# Studying Dynamic Neural Interactions with MEG

## Jan-Mathijs Schoffelen and Joachim Gross

**Abstract** Interactions between functionally specialized brain regions are crucial for normal brain function. Magnetoencephalography (MEG) is suited to capture these interactions because it provides whole head measurements of brain activity with temporal resolution in the millisecond range. Many different measures of connectivity exist and in order to take the connectivity analysis results at face value one should be aware of the strengths and weaknesses of these measures. Next to this, an important challenge in MEG connectivity analysis lies in the fact that more than one sensor picks up the activity of any underlying source. This field spread severely limits the utility of connectivity measures computed directly between sensor recordings. As a consequence, neuronal interactions should be ideally studied on the level of the reconstructed sources. MEG is well suited for this purpose, since its signal properties and high spatial sampling allows for relatively accurate unmixing of the sensor recordings. This chapter provides some necessary background on connectivity analysis in general, and proceeds by describing the challenges that are associated with the analysis of MEG-based connectivity at the sensor level. Source level approaches are described and some recent advances with respect to MEG-based connectivity during the resting state and graph theoretic approaches are described.

**Keywords** MEG · Magnetoencephalography · Connectivity · Coherence · Synchronization · Source localization · Field spread · Resting-state networks · Graph theory

---

J.-M. Schoffelen
Centre for Cognitive Neuroimaging, Donders Institute for Brain, Cognition and Behaviour, Radboud University Nijmegen, Nijmegen, The Netherlands

J.-M. Schoffelen
Max Planck Institute for Psycholinguistics, Nijmegen, The Netherlands

J. Gross (✉)
Department of Psychology, Centre for Cognitive Neuroimaging (CCNi), University of Glasgow, Glasgow, UK
e-mail: Joachim.Gross@glasgow.ac.uk

S. Supek and C. J. Aine (eds.), *Magnetoencephalography*,
DOI: 10.1007/978-3-642-33045-2_18,

# 1 Introduction

Magnetoencephalography (MEG) as a technique is ideally suited to study activity of the human brain on the time scale of cognitive and behaviorial processes. It provides measurement of brain activity by covering the whole head with a high number of sensors, and is increasingly used to study networks of interacting brain regions. The purpose of this chapter is to provide some background on connectivity analysis with MEG and to highlight some recent methodological developments, which enable researchers to study the interaction between brain regions based on these non-invasively obtained electrophysiological measures of neuronal activity.

The structure of this chapter is as follows: first we review some of the measures that are commonly used to analyze connectivity. Then we will discuss the problems related to electromagnetic field spread in the context of connectivity analysis at the MEG sensor level. Next we will describe approaches that analyze connectivity in source space. Following this, we will discuss the emerging fields of studying connectivity in the brain at rest with MEG and graph theoretic analysis of MEG-based connectivity metrics.

# 2 Measures of Connectivity

When faced with the possibility to analyse connectivity in MEG, the researcher can employ a vast number of different measures and analysis approaches to quantify this. Each of the different measures of connectivity has its merits and disadvantages with respect to what can be interpreted from those measures, and the ease with which they can be computed. This section provides an overview of the measures most commonly used, without having the intention to be comprehensive. The different metrics that are mentioned are shown in Table 1.

## *2.1 Connectivity Measures can be Grouped Along Different Dimensions*

It may be useful to group the different connectivity measures along several different dimensions. One key distinction which is often made is that of functional versus effective connectivity (Friston 1994). Measures of functional connectivity (undirected interaction measures) quantify statistical dependencies between neuronal signals, without explicitly addressing directed interactions. On the other hand, measures of effective connectivity (or directed interaction measures) quantify the directed influence of one neuronal system over another. This distinction has its implications for the interpretation of the analysis results. Per

**Table 1** Overview of different connectivity measures and their main characteristics

| | Directed interactions | Freq/time domain | Multi/bivariate | Linear | Sensitive to field spread |
|---|---|---|---|---|---|
| Amplitude envelope correlation | – | f | b | + | + |
| Coherence | – | f | b | + | + |
| Cross-correlation function | + | t | b | + | + |
| Cross-frequency interactions | – | f | b | – | + |
| Directed transfer function | + | t | m | + | + |
| Dynamic causal modelling | + | t/f | m | – | + |
| Granger causality | + | t/f | b | + | + |
| Imaginary part of coherency | + | f | m | – | – |
| Mutual information | – | t/f | b | – | + |
| Partial directed coherence | + | f | m | + | + |
| Phase lag index | + | f | b | – | – |
| Phase locking value | – | f | b | – | + |
| Phase slope index | + | f | b | – | – |
| Synchronization likelihood | + | t | b | – | – |
| Transfer entropy | + | t/f | b | – | – |

definition, undirected interaction measures do not allow for an interpretation of causality.

Another important distinction is that between time and frequency domain measures of connectivity. This directly refers to the underlying physiological mechanisms by means of which neuronal interactions are thought to occur. One view, which has gained a lot of interest in the past few decades, is that neural interactions are reflected in changes in the synchronization of rhythmic activity between brain regions (Fries 2005). In light of this proposed mechanism of interaction, it makes sense to use connectivity measures that are defined in the frequency domain, and where an estimate of the phase difference is used to compute the connectivity.

Yet another distinction pertains to whether the connectivity measure is a bivariate or a multivariate one. Although typically connectivity measures are estimated between pairs of signals, some measures account for the influence of ‘third party signals’ on the connection under consideration, yielding a potentially clearer interpretation of the interaction being direct or indirect (e.g. due to common input from a third source of activity).

Some connectivity measures assume the interaction between signals to be linear and/or use linear estimation techniques. Other measures don’t rely on these assumptions. This constrains the interpretation of the estimated connectivity results. Also, in general non-linear measures are often based on estimates of probability distributions and require more computing time, and also more data to be computed reliably.

Finally, in the context of MEG, it is crucial to consider whether the connectivity measure is sensitive to the effects of electromagnetic field spread. This will be outlined and discussed in more detail in Sect. 3.

## 2.2 Frequency Domain Measures of Undirected Interactions

*Amplitude envelope correlation* refers to the correlation coefficient between amplitude envelope time courses, which are typically computed on bandpass-filtered data, and as such this measure classifies as a frequency domain connectivity measure.

*Coherence* (Gross et al. 2001) is the frequency domain analogue of the cross-correlation coefficient, and is usually computed using non-parametric spectral estimation techniques, such as the Fourier transform, or a wavelet transform. As such coherence confounds the estimated consistency of a fixed phase difference with the correlation of the signals' amplitudes. It's a very popular measure, because it's easy to compute and it has a straightforward interpretation in terms of frequency-resolved linear predictions.

Amplitude effects can be disentangled from the consistency of the phase difference by means of the *phase locking value* (PLV). This measure can be obtained by normalising the complex-valued frequency domain single trial values with respect to their amplitudes, prior to estimating the interaction between the signals (Lachaux et al. 1999). This phase synchronisation analysis has been used in source connectivity analysis to complement traditional coherence analysis (Jerbi et al. 2007). Both coherence and PLV are symmetric measures and do not allow direct inference about directionality of information flow between areas. However, time delays can be estimated from the slope of the cross-spectral densities between time series under favourable conditions (Nolte et al. 2008).

Recent years have seen an increased interest in *cross-frequency interactions*, inspired by the notion that neuronal signals typically show rhythmic activity in several distinct frequency bands, and that neuronal interactions thus may also be reflected in statistical dependencies between these frequency bands (Jensen and Colgin 2007). Several types of interactions can be considered here, e.g. amplitude-amplitude coupling (where there is a correlation across observations of the amplitude envelopes of different frequency bands) or phase-amplitude coupling (where the phase of a slow oscillation systematically modulates the amplitude of a fast oscillation).

### *2.3 Measures of Directed Interactions*

Directed interactions can be inferred in one of the following conceptually different ways. The simplest concept is based on estimating the time lag between events occurring in a pair of signals (Nolte et al. 2008; Gross et al. 2000). This is linked to the principle that a cause must precede its effect, but it should be noted that temporal precedence does not provide direct evidence for causal interactions (Atukeren 2008). In the time domain, the cross correlation function can be used to estimate time lags between signals. However, this technique is hardly used in MEG-research. It is more common to explore the time lag in the frequency domain, where one can exploit the principle that a fixed time delay translates into linearly increasing phase differences with increasing frequency. Hence, the slope of the phase difference spectrum is a direct estimate of this time-delay. The *phase slope index* (Nolte et al. 2008; Haufe et al. 2013) is a measure that is based on this principle. The *phase lag index* (PLI) (Stam et al. 2007) quantifies the deviation of the phase difference distribution from 0, thus allowing for the inference of one signal leading (or lagging) the other.

Related to the concept of temporal precedence is the concept of *Wiener-Granger causality* (Bressler and Seth 2011), which is based on the prediction of a signal (let's call this signal A for the time being) based on the past values of itself, and based on the past values of another signal (signal B). If the quality of the prediction of signal A is substantially improved when past values of B are taken into account, signal B is said to cause signal A. This principle has been originally formulated by Wiener (1956), and is operationalized in the measure of Granger causality (Granger 1969). Granger causality in its original formulation is defined in the time domain. It is usually implemented by means of fitting a series of multivariate autoregressive models (MVAR-models) (Schloegl et al. 2006) and by exploring the residuals of the model fit. Based on work by Geweke, frequency-resolved Granger causality can also be computed, and from the Fourier transform of the autoregressive model coefficients a series of related measures can be derived such as the *directed transfer function* (DTF) (Kaminski and Liang 2005) and *partial directed coherence* (PDC) (Baccala and Sameshima 2001). Common to these measures is that they assume that the interaction is linear. *Transfer entropy* (TE Schreiber (2000)) is an implementation of Wiener's principle of causality that is free of an explicit model of the signals and their interaction. A non-linear formulation of Granger causality also exists (Marinazzo et al. 2011).

Finally, rather than using a data-driven approach, one can try and create generative model of the measured data, where the model entails not only the activation patterns of the underlying neural sources, but also their interactions. This approach is implemented in *Dynamic Causal Modelling* (DCM) (Moran et al. 2007; Kiebel et al. 2008; David and Friston 2003). The generative model specifies how input activates a system of pre-specified interconnected neuronal populations, leading to the measured signal. As such DCM provides an estimate of coupling parameters and source parameters in a single step (Kiebel et al. 2008). DCM had originally been devised for the analysis of evoked responses (Garrido et al. 2007). Recent developments have extended the functionality of this promising technique to induced responses (Chen et al. 2008), steady state responses (Moran et al. 2007) and phase-coupling (Penny et al. 2009).

## 3 MEG Sensor Level Connectivity Analysis

A central issue in the interpretation of MEG data is the problem of electromagnetic field spread. Although it is a well-known problem and described elsewhere (Winter et al. 2007), it merits discussion in the context of connectivity analysis because it severely confounds many connectivity measures and therefore complicates the correct interpretation of the results. In the following sections we will outline this problem in the context of connectivity analysis, and describe two strategies, which attempt to diminish this problem: the analysis of experimental contrasts, and the use of connectivity measures that are less sensitive to electromagnetic field spread.

### *3.1 Electromagnetic Field Spread*

Field spread refers to the phenomenon that the magnetic fields that are associated with electrical currents (of neural and non-neural origin) are not confined to the vicinity of the current generators, but are measurable far away from their source. For any neuronal source this leads to a widespread representation at the level of the sensor array. As a matter of fact, thanks to this feature, it is possible in the first place to measure MEG extracranially and to build models of the underlying neural sources. Yet, electromagnetic field spread also has important consequences for the interpretability of connectivity measures estimated between pairs or sensors. The reason for this is that any single source of neural (or non-neural) electric activity is visible to many sensors at once. This is illustrated by Fig. 1a. The spatial topography shows the correlation between one channel and the rest, from simulated data containing one single dipole plus uncorrelated sensor noise. Obviously, MEG sensor recordings represent the superposition of the activity of multiple sources, which are either or not functionally connected. Also with multiple sources present, even if the underlying sources are ‘unconnected’, many connectivity measures estimated between pairs of sensors will yield spurious estimates due to the instantaneous mixing process. To illustrate this we simulated the activity of 821 temporally uncorrelated dipoles, with an orientation parallel to the axis between the nasion and the midpoint of the interauricular line, and that were randomly distributed on the cortical sheet. Clearly, the orientations chosen are physiologically not meaningful, but are appropriate to demonstrate the effect of field spread on connectivity analysis. Using FieldTrip (Oostenveld et al. 2011), we simulated 50 s of data for a 275-channel CTF axial gradiometer system, by using a single shell

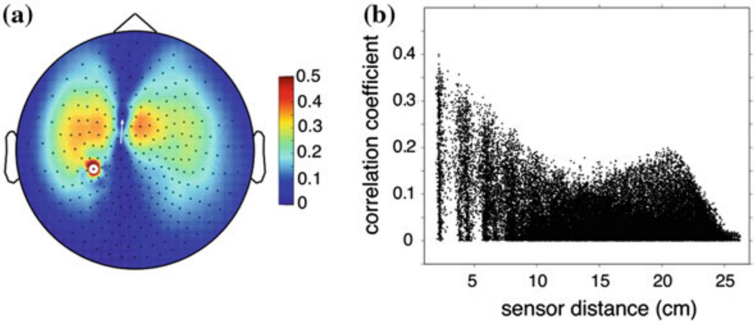

**Fig. 1** The effects of field spread confound sensor level estimates of connectivity measures. **a** Sensor-level connectivity between a seed sensor and the rest of the sensor array in the presence of a single underlying source. **b** The absolute value of the correlation coefficient between all pairs of measured signals as a function of sensor distance, where the underlying 821 sources were uncorrelated

volume conductor model (Nolte 2003) and uncorrelated sensor noise. Figure 1b shows the absolute value of the correlation coefficient between all MEG sensor pairs as a function of their distance. Even though the underlying source activities are temporally uncorrelated, many sensor pairs show high values of correlation.

### *3.2 Addressing Electromagnetic Field Spread with Statistics*

In order to reduce the interpretational difficulties caused by field spread, one potential strategy could be to analyze changes in connectivity caused by an experimental manipulation, rather than the strength of the connectivity as such. The rationale for using experimental contrasts in this context is based on the assumption that the effects of electromagnetic field spread are identical across the experimental conditions and therefore subtract out. Unfortunately, the spatial structure of field spread is highly dependent on changes in the signals, and on changes in the noise. As a consequence, estimated modulations in connectivity do not necessarily always reflect modulations in actual connectivity between relevant neuronal sources. Experimental manipulations will most likely always lead to changes in activity of the underlying sources, or in the activation of different sources. Also, in studies that involve the comparison between different groups of subjects (e.g. patients versus controls), it is not unlikely that difference in the distribution and activity of the underlying sources exist. These potential confounds in the interpretation of estimated differences in connectivity should therefore always be taken into account. This is illustrated in Fig. 2. Here, we simulated two dipoles oscillating at 20 Hz in left and right ‘motor cortex’, at a phase difference of 90°, against a background of 821 uncorrelated dipoles evenly distributed across the cortical sheet. We generated 2 conditions of data where the amplitude of the motor

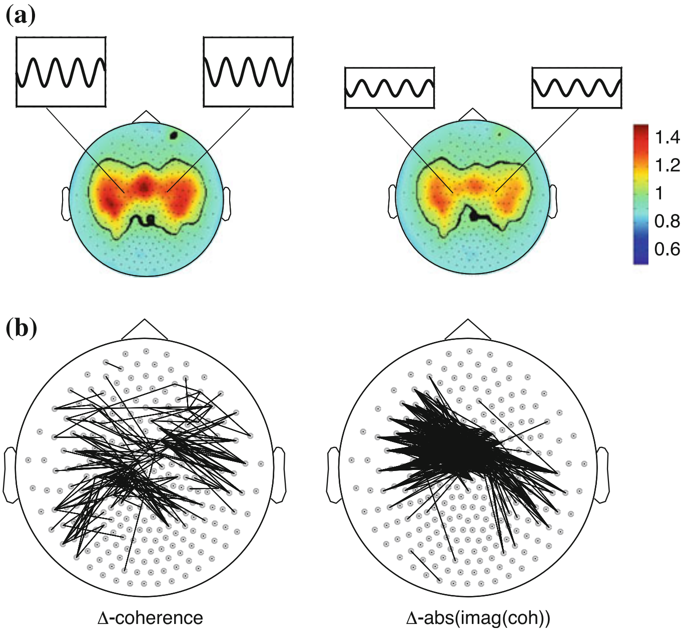

**Fig. 2** Changes in source strength yield widespread changes in sensor-level connectivity. **a** spatial topography of simulated activity with 821 randomly distributed, uncorrelated dipoles, and 2 strong, highly correlated dipoles in approximately *left* and *right* motor regions. The amplitude of the 'motor' sources is two times higher in the *left* panel than in the *right* panel. **b** Thresholded differential connectivity patterns (high amplitude condition minus low amplitude condition), where each line represents a sensor pair where the differential connectivity exceeded a threshold of 0.2. Two different connectivity metrices were used: coherence (*left* panel) and the imaginary part of coherency (*right* panel)

cortex dipoles was twice as large in condition 1 compared to condition 2 (Fig. 2a). We computed coherence and the imaginary part of coherency (see Sect. 3.3) across all channel pairs and display the sensor pairs in which the difference in connectivity across the conditions exceeded a certain threshold. Clearly there is interesting spatial structure in the differential coherence and imaginary coherency maps, that cannot be accounted for by a change in actual connectivity (which as a matter of fact in both conditions was simulated to be equal to 1).

For the reasons outlined above, field spread is problematic in the interpretation of sensor-level connectivity estimates, and an important motivation to perform the connectivity analysis at the source level. Also, contrasting connectivity between two experimental conditions in sensor space will likely reduce (but not abolish) negative effects of field spread (Schoffelen and Gross 2009). In addition to this, there are other important motivations to perform the analysis on the source level. First of all, there is a more direct indication of the anatomical location of the interacting brain regions. Secondly, source level analysis facilitates subsequent group analysis because the data can be averaged in a meaningful standardized space.

### 3.3 Addressing Electromagnetic Field Spread with Clever Measures of Connectivity

Another strategy to address interpretation problems associated with electromagnetic field spread is to use connectivity measures that are insensitive to this effect. In general, this type of measure can be divided into two categories. The first category consists of measures that are derived from conventional linear measures. The imaginary part of coherency (Nolte et al. 2004) is a well-known example of this type of measure. Another example is amplitude-envelope correlation with the zero time-lag correlation removed (Hipp et al. 2012) (see Sect. 5). The other category consists of measures that are derived from the non-linear dynamics framework. This type of measure includes the phase lag index (Stam et al. 2007) synchronization likelihood (Stam and Van Dijk 2002) and transfer entropy (Vicente et al. 2011).

Measures that are insensitive to field spread usually exploit the fact that field spread caused by point sources has an instantaneous effect on the sensors. In other words, field spread causes cross-correlation effects between sensors at a time lag of 0 ms, or equivalently at a phase difference of 0 or 180°. Explicitly removing the zero ms time lag contribution to the estimate of connectivity reduces the risk of falsely interpreting the estimate as true interaction. In the case of the imaginary part of coherency the removal of the 0° phase difference contribution is achieved by projection of the vector representation of the complex-valued coherency onto the imaginary axis.

An important caveat needs to be raised here, which is related to the fact that spurious connectivity is addressed only when contributing sources can be modeled as single point sources (equivalent current dipoles). This is illustrated in Fig. 3 where we present results of an analysis of the weighted phase lag index (WPLI) at 10 Hz (Vinck et al. 2011). For each channel, we computed the average WPLI between that channel and the rest of the channels and represented this in a spatial topography (panel A). Red here means that the underlying channels on average have a positive phase difference with the other channels, blue means that the underlying channels on average have a negative phase difference with the other channels. Thus the picture suggests a fronto-occipital gradient of time-lagged neural oscillations at 10 Hz, where the frontal channels ‘lead’ the occipital channels. However, the data that was used to generate this topography was constructed by back-projecting two independent components that were estimated from a few minutes of resting state MEG data. The time course of these components and their corresponding spatial topographies are shown in panel B. Clearly, these two components mainly represent cardiac activity. The slight time lag between the individual components in combination with the different topographies leads to a non-trivial mixing with significant interaction at non-zero time lag.

For the reasons outlined above it is increasingly acknowledged that the functional interactions should be studied at the level of the neuronal sources.

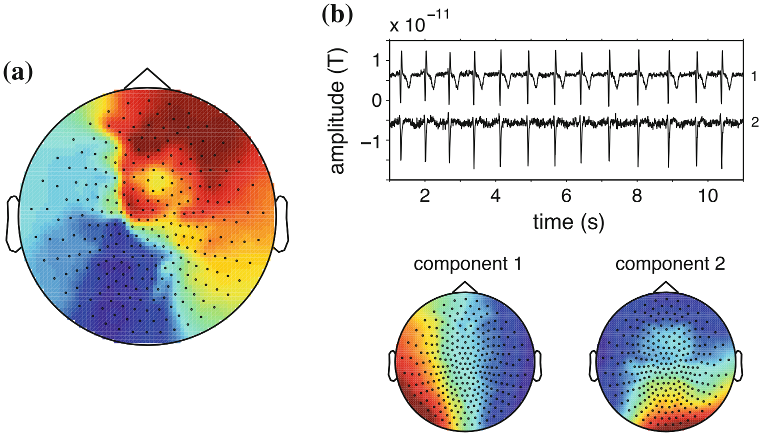

**Fig. 3** Sources that cannot be described as a single equivalent dipole yield non-zero phase-lagged connectivity estimates. **a** Spatial topography displaying for each sensor the average of the weighted-phase lag index between that sensor, and the rest of the sensor-array, yielding a distinct pattern of 'information flow' from frontal to posterior sensors. **b** Fragment of the time courses and spatial topographies of the independent components underlying the data that was used to generate the topography in panel (**a**)

## 4 MEG Source Level Connectivity Analysis

In this section we will provide an overview of the main methods that have been suggested for MEG source connectivity analysis. Most methods essentially adopt a two-step procedure. Firstly, an estimate of the activity of the neuronal sources is obtained by applying an inverse method (for a review, see Baillet et al. (2001)). Secondly, an analysis of connectivity is performed, in which researchers usually restrict themselves to a set of pre-specified seed regions-of-interest (ROIs). A notable exception to this two-step approach is Dynamic Causal Modelling, which will be described below. It is beyond the scope of this chapter to present in a comprehensive discussion the advantages and disadvantages of all connectivity measures and inverse methods; thus we will focus on some applications of connectivity measures in source space.

Typically, MEG source connectivity analysis is performed on the basis of a few selected regions of interest (ROIs). Connectivity measures are computed between all combinations of ROIs or ROIs are used as seeds to compute connectivity between activity at the seed location and all other voxels. Several strategies for the selection of ROIs exist:

*A priori selection*. A priori knowledge from previous functional imaging studies can be used to select ROIs (Astolfi et al. 2005). These areas can be identified in the individual anatomical MRI or coordinates in Talairach-MNI space can be transformed into individual coordinates. A related approach has been proposed by Haerle et al. (2004). Minimum norm source estimates were computed for 350 voxels to study steady-state auditory responses. Subsequently, coherence was computed between all pairs of voxels.

*Cortico-peripheral coherence*. In this approach an external signal serves as a reference signal. This can be a kinematic or electromyographic recording or even a continuous stimulus signal (such as speech). Coherence is computed between the reference signal and brain activity reconstructed at a discretized grid. This method allows the identification of brain areas where the activity is modulated by rhythmic processes in the peripheral signal. This strategy has been used successfully for oscillatory components in movements as recorded with electromyography and movement tracking devices (Gross et al. 2001, 2002; Schoffelen et al. 2008), and for localizing activity in auditory cortex using the speech signal as reference signal (Peelle et al. 2012). The local maxima in the cortical coherence map can be used as seed voxels for the analysis of cerebro-cerebral connectivity.

*Power maps*. Possibly the most widely used strategy is a selection of ROIs based on maps of neural activation or the statistical contrast in activation between experimental conditions. This approach has been successfully applied in a number of studies (David et al. 2002, 2003; Jerbi et al. 2007; Hipp et al. 2011).

*Connectivity-based methods*. Recently, several studies have performed the computation of connectivity between all pairs of voxels. Palva et al. (2010) computed phase locking on MEG minimum norm estimates to identify networks in a working memory task (see also Sect. 6). Hipp et al. (2011) developed a 6-dimensional cluster method to identify coherent networks from beamformer-localised EEG data. Kujala and co-workers suggested a technique that identifies highly connected areas by computing the connection density throughout the brain (Kujala et al. 2007). These ‘hubs’ can then be used as ROIs for a more detailed analysis of connectivity.

Source level connectivity analysis has become a powerful tool to identify networks of interacting brain regions and to study task-related changes in these networks. Several consistent findings seem to emerge from these studies. Network interactions seem to be highly specific regarding the frequency band and have modulatory effects on behavioural performance. Phase synchronization in the beta frequency band engaging a fronto-parietal network has been related to successful target detection (Gross et al. 2004). Interestingly, this study also demonstrated that desynchronisation in the network after target detection is important to facilitate detection of a subsequent target. Another study showed beta synchronization in a similar fronto-parietal network related to the perception of ambiguous audiovisual stimuli (Hipp et al. 2011). Again, beta synchronization distinguished between different percepts of the same stimuli. These results are consistent with the involvement of beta band synchronisation in top-down processes.

Another study nicely demonstrates that connectivity between brain areas is task-dependent. Siegel and colleagues studied connectivity between visual, parietal and frontal brain areas in both hemispheres during a visuospatial attention task (Siegel et al. 2008). Interestingly, shifting visuospatial attention to one hemifield (while maintaining central fixation) leads to increased gamma synchronisation between visual, parietal and frontal areas specifically in the contralateral hemisphere. These findings generalise beyond cognitive processes related to attention and perception. Palva et al. (2010) have studied phase synchronisation in a working memory task. They reported frequency-specific networks with low-frequency phase synchronisation predicting task performance.

## 5 Resting-State Connectivity

Human electrophysiological brain activity during rest has been studied since 1929, when Hans Berger performed the first human EEG recordings (Berger 1929). He discovered prominent rhythmic fluctuations in the signal at a rate of about 10/s. We now know that this so-called alpha oscillation dominates resting state activity, is strongest over occipital brain areas, and it reflects excitability changes in the generating neuronal populations (Niedermeyer and Silva 2004; Romei et al. 2008).

A vast number of MEG/EEG studies have been performed to study resting state activity in healthy participants and patients. In recent years functional connectivity has been studied in the resting state with MEG/EEG (Stam and van Straaten 2012; Stam 2010). Here, we focus on research that studies resting-state connectivity in source space. First, we present the commonly used methods to study resting-state connectivity and then we proceed to a discussion of the main findings.

### *5.1 Methodological Overview*

It seems surprising that specific methods have been developed to study resting-state connectivity since the overall aim of this analysis is similar to the connectivity analysis for other types of data—namely the identification of significant functional interactions between the time series of different brain areas. However, connectivity analysis in cognitive studies generally relies on the statistical comparison of two conditions, or an 'active' period of time and a baseline—a procedure that is known to reduce (but not abolish) the effect of field spread (see Sect. 3.2). No such comparison is available for resting state data (although surrogate data can be used (Ghuman et al. 2011)). Therefore, researchers have focused on methods that are more robust against contamination by field spread—mostly relying on amplitude correlations.

Most resting state connectivity methods rely on independent component analysis (ICA), albeit at different stages in the processing pipeline. One method has been proposed by Brookes et al. (2011). Beamforming is used to compute time series of activation for individual voxels from bandpass filtered resting-state data (Fig. 4a). ICA is performed on the amplitude envelopes of the band-limited voxel time series to identify independent temporal components with corresponding spatial maps.

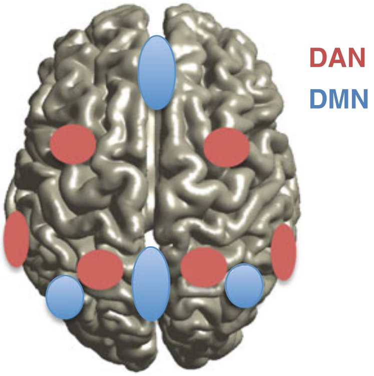

**Fig. 4** Schematic illustration of two resting-state networks. *DAN* Dorsal Attention Network, *DMN* Default Mode Network. Locations are taken from (de Pasquale et al. 2010; Brookes et al. 2011)

In a recently proposed method (de Pasquale et al. 2010; Mantini et al. 2011) ICA is used as a first step to decompose the signal into statistically independent components that often correspond to different types of artefacts (e.g. eye blinks and cardiac artefacts) and different activated brain areas (Makeig et al. 2002). In a second step neural generators of non-artifactual components are localised using standard source localisation techniques such as minimum norm or beamforming methods (Fig. 4b). The time series at any voxel in the brain is then computed from the summation of IC timecourses weighted by the amplitude of their source reconstruction at that voxel. A bandpass filter is then applied and the amplitude envelope is computed as the absolute value of the hilbert transform of the filtered signal. Amplitude correlations are computed between a seed voxel and all other voxels.

A promising extension of the seed-based approach has been presented by Hipp et al. (2012). Similar to the approach by Brookes et al. bandpass-filtered data is subjected to beamformer analysis to derive a time series for individual voxels. However, each pair of time series (corresponding to seed voxel and target voxel) was first orthogonalised to remove common components with zero delay—the hallmark of components related to field spread (see Sect. 3).These resting-state methods typically use amplitude correlations based on downsampled amplitude envelopes. The optimal integration window seems to be in the order of 1–4 s (Luckhoo et al. 2012).

Gomez-Herrero et al. combined ICA with multivariate autoregressive (MVAR) models to study directionality in resting-state data (Gomez-Herrero et al. 2008), see also (Haufe et al. 2010). The analysis pipeline (see also Sect. 4) consisted of PCA for dimensionality reduction, followed by estimation of a MVAR model. Residuals of the model were then subjected to ICA decomposition to estimate cortical generators with a source reconstruction method. ICA components were then combined with the coefficients of the MVAR model to compute measures of directed interactions (in this case directed transfer function) in source space.

Alternative approaches have been introduced that do not rely on ICA. Hillebrand et al. (2012) proposed to use beamforming to estimate time series of activation for regions of interest (ROIs) derived from an anatomical atlas. Spatial normalisation of individual MRIs is used to identify corresponding atlas-based ROIs in the individual brain. The study demonstrated that problems associated with field spread are reduced by using the Phase-Lag Index (Stam et al. 2007). A similar approach was used to study resting-state connectivity based on imaginary coherence in stroke patients (Guggisberg et al. 2008; Westlake et al. 2012).

## *5.2 Functional Connectivity in Resting-State Networks*

The analysis of resting state connectivity in functional MRI has recently attracted significant interest (Beckmann et al. 2005; Deco and Corbetta 2011). This is at least partly due to the seminal study by Biswal and colleagues who demonstrated spatially specific correlations in the temporal activation of brain areas during rest (Biswal et al. 1995). These correlations are driven by slow temporal fluctuations with frequencies around or below 0.1 Hz. However, until recently is has been unclear if and how these correlation patterns are represented in electrophysiological recordings. Recent developments in data analysis methods (reviewed in the previous section) have facilitated the identification of similar spatio-temporal correlation pattern in MEG/EEG signals of the resting brain. Due to their excellent temporal resolution MEG/EEG contribute complementary information to the fMRI-studies of human resting-state connectivity.

De Pasquale and colleagues used a seed-based correlation approach (see previous section) to identify the default mode network (DMN) and the dorsal attention network (DAN) from MEG data (Fig. 5). Both networks showed high spatial overlap with the corresponding networks identified in fMRI data. Interestingly, the high temporal resolution of MEG recordings afforded the investigation of this correlation structure in different frequency bands. DMN and DAN showed strongest amplitude correlations in the alpha (8–13 Hz) and beta (14–25 Hz) frequency bands with correlations that changed significantly over time. These temporal changes were further investigated in a subsequent study by the same authors (de Pasquale et al. 2012). Here, the DMN emerged as the network with strongest cross-network interactions with the posterior cingulate cortex as the most important node in the DMN. The DMN preferentially engages with nodes of another network when the within-network interactions of this other network are low.

Using a data-driven approach that is not based on seed voxels Brookes and colleagues largely corroborated these results by identifying several resting-state networks (including DMN and DAN) with dominant interactions in the beta band (Brookes et al. 2011). The frequency-specific nature of correlations in these (and other) studies convincingly implicates brain oscillations as the basis for these network interactions.

The orthogonalisation introduced by Hipp et al. (2012) improved spatial resolution of correlation maps with interesting results. Significant interhemispheric

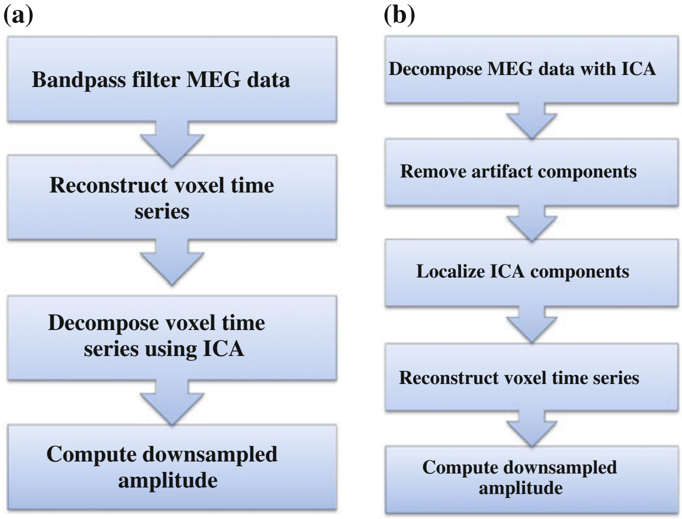

**Fig. 5** Two analysis pipelines for resting state MEG data. **a** Analysis approach used by Brookes et al. 2011). **b** Analysis approach used by de Pasquale et al. (2010), (Mantini et al. 2011)

amplitude correlations emerged in the beta frequency band between homologous sensory (auditory, somatosensory, visual) areas.

In summary, recent MEG resting-state connectivity studies in source space independently confirm the existence of resting-state networks previously discovered in fMRI data. Interestingly, MEG studies demonstrate that the correlation pattern in these networks is mediated by brain oscillations (predominantly in the alpha and beta frequency band) and that these correlations show strong temporal modulations that coincide with state transitions of between-network interactions.

## 6 Graph Theory

Although Graph Theory has been developed decades ago (Erdoes and Renyi 1959) it has only recently found a widespread use in the investigation of brain networks. This interest likely originates from a challenge that researchers face when they investigate anatomical or functional brain connectivity—namely its complexity. Human brain connectivity studies typically work with anatomical or functional data at a spatial resolution of 1–10 mm, leading to thousands of voxels. Each voxel can have anatomical or functional connections to many other voxels. In addition, functional connections are often evaluated in different frequency bands, experimental conditions, and may change over time. A meaningful low-dimensional characterization of this complex, high-dimensional data would greatly facilitate the identification of systematic differences between experimental conditions, or patients and healthy controls and could lead to a better understanding of the aspects of these complex networks that are essential for the functioning of the human brain. We will first introduce basic concepts of Graph theory, then present applications for MEG connectivity studies and, finally, discuss some limitations.

Networks of interacting brain areas can be represented by graphs. Graphs consist of nodes (or vertices) representing the brain areas, and connections (or edges) that represent the interactions between pairs of brain areas. Furthermore, information about directed information flow can be represented in directed graphs and information about connection strength can be represented in weighted graphs.

The topology of graphs can be characterized in a meaningful way by a number of measures that characterize different aspects of the graph. Here, we describe three important measures and refer the interested reader to more comprehensive material (Sporns 2011; Stam and van Straaten 2012; Ioannides 2007; Bullmore and Basset 2011).

| | |
|---|---|
| *Characteristic path length* | This is the average number of nodes on the shortest path between two nodes |
| *Degree distribution* | The degree of a node is the number of connected nodes. The distribution of degree across all nodes of a graph is the degree distribution |
| *Clustering coefficient* | For a given node the clustering coefficient is the ratio of the number of existing to the number of possible connections between all neighbours of the node |

Other measures such as *modularity* or *efficiency* have been introduced to characterise brain networks (Bullmore and Bassett 2011) with the aim to capture basic network characteristics that relate in a meaningful way to aspects of brain function or dysfunction.

Bassett and colleagues have used this approach successfully (Bassett et al. 2009). They demonstrated a positive correlation between performance in a working memory task and cost efficiency of network nodes. Consistent with the majority of MEG/EEG studies in this field individual sensors were taken as nodes. Various connectivity measures (see Sect. 2) can be used to quantify interactions between the signals of sensor pairs. Here, authors used mutual information in different frequency bands ranging from 1–60 Hz. Mutual information between all pairs of sensors signals results in a symmetric connectivity matrix. This matrix (that can also be computed from other connectivity measures such as coherence or phase synchronisation) is then converted into a graph. This conversion involves a thresholding and binarization of the matrix. The binarization sets every element with a value below threshold to zero and every element with a value above threshold to 1. The graph measure used by the authors was cost efficiency, which is inversely related to minimum path length computed at different thresholds. The authors observed significant correlation between cost efficiency and behavioral performance over left temporal and parietal areas and over midline frontal areas. This correlation was strongest in the beta band (12–30 Hz).

The possibility to describe topological aspects of a complex network with a few measures is particularly attractive for clinical studies since some of these measures could potentially be used as biomarkers for pathological changes associated with specific brain dysfunctions. Stam and colleagues have used Synchronization Likelihood (SL), a nonlinear measure of statistical interdependency, to study disease-related changes in functional brain networks. Again, SL values between pairs of MEG signals are used to build an association matrix that is converted into a graph before graph measures are computed. This approach has been used to uncover changes in network topology in different disorders such as Parkinson's and Alzheimer disease and is reviewed in (Stam 2010).

One of the most consistent findings emerging from these studies is that the functional network architecture of the human brain shows small-world properties (Stam 2004; Bassett et al. 2006). Small-worldness refers to networks that are characterised by high clustering but small path length. This is achieved by adding a few long-range connections to networks with predominantly short-range connections.

A limitation of these studies is that they use MEG sensors as graph nodes. This is problematic for at least two reasons (Schoffelen and Gross 2009). First, it is difficult to infer the involvement of specific brain areas from the location of MEG sensors. Second, the signal recorded by any given MEG sensor is typically a linear combination of the activity of several brain areas. Consequently, the topology of graphs constructed from sensor signals can be significantly affected by the sensitivity profile of the MEG sensor type and the specific configuration of active brain areas. Only few studies have addressed this problem by computing graphs from MEG data after source localization. Palva and colleagues studied functional connectivity in source space during visual working memory (Palva et al. 2010) and used graph theory to characterize the network. They localized bandpass filtered single-trial data using cortically constrained minimum-norm estimates. Phase-locking value was computed between pairs of cortical patches to build the association matrix. After thresholding based on group statistics, they used the node degree and related measures to identify hubs in frequency-dependent networks. The alpha-band network showed a hub in frontal cortex whereas for the beta-band hubs emerged in parieto-occipital cortex. Major hubs in the gamma-band were intraparietal sulcus (IPS) and superior parietal gyrus. Phase synchronization between brain areas was shown to correlate with behavioral performance. IPS was again the major hub in these performance-related networks.

This study nicely demonstrates the benefit of performing MEG connectivity analysis together with graph theory at the level of brain areas (as opposed to MEG sensor signals). Since here the graph nodes corresponded to anatomical brain areas results inferred from the functional data increase our understanding of specific brain networks and results can be related to findings from fMRI studies.

Although Graph Theory is a promising approach for the characterization of complex brain networks it has limitations. One main limitation is the loss of information during the computation of graphs (see Fig. 6). Following connectivity analysis the association matrix contains information about the strength of

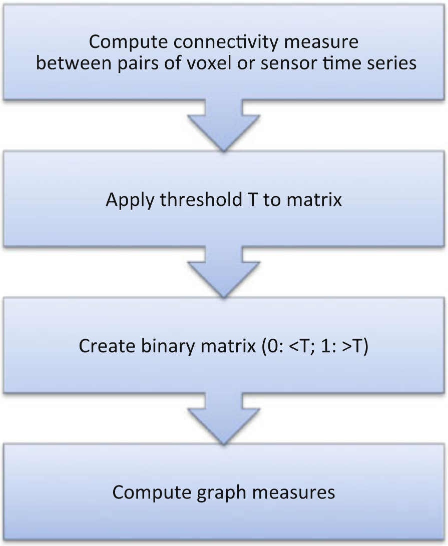

**Fig. 6** Typical pipeline for applying Graph Theory to MEG connectivity results

interactions between all pairs of nodes (where nodes could be brain areas or MEG sensors). In addition, some connectivity measures provide information about the direction of information flow (e.g. Granger causality or transfer entropy) leading to a non-symmetric association matrix (different values for the connection from node x−y compared to y−x). Most connectivity studies using graph theory measures however use undirected, unweighted graphs. Converting the association matrix into an undirected, unweighted graph involves thresholding. In most cases there is no objective way for selecting the threshold so one or several arbitrary thresholds are often used. This is problematic since the choice of threshold can affect the results. It is also unclear if different thresholds should be used (e.g. with respect to the distribution of values in the association matrix) when two or more experimental groups are compared.

## 7 Conclusion and Outlook

MEG connectivity analysis aims to understand the mechanisms underlying information processing in the complex human brain network. This poses a formidable challenge for a number of reasons. Although the location of specialised anatomical areas does not change over time, studies investigating neural plasticity demonstrate that their anatomical and functional properties and their interactions with other brain areas change at different time scales. In addition, connectivity studies have to account for the highly dynamic nature of interactions between brain areas that quickly adapt to changes in incoming sensory information or task demands. As discussed in this chapter, there is now compelling evidence that functional brain connectivity has to be studied in different frequency bands to account for the potentially different functional roles of these different frequency bands in neural communication. To further add to the complexity, different coupling mechanisms exist both, within and between different frequency bands and may involve phase and/or amplitude dynamics (Jensen and Colgin 2007). Further complications arise from the difficulty in distinguishing real interactions between brain areas from artifacts due to field spread (see Sect. 3).

Despite these challenges, MEG connectivity analysis is a highly active, successful and promising area of research (Palva and Palva 2012; Siegel et al. 2012; Schnitzler and Gross 2005). Significant progress has been made along different dimensions. First, methods have been developed that are more robust against or aim to circumvent the effects of field spread. Second, the development and application of biophysically meaningful generative models such as DCM provide a promising way to model dynamic interactions in brain areas. Third, recent advances of analysing resting-state connectivity with MEG have been able to identify networks that are consistent with results from fMRI studies. Here, MEG can contribute temporally and spectrally resolved information about these networks at a resolution that cannot be achieved with fMRI. Fourth, graph theory has become an increasingly useful tool to characterise the topology of complex anatomical or functional brain networks. This progress has significantly improved our understanding of functional connectivity in the human brain.

## References

Astolfi L, Cincotti F, Mattia D, Babiloni C, Carducci F, Basilisco A, Rossini PM, Salinari S, Ding L, Ni Y et al (2005) Assessing cortical functional connectivity by linear inverse estimation and directed transfer function: simulations and application to real data. Clin Neurophysiol 116(4):920–932

Atukeren E (2008) Christmas cards, easter bunnies, and granger-causality. Qual Quant 42(6):835–844

Baccala LA, Sameshima K (2001) Partial directed coherence: a new concept in neural structure determination. Biol Cybern 84(6):463–474

Baillet S, Mosher JC, Leahy RM (2001) Electromagnetic brain mapping. Sig Process Mag IEEE 18(6):14–30

Bassett DS, Bullmore ET, Meyer-Lindenberg A, Apud JA, Weinberger DR, Coppola R (2009) Cognitive fitness of cost-efficient brain functional networks. Proc Natl Acad Sci USA 106(28):11747–11752

Bassett DS, Meyer-Lindenberg A, Achard S, Duke T, Bullmore E (2006) Adaptive reconfiguration of fractal small-world human brain functional networks. Proc Natl Acad Sci USA 103(51):19518–19523

Beckmann CF, DeLuca M, Devlin JT, Smith SM (2005) Investigations into resting-state connectivity using independent component analysis. Philos Trans R Soc Lond B Biol Sci 360(1457):1001–1013

Berger H (1929) Über das elektrenkephalogramm des menschen. Eur Arch Psychiatry Clin Neurosci 87(1):527–570

Biswal B, Yetkin FZ, Haughton VM, Hyde JS (1995) Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. Magn Reson Med Off J Soc Magn Reson Med / Soc Magn Reson Med 34(4):537–541

Bressler SL, Seth AK (2011) Wiener-Granger causality: a well established methodology. NeuroImage 58(2):323–329

Brookes MJ, Woolrich M, Luckhoo H, Price D, Hale JR, Stephenson MC, Barnes GR, Smith SM, Morris PG (2011) Investigating the electrophysiological basis of resting state networks using magnetoencephalography. In: Proceedings of the national academy of sciences of the United States of America

Bullmore ET, Bassett DS (2011) Brain graphs: graphical models of the human brain connectome. Annu Rev Clin Psychol 7:113–140

Chen CC, Kiebel SJ, Friston KJ (2008) Dynamic causal modelling of induced responses. Neuroimage 41(4):1293–1312

David O, Cosmelli D, Hasboun D, Garnero L (2003) A multitrial analysis for revealing significant corticocortical networks in magnetoencephalography and electroencephalography. NeuroImage 20(1):186–201

David O, Friston KJ (2003) A neural mass model for MEG/EEG: coupling and neuronal dynamics. NeuroImage 20(3):1743–1755

David O, Garnero L, Cosmelli D, Varela FJ (2002) Estimation of neural dynamics from MEG/EEG cortical current density maps: application to the reconstruction of large-scale cortical synchrony. IEEE Trans Bio-Med Eng 49(9):975–987

de Pasquale F, Della Penna S, Snyder AZ, Lewis C, Mantini D, Marzetti L, Belardinelli P, Ciancetta L, Pizzella V, Romani GL, Corbetta M (2010) Temporal dynamics of spontaneous MEG activity in brain networks. Proc Natl Acad Sci USA 107(13):6040–6045

de Pasquale F, Della Penna S, Snyder AZ, Marzetti L, Pizzella V, Romani GL, Corbetta M (2012) A cortical core for dynamic integration of functional networks in the resting human brain. Neuron 74(4):753–764

Deco G, Corbetta M (2011) The dynamical balance of the brain at rest. Neuroscientist 17(1):107–123

Erdoes P, Renyi A (1959) On random graphs I. Publ Math 6:290–297

Fries P (2005) A mechanism for cognitive dynamics: neuronal communication through neuronal coherence. Trends Cogn Sci 9(10):474–480

Friston K (1994) Functional and effective connectivity in neuroimaging: a synthesis. Hum Brain Mapp 2:56–78

Garrido MI, Kilner JM, Kiebel SJ, Stephan KE, Friston KJ (2007) Dynamic causal modelling of evoked potentials: a reproducibility study. NeuroImage 36(3):571–580

Ghuman AS, McDaniel JR, Martin A (2011) A wavelet-based method for measuring the oscillatory dynamics of resting-state functional connectivity in MEG. NeuroImage 56(1):69–77

Gomez-Herrero G, Atienza M, Egiazarian K, Cantero JL (2008) Measuring directional coupling between EEG sources. Neuroimage 43(3):497–508

Granger CWJ (1969) Investigating causal relations by econometric models and cross-spectral methods. Econometrica 37:424–438

Gross J, Kujala J, Hamalainen M, Timmermann L, Schnitzler A, Salmelin R (2001) Dynamic imaging of coherent sources: studying neural interactions in the human brain. Proc Natl Acad Sci USA 98(2):694–699

Gross J, Timmermann L, Kujala J, Dirks M, Schmitz F, Salmelin R, Schnitzler A (2002) The neural basis of intermittent motor control in humans. Proc Natl Acad Sci USA 99(4):2299–2302

Gross J, Tass PA, Salenius S, Hari R, Freund HJ, Schnitzler A (2000) Cortico-muscular synchronization during isometric muscle contraction in humans as revealed by magnetoencephalography. J Physiol 527(Pt 3):623–631

Gross J, Schmitz F, Schnitzler I, Kessler K, Shapiro K, Hommel B, Schnitzler A (2004) Modulation of long-range neural synchrony reflects temporal limitations of visual attention in humans. Proc Natl Acad Sci USA 101(35):13050–13055

Guggisberg AG, Honma SM, Findlay AM, Dalal SS, Kirsch HE, Berger MS, Nagarajan SS (2008) Mapping functional connectivity in patients with brain lesions. Ann neurol 63(2):193–203

Haerle M, Rockstroh BS, Keil A, Wienbruch C, Elbert TR (2004) Mapping the brain's orchestration during speech comprehension: task-specific facilitation of regional synchrony in neural networks. BMC Neurosci 5:40

Haufe S, Tomioka R, Nolte G, Müller KR, Kawanabe M (2010) Modeling sparse connectivity between underlying brain sources for EEG/MEG. IEEE Trans Bio-med Eng 57(8):1954–1963

Haufe S, Nikulin VV, Müller KR, Nolte G (2013) A critical assessment of connectivity measures for EEG data: a simulation study. NeuroImage 64:120–133

Hillebrand A, Barnes GR, Bosboom JL, Berendse HW, Stam CJ (2012) Frequency-dependent functional connectivity within resting-state networks: an atlas-based MEG beamformer solution. NeuroImage 59(4):3909–3921

Hipp JF, Engel AK, Siegel M (2011) Oscillatory synchronization in large-scale cortical networks predicts perception. Neuron 69(2):387–396

Hipp JF, Hawellek DJ, Corbetta M, Siegel M, Engel AK (2012) Large-scale cortical correlation structure of spontaneous oscillatory activity. Nature Neurosci 15:884–890

Ioannides AA (2007) Dynamic functional connectivity. Curr Opin Neurobiol 17(2):161–170

Jensen O, Colgin LL (2007) Cross-frequency coupling between neuronal oscillations. Trends Cogn Sci 11(7):267–269

Jerbi K, Lachaux J-P, N'Diaye K, Pantazis D, Leahy RM, Garnero L, Baillet S (2007) Coherent neural representation of hand speed in humans revealed by MEG imaging. Proc Natl Acad Sci USA 104(18):7676–7681

Kaminski M, Liang H (2005) Causal influence: advances in neurosignal analysis. Crit Rev Biomed Eng 33(4):347–430

Kiebel SJ, Garrido MI, Moran RJ, Friston KJ (2008) Dynamic causal modelling for EEG and MEG. Cogn Neurodyn 2(2):121–136

Kujala J, Pammer K, Cornelissen P, Roebroeck A, Formisano E, Salmelin R (2007) Phase coupling in a cerebro-cerebellar network at 8–13 Hz during reading. Cereb Cortex 17(6):1476–1485

Lachaux JP, Rodriguez E, Martinerie J, Varela FJ (1999) Measuring phase synchrony in brain signals. Hum Brain Mapp 8(4):194–208

Luckhoo H, Hale JR, Stokes MG, Nobre AC, Morris PG, Brookes MJ, Woolrich MW (2012) Inferring task-related networks using independent component analysis in magnetoencephalography. NeuroImage 62(1):530–541

Makeig S, Westerfield M, Jung TP, Enghoff S, Townsend J, Courchesne E, Sejnowski TJ (2002) Dynamic brain sources of visual evoked responses. Science (New York, N.Y.) 295(5555):690–694

Mantini D, Della Penna S, Marzetti L, de Pasquale F, Pizzella V, Corbetta M, Romani GL (2011) A signal-processing pipeline for magnetoencephalography resting-state networks. Brain Connect 1(1):49–59

Marinazzo D, Liao W, Chen H, Stramaglia S (2011) Nonlinear connectivity by Granger causality. NeuroImage 58(2):330–338

Moran RJ, Kiebel SJ, Stephan KE, Reilly RB, Daunizeau J, Friston KJ (2007) A neural mass model of spectral responses in electrophysiology. Neuroimage 37(3):706–720

Niedermeyer E, Silva FLD (2004) Electroencephalography: basic principles, clinical applications, and related fields. Lippincott Williams & Wilkins, New York

Nolte G, Bai O, Wheaton L, Mari Z, Vorbach S, Hallett M (2004) Identifying true brain interaction from EEG data using the imaginary part of coherency. Clin Neurophysiol 115(10):2292–2307

Nolte G (2003) The magnetic lead field theorem in the quasi-static approximation and its use for magnetoencephalography forward calculation in realistic volume conductors. Phys Med Biol 48(22):3637–3652

Nolte G, Ziehe A, Nikulin VV, Schlogl A, Kramer N, Brismar T, Müller K-R (2008) Robustly estimating the flow direction of information in complex physical systems. Phys Rev Lett 100(23):234101–234104

Oostenveld R, Fries P, Maris E, Schoffelen JM (2011) FieldTrip: open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data. Comput Intell Neurosci 2011:156869

Palva JM, Monto S, Kulashekhar S, Palva S (2010) Neuronal synchrony reveals working memory networks and predicts individual memory capacity. Proc Natl Acad Sci USA 107(16):7580–7585

Palva S, Palva JM (2012) Discovering oscillatory interaction networks with M/EEG: challenges and breakthroughs. Trends Cogn Sci 16(4):219–230

Peelle JE, Gross J, Davis MH (2012) Phase-locked responses to speech in human auditory cortex are enhanced during comprehension, Cerebral cortex (in press)

Penny WD, Litvak V, Fuentemilla L, Duzel E, Friston K (2009) Dynamic Causal Models for phase coupling. J Neurosci Methods 183(1):19–30

Romei V, Rihs T, Brodbeck V, Thut G (2008) Resting electroencephalogram alpha-power over posterior sites indexes baseline visual cortex excitability. NeuroReport 19(2):203–208

Schloegl A, Supp G, Neuper Christa, Wolfgang K (2006) Analyzing event-related EEG data with multivariate autoregressive parameters. Event-related dynamics of brain oscillations. Elsevier, Amsterdam, pp 135–147

Schnitzler A, Gross J (2005) Normal and pathological oscillatory communication in the brain. Nat Rev Neurosci 6(4):285–296

Schoffelen J-M, Oostenveld R, Fries P (2008) Imaging the human motor system's beta-band synchronization during isometric contraction. NeuroImage 41(2):437–447

Schoffelen J-M, Gross J (2009) Source connectivity analysis with MEG and EEG. Hum Brain Mapp 30(6):1857–1865

Schreiber T (2000) Measuring information transfer. Phys Rev Lett 85(2):461–464

Siegel M, Donner TH, Oostenveld R, Fries P, Engel AK (2008) Neuronal synchronization along the dorsal visual pathway reflects the focus of spatial attention. Neuron 60(4):709–719

Siegel M, Donner TH, Engel AK (2012) Spectral fingerprints of large-scale neuronal interactions. Nat Rev Neurosci 13:121–134

Sporns O (2011) Networks of the brain. MIT Press, Cambridge

Stam CJ, van Straaten EC (2012) The organization of physiological brain networks. Clin Neurophysiol Off J Int Fed Clin Neurophysiol 123(6):1067–1087

Stam CJ (2004) Functional connectivity patterns of human magnetoencephalographic recordings: a 'small-world' network? Neurosci Lett 355(1–2):25–28

Stam CJ (2010) Use of magnetoencephalography (MEG) to study functional brain networks in neurodegenerative disorders. J Neurol Sci 289(1–2):128–134

Stam CJ, Nolte G, Daffertshofer A (2007) Phase lag index: assessment of functional connectivity from multi channel EEG and MEG with diminished bias from common sources. Hum Brain Mapp 28(11):1178–1193

Stam CJ, Van Dijk BW (2002) Synchronization likelihood: an unbiased measure of generalized synchronization in multivariate data sets. Physica D 163(3–4):236–251

Vicente R, Wibral M, Lindner M, Pipa G (2011) Transfer entropy–a model-free measure of effective connectivity for the neurosciences. J Comput Neurosci 30(1):45–67

Vinck M, Oostenveld R, van Wingerden M, Battaglia F, Pennartz CMA (2011) An improved index of phase-synchronization for electrophysiological data in the presence of volume-conduction, noise and sample-size bias. NeuroImage 55(4):1548–1565

Westlake KP, Hinkley LB, Bucci M, Guggisberg AG, Findlay AM, Henry RG, Nagarajan SS, Byl N (2012) Resting state alpha-band functional connectivity and recovery after stroke. Exp Neurol 237(1):160–169

Wiener N (1956) The theory of prediction, Modern mathematics for engineers. McGraw-Hill, New York, pp 165–190

Winter WR, Nunez PL, Ding J, Srinivasan R (2007) Comparison of the effect of volume conduction on EEG coherence with the effect of field spread on MEG coherence. Stat Med 26(21):3946–3957