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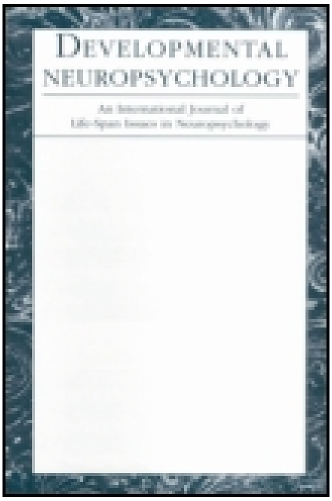

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Coherence, Phase Differences, Phase Shift, and Phase Lock in EEG/ERP Analyses

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Coherence, Phase Differences, Phase Shift, and Phase Lock in EEG/ERP Analyses

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Electroencephalogram (EEG) coherence is a mixture of phase locking interrupted by phase shifts in the spontaneous EEG. Average reference, Laplacian transforms, and independent component (ICA) reconstruction of time series can distort physiologically generated phase differences and invalidate the computation of coherence and phase differences as well as in the computation of directed coherence and phase reset. Time domain measures of phase shift and phase lock are less prone to artifact and are independent of volume conduction. Cross-frequency synchrony in the surface EEG and in Low Resolution Electromagnetic Tomography (LORETA) provides insights into dynamic functions of the brain.

Coherence is a measure of the variability of time differences between two time series in a specific frequency band. The Fourier transform provides a direct relationship between the time and frequency domains and represents time difference as a phase difference or phase angle. If the phase angle is stable and constant over time i.e., phase locked then coherence = 1.0 and if time differences between two time series varies from moment-to-moment then coherence = 0. Electroencephalogram (EEG) coherence is often interpreted as a measure of "coupling" and as a measure of the functional association between two brain regions (Nunez, 1981; Nunez, 1995; Thatcher, Krause, & Hrybyk, 1986; Thatcher, Walker, & Guidice, 1987; Walter, 1968). Coherence is a sensitive measure that can reveal subtle aspects of the network dynamics of the brain which complement the data obtained by the autospectrum. The earliest application of coherence measures to EEG was by Donald Walter in 1963 and since this time there have been hundreds of studies of EEG coherence. Here is a small sampling of EEG coherence studies since this time, for example, cognition (Babiloni et al., 2010; Giannitrapani, 1985; Kislova & Rusalova, 2009; Marosi et al., 1999; Martin-Loeches, Munoz-Ruata, Martinez-Lebrusant, & Gomez-Jari, 2001; Thatcher, North, & Biver, 2005), brain maturation (Gasser, Rousson, & Gasser, 2003; Hanlon, Thatcher, & Cline, 1999; Thatcher, 1992, 1998; Thatcher, North, & Biver, 2008a; Thatcher et al., 1987); heritability (van Baal, Boomsma, & de Geus, 2001; Van Beijsterveldt, Molenaar, de Geus, & Boomsma, 1998), gender differences (Hanlon et al., 1999; Koles, Lind, & Flor-Henry, 2010), directed coherence (Kamiński & Blinowska, 1991; Kamiński, Blinowska, & Szelenberger, 1997; Korzeniewska, Mańczak, Kamiński, Blinowska, & Kasicki, 2003; Tropini, Chiang, Wang, & McKeown, 2009), EEG and electromyography (Astolfi et al., 2010; Florin et al., 2010) and

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various clinical disorders (Babiloni et al., 2010; Barry, Clarke, McCarthy, & Selikowitz, 2002; De Vico Fallani et al., 2010; Hughes & John, 1999; John, 2009; John, Prichep, Fridman, & Easton, 1988; Kumar, Rao, Chandramouli, & Pillai, 2009; McAlaster, 1992; Shaw, Colter, & Resek, 1983; Thatcher, Biver, McAlaster, & Salazar, 1998).

The selection of a reference in recording EEG and in remontaging is a topic of extensive discussion and importance (Desmedt, Chalklin, & Tomberg, 1990; Dien, 1998; Nunez, 1981). Due to the use of differential amplifiers the electrical potential is the difference between two recording sites. The location and contribution of signals in a reference are therefore significant factors in the interpretation of the amplitudes and time differences in the EEG. This article is focused on measurements of phase and coherence, phase shift and phase lock and not on amplitude differences or the autospectrum of the EEG. It is important to read the papers by Yao and colleagues regarding this issue because the use of source analyses may be a solution to many of the reference problems that have historically plagued the field of EEG (Qin, Xu, & Yao, 2010; Yao, 2001).

EEG PHASE DIFFERENCES

EEG phase differences are often used to compute “directed coherence,” which is a measure of the directional flow of information between two EEG electrode sites (Kamiński & Blinowska, 1991; Kamiński, Blinowska, & Szelenberger, 1997). EEG phase differences are also used to estimate conduction velocities and synaptic integration times as one increases the inter-electrode distance in different directions (Nunez, 1981; Riddle & Baker, 2005; Suzuki, 1974; Thatcher, Krause, & Hrybyk, 1986; Thatcher, North, & Biver, 2008a). Volume conduction requires that phase differences = 0. Thus phase differences are very important in evaluating network dynamics that do not involve volume conduction. At the same time, zero phase lag relations exist across wide domains of the cerebral cortex due to the thalamus which is centrally located and can simultaneously activate neurons in distant cortical regions (Steriade, 2006). Therefore, just because phase difference = 0 does not mean that volume conduction explains the results, an underlying thalamic input to two or more locations can also explain the results. A method to distinguish zero phase lag due to volume conduction versus zero phase lag due to network connectivity is by phase reset measures that precisely define the onset and offset of phase shift in single pairs of electrodes which is by definition independent of volume conduction (Freeman & Rogers, 2002; Freeman, Burke, & Homes, 2003; Freeman, Homes, West, & Vanhatlo, 2006; Thatcher et al., 2008; 2009). Phase differences have a clear physiological basis such as conduction velocities in white matter tracks, synaptic delays, refractoriness and the rise times of synaptic potentials and the stability of physiologically generated phase differences as estimated by coherence. Therefore, it is important that the physiological time differences in the common reference recording are preserved prior to calculating coherence or mean phase difference. As mentioned previously all EEG recordings are actually bipolar recordings, that is, differences between two scalar electrical potentials applied to the inputs of a differential amplifier. This is important because it is an error to use vector multiplication of scalp electrical potentials when in fact electrical potentials are not vectors but rather they are scalars (Feynman, Leighton, & Sands, 1964; Malmivuo & Plonsey, 1995). This incorrect representation has resulted in confusion about the contribution of a common reference (Guevara et al., 2005). A common reference is a bipolar recording in which there is a shared reference for all scalp channels, for example, the same single input to one end of a differential amplifier (e.g., an ear, mastoid, physically linked ears or a single scalp location like Fpz) and the other end of the amplifier is attached to a scalp electrode site referred to as the "active" lead. This arrangement is repeated for all of the scalp EEG electrodes using the same or common reference. Standard bipolar recordings involving closely spaced pairs of electrodes do not satisfy this relationship because there is no single electrode that is a reference common to all other electrodes. This is important because of the algebra of common reference recordings using a scalar where, for example, the instantaneous phase difference between scalp electrode A and the common reference $R = 60^0$ and the instantaneous phase difference between scalp electrode B and the common reference $R = 45^0$, then $(A\text{-}R) - (B\text{-}R) = A\text{-}B = 60^0 - 45^0 = 15^0$ phase difference. In other words when a common reference is used in a differential amplifier then the phase or time differences due to the common reference electrode "R" cancels and drops out of the time series leaving the time difference between the two active scalp leads as the physiologically accurate measure, i.e., 15^0 instantaneous phase difference between locations A and B. This is important information because directed phase differences can be calculated based on this information, including epileptic spike propagation and many other neurophysiological processes such as inhibitory synaptic potential (IPSP) and excitatory synaptic potential (EPSP) durations (Nunez, 1981, 1995; Steriade, 2006). A limitation of the common reference is that it inflates coherence because the reference signal is in common with all of the recording channels. However, this is not a serious limitation in group analyses where the same common reference is used in each group of subjects and relative changes in coherence or absolute phase differences are of interest (e.g., pre treatment vs. post treatment EEG). Also, a common reference is not a limiting factor when measuring the duration of phase lock or phase shift in milliseconds because again the reference is in common to all of the recording electrodes and differences in phase shift or lock duration are a function of differences between the scalp recordings. The topic of phase shift and phase lock duration is discussed in a later section.

PROBLEMS WITH RE-MONTAGING AND DISTORTIONS OF THE ORIGINAL TIME SERIES

If the original EEG/event-related potential (ERP) time series is transformed into a second time series by using the average reference then the original phase differences from three electrode locations may be scrambled and lost. For example, with an average reference the entire surface of the brain is not measured, thus the averaging does not create a true zero potential at each instant of time. Also, a single large value from one electrode can distort and skew an entire distribution let alone distort the relationships in the original time series in the first place (Desmedt et al., 1990; Dien, 1998). Desmedt et al. (1990) show how "ghost" potentials can be produced by an average reference recording. High density electrode arrays help solve this problem, however, as pointed out by Desmedt et al. (1990) and Dien (1998) an accurate head model is needed, including measures from the underside of the brain in order to compute an accurate zero potential no matter how many scalp electrodes are used. This is why the average reference, especially with low density arrays, is not physiologically valid in the computation of coherence and has limited applicability to networks in the brain related to subtle and important physiological processes. The method of mixing phase differences precludes meaningful physiological or clinical correlations since measures such as conduction velocity or synaptic rise or fall times can no longer be estimated due to the average reference. The mixing together of phase differences in the EEG traces is also a problem when using the Laplacian transform which is a type of local average reference and, similarly, reconstruction of EEG time series using independent component analyses (ICA) or variations such as second order blind identification (SOBI), also replaces the original time series with an altered time series that eliminates any physiological phase relationships and therefore is an invalid method of calculating coherence. The reader is encouraged to test these facts in a tutorial at: http://www.appliedneuroscience.com/Tutorial%20on%20ICA%20Phase%20Adulteration.pdf

Similarly, Wavelet convolutions of the original time series may distort phase differences. One may obtain high reliability in test re-test measures of coherence using an average reference, however, the reliability is irrelevant because the method of computation using an average reference or a Laplacian is physiologically uninterpertable (Essl & Rappelsberger, 1998; Rappelsberger, 1989; Thatcher, 2010). A new method using inverse solutions to estimate 3-dimensional current sources called the “reference electrode standardization technique” (REST) is a promising method that can avoid the limitations of common references (e.g., inflation of coherence) and average references because the method is reference free (Qin et al., 2010; Yao, 2001).

Figure 1 shows the results of a validation test of coherence using a 1 uV sine wave as one channel and then progressively more Gaussian noise mixed with the 1 uV sine wave that is shifted by 30 degrees in order to systematically increase the signal-to-noise ratio. That is, 1 uV signal + 1 uV noise, 1 uV signal + 2 uV noise, 1 uV signal + 3 uV noise, and so on. According to the mathematics of coherence there should be a linear inverse relationship between coherence and signal-to-noise ratio and the 30 degree phase shift should be preserved. This is exactly what is seen in the left top (coherence) and left bottom (phase difference) of Figure 1 for the common reference. There is a clear inverse relationship between coherence and the signal-to-noise and mean phase is near to 30 degrees even though there is high variance at low signal-to-noise ratios. The middle top and bottom are the results of the test using an average reference and the right top and right bottom are the results of the test using the Laplacian transform. It can be seen in figure one that the mixing of signal and noise in all channels results in invalid coherence estimates and a complete loss of the 30 degree phase shift. This test can be performed by the interested reader for themselves if there is any doubt that the average reference and the Laplacian distort the original time differences and are therefore physiologically invalid when computing coherence.

EEG coherence and EEG phase delays are statistical estimates and are dependent on the number of degrees of freedom used to smooth or average spectra as well as the “reference” used to derive the data. Thus, while there is only one general mathematical equation for the computation of coherence, nonetheless, differences in the accuracy and sensitivity of the computation of coherence and phase delays depends on the amount of averaging across frequency bands or across records to achieve statistical stability in both ERP and EEG applications (Thatcher, Wang, Toro, & Hallett, 1994). Zaveri, Duckrow, and Spencer (2000) show how increased amplitude in a common reference “inflates” coherence for all electrode combinations but does not distort phase relationships for any given common reference electrode pair. Fein, Raz, Brown, and Merrin (1988) also showed that interhemispheric coherence was inflated when a common reference with a strong signal was used such as Cz. These authors also computed coherence using reconstructed “reference-free” signals using the source derivation method of Hjorth (1975) with ambiguous results. Again, the process of adding together all of the phase differences from all electrodes destroys the physiologically based time differences that were present in the original time series and replaces the original time series with scrambled phase and thus an inability to accurately

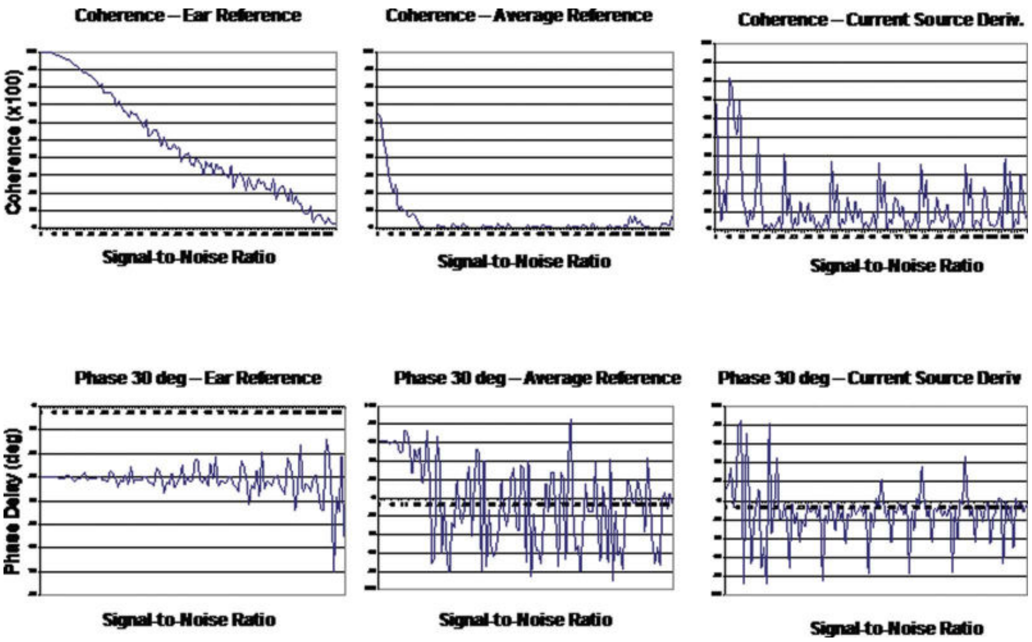

FIGURE 1 Calibration tests of coherence and phase differences using a 1 uV 5 Hz sine wave as a reference and then a 1 uV 30 deg phase shifted test sine wave + 1 uV of Gaussian noise, + 2 uV noise, + 3 uV noise, and so on to create a systematically reduced signal-to-noise ratio test. Top row is coherence, bottom row is phase difference in degrees. Left column is a common reference (one ear), middle column is the average reference, and the right column is the Laplacian. A linear relationship coherence and signal-to-noise ratio and preservation of the 30 degree phase differences shows that the common reference is valid. A scrambled relationship between coherence and signal-to-noise ratio and a loss of the 30 degree phase difference for the average reference and Laplacian demonstrates that these reference methods are physiologically invalid for the calculation coherence and phase differences. (color figure available online)

relate coherence and phase to an underlying neurophysiology. Using the same reference for all subjects and conditions helps minimize the effects of the reference electrode when computing coherence and phase differences.

This problem with the average reference was also pointed out by Nunez (1981) when he stated: “The average reference method of EEG recording requires considerable caution in the interpretation of the resulting record” (p. 194) and that “The phase relationship between two electrodes is also ambiguous” (p. 195). Rappelsberger (1989, p. 66) used EEG simulations to evaluate EEG coherence recorded with a single reference, the average reference and source derivation and concluded that EEG coherence is invalid using either the average reference or source derivation (e.g., “Tremendous distortions of the theoretical assumptions of common average reference recording and by source derivation are found in the coherence maps”). Directed coherence is another important example where distortions of the time series by the average reference or the Laplacian will obliterate and invalidate directed coherence (Kamiński and Blinowska, 1991; Kamiński et al., 1997; Korzeniewska et al., 2003). Another method that is invalidated by the average reference is Joint-Time-Frequency-Analyses like the Hilbert transform used to calculate instantaneous phase shift and phase lock in the time domain (Freeman et al. 2003; 2006; Thatcher, North, & Biver, 2008b; 2009a; Thatcher et al., 2009b).

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 for a period of time (Pikovsky, Rosenblum, & Kurths, 2003). Phase reset is made up of a shift in phase followed by phase stability to a new regime or state that is constant for a period of time. The amount of phase resetting per unit time is depicted by a phase reset curve 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 (Foss & Milton, 2000). The time interval between spike discharge and a post synaptic input can shift phase and firing patterns of neurons and the precise measurement of phase reset in recurrent neural loops has been well studied, see Foss and Milton (2000).

A useful method to measure phase resetting in EEG/ERP studies is to use of the Hilbert transform to compute a time series of instantaneous phase differences and then compute the first derivative of the time series of phase difference on the y-axis and time on the x-axis (Freeman 2002; 2006; Thatcher et al., 2008b; 2009a; 2009b). In the case of spontaneous or ongoing EEG where there is no evoking stimulus then a near zero 1st derivative of phase differences = phase lock while a significant positive or negative 1st derivative of the time series of phase differences represents a phase shift and both phase shift and phase lock = phase reset (Freeman et al., 2003; 2006; Thatcher et al., 2008b; 2009a). Phase reset is related to the onset of phase synchrony or phase locking and the period of near zero 1st derivatives in time is an example of a homeostatic and stable dynamical system (John, 2005; Pikovsky et al., 2003). 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.

Figure 2 illustrates the relationship between coherence, phase differences and 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 2 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 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. The word “instantaneous” refers to the mathematics of Joint-Time-Frequency-Analyses (JTFA) where there is a trade-off between time and frequency however the computation itself is at the resolution of the sample rate and not summed over epochs of time like with the FFT.

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

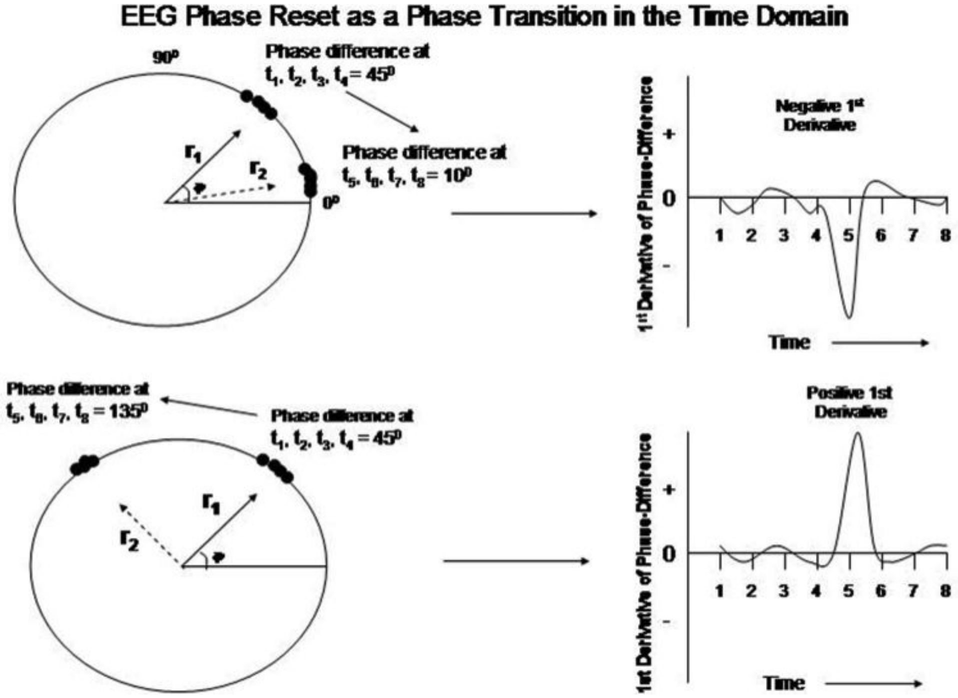

FIGURE 2 Illustrations of phase reset. Left is the unit circle in which there is a clustering of instantaneous phase angles and thus high coherence as measured by the length of the unit vector r. The vector $r1 = 45^0$ occurs first in time and the vector $r2 = 10^0$ and 135^0 occurs later in time. The 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 shift 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 electroencephalogram (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 (from Thatcher et al., 2009a).

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 (Klinshov & Nekorkin, 2008; Pikovsky et al., 2003).

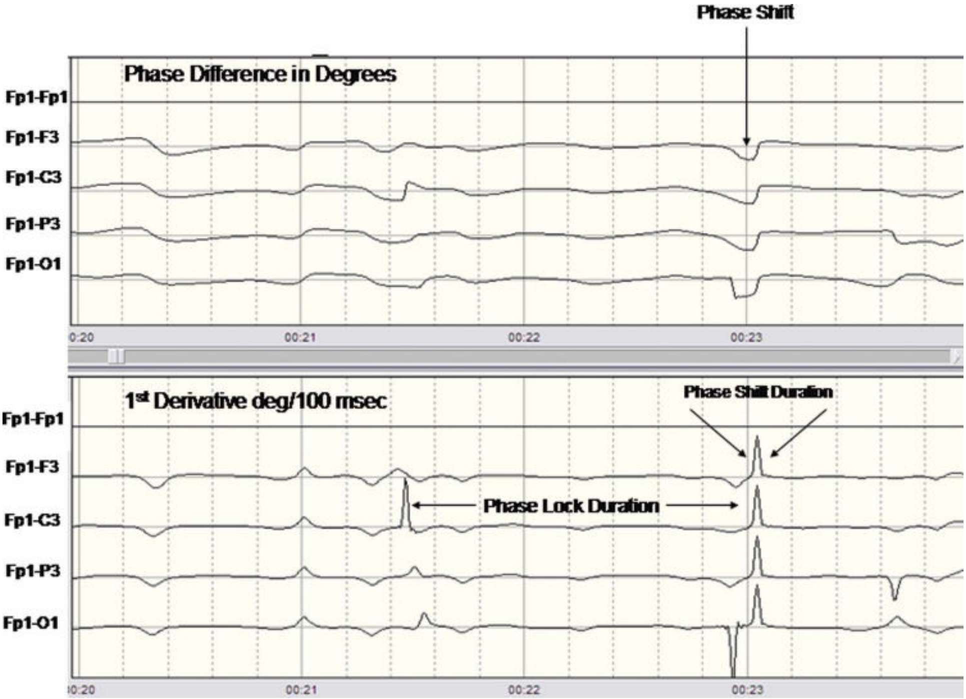

FIGURE 3 Example from one subject. Top are the EEG phase differences between Fp1-F3, Fp1-C3, Fp1-P3, and Fp1-O1 in degrees. Bottom are the 1st derivatives of the phase differences in the top traces in degrees/centiseconds. A 1st derivative $\geq 5^0$ /cs marked the onset of a phase shift and an interval of time following the phase shift where the 1st derivative ≈ 0 defined the phase locking interval as described in Figure 2. (color figure available online)

Figure 3 shows the relationship between the time series of phase differences (top) and the 1st derivative of the phase difference time series (bottom). Phase lock occurs when the 1st derivative of the time series approximates zero and phase shift is represented by a large 1st derivative of the time series of phase differences. The interval of time from the onset and offset of a peak in the 1st derivative of phase differences is defined as phase shift duration. The interval of time from the end of one phase shift and the beginning of a subsequent phase shift is defined as the duration of phase locking. For further details see Thatcher et al. (2008b, 2009a; 2009b).

Patterns of spontaneously occurring synchronous activity involve the creation of temporary differentiated neural assemblies with oscillations and covarying phase at local and large scales (Breakspear and Terry, 2002a; 2002b; Freeman and Rogers, 2002; Rudrauf et al., 2006; Stam & de Bruin, 2004; Thatcher et al., 2008b; Varela, 1995; Varela, Lachaux, Rodriguez, & Martinerie, 2001). The dynamic balance between synchronization and desynchronization is essential for normal brain function and abnormal balance is often associated with pathological conditions such as epilepsy (Chavez, Le Van Quyen, Navarro, Baulac, & Martinerie, 2003; Le Van Quyen, Martinerie, Navarro, & Varela, 2001; Lopes da Silva & Pijn, 1995; Netoff and Schiff, 2002), dementia (Stam et al., 2002a; 2002b) and autism (Thatcher et al., 2009b) and thalamo-cortical dysrhythmias (Llinás, Ribary, Jeanmonod, Kronberg, & Mitra, 1999; Jeanmonod et al., 2001; 2003). Measures of EEG phase reset have been correlated to various frequency bands during cognitive tasks (Kahana, 2006; Kirschfeld, 2005; Tesche & Karhu, 2000), working memory (Damasio, 1989; John, 1968; Rizzuto et al., 2003; Tallon-Baudry, Bertrand, & Fischer, 2001), sensory-motor interactions (Roelfsmema, Engel, Konig, & Singer, 1997; Vaadia et al., 1995), hippocampal long-term potentiation (McCartney, Johnson, Weil, & Givens, 2004), brain development (Thatcher et al., 2008a), intelligence (Thatcher et al., 2008b; Saseung & Klimesch, 2008), and consciousness (Cosmelli et al., 2004; Varela et al., 2001; John, 2002; 2005).

Myself and colleagues (Thatcher et al., 2008b) discovered opposite relations between phase shift duration and phase lock duration and intelligence with a positive correlation between intelligence and phase shift duration and a negative correlation to phase lock duration. A neural synchronization model was developed in which it was hypothesized that long phase shift durations represent an expanded neural recruitment process in which larger populations of neurons are recruited as phase shift duration lengthens. Phase shift duration was modeled by the duration of inhibitory burst activity in thalamo-cortical circuits in which the longer the inhibitory burst then the greater the phase shift duration (Thatcher et al., 2008b). Studies by Ermentrout and Kopell (1994), Ermentrout, Galán, and Urban (2007), and Tiesinga, and Sejnowski (2010) show that short distance couplings produce synchrony while long distance connections produce phase shift via a two step process: 1- arrival of long distance cortico-cortical excitatory synapses on dendrites in layer II-III (approx. 10 msec to 40 msec) often producing anti-phase relations to the local field potentials followed by, 2- local inhibitory feedback bursts of action potentials onto the cell body of cortical pyramidal neurons with a sustained durations of approximately 20 msec to 80 msec. The higher frequency long distance excitatory component that produces long-term potentiation (LTP) in loops is filtered by the extracellular space and requires micro-electrodes to accurately measure. The duration of the phase shift as measured at the scalp surface is approximately 40 msec to 80 msec (Freeman & Rogers, 2002; Freeman et al., 2003; Thatcher et al., 2008b; 2009a; Hughes & Crunelli, 2007). Phase shift is a critical process that initiates reverberation and long-term potentiation in nested loops of neurons with different spatial frequencies. Local synchrony is dependent on inhibitory neuron reaction to pyramidal cell bursting after the arrival of the excitatory long distance action potentials and competing loops that are in-phase and/or anti-phase with respect to the local field potentials (Buzsaki, 2006; Hughes & Crunelli, 2007). Phase shift is the domain of the higher frequencies in the EEG at the approximate 40 Hz to 150 Hz range and higher frequencies (Niedermeyer & Lopes da Silva, 1994). Cross-frequency coupling of theta and alpha to hi-gamma (80–150 Hz) is an example of local and global cross-frequency phase shifts over a wide frequency range in an EEG study (see Voytek et al., 2010).

Phase lock duration is not as well understood as phase shift duration. The studies of Tiesinga and Sejnowski (2010) show that a sustained hyperpolarization is necessary for phase lock, which is consistent with a long history of intracellular recordings that often show a rebound of excitation at the end of a prolonged inhibitory period (Steriade, 2006). Too long of a phase lock period then there is less cognitive flexibility and less neural resource available to be allocated at a given moment of time (Thatcher et al., 2008b). Follow-up studies in Autistic children indicated a deficiency of thalamo-cortical synchronization in which there is a low degree of neural resource recruitment resulting in a reduced number of neurons that are synchronized at each moment of time coupled with a prolonged period of phase locking that results in reduced flexibility and reduced capacity to recruit available neural resources to be phase locked at subsequent moments of time (Thatcher et al., 2009b).

COHERENCE AND VOLUME CONDUCTION

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 inside the volume at each moment of time with slight delays near to the speed of light (Feynmann et al., 1964). Sudden synchronous synaptic potentials on the dendrites of a cortical pyramidal cell result in a change in the amplitude of the local electrical potential referred to as an "Equivalent Dipole." The shape of the electrical potential at the scalp surface is different depending on the solid angle between the source and the electrode. Volume conduction involves near zero phase delays between any two points within the electrical field as collections of dipoles oscillate in time (Nunez, 1981). As mentioned previously, 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, imaginary spectrum, bi-coherence, phase reset, and coherence of long phase delays are so critical in measuring brain connectivity independent of volume conduction (Pascual-Marqui, 2007). When separated generators exhibit a stable phase difference at, for example, 10 degrees then this can not be explained by volume conduction because by definition phase = 0. As will be explained in later sections correlation coefficient methods such as the Pearson product 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 (Nolte, Bai, Wheaton, Mari, Vorbach, & Hallet, 2004; Pascual-Marqui, 2007; Langer et al., 2011).

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 (Eckhorn et al., 1988; Gray, Konig, Engel, & Singer, 1989, John, 2005; Thatcher et al., 1994). The thalamus is the master synchronizer of the EEG and "binding" at zero phase lag can easily be produced by the centrally located thalamus (see Steriade, 1995; 2006). Multiple unit recordings and magnetoelectroencephalography (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 contain "pacemaker" neurons and neural circuits that regularly synchronize widely disparate groups of cortical neurons at different frequencies (Steriade, 2006). 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, and so on. For example, if the phase difference uniformly equals zero in the space between two electrodes without a possible third common source then this is volume conduction. On the other hand if a point intermediate between two sources is not at phase = 0 then this can not be explained by volume conduction. Discrete inverse solutions are especially useful to identify intermediate non-zero phase shifted sources (Scherg, 1992; Thatcher et al., 1994). Distributed source inverse methods such as LORETA also distinguish between intermediate non-zero phase shifted sources, albeit larger volumes than with the discrete inverse solutions (Thatcher, Biver, & North, 2007).

CROSS-FREQUENCY PHASE SYNCHRONY OR m:n PHASE SYNCHRONIZATION

Cross-frequency phase synchrony is also called m:n phase synchronization (Schack, Vath, Petsche, Geissler, & Möller, 2002; Schack, Klimesch, & Sauseng, 2005). Phase synchronization is the process by which two or more cyclic signals tend to oscillate with a repeating sequence of relative phase angles. Cross-frequency phase synchrony occurs when there is a constant integer relationship between two frequencies such that the two cyclic signals share a repeating sequence of phase angles over consecutive cycles. These integer relationships are the so called Arnold Tongues, which follow from bifurcation of the circle map (Pikovsky et al., 2003).

Cross-frequency phase synchrony is mathematically defined by the average 2nd derivative of the instantaneous phase difference between two different frequency bands. Different frequencies, for example 4 Hz versus 7 Hz results in a continuum of changing phase differences and in beat frequencies (frequency mixing). However, when the two frequencies are phase locked and do not change over time (i.e., cross-frequency phase synchrony is contant), then the first derivative of the phase difference between two different frequencies is constant. That is, if two different frequencies are coupled over time then the 1st derivative is constant, although different depending on the difference in phase angle between the two frequencies (e.g., delta/theta or theta/beta or delta/alpha). As illustrated in Figure 4, in order to measure phase synchrony across frequencies it is necessary to compute the 2nd derivative of the phase differences because the 2nd derivative = 0 when the 1st derivative is constant which is the definition of cross-frequency phase locking. That is, a constant first derivative results in a zero 2nd derivative. Therefore, the instantaneous 2nd derivative is a direct measure of cross-frequency phase locking in the time domain. Measures of cross-frequency phase shift duration and cross-frequency phase lock duration are obtained using the same metrics as for phase reset within a frequency band (Thatcher, 2008b; 2009a). Figure 5 shows an example of cross-frequency power correlations in a single subject during wakefulness, drowsiness and sleep and Figure 6 shows an example of cross-frequency phase reset.

The EEG is a mixture of multiple sources of rhythms from infra slow <1 Hz to about 300 Hz that are present in all states of consciousness (Steriade, 2006; Buzsaki, 2006). Cortico-thalamic, septo-hippocampal, and intracortical loops resonate at different natural frequencies and cross-frequency phase locking and phase shift is a mechanism to organize multiple brain regions at the same time. For example, beta frequency bursts that ride on the crests of theta rhythms (Jensen & Lisman, 2005) or delta and beta cross-frequency coupling (Sauseng, Klimesch, Gruber, & Birbaumer, 2008) or theta and alpha cross-frequency coupling (Klimesch et al., 2004; Sauseng et al., 2002). The GABAenergic neurons in the nucleus reticularis control the pacemaker activity responsible for the waking EEG in the frequency range from about 2 to 13 Hz (Buzsaki,

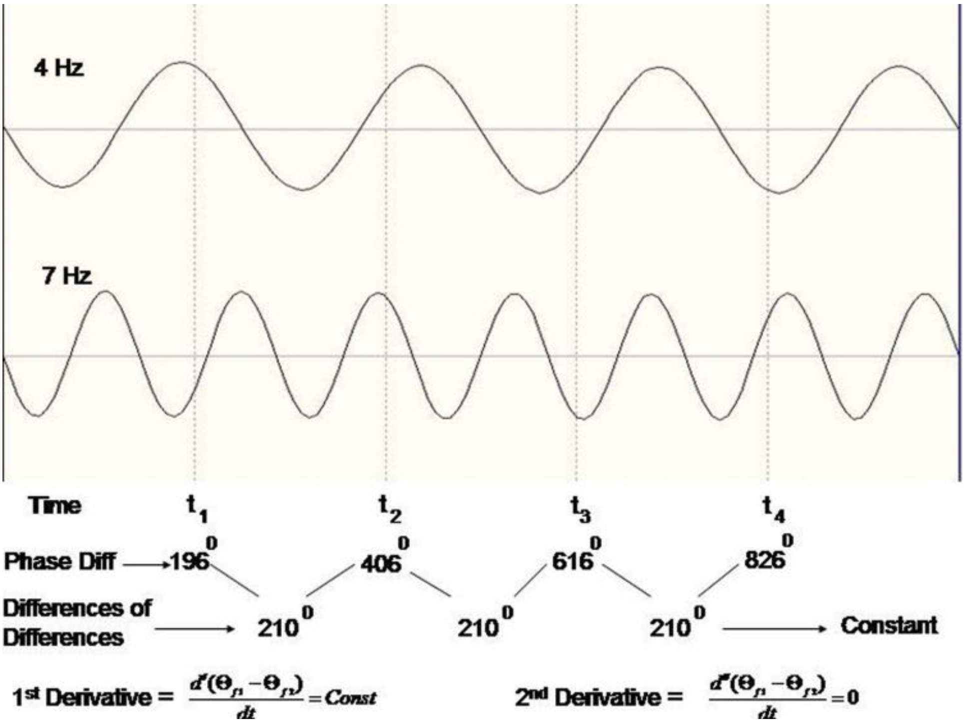

FIGURE 4 Illustrates the constant phase differences as a function of time when two different frequencies are phase locked. Cross-frequency phase locking and cross-frequency phase shift are measured by the 2nd derivative of instantaneous cross-frequency phase differences that = 0 when there is phase locking and is > 0 when there is a cross-frequency phase shift. (color figure available online)

2006; Steriade, 1994; 2006). Thalamic inhibitory burst activity shifts the phase of ongoing oscillations in cortico-thalamic loops and phase locking of reticular-limbic and reticular-frontal loops occurs via a spatial-temporal multiplexing. Phase locking of a multitude of frequencies for brief moments of time, approximately 100 msec to 300 msec is a powerful force that binds the action potential excitability cycles across widespread brain regions while complex sequential task activities are mediated. Buzsaki (2006) characterized the temporal nesting of multiplexed processes by a logrhythmic scale where fine detailed processes are nested within larger scaled processes as a function of 1/f. There is some debate about whether this is “pink” or “brown” noise (Freeman et al., 2006), however, this does not matter since what is important is the fact that relaxation oscillators are the basis functions and they are fit by a common exponential functions that govern the nesting of EEG frequencies from <0.1 to 300 Hz with different exponents. The pervasiveness of the 1/f function in EEG is also important because of its linkage to functional magnetic resonance imaging (fMRI) involving infra-slow rhythms of 10 to 70 sec with all of the EEG frequencies riding on the rising phase of a metabolic cycle (Monto, Palva, Voipio, & Palva, 2008; Raichle, 2010).

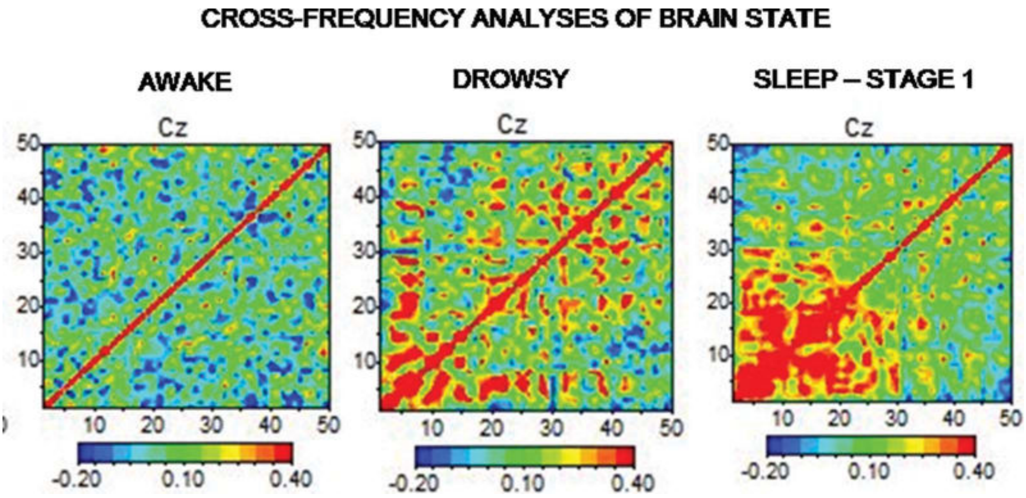

FIGURE 5 Example of Cross-Frequency Power Correlations from Cz referenced to linked ears during wakefulness, drowsiness, and sleep stage I in the same subject. The x-axis and y-axis is frequency from 0 to 50 Hz and the color bar shows the correlation coefficient from –0.2 to 0.4. Note the highly differentiated couplings during wakefulness that increase in magnitude, especially in lower frequencies during the transition from wakefulness to sleep. (color figure available online)

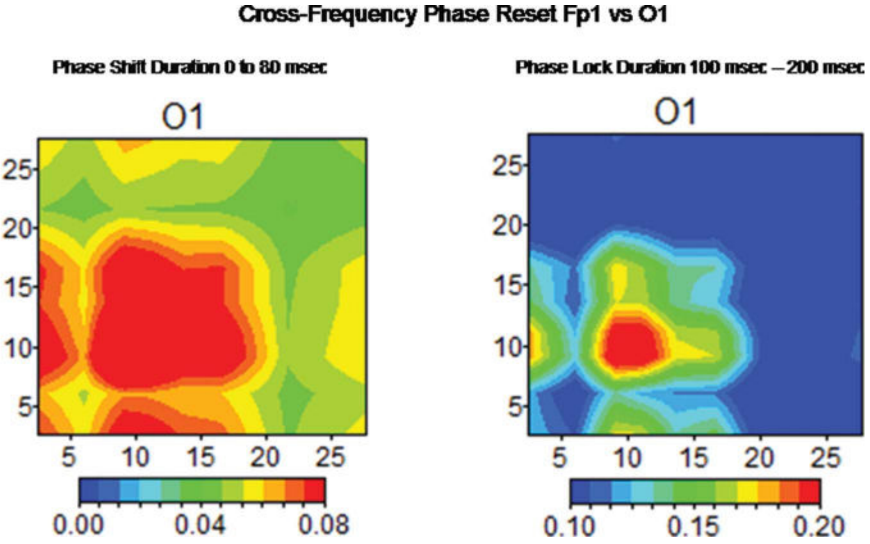

FIGURE 6 Example of Cross-Frequency Phase Reset between Fp1 and O1. Left is Cross-Frequency Phase Shift Duration 0 to 100 msec and right is Cross-Frequency Phase Lock Duration 100 msec to 200 msec. X & Y-axes are frequency from 0 to 30 Hz and color bar is seconds. (color figure available online)

LORETA SPATIAL TEMPORAL CORRELATIONS

A deeper understanding of cortical coupling is possible by studying the coherence and phase relations between 3-dimensional current sources derived from the surface EEG using an inverse method (Thatcher et al., 1994; 2007; Thatcher, North, & Biver, 2011; Thatcher, 1995; Pascual-Marqui, Koukkou, Lehmann, & Kochi, 2001; Hoechstetter et al., 2004). Myself and colleagues (Thatcher et al., 1994) recorded EEG during voluntary finger movement and co-registered the event related potential dipole sources to positron emission tomography (PET) scans obtained when subjects executed a thumb movement. The PET and EEG dipole co-registration of the motor potential was within a few millimeters and provided for the calculation of three dipole time series, similar to what is expected if implanted electrodes had been used. Coherence and phase differences were then computed for the dipole time series and revealed millisecond by millisecond switching networks that underlay voluntary finger movements. Other examples of source correlation, coherence and phase analyses are by Pascual-Marqui et al. (2001) a correlation between LORETA region of interests (ROIs) in schizophrenia patients and Hoechstetter et al. (2004) that used a discrete dipole solution and computed coherence between dipole time series using complex demodulation. Langer et al. (2011) used single LORETA voxels to compute 3-dimensional coherence that is important because averaging of voxels that comprise a Brodmann area or ROI can distort phase differences.

Myself and colleagues recently computed LORETA 3-dimensional source correlations during resting eyes closed conditions for 33 regions of interest within each hemisphere (Thatcher et al., 2005). Figure 7 is a typical contour map with frequency from 1 to 40 Hz on the x-axis and distance from a reference ROI on the y-axis with the magnitude of correlation represented on a color scale. The contour maps revealed regular spaced horizontal lines of increased and decreased coupling that had spacings that corresponded to the “U”-shaped cortico-cortical connection of the cerebral white matter. Vertical bands of high or low correlation at specific frequencies were also present and were unique to each ROI. The alpha frequency band was often prominent in occipital and parietal ROIs and less prominent in temporal and frontal ROIs. The frontal and temporal ROIs often showed maximal correlations at higher frequencies (e.g., 30–40 Hz), but each ROI showed maximal correlations at specific frequencies with single or a particular group of ROIs. These findings are similar to those reported by Shen, Nadkarni, and Zappulla (1999) using coherence of EEG recorded from subdural electrodes in which specific locations in the electrode grid exhibited high coherence to another location but at a specific frequency. In fact, the authors reported that each subdural electrode exhibited a unique spatial–frequency relationship to all other locations in the grid of electrodes; they presented a type of multiplexing model in which each domain of neurons communicated with all other domains but at specific frequencies. The findings by myself and colleques using LORETA source correlations are consistent with the Shen et al. (1999) “spatial-spectral signature of cortical synchrony” model of cortico-cortical coupling. According to this model, each ROI is connected to all other ROIs and a given region communicates with other regions at specific cross-frequency couplings. This same approach was recently used to replicate the anatomical connectivity of Hagmann et al.’s (2008) Diffusion Tensor Imaging “Modules” using LORETA source correlations (Thatcher et al., 2010).

This is another example of cross-frequency phase synchrony but in this case the phase synchrony is between 3-dimensional regions of interest. Multiplexing and coordination of

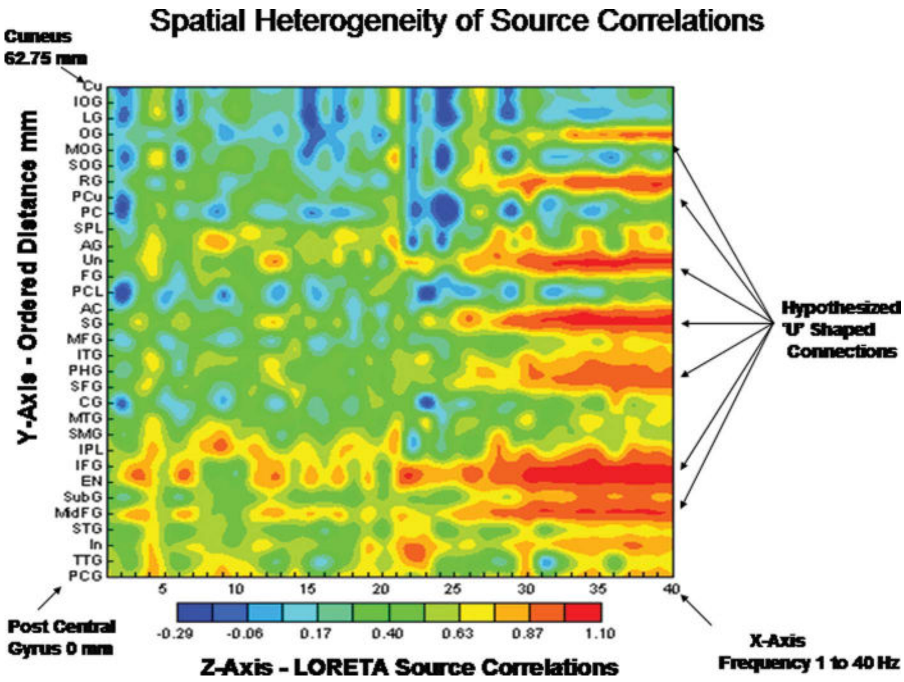

FIGURE 7 From Thatcher et al. (2007) and an exemplar of one of the subjects in this study demonstrating spatial heterogeneity of LORETA source correlations that cannot be explained by volume conduction. All subjects in this study exhibited similar spatially heterogeneous LORETA source correlations (see Thatcher et al., 2007 for further details). The two-dimensional contour map of the LORETA source correlations are ordered as a function of distance from a reference Brodmann area. The regions of interest (ROIs) are ordered from the left post central gyrus (Brodmann area 1) to the left cuneus (Brodmann area 17 that is 62.75 mm distant). The x-axis is frequency (1 to 40 Hz), the y-axis are ROIs and the ROIs are ordered as a function of distance from the post-central gyrus. The z-axis is the magnitude of the LORETA source correlation as represented by the color bar of the contour map. PCA = Posterior Pentral gyrus, TTG = Transverse Temporal gyrus, In = Insula, STG = Superior Temporal gyrus, MdFG = Middle Frontal gyrus, Sub G = Sub Gyral region, EN = Extra-Nuclear frontal gyrus, IFG = Inferior Frontal gyrus, IPL = Inferior Parietal lobule, SMG = Supramaginal gyrus, MTG = Middle Temporal gyrus, CG = Cingulate gyrus, SFG = Superior Frontal gyrus, PHG = Parahippocampal gyrus, ITG = Inferior Temporal gyrus, MFG = Medial Frontal gyrus, SG = Subcallosal gyrus, AC = Anterior Cingulate, PCL = Paracentral lobule, FG = Fusiform gyrus, UN = Uncus, AG = Angular gyrus, PC = Posterior Cingulate, PCu = Precuneus, RG = Rectal gyrus, SOG = Superior Occipital gyrus, MOG = Middle Occipital gyus, OG = Orbital gyrus, LG = Lingual gyrus, IOG = Inferior Occipital gyrus, Cu = Cuneus. (color figure available online)

cortical modules appears to be a basic brain mechanism and provides flexibility to temporally bind spatially widespread brain regions at different frequencies (Buzsaki, 2006; Steriade, 2006).

The REST method of referencing of the EEG utilizes scalp potentials to estimate equivalent 3D sources that do not depend on a scalp or average reference and mathematically provides a reference as a point at infinity. Recordings and simulation studies by Yao and colleques (Yao, 2001; Qin et al., 2010) show that the REST method is accurate and valid. However, no studies of phase shift or phase lock or n:m cross-frequency synchrony have been conducted to date to determine the effects of a point at infinity reference on these measures.

DISCUSSION

The choice of reference in the computation of EEG coherence is important in quantitative EEG. Any signal contained in a single reference will be shared by all of the scalp EEG electrodes and depends on the location of the reference also called a “common reference.” Coherence is a measure of phase consistency or phase stability over time but coherence can be globally inflated when a large signal is present in the reference such as a Cz reference (Fein et al., 1988). However, inflation of coherence is not a serious problem as long as the same common reference is used for all subjects and for all groups and conditions (Zaveri et al., 2000; Andino et al., 1990). The differences in coherence are of equal importance to absolute values of coherence, just as they are with a correlation coefficient.

It is easy to understand why coherence is neurophysiologically invalid when using an average reference from a low density array or a Laplacian since the summation of signals from all channels is “subtracted” or “added” to the electrical potentials recorded at each electrode. In the present article Figure 1 shows the results of a validation test using sine wave signals mixed with noise where the common reference behaves as expected and linearly decreases as a function of declining signal-to-noise ratio. In contract, the low density average reference and Laplacian fail to past this simple validation test. High-density recordings better approximate the point of zero potential but nonetheless are not perfect (Desmedt et al., 1990; Dien, 1998). The REST method of using a point at infinity for a reference by Yao and colleagues (Yao, 2001; Qin et al., 2010) has yet to be fully explored and tested but has promise to help reduce or eliminate reference problems.

Coherence is fundamentally a statistical measure of phase stability and varies from 0 to 1, like a squared correlation coefficient. In contrast, instantaneous time domain measures of the duration of phase lock and phase shift provide a direct linkage to underlying neurophysiological processes such as the average duration of IPSPs and EPSPs. Phase reset is made up of the two elemental components of phase lock and phase shift and is less prone to artifact and to problems with volume conduction. The nucleus reticularis contains powerful GABA energic inhibitory neurons and pacemaker neurons which control the frequency and phase of cortico-thalamic loops and is responsible for phase shift and phase lock durations in the EEG (Buzsaki, 2006; Thatcher et al., 2008b; 2009a; 2009b). Phase lock duration is positively correlated with coherence and provides a more fundamental measure of network dynamics than does coherence. Phase shift duration is correlated with cognitive function and appears to be related to recruitment of neural resources, the longer the phase shift duration then the larger the number of recruited neurons that are then phase locked to temporally mediate a give set of functions (Thatcher et al., 2008b).

Cross-frequency phase lock and cross-frequency phase shift are also important and reflect basic neurophysiological processes related to a wide range of cognitive functions and clinical disorders. Recent studies indicate that cortico-thalamic and septo-hippocampal loop systems are cross-frequency phase locked as part of a dynamic of information processing. The nucleus reticularis and zona incerta as well as intracortical inhibitory neurons are the likely candidates that control the duration of cross-frequency phase shift and phase lock and act as master synchronizers of cortical resources.

Finally, 3-dimensional source coherence and phase reset provides a powerful measure of intra-cortical synchronization and coordination of large modules in the brain (Hagmann et al., 2008). Source correlations and source coherence are less prone to volume conduction and reveal a dynamic spatio-temporal multiplexing of cortical modules that are dependent on short and long distance connections (Thatcher et al., 1994; 2005; 2010; 2011; Hoechstetter et al, 2004; Langer et al., 2011).

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