Synchronization Between Sources: Emerging Methods for Understanding Large-Scale Functional Networks in the Human Brain

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Abstract This chapter summarizes currently available techniques for measuring synchronization between neural sources identified through EEG and MEG recordings. First the evidence for the involvement of neural synchronization in the implementation of cognitive processes is described. This involvement is mainly through the provision of high-quality communication between active brain regions, allowing integration of processing activities through the exchange of information and control signals. Second, we describe several useful techniques for obtaining phase information from time series of EEG and MEG records, and measuring phase locking or phase coherence using these methods. These include wavelet analysis and the analytic signal using the Hilbert transform for obtaining phase information, and phase-locking value and coherence for obtaining useful indices of synchronization. Finally, we summarize several available techniques for locating neural sources of EEG and MEG records and describe the use of the phase-locking measurements in ascertaining synchronization between sources located with these techniques. The techniques include those involving blind separation of sources, such as independent component analysis or principle component analysis, and those involving use of brain anatomy to constrain source locations, such as beamformer or LORETA. We also provide a few examples of published or forthcoming research that has used these approaches. All of the techniques described are available either in commercial software (such as BESA and MATLAB) or in freeware that runs in MATLAB (such as EEGLAB, Fieldtrip, Brainstorm). Some custom programming might be required (e.g., in MATLAB using the Signal Processing Toolbox) to implement some of the measurements.

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1 Introduction: Oscillatory Synchronization and Dynamic Functional Neural Assemblies

The brain oscillates and synchronization of these oscillations have been theoretically and empirically linked to the dynamic organization of communication in the nervous system. Task-dependent neural synchronization is a general phenomenon. It has been observed at various scales ranging from single unit recordings to large-scale cortical dynamics, and has been associated with diverse functions including motor activity, working memory, associative memory, attention, object recognition, awareness, and perceptual organization (e.g., Schnitzler and Gross, 2005a; Tallon-Baudry et al., 1998; Miltner et al., 1999; Rodriguez et al., 1999; Bhattacharya et al., 2001; Doesburg et al., 2008; Burgess and Ali, 2002; Gruber et al., 2002). Moreover, disturbance of oscillatory rhythms and decreased synchronization have been associated with a wide ranging set of disorders including schizophrenia, Parkinson's disease, essential tremor, autism, dyslexia, and Alzheimer's disease (Llinás et al., 2005; Uhlhass and Singer, 2006; Schnitzler and Gross, 2005a). Given this evidence of involvement with both normal and abnormal psychological processes, it is not surprising that the study of oscillatory rhythms and their synchronization in the brain is a subject of growing interest. This chapter briefly summarizes the history of the field beginning with work performed using implanted electrodes and recordings from the scalp. Various approaches to the estimation of the brain generators giving rise to scalp activity, as well as how synchronization between those sources can be calculated, also will be surveyed. Calculation of synchronization between neural sources is a nascent field populated by several competing methods. We will discuss the strengths, weaknesses, and achievements of several of these approaches. It is beyond the purview of this chapter to provide a complete guide to synchronization analysis of EEG and MEG data. Instead, the chapter provides a guide for the investigator interested in surveying the available options or the student wishing an introductory overview. The chapter assumes a working knowledge of oscillation, synchronization, and basic signal processing (e.g., Fourier analysis).

Neurons oscillate, cortical columns oscillate, and from such choruses emerge large-scale oscillatory population dynamics reflecting the activity of millions of cells. When two neurons (or two neural populations) oscillate synchronously, bursts of action potentials can be consistently exchanged during the depolarized phase of the target neuron's ongoing membrane potential fluctuations, thereby increasing fidelity of communication between these neurons (Fries, 2005). This mechanism has been proposed as a means by which the brain is able to selectively integrate relevant neural populations at each moment in order to construct dynamic functional brain networks that perform various cognitive tasks, and/or to bind the spatially distributed brain representations of features of percepts (Varela et al., 2001). The first empirical evidence for this mechanism was the observation that gamma-band oscillations recorded from cat primary visual cortex synchronize when columns of neurons respond to a common object (Gray et al., 1989). It was subsequently observed that the perception of coherent, integrated objects also involves gamma-band synchronization across cortical regions (long-distance synchronization). This phenomenon expresses itself in EEG scalp recordings as synchronization between electrodes associated both with recognition of a familiar object, and with the perception of a meaningful figure in an ambiguous stimulus (Engel et al., 1991b, a; Frein et al., 1994; Gruber et al., 2002; Rodriguez et al., 1999). It is clear that selective synchronization of relevant neural populations across long distances is a general principle for organizing communication in the brain as it is also associated with many cognitive processes (Ward, 2003; Jensen et al., 2007). To refer such phenomena to a Hebbian frame, imagine that recurrently co-activated sets of connected neurons form stable, distributed networks relevant for a particular representation or function, and that when this constellation is ignited and integrated into a large-scale assembly it embodies the perception or task performance at hand (i.e., Hebb, 1949). Alternatively stated, the complex functions expressed by the brain require that particular sets of neural populations cooperate to perform a given task or to bind the features of a percept. Given the manifold mental processes that characterize human mental life, and the universe of perceptions of which we are capable, it must be the case that functional connectivity in the brain can be quickly reorganized, emerging from its constituent elements (Başar, 2006). Selective synchronization of oscillations between relevant neural populations provides a solution to this problem, as synchronously oscillating neurons exchange information more effectively (Varela et al., 2001; Fries, 2005).

2 Methods for the Analysis of Oscillatory Synchronization

Several different approaches have been employed for the calculation of synchronization between oscillating signals. Most successfully employed among these are the phase-locking value (PLV) approach, in which the phases of oscillators are obtained using wavelet analysis or by calculating the analytic signal using the Hilbert transform, and phase cross-coherence analysis. Such methods aim to identify the phases of pairs of oscillators within a relatively narrow bandwidth of frequency, and to assess synchronization between those oscillators by quantifying the stability of the phase relationship between the two. The PLV and coherence techniques will be reviewed here, as they constitute the core methods for the study of synchronization between localized sources of brain activity. Alternative methods exist for the analysis of synchronization, such as mutual information, Shannon entropy, and synchronization likelihood. We shall focus our discussion here, however, on PLV and phase cross-coherence analysis, as these have been most successfully employed in EEG and MEG studies. An important decision lies in the choice of how one partners a particular form of synchronization analysis with any of the numerous approaches to source analysis, and successful marriages of such techniques will be discussed later. It should also be noted that synchronization between EEG and MEG signals draws upon a rich body of work addressing oscillatory synchronization as a general concept for physical systems, and the aspiring investigator would be well served to seek an understanding of such principles (e.g., Pikovski et al., 2001).

2.1 Wavelet Analysis: Application to Phase-Locking Analysis

The most common method to obtain the phase of an oscillator for EEG and MEG PLV analysis is wavelet analysis. Here, instead of decomposing a signal into cosine waves with different phase offsets, as is done in Fourier analysis, the signal is decomposed into various versions of a standard wavelet (a short section of a cosine wave). The wavelet coefficients, which are the output of this analysis, represent the similarity of a particular wavelet, usually the Morlet wavelet (which is the product of a sinusoidal wave with a Gaussian or normal probability density) to the signal at various times and in various relevant frequency bands. In most applications (e.g., Le Van Quyen et al., 2001) an EEG or MEG signal, $h(t)$, is filtered into small frequency ranges using a digital band-pass filter and then the wavelet coefficients, $W_h(\tau, f)$, which are complex numbers, are computed as a function of time, τ, and center frequency of each band, f, from

$$W_h(\tau, f) = \int_{-\infty}^{\infty} h(t)\, \Psi^*_{\tau,f}(u)\, du \tag{1}$$

where $\Psi^*_{\tau,f}(u)$ is the complex conjugate of the Morlet wavelet defined by

$$\Psi_{\tau,f}(u) = \sqrt{f}\; e^{i2\pi\, f(u-\tau)}\; e^{-\frac{(u-\tau)^2}{2\sigma^2}} \tag{2}$$

The complex conjugate of a complex number $z = x + iy$ is defined as $z^* = x - iy$. For a given time and frequency, $\Psi^*_{\tau,f}(u)$ is a function only of σ, the standard deviation of the Gaussian density function (proportional to the inverse of f), which determines how many cycles of the wavelet are to be used. The number of cycles, $nc = 6f\sigma$. The frequency resolution of the analysis, i.e., the frequency range for which the phase is measured, is determined by σ because the range of frequencies analyzed is about from $f - 4f/nc$ to $f + 4f/nc$. For 40 Hz, for example, the frequency range would be from 20 to 60 Hz for $nc = 8$. This is in spite of the fact that we may have filtered so that the signal being analyzed is narrow band and only ranges from, say, 38 to 42 Hz. This illustrates an important property of wavelet and other multiresolution analyses: at low frequencies, frequency resolution is good but time resolution is poor whereas at high frequencies time resolution is good but frequency resolution is poor. Note that the poorer the frequency resolution, the less meaningful the phase. It is a common practice (e.g., Delorme and Makeig, 2004; Le Van Quyen, et al., 2001) to use fewer cycles of the wavelet for lower frequencies (e.g., three cycles for 6 Hz) and more cycles for higher frequencies (e.g., eight cycles for 40 Hz) with number of cycles increasing roughly linearly with frequency between these limits.

The wavelet transform supplies both the amplitude of the envelope of the signal and the phase at each time point available (see Fig. 1). This is because the wavelet is passed along the signal from time point to time point, with the wavelet coefficient for each time point being proportional to the match between the signal and the

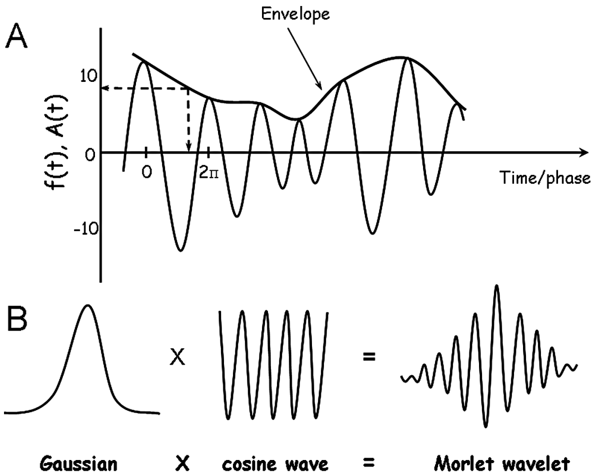

Fig. 1 (**A**) The amplitude envelope and phase of a sinusoidal signal. (**B**) A Morlet wavelet-like those used in wavelet analysis to obtain amplitude and phase of a sinusoidal signal like that in (**A**)

wavelet in the vicinity of that time point; this is closely related to the amplitude of the envelope of the signal at that time. The instantaneous phase at that time point, on the other hand, is the phase offset between the natural oscillation of the wavelet and the oscillation of the signal. Both of these are reflected in the wavelet coefficients. The difference between the phases of two signals, j and k, say one from each of two neural sources, can be computed from the wavelet coefficients for each time and frequency point from

$$e^{i(\phi_j(\tau,f)-\phi_k(\tau,f))} = \frac{W_j(\tau,\, f)\; W_k^*(\tau,\, f)}{\left|W_j(\tau,\, f)\; W_k(\tau,\, f)\right|} \tag{3}$$

Relative stability of this phase difference across time represents stochastic phase locking between the signals.

2.2 The Hilbert Transform: Application to Phase-Locking Analysis

Another effective technique available for obtaining the instantaneous phase of a signal is to use the Hilbert transform to obtain the analytic signal. The analytic signal, invented by Gabor (1946), is defined for a measured function of time, $h(t)$, as

$$\varsigma(t) = h(t) + i\,\tilde{h}(t) = A(t)e^{i\phi(t)} \tag{4}$$

where $\tilde{h}(t)$ means the Hilbert transform of $h(t)$,

$$\tilde{h}(t) = \frac{1}{\pi} P.V. \int_{-\infty}^{\infty} \frac{h(t)}{t-\tau}\, d\tau, \tag{5}$$

$i = \sqrt{-1}$, and P.V. indicates a special meaning of the improper integral (Pikovski et al., 2001). The Hilbert transform shifts a signal's phase by $\pi/2$. Thus, the real $(h(t))$ and imaginary $(i\tilde{h}(t))$ parts of the analytic signal are shifted by $\pi/2$.

In Eq. (4), the instantaneous amplitude is $A(t)$ and the instantaneous phase is $\phi(t)$. $A(t)$ is the amplitude of the envelope of the signal, and $\phi(t)$, the instantaneous phase, is the quantity that would be entered into computations involving measurement of synchronization, as when two sources are being compared (again, see Fig. 1). The Hilbert transform can be computed across relatively short epochs (say 1500 ms) or even across an entire EEG or MEG record (although available computer resources might make this infeasible). The latter approach should be viewed as preferable, given that the Hilbert transform produces distortions at the beginning and end of each analyzed data segment as it is based on an integral taken from $-\infty$ to $+\infty$. Such "edge effects" are particularly pronounced at lower frequencies. A practical solution for this problem is to apply the Hilbert transform to a time series that extends in both directions beyond the region of interest and to simply discard values near the beginning and end of each segment. Instantaneous phase is only meaningful for narrow band signals, so filtering must be done before the analytic signal is computed. This is usually accomplished, as for the wavelet analysis, by applying a digital band-pass filter to the recorded EEG or MEG signals. We have found that a filter having a pass-band of $f \pm 0.05f$ is effective (e.g., for $f = 10$ it is from 9.5 to 10.5 Hz).

2.3 Phase-Locking Value

Phase-locking value or PLV is a measure of synchronization that has been successfully employed in a variety of experiments and that we regard as the best method for the assessment of task-dependent EEG and MEG phase synchronizations. PLV measures the relative constancy of the difference of phases between two signals, here assumed to be from neural sources, as computed either by the wavelet transform or using the analytic signal, across the trials of an experiment. These trials are represented in the signals as epochs time-locked to a particular repetitive stimulus or response (Lachaux et al., 1999). PLV is defined as

$$PLV_{j,k,t} = N^{-1} \left| \sum_{N} e^{i[\phi_j(t) - \phi_k(t)]} \right| \tag{6}$$

where $\phi_j(t)$ and $\phi_k(t)$ are the phases of sources j and k at time point t for each of the N epochs considered (Lachaux et al., 1999). PLV ranges from a maximum of 1, when the phase differences are exactly the same across all N epochs, to a minimum of 0, when the phase differences vary randomly across the different epochs. In real data neither of these extreme values can be observed, but values close to 1 or 0 are often seen. PLV is the length of a resultant vector in the complex plane when each phase difference, $\phi_j(t) - \phi_k(t)$, is represented by a unit-length vector in the complex plane, and it is proportional to the standard deviation of the distribution of phase differences (see Fig. 2). Changes in PLV over time, in the absence of confounding factors such as volume conduction, reflect changes in the synchronization of the neural activity in a particular frequency band inferred from the sources.

If the recorded EEG or MEG signal is filtered into several frequency ranges, and PLV is then calculated for each sample point available for a particular pair of neural sources, then a time–frequency plot of PLV can be made. Typically baseline-corrected PLVs (written as $\mathrm{PLV_z}$) are plotted rather than raw PLVs. This is done to remove the record of ongoing synchronization unrelated to task demands. Normalization of PLVs is accomplished by subtracting the mean baseline PLV from the PLV for every data point and dividing the difference by the standard deviation of baseline PLV. We have found that a useful baseline is a time period of several hundred milliseconds just before the presentation of the stimulus to which the epochs are time-locked.

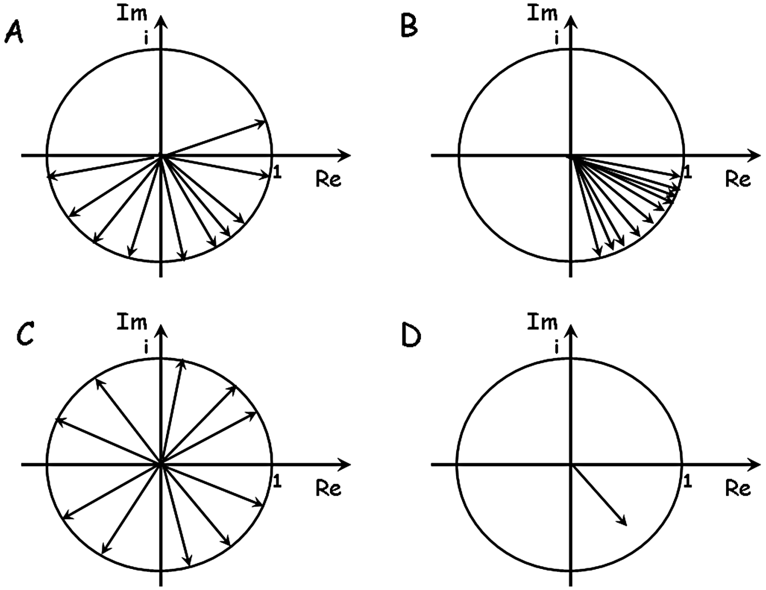

Fig. 2 (**A**) Unit vectors in the complex plane representing phase differences at a particular time–frequency point in the baseline period across 10 trials of an experiment. (**B**) Vectors representing phase differences that are more concentrated, and thus more phase locked, than during the baseline period, indicating an increase in synchronization. (**C**) Vectors representing a decrease in phase locking relative to the baseline period. (**D**) A vector representing a PLV value similar to that indicated by the fan of vectors in (**B**)

The study of phase synchronization in the human brain remains a nascent enterprise and consequently there is no developed statistical theory for the assessment of normalized PLVs, although progress in this direction has been made for phase concentration of single signals with respect to a repeated stimulus (e.g., Martínez-Montes et al., 2007). As we await the development of better techniques, surrogate statistics stand in as a common metric for ascertaining statistical reliability (Le Van Quyen et al., 2001). Surrogate $\mathrm{PLV_z}$ distributions are created for each frequency and time point available by randomly shuffling the epochs for one or both of the sensors and recomputing $\mathrm{PLV_z}$ for the scrambled data, a large number of times (in our work 200 times). As the temporal relationships between pairs of sources are random in the shuffled data, the surrogate distribution of $\mathrm{PLV_z}$ values represents a null distribution over the same actual data. If a $\mathrm{PLV_z}$ value exceeds either the 97.5th (or higher if a more conservative test is desired) or is less than the 2.5th (or lower) percentile of the surrogate distribution, then the $\mathrm{PLV_z}$ is considered to represent a significant increase (decrease) in synchronization at an alpha level of 0.05. Although our own analyses employ custom software, a similar PLV analysis has been implemented in commercially available EEG analysis software such as Brain Electrical Source Analysis (BESA 5.1, Megis Software, Germany). Moreover, the PLV analysis implemented in BESA has already been used to determine synchronization between neural sources (Sauseng et al., 2007).

2.4 Phase Cross Coherence in the Assessment of Human Brain Synchronization

Phase cross coherence should not be confused with linear coherence, which we do not recommend for estimating synchronization between EEG and MEG signals. Linear coherence (e.g., Delorme and Makeig, 2004) is defined in terms of wavelet coefficients as

$$LC_{1,2}(f,t) = \frac{\sum\limits_{k=1}^{N} W_{1,k}(f,t)W_{2,k}^{*}(f,t)}{\sqrt{\sum\limits_{k=1}^{N} \left|W_{1,k}(f,t)\right|^{2}}\sqrt{\sum\limits_{k=1}^{N} \left|W_{2,k}(f,t)\right|^{2}}} \tag{7}$$

where $W_{1,k}(f,t)$ is the wavelet coefficient for signal 1 at frequency f and time t and $W_{2,k}^{*}(f,t)$ the complex conjugate of the corresponding wavelet coefficient for signal 2. The problem with linear coherence is that it confounds phase synchronization with correlated amplitude changes between the signals. It is not useful for EEG and MEG synchronization analysis because phase synchronization and local amplitude changes can reflect very different neural processes (i.e., Palva and Palva, 2007). Phase cross coherence between signals across trials, N, is a much more desirable measure as it does not suffer from this defect. It is defined in terms of wavelet coefficients as

$$CC_{1,2}(f,t) = \frac{1}{N}\sum_{k=1}^{N}\frac{W_{1,k}(f,t)W_{2,k}^{*}(f,t)}{\left|W_{1,k}(f,t)W_{2,k}(f,t)\right|} \tag{8}$$

(e.g., Delorme and Makeig, 2004). In Eq. (8) the denominator, which is the magnitude of the cross product of the wavelet coefficients, is responsible for canceling out the amplitude information and thus leaving only a function of the phase difference to be averaged across trials. This index too varies between 1 (for perfect phase locking) and 0 (for a random phase relationship). Phase coherence analysis can be implemented using freely downloadable EEG analysis toolboxes which run in MATLAB (The MathWorks, Inc.), such as EEGLAB (Delorme and Makeig, 2004).

3 Dynamic Brain Networks: Synchronization Between Sources

Although determination of synchronization between electrical or magnetic signals recorded from the human scalp has provided a vista of functional brain dynamics, such determinations inevitably suffer from an inability to claim any specifics about the putative brain regions involved in the generation of long-range synchronization effects. Determination of synchronization between scalp signals also suffers from contamination by volume conduction, which is the propagation of a signal from a single source to multiple recording sites, in this case giving rise to spurious synchronization (e.g., Doesburg et al., 2008; Lachaux et al., 1999). This problem is compounded by the certainty that any scalp-recorded signal consists of a superposition of signals from various neural sources (e.g., Domínguez et al., 2007; Menecke et al., 2005). Numerous advances have provided some means for the reduction of volume conduction and for the estimation of the magnitude of its effects (i.e., Doesburg et al., 2008; Nunez et al., 1997, 1999). Nevertheless, volume conduction and signal superposition remain concerns for studies reporting synchronization between electrodes or sensors placed on or near the scalp. Implanted electrodes, conversely, leave no doubt that their signals originate from near the sensor, but such studies are blind to any activity occurring away from the recording sites. This is a particularly pronounced deficit in studies using electrodes implanted in humans, as the placement of these sensors is typically performed according to the goals of medical procedures and not those of scientific investigation.

Elucidation of dynamic, synchronously oscillating networks in the brain requires the localization of the generators of task-relevant oscillatory brain activity, and subsequently, estimation of phase synchronization between those sources. This step is necessary if strong claims are to be made about the putative engagement of specific brain regions in large scale, synchronous, oscillatory brain networks. Moreover, such analyses make some progress toward solving the related problems of spurious synchronization induced by volume conduction and by signal superposition. In pursuit of this end, we will summarize various approaches to EEG/MEG source localization, survey their relative strengths and weaknesses, and discuss some studies that have successfully combined source localization with long-distance phase synchronization measures. We will also point to available software for the implementation of each of the source-localization techniques. The nascent merger of source localization with synchronization analysis signifies the crossing of an important threshold in the study of neural dynamics, and the perfection of such unions will be critical to further advances in the field.

3.1 Synchronization Between Sources Using "Blind" Source Separation

Source localization techniques used in EEG and MEG analysis fall broadly into two categories, those that are "blind" and rely solely on the identification of statistically independent components that account for some portion of the variance in the signal, and those that utilize some form of model of the human head, accounting for its dimensions and conductivities in an attempt to relate signals measured at the scalp to their neural origins. Blind source-separation techniques for EEG and MEG data most commonly employ either independent component analysis (ICA) or principal component analysis (PCA). ICA attempts to separate the superimposed recorded time series of potential, current, or magnetic field variations arising from different neural sources by reversing the superposition of such signals (Onton et al., 2006). This is accomplished for the recorded data matrix, X, consisting of n channels by t time points, by using a neural network to discover an "unmixing" matrix, W, that when multiplied by the data matrix produces a matrix, U, of maximally temporally independent components: $U = WX$. The criterion for independence is a non-parametric, informational one, i.e., the components of U share minimal mutual information with each other (e.g., Ungureanu et al., 2004). Thus, the various independent components also have minimal, higher-order statistical relationships with one another although they are *not* necessarily (or typically) orthogonal in the correlation sense. Scalp maps of the independent components that account for significant amounts of the variance in the recorded signal can be computed from the inverse of the unmixing matrix, W^{-1}, and these can be used to fit equivalent dipoles to characterize the anatomical location of the neural sources presumed to be responsible for those components. Equivalent dipole fitting can be accomplished using a range of software packages including BESA (BESA 5.1, Megis Software, Germany) and EEGLAB (dipfit 2 plugin, Delorme and Makeig, 2004). Often the location of the best-fitting dipole is anatomically implausible, i.e., outside the head or in white matter; such components are probably artifacts of some sort (e.g., muscle movements) and can be eliminated from consideration. When the location is anatomically plausible, and the fit is good enough, then the dipole can be taken to be a useful representation of a neural source and its relationships to other such sources can then be ascertained.

One problem that arises with the fitting of dipoles, unlike other source-localization methods discussed below, is that it does not result in a unique solution. Or rather, many different solutions with the same number of dipoles, varying only slightly in location, orientation, and strength, and having nearly the same residual variances, are possible. Moreover, by adding dipoles to the solution set, ever better solutions can be found. Thus, assumptions brought to bear by the researcher, such as whether or not bilateral activation is expected, must be used to discover the most useful solution. One approach that is relatively free of biases is to insist that each independent component be accounted for by a single, best-fitting dipole that has residual variance less than some criterion (often 5%) and is anatomically plausible or even predicted before the experiment. This ensures that researcher biases will not result in over-interpretation of the data.

ICA analysis has proven to be well suited to source localization in the study of dynamic networks, as many of the components identified by this method do represent the activities of single anatomical sources. Importantly, when the number of recorded data channels is large enough (31 or more), ICA can reveal multiple sources of this type (Onton and Makeig, 2006; Onton et al., 2006). Given this, it is unsurprising that ICA has been successfully combined with phase cross coherence analysis in high-density EEG data, such as in the study of oscillatory synchronization in pain networks (Drewes et al., 2006).

Synchronization between oscillatory sources, it should be noted, is itself a form of temporal dependency. The study of task-dependent phase synchronization, however, has found many synchronization effects to be relatively short lived, and transient synchronization effects are thus possible between components identified as independent over entire data segments. This is particularly true when ICA is applied to a time series of recordings before they have been divided into stimulus- or response-relevant epochs. Also, the maximal informational independence criterion in ICA implies only that a solution is found in which mutual information among all possible pairs of components is minimal, not zero. Moreover, mutual information is minimized for the total signal, which contains a mixture of amplitude and phase information, whereas the phase cross-coherence measure is unaffected by any correlations, or lack thereof, of the amplitude envelopes of the two sources. Thus phase cross-coherence can be observed between two sources even when variations in their activity over time have been identified as maximally temporally independent. Another practical question is whether ICA is to be applied to data that have already been subjected to narrow band-pass filtering or whether it is used to identify components of broadband signals and spectral information from these sources is determined thereafter. Identification of components within specific frequency ranges carries greater neural meaning. It is more likely, however, that task-relevant synchronization would be preserved between components showing maximal temporal independence across a wider frequency spectrum, given that functional synchronization is typically expressed in a narrow frequency range.

Principal component analysis is another method of blind separation that has been effectively employed for EEG source localization. It is a parametric method that creates a series of mutually orthogonal components that each explain as much of the remaining data variance as possible. It utilizes the linear correlations between pairs of signals as a starting point and creates successive components all of whose pairwise correlation coefficients are zero. Principal component analysis can be used to separate multichannel EEG or MEG data into temporally and spatially independent components that can often be associated with particular neural generators, as in ICA (Chapman and McCrary, 1995). Such neural sources could then be studied for synchronization in the same way as those derived from ICA. One drawback of PCA is that it attempts to lump together as much of the data variance as possible into each component, even though it may include several temporally independent sources. In contrast ICA attempts to split apart such sources. Thus, ICA is probably the preferred technique to discover temporally independent neural sources. In the context of oscillatory dynamics, however, it should be noted that PCA can also be used to decompose EEG data into its composite time–frequency components (Lagerlund et al., 2004; Bernat et al., 2005). PCA is a widely used tool in EEG analysis and is implemented in various software analysis suites, such as BESA and EEGLAB.

3.2 Synchronization Between Neural Sources Identified Using Anatomical Constraints

A second family of analysis techniques that has proven to be useful in the localization of EEG and MEG generators uses some form of head model to constrain solutions. Like “blind” separation techniques, this group of methods also uses spatial and temporal independence to assign activations to various neural locations. Such activations, however, are assigned directly in “brain space” by applying models of the human head that take into account various properties, such as the conductance of the skull, scalp, and brain.

A preeminent technique for the localization of oscillatory sources in cognition that has borne increasingly promising fruit is beamformer analysis. Beamformer analysis produces an estimate of the unique contribution of each voxel in a source space to activity measured at or near the scalp. It does this by creating a set of spatial filters that linearly pass contributions from a given voxel while reducing contributions from all other voxels within a designated time–frequency window (Van Veen et al., 1997). Beamformer and all similar approaches begin by assuming the equivalent dipole model of a neural generator for each voxel in a source space (brain). Here, however, additional constraints, such as minimizing the variance of the filter output while allowing the entire signal at the selected voxel to pass (Van Veen et al., 1997), are imposed that yield a unique solution, unlike unconstrained dipole fitting. Perhaps most seminal and prolific among this family is the “dynamic imaging of coherent sources” (DICS) approach, which has been principally employed in the study of functional networks in the motor system (Gross et al., 2001; Schnitzler and Gross, 2005b). The DICS method was designed specifically for the study of coherence across multiple localized sources of oscillatory activity and its efficacy has been robustly demonstrated in imaging task-dependent activation in the motor system (i.e., Pollok et al., 2005; Timmermann et al., 2004). Although much published work using DICS has been performed by the progenitors of the technique, it has now been implemented in software analysis packages such as Fieldtrip, which runs as a toolbox in MATLAB.

Other variants of beamformer analysis suitable for the determination of multiple sources can be found in commercially available software such as the BESA suite (BESA 5.1; Megis Software, Germany). Such software applications have proven to be effective in revealing the sources and timing of oscillations relevant to cognitive processes such as endogenous attention control. For example, Green and McDonald (2008) used BESA beamformer to uncover a series of activations in theta-band-filtered EEG signals as human subjects performed a visual attention orienting task. The order and timing of activations (early visual cortex, parietal lobe, frontal cortex, parietal lobe, and early visual cortex again) corresponded to the expected sequence of activations involved in orienting visual attention to a specific region of visual space under endogenous control. Recently we combined theta-band beamformer sources identified from EEG data by BESA with PLV analysis to reveal task-dependent synchronization effects between sources in the context of both auditory and visual endogenous attention orienting. In our analysis of visual attention orienting, parietal and occipital sources identified by Green and McDonald (2008) were synchronized in the alpha band, continuously from about 300 ms after cue onset until the target appeared, on the side contralateral to the visual field toward which orienting was taking place (Doesburg et al., 2008, unpublished). In our analysis of auditory attention orienting, synchronization between activated brain areas occurred mainly when activity in one area was declining while activity in another was increasing, indicating that information resulting from processing in the earlier area was being passed to the next area in the sequence (Green et al., 2008, unpublished). BESA beamformer is also effective at identifying neural sources within relatively short time windows, allowing for the mapping of sequentially activated sets of cortical regions embodying organized stages of processing underlying a complex process (Green and McDonald, 2008). Moreover, when PLVs are computed between generators identified in this manner, complementary long-range phase synchronization effects are revealed, suggesting that this method may prove fruitful in illuminating the evolution of functional network dynamics over relatively short periods of time (Green et al., 2008, unpublished).

Another productive manifestation of beamformer analysis can be found in synthetic aperture magnetometry (SAM) developed for MEG analysis (Vrba and Robinson, 2001). Event-related SAM (erSAM) has been used to uncover sources of neuro-magnetic activity associated with cognitive processing (Herdman et al., 2007; see Hillebrand and Barnes, 2005 for a review). Studies employing a combination of the beamformer technique (using both BESA algorithms and SAM) with PLV analysis have proven to be effective for elucidation of large-scale oscillatory synchronous brain networks. An example of this can be found in the analysis of phase synchronization between reconstructed sources of oscillatory activation. Convergent results have been found using BESA beamformer algorithms (EEG) and SAM analysis (MEG) in conjunction with the PLV technique (analytic signal approach). In both cases, when attention is endogenously deployed to one visual hemifield, increased synchronization in the alpha band is observed between reconstructed occipital and parietal sources in the contralateral hemisphere (Doesburg

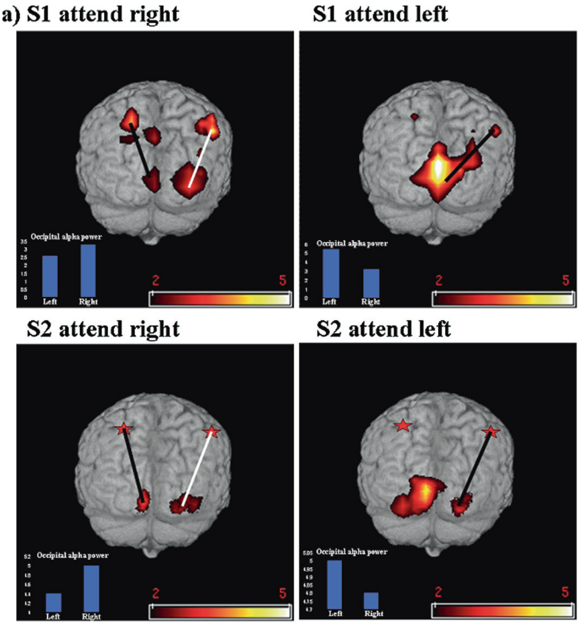

Fig. 3 Example of synchronization between SAM beamformer sources. *Black* (*white*) lines represent synchronization (desynchronization). *Reddish* areas represent alpha sources and *blue bars* represent local alpha power in early visual cortex for each hemisphere

et al., 2007, 2008, unpublished). Figure 3 shows SAM beamformer sources from the MEG experiment projected to the cortical surface, along with an indication of which sources are synchronized or desynchronized at the moment depicted (800 ms after an orienting cue was presented; black (white) lines indicate synchronization increases (decreases)). Interestingly, this lateralization of long-distance synchronization is inversely related to local occipital alpha power measurements in the same frequency range (Fig. 3, blue bar graphs), illustrating the complexity of the relationship between oscillatory synchronization and cognitive processing. More importantly, such results highlight the importance of using analysis techniques that separate phase synchronization from correlated local amplitude changes.

Perhaps the most elegant technique for the determination of locally coherent oscillatory sources and the extraction of epoched signals for phase-locking analysis is one in which minimum norm current solutions are employed in an iterative sequence to determine intertrial coherence and coherence between adjacent voxels for source reconstruction (David and Garnero, 2002; David et al., 2002, 2003). To date, however, this technique has only been used in the processing of brain responses entrained by flickering stimuli and has not been employed for the estimation of endogenous oscillatory activity (e.g., Cosmelli et al., 2004). Unfortunately, no widely accessible software exists for the performance of this state-of-the-art analysis. These methods, however, are well documented in the literature (above) and await reimplementation by an enterprising investigator.

Autoregressive techniques also have been employed for the estimation of multiple sources of task-relevant oscillatory activation within a particular frequency band. Sources identified using this method can be successfully combined with PLV analysis, as has been eloquently demonstrated in the study of gamma oscillations in the human object recognition network (Supp et al., 2007). The reliability of effects gained using this method has been demonstrated through replication (Gruber et al., 2008). Moreover, these source-localization effects and corresponding phase synchronization effects were obtained for high-frequency gamma-band signals. Localization of such rhythms is difficult as this frequency range contributes little to overall spectral power, but has been profusely evidenced as important to information processing in the cerebral cortex (Kaiser and Lutzenberger, 2005). Another advantage of this approach is that it has proven to be compatible with available methods for the calculation of Granger causality measures that can be used to index the causal direction of information flow between sources (Baccala and Sameshima, 2001). This is attractive because phase synchronization in the brain, which has been theoretically related to increased causal interaction, can thus be directly compared with just such a measure. The open source software used in all stages of this analysis, BioSig (Version 1.95), is freely available online at http://biosig.sourceforge.net/

Low resolution brain electromagnetic tomography (LORETA) (Pascual-Marqui et al., 1994) is another functional imaging method based on electrophysiological and neuroanatomical constraints. LORETA and its variants have been employed by many studies seeking to analyze ERP components as well as spectral components of EEG activation (see Pascual-Marqui et al., 2002 for a review). In view of this track record, LORETA also promises to be a useful method for the localization of neural generators in the study of long-distance neural synchronization.

4 Summary and Conclusion

The study of dynamic functional networks in the brain will require techniques to localize sources of activation and to determine synchronization between such sources. From our current point of departure there are many viable paths toward this goal. Which road is best will depend largely on the questions being addressed, and careful consideration must be given to which methods of synchronization analysis are combined with particular means of source imaging—not all methods may be compatible. Because these two streams of understanding have evolved, until relatively recently, as separate enterprises, the choosing of an appropriate pairing will be important. As the terrain here is varied, it is beyond the reach of this chapter to provide a walkthrough of each method, and providing one method would not adequately service those interested in various researches into this subject. We have accordingly provided an overview and primer to the various approaches thus far used to study synchronization between sources of brain activity.

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