delay analysis to noise. There is no change in the final conclusion drawn in Fig. 11 except for the increase in the error-bar of the delay estimate. The results of the partial coherence analysis remain consistent with Fig. 1(k). Based on the delay values, in Fig. 1k, we draw the arrows from source (which is \( X_2 \) signal) to targets (which are \( X_1 \) and \( X_2 \)). Further there is a delayed flow of information from \( X_1 \) to \( X_3 \), and hence we have drawn an arrow from \( X_1 \) to \( X_3 \). Although partial coherence analysis has wrongly identified \( X_3 \) as the mediator between the two
signals (Fig. 1d), a slight reduction in the (partial) coherence values in Fig 1 g and h when X3 is partialised for X1 and X2 (compare to Fig. 1c and 1f, respectively) indicates that X1 and X2 are also directly connected or share a common source with X3. If X3 had been the sole source as identified by the partial coherence analysis in Fig. 1d, its coherence with the other two signals should not have diminished when partialised for the third signal. Thus, based on the delay analysis and from the above discussion we establish the connectivities between the variables of the model as shown in Fig. f.

If we consider an another different situation in the above model, with \( \text{var}(\eta_2 = 0) \) and \( \text{var}(\eta_1), \text{var}(\eta_3) \) are non-zeros, and with \( \text{var}(\eta_2) > \text{var}(\eta_1) \), then the results of the partial coherence will clearly identify that the connection between X1 and X3 are established through X2 indicating that X2 is the source signal. Delay analysis will also yield similar results. However, in this case, as well as in the above scenario, though we can argue the connection (direction of the information flow) between two centers based on the delay analysis we cannot clearly judge whether or not they are directly or indirectly coupled. Thus, the results of both analyses should be interpreted with great care in the presence of cross-channel relations.

Further, for the above model, one can obtain similar results by cross-correlation analysis or by phase synchronisation analysis (Rybski et al. 2003). But for biological data, we are interested in the nature of interaction between the two signals in a particular frequency band. So in the next section we continue to use the maximising coherence method.

### 4 Application to Biological systems

In this section we perform the delay and partial coherence analyses to identify the connection between the cortical and muscle signals by applying them to (i) the EEG and EMG time series in ET patients (ii) the EEG of normal subjects while performing rhythmic bimanual tapping of their index fingers. We also show that the results of partial coherence analysis tend to identify the signal with the highest SNR as the mediator through which the connection between the other two signals is established. We calculate the signal to noise ratio (SNR) of the signal by considering the ratio of the power at the desired frequency to noise level. We use the mean value of power in the frequency range of 100 to 200 Hz as noise level (upper cut off of our filter is at 200 Hz). Connections and nature of interactions identified by delay analysis are different from those identified by partial coherence analysis and provide biologically conceivable interpretation.

Before proceeding any further, we construct cortico-muscular isocohereence maps (Raethjen et al. 2005; Govindan et al. 2005) for all the cases discussed below. In the case of ET, there are two distinct regions (hot spot) with significant cortico-muscular coherence at the tremor frequency, one in the frontal and midline regions, and another in the region of the contralateral primary sensorimotor cortex. In the normal subjects the voluntary rhythms of both hands are represented in the right and left sensorimotor areas and also in the frontal/midline region. As in the tremor patients this secondary hot spot likely reflects an involvement of premotor cortical areas (e.g.) SMA (Raethjen et al. 2005). In both cases we take an electrode from each region displaying maximum cortico-muscular coherence to identify the connections between the different cortical areas.

#### 4.1 Application to ET

ET is a common movement disorder characterised by postural tremor of the arms (Deuschl et al. 1998). Other neurological abnormalities are typically absent in essential tremor (Findley and Koller 1987). Experimental studies on animals (Llinás and Volkind 1973; Lamare 1984) and on human beings (Jenkins et al. 1993; Hallett and Dubinsky 1993; Bucher et al. 1997) show that different parts of the brain are involved in essential tremor. Evidence for the involvement of the thalamus in the tremor oscillations is also known (Hua et al. 1998; Benabid et al. 1991; Schuurman et al. 2000). The role of cortical motor centers is currently under debate (Halliday et al. 1998; Raethjen et al. 2005; Hellwig et al. 2001). We consider two ET patients which we label ET1 and ET2. These two subjects display cortico-muscular coherence at the tremor frequency (4 and 5 Hz) in a frontal area close to the midline, possibly supplementary motor area (SMA) and in the area of the sensorimotor cortex (MC). We are interested in the tremor related connectivities of these two motor regions with each other and with the periphery. For ET1, results of delay, coherence and partial coherence analyses are given in Fig. 2.

**Figure 2** will appear here.

The muscle spectrum in Fig. 2j shows tremor oscillations around 4 Hz. Fig. 2b displays the cortico-cortical coherence between F2 (SMA) and C2 (MC). There is a significant coherence at the tremor frequency of 4 Hz. Fig. 2(c,f) display a significant cortico-muscular coherence at the tremor frequency of 4 Hz (Mima and Hallett 1999a; Mima and Hallett 1999b; Mima et al. 2000b; Halliday et al. 1998). In Fig. 2d, (partial) coherence between F2 and C2 accounting for the common influence of EMG is vanished at the tremor frequency of 4 Hz seemingly indicating that the external tremor is mainly responsible for the coupling between these areas. However, in Fig. 2(g,h) partial cortico-muscular coherence accounting for the other cortical area is also slightly reduced compared to the coherences shown in Fig. 2(c,f). This indicates that these two regions are also coupled (Raethjen et al. 2005). Thus the partial coherence analysis seems to support the notion that all recording sites are connected...
in a motor network with the peripheral tremor being the leading influence of tremor related activity. SNR of F2, C2 and EMG are 1.52, 10.25 and 70.58, respectively. By comparing the SNR values we see that partial coherence analysis has identified the signal with the highest SNR as the main mediator within the cortico-muscular network as predicted by the model (Albo et al. 2004).

To establish the direction of the different connections we again perform the delay analysis. We choose the tremor frequency of 4 Hz as $\omega_0$. Fig. 2a shows a delay of $7 \pm 0.67$ ms from C2 to F2 and $3 \pm 0.88$ ms from F2 to C2 and the significances of deviation from the surrogates are $S(7) = 4.72$ and $S(3) = 3.36$. Fig. 2e shows a delay of $19 \pm 9.78$ ms from F2 to EMG and the significance of deviation from the surrogates is $S(19) = 2.86$. Fig. 2i shows a delay of $9 \pm 3.83$ ms from EMG to C2 and $11 \pm 3.71$ ms from C2 to EMG and the significances of deviation from the surrogates are $S(9) = 15.82$ and $S(11) = 15.83$. Significance of deviation from the surrogates in all the cases are greater than 2 standard deviations indicating $C(\tau)_{\omega_0}$ is not due to spurious correlations. There is a uni-directional flow from F2 to EMG and a bi-directional flow between F2 and C2. Also there is a bi-directional flow between C2 and EMG. Thus the cortical areas both influence each other while the EMG only exerts some influence on one of the cortical sites. This dominance of cortico-muscular flow and relative lack of musculo-cortical interaction indicates that the EMG cannot be the main influence responsible for the cortico-cortical interaction as inferred from the partial coherence analysis. On the contrary the two cortical areas mutually exchange information and both project to the EMG thereby contributing to the peripheral tremor rhythm. Cortico-cortical connections and the cortico-muscular connections based on the delay analysis are shown in Fig. 2i. For the details of discussion of cortico-muscular and musculo-cortical delays we also refer to (Govindan et al. 2005).

Figure 3 will appear here

The results of delay, coherence and partial coherence analyses for ET2 are shown in Fig. 3. As seen for ET1, there is a significant cortico-cortical coherence between FCZ (SMA) and C4 (MC) (see Fig. 3b) at the tremor frequency of 5 Hz shown in Fig. 3j. Also, there is a significant cortico-muscular coherence for both SMA (FCZ) and MC (C4) as shown in Fig. 3(c,f) at the tremor frequency of 5 Hz. In Fig. 3d partial coherence between FCZ and C4 accounting for the common influence of EMG is insignificant again seemingly indicating that EMG is mainly responsible for the tremor related correlations between FCZ and C4. As seen in Fig. 2(g,h) for ET1, also for ET2 (see Fig. 3(g,h)), the partial cortico-muscular coherence accounting for the common influence of the other cortical region is significant but has slightly reduced compared to their corresponding coherences shown in Fig. 3(c,f). This again shows (as concluded for ET1) that these two regions also seem to couple leading to a reduction in the coherence when the influence of the other cortical region is removed. The SNR values for FCZ, C4 and EMG are 20.25, 26.64 and 161.22, respectively. Thus the partial coherence has again identified the EMG signal with the highest SNR as the mediator.

For delay analysis, we choose $\omega_0$ as 5 Hz which is the tremor frequency. In Fig. 3a, there is a delay of $3 \pm 1.92$ ms from FCZ to C4 and the significance of deviation from the surrogates is $S(3) = 14.06$. In Fig. 3e, there is a delay of $25 \pm 10.42$ ms from FCZ to EMG and the significance of deviations from the surrogates is $S(25) = 5.05$. In Fig. 3i, there is a delay of $18 \pm 9.21$ ms from C4 to EMG and the significance of deviation from the surrogates is $S(18) = 13.01$. In all the cases the significance of deviations from the surrogates is greater than 2 standard deviations indicating that the correlations in $C(\tau)_{\omega_0}$ are not spurious. There is a clear uni-directional flow from FCZ to C4 in Fig. 3a. Also there is uni-directional flow from FCZ to EMG in Fig. 3e. In Fig. 3i there is uni-directional flow from C4 to EMG. There is no flow from EMG to the cortical centers to account for the cortico-cortical connection as suggested by the partial coherence analysis. Based on the delay analysis, the cortico-cortical connections and the cortico-muscular connections are given in Fig. 3i and this conclusion is different from the conclusion drawn from partial coherence analysis (see Fig. 3k).

In both cases, there is a cortico-muscular delay of 11-20 ms from MC to muscle. This is in keeping with the experimentally observed conduction time of 15 ± 2 ms between cortex to muscle (Rothwell et al. 1991). The longer cortico-muscular delay of 19-25 ms between the frontal (SMA) region and muscle may indicate a different pathway or mode of interaction with the periphery. The musculo-cortical delay (EMG-MC) found in ET1 is in keeping with normal latencies of somatosensory evoked cortical potentials and indicates that the peripheral tremor is also fed back to cortex. The cortico-cortical delay of 3-7 ms between SMA and MC is in agreement with the delay of 3-6 ms between premotor stimulation and its effect on the motor cortex recently studied with transcranial magnetic stimulation (Civardi et al. 2001).

In the above examples, EMG has the highest SNR and hence it is identified as the main mediator, through which the (tremor related) cortical connections are established, by partial coherence analysis. This would imply feedback of the tremor rhythm to the cortex as the main mechanism for the cortico-muscular and cortico-cortical coherence. But, based on the delay analysis we can clearly show that the SMA and MC both share tremor related activity themselves which in turn is transmitted to the muscle. This is an argument that the cortex being part of the central generating network of ET (Hellwig et al. 2001; Raethjen et al. 2004). While the disappearance of the cortico-cortical coherence when the common influence of the EMG is removed, is a method-
ological artefact the remaining albeit slightly reduced cortico-muscular coherence after accounting for the influence of the other cortical signal is interpretable. It indicates a somewhat independent connection of both areas with the peripheral tremor possibly intermittently sharing their tremor related activity (Raethjen et al. 2005). This tremor related cortico-cortical interaction is bidirectional in the first example. In the second presented case the main information flow seems to be from SMA to MC. In summary, this study provides evidence that tremor related correlations are transmitted from SMA or MC to muscle, but due to the low (tremor related) signal content in the cortex this connection is not correctly identified by partial coherence analysis.

4.2 Application to cortical activity related to bimanual rhythmic movements in Normal subjects

In this section we perform the time delay analysis to identify the interaction between the left and right sensorimotor cortices and the midline area of healthy subjects during bimanual rhythmic movements of the index fingers. This study will throw light on the cortical network involved in bimanual movements. In a recent study (Pollok et al. 2004), it has been shown that the rhythm of voluntary unilateral hand movements is represented in the contralateral sensorimotor cortex as part of the central generating network of these voluntary rhythms. For bimanual movements it has been postulated that the cortical midline areas (especially SMA) play a major role (Jäncke et al. 2000; Lang et al. 1990; Stephan et al. 1999; Donchin et al. 2001; Immisch et al. 2001). On the other hand the interhemispheric connections via the corpus callosum between the primary sensorimotor cortices on both sides seem to be important (Eliassen et al. 2000; Brinkman and Kuypers 1973; Andres et al. 1999). As the more bilaterally organised SMA and the more lateralized primary sensorimotor cortices are also tightly linked by projection fibers, one may postulate that all three cortical areas take part in the control of bilateral movements. It has recently been proposed on the basis of monkey experiments that the SMA is not a superordinate center for bimanual movement coordination but only part of an interconnected cortical network in both hemispheres (Kazennikov et al. 1999).

We consider two subjects, hs1 and hs2. All the cortical areas (electrodes) used for this study displayed significant cortico-muscular coherence at the tapping frequency. But in this study we are interested in the movement related cortico-cortical connections. Again we compare the results of the delay analysis with the partial coherence analysis. The results of partial coherence analysis are also compared with the SNR of the cortical signals.

For hs1, the results of the delay, coherence and partial coherence analyses are given in Fig. 4. There is a significant synchronised activity between the two index finger extensor and flexor muscles around 4 Hz as displayed by their coherence spectrum in Fig. 4j. Fig. 4(b,c,f) display significant cortico-cortical coherence at the tapping frequency of 4 Hz (see Fig. 4j) as well as in other frequency bands. In Fig. 4d, the partial coherence between the cortical signals from the left and right hemispheres, accounting for the common influence of the midline area (represented by CPZ) is insignificant at the tapping frequency as well as in the other frequency bands. This seemingly indicates that the tapping related activity in the two hemispheres is coupled through the midline area (CPZ). In Fig. 4(g,h) the partial coherences between one of the hemispheres and the midline accounting for the influence of the other hemisphere remain significant but have also slightly reduced compared to coherence shown in Fig. 4(c,f), respectively. This indicates that these areas also share some tapping related and other activities between them. Based on these arguments one would conclude in Fig. 4k that the midline region is the main mediator bringing in the coupling between the two hemisphere. However, the reduction of the partial coherence accounting for the influence of the lateral cortical areas (C4/C3) indicates that they also have direct connections. The SNR values for C3, C4 and CPZ are 51.28, 53.02 and 82.59, respectively. Thus, the partial coherence analysis detects the recording site with the highest SNR as the leading influence among the three (Albo et al. 2004). Now we look at the results of the delay estimation.

Figure 4 will appear here

We choose $\omega_0$ as 4 Hz at which there is a synchronised activity between the two fingers. In Fig. 4a there is a delay of $6 \pm 0.88$ ms from C4 to C3 and the significance of deviation from the surrogates is $S(6) = 78.64$. In Fig. 4e, there is a delay of $2 \pm 0.41$ ms from CPZ to C3 and the significance of deviation from the surrogates is $S(2) = 89.79$. In Fig. 4i there is a delay of $3 \pm 0.74$ ms from C4 to CPZ and the significance of deviation from the surrogates is $S(3) = 150.2$. In all the cases, the (significance of) deviation from surrogates is greater than 2 standard deviations indicating that $C(\tau)_{\omega_0}$ obtained in all the cases are not spurious. In Fig. 4a there is a uni-directional flow from C4 to C3. Fig. 4e, shows a uni-directional flow from CPZ to C3. In Fig. 4i there is a uni-directional flow from C4 to CPZ. Based on these results, we can conclude that there is a movement related information flow directly from right to left hemisphere via the midline area. Interestingly, the sum of the delay from C4 to CPZ and from CPZ to C3 (5 ms) is very close to the direct delay between C4 and C3 (6 ms). Thus, we cannot exclude that the transmission between C4 and C3 calculated by maximising coherence only reflects the indirect transmission via the midline area (CPZ) which was detected as the main mediator in the partial coherence analysis. However, the fact that partial coherence results are also in keeping with direct connections between C4 and C3 and that the midline has the highest
SNR are arguments against the midline being the sole factor in connecting the three cortical areas. In fact, the delay analysis shows that the midline area (CPZ) only projects to C3 while C4 projects both to C3 and CPZ thus being the most influential area within this network of three cortical areas. Connections based on the delay estimation are shown in Fig. 4l.

Next we consider hs2 for which the results of the delay, coherence and partial coherence analyses are given in Fig. 5. In an earlier work (Pollok et al. 2004), it has been shown that healthy subjects while performing bimanual movements exhibited significant cortico-muscular coherence at the movement frequency and also at double the movement frequency. The coherence at both frequencies are considered to be the movement related cortical representations. In this subject, we observe cortico-cortical coherence at the tapping frequency and/or at double the tapping frequency. Based on the results of earlier work (Pollok et al. 2004), we interpret a complete loss of coherence between two cortical areas at both the frequencies (tapping and double the tapping frequency) when the common influence of the third cortical area is removed, as the insignificant partial coherence. There is a significant coherent rhythm in both index fingers at 3-6 Hz shown in Fig. 5j. In Fig. 5(b,c) there is a significant cortico-cortical coherence between midline and lateral electrodes that showed coherence with the peripheral voluntary movement rhythm. However the coherence is significant between the hemispheres only at double the tapping frequency (6-7 Hz) (see Fig. 5f). In Fig. 5h, the partial coherence between the two hemispheres accounting for the common influence of the midline region is insignificant, seemingly indicating that the connection between the hemispheres is established through the midline. In Fig. 5d there is a reduction in the partial coherence at double the tapping frequency (compare to Fig. 5b), between FCZ and C3 when the common influence of C4 is removed but the coherence at the tapping frequency remains almost the same. In Fig. 5g, the partial coherence almost the same (see Fig. 5c) at the basic as well as double the tapping frequency between FCZ and C4 when the common influence of C3 is removed. The SNR of FCZ, C3 and C4 are 44.07, 29.65 and 35.01, respectively. They are almost comparable to each other. Fig. 5k shows the main cortico-cortical connections based on the results of partial coherence analysis.

Figure 5 will appear here.

We choose $\omega_0$ as 6 Hz as there is significant coherence at this frequency in all the three pairs. In Fig. 5a there is a delay of $6 \pm 1.83$ ms from C3 to FCZ and a delay of $15 \pm 3.3$ ms from FCZ to C3. The significances of deviation from the surrogates are $S(6) = 9.86$ and $S(15) = 10.26$, respectively. In Fig. 5e, there is delay of $16 \pm 6.17$ ms from FCZ to C4 and the significance of deviation from the surrogates is $S(16) = 15.61$. In Fig. 5i, there is a delay of $14 \pm 6.29$ ms from C4 to C3 and the significance of deviation from the surrogates is $S(14) = 5.68$. In all the cases, the significance of deviation from the surrogates is greater than 2 standard deviations indicating that the correlations in $C(\tau)_{\omega_0}$ are not spurious. In Fig. 5a, there is a bi-directional flow between FCZ and C3. In Fig. 5e, there is a uni-directional flow from FCZ to C4. In Fig. 5i, there is a uni-directional flow from C4 to C3. Based on these arguments the cortico-cortical connections with the direction of the information flows are given in Fig. 5l. Based on the results of partial coherence analysis, one would expect a tapping related synchronisation between FCZ and C4 and that C3 gains access to C4 mainly through FCZ. This is in keeping with the connections obtained from the delay analysis. Again the reduction in the partial coherence between FCZ and C3 accounting for the common influence of C4 indicates that there also is a direct connection between C4 and C3 with a flow mainly from C4 to C3. This is exactly what we find in the delay analysis. Thus, in this case the results obtained from both the analyses are not contradictory because the SNR at the three recording sites are comparable and are in accordance with our starting hypothesis the partial coherence analysis yielded valid results in this case.

Taking into account the relatively large variability (error-bars), the delay between the right and left sensorimotor cortices of 6 and 14 ms is in keeping with the well known latencies of transcallosal inhibition around 8-15 ms (Meyer et al. 1995; De Gennaro et al. 2004; De Gennaro et al. 2004; Schmidt et al. 2000). The delay between the midline area and the sensorimotor cortex is slightly shorter than the transcallosal delay which is in keeping with the shorter latencies of inhibitory effects on the primary motor cortex evoked by premotor cortex stimulation (3-6 ms) in humans (Civardi et al. 2001).

The results of our analyses in these two cases show that all three (bilateral sensorimotor cortices and midline area) cortical areas are connected and that the midline area (possibly SMA) is not necessarily the leading source of the activity related to bimanual rhythmic movement. Thus our data support the hypothesis that a bilateral interconnected cortical network including midline structures (e.g. SMA) is involved in bimanual coordination (Kazennikov et al. 1999).

5 Conclusion

In order to understand the complex interactions between 3 or more signals, partial coherence is used as a potential tool. But partial coherence analysis is sensitive to SNR (Albo et al. 2004). On the other hand, for data from multichannels, multivariate analysis has been shown to perform well in terms of identifying the complex interaction patterns underlying the system compared to the pair-wise analysis (Kus et al. 2004). In many physiological situation there will be delay between the signals (Müller 2003; Timmermann et al. 2003; Govindan et
al. 2005; Pollok et al. 2004). In this work, as a complementary approach to partial coherence analysis, we use delay analysis to identify the connections and the nature of interaction between the signals.

In cases where results of partial coherence are affected by SNR, we establish the connections between centers based on the delay. As mentioned in the introduction, though we can argue about the direction of information flows based on the delay analysis, it cannot distinguish between direct or indirect connection. However, as shown in our examples delay analysis can often help to detect spurious overall results of the partial coherence analysis. In these cases some reduction in partial coherence compared to coherence is typically seen also for those two connection that remained after partialization. This hints at a weaker direct connection also between those two centers for which partial coherence became insignificant, and it justifies to interpret the delay between them as direction of at least some flow of information.

The application to EEG and EMG data shows that the combination of both methods while monitoring the SNR of all recording sites greatly improves the interpretation of the results. In case of biological systems, there is a large variability (as revealed by surrogate analysis) in the delay estimated by maximising coherence analysis. Though this can partly be attributed to methodological problems, the major reason for this variation may be the complex connections and the mode of interaction between cortical and subcortical centers (Williams et al. 2002; Marsden et al. 2000; Marsden et al. 2001). Application of time delay analysis to complex (theoretical) networks may help to understand the delay results of biological systems. This will be pursued in our future work.

Even though there is a large variability in the magnitude of the delay, direction of information flow is clearly revealed by the delay analysis. However, the whole idea of using delay analysis to identify the connection and interaction is valid only when there is a non-zero delay between two signals. In case of zero delay between two signals, and to find out the direct and indirect coupling, one has to opt for methods like Extended Granger Causality (Chen et al. 2004) to identify the connections and interactions between the signals but this is beyond the scope of the current work.

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Figure captions

Fig. 1 Results of delay, coherence and partial coherence analyses for model system. In \( b,c,f \) coherence between the time series \( X \) and \( Y \) is displayed and is indicated by \( X \rightarrow Y \). In \( d,g,h \) partial coherence between the time series \( X \) and \( Y \) accounting for the common influence of the third time series \( Z \) is displayed and is indicated by \( X \rightarrow Y/Z \). Horizontal dotted lines in \( b,c,f \) and \( d,g,h \) represent the 99% confidence limit for coherence and partial coherence, respectively. In \( a,e,i \) results of the delay analysis between the time series \( X \) and \( Y \) is displayed and is indicated by \( X \rightarrow Y \). Here, as well as in the foregoing discussions, negative values of \( \tau \) indicate that the time series of \( X \) is shifted backwards in time to identify the delayed flow of information from \( X \) to \( Y \). In \( d \) partial coherence between \( X_1(t) \) and \( X_2(t) \) accounting for the common influence of \( X_3(t) \), is insignificant indicating that \( X_1(t) \) and \( X_2(t) \) are communicating mainly through \( X_3(t) \). a There is a delay of 3 ms from \( X_2(t) \) to \( X_1(t) \). e There is a delay of 2 ms from \( X_1(t) \) to \( X_2(t) \). i There is a delay of 5 ms from \( X_2(t) \) to \( X_3(t) \). j Connections and the directions of interactions used in the model. k Main connections identified by partial coherence analysis. However, though there is a significant (partial) coherence in \( (g,h) \), a reduction compared to the coherence in \( (c,f) \) indicates a weaker direct connection also between \( X_1(t) \) and \( X_2(t) \). l Connections and the directions of interaction identified by delay analysis.

Fig. 2 Results of delay, coherence and partial coherence analyses for ET1. Quantities plotted in \( a-i,k,l \) have the same meaning as in Fig. 1. In \( b,c,f \) there is a significant coherence between the time series \( X \) and \( Y \) (indicated by \( X \rightarrow Y \)) at the tremor frequency of 4 Hz which is shown in \( j \). In \( d \) partial coherence between \( F2 \) and \( C2 \) accounting for the common influence of EMG, is insignificant (at the tremor of 4 Hz) indicating that the connection between \( F2 \) and \( C2 \) is established mainly through the EMG. In \( g,h \) there is a significant partial cortico-muscular coherence between the time series \( X \) and \( Y \) (indicated by \( X \rightarrow Y \)) at the tapping (coherent) frequency of 4 Hz which is shown in \( j \). Also, there is a significant coherence in all the other frequency bands. In \( d \) partial coherence between \( C3 \) and \( C4 \) accounting for the common influence of CPZ, is insignificant (at the tapping frequency of 4 Hz as well as in the other frequency bands) indicating that the connection between \( C3 \) and \( C4 \) is established mainly through CPZ. In \( g,h \) there is a significant partial cortico-cortical coherence between left/right hemisphere with the midline region when the influence of the other hemisphere is removed. However, a slight reduction in the partial coherence compared to the coherence shown in \( (c,f) \) indicates that these two hemispheres are also (weakly) coupled. a There is a delay of 6 ms from \( C4 \) to \( C3 \). e There is delay of 2-3 ms from CPZ to \( C3 \). i There is a delay of 3-4 ms from \( C4 \) to CPZ. For the sake of clarity, the abscissas in \( a,e,i \) are plotted in different scales.

Fig. 3 Results of delay, coherence and partial coherence analyses for hs2. Quantities plotted in \( a-i,k,l \) have the same meaning as in Fig. 1. In \( b,c,f \) there is a significant coherence at the tapping frequency of 4 Hz between the EMG recorded from both fingers. In \( b,c,f \) there is a significant coherence between the time series \( X \) and \( Y \) (indicated by \( X \rightarrow Y \)) at the tapping (coherent) frequency of 4 Hz which is shown in \( j \). Also, there is a significant coherence in all the other frequency bands. In \( d \) partial coherence between \( C3 \) and \( C4 \) accounting for the common influence of CPZ, is insignificant (at the tapping frequency of 4 Hz as well as in the other frequency bands) indicating that the connection between \( C3 \) and \( C4 \) is established mainly through CPZ. In \( g,h \) there is a significant partial cortico-muscular coherence when the influence of the other cortical area is removed, but it has reduced compared to the cortico-muscular coherence (shown in \( c,f \)) indicating an indirect connection also between the two cortical areas. a There is a delay of 3 ms from FCZ to \( C4 \). d There is a delay of 25 ms from FCZ to EMG. i There is a delay of 20 ms from \( C4 \) to EMG. For the sake of clarity, the abscissas in \( a,e,i \) are plotted in different scales.

Fig. 4 Results of delay, coherence and partial coherence analyses for hs1. Quantities plotted in \( a-i,k,l \) have the same meaning as in Fig. 1. In \( j \) there is a significant coherence at the tapping frequency of 4 Hz between the EMG recorded from both fingers. In \( b,c,f \) there is a significant coherence between the time series \( X \) and \( Y \) (indicated by \( X \rightarrow Y \)) at the tapping (coherent) frequency of 4 Hz which is shown in \( j \). Also, there is a significant coherence in all the other frequency bands. In \( d \) partial coherence between \( C3 \) and \( C4 \) accounting for the common influence of CPZ, is insignificant (at the tapping frequency of 4 Hz as well as in the other frequency bands) indicating that the connection between \( C3 \) and \( C4 \) is established mainly through CPZ. In \( g,h \) there is a significant partial cortico-cortical coherence between left/right hemisphere with the midline region when the influence of the other hemisphere is removed. However, there is a significant coherence between the time series \( X \) and \( Y \) (indicated by \( X \rightarrow Y \)) at the tremor (coherent) frequency of 4 Hz which is shown in \( j \). In \( f \) there is a significant coherence at double the tapping frequency, 6-7 Hz. In \( h \) partial coherence between \( C3 \) and \( C4 \) accounting for the common influence of FCZ, is insignificant indicating that the connection between \( C3 \) and \( C4 \) is established mainly through FCZ. In \( d,g \) there is a significant partial coherence between left/right hemisphere with the central region when the influence of the other hemisphere is removed but the slight reduction (compared to the coherence shown in \( b,c \)) indicates that these hemispheres are also (weakly) coupled. However, though there is a significant (partial) coherence in \( (d,g) \), a reduction compared to the coherence (at double the tapping frequency) in \( (b,c) \) indicates a weaker direct connection also between \( C3 \) and \( C4 \). a There is a delay of 6 ms from \( C3 \) to FCZ and a delay of 15 ms from FCZ to \( C3 \). e There is a delay
of 16 ms from FCZ to C4. There is a delay of 14 ms from C4 to C3. For the sake of clarity, the abscissas in a, e, i are plotted in different scale.
(a) $C_{3-4}$
(b) $C_{3-4}$
(c) $C_{3-CPZ}$
(d) $C_{3-4}/CPZ$
(e) $C_{3-CPZ}$
(f) $C_{4-CPZ}$
(g) $C_{3-CPZ}/C4$
(h) $C_{4-CPZ}/C3$
(i) $C_{4-CPZ}$
(j) EMG–EMG
(k) C3 -> C4 -> CPZ
(l) C3 -> C4 -> CPZ
