Analyzing Neural Time Series Data: Theory and Practice

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This book was set in ITC Stone Serif Std by Toppan Best-set Premedia Limited, Hong Kong. Printed and bound in the United States of America.

Library of Congress Cataloging-in-Publication Data

Cohen, Mike X, 1979–
Analyzing neural time series data : theory and practice / Mike X Cohen.
pages cm.—(Issues in clinical and cognitive neuropsychology)
Includes bibliographical references and index.
ISBN 978-0-262-01987-3 (hardcover : alk. paper) 1. Neural networks (Neurobiology) 2. Neural networks (Computer science) 3. Computational neuroscience. 4. Artificial intelligence—Biological applications. I. Title.
QP363.3.C633 2014
612.8'2339—dc23
2013016461

10 9 8 7 6 5 4 3 2 1

25 Introduction to the Various Connectivity Analyses

How brain networks develop, function, and support cognition is a large and growing topic in many branches of neuroscience (Sporns 2011). Neural networks operate at multiple spatial and temporal scales (Varela et al. 2001), and considerable empirical research from multiple species, theories, and mathematical models over the past several decades points to oscillatory synchronization as being a key mechanism by which neural populations transmit information and form larger networks (Fries 2005; Salinas and Sejnowski 2001; Singer 1993). The purpose of this chapter is to provide an overview of the methods most commonly used to assess connectivity in cognitive electrophysiology and the issues involved in those analyses.

The term "connectivity" is used here to refer to any analysis for which more than one signal is considered at a time. This mostly refers to two signals from two different electrodes but can also refer to two signals from the same electrode or multiple signals from multiple electrodes. The term connectivity includes measures based on phase and on power using a variety of linear and nonlinear methods. These analyses often have disparate assumptions and utilize different aspects of the EEG signal but share the common goal of identifying brain connectivity; thus, the term connectivity is used to refer generally to all analyses that share this goal.

25.1 Why Only Two Sites (Bivariate Connectivity)?

Most but not all brain connectivity measures are bivariate, meaning that they involve interactions between only two brain regions/electrodes. Some brain connectivity measures may initially seem multivariate (one-to-all or all-to-all connectivity) but are in fact mass-bivariate measures because each step of the analysis involves connectivity between only a pair of electrodes.

Why are most connectivity measures bivariate? Perhaps this is related to our still-infantile view of brain interactions in which there are few detailed models of multinode networks that are widely used in cognitive electrophysiology. This is possibly due to a paucity of approachable and intuitive mathematical/statistical analyses for quantifying larger and more complex networks. From a practical perspective, increasingly complex models of multinode brain interactions become increasingly difficult to conceptualize, and thus, it is easier to break them down into a set of simpler bivariate cases. For this reason, bivariate connectivity analyses are easier to implement, interpret, and test with established statistical procedures. Another possible reason for the abundance of bivariate connectivity methods is that the brain really works that way, and bivariate connections are the most relevant types of connections for many cognitive functions.

The focus in this book on bivariate connectivity methods is due to the practical reason listed above: bivariate methods are easier to understand, implement, visualize, and statistically quantify. This is in no way a rebuke of multivariate connectivity methods or an endorsement of the idea that only bivariate connections are relevant to brain function. The chapter on graph theory (chapter 31) provides an introduction to some multivariate network analyses.

You should be aware that bivariate correlations can inflate or misrepresent estimates of relationships if the network structure is actually multivariate (an example of this is shown in figure 25.1A). This is particularly relevant for brain connectivity because the brain is a highly multivariate system. For task-related connectivity this potential inflation is mitigated somewhat by condition comparisons because inflated connectivity estimates should affect all conditions, and therefore, the inflation should subtract out during condition comparisons of connectivity.

25.2 Important Concepts Related to Bivariate Connectivity

The following five points should be kept in mind when you are interpreting results of bivariate connectivity analyses.

First, for many (though not all) types of connectivity analyses, the phase lag between the two electrodes is not taken into consideration. What matters is that the phase lag is consistent across time and/or trials. This means that connectivity between a pair of electrodes that are 0 ms, 10 ms, or 100 ms lagged from each other can be equally strongly synchronized. Most measures of connectivity provide information regarding the phase lag, although this can be difficult to interpret in some cases (see next paragraph and figure 25.1).

Second, a nonzero phase lag in connectivity does not necessarily imply a causal or directed relationship. Nonzero connectivity lag can be considered supporting evidence consistent with a causal or directed relationship, but this should be interpreted cautiously. For example,

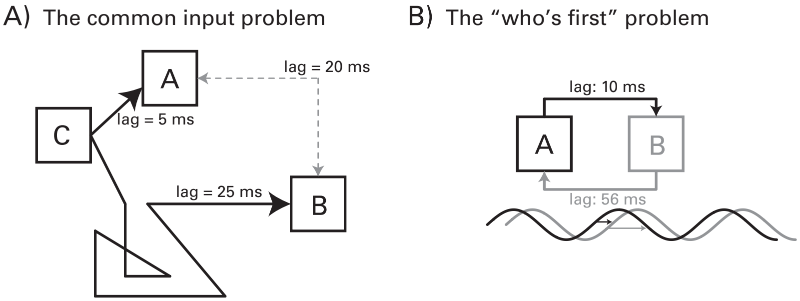

Figure 25.1
Two scenarios to keep in mind when interpreting temporally lagged bivariate connectivity results.

if region A and region B each are entrained with region C, and if the C → A connection is faster than the C → B connection, there may appear to be phase-lagged connectivity between A and B without a causal or even a direct interaction between them (figure 25.1A). This example also highlights a danger of interpreting a bivariate correlation in a multivariate network. Another example: given a phase lag of 10 ms between regions A and B that are synchronous at 15 Hz, it may be difficult to determine whether A leads B by 10 ms, or whether B leads A by 56 ms (figure 25.1B). An additional complication of interpreting phase lags between electrodes is that phase (and thus, the phase lag between two electrodes) may be influenced by the relative dipole orientations of the sources measured by the electrodes.

Some measures such as Granger prediction (chapter 28) and the phase-slope-index (chapter 26) provide better evidence for directed connectivity compared to connectivity measures based on phase angle distributions (chapter 26) or power correlations (chapter 27). Nonetheless, because the brain is an enormously complex and dynamic system, because it is not possible to record from all components of this system at the same time, and because data contain noise, it is difficult to determine unambiguously whether a pattern of bivariate connectivity is truly causal. If claims about directionality or causality are important for your experiment and for interpreting your results, use directional methods such as Granger prediction and try to buttress your interpretation of causality or directionality with theory, known anatomical directional connectivity, previous relevant research, and, if possible, causal interference methods such as transcranial magnetic or electrical stimulation.

Third, phase-based and power-based measures of connectivity tend to reveal different patterns of results. This is not surprising from a mathematical perspective because phase and power are mostly independent measures. Phase and power likely reflect different neurophysiological dynamics, with phase likely reflecting the timing of activity within a neural population and power likely reflecting the number of neurons or spatial extent of the neural population (chapter 21). However, the neurophysiological processes that contribute to phase-based versus power-based connectivity are not entirely clear, and too little cognitive electrophysiological research has been done to know when it is best to use phase-based versus power-based connectivity analyses, although phase-based connectivity is more commonly used in the literature. In general, however, phase-based connectivity analyses are useful for hypotheses concerning instantaneous connectivity (that is, at the same time, not necessary at zero phase lag), whereas power-based connectivity analyses are more robust to temporal offsets and jitters.

Fourth, a distinction can be made between functional and effective connectivity. Functional connectivity refers to linear or nonlinear covariation between fluctuations in activity recorded from distinct neural networks, and effective connectivity refers to a causal influence of activity in one neural network over activity in another neural network (Friston 1994). Thus, the distinction between functional and effective connectivity is analogous to a distinction between correlation and causation.

Fifth, many connectivity results can be confounded by volume conduction. Care must be taken to investigate and address this alternative hypothesis, and results must be interpreted cautiously in light of this potential confound and the ways to address it. This topic is discussed further in section 25.10.

25.3 Which Measure of Connectivity Should Be Used?

There are several classes of bivariate connectivity analyses (e.g., phase based vs. power based), several different analyses within each class, and several parameters and analysis options of each analysis. Each analysis has its advantages and limitations, and different measures are better suited for different purposes or assumptions about underlying neurocognitive processes. The following sections briefly describe the connectivity analyses discussed in this book and their advantages and limitations.

There is no correct or best connectivity method. Even when simulated data with known connectivity patterns are used, there may be no clear “winner” method that outperforms all other methods in all situations (Ansari-Asl et al. 2006; David, Cosmelli, and Friston 2004; Wendling et al. 2009). Some methods are more amenable to hypothesis testing, whereas others are more amenable to exploratory analyses. Some methods have a clear neurophysiological interpretation, whereas others are more based on computer science and engineering principles. Some methods are established and widely used, and other methods are novel and more open to development and validation. Although this plethora of connectivity methods may seem to complicate cognitive electrophysiology research, it also provides increased flexibility for custom-tailoring analyses to specific research questions or goals.

If you would like to test for connectivity but do not know which measure you should use, first consider your hypotheses and expectations and which methods are best suited to address your research questions. You can also use the same connectivity methods used in publications that have a similar experiment design or similar kind of data. In general, it is a good idea to start with commonly used connectivity methods that are appropriate for your hypotheses and apply more sophisticated or less established connectivity measures only when your questions are not addressed by the less sophisticated methods or when the less sophisticated methods are difficult to interpret (e.g., if spurious connectivity due to artifacts cannot be ruled out).

25.4 Phase-Based Connectivity

Phase-based connectivity analyses (described in greater detail in chapter 26) rely on the distribution of phase angle differences between two electrodes, with the idea that when neural populations are functionally coupled, the timing of their oscillatory processes, as measured through phase, becomes synchronized. The mathematics of phase-based connectivity analyses is similar to that underlying ITPC (chapter 19).

There are several advantages to phase-based connectivity analyses. They are widely used in many experiments and across many species, and they have been used to examine network formation and network dynamics on many spatial and temporal scales. This is partly because phase-based connectivity analyses have a neurophysiological interpretation. These analyses are computationally fast, and thus, the results can be inspected quickly, and the analyses require few assumptions or parameter selections other than the parameters already selected for the time-frequency decomposition. Some phase-based analyses are also insensitive to time lag (others are sensitive to lag), meaning that as long as the temporal relationship between activity at two electrodes is consistent over time and/or trials, the phase lag will not affect the strength of the connectivity.

There are also a few disadvantages. Phase-based measures rely on precise temporal relationships, usually in the identical frequency band, and are therefore susceptible to temporal jitter or uncertainty in the precise timing of experiment events. These temporal uncertainties can have more significant effects at higher frequencies, as discussed in chapter 19. Second, phase-based measures do not provide compelling evidence for directionality for reasons outlined in section 25.2 and figure 25.1B.

25.5 Power-Based Connectivity

Power-based connectivity analyses (described in greater detail in chapter 27) involve correlating time-frequency power between two electrodes across time or over trials. These correlations can be computed between activity in the same or different frequencies and at the same or different time points.

Power-based connectivity measures provide ample opportunities for flexible analyses that can be custom-tailored toward testing specific hypotheses, and they can also be used for data-driven exploratory analyses. Power-based connectivity measures are arguably the most similar to connectivity measures often used in fMRI such as the psychophysiological interaction (which is based on correlating the BOLD time series between pairs of voxels), because the correlated fluctuations in activity are relatively slower, compared to phase-based connectivity measures. Power-based connectivity measures are also relatively insensitive to temporal jitter and uncertainty, as was shown in figure 19.9.

25.6 Granger Prediction

Granger prediction (also called Granger causality; described in greater detail in chapter 28) tests whether variance in one signal can be predicted from variance in another signal earlier in time. Granger prediction is similar to, and in some cases identical to, other autoregression-based estimates of directed connectivity, including the directed transfer function (Kaminski et al. 2001) and partial directed coherence.

The main advantages of Granger prediction are that it tests for and can dissociate directional connectivity, that is, $A \rightarrow B$ versus $B \rightarrow A$ connectivity. It can ignore simultaneous connectivity, which makes it less susceptible to volume conduction. There are several sophisticated analyses of multivariate networks that are based on Granger prediction, although usually in the literature (and in this book), the "basic" bivariate Granger prediction analyses are applied.

There are a few disadvantages of Granger prediction. It is sensitive to violations of stationarity, can be computationally time-consuming to perform, and doubles the number of results because each pair of electrodes contains two connectivity values (estimates of both $A \rightarrow B$ and $B \rightarrow A$ connectivity). If Granger prediction is used in an exploratory fashion, there will be twice the number of statistical comparisons that need to be controlled for, and thus, Granger prediction may become tedious for large-scale exploratory analyses.

25.7 Mutual Information

Mutual information is a simple but robust method of detecting shared information between two variables. It is computed based on the distributions of values within variables and the joint distribution of two (or more) variables (see it described in greater detail in chapter 29).

There are several advantages of mutual information analyses. First, mutual information can detect many kinds of relationships, including linear and nonlinear interactions that a correlation would fail to identify. For example, a circle has a correlation coefficient of zero but a mutual information value greater than zero. Second, mutual information has a long tradition of use and development in engineering and information technology. Finally, there are also several extensions for using mutual information and entropy to estimate system complexity or signal transmission integrity (e.g., channel-coding theorem).

There are also a few disadvantages of using mutual information for examining brain connectivity. First, mutual information does not provide information as to whether a relationship is linear or nonlinear, or positive or negative. Second, it is sensitive to the number of histogram bins. This is easy to control for but could be a significant confound if not addressed during analyses. Third, it can be computationally intensive, particularly if used for exploratory analyses. Finally, although it is a widely used signal-processing technique and may be particularly advantageous for quantifying nonlinear interactions, it does not have a clear neurophysiological interpretation.

25.8 Cross-Frequency Coupling

Cross-frequency coupling (described in greater detail in chapter 30) refers to a statistical relationship between activities in two different frequency bands. It can be used to infer local organization (when measured at a single electrode) and long-range connectivity (when activity from the two frequency bands is measured from different electrodes). Cross-frequency coupling has been observed in several species and has been linked to cognitive and perceptual processes (Canolty and Knight 2010) and disease states (Allen et al. 2011).

There are several advantages of cross-frequency coupling. It provides findings that can be linked across species and to computational models, and there are theories proposing a key role of cross-frequency coupling in information processing in the brain (e.g., Lisman 2005). Cross-frequency coupling might also help identify task-related high-frequency power, which may be difficult to identify with EEG in trial-averaging-based analyses (Nunez and Srinivasan 2010).

The main disadvantage (which can be an advantage if you enjoy exploratory data mining) is that there is a potentially huge search space (frequencies × frequencies × electrodes × electrodes × conditions × time), which means that cross-frequency coupling analyses can be time-consuming and that there are many tests to control for during statistical evaluation. These can be minimized if you have hypotheses to help constrain the analyses.

25.9 Graph Theory

Graph theory (described in greater detail in chapter 31) is a mathematical framework for characterizing networks that can be represented as graphs containing nodes and vertices (for EEG connectivity, nodes and vertices are, respectively, electrodes and connectivity strengths). There are many analyses that fall under the umbrella term graph theory, and they are generally useful for providing summary information regarding large-scale or multivariate network dynamics.

There are several advantages of graph-theory-based analyses. They provide useful and often easy-to-interpret characterizations of multivariate networks. Because graph theory provides a general mathematical framework for conceptualizing networks, the same analyses can be applied to very different kinds of data, and high-level summary variables can be directly compared across, for example, EEG connectivity, diffusion MRI connectivity, and interneuron spike co-timing. Thus, graph-theory-based approaches can facilitate cross-methods and cross-species comparisons. Graph theory is arguably an underutilized analysis framework in cognitive electrophysiology that may provide novel insights into the electrophysiological network-level mechanisms of cognitive processes.

The main disadvantage of graph-theory-based measures is that they are often (although not always) used in exploratory data-mining analyses that lack a theoretical framework within which to understand the findings and link the results to other known functional properties of the brain. The reason this can be a disadvantage is that there are many graph-theory-based metrics that are used and relatively few applications, and it can be difficult to compare findings across studies that use different methods and that do not test specific hypotheses.

25.10 Potential Confound of Volume Conduction

Volume conduction is a potential confound that can lead to spurious connectivity results. There are two related concerns. First, sources in the brain generate large electromagnetic fields that are measured by more than one EEG electrode or MEG sensor, thus introducing

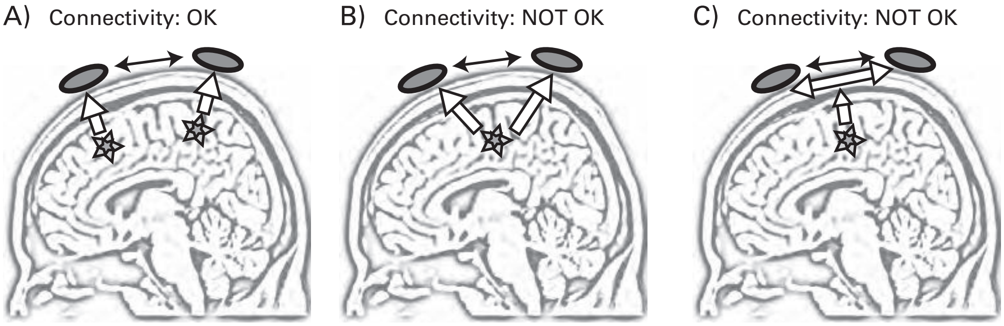

Figure 25.2
Illustration of the danger of volume conduction for interpreting interelectrode connectivity results. The black/gray rings represent electrodes, the black arrow between them illustrates measured connectivity, the stars represent neural sources in the brain, and the white arrows represent the path of electrical or magnetic activity from those sources. Ideally (panel A), each electrode measures only neural activity below the electrode, and thus, connectivity between two electrodes reflects connectivity between two physically distinct brain regions. Unfortunately, however, this situation cannot be assumed for EEG analyses: each electrode measures activity from overlapping brain regions (panel B), thus leading to the possibility that connectivity between two electrodes simply reflects those electrodes measuring activity from the same brain source. Furthermore, electrical fields can spread tangentially through the skull/scalp, causing further concern for EEG connectivity analyses (panel C).

spatial autocorrelation at the electrode level (figure 25.2B). This problem affects both EEG and MEG. The second issue is that electrical fields spread "laterally" through head tissues (skull, skin, etc.) and thus spread to neighboring electrodes (figure 22.1A and figure 25.2C). This problem affects EEG only; magnetic fields pass through these tissues undisturbed.

Volume conduction precludes an easy interpretation of brain localization based on electrode data, and it presents potential confounds for many but not all connectivity analyses. The confound is that connectivity between two electrodes could reflect true connectivity between different brain regions or could be due to those two electrodes measuring activity from the same brain sources (figure 25.2).

There are several options for addressing these potential confounds for connectivity analyses. No single option is optimal in all situations; instead, how you address this confound depends on the type of analysis performed and on the experimental design. It also depends on how hypothesis-driven versus exploratory your analyses are. Hypothesis-driven analyses typically involve a small number of tests. Thus, you might want to use analysis methods that have maximal sensitivity to detect true brain connectivity and then examine each effect for potential confounds. On the other hand, exploratory analyses typically involve a very large number of tests, and it is impractical to examine whether each finding may be contaminated by volume conduction. Thus, you might want to use methods that are insensitive to volume conduction even though those methods may have decreased sensitivity to detect true brain connectivity.

If your connectivity finding is an artifact of volume conduction, you can expect the following pattern of results:

1. *Zero or π phase lag* Because volume-conducted activity is recorded instantaneously at multiple electrodes (within measurement capabilities), spurious connectivity due to volume conduction will have zero phase lag (or π phase lag if the electrodes are on opposite sides of the dipole). However, this is complicated by the fact that there is true zero-phase-lag connectivity in the brain (Chawla, Friston, and Lumer 2001; Roelfsema et al. 1997; Viriyopase et al. 2012). Thus, zero-lag or π-lag connectivity can reflect volume conduction, or it can reflect true zero-phase-lag brain connectivity.
2. *Very strong connectivity at neighboring electrodes and a decrease of connectivity strength with increasing interelectrode distance* The relationship between connectivity and interelectrode distance is somewhat complicated by cortical anatomy and dipole orientation, but in general, spurious connectivity due to volume conduction will be stronger with electrodes that are closer to each other, particularly for EEG. An example of this is shown in figures 22.7 and 22.8.
3. *Positive correlations* In the frequency and time-frequency domains, spurious connectivity due to volume conduction can only cause positive correlations. Time-domain connectivity would show negative correlations if the two electrodes are on opposite sides of the dipole.
4. *Positive correlations between connectivity and power in the same frequency band* If volume conduction is driving the connectivity, changes in power should correlate with changes in connectivity.

If your connectivity results are consistent with these four predictions, you should be concerned that those connectivity results are artifacts of volume conduction. On the other hand, if your results fail to conform to these predictions, it is unlikely that your connectivity results are due to volume conduction.

There are at least 10 approaches to addressing the potential contamination of volume conduction. Some of these approaches help minimize but do not necessarily completely eliminate volume conduction; thus, you may need to combine several of the following strategies.

1. Apply a spatial filter prior to computing connectivity, such as the surface Laplacian or source imaging. Most spatial filters will attenuate effects of volume conduction and therefore

render the data more appropriate for connectivity analyses. The surface Laplacian is a good spatial filter for electrode-level analyses, and distributed adaptive source solutions such as beamforming are good spatial filters for source-space analyses. However, spatial filtering does not guarantee that volume conduction is completely eliminated (particularly for neighboring electrodes or neighboring voxels), so you should still be cautious of connectivity results after application of a spatial filter, particularly for electrodes that are physically close to each other.

2. Examine only negative correlations in the frequency or time-frequency domains. Negative correlations in power at the same frequency band cannot be due to volume conduction. This option is not always a feasible approach because whether negative correlations can be expected depends on your task and on your hypotheses.

3. Test for temporally lagged connectivity rather than zero-phase connectivity. Because volume conduction is instantaneous, temporally lagged connectivity is less affected by volume conduction. Keep in mind, however, that temporally lagged connectivity does not necessarily eliminate volume conduction for all analyses because of temporal autocorrelation. Imagine that you have a signal comprising random numbers that you filter at 5 Hz, and then you correlate that signal with a 10-ms-lagged version of itself. You would still see a strong correlation between the "two" signals because at 5 Hz, the activity at one point in time is strongly correlated with activity 10 ms later due to temporal autocorrelation (see figure 25.3). The strength of temporal autocorrelation depends on the time-frequency decomposition characteristics and on the frequency (lower frequencies have stronger temporal autocorrelation). Thus, temporally lagged connectivity measures help minimize volume conduction, but they do not eliminate it, particularly when the signals are first bandpass filtered.

4. Test for condition differences in connectivity rather than single-condition effects. Some types of biases that are introduced by connectivity analyses will affect all conditions equally. Thus, subtracting connectivity between conditions (or, in some cases, between electrode pairs) will attenuate biases and thus may also attenuate the effect of volume conduction. One example of this is shown in figure 25.3. This figure shows that spurious connectivity resulting from bandpass filtering a signal made from random numbers is attenuated when connectivity results are compared across "conditions" (in this case, conditions are simulated simply as two different signals).

5. Test for a cross-frequency correlation (e.g., whether 6-Hz activity in one electrode correlates with 20-Hz activity in another electrode). If the 6-Hz and 20-Hz power activities are not correlated within each electrode, the correlation across electrodes cannot be due to volume conduction. Correlations across frequency bands should be interpreted cautiously if activity at those two frequency bands is correlated within one or both electrodes individually. For

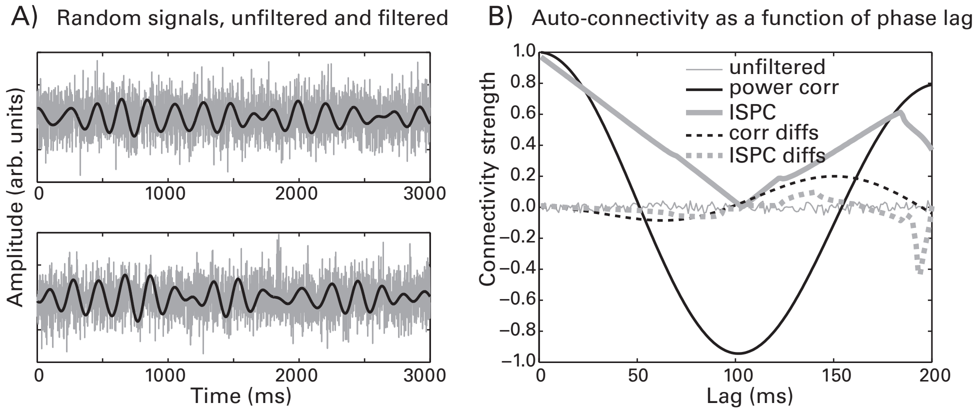

Figure 25.3
Illustration of how autocorrelation can be induced from bandpass filtering and how condition subtractions can attenuate the autocorrelation inflations. Panel A shows two signals generated by random numbers (gray lines) and the result of bandpass filtering each of those signals at 5 Hz (black lines; this was achieved by taking the real part of a convolution between the signals and a 5-Hz wavelet). Panel B shows autoconnectivity as a function of lag. Connectivity was computed between one signal and a lagged version of itself for 200 ms of lags (this corresponds to one cycle at 5 Hz). The y-axis refers to Pearson correlation ("power corr") or a measure of phase-based connectivity that is discussed in chapter 26 ("ISPC"). The thin gray line shows that before bandpass filtering, there is no autoconnectivity, whereas autoconnectivity is introduced by bandpass filtering. Subtracting the autoconnectivity values between signals ("diffs"; analogous to condition differences) attenuates the spurious connectivity. Some residual spurious connectivity after condition differences would be further attenuated when averaging is done over many trials.

example, if one electrode exhibits a correlated gamma power increase and an alpha power decrease, then negative correlations between alpha at that electrode and gamma at a different electrode could reflect volume conduction of the combined alpha/gamma effect.

6. Test for a statistical or qualitative dissociation between connectivity and power. For example, if connectivity between electrodes A and B increases but power simultaneously decreases, the connectivity cannot be due to volume conduction. A distinction between dynamics in power and dynamics in connectivity could be examined in several ways other than trial-averaged results. For example, you could test whether trial-to-trial fluctuations in connectivity and power covary with trial-to-trial fluctuations in behavior or stimulus properties. If connectivity correlates with behavior but power does not, the connectivity is thus decoupled from the power. Any dissociation between connectivity between electrodes and power at one or both electrodes provides evidence against volume conduction. These results should also be

interpreted with caution: a correlation between power and connectivity does not necessarily mean that the connectivity is due to volume conduction, but such a correspondence makes it more difficult to rule out the volume conduction alternative explanation.

7. Test whether the phase lag of connectivity between electrodes is significantly different from zero or π. Although zero-phase-lag connectivity can reflect true brain connectivity or volume-conducted activity, nonzero phase lag cannot be due to volume conduction. One limitation of this approach is that phase lags that are not zero but are close to zero may still be statistically indistinguishable from zero (section 26.10 provides a statistical test for phase angles).

8. For phase-based connectivity, you can use measures that are insensitive to volume conduction such as imaginary coherence, phase-lag index, weighted phase-lag index, or phase-slope-index.

9. For power-based connectivity, you can compute partial correlations between two electrodes holding constant a third electrode. This third electrode can be a neighbor of one of the electrodes. The idea is that the power time series of two neighboring electrodes are strongly correlated because of volume conduction; by computing partial correlations, shared variance that is mainly due to volume conduction with a neighboring electrode will be removed (section 27.4).

10. For power-based connectivity you can modify pairs of time series before calculating connectivity such that the coherent real parts (which include volume conduction effects) are removed, thereby removing any potentially volume-conducted signals (Hipp et al. 2012). This is complementary to using volume-conduction-independent measures because instead of ignoring potentially volume-conducted activity during the analysis, parts of the data that potentially contain volume-conducted signal are removed.