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

30 Cross-Frequency Coupling

Cross-frequency coupling refers to a statistical relationship between activities in two different frequency bands, has been observed in many species and in many brain regions, and has been linked to several cognitive processes and disease states (Canolty and Knight 2010). Cross-frequency coupling analyses require both the high temporal resolution and the high temporal precision of electrophysiological measurements. Therefore, you should perform cross-frequency coupling analyses on high-sampling-rate data. You should also carefully select your time-frequency decomposition analysis parameters: try to select parameters that increase temporal precision even though this entails some reduction of frequency precision. Although this will have implications for interpreting the results—for example, it may be difficult to determine whether theta phase is maximally coupled with 40-Hz or 55-Hz power—having a high temporal precision will provide greater sensitivity to detect true cross-frequency coupling.

There are several different manifestations of cross-frequency coupling and several ways to test for cross-frequency coupling; this chapter presents a few of the more commonly used approaches. The mathematical principles underlying several of the analysis techniques in this chapter are based on Euler's formula and on the use of Euler's formula for averaging phase values. Thus, before reading this chapter, make sure you are familiar with the material presented in chapters 13 and 19 (in particular, section 19.7).

30.1 Visual Inspection of Cross-Frequency Coupling

Even without performing any analyses you may see patterns in your data that suggest the presence of cross-frequency coupling. If you look at the time course of band-specific power, particularly above 20 Hz, you will probably see that power is not constant over time but rather appears in bursts that sometimes seem to occur at regular intervals. Figure 30.1 shows an example of 25-Hz power from the first trial at electrode O1. It seems from visual inspection

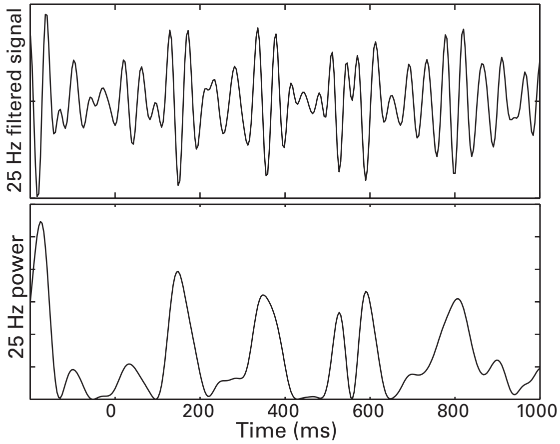

Figure 30.1
From visual inspection of one trial of 25-Hz power, it seems that there may be cross-frequency coupling between 25-Hz power and 5-Hz phase—note the approximate 200-ms rhythmicity in power bursts. This pattern of results was not robust over trials.

that 25-Hz power occurs in bursts at intervals of around 200 ms, suggesting cross-frequency coupling between 25-Hz power and 5-Hz phase. Of course this is an anecdotal observation of a single trial that requires quantitative statistical confirmation before being interpreted, but visual inspection often provides an informative and encouraging first step. In fact, this relationship is not robust over trials, which is demonstrated in the online Matlab code. This is therefore a useful illustration of how a small amount of "representative data" can be enticing and encouraging but should not be overly trusted.

30.2 Power-Power Correlations

There are two methods for computing power-power cross-frequency coupling; both were introduced in chapter 27. One method is to correlate two power time series over time, where the two time series are taken from different frequency bands (at the same or different electrodes). The second method for computing power-power cross-frequency coupling is cross-trial time-frequency power correlations, which was shown in figure 27.6C (plate 19).

30.3 A Priori Phase-Amplitude Coupling

Phase-amplitude coupling is perhaps the most commonly used method of computing cross-frequency coupling (Canolty et al. 2006) and has been confirmed in physiology studies (Bragin et al. 1995; Jensen and Colgin 2007; Lakatos et al. 2005) and computational and theoretical simulations (Lisman 2005; Zhang et al. 2012). Phase-amplitude coupling involves testing for a relationship between the phase of one frequency band and the power of another, typically relatively higher, frequency band. Thus, within phase-amplitude coupling, you refer to the "frequency for phase" and the "frequency for power."

A distinction here is made among "a priori phase-amplitude coupling," "mixed a priori/exploratory phase-amplitude coupling," and "exploratory phase-amplitude coupling." The differences are that with a priori phase-amplitude coupling you specify both frequency bands between which to assess cross-frequency coupling (e.g., based on a priori hypotheses); with mixed a priori/exploratory phase-amplitude coupling you specify one of the two frequency bands while using exploratory analyses for the other frequency band; and with exploratory phase-amplitude coupling you do not specify either frequency band but, rather, search through a frequency-frequency space and evaluate the strength of the phase-amplitude coupling at each frequency pair.

Some of the analyses in this chapter will use sample data recorded from the human nucleus accumbens (available with the online Matlab code) because they show strong alpha-gamma coupling (Cohen et al. 2009). One second of this 8-s snippet of data is shown in figure 30.2, along with the bandpass-filtered signal at 70 Hz (the real part of the result of convolution between the data and a 70-Hz wavelet) and power at 70 Hz. As with figure 30.1, visual inspection suggests that 70-Hz power contains bursts that occur around every 90 ms (you can count 12–13 peaks in this 1-s period).

Before learning about the mathematical quantification of phase-amplitude coupling, consider visual representations of the relationship between the 70-Hz power and 10-Hz phase. Figure 30.2 shows this relationship in three different ways: plotted simultaneously over time (figure 30.3A), 70-Hz power as a function of 10-Hz phase in polar space (figure 30.3B), and a histogram of 70-Hz power values over 10-Hz phase values (Figure 30.3C). The null hypothesis—that 70-Hz power is unrelated to 10-Hz phase—would produce uniformly distributed black dots in panel B (that is, a perfect circle) and a flat histogram in panel C. The lack of uniform distribution in panels B and C suggests that relative increases in 70-Hz power occur preferentially at certain regions of the 10-Hz phase distribution.

The quantification of phase-amplitude coupling is based on Euler's formula. Recall that Euler's formula (e^{ik}; section 13.4) can be used to represent a phase angle as a unit-length vector in a circle, and it can also be used to weight phase values by some trial-varying variable to test for a relationship between that variable and phase (wITPC; section 19.7). Phase-amplitude coupling is similar to wITPC except that instead of using a trial-varying weighting such as reaction time, phase-amplitude coupling uses the time-varying power time series from a higher frequency band. In other words each vector in polar space (one vector per

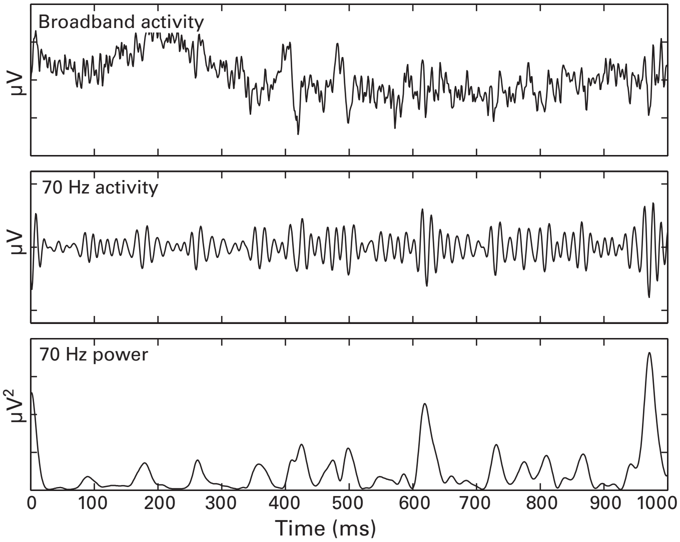

Figure 30.2

Broadband, 70-Hz-filtered, and 70-Hz power time series data from 1 s of recordings from the human nucleus accumbens. The data were sampled at 1000 Hz.

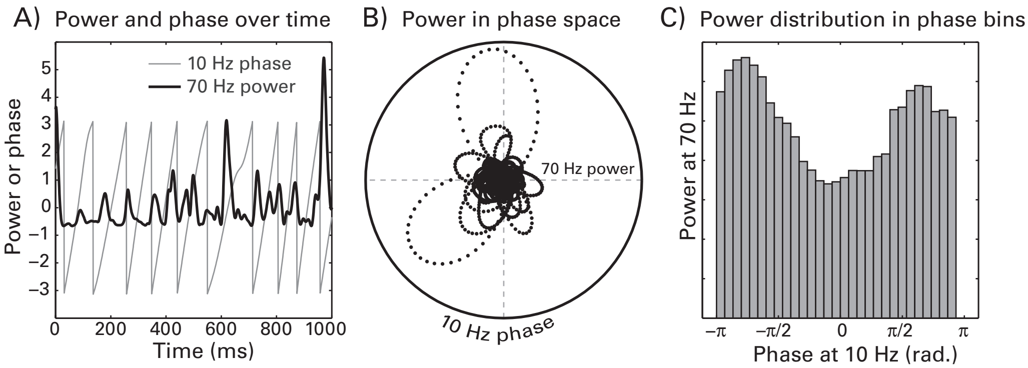

Figure 30.3

Different ways of showing power and phase data from different frequency bands. Data from only the first second of 8 s are shown in panel A for visibility. The "loops" in panel B result from the power increasing and decreasing over time (each dot is a time point).

time-frequency point) is defined as the angle from the 10-Hz phase angle time series and the length from the 70-Hz power time series. This is easy to see in figure 30.3B by imagining that each dot is the endpoint of a vector to the origin. The length of the average vector is the measure of phase-amplitude coupling (PAC) (Canolty et al. 2006):

$$PAC = \left| n^{-1} \sum_{t=1}^{n} a_t e^{i\phi_t} \right| \tag{30.1}$$

in which t is time point, a is the power at 70 Hz at time point t, i is the imaginary operator, ϕ is the phase angle (in radians) at 10 Hz at time point t, and n is the total number of time points. You should use the raw, untransformed power time series because this will ensure that all vectors have positive length.

There are three confounds of assessing phase-amplitude coupling via equation 30.1, but fortunately, there is one solution that solves them all. The first confound is related to the scale of the result of this equation. Similar to wITPC, PAC values from equation 30.1 are not bound by 1.0 but instead can be arbitrarily large. In fact, simply multiplying the power values by 10 will increase PAC, even though the relationship between relative fluctuations in power and phase has not changed (figure 30.4B). This is not good: a measure of cross-frequency coupling should reflect the relationship between power and simultaneous phase, and it should not be arbitrarily influenced the magnitude of the power values. Although it

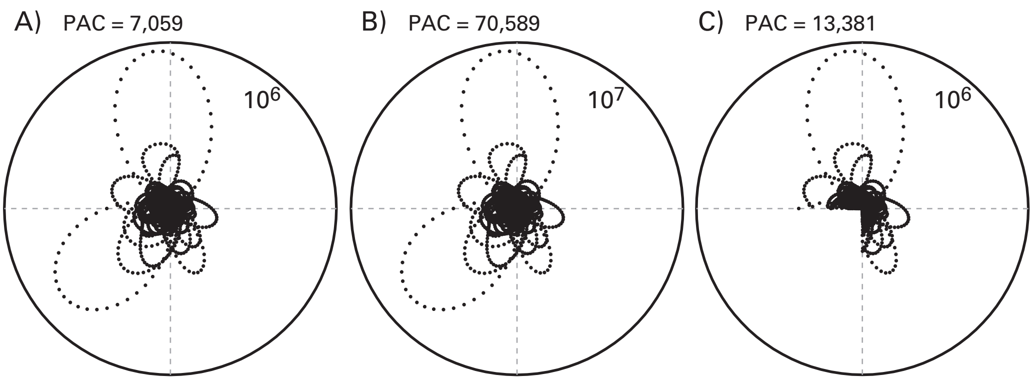

Figure 30.4
Three potential confounds of measuring phase-amplitude coupling via equation 30.1. First, the PAC value scales arbitrarily with power values (panel B; in this case, the power data were multiplied by the number 10). Second, nonuniform phase angle distributions will artificially increase phase-amplitude coupling strength (panel C). Third, outliers or large power fluctuations may increase PAC strength. Numbers near the outer circle indicate 70-Hz power (arbitrary units).

is possible to address this issue either by scaling the PAC measure by the power (Ozkurt and Schnitzler 2011) or by converting power values to rank and applying Moore's modification of the Rayleigh test (Zar 1999, p. 641), there are other potential concerns that favor an alternative option.

The second confound afflicting equation 30.1 is that a nonuniform distribution of phase angles will bias the result of equation 30.1. This can be seen in figure 30.4C. Removing phase angles selectively from one region of phase space nearly doubled the measure of phase-amplitude coupling strength defined by equation 30.1, although the relationship between power and phase at existing phase points has not changed. This may seem like an extreme and unrealistic illustration, but nonuniform phase angle distributions often occur after experiment events (see figure 19.2 for an even more extreme example using real data). Even if the distribution is full but not uniform, the violation of a von Mises distribution (the circular equivalent of a normal distribution) will bias the result of equation 30.1. In theory, you could statistically test each phase angle distribution to determine whether it is von Mises distributed, but this is not practical when testing for phase-amplitude coupling over time, frequencies, conditions, electrodes, and subjects.

The final confound associated with equation 30.1 is that very large power fluctuations that may be outliers can unfairly influence PAC. Figure 30.3 illustrates this concern. There are two bursts that can be seen in the power time series data. These bursts might reflect noise, or they might be driven by true (that is, of neural origin) brief large-amplitude bursts of power, but either way, they have a disproportionate effect on phase-amplitude coupling as defined by equation 30.1. Situations like this will often arise in power data, and it is generally not feasible to inspect each phase-amplitude coupling result to determine whether that result may have been unduly influenced by brief large-amplitude fluctuations that happened to occur at a specific region of phase space. Thus, a useful measure of cross-frequency coupling must be robust to large fluctuations in power that are outliers or otherwise nonrepresentative of the power time series.

Fortunately, there is a single solution to all three potential confounds listed here. Furthermore, this solution has the added benefit of making phase-amplitude coupling strength more amenable to statistical evaluation and condition comparisons, both at the single-subject level and across subjects at the group level. The solution is to apply nonparametric permutation testing (discussed in more detail in chapter 33) to determine how the PAC value compares to a distribution of phase-amplitude coupling values expected under the null hypothesis. The null hypothesis, that there is no temporal relationship between phase and power, implies that if the two time series (power and phase) are shuffled with respect to each other, this will not have an effect on the phase-amplitude coupling value shown in equation 30.1. Permutation testing for phase-amplitude coupling therefore involves temporally shifting the power time series by a random temporal offset without changing the phase angle time series. The phase-amplitude coupling value is then computed according to equation 30.1, producing one phase-amplitude coupling value under the null hypothesis. This procedure is then repeated hundreds or thousands of times, generating a distribution of phase-amplitude coupling values expected under the null hypothesis. The observed PAC (that is, the result of equation 30.1 without altering the data) is compared to the distribution of PAC values under the null hypothesis by subtracting the mean and dividing by the standard deviation (figure 30.5). This creates a standardized *Z*-value of PAC, or PAC_z.

There are several advantages to interpreting the PAC_z instead of the "raw" PAC value: normal-*Z* values are independent of the scale of the original data (this addresses the first

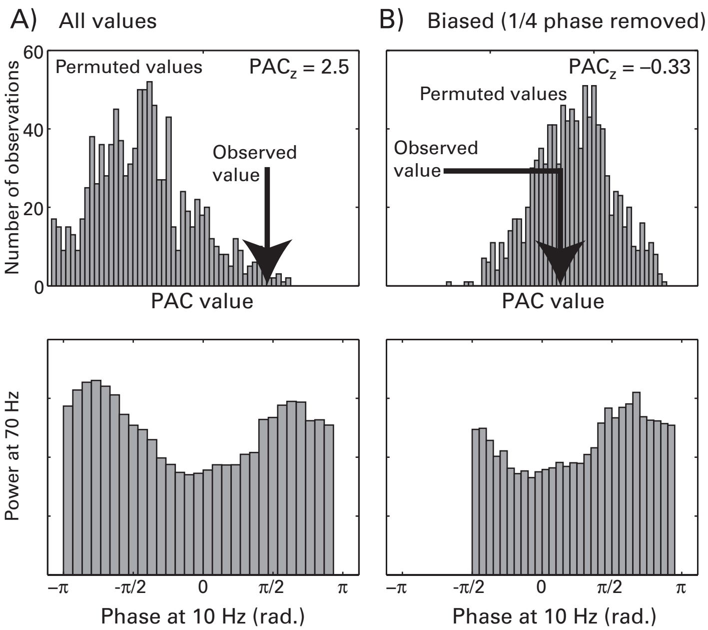

Figure 30.5
Illustration of PAC_z. Repeatedly assessing PAC with a randomly permuted power time series yields a distribution of PAC values expected under the null hypothesis (panels A and B, top row). The PAC value observed without shuffling the time series (see black arrow) is normalized with respect to this distribution. The normalized PAC, or PAC_z, is in standard deviation units and is unrelated to the scale of the power data. The bottom rows show the distribution of 70-Hz power values over 10-Hz phase bins from the observed data.

confound associated with equation 30.1), they are based on the observed phase distribution and thus are not influenced by violations of a von Mises distribution (this addresses the second confound), and the result is not influenced by large power fluctuations because those fluctuations will be paired with different phase values in different permutations (this addresses the third confound). PAC_z values have additional advantages: they have a straightforward statistical interpretation (standard deviation units), are easily evaluated in a statistical sense within the context of permutation testing (normal-*Z* values can be converted to *p*-values), and are potentially suitable for group-level parametric statistical tests (because they have an average value of zero and variance of 1 under the null hypothesis).

There are several ways to shuffle the power time series. One is to cut the power time series at a random point and put the postcut time series before the precut time series. A second way is to completely randomize the time points, which destroys the temporal characteristics of the original power time series. A third method is to use a frequency domain randomization procedure, which involves taking the FFT of the power time series, shuffling the phases of the FFT, and taking the inverse FFT. This method generally provides similar results as the first method and often removes nonrepresentative large-amplitude peaks, although it changes the values from the original power time series. The random shuffling method is the least preferred because it eliminates the temporal structure of the power time series, and thus may inflate the statistical significance in some cases. The online Matlab code shows you how to implement each of these methods, and their results are compared in figure 30.6. In all of these examples the power time series was shuffled while the phase angle time series was left intact, but you could also shuffle the phase angle time series while leaving the power time series intact. In theory, you could also shuffle both the power time series and the phase angle time series, although this will not provide any better test of the null hypothesis than shuffling only one of the time series.

So far, cross-frequency coupling has been computed in one time segment. Assessing changes in cross-frequency coupling over time can be done by computing PAC_z over successive time segments to create a time series of PAC_z values. An example result is shown in figure 30.7.

How much data do you need for reliable estimates of phase-amplitude coupling? You need at least one full cycle of the lower frequency in order to build a distribution of higher-frequency power values; otherwise you will create a situation like that presented in figure 30.4C. But using data from only one cycle will not provide a robust estimate of phase-amplitude coupling. This is in part because of the relatively lower signal-to-noise ratio of high-frequency activity, particularly in noninvasive recordings. On the other hand, if the cross-frequency coupling is transient, using too many cycles in the analysis may

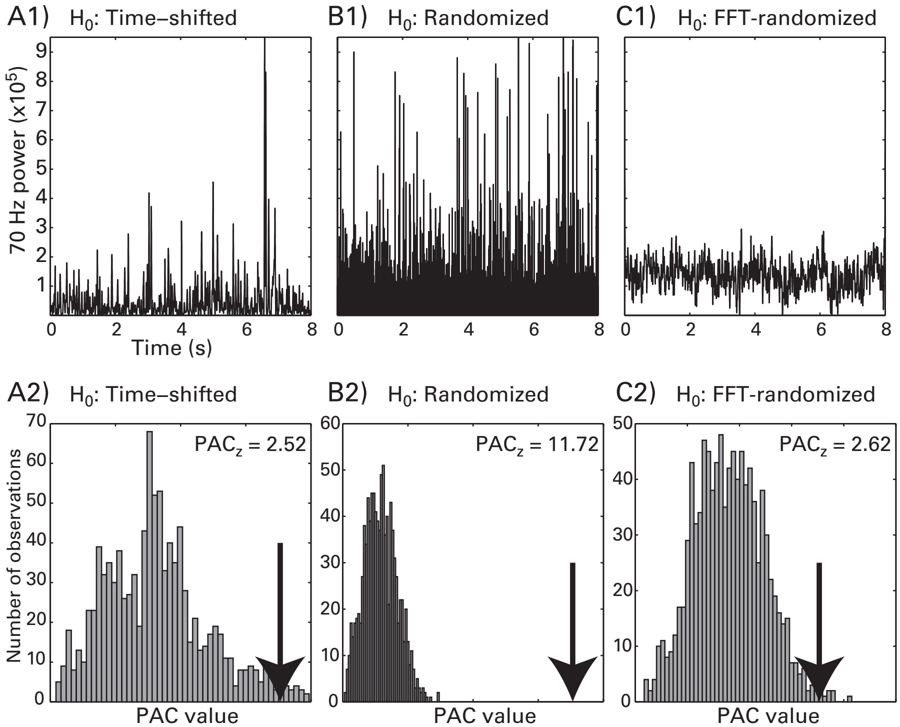

Figure 30.6
Different methods for constructing the null hypothesis power time series when computing phase-amplitude coupling and the resulting estimates of PAC_z. The top row shows examples of one (out of 1000) permuted power time series, and the bottom row shows the distribution of PAC values under the null hypothesis (gray bars) and the observed PAC value (black arrow). The observed PAC value is identical in all situations, but the distributions of null-hypothesis PAC values are different for the different ways of constructing the null hypothesis.

decrease temporal precision to the point of losing sensitivity for detecting transient effects. Fortunately, having many trials will help increase the signal-to-noise ratio because you can concatenate data from a small number of cycles over many trials. For example, if you use 5 Hz as the frequency for phase, three cycles (corresponding to 600 ms) may provide too little data for a robust estimate of cross-frequency coupling, but if you concatenate three cycles at the same time segment (e.g., 200–800 ms poststimulus) over 100 trials, the cross-frequency coupling analysis will be performed using 300 cycles, which should be sufficient to detect true task-related phase-amplitude coupling in the presence of noise (Tort et al. 2010). Pooling the data from small time segments over many trials is also advantageous

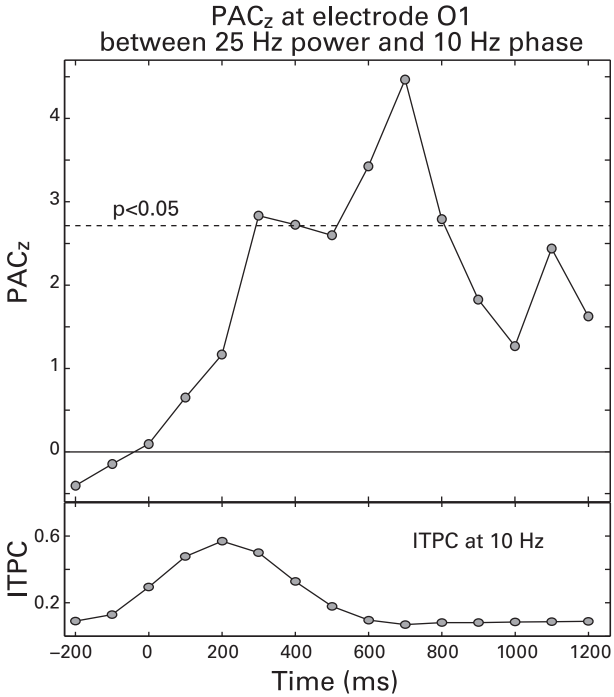

Figure 30.7
PAC_z over time, computed between 10-Hz phase and 25-Hz power from electrode O1 of the sample scalp EEG data. The dotted horizontal line corresponds to $p < 0.05$ Bonferroni-corrected for multiple comparisons across time bins. The lower plot shows the time course of ITPC, which demonstrates that the PAC_z does not temporally co-peak with stimulus-locked ITPC (discussed in section 30.4).

for highlighting task-related changes in cross-frequency coupling because only the phase-amplitude coupling results that are consistent over trials will be identified.

30.4 Separating Task-Related Phase and Power Coactivations from Phase-Amplitude Coupling

Imagine a burst of gamma power that is time-locked to a stimulus and also an increase in alpha ITPC time-locked to that same stimulus. The likely PAC result is that gamma power will be time-locked to alpha phase. This could reflect true phase-amplitude coupling, but it could also be a spurious result driven by gamma power and alpha phase being independently time-locked to the stimulus onset.

There are several ways to avoid misinterpreting this possible spurious result. First, you can plot ITPC from the lower frequency to show that PAC_z and ITPC do not temporally co-occur (as is shown in figure 30.7). Second, you can simply avoid analyzing cross-frequency coupling during time periods with strong ITPC in the lower-frequency phase or mention explicitly the time periods in which phase-amplitude coupling is difficult to interpret because of ITPC. This would be appropriate if the PAC_z shown in figure 30.7 were statistically significant around 100–400 ms. Third, you can subtract the ERP from the single-trial EEG data before computing phase-amplitude coupling, as was done to compute the non-phase-locked power in chapter 20. This will eliminate ITPC while leaving the upper frequency-power time series mostly unchanged (the power time series will remain mostly unchanged because activity from frequencies above around 20 Hz generally do not contribute to ERPs, particularly after the first 200 ms of the ERP).

30.5 Mixed A Priori/Exploratory Phase-Amplitude Coupling

So far in this chapter, frequency bands for phase and for power were selected, and PAC_z was computed only between those two bands. This is a useful approach if you can select frequency bands based on hypotheses or previous studies or based on an analysis of task-related power and phase. The advantages of this a priori approach are that it is hypothesis driven, fast (because it involves only one pair of frequency bands), and maximally sensitive to detecting an effect at the hypothesized frequency bands. The increased sensitivity is due to having only one statistical test (or a small number of statistical tests), so a *p*-value of 0.05 can be used without correcting for multiple comparisons over dozens or hundreds of frequency-frequency pairs. The main two limitations are that you cannot determine whether the effect is selective to those frequency bands and that you may not have precise hypotheses about which frequency bands to use for power or phase.

The mixed a priori/exploratory phase-amplitude coupling method is useful when you have an a priori reason to select one frequency band but would like the flexibility to find the other frequency band using data-driven techniques. There are two options—you select the lower frequency for phase and then use an exploratory approach to find the best-fitting frequency for power, or you select the higher frequency for power and then use an exploratory approach to find the best-fitting frequency for phase.

In the first example the frequency for power was selected, and an exploratory method was applied to find the best frequency for phase (that is, the frequency for phase at which the strongest coupling with the frequency for power can be observed). This exploratory method involves looping through several frequency bands (here, from 2 to 20 Hz) and repeatedly

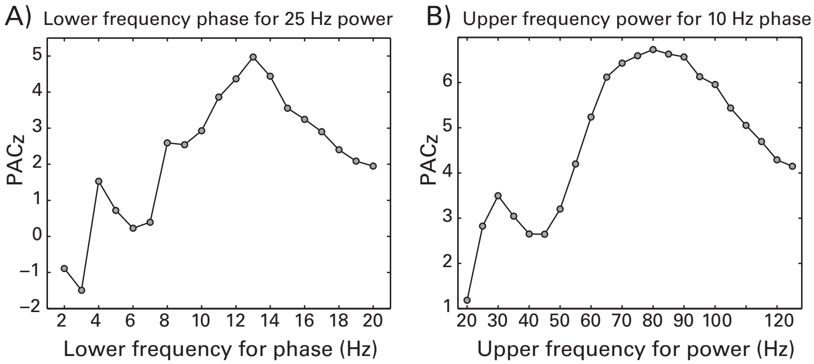

Figure 30.8
Results from mixed a priori/exploratory phase-amplitude coupling. Panel A illustrates the situation in which the frequency for power is selected a priori (in this case, 25 Hz), and an exploratory procedure is taken to identify the frequency for phase that has the strongest PAC_z with the power time series. Panel B illustrates the complementary situation, in which the frequency for phase is selected a priori (in this case, 10 Hz), and an exploratory procedure is applied to higher-frequency power.

computing PAC_z for each frequency band (figure 30.8A). It can be seen in the figure that the phase at 13 Hz was most robustly coupled with power at 25 Hz.

In the second example the frequency for phase was selected a priori, and an exploratory method was applied to determine the best frequency for power. Results are shown in figure 30.8B. Power at 80 Hz was most robustly coupled with the phase at 10 Hz. Note that because of the randomization involved in permutation testing (discussed more in section 33.4), it is possible that the frequencies with maximum PAC_z will differ slightly when this analysis is repeatedly performed. The differences, however, should be minor. For example, in different repetitions the analyses for figure 30.8B produced 75, 80, and 85 Hz as the peak frequency. Arguably, slight differences in peak frequency are not a major concern because the time-frequency decomposition parameters should be focused on temporal precision at the expense of frequency precision. Thus, there is likely little unique information between power at 75 Hz and power at 85 Hz. Using data with a higher sampling rate should improve the signal-to-noise ratio at higher frequencies.

The results of a mixed a priori/exploratory phase-amplitude coupling analysis should be treated appropriately to avoid making circular inferences (also sometimes called "double-dipping"; this is discussed more in section 35.1). For example, based on the results presented in figure 30.8A, it is inappropriate to select 13 Hz for phase and then statistically test for the coupling between 13 Hz phase and 25 Hz power using a statistical significance threshold of $p < 0.05$. This is inappropriate because the frequency band was selected based on that frequency pair showing a strong effect. There are two ways to approach the mixed a priori/exploratory phase-amplitude coupling that avoids circular inference. The first approach is to test for statistical significance of the 13 Hz phase result while appropriately correcting for multiple comparisons across 19 frequency bands that were examined (see chapter 32 for a discussion on strategies for correcting for multiple comparisons). The second approach is to use the exploratory results as a means of selecting data for a subsequent orthogonal condition comparison. For example, imagine that figure 30.8A was generated based on all trials from all conditions in the experiment. This result shows that, across all conditions, 13-Hz phase is most strongly coupled with 25-Hz power. Rather than assessing whether that PAC_z is significant per se, you use this as a selection procedure for condition differences. That is, based on this result, you can compute phase-amplitude coupling strength between 13-Hz phase and 25-Hz power separately for condition A and condition B and then test whether the phase-amplitude coupling strength is significantly different between those two conditions. In this scenario the statistical comparison of PAC_z strengths across conditions is not biased by the procedure used to identify the two frequency bands for PAC_z.

Studies on phase-amplitude coupling sometimes show time-frequency plots of power time-locked to the lower frequency phase (e.g., Figure 1B in Canolty et al. 2006). To create these plots, perform a time-frequency decomposition to create a time-frequency power plot as you would to create a normal task-related time-frequency power plot. However, instead of using a stimulus or other experiment event as time = 0, you use the troughs (or peaks) of the lower-frequency phase angle time series. Thus, the time-frequency power plot is time-locked to an internal event (a particular phase of a slower oscillation) rather than being time-locked to an external event (a stimulus onset). To normalize the power over frequencies so that a wide range of frequencies can be viewed on the same plot, power from each frequency can be normalized to the pretrial power (as is done for typical time-frequency power plots), or it can be normalized by taking the *Z*-transform of each time series surrounding each trough. The latter option is a sensible approach because for phase-amplitude coupling you are not interested in the overall power of high-frequency activity relative to the power during a baseline period; rather, you are interested in the local fluctuations in power that surround lower-frequency phase dynamics. An example of a time-frequency plot is shown in figure 30.9 (color plate 23).

30.6 Exploratory Phase-Amplitude Coupling

This final method of computing phase-amplitude coupling is useful when you have no a priori reason to select either frequency band or if you want to confirm the frequency-frequency selectivity of a phase-amplitude coupling result that was defined based on a

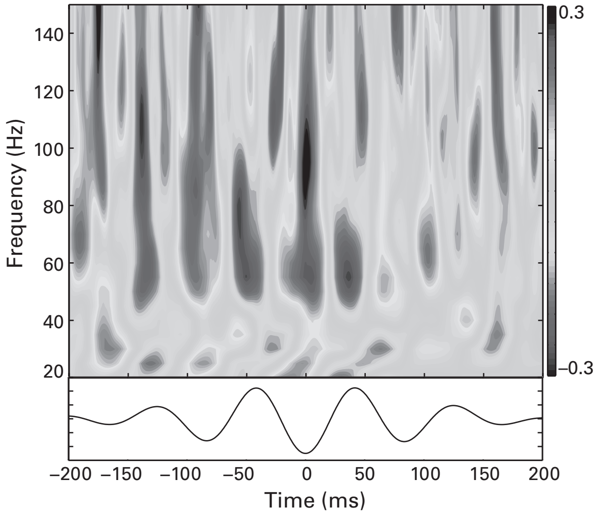

Figure 30.9 (plate 23)
Time-frequency power plot showing *Z*-normalized high-frequency power time-locked to alpha-band-filtered troughs. These data are from the nucleus accumbens recording.

priori–specified frequency bands. The advantage of this exploratory method is that it offers the flexibility to identify phase-amplitude coupling patterns in any pairs of frequency bands. The disadvantage is that because of the large number of tests performed, which could number in the hundreds or thousands, an appropriately conservative statistical threshold must be applied to address the multiple comparisons.

In light of the previous sections it should be sensible that, to compute exploratory phase-amplitude coupling, you combine the exploratory approaches for phase and power. This produces a two-dimensional (2-D) matrix, and the value at each point in this matrix is the PAC_z between the corresponding phase and power frequencies. An example result is shown in figure 30.10 for the nucleus accumbens recordings. The most robust feature in this frequency-frequency space is the coupling between 10- and 13-Hz phase and 55- to 105-Hz power. Thus, this 8-s segment of data replicates the effects observed over many dozens of trials and patients (Cohen et al. 2009).

30.7 Notes about Phase-Amplitude Coupling

Here are six notes and hints about computing phase-amplitude coupling. First, phase-amplitude coupling is best done using wavelet convolution or filter-Hilbert because these methods return phase angle time series (that is, estimates of instantaneous phase angles).

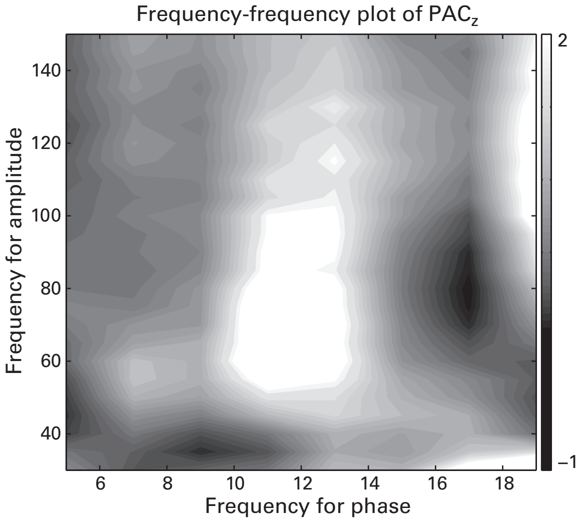

Figure 30.10
Exploratory PAC$_z$, which is useful (1) when you have no a priori hypotheses about which frequency band pairs to use for phase-amplitude coupling, or (2) to confirm the specificity of frequency band pairs that were selected based on a priori hypotheses.

Second, because the timing of the high frequency power is critical for the sensitivity of these analyses, you should use time-frequency decomposition parameters that highlight temporal precision over frequency precision. That is, use wavelets with a small number of cycles (three to five) or filter-Hilbert with relatively wide frequency bands.

Third, when implementing equation 30.1 in Matlab, make sure you write `abs(mean(. . .))` and not `mean(abs(. . .))` (this was also discussed in chapter 19).

Fourth, keep in mind that there is reduced signal-to-noise ratio at higher frequencies, particularly as those frequencies approach the Nyquist frequency. You can be more confident about your results if you have at least five samples of power per cycle of phase. For this reason if you plan on analyzing cross-frequency coupling, try to record the data with a relatively high sampling rate, for example, 1000 Hz. Figure 30.11 illustrates the number of time points of power per cycle of phase using a sampling rate of 256 Hz. The plot shows the logarithm of counts to facilitate comparison. If you have fewer than five power time points per cycle of phase, try to offset the balance by using more data to estimate PAC$_z$.

Fifth, edge artifacts from time-frequency decomposition can cause spurious phase-amplitude coupling (Kramer, Tort, and Kopell 2008). Avoid including potential edge artifact periods in the analyses and try to use clean data with no noise spikes or brief amplifier

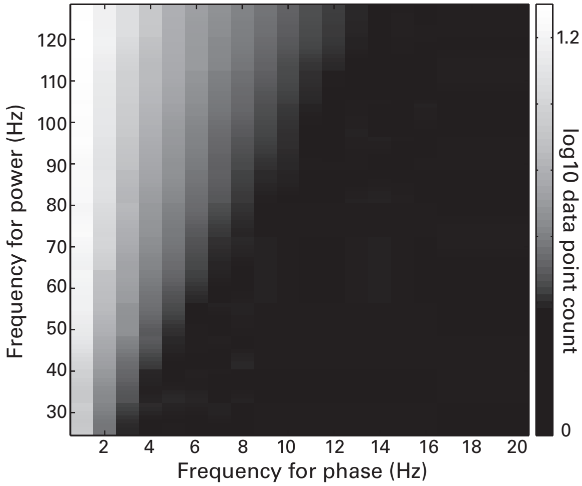

Figure 30.11
Illustration of the number of data points per cycle of frequency for power that fit into one cycle at each frequency for phase, as a function of frequencies. The numbers were scaled by logarithm-base-10 to facilitate visual inspection; the brightest white color corresponds to 20 data points. These results are based on a sampling rate of 256 Hz, so there would be about four times as many data points per phase cycle using a sampling rate of 1000 Hz. Note also that this is points per phase cycle, and normally you would have dozens or hundreds of phase cycles per analysis.

saturations that might cause edge artifacts. Permutation testing will also help to minimize the negative impact of noise spikes because those noise spikes will be paired with different phase values in different iterations during permutation testing.

Finally, phase-amplitude coupling analyses typically involve a very large search space with commensurately large multiple-comparisons concerns. One general strategy for minimizing multiple comparisons while preserving the freedom to use exploratory data-driven approaches is the following (a similar procedure was also described in section 30.5): compute exploratory phase-amplitude coupling for broad frequency ranges (e.g., 2–15 Hz for phase and 20–100 Hz for power), collapsing over all conditions. Find a region in this phase-power space that shows significant phase-amplitude coupling across all conditions, appropriately correcting for multiple comparisons (e.g., using strategies presented in chapter 33). Next, compute phase-amplitude coupling only for this frequency pair, separately for each condition. Condition differences can now be tested without multiple comparisons across all phase and power-frequency combinations. Depending on your specific design and analysis, it is possible that you will still need to correct for multiple comparisons across electrodes or conditions or time points, but at least the multiple comparisons problem has been reduced from hundreds of comparisons to a few comparisons.

30.8 Phase-Phase Coupling

So far, power-power coupling and phase-amplitude coupling have been discussed. You can probably guess that the third type of cross-frequency coupling analysis is based on phase-phase coupling.

Consider that the upper frequency power time series itself can be conceptualized as an oscillatory signal from which phase values can be extracted. Then, phase synchronization can be computed between the phase of the upper-frequency power time series and the phase of the lower frequency (Mormann et al. 2005). This method is frequently used in the literature (Cohen 2008; Penny et al. 2008; Vanhatalo et al. 2004; Voytek et al. 2010). A graphical overview of phase-phase coupling is shown in figure 30.12. To isolate the lower-frequency component in the upper-frequency power time series, you can filter the upper-frequency power time series using the same filter characteristics as were applied to the lower frequency. This can be done by applying the filter-Hilbert method to the power

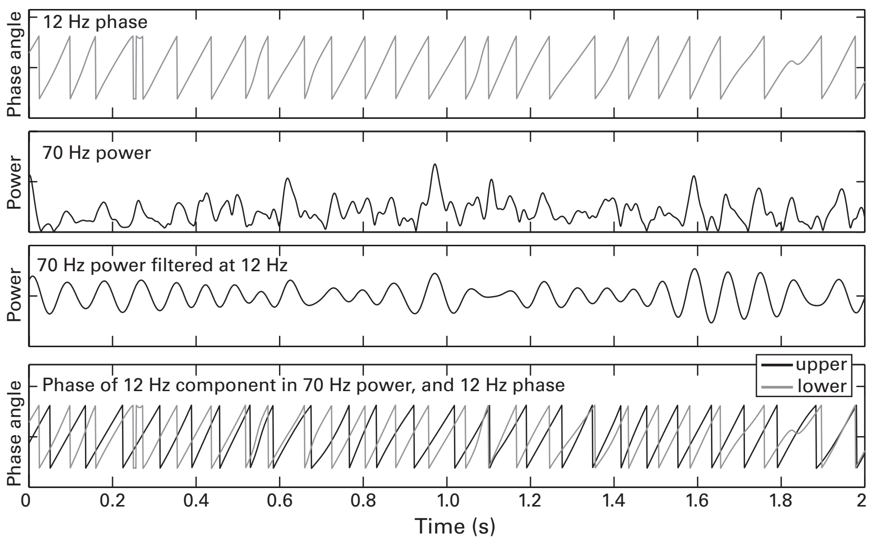

Figure 30.12
Overview of phase-phase cross-frequency coupling method. The first 2 s of 8 s of data are shown. This figure is partly modeled after figure 1 in Penny et al. (2008).

time series or convolving the upper-frequency power time series with the same wavelet used for the lower-frequency phase angle time series (in this case, the 12-Hz wavelet; this is the approach used in the online Matlab code and in figure 30.12). In the data shown in figure 30.12 the phase-phase coupling between the phase angle time series of 12 Hz and the phase of the 70-Hz power time series was 0.275, which is statistically significant considering that 8000 time points were used for the statistical measure (chapter 34 shows methods for computing statistics on mean vectors of phase values).

30.9 Other Methods for Quantifying Cross-Frequency Coupling

This chapter focuses on phase-amplitude coupling via an extension of Euler's formula, which reflects that this approach is the most commonly used in the literature. But there are several other approaches for assessing cross-frequency coupling. For example, the general linear model can be used to test whether variance in phase can account for variance in power (Penny et al. 2008). You can also compute the nonuniformity of a power distribution over phase bins (Tort et al. 2010), which is particularly useful if there are multiple power peaks in phase space. Another method of phase-phase coupling is called "n:m" phase coupling (Tass et al. 1998), which involves multiplying the phase angles from two different frequency bands by integer multiples, such as 1:2, 1:3, 1:4, etc. There are decomposition methods that might be useful in situations of low signal-to-noise ratio (Nikulin, Nolte, and Curio 2012). There has also been a recent extension of phase-amplitude coupling for multivariate networks (Canolty et al. 2012).

30.10 Cross-Frequency Coupling over Time or over Trials

The analyses discussed in this chapter are focused on cross-frequency coupling over time. This is sensible because cross-frequency coupling relies on precise timing between signals at two frequency bands, and thus, even small jitters in cross-trial timing or a lack of phase-locking to a stimulus suggests that cross-frequency coupling may be better measured using methods that can detect non-phase-locked activity. However, as with most connectivity measures, phase-amplitude coupling can also be performed at each time point over trials (Voytek et al. 2013).

30.11 Describing This Analysis in Your Methods Section

Cross-frequency coupling analyses often involve many steps and are infrequently used in the literature. Therefore, be clear about your motivations for performing cross-frequency coupling. Make sure the description of the methods is clear because cross-frequency coupling analyses typically involve several steps. If you had a priori motivations for selecting particular frequencies, justify those choices as being based on hypotheses, previous experiments, or orthogonal data selection from within your results. A clear description of the statistical analyses and the control of multiple comparisons is particularly important because cross-frequency coupling analyses often involve a large number of tests.

30.12 Exercises

1. Online Matlab code is not provided for figure 30.9 (color plate 23). Recreate this plot using the sample data recorded from the nucleus accumbens. Here is a Matlab tip to help you identify local minima of a time series vector `data` that contains a bandpass-filtered signal (change the “>0” to “<0” to identify local maxima):

```
troughs=find(diff(sign(diff(data)))>0)+1;
```

2. Recreate figure 30.10 (exploratory PAC_z) for two electrodes from the sample scalp EEG dataset, one electrode from the front of the head and one electrode from the back of the head. Are there any noticeable features in the PAC_z from the two electrodes, and are there any frequency pairs that seem to show cross-frequency coupling, and are there any visually striking differences between the two electrodes?