

Towards a Coherent View of Brain Connectivity

Thomas F. Collura, Ph.D., P.E.

ABSTRACT

The electroencephalogram provides a myriad of opportunities to detect and assess brain function in general, and brain connectivity in particular. This article describes the relationship between local and nonlocal brain activation and synchrony, and motivates the use of appropriate metrics to study and train functional brain connectivity. Specific metrics are described including coherence, phase, synchrony, correlation, and comodulation. These are contrasted and compared in terms of their ability to detect particular aspects of connectivity, and their usefulness for training. Finally, the importance of normative assessment and continued guidance during connectivity training is explained.

INTRODUCTION

The EEG is a uniquely powerful and revealing indicator of brain function, and is one of the best methods available for assessing and monitoring neural activity in real time. It owes much of its value to its sensitivity to neuronal synchrony. The primary mechanism that produces measurable scalp EEG is the summation, through volume conduction, of post-synaptic potentials that occur in pyramidal cells within the cerebral cortex. When cells polarize (or depolarize) in unison, the resulting potentials are added in the conducting media, leading to external fields that can be measured. This phenomenon is so pronounced that a mere 1% of cortical cells in a 1 cm² area of cortex, when acting in synchrony, are sufficient to account for more than 96% of the EEG signal (Shaw 2003). In other words, the very existence of an EEG potential implies some degree of local synchrony within a population of cells lying beneath the affected sensor. By an extension of this logic, if a mere 1% of cortical cells are coordinated in some way with 1% of the cells in some

other location, then 96% of the connectivity might be accounted for in the EEG. The question is, how do we define this connectivity, and how do we measure it?

This point of view can be extended to the understanding of brain connectivity as revealed by the EEG. When two or more distinct brain locations exhibit some form of synchrony or coordinated activity, their relationship can be revealed by EEG measures that are derived from two or more channels. In this discussion, we shall examine the types of coordinated activity that can be revealed by the EEG, and how this activity can be reflected in appropriate metrics.

When we look at brain connectivity and function, we see that there is a continuum of relationships between different brain centers. The brain is comprised of cortical centers and connections between and among them, and including subcortical structures, most notably the thalamus. Intracortical connections include short-range connections between neighboring locations, as well as long-range connections that connect distant locations. Connectivity metrics are intended to detect these connections and their function, as well as short-term and long-term changes in the dynamics of the interconnections. When neighboring locations act in a synchronize manner, local amplitudes are increased, and manifest as the presence of a measurable EEG wave. Local synchrony can thus be detected with a single sensor that lies over the involved area. When more distant locations interconnect and communicate, the possibility arises of detecting this through relationships between EEG signals recorded with two or more sensors.

INSERT FIGURE 1 HERE

From the brain's point of view, there are important functional differences between short-range and long-range connections. Therefore, connectivity measures provide a window into the brain that is fundamentally different from that provided by a single sensor. Connectivity metrics extend our existing knowledge to incorporate increasing distances, thus reflecting whole brain function as extensions and generalizations of the concepts implicit in localized brain function.

There has been a historic tendency to use the term “coherence” for any EEG metric that reveals coordinated neural activity, regardless of its intent or definition. This has resulted in some confusion when attempts are made to compare or contrast differing methods. We will attempt here to clarify the salient definitions, and to outline a consistent terminology that can serve for future development and discussion. The primary intent of any connectivity measure is to assess the similarity between channels in some relevant signal dimension. Connectivity measures can be applied in one or both of two important contexts, those being real-time and post-processed.

When real-time performance is required, time response becomes significant. Generally, FFT-based methods will have slower time response, owing to the need to acquire an epoch of data (on the order of 1 second) before the estimate can be made. Tapering windows further confound this delay by emphasizing wave components in the center of the window, thus imposing a firm delay of $\frac{1}{2}$ the epoch size, thus incurring a delay of 500 milliseconds, which is detrimental to EEG biofeedback applications. Digital filters and related methods including “complex demodulation” and “joint time-frequency analysis” can provide real-time performance, while retaining generality and accuracy (Collura 1990). The main “cost” of such approaches is the need to predefine the component band of interest, e.g. 8-12 Hz. When assessment is the need, FFT and other transform-based methods are sufficient, and can provide a level of precision and understandability that is of value in normative applications. Nonetheless, it is becoming increasingly important to construct normative databases around digital filter based methods, thus extending the benefits of real-time measurement into the assessment. Whenever a metric is defined in terms of a particular component band (e.g. theta, alpha, etc.), it is necessary to provide a measurement that applies to the bandlimited signal.

The ultimate goal of any EEG connectivity metric is to reflect relevant similarities between the EEG signals arising from the two or more sites of interest. There are many ways in which a

similarity can be manifest. This is not unlike trying to assess the similarity between any two entities, be they signals, human beings, automobiles, or whatever. The ultimate goal is to detect a relevant similarity and reflect it in a useful metric, and there are a wide range of methods that can be employed in pursuit of this goal. From this point of view, we can understand and appreciate the value of various metrics and their application. Any metric that reflects the relationship between two sites has potential merit. It may reflect the amount of information shared, or the speed of information sharing. It may be applicable in real-time, or in a postprocessed EEG. As long as it has value in assessing or training brain function, it should be considered among candidate methods. All such methods take us beyond simple amplitude training, and enter the realm of the integrated function of the brain.

It must also be appreciated that any metric falls within the realm of system identification and parameter estimation in a general sense. Systems have many properties. In the purest sense, systems have real properties. However, we are not able to access these directly. Rather, by making assumptions, we derive an ideal property, which we may seek to measure. Through appropriate definitions, measurements, and computations, we arrive at an estimate of a quantifiable property, which always puts us into an abstract realm. For example, we can never measure temperature directly. Rather, by making assumptions and using definitions, we measure some other property such as the length of a column of mercury or alcohol, the deflection of a metal strip, the presence of electromagnetic radiation, and so on. By recording such physical entities and interpreting them in an agreed-upon way, we arrive at a measurement that we all agree to call “temperature.” The situation is not so different in the case of brain connectivity. What we actually record is one or more electrical potentials that we subject to computations, and an agreed-upon representation. Such computations produce an estimate of some quality, which we interpret generally as the similarity between activity in the brain, and use in the pursuit of brain connectivity assessment or training.

INSERT FIGURE 2 HERE

We may thus appreciate that particular brain connectivity metrics may or may not have sensitivity to various properties of the signals. For example, a given metric may be sensitive to the phase of the signals, or it may ignore this property. It may be sensitive to the absolute or relative amplitudes of the signals, or it may ignore them. It may measure quantities across frequency, across time, or both. Furthermore, the source of the data may be any of a range of sources, including raw waveforms, transformed quantities using Fourier or other methods, or it may use filtered waveforms produced by digital filters or complex demodulation. All of these alternatives provide us with options for pursuing brain connectivity, and none of them should be considered as hard and fast requirements for the general pursuit of this domain. With this understanding, we can investigate the predominant metrics, and describe their properties, including strengths and weaknesses in practical applications.

It should be emphasized at the outset that providing a formula for a metric in no way provides a “recipe” for implementing it in a real system, any more than being told that cheesecake contains certain ingredients is a recipe for success. Critical issues such as timing, measurement of quantities, and order of computations, affects the outcome. It is relatively simple to produce a metric that seems to behave as intended, but there are a wide range of considerations that must be addressed for a useful metric to be produced. Thatcher (2003) addresses these issues well in the case of classical coherence, which is described below. Particular issues for other metrics differ, and are part of the art of implementing useful biofeedback systems.

SPECIFIC METRICS AND THEIR USE

Classical or “pure” coherence is a measure that is derived from the engineering field, and which is designed to reveal connectivity as reflected in a consistent phase relationship between two or more signals. It is defined as the “cross-spectra normalized to the product of the auto-spectra,”

and can be interpreted as a generalization of the Pearson correlation coefficient to variables expressed in the complex frequency domain. It has widespread use in time-series analysis (Carter 1987) and can be expressed mathematically as:

$$COHERENCE = \frac{|H_{xy}|^2}{|H_{xx}| |H_{yy}|}$$

In this representation, the numerator is the “cross-spectrum” between the two signals, and the two terms in the denominator represent the “auto-spectra” of the individual signals. The metric can be defined for any frequency component band or bin. When calculated across frequencies, it produces the “coherence spectrum.”

Pure coherence is independent of the absolute phase separation between the signals. It is also independent of the individual amplitudes of the signals, in that it is possible to have high coherence between two small signals, and it is possible to have low coherence between two large signals. It is also possible to have high coherence between a large signal and a small signal. Note that the spectral energy of interest can be estimated by more than one method, although the classical approach is to use the Fourier Transform. When a transform is used, certain decisions are already implicit, such as the signal sampling rate, the epoch or window used for analysis, choice of windowing factors such as Hamming, Hanning, and so on, as well as smoothing factors used in the computations. Similarly, when complex demodulation is used to recover the coefficient estimates, characteristics such as filter bandwidth, type, and order become significant, as well as internal smoothing and shaping factors applied to the coefficients. Changes in any of these parameters will affect the result, in terms of its time behavior, its precision, its accuracy, and its ultimate usefulness. Ultimately, it is from the skill applied in determining and implementing such details that specific instrumentation and software derive their relative usefulness and efficacy.

The following graph demonstrates the concordance between two different implementations of this type of coherence metric. It compares 1-minute averages of a real-time coherence data from an EEG training system (BrainMaster) with postprocessed results (1-minute samples of EEG) from a clinical QEEG assessment system (NeuroGuide). 20 points are shown, representing 5 electrode pairs and 4 frequency bands. While the BrainMaster system uses optimized real-time quadrature filters with built-in coherence detectors, NeuroGuide uses FFT's of successive epochs of a 1-minute EEG record to estimate the spectral parameters. While the BrainMaster data is available 30 times per second during the entire minute, the NeuroGuide data requires the session to be over before results can be computed. These are thus two rather different approaches to extracting the relevant signal energy. Nonetheless, the average of the real-time data are found to agree well with the aggregate data computed from the entire minute. This agreement in the results illustrates the ability to produce a good match across the range of coherence values from 2 to 70 percent. It further illustrates the fact that the metric can be expressed either in power or in amplitude units. It is thus reasonable (and necessary) in this example to take the square of one metric in order to produce agreement with the other. This demonstrates that, based upon consistent use of definitions, associated time constants and parameters, it is possible to reach significant agreement, even between a metric that is real-time, and a metric that is postprocessed.

INSERT FIGURE 3 HERE

For clarification, it should be noted that there are two different uses of the term “coherence” in physics, and that both of these appear in the study of biological signals. One of these, which can be computed using only one signal, is more properly called “self-coherence”, and is a measure of the spectral purity of the energy the signal. This measure is also applied in the field of heart-rate variability (HRV), and is, properly, called “coherence” in HRV instrumentation and literature. This should not be confused with the use of the previously described definition that is used generally in EEG, in which the measure is not made within one signal, but between two signals.

Spectral Correlation Coefficient (SCC) is a metric that was defined by Joffe and first implemented in the Lexicor (Boulder, CO) equipment produced beginning in the 1980's. This metric is based upon amplitude data provided by the FFT, and is designed to reveal similarities in the shape (profile) of the FFT frequency spectral data. It asks, "do the frequency spectra look similar across frequency," and employs a metric that is a standard Pearson correlation of the amplitude data within a designated frequency band. It was described by Joffe as a "spectral morphology comparison using the formula:"

$$SPECTRALCORRELATION = \frac{\left(\sum |X_f| |Y_f|\right)^2}{\left(\sum |X_f|^2 \sum |Y_f|^2\right)}$$

Expressed in percent, where X and Y represent the Fourier magnitude series of the two channels" (Joffe 1989). This is thus a measure of how similar the two signals' FFT spectra are in shape, regardless of phase, and independent of their absolute or relative magnitudes. The metric can be further extended to become a function of time, by taking successive samples into the analysis.

The following plots document the concordance between two independent implementations of the SCC metric (Lexicor NRS-2D and BrainMaster 2EW). The agreement is best at low frequencies and diverges at high frequencies, at which the individual response characteristics of the amplifiers dominates the computation. This illustrates the importance of matching the frequency response of a system, when implementing a metric. In this particular case, the tuning of the system to match the desired values consists of reducing the high-frequency response to match that of the less responsive amplifier. It is visually evident that by introducing a falloff in frequency response that has increasing effect at higher frequencies, the two metrics could be brought into well within 1% agreement.

INSERT FIGURE 4 HERE

SCC can be computed for any epoch that produces an estimate of the FFT spectral energy, which is to say that it is meaningful for a single FFT sample. Thornton has found this metric to be of significant value in the assessment and training of children with learning disabilities and related disorders. To this end, he has constructed a database of normative values, as well as clinical procedures leading to effective training.

The metric known as Comodulation was described by Sterman and Kaiser, and was intended as a means of assessing similarity in the time behavior of EEG component amplitudes. It asks, “do the signals wax and wane in a correlated manner”? In its definition, comodulation again looks like a standard Pearson correlation coefficient:

$$COMODULATION = \frac{\left(\sum |X_t| |Y_t|\right)^2}{\left(\sum |X_t|^2 \sum |Y_t|^2\right)}$$

In this expression, the X and Y values represent successive measurements of the signal amplitudes across time for signals X and Y, respectively. Comodulation is measured across time, so that it is necessary to define the time duration, as well as the intervals of measure, for the computation. Comodulation values depend strongly on these parameters, as well as the exact conditions of the detection of the amplitude data.

Phase itself is an important metric. There are various methods of measuring phase. The traditional way to compute phase is to use the arctangent of the ratio of quadrature components derived from the FFT. Such computations suffer from problems including “wraparound” and related stability issues. That is, if two signals are continually sliding in phase, there comes a time when they are again in phase and the metric needs to “snap” back to zero. The conditions of this

transition introduce ambiguities in the definition and use of the metric. Collura described a metric that is sensitive to phase, and can be derived from complex demodulation in real time. Thatcher has also recently introduced a dynamic phase metric based upon complex demodulation, as well as a practical method of assessing (and training) phase resetting. The phase of a particular signal is generally defined as:

$$PHASE = Arc \tan \left(\frac{b}{a} \right)$$

In which b represents the “imaginary” or “out-of-phase” component, and a represents the “real” or “in-phase” component of the signal. While this definition is clear for a defined signal, estimating the phase of an actual time-series is more complex. a and b can be determined by Fourier Transform, complex demodulation, or any other applicable method. The phase separation between two signals is computed by subtracting their individual phases:

$$PHASEDIFFERENCE = Arc \tan \left(\frac{b_2}{a_2} \right) - Arc \tan \left(\frac{b_1}{a_1} \right)$$

This metric has issues having to do with “wraparound,” as well as stability and accuracy concerns raised by the need to take a ratio of two number that may be very small, or very different in magnitude. In particular, if two signals “slide” alongside each other, there is a discontinuity in this value resulting in a need to “snap” the values back into alignment. Alternate forms of phase relationships can be derived, which have different properties for specific uses. There are options for expressing the reported phase metric, including degrees or percentages, in which 100 percent may mean either “zero degrees out of phase” (Joffe) or, alternatively, “180 degrees out of phase.” (Collura)

Collura describes a measure of “similarity” that is similar to that of classical coherence, but which has several important differences. The first is that it is maximized when the signals are in phase, which is to say that their phase difference is zero. It is thus a measure of synchrony, not just phase stability. A second difference is that it is maximized when the signals are of similar size. The general form of this metric’s sensitivity is given by:

$$SIMILARITY_{[A,B]} = \frac{2AB}{A^2 + B^2}$$

In which A and B are the complex quantities of the two signals. This reaches unity when A and B are identical in both amplitude and phase. This metric thus produces a value that is relevant to EEG synchrony, as a special case of EEG coherence. In addition to being useful for EEG biofeedback assessment and training, it has found particular value in the assessment of consciousness in the application of intraoperative monitoring (Alshab et. al. 2005).

Asymmetry may also be regarded as a connectivity metric, in that it reflects relative activation between the sites of interest. Asymmetry can be measured in any manner that reveals differences in signal amplitudes. Rosenfeld has derived a particularly useful metric, which takes the form of the difference between the signal amplitudes normalized to the sum of their amplitudes. This metric takes the form:

$$ASYMMETRY = \frac{A - B}{A + B}$$

In which A and B are the instantaneous values of a given estimate, typically alpha amplitude, in the two channels of interest. This metric has the benefit of being independent of the individual signal amplitudes, and also preferring either very large amplitude differences, or lower amplitude in both signals.

EEG asymmetry is of particular value in working with interhemispheric EEG, in particular that of the frontal lobes. It has been found to correlate with mood in general, and depression in particular. The measurement and training of frontal EEG asymmetry has become an important avenue in clinical neurofeedback when applied to depressed patients. It is also of potential value when used intrahemispherically, particularly front-to-back, in which posterior amplitudes can be trained in relation to anterior amplitudes, to seek normal relationships.

Another highly useful method is to simply add (and/or subtract) the EEG signals as raw waveforms, and process the resulting signals in a conventional manner. This method was applied by Crane (1995) in the Capscan system and by Fehmi, and has been further developed by others. This method has the benefit of being easy to understand and interpret. It is also simple to use, in that the signal recombination simply produces another signal, which may then be subjected to any of the methods used for signal processing, including transforms, digital filtering, joint time-frequency analysis, and so on. The dependence of the channel sum or difference on the individual signal amplitudes and phases is easy to determine and describe. This approach avoids the pitfalls implicit in deriving a new metric, implementing and validating it, and interpreting the results. It further simplifies the implementation on different platforms, since the core signal processing consists solely of algebraic combination of the two or more raw signals.

The following time-frequency plot illustrates the difference between the spectral energy in the sum (left) and the difference (right) of signals recorded from T3 and T4. It is immediately visually evident that, whereas these signals have significant shared (synchronous) energy in the theta band, their activity in the alpha and low beta bands are predominantly independent (asynchronous). This insight is significant when choices are made to train either monopolarly or bipolarly.

INSERT FIGURE 5 HERE

SUMMARY OF METRICS

The following table summarizes the definitions and sensitivities of the major EEG connectivity metrics that have been discussed. This analyzes each of the metrics in terms of the method used, what it looks primarily at, what question it asks, and whether it has sensitivity to amplitude or phase relationships.

INSERT TABLE 1 HERE

The following table summarizes the training capabilities of the EEG connectivity metrics. In each case, we analyze whether the metric can be used, as defined, to train neuronal connectivity as expressed by coherence, synchrony, and general dependence or independence of the recorded areas.

INSERT TABLE 2 HERE

THE IMPORTANCE OF NORMATIVE ASSESSMENT

Connectivity assessment and training provide a significant challenge in that it is not generally clear what is “good” in terms of any particular metric between specific locations and within a component band of interest. With very few exceptions, connectivity in the brain has what David Kaiser has referred to as a “Goldilocks” aspect. That is to say, it might be too low, or too high, but it needs to be “just right” to ensure optimal brain functioning. For this reason, the availability of normative data is crucial for the proper interpretation and use of connectivity measures.

Walker has found, for example, that training coherence without short-term guidance can lead to coherence abnormalities that have clinical significance. When coherence is too high, it is referred to as “hyper-coherence” and when it is too low, it is referred to as “hypo-coherence.” Either of these conditions can be adverse. In particular, when the language areas are involved, for instance, either hyper-coherence or hypo-coherence can be accompanied by dysfunctions such as stuttering, word grasping, and related disorders of speech and language.

As another example, since bipolar (channel difference) techniques are known to have a general effect of decreasing coherence in any bands that are trained up, this consideration is particularly relevant to such protocols. This phenomenon likely plays a large role in the experience that bipolar training between T3 and T4, for example, may lead to unpredictable and uncontrolled effects, requiring frequent interviewing and coaching of the trainee. If normative data and controlled coherence training were applied in such situations, we should anticipate improved control and predictability of training, and a reduction in adverse or unpredictable outcomes.

Thornton has described a successful clinical approach using spectral correlation coefficient, applied to trainees with learning disabilities. He developed his own database of normative scores, and uses this in the assessment of clients, and the application of neurofeedback protocols. In this approach, he honors the need for the SCC to be within a normative range. When excessive scores

are seen, downtraining is indicated, and when low scores are seen, they are uptrained. A particular challenge with this approach is the fact that the normative scores are dedicated to a particular instrument (Lexicor) and do not generalize a priori to other systems. Training is based upon raw scores, so that, for example, an SCC which may be low, with a value of, say, 70, needs to be trained up to a normal value of, say, 80, but not up to an abnormal level of 90. The exact scores must be set into the protocol and carefully watched during the training process. Normal scores depend on the sites involved, the frequency bands studied, and the age of the trainee, among other factors. The construction of a useful clinical database is time-consuming, and does not generalize to other metrics. For this reason, an overt effort must be made to implement a comparable metric on other platforms, and to validate it before this approach can be used on them. A project with this goal is presently underway between Thornton and the author. It is found that the SCC metric depends on the specific frequency response of the amplifiers. Therefore, whereas it is straightforward to match scores in midband components (theta, alpha, beta), they do not match in bands in which the amplifiers differ in frequency response. In order to produce matching measurements, it is therefore necessary to “tune down” the frequency response of the more modern amplifiers, to cause them to match the lower frequency response of their predecessors.

Collura and Thatcher have developed a method based upon an embedded database, that provides real-time z-scores and a specially tailored training system. When this approach is used, metrics that are expressed as z scores include, in addition to amplitude-based values, z scores for asymmetry, coherence, and phase. Real-time z-scores differ from conventional QEEG z scores in two important ways. The first is that the scores are derived from real-time complex demodulation instead of the conventional FFT, and are thus available in real time with minimal delay. The second important factor is that real-time z-scores are computed based upon within-subject short-term variations in addition to across-subject variations, while conventional QEEGs employ only

across-subjects statistics. For this reason, the standard deviations for real-time z scores are higher, and the resulting z scores are typically lower. Thus, real-time z-scores tend to be more “forgiving,” and are more likely to appear normal.

When z-scores are used for EEG training, a variety of targeting options are available. The most obvious is to train “toward the norm,” in which the protocol is designed to guide the trainee into the normal range. There are various options available when using this approach, owing to the variety of z-scores available, and choices regarding the provision of reinforcement feedback. When doing connectivity training, this is the most obvious approach, and provides significant benefits. The first is that it clearly avoids the pitfalls of training either hypercoherence or hypo-coherence. Another is that such protocols can “autoselect” the variables that are trained, in that they will automatically ignore normal scores, and only use abnormal scores to produce the contingent feedback. This is of particular significance in light of the fact that it is known that connectivity metrics that were normal may become abnormal in the course of training. The use of z-scores in this situations can relieve practitioners of some of the burden of a repeated cycle of QEEG / protocol design / training / repeat QEEG / etc.

The ability to automatically train toward normal can be used in conjunction with other training protocols, as part of a comprehensive approach. For example, a coherence “guard” can be provided, to ensure that feedback for amplitude-based conditions provides reinforcement only when coherences are normal. Such combined training may be likened to a complex task, in which the brain learns not just a single targeting experience, but learns to maintain a balance of activation, relaxation, and connectivity all in one protocol.