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Hand Calculator Calculations of EEG Coherence, Phase Delays and Brain Connectivity

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1 - Introduction

Measurements of real-time and off-line electrodynamics of the human brain have evolved over the years and one purpose of this paper is to provide simple hand calculator equations to facilitate standardization and the implementation of standardized methods. We begin with the fact that the brain weighs approximately 2.5 pounds and consumes approximately 60% of blood glucose (Tryer, 1988) and consumes as much oxygen as our muscles consume during active contraction, 24 hours a day. How is this disproportionate amount of energy used? The answer is that it is used to produce electricity including synchronized and collective actions of small and large groups of neurons linked by axonal and dendritic connections. Each neuron is like a dynamically oscillating battery that is continually being recharged (Steriade, 1995). Locally connected neurons recruit neighboring neurons with a sequential build up of electrical potential referred to as the recruiting response and the augmenting response also called EEG "burst activity" and "spindles" (Thatcher and John, 1977; Steriade, 1995). EEG burst activity is recognized by spindle shaped waves that wax and wane (i.e., augmenting by sequential build up, then asymptote and then decline to repeat as a waxing and waning pattern) are universal and are present in delta (1 – 4 Hz) theta (4-7.5Hz), alpha (8 to 12 Hz), beta (12.5 Hz to 30 Hz) and gamma (30 Hz – 100 Hz) frequency bands during waking in normal functioning people. Another fundamental fact is that only synchronized cortical neurons produce the electricity called the electroencephalogram and the generators are largely located near to the electrode location within a 6 cm radius below the recording electrode (Nunez, 1981; 1995). Unrelated distant sources produce lower amplitude potentials by volume conduction that add or substract at a zero phase difference between the source and the surface sensors. Locally synchronized neurons are connected to distant groups of neurons (3 cm to 21 cm) via cortico-cortical connections (Braitenberg, 1978; Schulz and Braitenberg, 2002) and are connected to clusters or populations of neurons which exhibit significant phase differences due to axonal conduction velocities, synaptic rise times, synaptic locations and other neurophsyiological delays which simply can not be produced by volume conduction. Connectivity is defined as the magnitude of coupling between neurons, independent of volume conduction. This is because in this paper we are interested in the synchronous coupling and de-coupling of local and long distance populations of neurons that add together and give rise to the rhythmic patterns of the EEG seen at the scalp surface (i.e., dynamic connectivity). Much has been learned about brain function in the last few decades and EEG biofeedback to control robotic limbs coupled with PET and fMRI cross-validation of the location of the sources of the EEG shows that the future of EEG is very bright and positive because of the reality of the neurophysics of the brain and high speed computers. 3-dimensional EEG source localization methods have proliferated with ever increased spatial resolution and cross-validation by fMRI, PET and SPECT. Understanding measurements of coupling between populations of neurons in 3-dimensions using Low Resolution Electromagnetic Tomography is critical to understand how widely distant regions of the brain communicate (Pascual-Marqui, 1999; Pascual-Marqui et al, 2001; Thatcher et al, 1994; 2005a; 2005b; 2006). It is in recognition of the importance of understanding brain connectivity especially using explicit and step by step methods that the present paper was undertaken. We attempt to use hand calculator simplicity when ever possible and this is why the cospectrum and quadspectrum are in simple notation such as a(x) or u(y) to represent different values that are added or multiplied. The hand calculator equations in section 9 are important as a reference for a programmer or a systems analysist to implement in a digital computer and thereby provide testable standards and simplicity.

2- EEG Amplitude

Nunez (1994) estimated that 50% of the amplitude arises from directly beneath the scalp electrode and approximately 95% is within a 6 cm diameter. Cooper et al (1965) estimated that the minimal dipole surface area necessary to generate a potential measurable from the scalp surface is 6 cm^2 which is a circle with a diameter = 2.76 cm. However, the amplitude of the EEG is not a simple matter of the total number of active neurons and synapses near to the recording electrode. For example, volume conduction and synchrony of generators are superimposed and mixed in the waves of the EEG. Volume conduction approximates a gaussian spatial distribution for a given point source and volume conduction of the electrical field occurs at phase delay = 0 between any two recording points (limit speed of light) (Feinmann, 1963). If there is a consistent and significant phase delay between distant synchronous populations of neurons, for example, a consistent 30 degree phase difference which can not be explained by volume conduction and network properties are necessary to explain the EEG findings.   This emphasizes the importance of phase differences and the importance of complex numbers when measuring the EEG because phase differences can only be measured using complex numbers.

The importance of the synchrony of a small percentage of the synaptic sources of EEG generators is far greater than the total number of generators. For example, Nunez (1981; 1994) and Lopes da Silva (1994) have shown that the total population of synaptic generators of the EEG are the summation of : 1- a synchronous generator (M) compartment and, 2- an asynchronous generator (N) compartment in which the relative contribution to the amplitude of the EEG = $M\sqrt{N}$.   This means that synchronous generators contribute much more to the amplitude of EEG than asynchronous generators.   For example, assume 10^5 total generators in which 10% of the generators are synchronous or M = 1 x 10^4 and N = 9 x 10^4 then EEG amplitude = $10^4\sqrt{9x10^4}$, or in other words, a 10% change in the number of synchronous generators results in a 33 fold increase in EEG amplitude (Lopez da Silva, 1994).   Blood flow studies of intelligence often report less blood flow changes in high I.Q. groups compared to lower I.Q. subjects (Haier et al, 1992; Haier and Benbow, 1995; Jausovec and Jausovec, 2003). Cerebral blood flow is generally related to the total number of active neurons integrated over time, e.g., 10 – 20 minutes (Yarowsky et al, 1983: 1985; Herscovitch, 1994).   In contrast, EEG amplitude as described above is influenced by the number of synchronous generators much more than by the total number of generators and this may be why high I.Q. subjects while generating more synchronous source current than low I.Q. subjects often fail to show greater cerebral blood flow (Thatcher et al, 2006).

3- What is Volume Conduction and Connectivity?

Connectivity is defined as the magnitude of coupling between different electrical energies recorded from different locations of the brain independent of volume conduction. Coupled oscillators are the topic of this paper starting with the genesis of the electrical potentials being ionic fluxes across polarized membranes of neurons with intrinsic rhythms and driven rhythms (self-sustained oscillations) as described by Steriade (1995) and others (Thatcher and John, 1977).

Electrical events occur inside of the human body which is made up of 3-dimensional structures like membranes, skin and tissues that have volume. Electrical currents spread nearly instantaneously throughout any volume. Because of the physics of conservation there is a balance between negative and positive potentials at each moment of time with slight delays at the speed of light (Feynmann, 1963). Sudden synchronous synaptic potentials on the dentrites of a cortical pyramidal cell result in a change in the local electrical potential referred to as a “Dipole”. Depending on the solid angle between the source and the sensor (i.e., electrode) the polarity and shape of the electrical potential is different. Volume conduction involves near zero phase delays between any two points within the electrical field as collections of dipoles oscillate in time (Nunez, 1981). Zero phase delay is one of the important properties of volume conduction and it is for this reason that measures such as the cross-spectrum, coherence, bi-coherence and coherence of phase delays are so critical in measuring brain connectivity independent of volume conduction. When separated generators exhibit a stable phase difference of, for example, 30 degrees then this can not be explained by volume conduction. As will be explained in later sections correlation coefficient methods such as the Pearson product correlation (e.g., “co-modulation” and “Lexicor correlation”) do not compute phase and are therefore incapable of controlling for volume conduction. The use of complex numbers and the cross-spectrum is essential for studies of brain connectivity not only because of the ability to control volume conduction but also because of the need to measure the fine temporal details and temporal history of coupling or “connectivity” within and between different regions of the brain.

Figure 1 is an illustration of the cross-spectrum of volume conduction vs. connectivity in which a sine wave is generated inside a sphere with sensors on the surface. The top shows the zero phase lag recordings of a sine wave and illustrates volume conduction in which the solid angle from the source to the surface is equal in all directions. The bottom shows recordings with significant phase differences which can not be accounted for by volume conduction and must be due to “connections” in the interior of the sphere. As discussed in more detail in section 9, the cross-spectrum is the sum of the in-phase potentials (i.e., cospectrum) and out-of-phase potentials (i.e., quadspectrum). The in-phase component contains volume conduction and the synchronous activation of local neural generators. The out-of-phase component contains the network or connectivity contributions from locations distant to a given source. In other words, the cospectrum = volume conduction and the quadspectrum = non-volume conduction which can be separated and analyzed by independently evaluating the cospectrum and quadspectrum (see section 9).

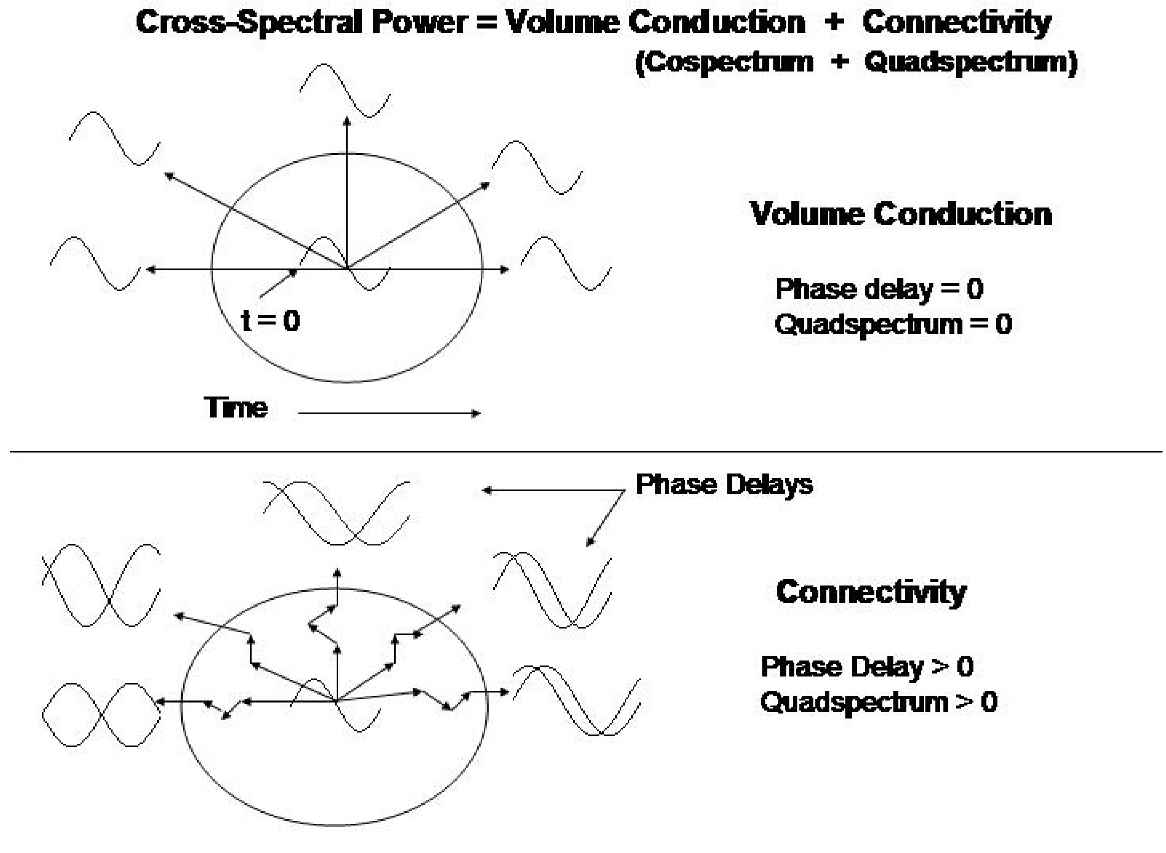

Fig. 1 – Illustration of volume conduction vs. connectivity. Top is a sine wave generator in the center of a sphere with sensors on the surface of the sphere. The sine wave generates zero phase lag square waves at all points on the surface of the sphere due to volume conduction. The cospectrum is high and the quadspectrum = 0. The bottom is the same sine wave generator in the center of the sphere but with network connections in the interior of the sphere. As a consequence there are phase differences in the surface recordings which are detected in the quadspectrum component of the cross-spectrum. See section 9 for details.

Another illustration of the relationship between "In-Phase" and volume conduction vs. "Out-of Phase" and connectivity is in figure 2.

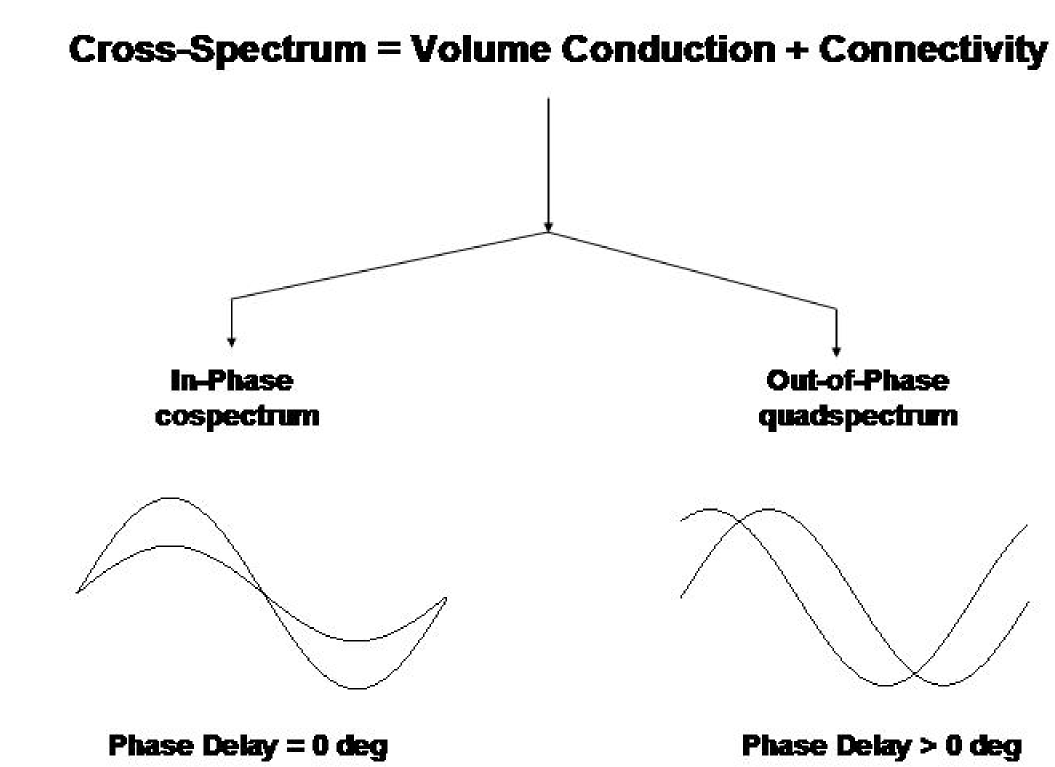

Fig. 2- Illustration of the "In-Phase" volume conduction vs. "Out-of-Phase" connectivity components of the Cross-Spectrum. See section 9 for more details.

4- How is network zero phase lag different from volume conduction?

Spatially distributed neurons exhibit near zero phase difference, referred to as a "binding" or "synchrony" within a network of neurons, which is independent of volume conduction (Ekhorn et al, 1988; Gray et al, 1989, John, 2005; Thatcher et al, 1994). Multiple unit recordings and Magnetic electroencephalography (MEG) which is invisible to volume conduction have firmly established the scientific validity of network zero phase lag independent of volume conduction (Rogers, 1994). The thalamus and septo-hippocampal systems are centrally located inside of the brain and contains "pacemaker" neurons and neural circuits that regularly synchronize widely disparate groups of cortical neurons (Steriade, 1995). As illustrated in Figure 3, a centrally synchronizing structure "C" can produce zero phase lag and simultaneously synchronize neural populations "A" and "B" without any direct connection between "A" and "B". As shown in figure 3 the cross-spectrum of coherence and phase difference can distinguish between volume conduction and network zero phase differences such as produced by the thalamus or the septal-hippocampus-entorhinal cortex, etc. For example, if the phase difference is uniformly zero in the space between "A" and "B" then this is volume conduction. On the other hand if the phase difference is not zero at points spatially intermediate between "A" and "B" then this is an example of zero phase difference independent of volume conduction. This is why a larger numbers of electrodes is important. The study by Thatcher et al, 1994 is an example of significant phase differences at intermediate short distances in contrast to zero phase difference between more distant locations which can not be explained by volume conduction.

In the chapters below we begin with a discussion of correlation, then coherence and phase difference and then bi-spectra. We show that there is a commonality shared by all of these measures – the commonality is the statistical "degrees of freedom". Each measure of cortical network dynamics involves the detection of a "signal" within "noise" and each measure shares the same statistical properties, namely, increased sample sizes are proportional to increased sensitivity and increased accuracy of the estimates of coupling.

5- Pearson product correlation ("co-modulation" and Lexicor "spectral correlation coefficient")

The Pearson product correlation coefficient is often used to estimate the degree of association between amplitudes or magnitudes of the EEG over intervals of time and frequency (Adey et al, 1961). The Pearson product correlation coefficient does not calculate a cross-spectrum and therefore does not calculate phase nor does it involve the measurement of the consistency of phase relationships such as with coherence and the bi-spectrum. However, coherence and the Pearson product correlation coefficient are statistical measures and both depend on the same number of degrees of freedom for determining the accuracy of the measure as well as the same levels of statistical significance. The Pearson product correlation coefficient is a valid and important measure of coupling and it is normalized and independent of absolute values.

The Pearson product correlation coefficient (PCC) has been applied to the analysis of EEG spectra for over 40 years, for example, some of the earliest studies were by Adey et al (1961); Jindra (1976) Paigacheva, I.V. and Korinevskii (1977). The general method is to compute the auto power spectrum for a given epoch and then to compute the correlation of power or magnitude over successive epochs, i.e., over time. The number of degrees of freedom is determined by the number of epochs. Neuroscan, Inc. offered this method of EEG analysis in the 1980s. Recently, the application of the Pearson product correlation coefficient (PCC) for magnitude has been called "co-modulation" (Sterman and Kaiser, 2001). Below is the general equation for the computation of "spectral correlation" or "spectral amplitude correlation" and the recent term "co-modulation" which is a limited term because it fails to refer to the condition of a 3rd source affecting two other sources without the two sources being directly connected. The term "co-modulation" has a different meaning than "synchronization" (Pikovsky et al, 2003) and in order to reduce confusion it is best to simply refer to the correlation itself. In other words, it is best to use the term "Correlation" or "Pearson product correlation coefficient" (PCC) unless additional path analyses or partial correlation analyses were used to show that "co-modulation" and not a 3rd modulator "C" is the correct model or that there is no synchrony involved. Figure 3 illustrates the differences in meaning when using the terms "Pearson Product Correlation Coefficient" vs the term "Co-Modulation".

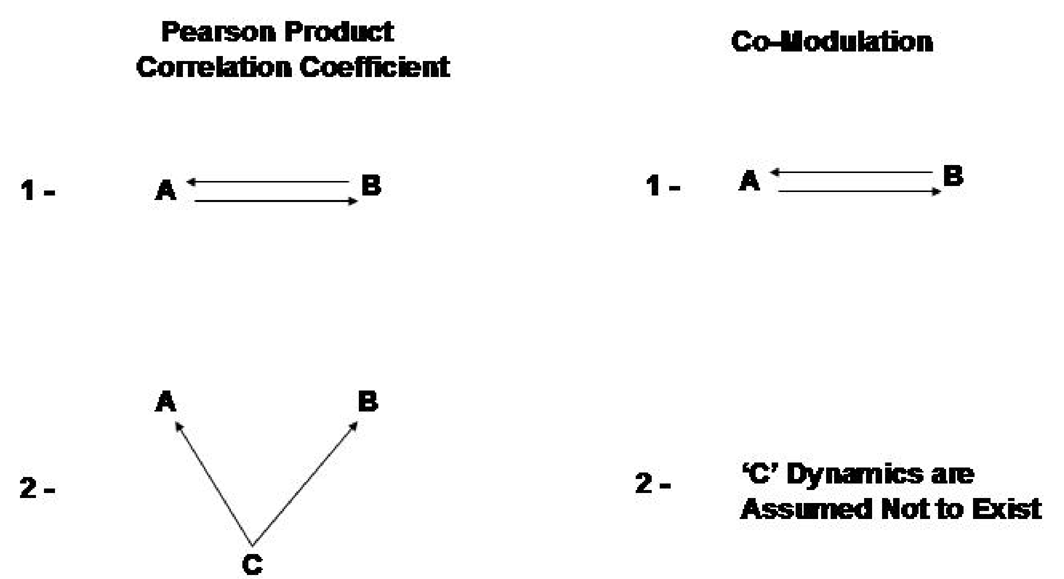

Fig. 3 – Pearson product correlation coefficient (and coherence) includes at least two possible couplings and mixtures of these two types of coupling: 1- where neuron A

influences neuron B and vice versa and, 2- where a third neuron ‘C’ influences neuron A and neuron B and there is no connection between A and B. Co-modulation omits the standard ‘C’ possibility and is limited to where neuron A influences neuron B and vice versa. The limitation of the term “co-modulation” is that without partial correlation analyses or path analyses it is not possible to omit coupling number 2 which means that the term co-modulation can be misleading unless these additional analyses are done.

As discussed by Pikovsky et al (2003) the term modulation is complicated and it is possible for there to be modulation without synchronization and synchronization without modulation. As stated by Pikovsky et al (2003, p. 77) “Generally, modulation without synchronization is observed when a force affects oscillations, but cannot adjust their frequency.” Without further analyses to determine this distinction it is best to simply refer to correlation.

The distinguishing characteristic of application of the Pearson product correlation coefficient is the computation of the time course of the normalized covariance of spectra over an interval of time:

Eq. 1-

$$\boldsymbol{r} = \frac{\sum_{N}(\boldsymbol{X} - \overline{\boldsymbol{X}})(\boldsymbol{Y} - \overline{\boldsymbol{Y}})}{\sqrt{\sum_{N}(\boldsymbol{X} - \overline{\boldsymbol{X}})^2 \sum_{N}(\boldsymbol{Y} - \overline{\boldsymbol{Y}})^2}}$$

or the computationally simpler equation that one can compute more easily using a hand calculator:

Eq. 2 -

$$\boldsymbol{r} = \frac{\boldsymbol{N}\sum \boldsymbol{XY} - \sum \boldsymbol{X} \sum \boldsymbol{Y}}{\sqrt{(\boldsymbol{N}\sum \boldsymbol{X}^2 - (\sum \boldsymbol{X})^2)(\boldsymbol{N}\sum \boldsymbol{Y}^2 - (\sum \boldsymbol{Y})^2)}}$$

For example, if one computes the FFT over 1 second epochs for a 60 second recording period, i.e., N = 60, then the number of degrees of freedom in the spectral correlation coefficient (PCC) for channels X and Y = 60 – 1 = 59. For 59 degrees of freedom then a correlation of 0.258 or higher is statistically significant at $P < .05$. This is a valid and commonly used connectivity measure, however, it is important to remember that the correlation coefficient includes volume conduction + network connectivity, i.e., they are inextricably confounded. This is because the correlation coefficient omits phase difference and is the “in-phase” or autospectral values and therefore volume conduction can not be separated and eliminated. This makes it more difficult to know if factors such as the number and strength of connections are what are changing due to experimental control or is it the "volume conduction" that is changing? As explained in section 8, coherence using complex numbers and phase differences separate volume conduction from network dynamics and automatically solve this problem.

Another method of applying the Pearson Product correlation (PCC) was developed by Lexicor, Inc. in the 1990s. This method computes the correlation between EEG spectra measured from two different locations and uses the individual spectral bin values within a frequency band. For example, if there are five frequency bins in the alpha frequency band (i.e., 8Hz, 9Hz, 10Hz, 11Hz and 12Hz), then N = 5 and the number of degrees of freedom = N – 1 = 4. When the degrees of freedom = 4 then a correlation coefficient of 0.961 or higher is necessary in order to achieve statistical significance at $P < .05$. Equations 1 and 2 are used to calculate the Pearson product correlation in both instances.

Dr. Thomas Collura recently evaluated the commonalities and differences between "co-modulation" and the Lexicor application of the Pearson product correlation (Collura, 2006). It was shown that the difference between the "co-modulation" and Lexicor methods is primarily in terms of the number of degrees of freedom as well as the evaluation of covariance of spectral energies over time in the former application of the Pearson Product correlation (PCC) versus within frequency band covariation across channels in the Lexicor method of applying the Pearson product correlation (PCC).

Below is a hand calculator example of a Lexicor application of the Pearson product correlation coefficient (PCC) for the alpha frequency band (8 – 12 Hz column on the left) between channel X and channel Y using easy numbers for a hand calculator using equation 2 with N = 5 (i.e., number of spectral bins within a band).

Table I

	X (uV)	Y (uV)	X^2 (uV^2)	Y^2 (uV^2)	XY
8Hz	1	2	1	4	2
9Hz	2	1	4	1	2
10Hz	3	2	9	4	6
11Hz	3	1	9	1	3
12Hz	4	2	16	4	8
	$\sum X = 13$	$\sum Y = 8$	$\sum X^2 = 39$	$\sum Y^2 = 18$	$\sum XY = 21$

$$r = \frac{N\sum XY - \sum X \sum Y}{\sqrt{(N\sum X^2 - (\sum X)^2)(N\sum Y^2 - (\sum Y)^2)}}$$

$$r = \frac{5 \times 21 - 13 \times 8}{\sqrt{(5 \times 39 - 13^2)(5 \times 18 - 8^2)}}$$

$$r = \frac{1}{\sqrt{26 \times 26}} = +0.001479$$

Fig. 4 shows the results of the BrainMaster implementation of the Lexicor spectral correlation method in which very high correlation values are present because of the low number of degrees of freedom and especially the divergent differences at higher frequencies because of slight differences in filtering. This figure emphasizes that extreme caution should be used when computing a correlation coefficient using the Lexicor method with low degrees of freedom.

Comparison of Lexicor SCC and BrainMaster SCC

Trial Run 8/31/06

	LEXICOR	RUNTIME	REPLAY NOTCH OFF	REPLAY 60 Hz NOTCH ON	REPLAY 60 & 50 Hz NOTCHES ON
DELTA	92.4	94.77	92.12	92.19	92.16
THETA	93.4	95.79	92.77	92.86	92.93
ALPHA	90.9	95.91	92.12	92.26	91.98
BETA	84.6	83.56	86.19	85.42	84.23
GAMMA	88.6	63.05	93.35	78.7	70.42

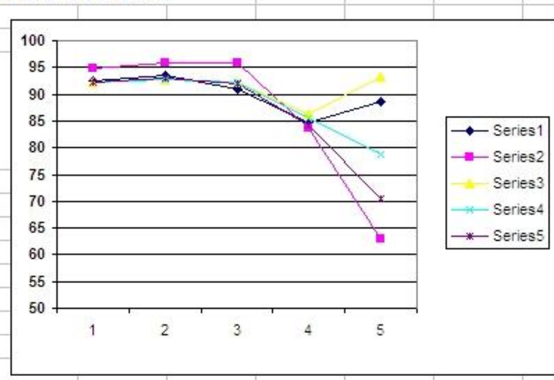

Fig. 4 - Comparisons between the BrainMaster and Lexicor implementation of the spectral correlation method. The correlation values are all very high due to the low degrees of freedom and miss-match of calculation occurs at the higher frequencies depending on the filter parameters (From Collura, 2006).

LORETA source correlations are another example of the application of the Pearson product correlation coefficient (Thatcher et al, 2006). Below are examples of the relationship between cortico-cortical connectivity and distance from a point source using LORETA current sources and the Pearson product correlation coefficient (PCC) as applied to sequential epochs of time. The degrees of freedom ranged from 29 to 60 in which a correlation of 0.367 to 0.254 is necessary for $P < .05$.

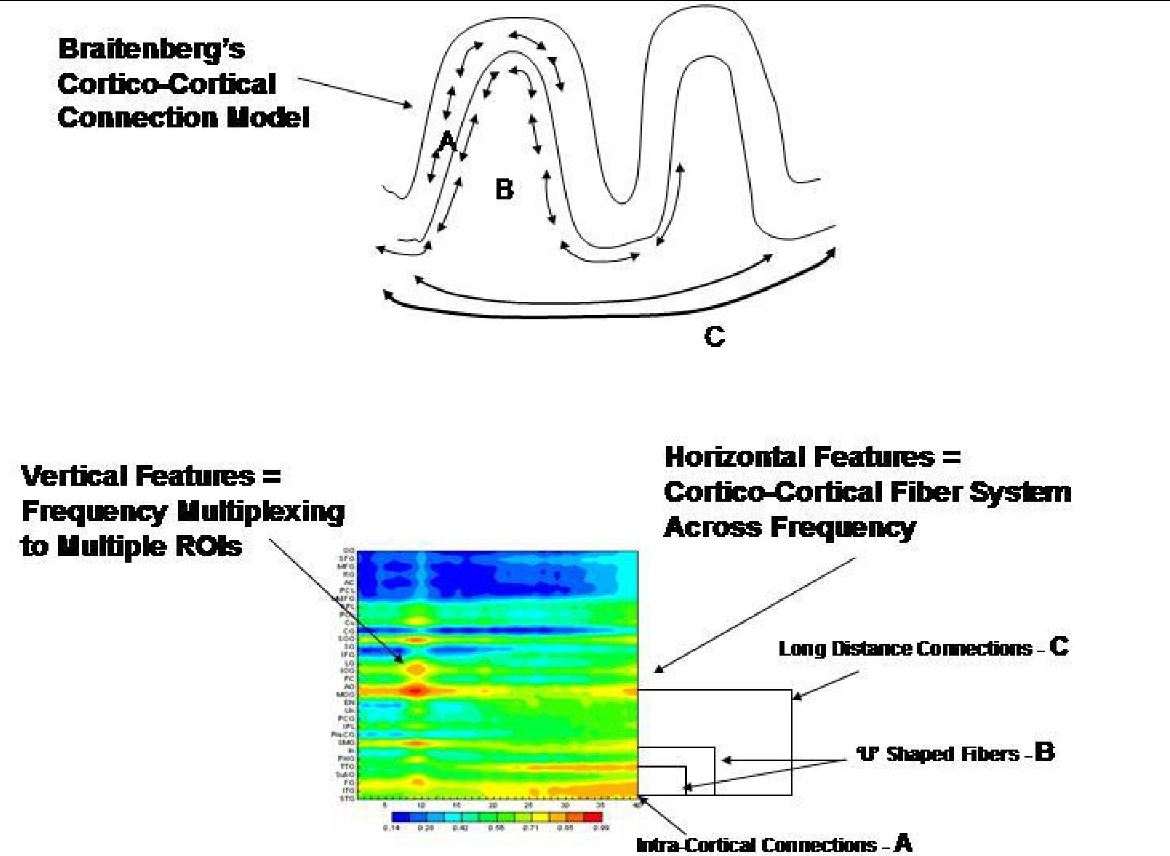

Fig. 5 - Illustration of a cortico-cortical connection model. Top is the organization of intra-cortical connections according to Schulz and Braitenberg (2002). A = gray matter intra-cortical connections, B = 'U' shaped white matter connections and C = long distance white matter connections. Bottom is an exemplar contour map of source correlations in which the horizontal bands of increasing and decreasing source correlations correspond to the different cortico-cortical connection systems as described in the top of the figure. From Thatcher et al, 2006.

6- What is Coherence?

Coherence is a measure of the amount of association or coupling between two different time series. Coherence combines something analogous to the "Pearson product-moment correlation" with the additional information of a cross-correlation function of phase angles between two signals at different frequencies. When the phase difference between two signals is constant than coherence = 1, when the phase difference between signals is random then coherence = 0. Coherence is mathematically analogous to a Pearson product-moment correlation, however, coherence measures phase differences and yields a much finer measure of shared energy between mixtures of periodic signals than can be achieved using the

Pearson product-moment correlation coefficient. In fact, coherence is essential because the degree of relationship or coupling between any two living systems cannot be fully understood without knowledge of its frequency structure over a relative long period of time. Another advantage of Coherence, as mentioned previously, is its dependence on the consistency of the average phase difference between two time series, where as the Pearson product-moment correlation coefficient is independent of phase differences. The fine details of the temporal relationship between coupled systems is immediately and sensitively revealed by coherence.

In this paper we will first describe the mathematics of the autospectrum and power spectrum as they apply to EEG coherence by using simple hand calculator instructions so that one can step through the mathematics and understand coherence and phase at a basic level (some of the deeper mathematical detail is in the Appendix). We will step the reader through simple examples that can be solved with a hand calculator (scientific calculator is recommended) to further illustrate how coherence is computed and to demonstrate by simulation of EEG signals and noise. We will also address the statistical properties of the power spectrum, coherence and phase synchrony using calibration sine waves and the FFT in order to illustrate the nature of coherence and phase angle (i.e., phase difference and direction) and finally, a statistical standard by which the signal-to-noise ratio and degrees of freedom in the computation of EEG coherence are measured using a hand calculator and by computer simulation of the EEG. Computer signal generators not only verify but most importantly also explore a rich universe of coherence and phase angles with a few mouse clicks (download a free EEG simulator at: http://www.appliedneuroscience.com and download the NeuroGuide demo program. Click File > Open > Signal Generation to simulate the EEG, including "Spindles" and inter-spindle intervals, etc. Another free EEG simulation program is at: http://www.besa.de/index_home.htm , a third free EEG simulation program (purchase of MatLab required) is at: http://www.sccn.ucsd.edu/eeglab/index.html and a fourth simulation program for the mathematics of the Fourier series is: http://www.univie.ac.at/future.media/moe/galerie/fourier/fourier.html#fourier

Mathematical and statistical standardization of EEG coherence are best understood using a hand held calculator and then by simulation of the EEG.

Coherence arises from Joseph Fourier's 1805 fundamental inequality where by the ratio of the cross-spectrum/product of auto-spectrum < 1.

Coherence is inherently a statistical estimate of coupling or association between two time series and is in essence the correlation over trials or repeated measures. As mentioned previously, the critical concept is "phase consistency", i.e., when the phase relationship between two time series is constant over trials than coherence = 1.

7- How Does One Compute Coherence?

The first step in the calculation of the coherence spectrum is to describe the activity of each raw time-series in the frequency domain by the "auto-spectrum" which is a measure of the amount of energy or "activity" at different frequencies. The second step is to compute the "cross-spectrum" which is the energy in a frequency band that is in common to the two different raw data time-series. The third step is to compute coherence which is a normalization of the cross-spectrum as the ratio of the auto-spectra and cross-spectra. To summarize:

1- Compute the auto-spectra of channels X and Y based on the "atoms" of the spectrum
2- Compute the cross-spectra of X and Y from the "atoms" of the spectrum
3- Compute Coherence as the ratio of the auto-spectra and cross-spectra

8- First Compute the auto-spectra of channels X and Y based on the "atoms" of the spectrum

Joseph Fourier in his thesis of 1805, benefiting from almost a century of failed attempts, finally correctly showed that any complex time-series can be decomposed into elemental "atoms" of individual frequencies (sine and cosine and linear operations). Fourier defined the autospectrum as the amount of energy present at a specific frequency band. He showed that the autospectrum can be computed by multiplying each point of the raw data by a series of cosines, and independently again by a series of sines, for the frequency of interest. The average product of the raw-data and cosine is known as the cosine coefficient of the finite discrete Fourier transform, and that for the sine and the raw data as a sine coefficient. The relative contributions of each frequency are expressed by these cosine and sine (finite discrete Fourier) coefficients. The cosine and sine coefficients constitute the basis for all spectrum calculations, including the cross-spectrum and coherence. Tick (1967) referred to the sine and cosine coefficients as the "atoms" of spectrum analysis. For a real sequence $\{x_i, i = 0, \ldots, N-1\}$ and Δt = the sample interval and f = frequency, then the cosine and sine transforms are:

Eq.3 - The cosine coefficient = $a(n) = \Delta t \sum_{i=1}^{N} X(i) \cos 2\pi f i \Delta t$

Eq.4 - The sine coefficient = $b(n) = \Delta t \sum_{i=1}^{N} X(i) \sin 2\pi f t \Delta t$

The hand calculation of the individual coefficients is complicated and here are some steps that are helpful:

1- Evaluate i * Δt * f * 2л = θ.
2- Compute cos θ and then sin θ.
3- Compute x_i cos θ, and then x_i sine θ.
4- Accumulate both sums.
5- Increment i; return to step 1.

A numerical example of the computation of the Fourier Transform is shown in Table II. The data is from Walter (1969) which served as a numeric calibration and tutorial of EEG coherence in the 1960s (see also Jenkens and Watts, 1969 and Orr and Naitoh, 1976). This 1960s dataset is still useful for explaining the concept of spectral analysis as it applies to the Electroencephalogram as QEEG was developed in the 1950's and used at UCLA and other universities giving rise to a large number of publications and the development of the BMDP Biomedical statistical programs in the 1960s. The Walter (1969) data are 8 digital time points that were sampled at 100 millisecond intervals (0.1 sec. intervals) with 3 separate measurements (i.e., repetitions). The highest frequency resolution of this data set is defined as 1/T = 1/0.8 sec. = 1.25 Hz. The highest discernable frequency is 5 Hz (Nyquist limit) and thus the data are bounded by 1.25 Hz and 5 Hz, with values at every 1.25 Hz. We will use the same historic examples that pioneers used in the early development of quantitative EEG used in the 1950s - 1970s. The analyses below are based on the careful step by step evaluation of the Walter (1969) paper by Orr, W.C. and Naitoh, P. in 1967 which we follow.

The Walter (1969) cosine and sine coefficients in Table II will be used for the purpose of this discussion. The focus will be on the use of a hand calculator to compute coherence using the values in Table II and not on the computation of the coefficients themselves.[1] The reader is encouraged to either write intermediate values on a piece of paper or to store temporary variable values using the memory keys of their hand calculator.

Table II
Example of Raw Data

Table of Observation (seconds)	Channel X 0.0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	Table of Observation (seconds)	Channel Y 0.0	0.1	0.2	0.3	0.4	0.5	0.6	0.7
Record 1	3	5	-6	2	4	-1	-4	1	Record 1	-1	4	-2	2	0	-0	2	-1
Record 2	1	1	-4	5	1	-5	-1	4	Record 2	4	3	-9	2	7	0	-5	1
Record 3	-1	7	-3	0	2	1	-1	-2	Record 3	-1	9	-4	-1	2	4	-1	-5

Hand Calculator Example of Cosine and Sine Coefficients

Channel X Cosine Coefficients a(x)					Channel Y Cosine Coefficients b(y)				
f (Hz)	1.25	2.5	3.75	5.0	f (Hz)	1.25	2.5	3.75	5.0
Record 1	0.634	4.25	-1.134	-1.25	Record 1	-0.073	-0.25	-0.427	-0.75
Record 2	0.634	2.0	-1.134	-0.875	Record 2	-0.398	6.5	-1.106	-1.25
Record 3	-0.043	1.75	-1.457	-1.375	Record 3	-0.368	1.5	-0.934	-1.375
Average	0.408	2.667	-1.242	-1.167	Average	-0.272	2.583	-0.822	-1.125

Channel X Sine Coefficients b(x)					Channel Y Sine Coefficients b(y)				
f (Hz)	1.25	2.5	3.75	5.0	f (Hz)	1.25	2.5	3.75	5.0
Record 1	0.737	0.25	1.737	0.000	Record 1	0.237	0.75	2.237	0.000
Record 2	0.487	-3.25	1.987	0.000	Record 2	-0.043	0.00	1.457	0.000
Record 3	0.414	2.5	2.414	0.000	Record 3	0.641	4.75	2.341	0.000
Average	0.546	-1.67	2.048	0.000	Average	0.345	1.833	2.012	0.000

Autospectrum X **Autospectrum Y**

[1] A Matlab computation of the sine and cosine coefficients using the raw data in Table II produced the following coefficients 2.5355- 2.9497i, 17.0000- 1.0000i, -4.5355- 6.9497i using the complex notation a + ib. Even though different coefficients may be produced than those published by Walter (1969) let us continue to use the Walter (1969) coefficients because the procedures to compute coherence and not the coefficients are what are of interest in this paper. We will produce an updated table and set of numbers in a future revision.

f (Hz)	1.25	2.5	3.75	5.0	f (Hz)	1.25	2.5	3.75	5.0
Record 1	**0.945**	**18.125**	**4.303**	**1.563**	**Record 1**	**0.061**	**0.625**	**3.186**	**0.561**
Record 2	**0.639**	**14.563**	**5.234**	**0.766**	**Record 2**	**0.159**	**42.25**	**3.342**	**1.563**
Record 3	**0.173**	**9.313**	**7.95**	**1.891**	**Record 3**	**1.036**	**24.813**	**6.353**	**1.891**
Average	**0.586**	**14.00**	**5.838**	**1.407**	**Average**	**0.419**	**22.561**	**4.96**	**1.339**

The frequency analysis of a time series of finite duration "at" a chosen frequency does not really show the activity precisely at that frequency alone. The spectral estimate reflects the activities within a frequency band whose width is approximately 1/T around the chosen frequency. For example, the activity "at" 1.25 Hz in the example in Table II represents in fact the activities from 0.625 Hz to 1.875 Hz (or equivalently, 1.25 Hz ± 0.625 Hz).

The autospectrum is a "real" valued measure of the amount of activity present at a specific frequency band. The autospectrum is computed by multiplying the raw data by the cosine, and independently, by the sine for the frequency of interest in a specific channel. The average product of the raw-data and cosine is referred to as the "cosine coefficient" of the finite discrete Fourier transform, and the average product of the sine and the raw-data is referred to as the sine coefficient. Let N, f and a(x) represent the number of observed values for a time series x(i), the frequency of interest, and a cosine coefficient n, then the summation or necessary "smoothing" is defined as:

Eq. 5 - The average cosine coefficient = $a(n) = \frac{1}{N}\sum_{i=1}^{N} X(i)\cos\left(\frac{2\pi i f}{N}\right)$

Eq.6 - The average sine coefficient = $b(n) = \frac{1}{N}\sum_{i=1}^{N} X(i)\sin\left(\frac{2\pi i f}{N}\right)$

Each frequency component has a sine and cosine numerical value. The actual autospectrum value is arrived at by squaring and adding the respective sine and cosine coefficients for each time series. The power spectral value for any frequency intensity is:

Eq. 7 - $F(x) = (a^2(x) + b^2(x))$,

That is, the power spectrum is the sum of the squares of the sine and cosine coefficients at frequency f as shown in Table II.

9- Second Compute the cross-spectra of X and Y from the "atoms" of the spectrum

To calculate the cross-spectrum, it is necessary to consider the "in-phase" and "out-of-phase" components of the signals in channels X and Y. The former is referred to as the co(incident) spectrum or cospectrum and the latter is referred to as the guadrature spectrum or quadspectrum. The "in-phase" component is computed by considering the sine coefficients as well as the cosine coefficients of X and Y. The "out-of-phase" component concerns relating the cosine coefficient of time series X to the sine coefficient of times series Y, and similarly the sine coefficient of times series X to the cosine coefficient of time series Y.

A simple hand calculator test will show that the quadspectrum = 0 for any two in-phase sine waves (i.e., phase difference = 0). This simple test is important when eliminating or separating the "volume conduction" contribution to the cross-spectra generated by the brain network or brain "Connectivity" aspects of EEG as discussed in section 2. For example, non-volume conduction measures where there are statistically significant phase differences of less than 1 degree have been published (Ekhorn et al, 1988; Barth, 2003). Long electrical phase differences of 5^0 to 30^0 simply can not be explained by volume conduction as a matter of physics.

10- How to Compute the cospectrum and quadspectrum

Below is a hand calculator example of how to compute the coherence spectrum. Step 1 is to calculate the cospectrum and quadspectrum:

a(x) = cosine coefficient for the frequency (f) for channel X
b(x) = sine coefficient for the frequency (f) for channel X
u(y) = cosine coefficient for the frequency (f) for channel Y
v(y) = sine coefficient for the frequency (f) for channel Y

The cospectrum and quadspectrum then are defined as:

Eq. 8 - Cospectrum (f) = a(x) u(y) + b(x) v(y)

Eq. 9 - Quadspectrum (f) = a(x) v(y) – b(x) u(y)

The cross-spectrum **power** is real valued and defined as:

Eq. 10 - (f) $= \sqrt{(\cos pectrum(f)^2 + quadspectrum(f)^2)}$

Eq. 11- $= \sqrt{((\boldsymbol{a}(x)\boldsymbol{u}(y) + \boldsymbol{b}(x)\boldsymbol{v}(y))^2 + (\boldsymbol{a}(x)\boldsymbol{v}(y) - \boldsymbol{b}(x)\boldsymbol{u}(y))^2}$

That is, the cross-spectrum **power** is the absolute value of the complex-valued cross-spectrum. The cross-spectrum **power** is a measure of connectivity based on the total shared energy between two locations at a specific frequency and it is a mixture of in-phase and out-of-phase activity (i.e., local and distant). The cross-spectrum power is a real number because a complex number times the complex conjugate is a real number. **Coherence** is a normalization of the cross-spectral power by dividing by the autospectra or the in-phase component and, therefore, coherence is independent of autospectral amplitude or power and varies from 0 to 1.

Table III is an illustration of the computational details of coherence based on the FFT auto and cross-spectra in Table II:

Table III
Hand Calculator Example
Cospectrum, Quaspectrum and Ensemble Smoothing

F (Hz)	**Cospectrum**				**Quaspectrum**			
	1.25	**2.50**	**3.75**	**5.00**	**1.25**	**2.50**	**3.75**	**5.00**
Record 1	**0.128**	**-0.875**	**4.375**	**0.938**	**0.204**	**3.25**	**-1.795**	**0.000**
Record 2	**-0.272**	**13.00**	**4.147**	**1.094**	**-0.22**	**-21.125**	**0.541**	**0.000**
Record 3	**0.363**	**14.50**	**7.012**	**1.891**	**0.108**	**4.563**	**-1.156**	**0.000**
Average	**0.073**	**8.875**	**5.176**	**1.307**	**0.031**	**-4.438**	**-0.803**	**0.000**

Cospectrum (1.25 Hz) = 0.634(-0.073) + 0.737(0.237) = 0.128

Quadspectrum (1.25 Hz) = 0.634(0.237) – 0.737(-0.073) = 0.204

Cross-spectrum (1.25 Hz) = 0.128 + sq. root -1 (0.204) and

Cross-spectrum power (1.25 Hz) = $(0.128^2 + 0.204^2)$ ½ = 0.241

This computation is repeated for each frequency component to yield the complete cross-spectrum.

As mentioned previously in section 3, the cross-spectrum is the sum of the in-phase potentials (i.e., cospectrum) and out-of-phase potentials (i.e., quadspectrum). The in-phase component contains volume conduction and the synchronous activation of local neural generators. The out-of-phase component contains the network or connectivity contributions from locations distant to a given source. In other words, the cospectrum = volume conduction and the quadspectrum = non-volume conduction which can be separated and analyzed by independently evaluating the cospectrum and quadspectrum. Figure 6 is an example of the differences between the in-phase and out-of-phase components of the cross-spectrum in a right hemisphere hematoma patient. The cospectrum shows high focal sources and little distant zero phase lag relations. This is indicative of a source near to the surface of the scalp at P4 and C4. The quadspectrum shows high out-of-phase power or network connections between P4 and the distant left hemisphere and especially F3 that are highly out-of-phase. In general the right parietal lobe is out of phase with respect to the spatially distant left hemisphere.

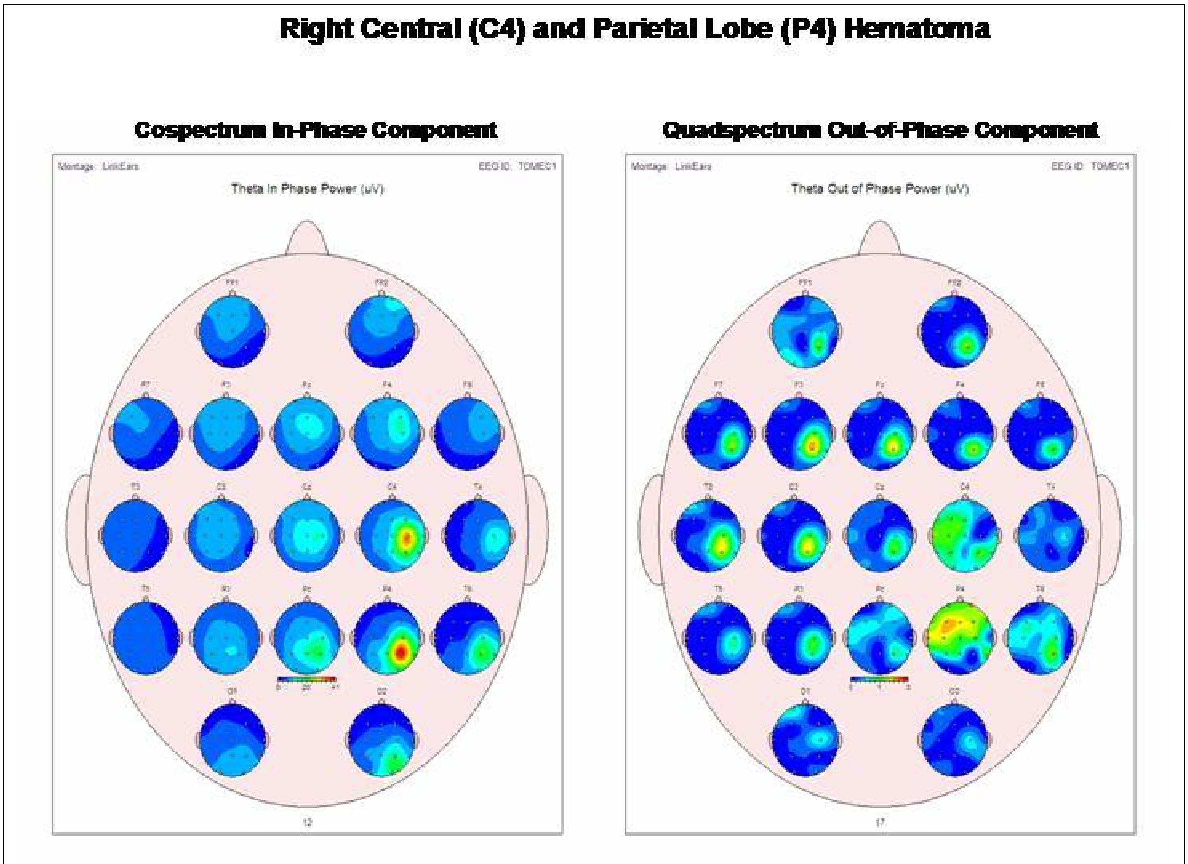

Fig. 6 – Left is the cospectral power or In-Phase power in all 171 electrode combinations of the 10/20 system. Right is the quadspectral power or Out-of-Phase relationships. P4 and C4 are near to the location of the right hemisphere hematoma. P4 is out-of-phase with a large number of locations, especially the left hemisphere (from NeuroGuide Demo).

11- Third Compute Coherence as the ratio of the auto-spectra and cross-spectra

Coherence is usually defined as:

Eq. 12 - Coherence (f) = $$\frac{|Cross - Spectrum(f)XY|^2}{(Autospectrum(f)(X))(Autospectrum(f)(Y))}$$

However, this standard mathematical definition of coherence hides some of the essential statistical nature and structure of coherence. To illustrate the fundamental statistics of coherence let us return to our simple algebraic notation:

Eq. 13 -

$$\text{Coherence (f)} = \frac{(\sum_N (a(x)u(y)+b(x)v(y)))^2 + (\sum_N (a(x)v(y)-b(x)u(y)))^2}{\sum_N (a(x)^2+b(x)^2)\sum_N u(y)^2+v(y)^2)}$$

Where N and the summation sign represents averaging over frequencies in the raw spectrogram or averaging replications of a given frequency or both. The numerator and denominator of coherence always refers to smoothed or averaged values, and, when there are N replications or N frequencies then each coherence value has 2N degrees of freedom. Note that if spectrum estimates were used which were not smoothed or averaged over frequencies nor over replications, then coherence = 1 (Bendat and Piersol, 1980; Benignus, 1968; Otnes and Enochson, 1972). In order to compute coherence, averaged cospectrum and quaspectrum smoothed values with degrees of freedom > 2 and error bias = 1/N is used.

The numerical example of coherence used the average cospectrum and quadspectrum across replications in Table III. For example from Table III the coherence at 1.25 Hz is:

$$\text{Eq. 14 - Hand Calculator Coherence (1.25 Hz)} = \frac{0.073^2 + 0.031^2}{0.586(0.419)} = 0.026$$

This computation is repeated for each frequency component to yield the complete coherence spectrum, a typical plot of coherence is frequency on the horizontal axis (abscissa) and coherence on the vertical axis (ordinate). Coherence is sometimes defined and computed as the positive square-root and this is referred to as "coherency".

12- Some Statistical Properties of Coherence

How large should coherence values be before they can be considered reliable? The answer is it depends on the true coherence relationship and the degrees of freedom used in the averaging computation in equation 13. In general the degrees of freedom increase as a square root of N (i.e., the amount of smoothing) and the more the degrees of freedom the better (i.e., averaging across frequency and/or across repetitions or "smoothing"). The trade off is between frequency resolution and reliability, the longer the interval of time over which averaging occurs or the larger the number of repetitions then the greater are the degrees of freedom. Short time intervals of low frequencies by their nature have low degrees of freedom. For this reason the NeuroGuide uses the default of a 1 minute sample, e.g., the theta frequency band 4 – 7 Hz NeuroGuide EEG coherence for a 1 minute sample = 7 (0.5 Hz bins) + 117 FFTs = 124 x 2 = 248 degrees of freedom. To test the statistical properties of coherence select shorter segments of simulated EEG and systematically change the signal-to-noise ratio in the NeuroGuide demo signal generator at www.appliedneuroscience.com. After launching the NeuroGuide demo click Open > Signal Generation.

13- How large should coherence be before it can be regarded as significantly larger than zero?

Low degrees of freedom always involve "Inflation" of the true signal-to-noise relationship between two channels when a Pearson product correlation coefficient is computed. EEG coherence is no exception and this explains why coherence is highly inflated when the degrees of freedom are low and the bandwidth is small. For example, figure 7 shows the inflation of coherence (y-axis) when a signal in one channel (4 Hz – 19 Hz sine wave) is compared to random noise in a second channel with increasing degrees of freedom (x-axis) and different bandwidths. The ideal is coherence = 0.

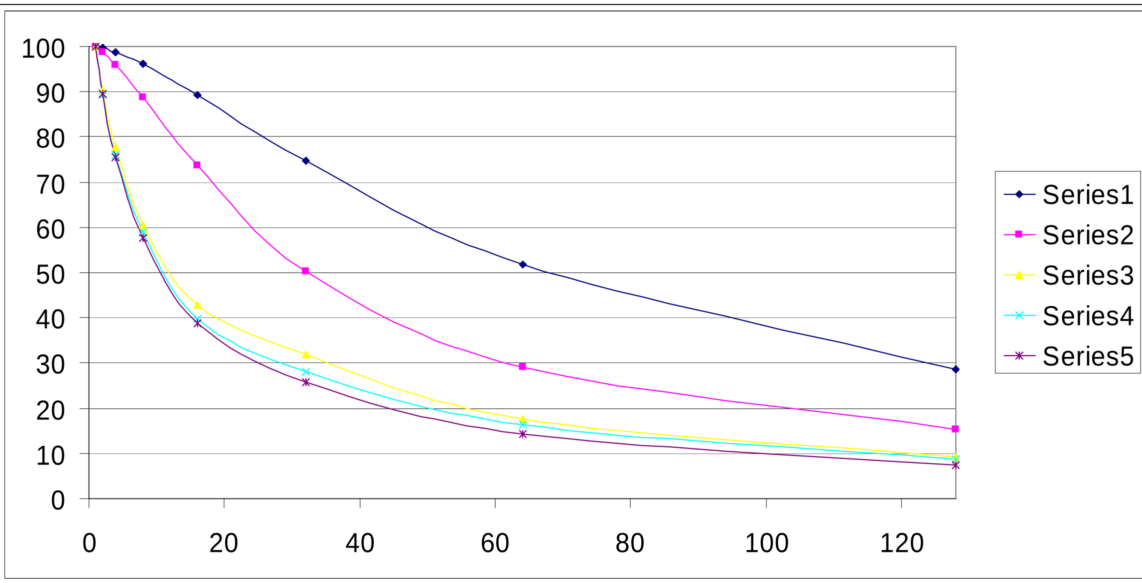

Figure 7 – Coherence (y-axis) vs. number of time samples (y-axis). Sample rate = 128 Hz. The five curves are for different band widths. Series 1 = 4 Hz, series 2 = 6 Hz, series 3 = 8 Hz, series 4 = 10 Hz and series 5 = 12 Hz bandwidths. The wider the band width the more stable and accurate is coherence.

The digital reality of low degrees of freedom using a 2 Hz bandwidth are also shown in figure 7. The y-axis is coherence (x100). The x-axis are the number of time samples at a sample rate of 128 Hz using a digital filter (complex demodulation) to compute coherence. The five curves represent different bandwidths (4 Hz, 6 Hz, 8 Hz, 10 Hz & 12 Hz). The ideal coherence value = 0 at infinity and series 5 with a 12 Hz band width is approximately 9% at 128 time samples. Mathematically coherence inflation is defined as:

Eq. 15 – Inflation of Coherence = white noise - signal = [Observed white noise coherence].

The curves in Figure 7 show that after 1 second of averaging the EEG coherence inflation values ranged from 1 to 0.10 (or 10%). Figure 1 also shows that the wider the band width then the larger the number of degrees of freedom. The equation to compute the degrees of freedom when using complex demodulation is:

Eq. 16 - Df = 2BT

Where B = bandwidth and T = time samples (Otnes and Enochson, 1972 and Appendix-B).

Bendat and Piersol (1980) as elaborated by Nunez et al (1997) provide another measure of the 95% interval for coherence which is expressed as:

Eq. 17 - $$\frac{F(i)}{1+2e} \leq F(i) \leq \frac{F(i)}{1-2e}$$

Where F(i) applies to the auto or cross spectral density or coherence. The confidence interval depends on the error term e defined as the RMS error (i.e., root mean square error). In general, the error may be estimated by:

Eq. 18 - $$e_f = \frac{1}{\sqrt{N}}$$

14- Is there an inherent time limit for EEG Coherence Biofeedback?

The answer is yes, because coherence is unique in EEG biofeedback because it depends upon averaging the phase angles or phase differences. The lower the variance or the more constant the phase differences (or the greater the phase synchrony or phase locking) then the higher the coherence.

Similarly, as a property of statistics the greater the degrees of freedom then the less the statistical inflation of the real coherence value. Based on operant conditioning studies the feedback interval or feedback delay is crucial for the ability of the brain to link together two past events. Too short an interval or too long an interval reduces the likelihood of a person making a "connection" between the biofeedback display/sound or signal and the brain's electrical state at a previous moment in time. In the case of amplitude and phase difference the calculation does not depend upon an average as it does when computing coherence. Thus, coherence EEG biofeedback inherently requires a longer feedback delay than does the nearly instantaneous computations of power, ratios of power, relative power, amplitude, amplitude asymmetries, phase difference (or phase angle), etc. To the best of our knowledge the minimum amount of inflation that leads to the greatest efficacy of biofeedback training using EEG coherence has not yet been published. The minimal interval is a function of at least two factors: 1- the stability of the signal being fed back, i.e., a noisy and jumpy signal has no connection formation value and, 2- the interval of time between the brain event and the feedback. Both are critical and seconds and milliseconds are the domain.

15- What is Phase Difference?

Coherence and phase difference (measured in angles) are linked by the fact that the average temporal consistency of the phase difference between two EEG time series (i.e., phase synchrony) is directly proportional to coherence. For example, when coherence is computed with a reasonable number of degrees of freedom (or smoothing) and approaches unity, then the phase difference between the two time-series becomes meaningful because the confidence interval of phase difference is a function of the magnitude of the coherence and the degrees of freedom. If the phase angle is random between two time series then coherence = 0. Another way to view the relationship between phase consistency (phase synchrony) and coherence is to consider that if Coherence = 1, then once the phase angle relation is known the variance in one channel can be completely accounted for by the other. The phase relation is also critical in understanding which time-series lags or leads the other or, in other words the direction and magnitude of the difference. However, when using circular statistics the mean phase angle or phase difference is relative to an arbitrary reference and the magnitude and direction of a shift in phase angle is all that is relevant (see section 15).

The phase difference is defined as:

Eq. 19 - Phase difference (f) = Arctan $\frac{(Smoothedquadspectrum(f))}{(Smoothed\cos pectrum(f))}$

In the numerical example in Table II,

Phase difference (or angle at 1.25 Hz) = Arctan 0.031/0.073 = 22.7^o

Two oscillators are *frequency locked* when the first derivative of the phase difference has a stable periodic orbit even if there is a difference in phase between the two oscillators. Two oscillators are *entrained* when they are frequency locked in a 1:1 fashion with no phase difference. Two oscillators are phase locked where there is a stable phase difference that is not 1:1 (e.g., 2:3). Two oscillators are *synchronized* when they are phase locked independent of the absolute value of the phase difference, e.g., when the 1st derivative of the time series of phase ≈ 0. Synchronization is *in-phase* when the phase difference = 0 and *out-of-phase* is when the phase difference ≠ 0. Two oscillators are said to be synchronized in *anti-phase* when the phase difference = 180^0. Frequency locking without phase locking is called *phase trapping*. The relationship between all of these definitions is depicted in figure 8.

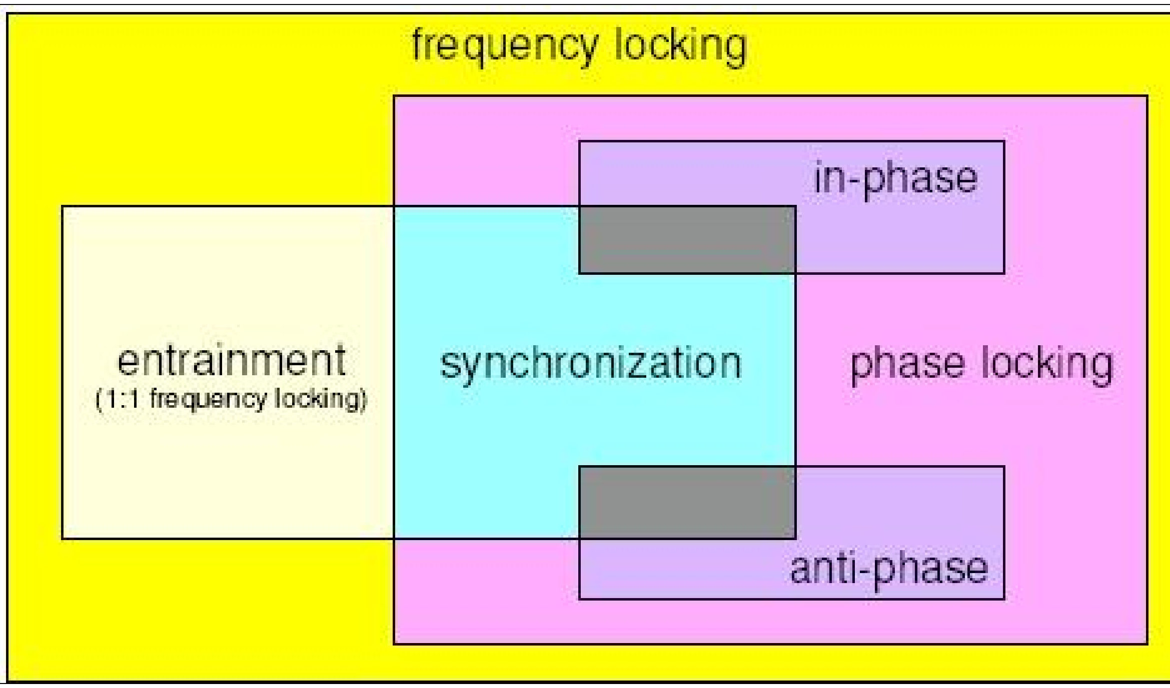

Fig. 8 – Various degrees and types of locking of oscillators. From Izhikevich

and Kuramoto, 2005).

16 – What is Phase Resetting?

Coupled oscillators often drift apart in their phase relationship and a synchronizing pulse can shift the phase of one or both of the oscillations so that they are again in phase or phase locked (Pikovsky et al, 2003). Synchrony is defined as "an adjustment of rhythms of self-sustaining oscillators due to their weak interactions" (Pikovsky et al, 2003). Phase reset marks the onset of phase locking. Phase locking and the term "entrainment" are synonymous. The amount of phase resetting per unit time is depicted by phase reset curves or PRC = (new phase – old phase). Positive values of the PRC correspond to phase angle advances, negative values correspond to phase angle reductions. Weak coupling typically exhibits a slow and smooth PRC whereas strong coupling between oscillators often results in abrupt or a discontinuous PRC. A useful method to measure phase resetting is by computing the first derivative of the time series of phase difference on the y-axis and time on the x-axis. A significant positive or negative first derivative of the time series of phase differences represents the magnitude of phase resetting (the second derivative of the phase shift is also useful in this computation). Phase reset is related to onset of phase synchrony or phase lacking and the period of near zero 1st derivatives in time is an example of a homeostatic and stable dynamical system (Pikovsky et al, 2003; John, 2005). Two interesting properties of phase reset are that minimal energy is required to reset phase between weakly coupled oscillators and phase reset occurs independent of amplitude. In weakly coupled chaotic systems amplitude can vary randomly while phase locking is stable.

Phase reset is defined as a significant positive or negative first derivative of the time series of phase difference between two channels, i.e., d($\varphi_t - \varphi'_t$_/t > 0 or < 0. Phase locked or phase synchrony is defined as that period of time where there is a stable near zero first derivative of the instantaneous phase difference between d($\varphi_t - \varphi'_t$_/t ≈ 0. A high coherence value is related to extended periods of phase locking. A significant positive first derivative of the time series of coherence marks the onset of phase locking and a significant negative first derivative of the time series of coherence marks the onset of phase dispersion over an interval of time. The significance level can be determined by computing the means and standard deviations of the first derivative for each time series and then computing a Z score for each time point with alpha at $P < .05$ or $\boldsymbol{Z} = \frac{\boldsymbol{u} - \boldsymbol{x}}{\boldsymbol{SD}}$ where u = mean and x = the instantaneous first derivative at t and SD = standard deviation. For example, depending on the method of computation, values near zero st. dev. or < 1.64 st. dev may define the state of "Phase Locking". Values > 2 st. dev. may define the state of "Phase Transition" or "Phase Reset" (the alpha threshold is a matter of observation and test).

Figure eight illustrates the concept of phase reset. Coherence is a measure of phase consistency or phase clustering on the unit circle as measured by the length of the unit vector r. The illustration in figure 9 shows that the resultant vector $r_1 = r_2$ and therefore coherence when averaged over time is constant even though there can be a shift in the phase

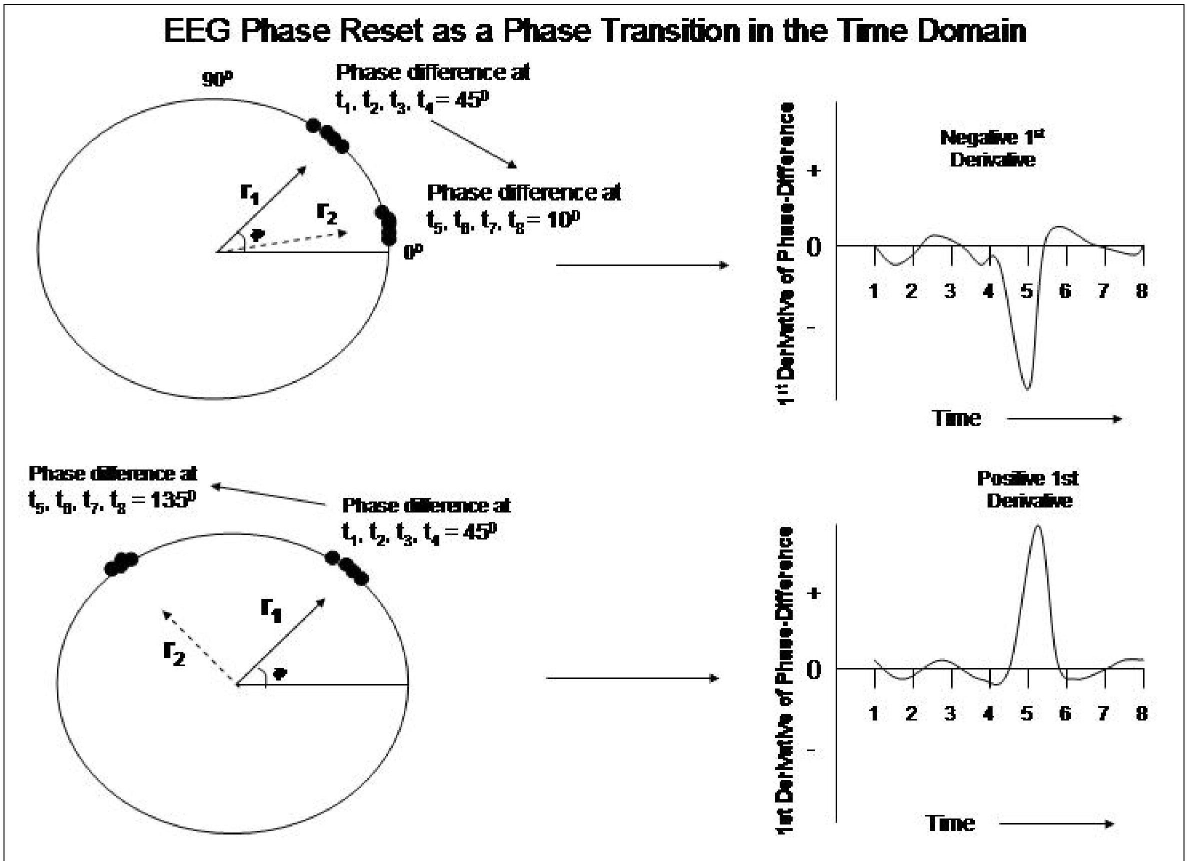

Fig. 9 – Illustrations of phase reset. Left is the unit circle in which there is a clustering of phase angles and thus high coherence as measured by the length of the unit vector r. The vector r1 = 45^0 occurs first in time and the vector r2 = 10^0 and 135^0 occurs later in time. The transition is between time point 4 and 5 where the 1st derivative is a maximum. The right displays are a time series of the approximated 1st derivative of the instantaneous phase differences for the time series t_1, t_2, t_3, t_4 at mean phase angle = 45^0 and t_5,t_6,t_7, t_8 at mean phase angle = 10^0. Phase reset is defined as a significant negative or positive 1st derivative (y' < 0 or y' > 0). The 1st derivative near zero is when there is phase locking

or phase stability and little change over time. The sign or direction of phase reset is arbitrary since two oscillating events are being brought into phase synchrony and represent a stable state as measured by EEG coherence independent of direction. The clustering of stable phase relationships over long periods of time is more common than are the phase transitions. The phase transitions are time markers of the thalamo-cortical-limbic-reticular circuits of the brain (John, 2005; Thatcher and John, 1977).

angle (i.e., phase difference) that occurs during the summation and average of the computation of coherence. This illustrates the advantage of phase differences which are "instantaneous" and not a statistical average like coherence and a correlation coefficient. Details for computing complex demodulation and instantaneous spectra are in Appendix-B.

As mentioned previously, an important property of phase reset is that it requires essentially zero energy to change the phase relationship between coupled oscillators and by this process rapidly create synchronized clusters of neural activity. In addition to phase reset without any change in frequency or amplitude of the EEG spectrum is that it can also be independent of phase history. That is, phase reset occurs independent of magnitude and direction of the phase difference that existed before the onset of the reset pulse (Kazantsev et al, 2004). What is important in the computation of the first derivative of the time series of phase is the rate of change of phase over time and not the absolute magnitude of phase.

Figure 10 shows the relationship between phase differences using Cz as a reference and phase reset as measured by the 1^{st} derivative of the phase difference time series.

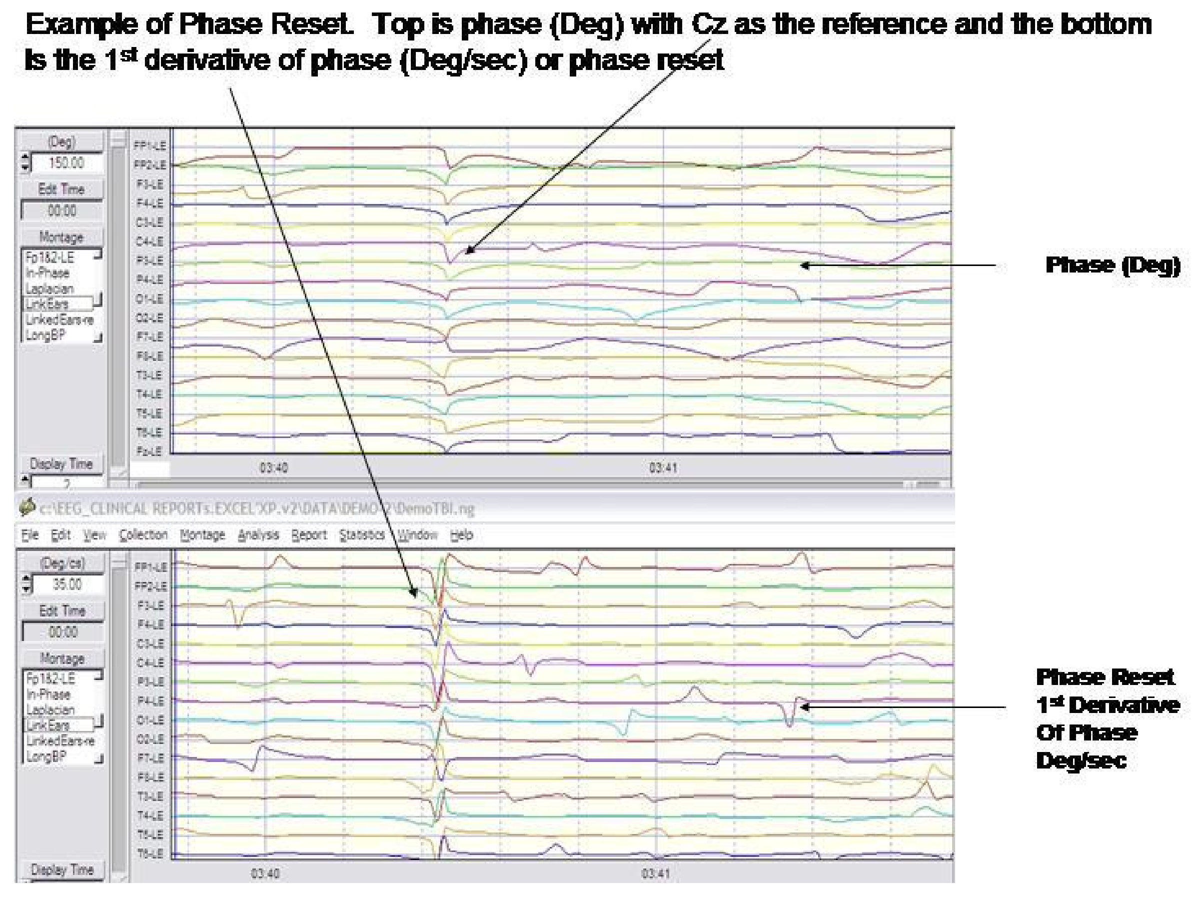

Fig. 10 – Example of phase difference time series with Cz as the reference (Top) and the 1st derivative of the phase difference time series (Bottom) or phase reset. Analyses were produced using the NeuroGuide Lexicor demo from the download at www.appliedneuroscience.com

Figure 11 shows examples of phase synchrony or phase locking when the first derivative of the phase difference time series ≈ 0 and phase reset when the 1st derivative of the phase difference time series ≠ 0. Global phase reset is defined as > 90% of the channels exhibiting simultaneous phase reset and local phase reset is defined as 1 or a few channels exhibiting phase reset. The intervals of time between phase reset are periods of phase synchrony.

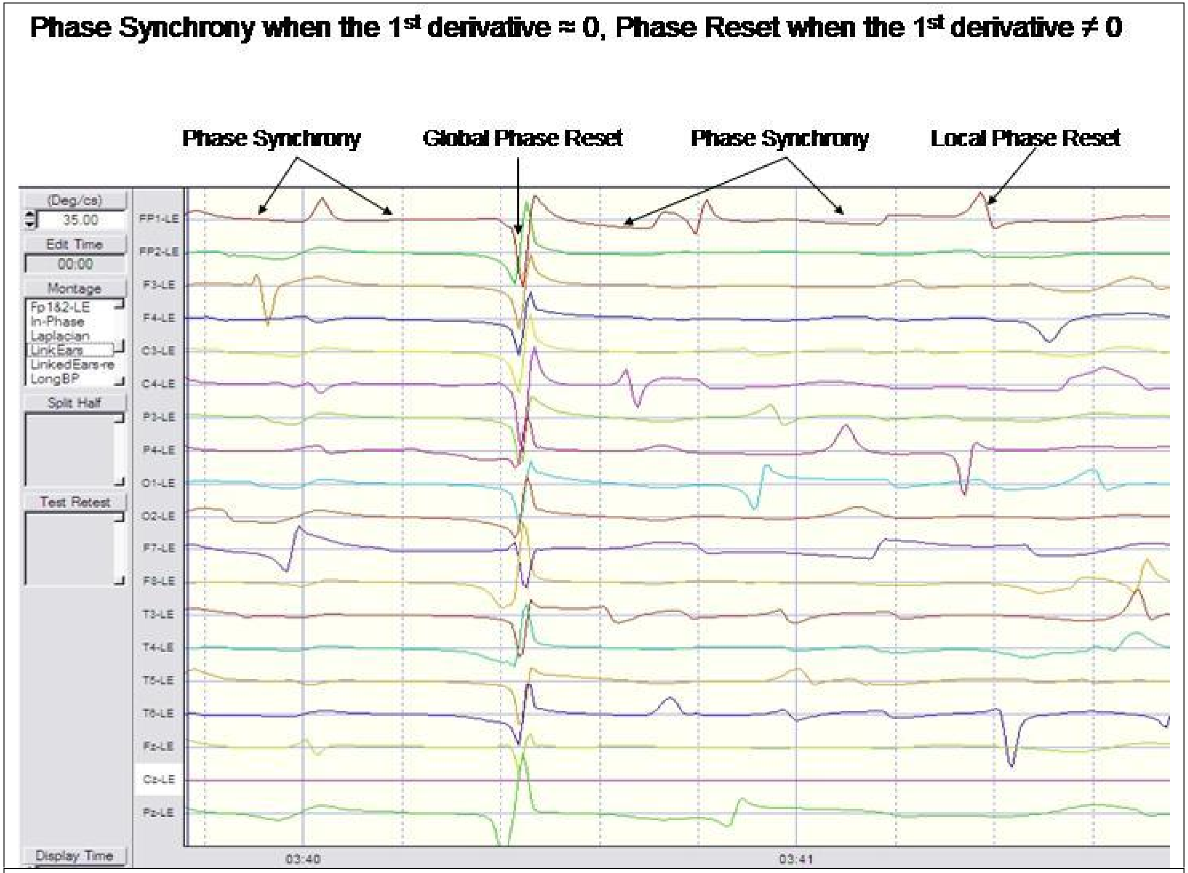

Figure 11 shows examples of phase synchrony or phase locking when the first derivative of the phase difference time series ≈ 0 and phase reset when the 1st derivative of the phase difference time series ≠ 0. Global phase reset is defined as > 90% of the channels exhibiting simultaneous phase reset and local phase reset is defined as 1 or a few channels exhibiting phase reset. The intervals of time between phase reset are periods of phase synchrony also called "phase locking". Analyses were produced using the NeuroGuide Lexicor demo from the download at www.appliedneuroscience.com

17- How large should coherence be before Phase Difference can be regarded as stable?

As mentioned previously, the confidence internal for the estimation of the average phase angle between two time series is related to the magnitude of coherence. When coherence is near unity then the oscillators are synchronized and phase and frequency locked. This means that when coherence is too low, e.g., < 0.2, then the estimate of the average phase angle may not be stable and phase relationships could be non-linear and not synchronized or phase locked. An example of a 30 degree phase angle using the NeuroGuide signal generation program is shown in figure 12:

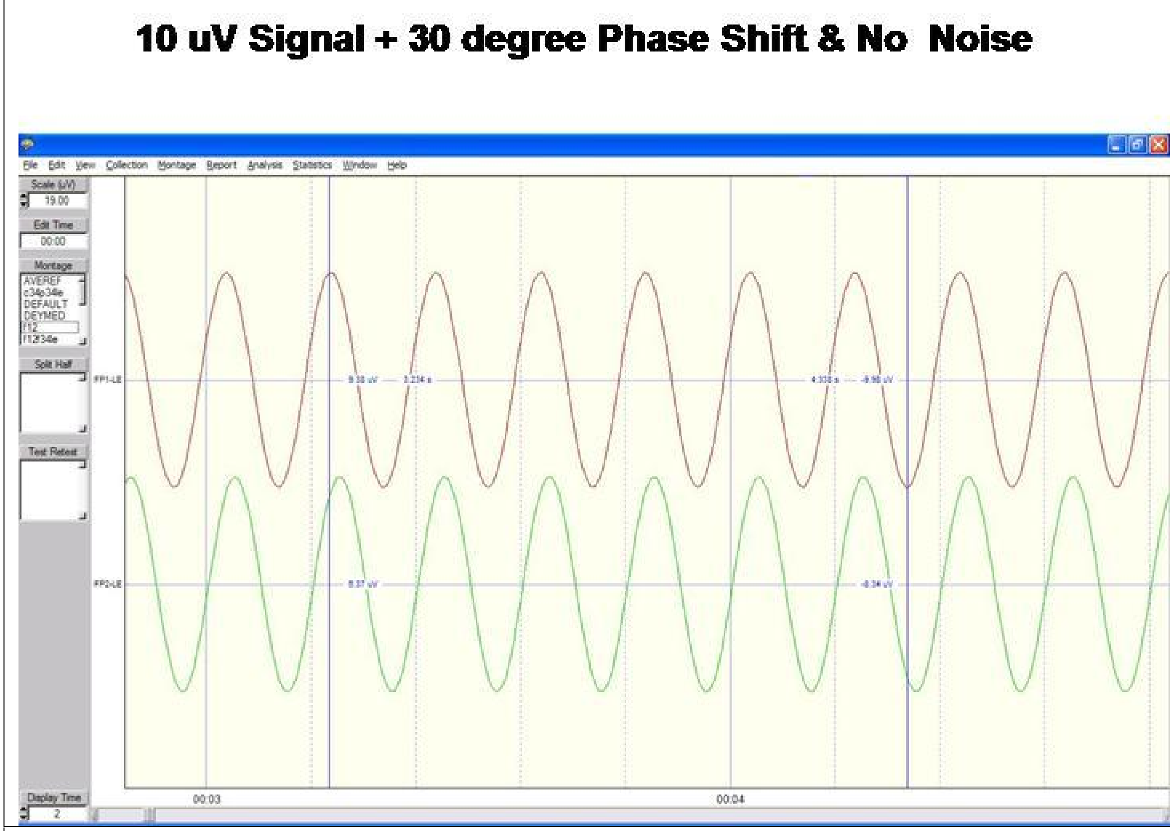

Figure 12 shows an example of two 10 uV sine waves with the second sine wave shifted by 30 degrees with increasing amounts of noise added to the signal in one channel (signal-to-noise ratio). The data is 60 seconds sampled at 128 Hz.(from Thatcher et al, 2004). Analyses were produced using the NeuroGuide Lexicor demo from the download at www.appliedneuroscience.com.

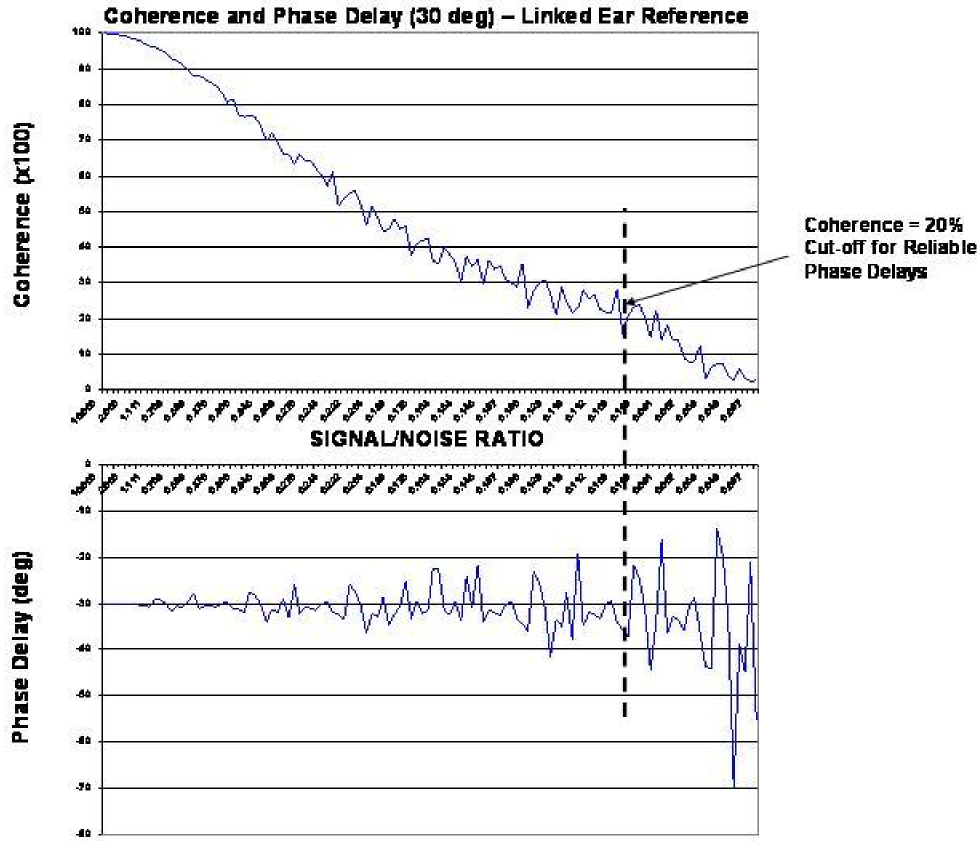

Fig – 13. Top is coherence (y-axis) vs signal-to-noise ratio (x-axis). Bottom is phase angle on the y-axis and signal-to-noise ratio on the x-axis. Phase locking is minimal or absent when coherence is less than approximately 0.2 or 20%.

Figure 13 (from Thatcher et al, 2004) shows increased variability of EEG phase angle or difference as noise is systematically added to the 30 degree shifted sine wave. Note that non-linear dynamical processes are suggested by the fact that the mean = 30 degrees when coherence < 0.2. Chaotic dynamics and reproducible correlations are often embedded in similar time data.

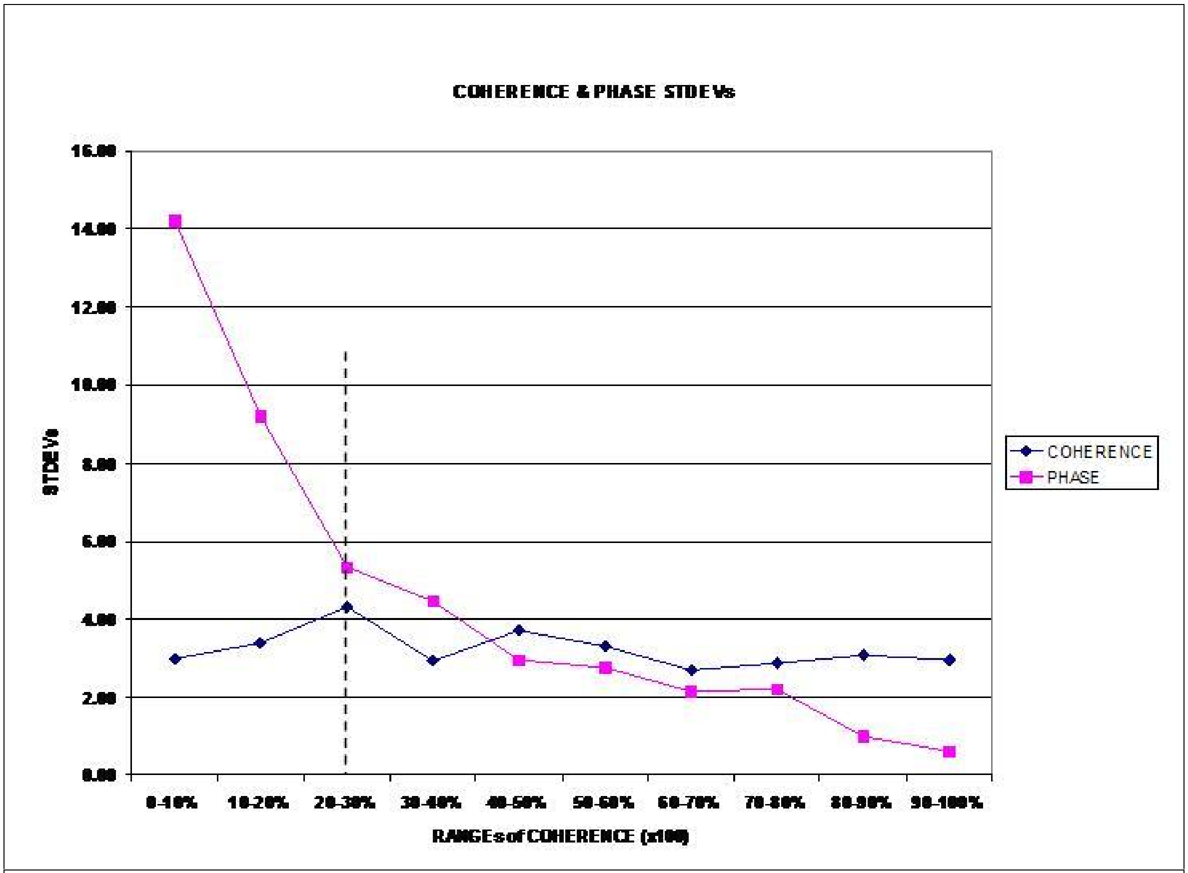

Figure 14 – The x-axis are different ranges of coherence (x100). The y-axis is the standard deviation of coherence (blue circles) and phase angles (pink squares). The dashed vertical line shows the level of coherence (20% or 0.2) when the variance of the phase angle becomes very high. High variance of the phase angle means that there is minimal or no phase locking.

Figure 14 (from Thatcher et al, 2004) shows that EEG coherence linearly decreases as a function of the signal-to-noise ratio. It can be seen that phase angles even with 248 degrees of freedom are instable and poorly estimated as coherence decreases. EEG coherence at 0.2 or less is used as a cut-off for accepting phase as a valid and stable linear measure. The instability of a non-linear system may be present because the mean phase angle = 30 degrees when coherence is less than 0.2, see Figure 13.

The test signals were computed using the NeuroGuide signal generation program and by systematically increasing the amount of white “noise” added to one of the channels used to compute coherence and phase angle. In general, as the value of coherence decreases below approximately 0.2 or 20% (i.e., coherence x100) then phase angles are extremely variable and unstable even using 248 degrees of freedom.

The calculations exceed what is possible using a hand held calculator, however, computer simulations can produce results much faster than a hand calculator. The understanding of coherence and phase can be explored by any one who downloads the free NeuroGuide demo at: www.appliedneuroscience.com and tests coherence and phase for themselves.

18- Why the average reference and Laplacian fail to produce valid coherence and phase measures.

It is easy to understand why coherence is invalid when using an average reference since the summation of signals from all channels is "subtracted" or 'added' to the electrical potentials recorded at each electrode. Figure 15 below shows the results of the average reference where noise and signal from each channel is incorporated into all of the channels by being "subtracted" from the electrical potential recorded from each channel. Thus, signals and noise are mixed and added to the recordings from each channel making coherence and phase differences invalid. A similar situation prevails with source derivation or the Laplacian reference (Figure 16) since spatially weighted signals and noise from other channels are averaged and subtracted from the electrical potential recorded from each electrode site. Coherence when using the average reference or source derivation is especially sensitive to the presence of artifact or noise since the artifact will be mixed with and added to all channels.

Figure 15 are the results of the computation of EEG coherence and EEG phase differences using the average reference EEG simulation. The y-axis in figure 15 (top) is coherence and the x-axis is the signal-to-noise ratio (S/N). The y-axis in figure 15 (bottom) is phase difference (degrees) and the x-axis is the same signal-to-noise ratio (S/N) as in figure 13. It can be seen in Figure 15 that coherence is extremely variable and does not decrease as a linear function of signal-to-noise ratio. It can also be seen in Figure 15 that EEG phase differences never approximate 30 degrees and are extremely variable at all levels of noise.

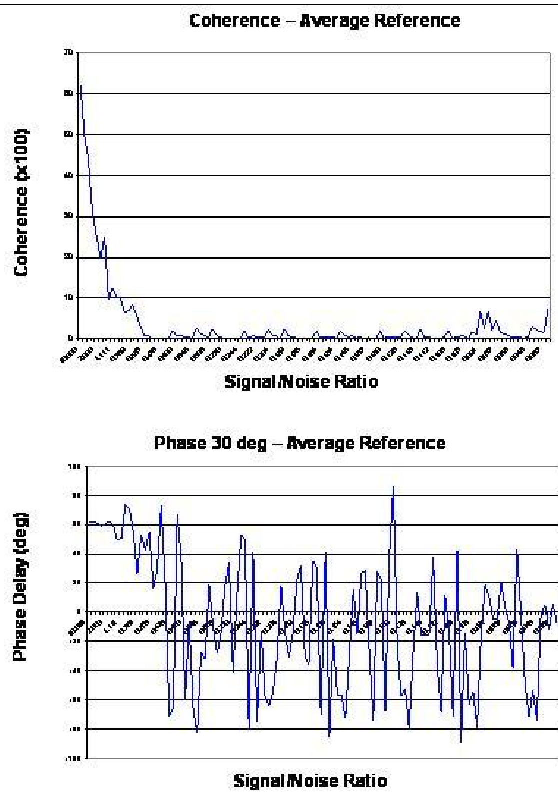

Fig – 15. Top is coherence (y-axis) vs signal-to-noise ratio (x-axis). Coherence drops off Rapidly and is invalid. Bottom is phase angle on the y-axis and signal-to-noise ratio on the x-axis. Phase locking is minimal or absent and unstable throughout the entire simulation and fails to exhibit the 30 degree phase difference.

Figure 16 are the results of the computation of EEG coherence and EEG phase differences using the Laplacian reference EEG simulation. The y-axis in figure 16 (top) is coherence and the x-axis is the signal-to-noise ratio (S/N). The y-axis in figure 16 (bottom) is phase difference (degrees) and the x-axis is the same signal-to-noise ratio (S/N) as in figure 13. It can be seen in Figure 16 that coherence is extremely variable and does not decrease as a linear function of signal-to-noise ratio. It can also be seen in Figure 16 that EEG phase differences are invalid and never approximate 30 degrees with high variance at all levels of noise.

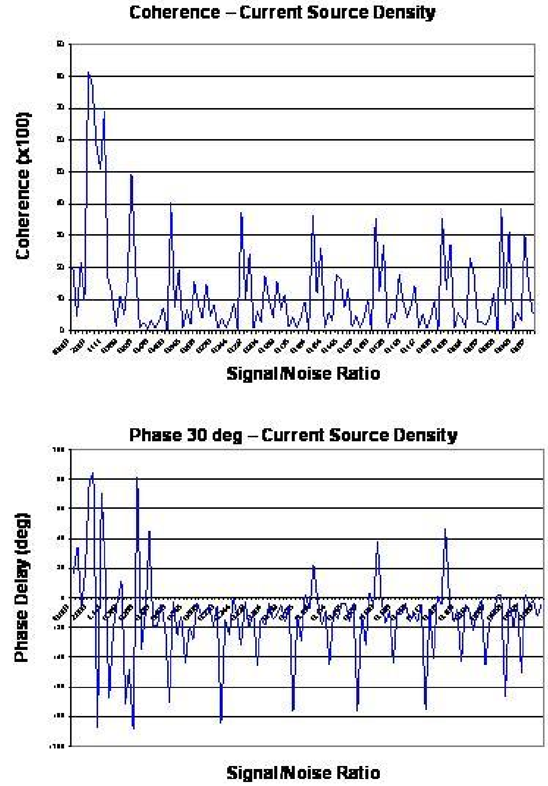

Fig – 16. Top is coherence (y-axis) vs signal-to-noise ratio (x-axis). Coherence drops off Rapidly and is invalid. Bottom is phase angle on the y-axis and signal-to-noise ratio on the x-axis. Phase locking is minimal or absent and unstable throughout the entire simulation and fails to exhibit the 30 degree phase difference.

The results of these analyses are consistent with those by Rappelsberger, 1989 who emphasized the value and validity of using a single reference and linked ears in estimating the magnitude of shared or coupled activity between two scalp electrodes. The use of re-montage methods such as the average reference and Laplacian source derivation are useful in helping to determine the location of the sources of EEG of different amplitudes at different locations. However, the results of this study which again confirm the findings of Rappelsberger and Petsche, 1988 and Rappelsberger, 1989 which showed that coherence is invalid when using either an average reference or the Laplacian source derivation. This same conclusion was also demonstrated by Korzeniewska, et al (2003).

19- What is “Inflation” of Coherence (and correlation)?

Coherence inflation is defined as any value of coherence (x) greater than zero when coherence (or correlation) is computed using pure Gaussian noise in one of the two channels and a pure sine wave in the other channel.

Eq. 20- Coherence Inflation → $x > 0$

This is the error term when one of the channels is pure Gaussian noise and the second channel is signal. Any value of coherence > 0 is due to error attributable to low degrees of freedom, inadequate signal resolution or too short of measurement interval, or improper sample rates within that interval, etc.

Figure 17 below shows an example of a 5 Hz 10uVsine wave in one channel and 100 uV (p-p) gaussian noise in the second channel. The power spectrum of the two channels is shown in the upper right panel. Figure 17 is just one example of the analyses performed by the NeuroGuide Signal Generator that directly test EEG simulated EEG cross-spectra.

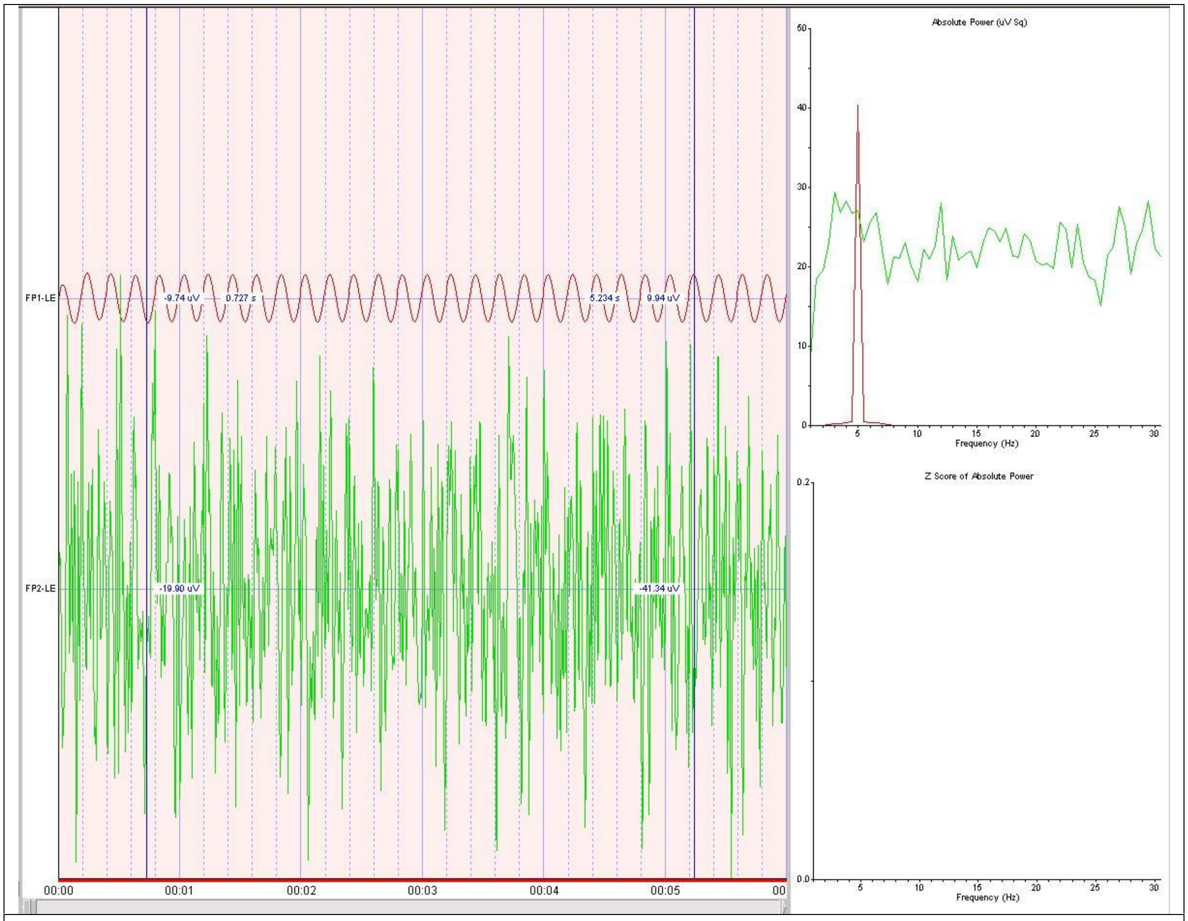

Figure 17. Screen capture of the NeuroGuide signal generation program.

Top trace is a 5 Hz 10 uV sine wave + 0 noise and the bottom trace is the mixture of a 5 Hz 10 uV sine wave + 100 uV Gaussian noise.

20- What are the limits of EEG Correlation, Coherence and Phase Biofeedback

As explained above, correlation and coherence requires averaging of time series data points in order to converge to an accurate estimate of shared activity between two time series. This means that correlation and coherence, unlike absolute power, are not instantaneous and always require time to compute. The most important factors in EEG correlation and coherence biofeedback are: 1- The band width, 2- Sample rate and , 3- Interval of time over which Averaging occurs.

Band width is directly related to the number of degrees of freedom. The wider the band width, the larger the number of degrees of freedom. However, with increased band width then there is reduced frequency resolution. In general, the standard band widths of EEG which are adequate such as theta (4 – 7.5 Hz), Alpha (8 – 12 Hz), Beta (12.5 – 22 Hz) and Gamma (25 – 30 Hz), etc. With narrow bandwidths, for example 0.5 Hz or 1 Hz then coherence will equal unity unless there are sufficient degrees of freedom to resolve true “signals” in the brain, which in the case of the human scalp EEG a 1,000 Hz sample rate is more than adequate.

Figure 18 below shows the results of tests using mixtures of signal and noise as in Figure 10 in which mean coherence is the Y – Axis as a function of sample rate (i.e., 512 Hz top left, 256 top right, 128 bottom left & 64 Hz bottom right). This figure will be replaced with a series of more clearly labeled figures in the next version of this paper. For the moment, accept the fact that the amount of time for averaging on the X - axis (125 msec., 250 msec., 500 msec. and 1,000 msec. results in lower coherence values, i.e., lower coherence inflation. This test involved computing coherence between one channel of pure sine waves (10 uV p-p) at different frequencies (theta, alpha, beta & gamma) and a second channel with pure Gaussian noise (also 10 uV p-p). It can be seen that the most important factor in determining coherence “Inflation” is the length of time for averaging. 1,000 msec. produces coherence = 0.1 (or 10%) inflation. Inflation is defined above as any value > 0 when pure Gaussian noise is in one of the channels. 500 msec produces coherence inflation = 0.2 (or 20%) inflation while 250 msec produces coherence inflation = 0.3 to 0.4 and 125 msec = 0.5 to 0.6 inflation. The coherence inflation is independent of band width, frequency and sample rate. The only critical factor is the interval of time over which the average is computed, the longer the interval the lower the inflation.

The results of these analyses are that a minimum of a 500 millisecond difference is required when using EEG biofeedback in order to compute an accurate estimate of coherence or coupling between two time series. With a 500 millisecond average then the amount of inflation is relative low (e.g., 0.2 or 20%) and as long as the same interval of time of averaging is used with a normative database, then the Z scores of real-time coherence will be valid and accurate. As seen in Fig. 18 a sample rate of 1,000 produces even lower inflation, however, a 1 second difference between a brain event and the feedback signal may be too long for connection formation in a biofeedback setting.

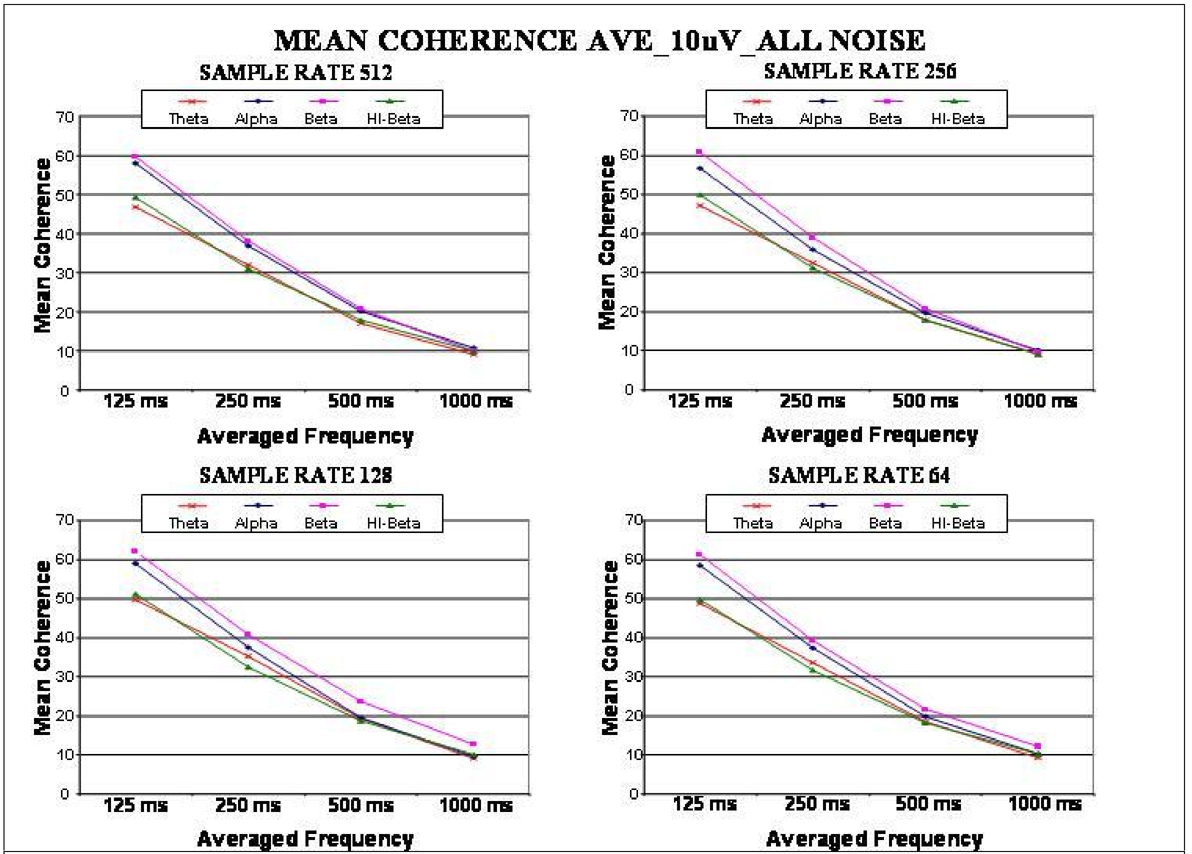

Figure 18. Mean coherence (y-axis) and the integration window size in milliseconds (x-axis). Top left is sample rate = 512 Hz, top right sample rate = 256 Hz, bottom left sample rate = 128 Hz and bottom left sample rate = 64 Hz. The amount of averaging from 125 msec. to 1,000 msec is the critical variable in minimizing "inflation" and not the sample rate.

Figure 19 below is the same as figure 18, but contains the standard deviations. A 500 msec. averaging delay = 0.15 standard deviation while 1,000 msec = 0.1 standard deviation. This figure shows that the choice of a 500 millisecond integration delay yields a reasonably stable estimate of coherence when using EEG biofeedback but that shorter intervals, such as 125 msec or 250 msec produce high inflation and high standard deviations and will not provide a valid "feedback" signal and thus less averaging will likely reduce neurotherapy efficacy.

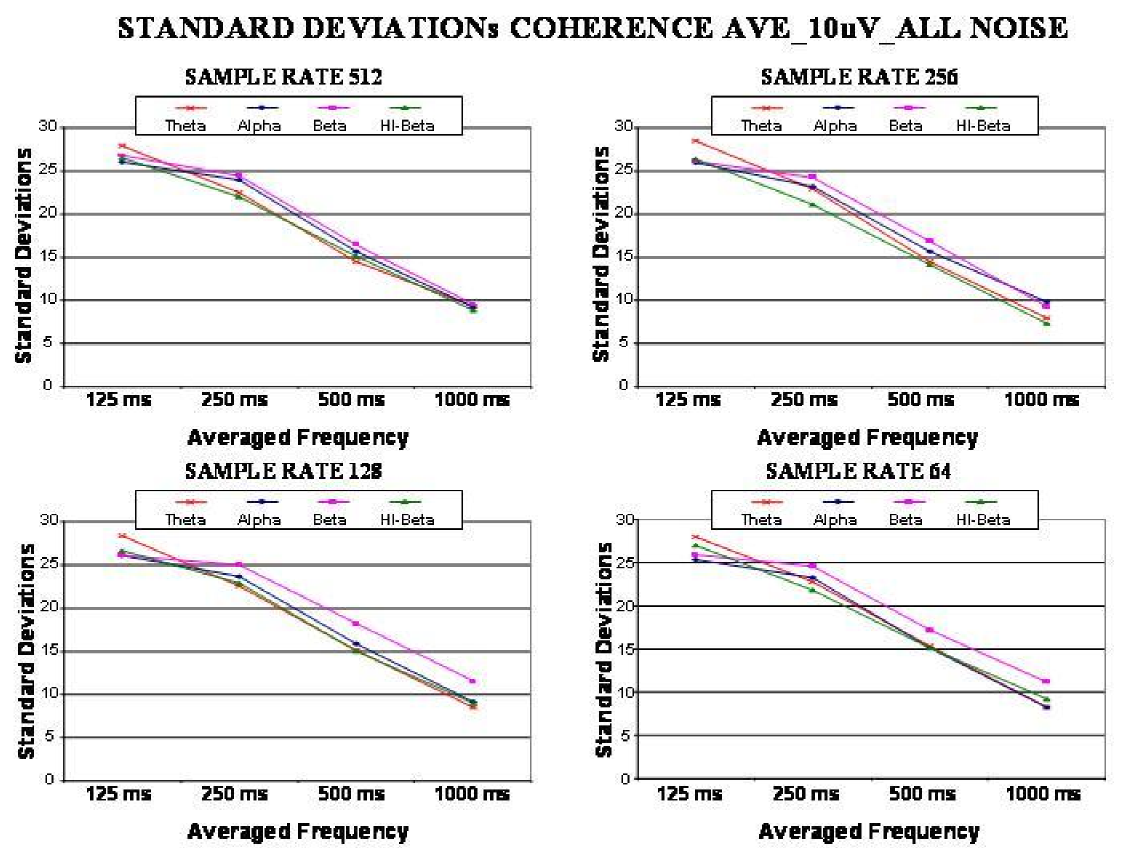

Figure 19. Standard deviations of coherence (y-axis) and the integration window size in milliseconds (x-axis). Top left is sample rate = 512Hz, top right sample rate = 256 Hz, bottom left sample rate = 128 Hz and bottom left sample rate = 64 Hz.

EEG phase is not the same as coherence and it can be computed instantaneously without averaging. Phase reset curves without averaging provide a detailed picture of the phase stability between coupled oscillators.

Nonetheless, “instantaneous” phase is variable and it is advisable to average the phase angles over intervals of time if greater stability is required especially when using Z score biofeedback.

21 – Coherence, Phase and Circular Statistics

Phase angle has an intrinsic discontinuity, for example consider the linear and circular distributions of 360 equidistant points. In the linear distribution 0 and 360 are at opposite ends while in the circular distribution $0^0 = 360^0$ (Jammalamadaka and SenGupta, 2001). To evaluate phase angles it is necessary to use vector algebra and compute a mean vector with magnitude or length r, and a direction Θ and to calculate the average x and y components of the mean vector:

Eq. 21 - $$\bar{x} = \frac{1}{n}\sum_{i-1}^{n}\left[\sin(\alpha_1) + \sin(\alpha_2) + \sin(\alpha_3) + \ldots \sin(\alpha_n)\right]$$

Eq. 22 - $$\bar{y} = \frac{1}{n}\sum_{i-1}^{n}\left[\cos(\alpha_1) + \cos(\alpha_2) + \cos(\alpha_3) + \ldots \cos(\alpha_n)\right]$$

where n is the number of observations and α_i is the ith observation.

The length or magnitude of the mean vector is:

Eq. 23 - $$r = \sqrt{\bar{x}^2 + \bar{y}^2}$$

And the vector mean direction is:

Eq. 24 - $$\overline{\Theta} = \arctan(\bar{x} / \bar{y})$$

The magnitude of the mean vector gives an indication of the relative dispersion or coherence of the observations. The range of r is 0.0 to 1.0. If the phase angles or differences are clustered or clumped together in one direction then r will approximate 1. If the phase differences are random over the interval, then r will be small and approximate 0. The statistical computation of the cross-spectral “atoms” provides a complete description of the EEG phase locking, synchrony and phase angles (also phase resetting if differences or derivatives as a function of time are used).

Eq. 25 - Angular variance: $s^2 = 2(1-r)$

This is equivalent to variance in linear statistics.

Eq. 26 - Angular deviation: $s = 2(1-r)^{1/2}$

This is equivalent to standard deviation in linear statistics.

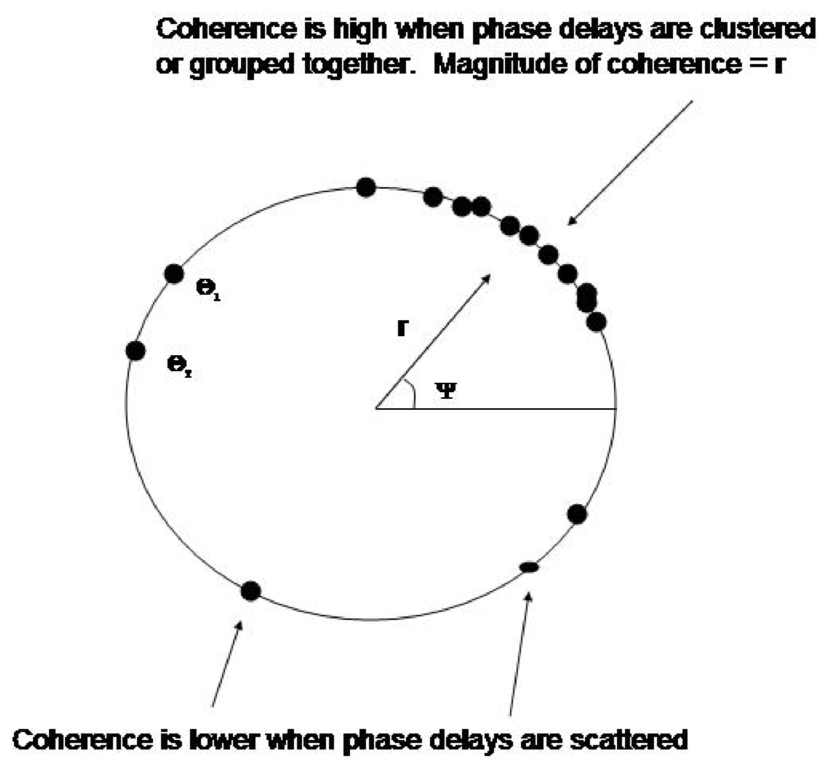

Fig. 20 – Circular synchronization index. r = magnitude of coherence

22 – Phase straightening

As mentioned previously phase angle has an intrinsic discontinuity, where 0 and 360 are at opposite ends while in the circular distribution $0^0 = 360^0$ (Jammalamadaka and SenGupta, 2001). A method to remove discontinuities due to the mathematical limit of the arctangent is a procedure called "phase straightening" by Otnes and Enochnson (1972, p. 238). The procedure involves checking for a large jump which happens when the phase goes from + 180^0 to – 180^0 and then adding or subtracting 360^0 depending on the direction of sign change. For example, $\Delta\theta = (180 - \varepsilon)^0 + (180 - \varepsilon)^0 =$

360^0 - 2ε which is the same as 2ε since $-(180 – ε)^0 = 180 + ε$. This procedure results in phase being a smooth function of time or frequency and removes the discontinuities. The programmer needs only to keep track of the number of winds around the circle also called the "winding number" if absolute phase differences are needed.

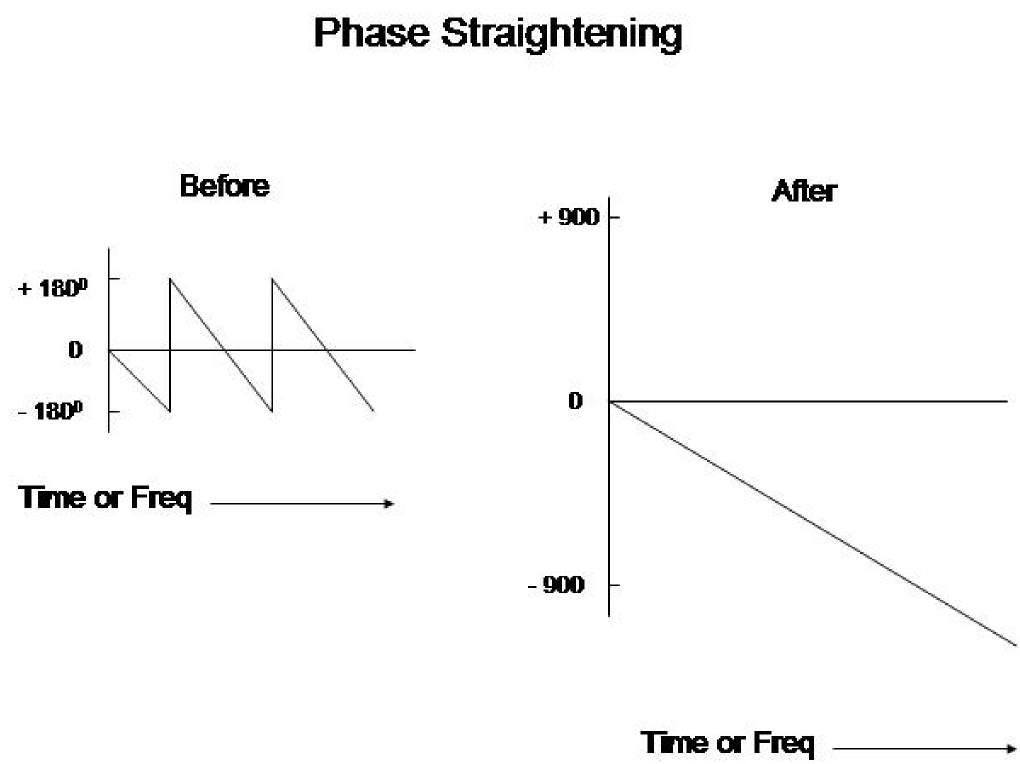

Fig. 21 – Illustration of phase straightening where the change or discontinuity from – 180^0 to + 180^0 is removed by adding or subtracting 360^0 depending on the direction of change (adapted from Otnes and Enochson, 1972).

Phase straightening is important when computing the first and second derivatives of the time series of phase differences because the discontinuity between – 180^0 to + 180^0 can produce artifacts. All of the derivatives and phase reset measures in this paper were computed after phase straightening in order to avoid possible artifact.

23 – EEG Spindles and Burst Activity

The human Electroencephalogram is characterized by electrical events that have a specific shape and physiological origin called "spindles" or “burst activity”. A spindle is defined as a rhythmic and sequential build up of EEG amplitudes that wax and wane and appears as an “envelope” structure. Spindles are also referred to as augmenting and recruiting responses (Steriade, 1995). Spindles are especially prevalent during late drowsiness and sleep, however, spindles also occur during waking and focused attention. In animal studies spindle like responses referred to as “augmenting responses” can be produced by thalamic stimulation and involve activation of the upper layers of the cortex and are typically negative in polarity as the first event in the sequential build up of voltages. “Recruiting responses” also have a spindle like structure but the first wave is positive in polarity at the scalp surface and involves activation of the lower layers of the cortex (Steriade, 1995). Both augmenting and recruiting responses exhibit the same spindle like “envelope” shape but have different initial polarities and are not easy to distinguish in the human EEG record. For this reason, Steriade (1995) recommends that one refer to all spindles as “augmenting responses”.

There are several methods that are used to quantify “spindle” or augmenting response structure such as the inter-spindle interval, spindle peak amplitude and spindle duration. Figure 22 shows an example of how NeuroGuide quantifies spindle activity using JTFA and the time series of instantaneous spectral measures (go to www.appliedneuroscience.com down load the free demo).

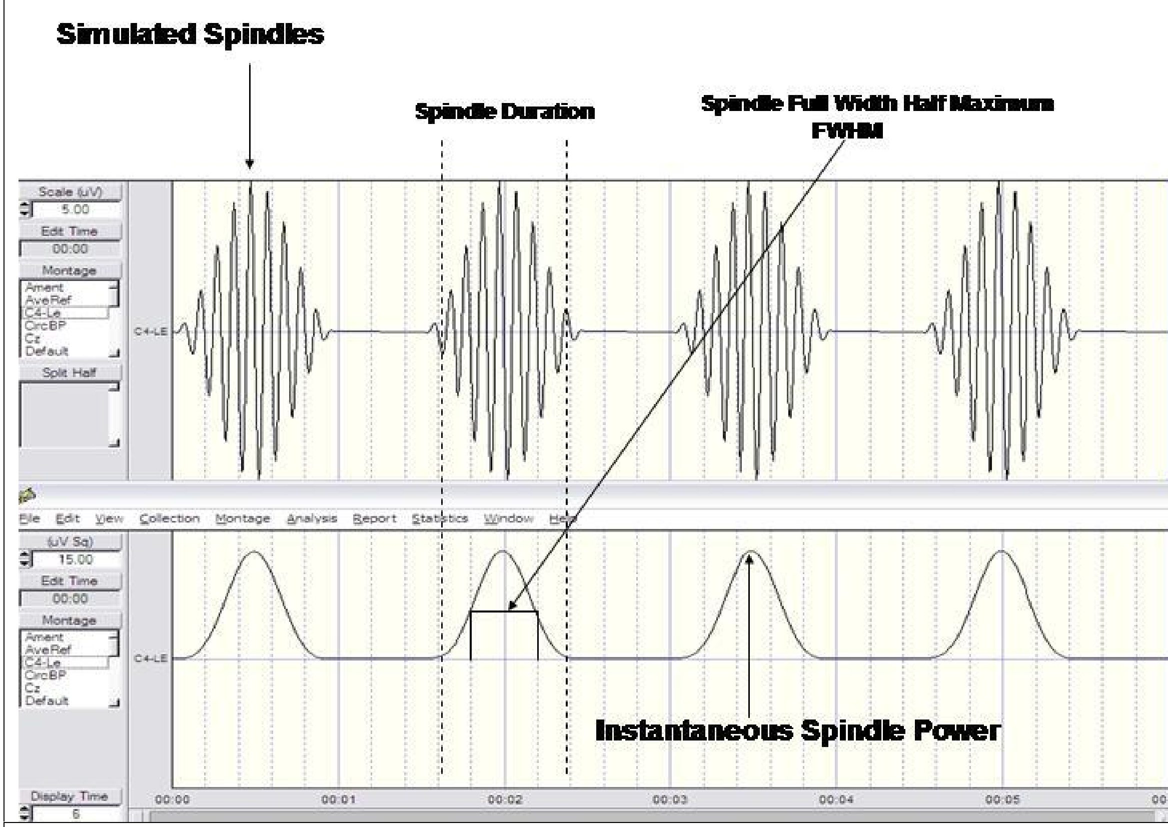

Fig. 22 – Top are simulated spindles and bottom is the time series of the instantaneous power of the spindles. Quantitative measures of spindle duration, intensity and average inter-spindle intervals are computed. The Full Width Half Maximum (FWHM) is a measure of the area under the curve and is also a measure of the duration of the spindle or "burst" activity. Example produced using NeuroGuide demo software from www.appliedneuroscience.com.

24 – The Bi-Spectrum and Bi-Coherence and Bi-Phase Difference

Another method to quantify spindle activity and brain connectivity as it relates to spindles is the Bi-Spectrum. There are two different definitions of the Bi-Spectrum. One is by Hasselman et al, (1963) as the 3rd moment statistical property called "skewness" which was used to detect nonlinear interacting ocean waves. Brillinger and Rosenblatt (1967) elaborated and described the computation of the tri-spectrum as the 4th power statistical moment or "kurtosis". The application of this definition of bi-spectra is purely statistical and it is primarily used to detect non-linearities. The second definition of bi-spectra is by Bendat and Pearsol (1980) in which bi-spectra are produced by partial-coherence analyses in order to isolate the covariances between different frequencies and locations. The bi-spectrum using partial-coherence is a measure of the association between different frequencies and different inputs, for example, a measure of the phase consistency and the phase difference between theta and beta frequencies. In the present paper we use the Bendat and Piersol (1980) approach to bi-spectra and bi-coherence to develop measures of coherence and phase differences between different frequencies within a single channel (auto bi-coherence and bi-phase) and the correlation between frequencies in different EEG channels or sensors (cross bi-coherence and cross bi-phase).

To calculate bi-coherence, it is necessary to multiply two complex domain transforms of the digital time series to obtain a 3rd order transform and because of the linearity of the transforms and the need for real-time computations we transform each instant of time for X_t to the complex domain by multiplying a time series by a sine and cosine sine wave at a specific center frequency and band width followed by low-pass filtering. This well established signal processing method is called "complex demodulation" (Otnes and Enochson, 1972) and we refer to it as a complex demodulation transform or "CDF" where each time point is represented as a point on the unit circle 0 to 2pi. This is an instantaneous cosine and sine representation of a time series from which the time series of the "cospectrum" and "quadspectrum" are computed from the cross-spectrum (see Appendix B for the mathematical details of complex demodulation). As described in section 9 the results of the CDF is the creation of a new real valued time series. The CDF real valued time series is then used as the input to spectral analyses for the computation of bi-coherence and bi-phase.

25- What is the physiological meaning of EEG bi-coherence and bi-phase?

Bi-coherence and Bi-phase measure the spatial and temporal relations between EEG "spindles" or "burst activity" and "rhythmic episodes" as well as the frequency structure of EEG burst activity in general. Complex demodulation of a EEG time series at a given center frequency measures the instantaneous power (uV^2) of activity at each instant of time in a frequency band, similar to a filter except that the time series is represented in the complex domain. The frequency spectrum of "spindle activity" at a given frequency measures spindle duration and inter-spindle intervals or how common spindles are within a record and auto bi-coherence shows the phase synchrony of spindle activity at different frequencies within a channel. Cross bi-coherence measures the phase synchrony of spindle or burst activity at the same or different frequency in different channels.

The FFT of the complex demodulation time series (x'_t) computes the inter-burst frequency and average burst duration and burst rise times because x'_t is the envelope of the spindle structure of EEG events. For example, long duration bursts result in high power in the lower frequencies of the FFT spectrum. Short inter-burst intervals result in high power at higher frequencies of the FFT spectrum.

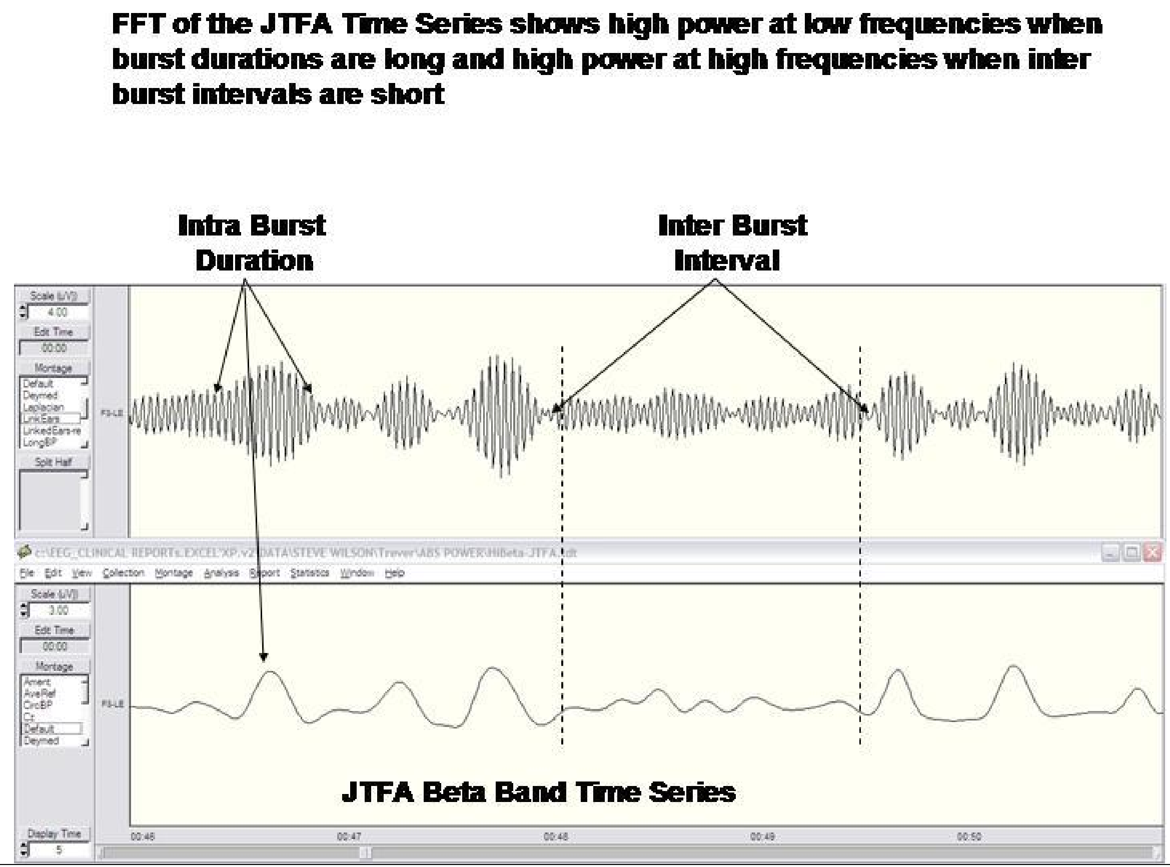

Fig. 23 – Top is filtered EEG at 25 – 30 Hz from F8 and reveals the burst structure of the EEG. Bottom is the complex demodulation (JTFA) time series of instantaneous power at 25 – 30 Hz (x'_t) and represents the integral or envelope of burst activity in the hi-beta frequency band. Long duration bursts result in high spectral power in the lower frequencies and short inter-burst intervals result in high spectral power in the higher frequencies of the spectrum. Analyses were produced using the NeuroGuide Lexicor demo from the download at www.appliedneuroscience.com

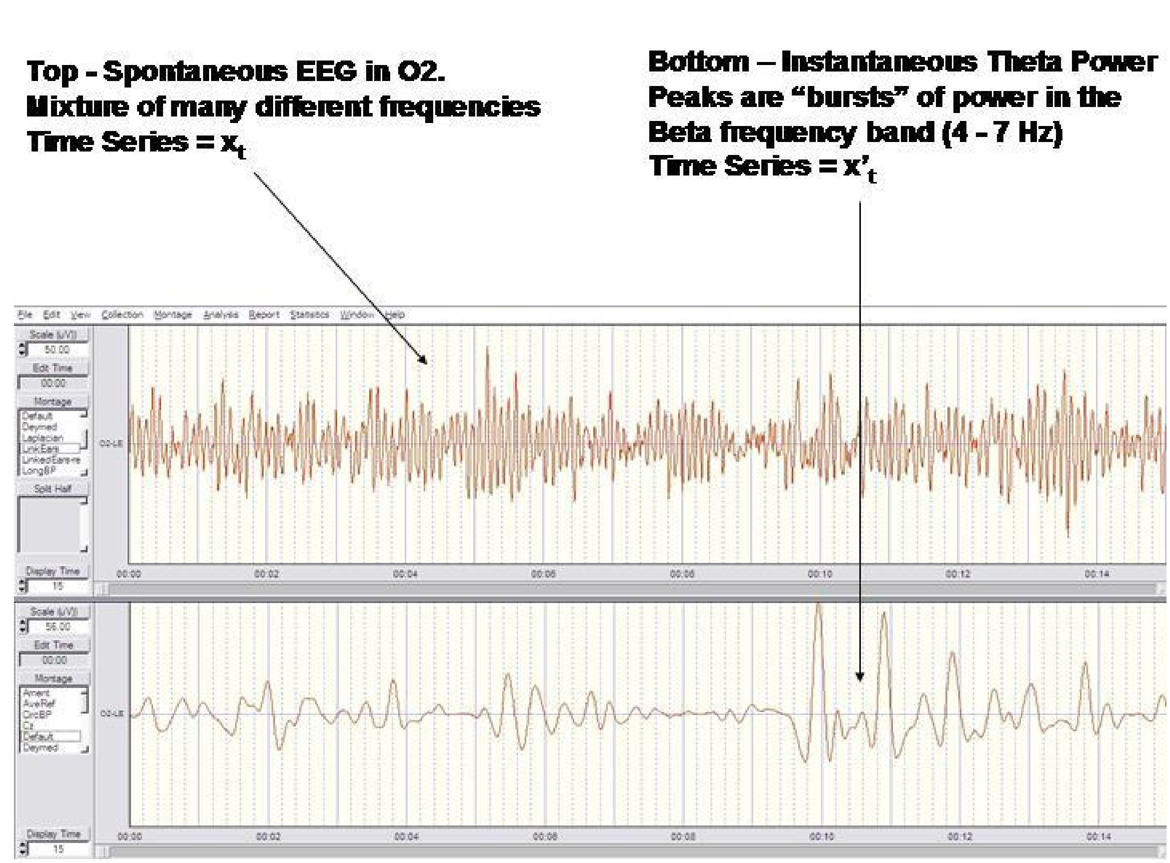

Fig. 24 - Top is the spontaneous EEG from O2. Bottom is the complex demodulation (JTFA) time series (x'_t) of the instantaneous power between 4 – 7 Hz. Peaks in the JTFA time series represent integrations or the instantaneous envelope of burst activity in the theta frequency band. Analyses were produced using the NeuroGuide Lexicor demo from the download at www.appliedneuroscience.com

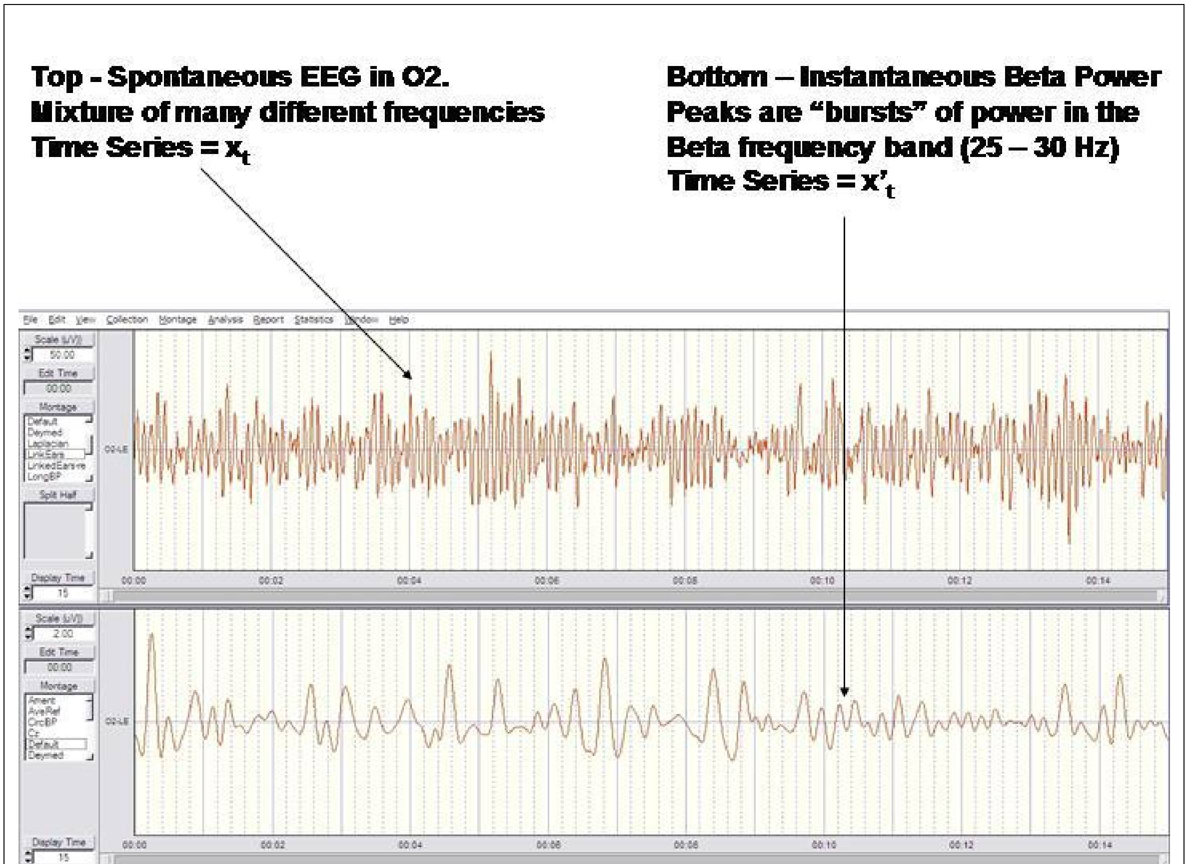

Fig. 25 - Top is the spontaneous EEG from O2. Bottom is the complex demodulation (JTFA) time series (x'_t) of the instantaneous power between 25 - 30 Hz. Peaks in the JTFA time series represent integrations or the instantaneous envelope of burst activity in the hi-beta frequency band. Bi-coherence between the two JTFA time series in fig. 19 and fig. 20 measure the phase synchrony of burst activity in the theta and beta frequency bands. Bi-phase measures the average time differences between theta and beta burst activity. Analyses were produced using the NeuroGuide Lexicor demo from the download at www.appliedneuroscience.com

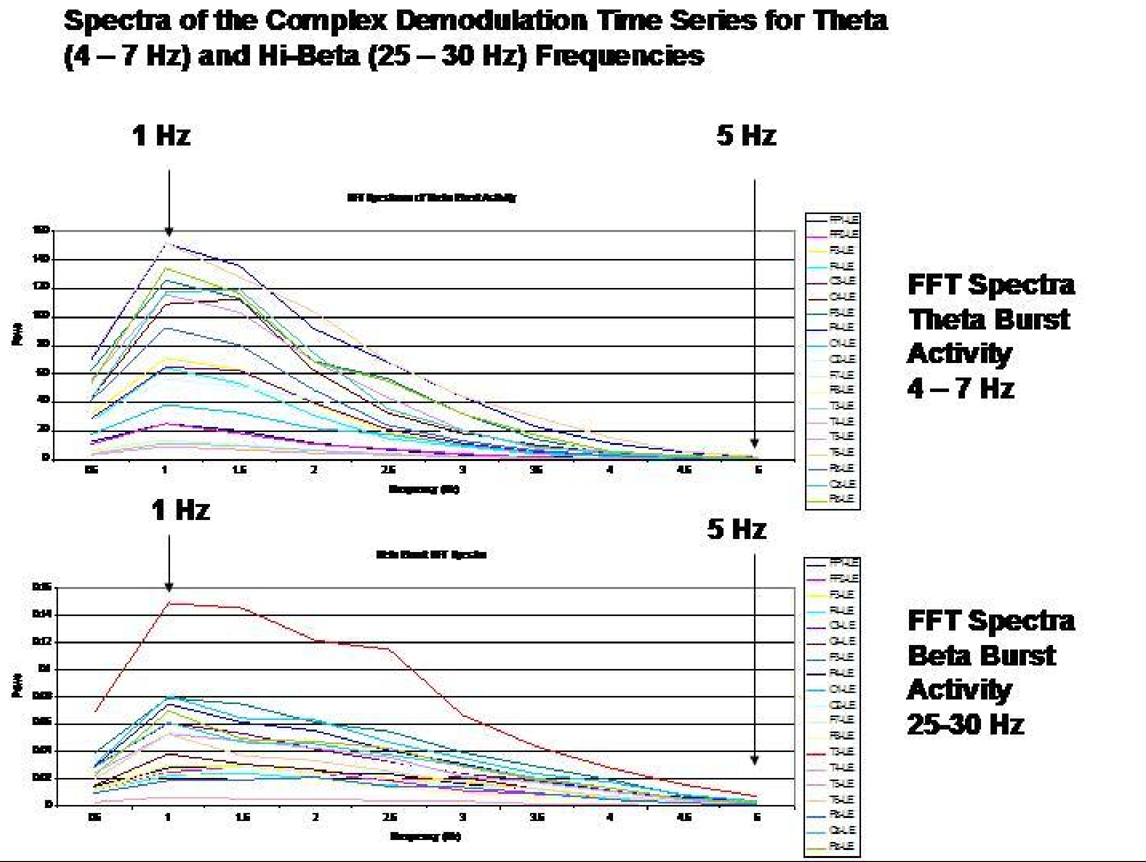

Fig. 26 – FFT analyses of the time series of instantaneous power over a 1 minute interval of time in the theta and beta frequency bands.

26- How to compute Auto Bi-Coherence (ABC)

The procedure is:

1- Transform the digital value of the EEG time series x_t in channel X to a new time series x'_t by multiplying each time point by a sine wave at frequency 1 and a cosine wave at frequency 1. Then, low pass filter and compute the square root of the sum of squares of the cospectrum and quadspectrum at each point of time to produce the new time series x'_t (see section 9).

2- Transform the digital value of the EEG time series x_t in channel X to a new time series x''_t by multiplying each time point by a sine wave at frequency 2 and a cosine wave at frequency 2. Then low pass filter and then compute the square root of the sum of squares of the cospectrum and quadspectrum at each point of time to produce the new time series x''_t (see section 9).

3- Compute the auto bi-coherence of the two time series x'_t and x''_t for the two frequencies 1 and 2 for each instant of time.

27- How to compute cross bi-coherence

The procedure is:

4- Transform the digital value of the EEG time series x_t in channel X to a new time series x'_t by multiplying each time point by a sine wave at frequency 1 and a cosine wave at frequency 1. Then, low pass filter and compute the square root of the sum of squares of the cospectrum and quadspectrum at each point of time to produce the new time series x'_t .

5- Transform the digital value of the EEG time series y_t in channel Y to a new time series y'_t by multiplying each time point by a sine wave at frequency 2 and a cosine wave at frequency 2. Then low pass filter and then compute the square root of the sum of squares of the cospectrum and quadspectrum at each point of time to produce the new time series x'_t .

Auto bi-phase and cross bi-phase are computed in the same manner as in previous sections but taking the arctangent of the ratio of the quadspectrum to the cospectrum at each moment of time.

In summary, there are four categories of the bi-spectrum for the purposes of relating different frequencies: 1- Cross Bi-spectral coherence, 2- Auto Bi-spectral coherence, 3- Auto bi-spectral phase and 4- Cross bi-spectral phase.

28- Auto Bi-Spectral Coherence is defined as the square of the ratio of the cross-spectra within a single channel at two different frequencies divided by the product of the auto-spectra. For example, the auto bi-spectrum between the EEG theta frequency (4 - 7 Hz) and the beta frequency band (25 – 30 Hz) as recorded from electrode location F3. To compute auto bi-spectral coherence one first transforms each time point to the complex domain using complex demodulation and then one computes the Fourier transform of the complex domain time series.

Eq. 27:

Auto Bi-Spectral Coherence (ABC) (f_1,f_2) after complex demodulation (x',y') is defined as

$$ABC = \frac{(\sum_N (a(x'\,f_1)u(x''\,f_2) + b(x'\,f_1)v(x''\,f_2)))^2 + (\sum_N (a(x'\,f_1)v(x''\,f_2) - b(x'\,f_1)u(x''\,f_2)))^2}{\sum_N (a(x'\,f_1)^2 + b(x'\,f_2)^2)\sum_N u(x''\,f_2)^2 + v(x''\,f_2)^2)}$$

Where x = frequency activity recorded from a single channel and x' = frequency 1 and x'' = frequency two recorded from the same channel. N and the summation sign represents averaging over frequencies in the raw spectrogram or averaging replications of a given frequency or both. The numerator and denominator of bi-coherence always refers to smoothed or averaged values, and, when there are N replications or N frequencies then each bi-coherence value has 2N degrees of freedom.

29- Cross Bi-Spectral coherence is a measure of the phase consistency between two different frequencies recorded from two different locations. For example, the phase consistency between theta (4-7 Hz) and High Beta (20 – 40 Hz) EEG signals in two spatially separated channels F3 and F4 of the 10/20 system of EEG electrode location.

The Cross Bi-spectral Coherence (CBC) is defined as the ratio of the auto-spectra and cross-spectra for two channels, X and Y and two frequencies f_1 and f_2. We again refer to the definitions of the cospectrum and the quadspectrum (see section 9) and then we define the cross bi-spectral coherence:

Eq. = 28

$$CBC = \frac{(\sum_N (a(x'\,f_1)u(y'\,f_2) + b(x'\,f_1)v(y'\,f_2)))^2 + (\sum_N (a(x'\,f_1)v(y'\,f_2) - b(x'\,f_1)u(y'\,f_2)))^2}{\sum_N (a(x'\,f_1)^2 + b(x'\,f_2)^2)\sum_N u(y'\,f_2)^2 + v(y'\,f_2)^2)}$$

Where x' = channel 1 and y' = channel 2, f_1 = frequency 1 in channel 1 and f_2 = frequency 2 in channel 2. N and the summation sign represents averaging over frequencies in the raw spectrogram or averaging replications of a given frequency or both. The numerator and denominator of bi-coherence always refers to smoothed or averaged values, and, when there are N replications or N frequencies then each bi-coherence value has 2N degrees of freedom.

30- Bi-Spectral Phase

Bi-spectral phase difference is generically defined as:

Eq. 29 –

$$\text{Phase difference } (f_1,f_2) = \text{Arctan } \frac{(\boldsymbol{Smoothedquadspectrum}(f_1, f_2))}{(\boldsymbol{Smoothed}\ \mathbf{cos}\ \boldsymbol{pectrum}(f_1, f_2))}$$

Like bi-coherence there are two subdivisions of bi-spectral phase: 1- Auto Bi-spectral phase and 2- Cross Bi-spectral phase.

31- Auto Bi-Spectral Phase Difference is a measure of the phase difference between two phase difference time series at two frequencies recorded from one location. Phase difference between two time series and two frequencies is defined as a point on the unit circle and is represented in degrees or radians and is "normalized" with respect to frequency (i.e., independent of frequency because r = 1). For example, a phase difference of 45^0 is the same for the standard EEG frequency bands of delta, theta, alpha, beta, gamma, etc. Because of this fact and because of the physics of superposition of waves the bi-spectral phase measure is a useful measure of local generator signals that are coupled at different frequencies and exhibit bi-frequency phase locking. The first and second derivatives of bi-frequency phase coupling are similar to the inter-coupling measures and are useful measures of "transition states" or bifurcation points and stability measures of homeostatic systems measured from a single location and given superposition of waves from many different locations.

The equation for use with a hand calculator to compute Auto Bi-Spectral Phase (f_1, f_2) **or ABP** is:

Eq. 30

$$ABP = Arc\tan\frac{\sum_{N}(a(x'\,f_1)v(x''\,f_2) - b(x'\,f_1)u(x''\,f_2))}{\sum_{N}(a(x'\,f_1)u(x''\,f_2) + b(x'\,f_1)v(x''\,f_2))}$$

Where x' = frequency 1 and x'' = frequency two recorded from the same channel and N = number of time samples (for cospectrum and quadspectrum calculation see section 9).

32- Cross Bi-Spectral Phase Difference is a measure of the phase difference between two real valued phase difference time series at two frequencies recorded from two different locations. This is an important measure of network dynamics and communication at different frequencies across space. Because instantaneous phase is a scalar and a real number then the commutation properties of algebra hold and the use of the Fourier transform is valid to compute the arctangent of the quadspectrum and cospectrum. Phase difference between two locations and two frequencies is defined as a point on the unit circle and is represented in degrees or radians and is "normalized" with respect to frequency (i.e., independent of frequency because r = 1). For example, a phase difference of 45^0 is the same for the standard EEG frequency bands of delta, theta, alpha, beta, gamma, etc. Because of this fact and because of the physics of superposition of waves the bi-spectral phase measure is a useful measure of local and distant coupling by frequency and phase locking. The first and second derivatives of bi-phase coupling are useful measures of "transition states" or bifurcation points and stability measures of homeostatic systems (similar to their application to phase reset described in section 9).

The equation for use with a hand calculator to compute Cross Bi-Spectral Phase **or CBP** is:

Eq. 31-

$$CBP = Arc\tan\frac{\sum_{N}((a(x'\,f_1)v(y'\,f_2) - b(x'\,f_1)u(y'\,f_2))}{\sum_{N}((a(x'\,f_1)u(y'\,f_2) + b(x'\,f_1)v(y'\,f_2))}$$

33- Coherence of Coherence

Defined as the average Coherence between two time series of instantaneous coherence for a pair of electrodes with a common reference.

The importance of a common reference is because algebraic subtraction occurs only by virtue of a common reference whereas an average reference or a Laplacian reference mixes signals from all leads into each of the remaining leads thus eliminating valid and meaningful algebra. A view of all pair wise combinations of "Coherence of Coherence" for 19 leads = 171 combinations using Cz as the reference electrode is in Figure 27.

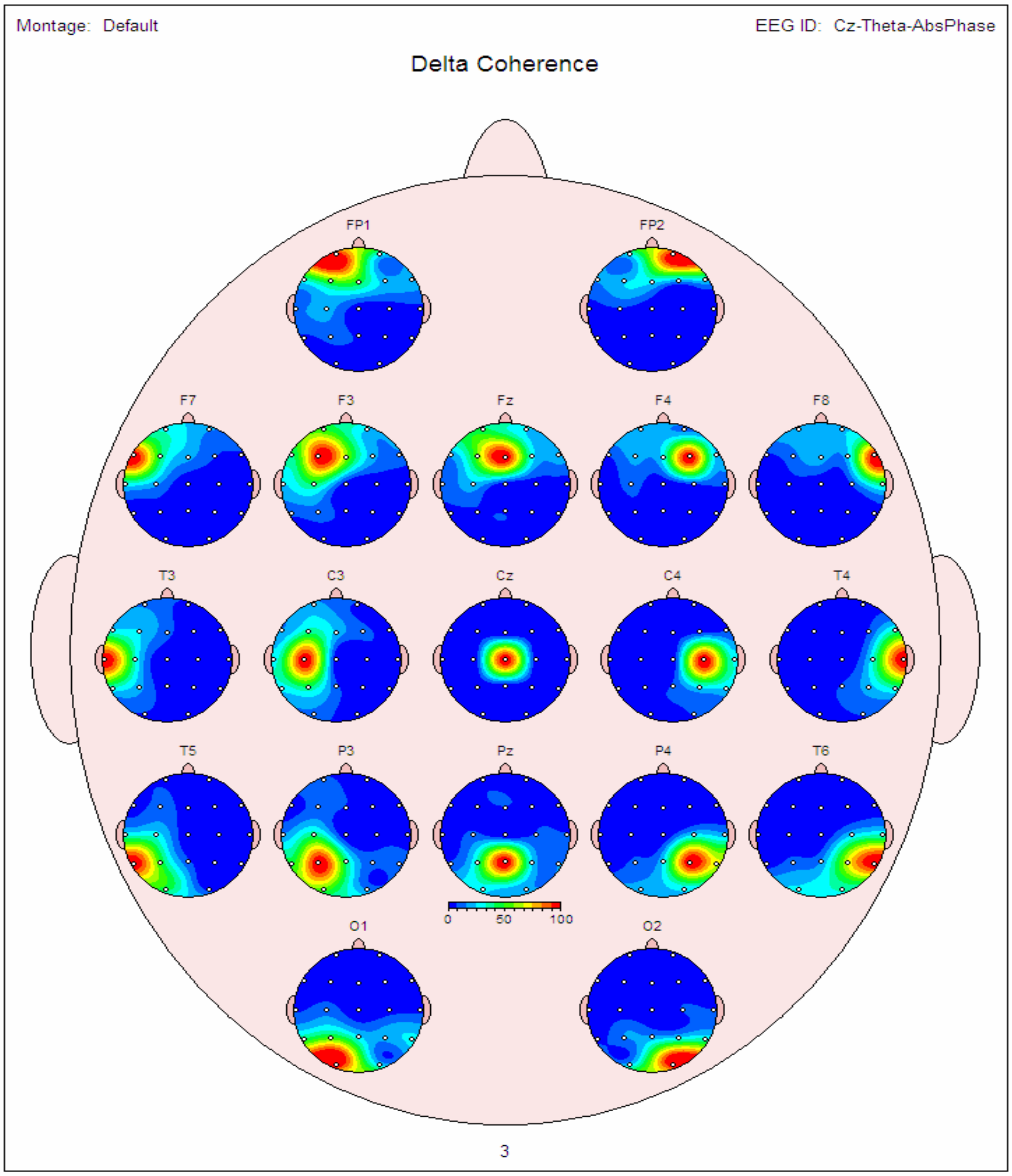

Fig. 27 – Example of coherence of coherence for all 171 combinations of 19 electrodes. Analyses were produced using the NeuroGuide Lexicor demo from the download at www.appliedneuroscience.com

34 – Phase Difference of Coherence

Defined as the average Phase difference of the time series of instantaneous coherence between any pair of electrodes with respect to a common electrode. For example, the two time series of instantaneous coherence between Cz-P3 and Cz-P4 are the input to the phase analysis in which the average phase difference between the two time series of coherence exhibits statistically significant phase stability over time (i.e., significant coherence values). An example of 19 leads = 171 combinations is in Figure 28.

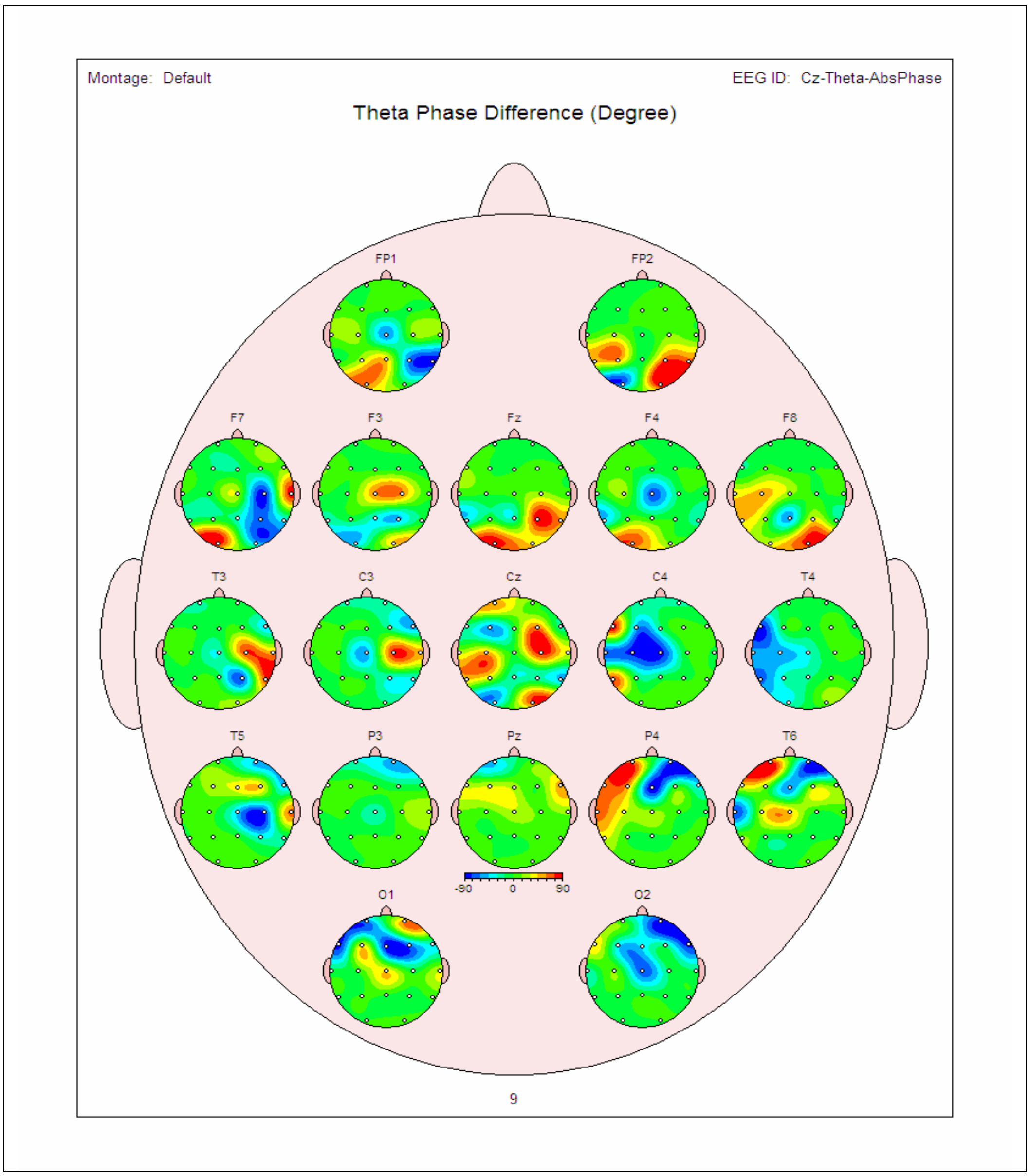

Fig. 28 – Example of phase difference of the time series of instantaneous coherence for all 171 combinations of 19 electrodes. Analyses were produced using the NeuroGuide Lexicor demo from the download at www.appliedneuroscience.com

35 – Coherence of Phase Differences

Defined as the average Coherence of the time series of instantaneous phase differences between any pair of electrodes with respect to a common electrode. For example, the two time series's of instantaneous phase difference between Cz-P3 and Cz-P4 are the input of the coherence analysis in which coherence between the two time series of phase difference exhibits statistically significant phase stability over time (i.e., significant coherence values). An example of 19 leads = 171 combinations is in Figure 29.

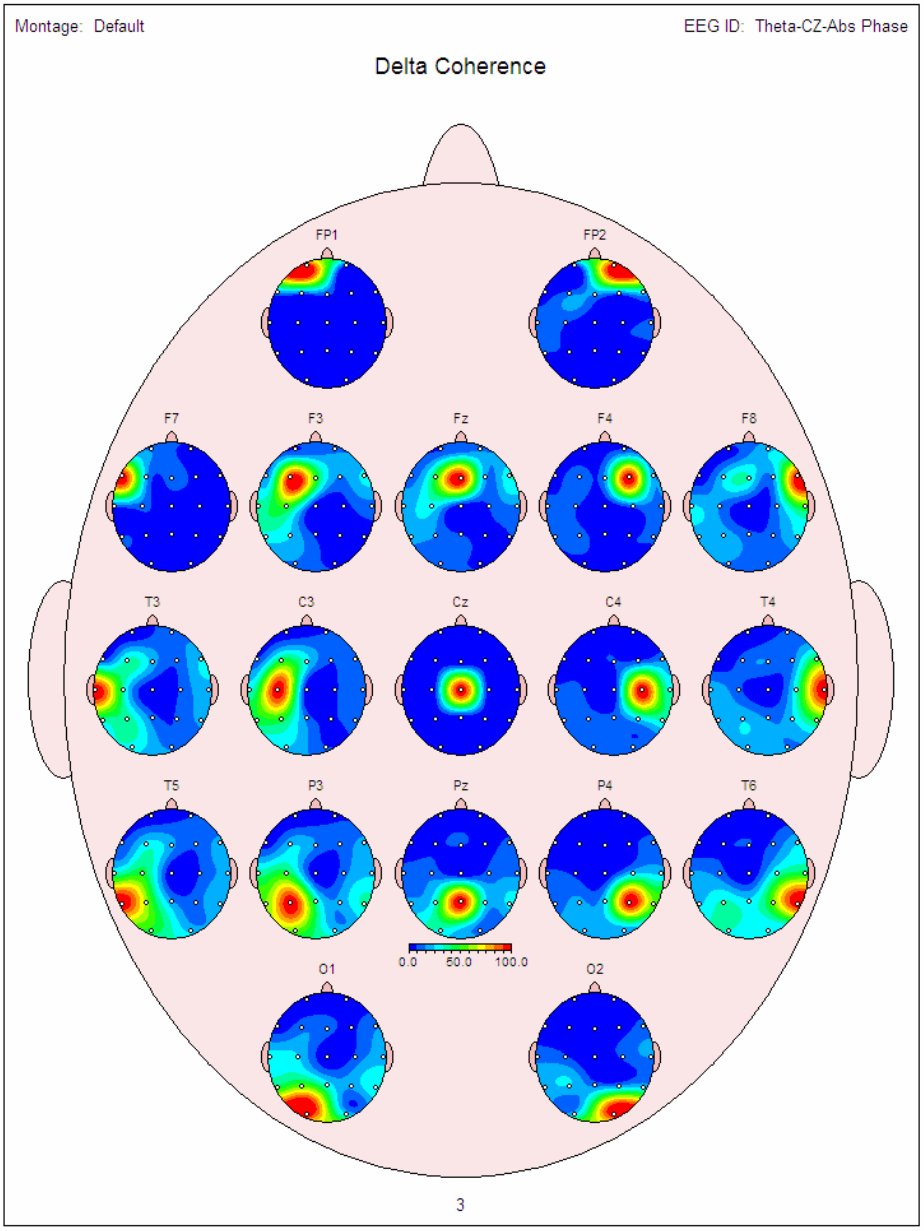

Fig. 29 – Example of coherence of the time series of instantaneous phase differences for all 171 combinations of 19 electrodes. Analyses were produced using the NeuroGuide Lexicor demo from the download at www.appliedneuroscience.com

36 – Coherence Between Two Time Series of Phase Resets

Defined as the average Coherence of the First Derivative of the Time Series of Instantaneous Phase Differences (i.e., “Phase Reset”) between any pair of electrodes with respect to a common electrode. For example, the two time series of phase resets for Cz-P3 and Cz-P4 are the input to the coherence analysis in which there is significant phase stability between the two time series of phase reset. See section 15 for an explanation of phase reset. An example of 19 leads = 171 combinations is in Figure 30.

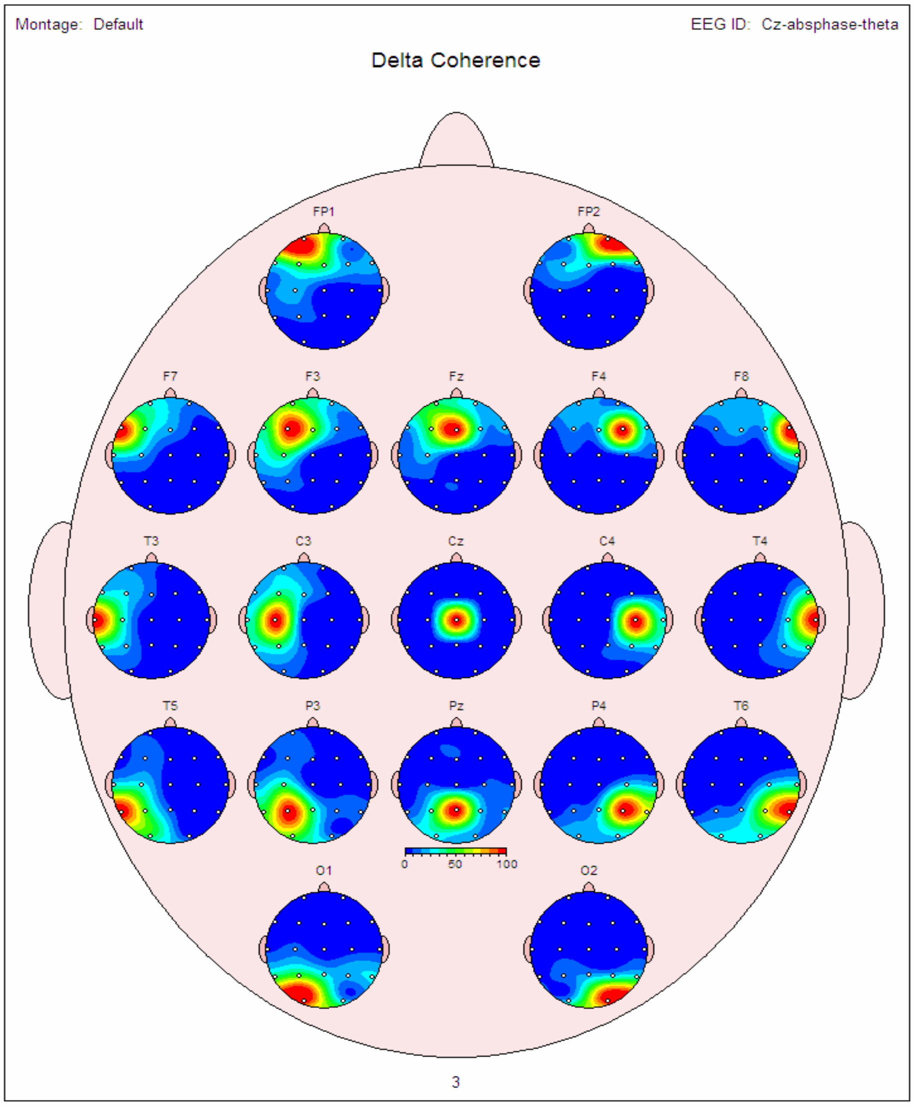

Fig. 30 – Example of coherence of the time series of instantaneous phase re-set for all 171 combinations of 19 electrodes. Analyses were produced using the NeuroGuide Lexicor demo from the download at www.appliedneuroscience.com

37 – Phase Difference Between Two Phase Difference Time Series

Defined as the average Phase difference of the Time Series of Instantaneous Phase Differences between two channels with respect to a common reference. A map of all pair wise combinations (19 leads = 171 combinations with respect to Cz) is useful to visualize the full manifold of relationships as defined by the phase difference of the time series of phase differences. An example of 19 leads = 171 combinations is in Figure 31.

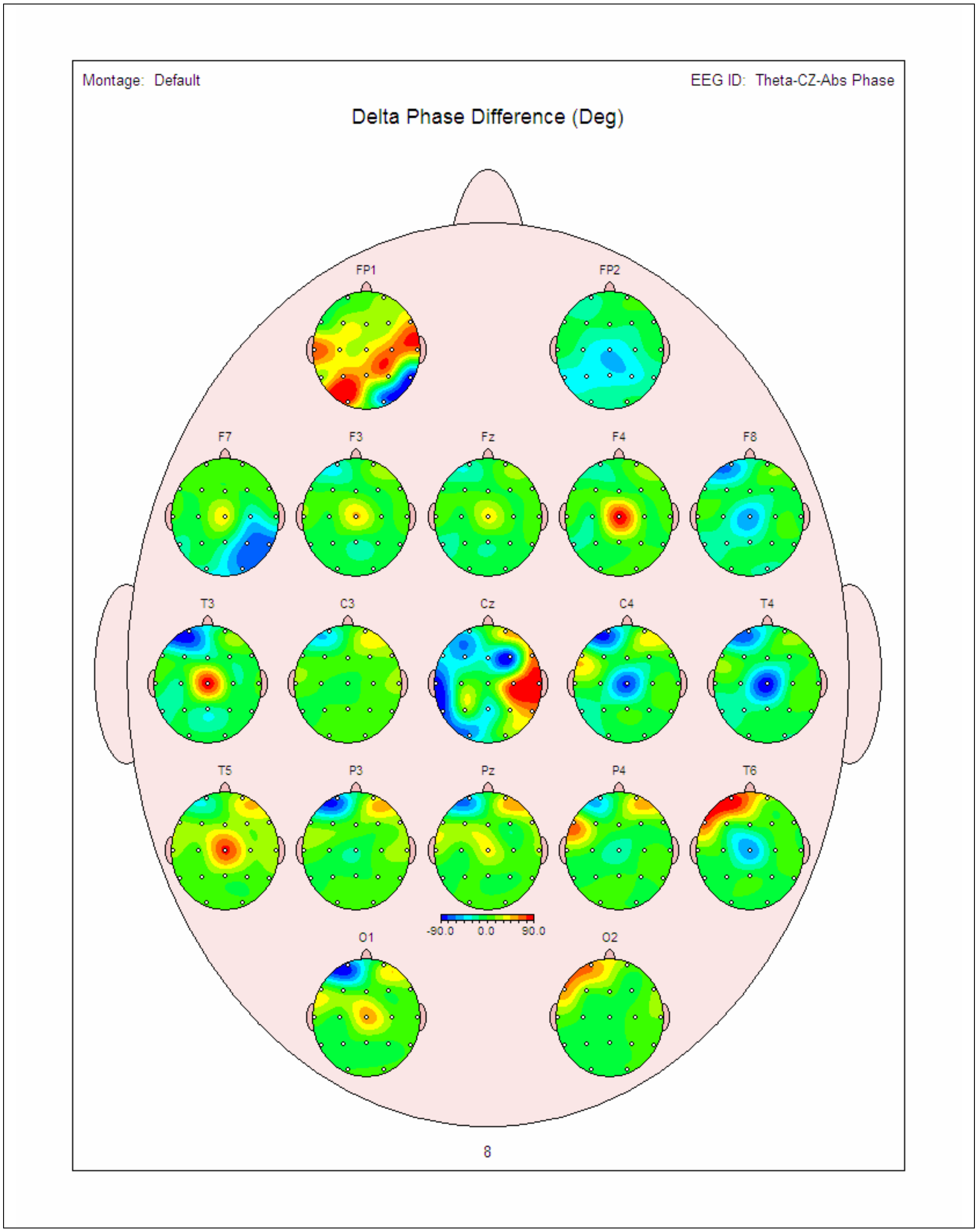

Fig. 31 – Example of phase difference of the time series of instantaneous phase differences for all 171 combinations of 19 electrodes. Analyses were produced using the NeuroGuide Lexicor demo from the download at www.appliedneuroscience.com

38 – Phase Difference of Phase Reset

Defined as the average phase difference of the First Derivative of the Time Series of Instantaneous Phase Differences (i.e., Phase Reset) between two electrode combinations referenced to a common reference as explained in section 34. See section 15 for an explanation of phase reset. An example of 19 leads = 171 combinations is in Figure 32.

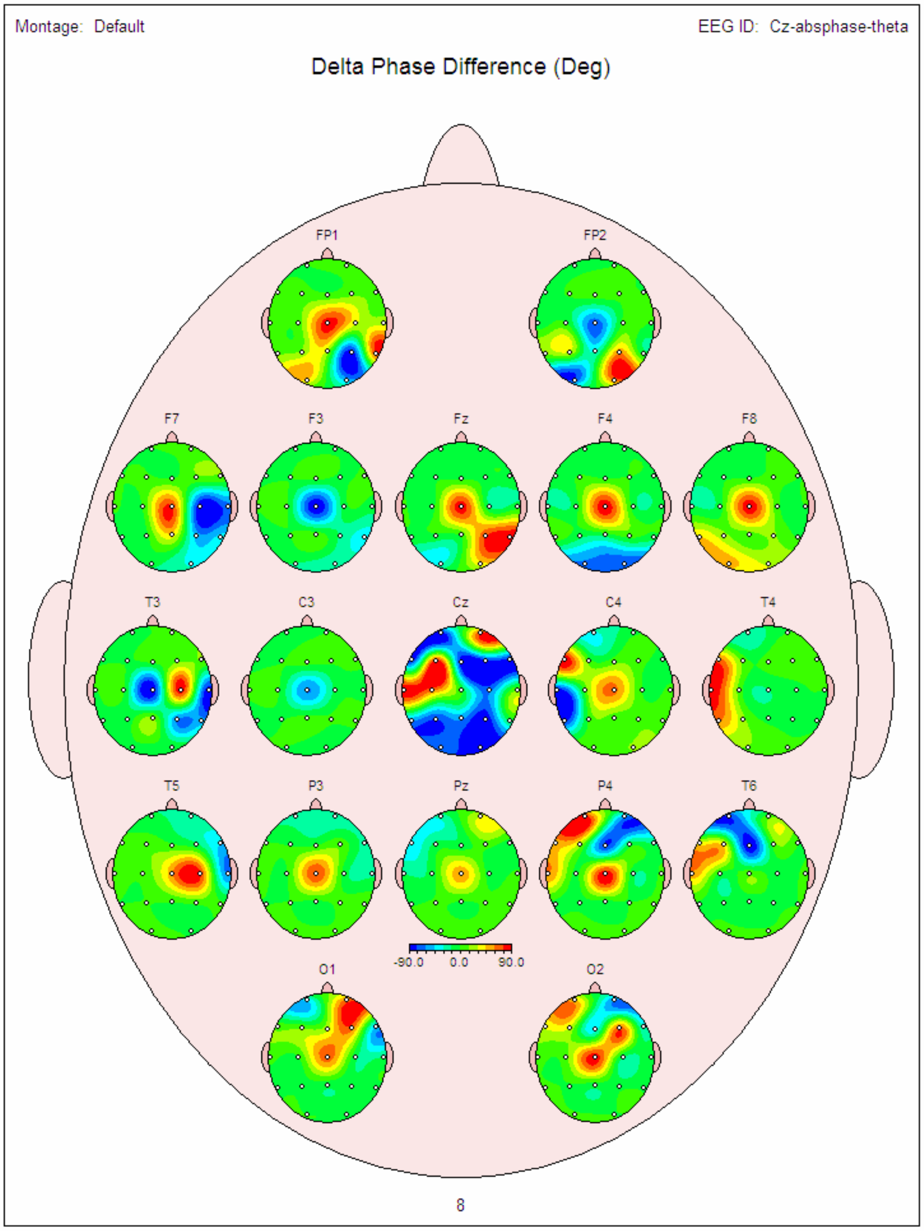

Fig. 32 – Example of phase differences of the time series of instantaneous phase re-set for all 171 combinations of 19 electrodes. Analyses were produced using the NeuroGuide Lexicor demo from the download at www.appliedneuroscience.com

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A.1 – Minimization of RMS Error

Time series are sequences, discrete or continuous, of quantitative data of specific moments in time. They may be simple such as a single numerical observation at each moment of time and studied with respect to their distribution in time, or multiple in which case they consist of a number of separate quantities tabulated according to a common time base (e.g., a mixture of sine waves beginning at time = 0).

The statistics of a time series is the science of predicting an immediate or long time future sequence based on a sample of past sequential quantitative data. In general, the longer the sample of past quantitative moments of time then the greater the accuracy of predicting future sequence(s).

The fine details of accuracy of prediction of the future based upon past samples is generally governed by the relationship of 1 / sq rt. of N. To understand why this is the case let us define a statistic of a time series based on the "signal" or "message" that is transmitted and the "noise" or randomness that the signal is embedded in. This relationship was described by the Nobel laureate Normbet Wiener (N. Wiener, Time Series, MIT Press, Cambridge, Mass., 1949) in which a time series is a combination of a signal + noise or the signal f(t) and the message g(t) + noise, where noise is defined as f(t) – g(t). In other words noise is defined as the difference between the "message" and the measured quantitative values or f(t) – g(t). For example, noise = 0 when f(t) – g(t) = 0.

Let us consider the output of an electrical circuit with input f(t). If the circuit has the response A (t) to a unit-step function, then the output is given by:

$$F(t) = \int_{0}^{+\infty} A'(\tau)\, f(t-\tau)\, d\tau + A(0)\, f(t)$$

The goal is to have F(t) approximate as closely as possible the message g(f). That is, we want to minimize [F(t) – g(t)]. As a criterion

The Ergotic goal of time series statistics is to minimize the difference between the measured values f(t) and the "signal" g(t).

The time series can be divided into two general categories: 1- the statistics of short-time biological data and other short-time interval events such as economic, sociological, etc. and 2- long time span events such as astronomical, meterological, geologic and geophysical data . . . . – to be continued

41- Appendix – B

Instantaneous Coherence and Phase Difference

Complex demodulation was used to compute instantaneous coherence and phase-differences (Granger and Hatanaka, 1964; Otnes and Enochson, 1972; Bloomfield, 2000). This method first multiples a time series by the complex function of a sine and cosine at a particular frequency followed by a low pass filter which removes all but very low frequencies and transforms the time series into instantaneous amplitude and phase and an “instantaneous” spectrum (Bloomfield, 2000). We place quotations around the term “instantaneous” to emphasize that there is always a trade-off between time resolution and frequency resolution. The broader the band width the higher the time resolution but the lower the frequency resolution and vice versa (Bloomfield, 2000). For example, if we multiply a time series $\{x_t, t = 1, \ldots, n\}$ by sine $\omega_0 t$ and cos $\omega_0 t$ and then apply a low pass filter F, we have

$$Z'_t = F(x_t \sin \omega_0 t)$$
$$Z''_t = F(x_t \cos \omega_0 t)$$

and $2\left[(Z'_t)^2 + (Z''_t)^2\right]^{1/2}$ is an estimate of the “instantaneous” amplitude of the frequency ω_0 at time t and $\tan^{-1} \frac{Z'_t}{Z''_t}$ is an estimate of the “instantaneous” phase at time t.

The instantaneous cross-spectrum is computed when there are two time series $\{y_t, t = 1, \ldots, n\}$ and $\{y'_t, t = 1, \ldots, n\}$ and if F [ ] is a filter passing only frequencies near zero, then, as above

$R_t^2 = F[y_t \sin \omega_0 t]^2 + F[y_t \cos \omega_0 t]^2 = \left| F[y_t e^{i\omega_0 t}]^2 \right|$ is the estimate of the amplitude of frequency ω_0 at time t and

$\varphi_t = \tan^{-1}\left(\frac{F[y_t \sin \omega_0 t]}{F[y_t \cos \omega_0 t]} \right)$ is an estimate of the phase of frequency ω_0 at time t and since

$$F[y_t e^{i\omega_0 t}] = R_t e^{i\varphi_t},$$

and likewise,

$$F[y'_t e^{i\omega_0 t}] = R'_t e^{i\varphi_t}$$

the instantaneous cross-spectrum is

$$V_t = F[y_t e^{i\omega_0 t}] F[y'_t e^{-i\omega_0 t}]$$

$$= R_t R'_t e^{i[\varphi_t - \varphi'_t]}$$

and the instantaneous coherence is

$$\frac{|V_t|}{R_t^2 R_t'^2} \equiv 1$$

however coherence is computed as the average of the sine and cosine functions over an interval of time or

$$\overline{C}(t,\omega) = \frac{|\overline{V}_t|}{R_t^2 R_t'^2}$$

The instantaneous phase-difference is $\varphi_t - \varphi'_t$ which is also the arctan of the imaginary part of V_t divided by the real part (or the quadspectrum divided by the cospectrum).

Computation of the First Derivatives of the Time Series of Coherence and Phase Angles

The first derivative of the time series of phase-differences between all pair wise combinations of two channels was computed in order to detect advancements and reset of phase-differences. The Savitzgy-Golay procedure was used to compute the first derivatives of the time series using a window length of 3 time points and the polynomial degree of 2 (Press et al, 1994). The units of the 1st derivative are in degrees/point which is normalized to degrees/second and degrees/millisecond in the case of EEG. The second derivative was computed using a window length of 5 and a polynomial degree of 3 and is in units of degrees/second^2 or degrees/millisecond^2 in the case of EEG. For simplicity, in NeuroGuide the units of the first derivative of a phase time series is degrees per centiseconds (i.e., degrees/cs^2 = degrees/100 msec.^{2}).

42- Appendix – C

Listing of the Relevant Connectivity Equations. All of the equations below can be evaluated using a hand calculator and the equations can be easily programmed by a competent programmer. See the sections above for details. The goal is to help develop standardization and simplification for the implementation of EEG connectivity measures:

1- Pearson Product Correlation Coefficient

$$r = \frac{N\sum XY - \sum X \sum Y}{\sqrt{\left[N\sum X^2 - (\sum X)^2\right]\left[N\sum Y^2 - (\sum Y)^2\right]}}$$

2- The cospectrum and quadspectrum (see section 9):
$a(xf_1)$ = cosine coefficient for the frequency (f_1) for channel X
$b(xf_1)$ = sine coefficient for the frequency (f_1) for channel X
$u(yf_2)$ = cosine coefficient for the frequency (f_2) for channel Y
$v(yf_2)$ = sine coefficient for the frequency (f_2) for channel Y

The cospectrum and quadspectrum are algebraically defined as:

Cospectrum $(f_1,f_2) = a(xf_1)\ u(yf_2) + b(xf_1)\ v(yf_2)$

Quadspectrum $(f_1,f_2) = a(xf_1)\ v(yf_2) – b(xf_1)\ u(yf_2)$

3- Auto-spectrum

$F(x) = (a^2 (x) + b^2 (x))$

4- The cross-spectrum amplitude:

$$= \sqrt{((a(x)u(y) + b(x)v(y))^2 + (a(x)v(y) - b(x)u(y))^2}$$

5- Coherence

$$\textbf{Coh (f)} = \frac{(\sum_N (a(x)u(y)+b(x)v(y)))^2 + (\sum_N (a(x)v(y)-b(x)u(y)))^2}{\sum_N (a(x)^2 + b(x)^2)\sum_N u(y)^2 + v(y)^2)}$$

6- **Phase Delay or phase difference**

$$\textbf{Phase difference (f) = Arctan } \frac{\sum_N (a(x)v(y) - b(x)u(y))}{\sum_N (a(x)u(y) + b(x)v(y))}$$

7- Auto Bi-Spectral Coherence (f_1,f_2) (ABC) after complex demodulation:

$$ABC = \frac{(\sum_{N}(a(x' f_1)u(x'' f_2) + b(x' f_1)v(x'' f_2)))^2 + (\sum_{N}(a(x' f_1)v(x'' f_2) - b(x' f_1)u(x'' f_2)))^2}{\sum_{N}(a(x' f_1)^2 + b(x' f_2)^2)\sum_{N} u(x'' f_2)^2 + v(x'' f_2)^2)}$$

8- Cross Bi-spectral Coherence (f_1,f_2) (CBC) for channels X and Y after complex demodulation

$$CBC = \frac{(\sum_{N}(a(x' f_1)u(y' f_2) + b(x' f_1)v(y' f_2)))^2 + (\sum_{N}(a(x' f_1)v(y' f_2) - b(x' f_1)u(y' f_2)))^2}{\sum_{N}(a(x' f_1)^2 + b(x' f_2)^2)\sum_{N} u(y' f_2)^2 + v(y' f_2)^2)}$$

9- Auto bi-spectral phase (f_1, f_2) (ABP) after complex demodulation

$$ABP = Arc\tan\frac{\sum_{N}(a(x' f_1)v(x'' f_2) - b(x' f_1)u(x'' f_2))}{\sum_{N}(a(x' f_1)u(x'' f_2) + b(x' f_1)v(x'' f_2))}$$

10- Cross Bi-Spectral Phase (f_1,f_2) (CBP) after complex demodulation

$$CBP = Arc\tan\frac{\sum_{N}((a(x' f_1)v(y' f_2) - b(x' f_1)u(y' f_2))}{\sum_{N}((a(x' f_1)u(y' f_2) + b(x' f_1)v(y' f_2))}$$

Equations for sections 31 to 36 will be added in a future update.