Real-Time Z Scores:
TECHNICAL AND CONCEPTUAL FOUNDATIONS

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1.0 - Design of the Instantaneous Z Score Normative Database

The central concept is the use of real-time Z scores to help guide or "re-tune" the EEG resonant frequencies and network patterns toward improved regulation of complex neural network systems using standard EEG biofeedback methods. That is, the goal is to not reinforce extreme instantaneous Z scores representing brief moments of 'chaos' or dysregulation. Instead reinforce periods of stability by reinforcing instantaneous Z scores that are moving in the direction of the center of a normal population or Z = 0. This is a general mathematical process only if the EEG is transformed to approximate a Gaussian distribution and the measures are from the same universe of measures. For example, Z scores are invalid if an apple is used as the standard for an orange even if they are both Gaussian.

The majority of cortical pyramidal neurons resonate at specific center frequencies depending on the membrane potential and ionic conductances and behave like "band pass" filters that gate action potentials. The pyramidal neuron resonances wax and wane and exhibit rhythmic bursts and periods of asynchrony in a non-Gaussian distribution as a function of time. It is necessary to mathematically transform EEG digital data to approximate a Gaussian in shape and then the EEG normative database can be cross-validated and estimates of error can be made. Z score biofeedback using the target of reinforcing toward of Z = 0 with respect to the center of an age matched group of healthy individuals is designed to reinforce increased information processing in networks of the brain. The real-time EEG Z score was conceived in 1994 and created in 2002 and started with the University of Maryland normative database of "normal" subjects (N = 625). An additional group of clinically healthy adult subjects (22 to 55) were added to the normative database using the Deymed amplifier. Standard equilibration of the amplifier frequency and gain characteristics was used to exactly match the Deymed amplifier to the University of Maryland amplifiers. The normative database includes clinical selection criteria, age range (2 months to 82 years), cross-validation tests, demographics, and other details of the Z score normative database have been published and are recommended reading for those interested in deeper details than is briefly reviewed in this document (see Thatcher, 1998a; 1998b; 2001; 200; Thatcher and Lubar, 2008).

The real-time Z score biofeedback method is called "Z Tunes" (ZT) in recognition of the neurophysiological linkage to resonant cortical pyramidal neurons

that operate by reinforcing a negative slope of outliers over a 10 second history in order to reinforce instantaneous brain states exhibiting increased stability in the direction of Z = 0.

Four Basic Concepts used in the Design of Real-Time Z Scores

1.1- Use of Gaussian Probabilities to Identify "De-Regulation" in the Brain

The central idea of the instantaneous Z score is the application of the mathematical Gaussian curve or 'Bell Shaped' curve by which probabilities can be estimated using the auto and cross-spectrum of the electroencephalogram (EEG) in order to identify brain regions that are de-regulated and depart from expected values. Linkage of symptoms and complaints to functional localization in the brain is best achieved by the use of a minimum of 19 channel EEG evaluation so that current source density and LORETA source localization can be computed. Once the linkage is made, then an individualized Z score protocol can be devised. However, in order to make a linkage to symptoms an accurate statistical inference must be made using the Gaussian distribution. The Gaussian distribution is a fundamental distribution that is used throughout science, for example, the Schrodinger wave equation in Quantum mechanics uses the Gaussian distribution as basis functions (Robinett, 1997). The application of the EEG to the concept of the Gaussian distribution requires the use of standard mathematical transforms by which all statistical distributions can be transformed to a Gaussian distribution (Box and Cox, 1964). In the case of the EEG, transforms such as the square root, cube root; $\log_{10}$, Box-Cox, etc. are applied to the power spectrum of the digital time series in order to approximate a normal distribution (Gasser, et al, 1988a; 1988b; John et al, 1987; 1988, Duffy et al, 1994; Thatcher et al, 2003; 2005a; 2005b). The choice of the exact transform depends on the accuracy of the approximate match to a Gaussian distribution. The fact that accuracies of 95% to 99% match to a Gaussian are commonly published in the EEG literature encouraged Thatcher and colleaques to develop and test the Z score biofeedback program in the first place.

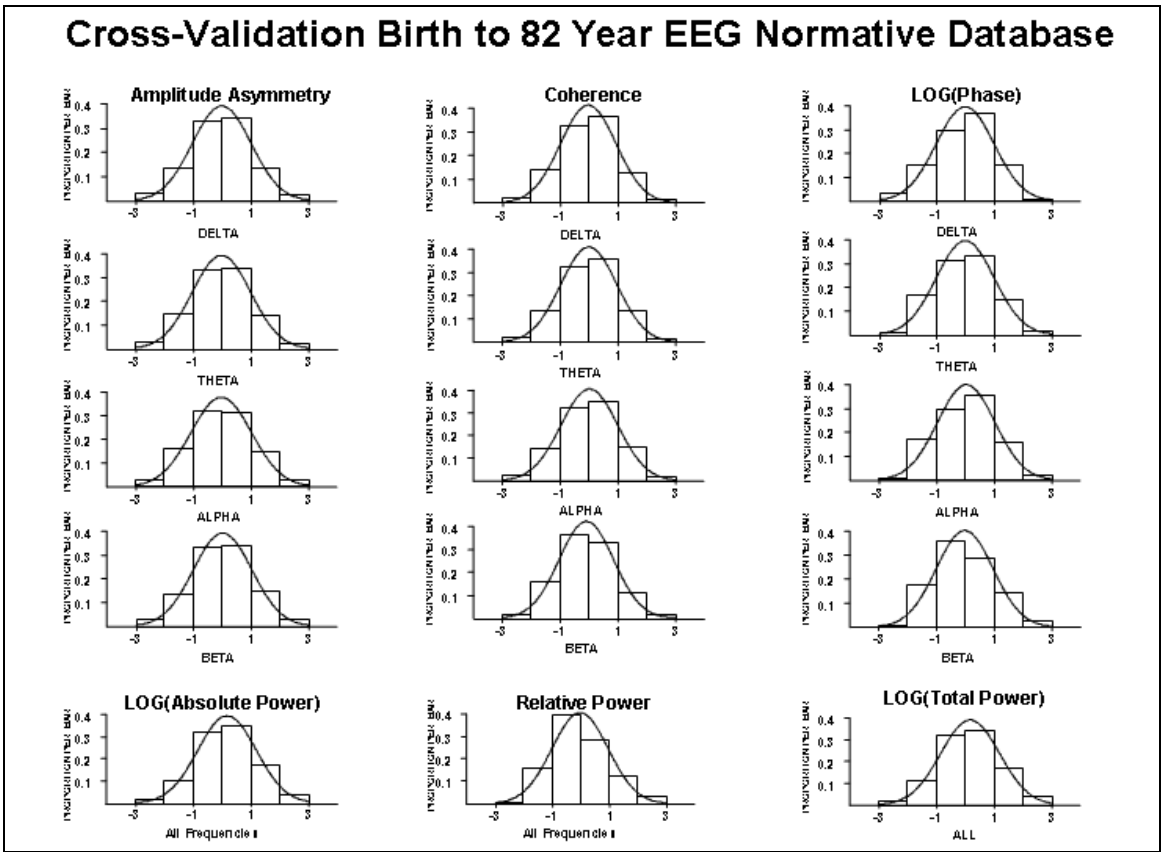

Fig. 1 – Example of Gaussian distributions of the Neuroguide "static" normative database. The distribution is subjects over age. From Thatcher et al, 2003.

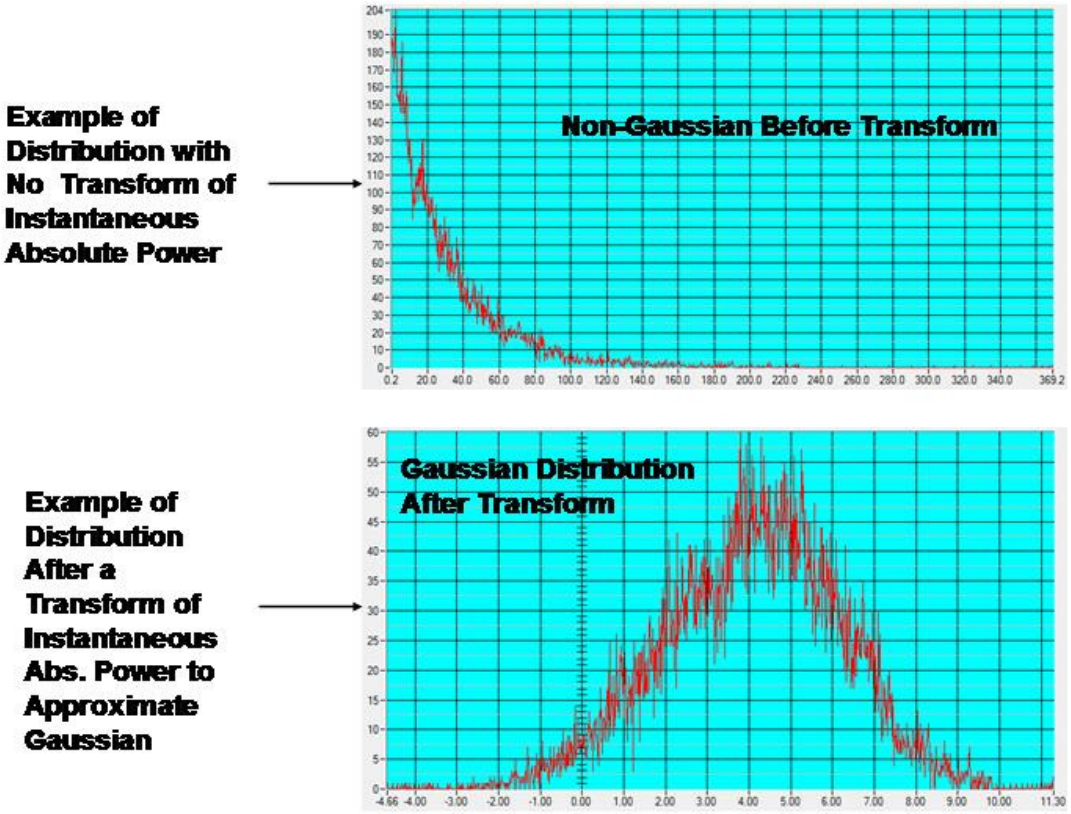

Fig. 2- Example of the distribution of instantaneous absolute values before and after a transform is applied to approximate Gaussian. If no transform is used then the instantaneous Z scores are totally invalid and should not be used.

1.2 – Sampling from the same population of measures of the human brain

The second design concept is the application of the Gaussian distribution to averaged "instantaneous" time domain spectral measures from groups of normal subjects and then to cross-validate the means and standard deviations for each subject for each instant of time with respect to the measurement (Thatcher, 1998a; 1998b, 2000a; 2000b). The cross-validation is directly related to the mean and variance of the distribution from which the same samples are obtained (Thatcher et al, 2003; 2005a; 2005b). This includes the physiological basis for the measures which must be the same because spatial and temporal localization validation is sufficient to prove validity. However, in order to achieve a representative sample of Z scores then the variables must be drawn from the same physiological population and be in agreement with respect to frequency and location. Over the last twenty five years, the NYU and ANI normative databases have been repeatedly and independently cross-validated and are used world wide in many institutions and serve as a historical reference in the history of qEEG normative databases (see Thatcher and Lubar, 2008 and brainmaster independent comparisons at: http://www.brainm.com/kb/entry/525/)

). Because of the 25 year history of high cross-validation the NYU and ANI databases in the "static" FFT domain then when used in the instantaneous domain they must also cross-validate between ANI and NYU. Testing the foundations and examining the statistics is a crucial part of this process and full disclosure of equations and procedures allows for independent replication and validation in the future. The good news is that a recent implementation of the NYU norms in the time domain matches the ANI time domain norms by a linear factor and appears to provide acceptable cross-validation (8% error) (http://www.brainm.com/kb/entry/525/).

In the case of the Fast Fourier Transform (FFT) there is a single spectral value for each subject and power at each frequency is computed over a one to several minute period and, therefore, there is only between subject variance in "static" qEEG normative databases that use non-instantaneous analyses such as the FFT "static" norms, i.e., the average of subjects over an age range. Instantaneous or JTFA raw digital values differ from the FFT by being measures of the "instantaneous" state of the brain as defined by the center frequency and band width of the JTFA time/frequency transform. In contrast, the FFT estimates the average spectral value over a period of time (e.g., 1 to 2 minutes) to produce a single value that is then added across subjects in a given age range. The sample size is usually around 30 to 70 subjects in an age group and not tens of thousands of instantaneous JTFA values with variance as a function of age.

The FFT and JTFA measure the same physiological processes in a statistically different manner and these two methods are essentially identical to each other when using large sample sizes and no FFT windowing. Nonetheless, an important difference is that the average spectral values produced by a FFT involve different mathematical procedures and require windowing. Therefore, the means are slightly different. Also, the variance is larger with the instantaneous JTFA than the distribution over age as with the FFT. For example, the FFT is calculated over an entire epoch of time (e.g., 1 or 2 seconds, etc) and must use windowing to prevent discontinuities in the computation and is noisy with low degrees of freedom. In contrast, JTFA methods compute spectral values at each instant of time, do not involve windowing, have higher degrees of freedom and a different non-Gaussain distribution than the FFT average over an age range.

Figure 3 is an example of the large and dramatic differences between the FFT and the Instantaneous spectrum over a two second period of time. The mismatch occurs in all frequencies. Also, the FFT requires windowing in order to eliminate discontinuities at the boundary of the epoch which produces ringing and false frequencies. Figure 3 top is the FFT computed over the 1st two seconds of the Neuroguide demo. Note the low degrees of freedom and noisy nature of the FFT. Figure 3 bottom is the JTFA over the same 2 second epoch of time and demonstrates a different measure set. Nonetheless, if one sums over the entire epoch then the statistical degrees of freedom between the FFT and JTFA more closely match and both methods produce approximately the same, but not identical values due to the FFT windowing.

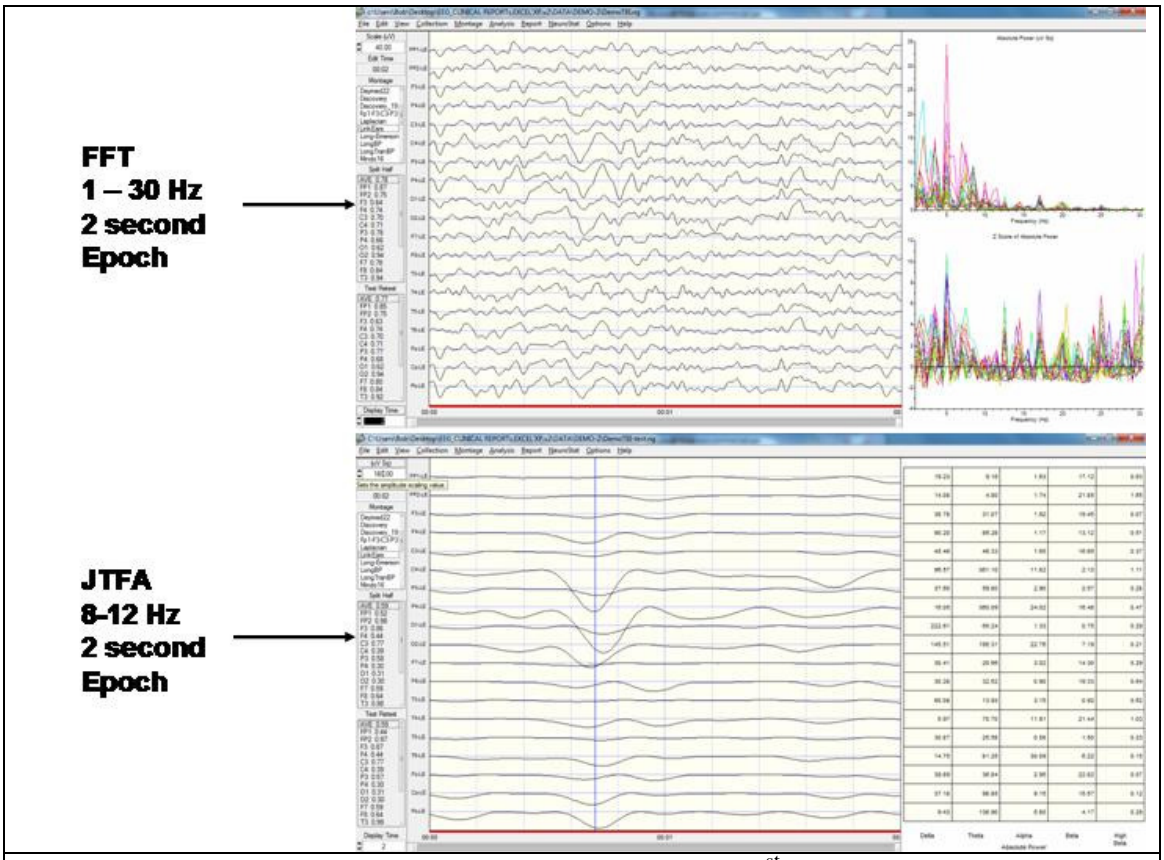

Fig. 3- Top is the FFT absolute power spectrum over the 1st 2 seconds of EEG and the bottom is the JTFA absolute power spectrum in the theta frequency band (4 - 8 Hz) over the same 2 seconds of EEG data. This figure shows the dramatic difference between the FFT and the JTFA at low degrees of freedom. The FFT requires windowing whereas the JTFA does not require windowing which results in slight differences in the total power measurements. Nonetheless, at high degrees of freedom then the JTFA and FFT converge to very similar values, but not identical values. The use of the FFT mean to calculate instantaneous Z scores is not optimal and presents scaling problems because of different mean values. The simple computation is JTFA means to calculate JTFA Z scores and FFT means to calculate FFT Z scores. As shown in figures 4 & 5, there are slight differences between the FFT and JTFA when testing with mathematically ideal sine waves.

Here is an exercise to compare FFT vs JTFA values using calibration sine waves with the NeuroGuide signal generator program.

1- Click File > Open > Signal Generator
2- Double click 10 Hz and type 10 to produce a 10 uV peak-to-peak sine wave
3- Click OK and in Neuroguide click Edit > Select All
4- Click View > Dynamic JTFA and select abs, power, average abs. power and click Apply

5- Note that the alpha band shows 49.98 which is also produced mathematically by squaring 7.07 RMS – This is the JTFA spectral test
6- For the FFT, deselect the JTFA and click > Report Selections
7- Select Spectral Values > Absolute Power and Raw Scores & OK
8- Click Report > Report Generate and note that

Figure 4 is a diagram to illustrate the relationship between the mean of a FFT based normative database versus the mean of an "instantaneous" or Joint Time Frequency Analysis (JTFA) database.

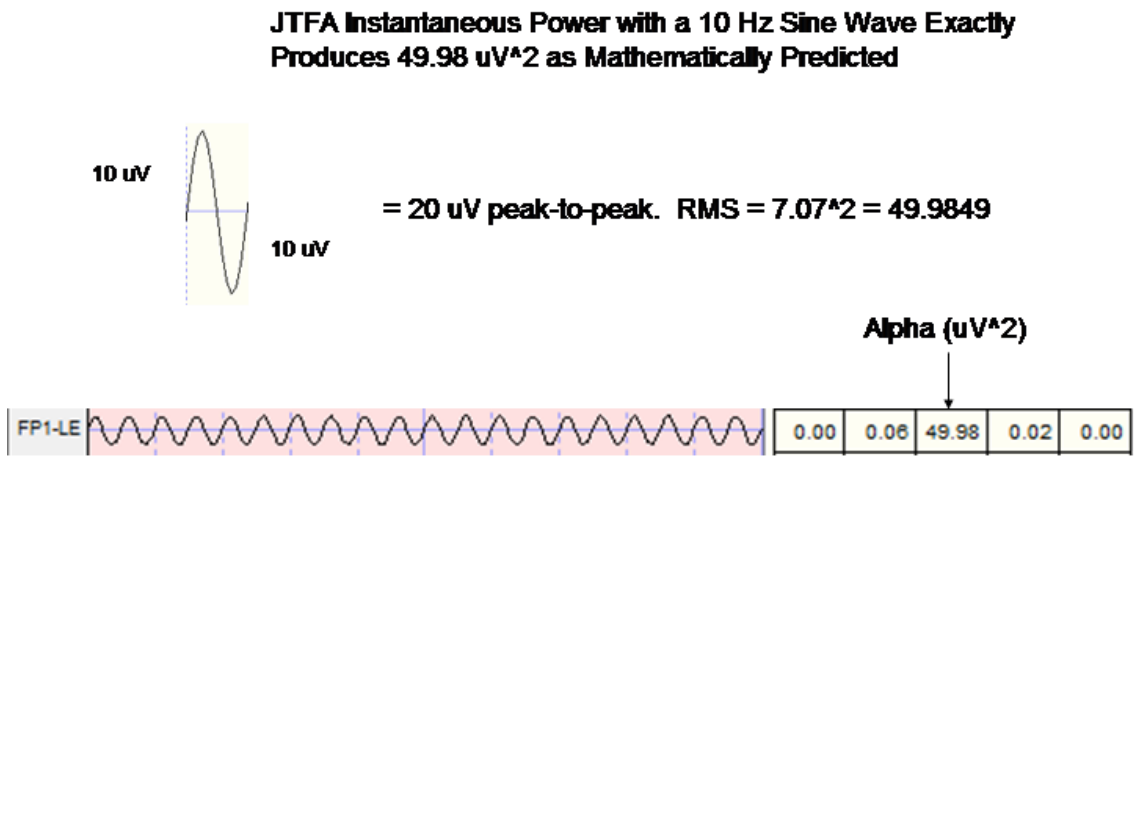

Fig. 4 – Top illustrates a 10 Hz & 10 uV sine wave. The expected power is the RMS value of the sine wave which = 7.07 ^ 2 = 49.9849 uV^2. The middle trace is a 10 Hz, 10 uV sine wave produced by the Neuroguide signal generator. Click View > JTFA > Absolute Power and select average of Absolute Values which produces 49.98 uV^2 which is exactly as mathematically predicted

This is good news because it shows a convergence or cross-validation of the same exact underlying EEG linearly scaled differently. However, this is not trivial in the statistics of sampling theory where one samples from two populations that have highly correlated and linearly scaled for each frequency. If a scaling factor is used to equate the JTFA and FFT absolute values then it is important to describe the procedure and method of linear scaling. If no FFT windowing is used then this too should be

stated. Without windowing then discontinuities at the beginning and end of the epoch will produce ringing and false frequencies. Neuroguide uses a cosine taper to window the FFT. A simpler approach is to use the instantaneous means and standard deviations from the outset and then there is no question that in fact apples are compared to apples and oranges are compared to oranges. The between subject variance using instantaneous means and standard deviations to calculate instantaneous Z scores is valid although with significantly lower degrees of freedom. ANI is currently comparing the instantaneous Z scores computed with and without within session variance and if the values are stable and valid than this method may be implemented so that the absolute value of Z scores more closely matches the static FFT Z scoresThis will result in larger Z scores that are closer to the mean of the FFT norms without relying on "static" age regressed means. The use of the instantaneous means is not more computationally taxing and it avoids the need to use FFT means and standard deviations from age regression norms.

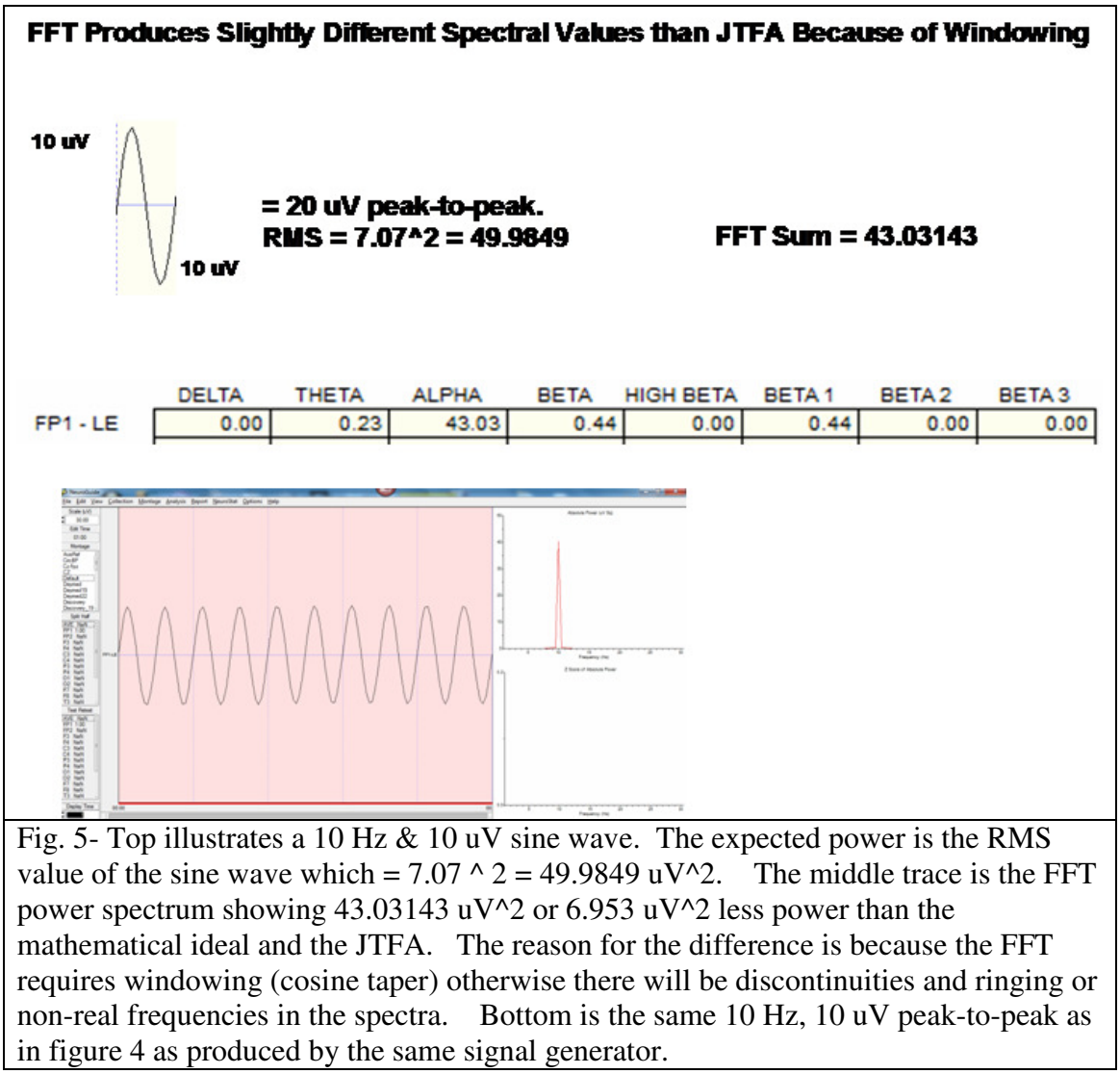

Fig. 5- Top illustrates a 10 Hz & 10 uV sine wave. The expected power is the RMS value of the sine wave which = 7.07 ^ 2 = 49.9849 uV^2. The middle trace is the FFT power spectrum showing 43.03143 uV^2 or 6.953 uV^2 less power than the mathematical ideal and the JTFA. The reason for the difference is because the FFT requires windowing (cosine taper) otherwise there will be discontinuities and ringing or non-real frequencies in the spectra. Bottom is the same 10 Hz, 10 uV peak-to-peak as in figure 4 as produced by the same signal generator.

1.4 – Simplification and Standardization

The third design concept is simplification and standardization of EEG biofeedback by the application of basic science. Simplification is achieved by the use of a single metric, namely, the metric of the "Z Score" for widely diverse measures such as power, coherence and phase delays. Standardization is also achieved by EEG amplifier matching of the frequency response of the normative database amplifiers to the frequency characteristics of the EEG amplifiers used to acquire a comparison subject's EEG time series.

2.0- sLORETA and LORETA Z Scores and the Cross-Spectrum

The computation of instantaneous Z scores for sLORETA and LORETA is different than for the surface EEG. This is because LORETA produces three orthogonal 3-dimensional current vectors from each voxel. That is, there are three time series in the x, y & z directions. The resultant vector is the square root of the sum of squares. A problem with the resultant vector is that the square of x, y & z rectifies the EEG current source time series or produces only positive values which doubles the frequency of the time series. In order to avoid frequency doubling ANI computes the mean time series or $(\sum x + y + z)/3$ = mean current source in each voxel. ANI also computes the x, y & Z mean and standard deviation and compared the average of the means to the average of the x, y & z vectors and found that they are essentially the same. Transforms were then applied to the average current source instantaneous time series in order to obtain Gaussian mean and standard deviation current sources from each voxel.

The mathematical details of using or not using complex numbers must be described and the methods of computation at each step. The case of the Neuroguide instantaneous norms the cross-spectrum is calculated in the x, y & z directions. The Z scores are computed from the mean of the x, y & z real and imaginary components and the resultant vector is not used in the calculation of coherence and phase differences. The 1^{st} and 2^{nd} derivatives of the phase difference time series is used to compute phase shift and phase lock duration with the same mathematics and methods as described by (Thatcher et al, 2008; 2009). The resultant vector is useful for co-modulation or covariant magnitudes between Brodmann areas computed by a correlation coefficient.

2.1 – Network Nodes and Connections

The 3D spatial Laplacian operator maximally smoothes the current source space in alignment with the physiological constraint of simultaneously active neurons that generate a spatially smeared distribution of current densities (see Pascual-Marqui, 1999). This means that adjacent voxels will be positively correlated and decrease smoothly with distance and as a consequence the center voxel of any given functional node will be representative of that node. For example, the correlation between the center voxel of a Brodmannn area and an adjacent voxel is about 0.99 and the correlation at the boundary or edge voxel is about 0.85 which is the case for all center voxels. Also, computing 6,230 combinatorial is a matrix of 19 million by 19 million in the complex domain which is not feasible to compute in real-time. As a consequence an accepted method of computing sLORETA coherence and phase of the EEG sources

is by using the center voxel of each functional region of interest or Brodmann area or node of an inter-connected network (Langer et al, 2011). The cross-spectrum is then calculated for all combinations of 88 Brodmann areas (N = 3,828) for each frequency band which is handled easily with today's computers in real-time.

3.0 – Z Tunes for Individualized EEG Biofeedback Protocols

A fourth and intertwined clinical concept in the design of Z score biofeedback is "individualized" EEG biofeedback and non-protocol driven EEG biofeedback. The idea of linking patient symptoms and complaints to functional localization in the brain and resonant frequencies of the EEG as evidenced by "de-regulation" of neural populations is fundamental to individualized biofeedback. For example, de-regulation is recognized by significantly elevated or reduced power or network measures such as coherence and phase within regions of the brain that sub-serve particular functions that can be linked to the patient's symptoms and complaints. The use of Z scores for biofeedback is designed to "re-regulate" or "optimize" the homeostasis, neural excitability and network connectivity in particular regions of the brain. The functional localization and linkage to symptoms is based on modern knowledge of brain function as measured by fMRI, PET, penetrating head wounds, strokes and other neurological evidence acquired over the last two centuries (see Heilman and Valenstein, 1993; Braxis et al, 2007 see the Human Brain Mapping database of functional localization at: http://hendrix.imm.dtu.dk/services/jerne/brede/index_ext_roots.html). Thus, the false concern that Z score biofeedback will make exceptional people dull and an average individual a genius is misplaced. The concept is to reinforce stability and not periods of "chaos" in networks linked symptoms and complaints and then monitor improvement or symptom reduction during the course of treatment using a single metric for all measures, i.e., the Z score. For peak performance applications, a careful inventory of the client's personality style, self assessment of weaknesses and strengths and identification of the client's specific areas that he/she wishes to improve must be obtained before application of Z score biofeedback. Then, the practitioner attempts to link the client's identification of areas of weakness that he/she wants improved to functional localization as expressed by "de-regulation" of deviant neural activity that may be subject to change.

As mentioned previously, the instantaneous Z scores are much smaller than the FFT Z scores in NeuroGuide™ which uses the same subjects for the normative database. Smaller Z scores when using the instantaneous Z scores is expected because of the necessary inclusion of the moment-to-moment within session variance. One should not be surprised by a 50% reduction in JTFA Z scores in comparison to FFT Z scores and this is why it is best to first use 19 channel EEG measures and the highly stable FFT Z scores to link symptoms to functional localization in the brain to the extent possible. Then use the Z Score program inside of NeuroGuide™ to evaluate the patient's instantaneous Z scores in preparation before the biofeedback procedure begins. This will allow one to obtain a unique picture of the EEG instantaneous Z scores of each unique patient prior to beginning Z score biofeedback. The clinician must be trained to select which Z scores best match the patient's symptoms and complaints. A general rule is choice of Z scores to use for biofeedback depends on two factors obtained using a full 19 channel EEG analysis: 1- scalp location(s) and, 2-

magnitude of the Z scores. De-regulation by hyperpolarization produces slowing in the EEG and de-regulation due to reduced inhibition produces deviations at higher frequencies. The direction of the Z score is much less important than the location(s) of the deviant Z scores and the linkage to the patient's symptoms and complaints.

Here is a step by step description of how to review your patient's EEG prior to designing a Z score biofeedback protocol. The Z score biofeedback program inside of NeuroGuide™ is the same program as used by Advanced Brain Monitoring, BrainMaster, Thought Technology, EEG Spectrum, Neurofeld Q20, Mind Media BV (NeXus) and Deymed.

3.1 – Step-by-Step Instantaneous Z Score Tutorial inside of NeuroGuide™

Before beginning the step by step tutorial, please download the free NeuroGuide Demo at http://www.appliedneuroscience.com/Contact%20Download1.htm. Install and launch NeuroGuide, accept the copyright agreement and then click Demo. If one is a current user of NeuroGuide™ then rename the file c:/program files/NeuroGuide/passKeyB to oldpassKeyB and then launch NeuroGuide and click Demo.

Step 1- Click File Open > Lexicor > Lexicor NRS24. This is the EEG from a 55 yr. old male who was struck by a bat near to his right parietal bone and suffered a slow bleeding epidural hematoma. The day following the incident the patient was found on the floor and unresponsive and the CT scan showed blood had pocketed in the occipital region and drainage of the blood in the occipital region was ordered. Two years post incident the patient has spatial neglect, is in a wheel chair due to paralysis of his left side and has denial of the extent of his disorder and problems recognizing emotions in others. We expect to find P4 to be deviant from normal based on clinical symptoms.

Step 2- In the Subject Information window, for age type 55 and select the eyes closed condition and click ok.

Step 3- Double click Linked Ears in the Montage list on the left side of the screen.

Step 4- Edit > Select All and then Click View > Dynamic FFT > Absolute Power and position the mouse over the Z score of Absolute Power panel and depress the left mouse button and move the mouse to 5.5 Hz and view the elevated Z scores in C4 and P4. Select all is not a recommended option in NeuroGuide™ because it contains artifact and is only used here for illustration purposes.

Step 5- Click View > Dynamic JTFA > Absolute Power

Step 6- Click View > Dynamic JTFA > Z Scores

Step 7- Click View > Dynamic JTFA > Color Maps

Step 8 – Depress the left mouse button and drag the mouse over the EEG tracings and view the dynamic Z scores in the delta, theta, alpha, beta and hi-beta frequency bands. Depress the left mouse button and move the mouse to the right border and automatically advance the instantaneous Z scores like a movie.

Step 9- Change the display time to 1 second (located in the lower left corner) and review your patient's instantaneous Z scores for all 19 locations like a temporal zoom lenz.

Figure 6 is an example of the instantaneous Z score screen inside of NeuroGuide™ while the instantaneous Z scores are being reviewed.

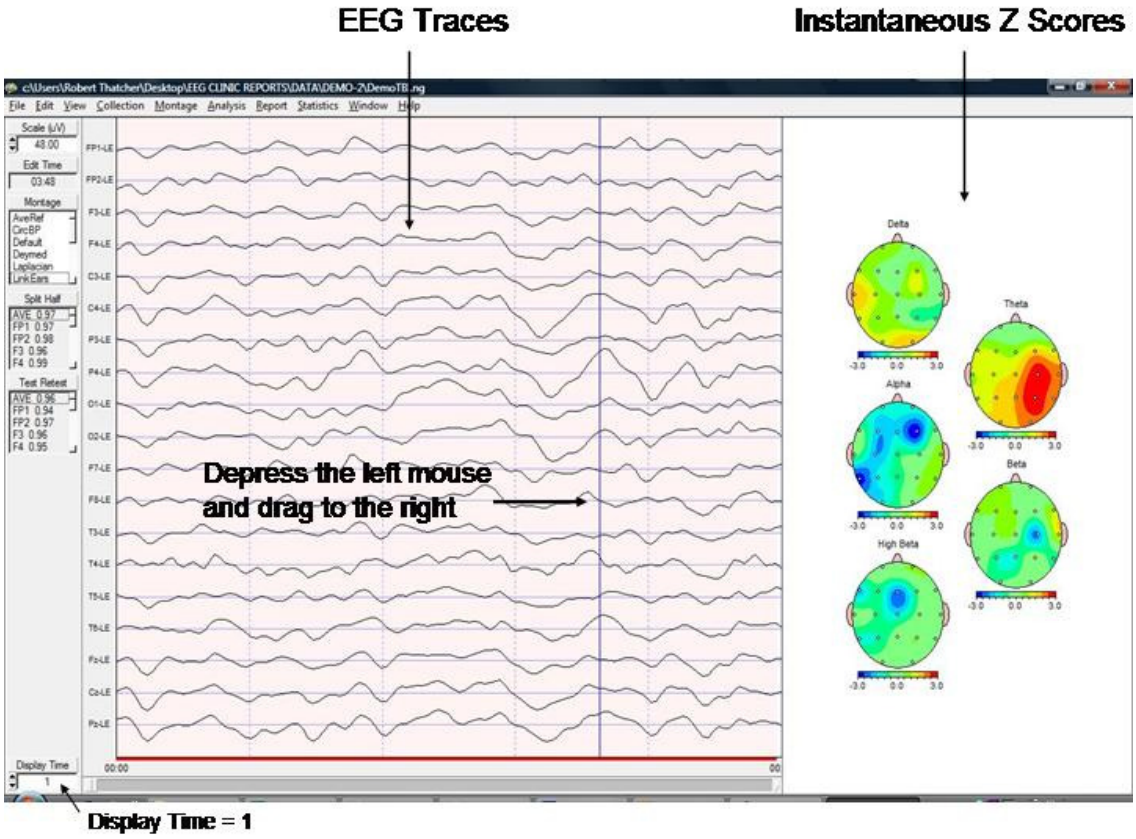

Fig. 6 – Screen capture from NeuroGuide™ in the Demo mode from a patient with right parietal and right central injury. Instantaneous Z scores are on the right, EEG traces are on the left. Depress the left mouse button move the mouse over the traces. Move the mouse to the right border and watch a movie of the dynamic Z scores. Download the free NeuroGuide™ Demo at www.appliedneuroscience.com

A P4 and C4 theta and delta deviation from normal is evident as well as bilateral occipital delta deviations from normal. There is diminished alpha and theta but in the instantaneous Z scores but on the average the dynamic FFT provides a much clearer picture of the right parietal and right central Z scores. For illustration purposes only, a

biofeedback protocol would be to reward Z score values less than and greater than 2 standard deviations in the theta frequency band in P4 and C4 and most of the feedback rewards will automatically occur in the delta and theta frequency band. As mentioned previously, the above is an example of an individualized Z score biofeedback procedure after reviewing the patent's EEG using the same instantaneous Z score program running in Advanced Brain Monitoring, BrainMaster, Neurofield Q20, Thought Technology, EEG Spectrum, Mind Media BV (NeXus) and Deymed.

3.2 - Implementation of the Z Score Biofeedback

Step one is to compute means and standard deviations of instantaneous absolute power, relative power, power ratios, coherence, phase differences and amplitude asymmetries on selected age groups of normal subjects from the 19 channel 10/20 electrode locations using the within session and between session variance as described previously. The inclusion/exclusion criteria, number of subjects, number of subjects per age group, cross-validation procedures and other details of the means and standard deviation computations is published (Thatcher et al, 1987; 2003) and shown in Figure 5. Step two is to develop a Dynamic Link Library or DLL that can be distributed to EEG biofeedback manufacturers such as Advanced Brain Monitoring, BrainMaster, EEG Spectrum, Thought Technology, Neurofield Q20, Mind Media BV (NeXus) and Deymed which allows the manufacturers to integrate the instantaneous Z scores inside of their already existing software environments. The dll involves only four command lines of code and is designed for software developments to easily implement the instantaneous Z scores by passing raw digital data to the dll and then organizing the Z scores that are returned in less than one microsecond. This rapid analysis and return of Z scores is essential for timely feedback when specific EEG features are measured by the Complex Demodulation JTFA operating inside of the dll.

3.3 – JTFA Complex Demodulation Computations

The mathematical details of complex demodulation used to compute the instantaneous Z scores as contained in the Applied Neuroscience, Inc. "dll" are provided in the Appendix section 4.0 and are described in Otnes and Enochson, 1977; Granger and Hatanaka, 1964; Bloomfield, 2000; Thatcher et al, 2007). Complex demodulation is a time domain digital method of spectral analysis whereas the fast Fourier transform (FFT) is a frequency domain method. These two methods are related by the fact they both involve sines and cosines and both operate in the complex domain and in this way represent the same mathematical descriptions of the power spectrum. The advantage of complex demodulation is that it is a time domain method and less sensitive to artifact and it does not require windowing nor even integers of the power of 2 as does the FFT. The FFT integrates power in a frequency band over the entire epoch length and requires windowing functions which can dramatically affect the power values whereas, as mentioned previously, complex demodulation does not require windowing (Otnes and Enochson, 1972). Complex demodulation was computed for the linked ears and eyes open and eyes closed conditions for all 625 subjects in the normative database.

Table I – Time Domain Conversion of Frequencies to Time of the Z Score Biofeedback DLL and NeuroGuide. The asterisk * = NeuroGuide Only

	Center Frequency	Band Width	Time Domain
Delta	2.5 Hz	1 – 4 Hz	1,000 ms to 250 ms
Theta	6.0 Hz	4 - 8 Hz	250 ms to 125 ms
Alpha	8.0 Hz	8 – 12 Hz	125 ms to 83 ms
Beta	18.5 Hz	12 – 25 Hz	83 ms to 40 ms
Hi-Beta	27.5 Hz	25 – 30 Hz	40 ms to 33 ms
Beta 1	13.5 Hz	12 – 15 Hz	83 ms to 67 ms
Beta 2	16.5 Hz	15 – 18 Hz	67 ms to 56 ms
Beta 3	21.5 Hz	18 – 25 Hz	56 ms to 40 ms
Alpha 1	9.0 Hz	8 – 10 Hz	125 ms to 100 ms
Alpha 2	11.0 Hz	10 – 12 Hz	100 ms to 83 ms
Gamma 1 *	FFT only	30 – 35 Hz	33 ms to 29 ms
Gamma 2 *	FFT only	35 – 40 Hz	29 ms to 25 ms
Gamma 3 *	FFT only	40 – 50 Hz	25 ms to 20 ms

Figure 7 is an illustration of the method of complex demodulation for the computation of power, coherence and phase. The mathematical details are in the Appendix, section 4.0.

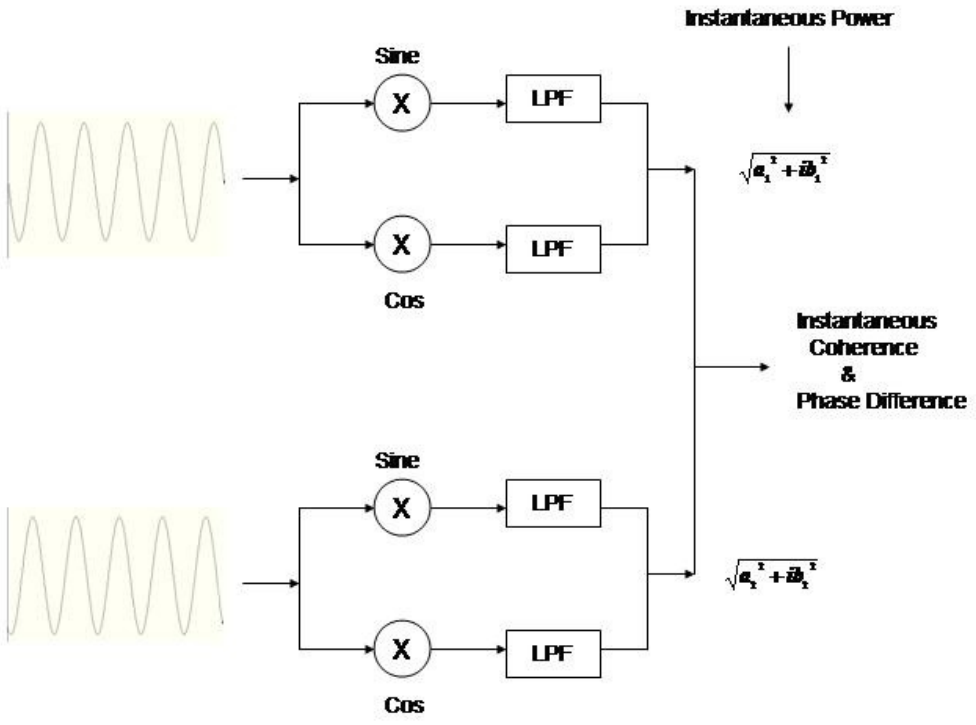

Fig. 7 – Diagram of complex demodulation. Left is a sine wave as input which is multiplied by the sine

and cosine waves at the center frequency of a given frequency band as described in Table I which transforms the digital time series to the complex plane. A 6th order Butterworth low-pass filter is used to shift the frequency to zero where power at the center frequency is then calculated using the Pythagorean theorem. Complex numbers are then used to compute coherence and phase as described in Appendix, section 4.0.

3.4 - Z Scores and qEEG Normative Databases

Matousek and Petersen (1973) computed means and standard deviations in one year age groups and were the first to use Z scores to compare an individual to the normative database means and standard deviations. The Z score is an excellent statistic defined as the difference between the value from an individual and the mean of the population divided by the standard deviation of the population or $Z = \frac{x_i - \bar{X}}{SD}$. John and colleques expanded on the use of the Z score for clinical evaluation including the use of multivariate measures such as the Mahalanobis distance metric. A direct normalization of the Gaussian distribution using Z scores is useful in comparing individuals to a QEEG normative database. That is, the standard score form of the Gaussian is where the mean = 0 and standard deviation = 1 or, by substitution into the Gaussian equation for a bell shaped curve, then

$Y = \frac{1}{\sqrt{2\pi}} e^{-z^2/2}$, where Y = Gaussian distribution and the Z score is a deviation in standard deviation units measured along the baseline of the Gaussian curve from a mean of 0 and a standard deviation = 1 and deviations to the right of the mean being positive and those to the left negative. By substituting different values of Z then different values of Y can be calculated. For example, when Z = 0, Y = 0.3989 or, in other words, the height of the curve at the mean of the normal distribution in standard-score form is given by the number 0.3989. For purposes of assessing deviation from normal, the values of Z above and below the mean, which include 95% of the area of the Gaussian is often used as a level of confidence necessary to minimize Type I and Type II errors. The standard-score equation is also used to cross-validate a normative database which again emphasizes the importance of approximation to a Gaussian for any normative QEEG database.

3.5 – Standardization by Amplifier Matching and qEEG Normative Databases

Surprisingly, matching of amplifier frequency characteristics as a standard was largely neglected during much of the history of qEEG normative databases. E. Roy John and colleagues (1982 to 1988) formed a consortium of universities and medical schools that were using qEEG who met several times over a few years and was one of the supporters of the edited volume by John titled “Machinery of the Mind” (John, 1990). One of the important issues consistently raised at the consortium meetings was the need for “standardization”. In the 1980s it was technically difficult to match different EEG systems because of the infantile development of analysis software. This history forced most qEEG uses to use relative power because absolute power was not comparable between different EEG machines. There was no frequency response standardization between different EEG machines and thus there was no cross-platform standardization of qEEG. It was not until the mid 1990s that computer speed and

software development made amplifier matching and normative database amplifier equilibration a possibility. The first use of standardized matching of amplifiers was to the University of Maryland (UM) database (Thatcher et al, 2003). The procedure involved injecting micro volt calibration sign waves into the input of amplifiers of different EEG machines and then inject the same micro volt signals into the normative database amplifiers thus obtaining two frequency response curves. Equilibration of a normative qEEG database to different EEG machines is the ratio of the frequency response curves of the two amplifiers that are then used as coefficients in the power spectral analysis. This was an important step because suddenly absolute power Z scores and normative database comparisons became possible. The frequencies in absolute power are independent of each other and are not distorted. It is always best to use absolute values when ever possible and not relative values or even ratios. A ratio can change due to the denominator or the numerator and one can not determine which has changed without evaluating the absolute values used to compute the ratios.

As illustrated in Figure 8, a simple method of amplifier equilibration to exactly match the frequency characteristics of different amplifiers is to calibrate the amplifiers using micro-volt sine waves at discrete frequencies from 1 to 40 Hz and injecting the sine waves into the inputs of the EEG amplifiers. Then take the ratio of the micro-volt values at each frequency and use the ratios to exactly equate the spectral output values at different frequencies for different amplifiers. This method creates a universal equilibration process so that micro-volts in a given amplifier are equal to micro-volts in all other amplifiers including the normative database amplifiers. By equilibrating amplifiers then direct comparisons between a given patient's EEG and the normative database means and standard deviations is valid and meaningful.

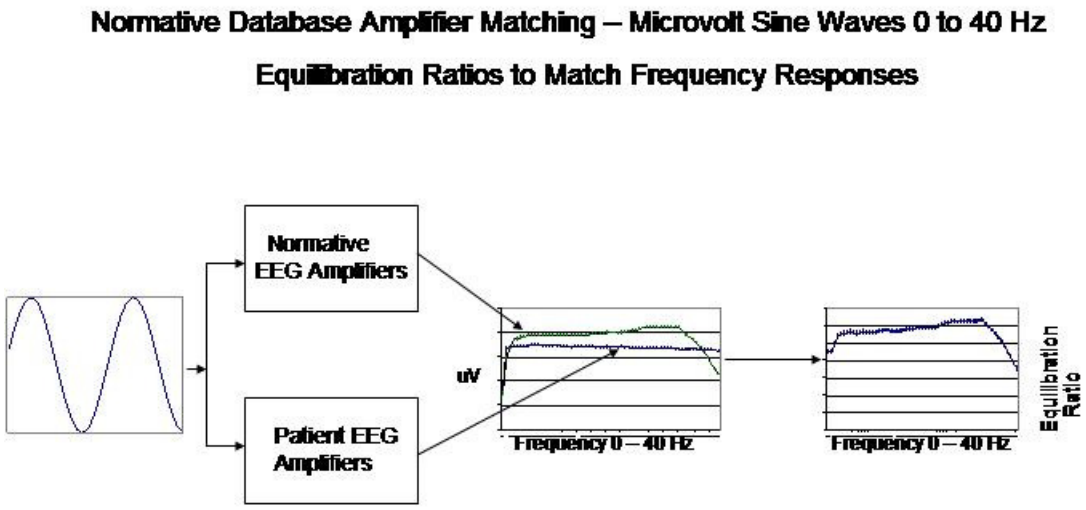

Fig. 8 – Flow chart of the amplifier standardization procedure. Micro volt sine waves are injected into the input of amplifiers and the frequency responses are calculated. The frequency response of the normative database amplifiers and the frequency response of other EEG amplifier systems are then equated and the spectral analysis is adjusted so that there is a standardized import and matching of amplifier systems with the common unit being micro volts (uV).

4.0 - General Method to Produce a Valid Instantaneous Z Score EEG Database

Figure 9 is an illustration of a step by step procedure by which the Z instantaneous score normative EEG database was validated and sensitivities calculated. The left side of the figure is the edited and artifact clean and reliable digital EEG time series which may be re-referenced or re-Montaged, which is then analyzed in either the time domain or the frequency domain.

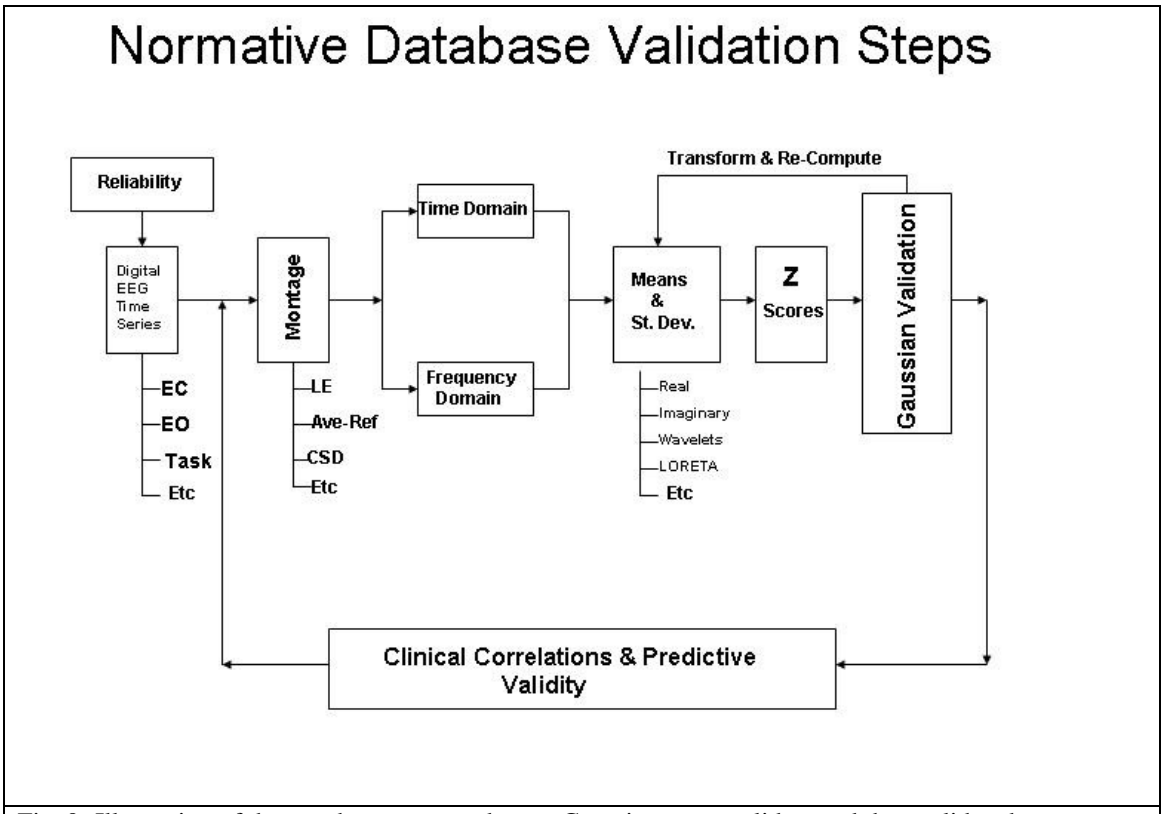

Fig. 9- Illustration of the step by step procedure to Gaussian cross-validate and then validate by correlations with clinical measures in order to estimate the predictive and content validity of any EEG normative database. The feedback connections between Gaussian cross validation and the means and standard deviations refers to transforms to approximate Gaussian if the non-transformed data is less Gaussian. The clinical correlation and validation arrow to the montage stage represents repetition of clinical validation to a different montage or reference or condition such as eyes-open, active tasks, eyes-closed, etc. to the adjustments and understanding of the experimental design(s). From Thatcher et al, 2003.

4.1 – Age Groupings of the Instantaneous Z Score Normative Population

The selected normal subjects are grouped by age with sufficiently large sample size and the means and standard deviations of the EEG time series and/or Frequency domain analyses are computed for each age group. Transforms are applied to approximate a Gaussian distribution of the EEG measures that comprise the means. Once approximation to Gaussian is completed, then Z scores are computed for each subject in the database and leave one out Gaussian Cross-Validation is computed in order to arrive at an optimum Gaussian Cross-validation sensitivity. Finally the Gaussian validated norms are subjected to content and predictive validation procedures such as correlation with Neuropsychological test scores and intelligence, etc. and also discriminant analyses and neural networks and outcome statistics, etc. The content validations are with respect to clinical measures such as intelligence, neuropsychological test scores, school achievement, clinical outcomes, etc. The predictive validations are with respect to the discriminative, statistical or neural network clinical classification accuracy. Both parametric and non-parametric statistics are used to determine the content and predictive validity of a normative EEG database..

Figure 10 shows the number of subjects per year in the normative EEG lifespan

database. It can be seen that the largest number of subjects are in the younger ages (e.g., 1 to 14 years, N = 470) when the EEG is changing most rapidly. As mentioned

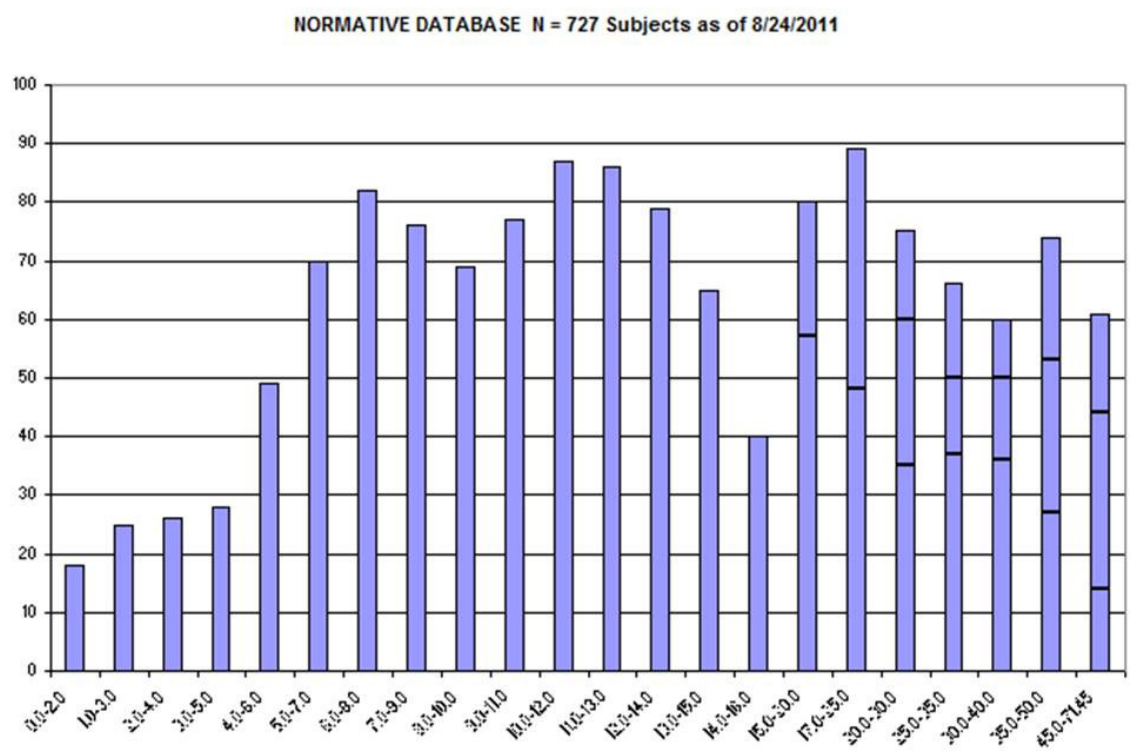

Fig. 10 - The NeuroGuide and the Z Tunes are the same and the total number of subjects = 727 in the Z score Lifespan EEG reference normative database. The database is a "life-span" database with the two months of age being the youngest subject and 82.3 years of age being the oldest subject. Two year means were computed using a sliding average with 6 month overlap of subjects. This produced a more stable and higher age resolution normative database and a total of 22 different age groups. The 22 age groups and age ranges and number of subjects per age group is shown in the bar graph.

previously, a proportionately smaller number of subjects represents the adult age range from 14 to 82 years (N = 208). The Z score normative database includes a total of 727 carefully screened individual subjects ranging in age from 2 months to 82 years. In order to increase the time resolution of age, sliding averages were used for the stratification in NeuroGuide™ and for instantaneous Z scores (Thatcher et al, 2003). Two year means were computed using a sliding average with 6 month overlap of subjects. This produced a more stable and higher age resolution normative database and a total of 22 different age groups. The 22 age groups and age ranges and number of subjects per age group is shown in the bar graph in figure 10.

4.2 – Z Tunes™ and Gaussian Weighted Resonance Matching

Two important facts should be considered when designing reward feedback with real-time Z scores: 1- the neurophysiologic fact that most cortical pyramidal neurons behave like "band pass" filters and are tuned to particular center frequencies and band widths and, 2- the Z scores are themselves a Gaussian probability distribution. The resonant properties of cortical pyramidal neurons are determined by the membrane potential, passive cable properties and ionic conductance channels of Na+, K+, Cl+ & Ca++ and the shape of the resonance is approximately 'Gaussian'. Therefore, the optimal biofeedback reward is one that reinforces the probability distribution of Z scores from a given patient for a given metric to better approximate the Gaussian probability distribution of the normative database. If one uses a simple window of e.g., ± 5 st. dev. without any weighting then a 4.9 st. dev. instantaneous Z score is treated the same as a 0.5 st. dev. instantaneous Z score and there is little information given to the brain to help shape the Z score probability distribution toward Z = 0. Tom Collura at Brainmaster experimented with a percentage control where only a percentage of instantaneous Z scores are required to be within a specific range in order to receive treatment and this is called "Z%ok", e.g., 70%. The criticism of this method is that outliers will also be reinforced and this should slow the rate of shaping the Z scores toward Z = 0.

A more complicated but a more direct method than Z%ok is the method that we refer to as "Z Tune" that is to calculate the slope of a 10 seconds history of Z scores and allow reinforcement to occur if outliers are moving in the direction of Z = 0. This is a type of adaptive filter designed to take advantage of the probability and Gaussian nature of neurons by weighting extreme or outlier instantaneous Z score by a probability of moving in the direction of Z = 0. In this way the most frequent events that approximate the center frequency and band width of cortical resonance in normal subjects is reinforced and the influence of outliers are minimized by lower weightings. Outliers are not ignored, they are reinforced when moving in the direction of greater stability and less "chaos". In other words, by using an adaptive real-time resonance slope then instantaneous Z scores that move toward the most probable state are reinforced more than events that move in the opposite direction or away from the most probable normative resonance.

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6.0 - **Appendix -**

Complex Demodulation and Joint-Time-Frequency-Analysis

Complex demodulation is used in a joint-time-frequency-analysis (JTFA) to compute instantaneous power, coherence, amplitude asymmetry and phase-differences (Granger and Hatanaka, 1964; Otnes and Enochson, 1978; Bloomfield, 2000; Thatcher et al, 2007) and then to compute a Z score based on these instantaneous values. Complex demodulation is an analytic linear shift-invariant transform that first multiplies a time series by the complex function of a sine and cosine at a specific center frequency (see Table I) followed by a low pass filter (6^{th} order low-pass Butterworth) which removes all but very low frequencies (shifts frequency to 0) 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, as with the Hilbert transform, 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. Mathematically, complex demodulation is defined as an analytic transform that involves the multiplication of a discrete time series $\{x_t, t = 1, \ldots, n\}$ by sine $\omega_0 t$ and cos $\omega_0 t$ giving

$$x'_t = x_t \sin \omega_0 t \tag{1}$$

and

$$x''_t = x_t \cos \omega_0 t \tag{2}$$

and then apply a low pass filter F to produce the instantaneous time series, Z_t' and Z_t'' where the sine and cosine time series are defined as:

$$Z'_t = F(x_t \sin \omega_0 t) \tag{3}$$

$$Z''_t = F(x_t \cos \omega_0 t) \tag{4}$$

and

$$2\left[(Z_t')^2 + (Z_t'')^2\right]^{1/2} \tag{5}$$

is an estimate of the instantaneous amplitude of the frequency ω_0 at time t and

$$\tan^{-1}\frac{Z_t'}{Z_t''} \tag{6}$$

is an estimate of the instantaneous phase at time t. At this step the complex demodulation transform is the same as the Hilbert transform (Pikovsky et al, 2003, p. 362; Oppenheim and Schaefer, 1975).

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 $R_t^2 = F\left[y_t \sin\omega_0 t\right]^2 + F\left[y_t \cos\omega_0 t\right]^2 = \left|F\left[y_t e^{i\omega_0 t}\right]^2\right|$ is the estimate of the amplitude of frequency ω_0 at time t and $\varphi_t = \tan^{-1}\left(\frac{F\left[y_t \sin\omega_0 t\right]}{F\left[y_t \cos\omega_0 t\right]}\right)$ is an estimate of the phase of frequency ω_0 at time t and therefore,

$$F\left[y_t e^{i\omega_0 t}\right] = R_t e^{i\varphi_t}, \tag{7}$$

and likewise,

$$F\left[y'_t e^{i\omega_0 t}\right] = R'_t e^{i\varphi_t} \tag{8}$$

The instantaneous cross-spectrum is

$$V_t = F\left[y_t e^{i\omega_0 t}\right] F\left[y'_t e^{-i\omega_0 t}\right] = R_t R'_t e^{i[\varphi_t - \varphi'_t]} \tag{9}$$

and the instantaneous coherence is

$$\frac{|V_t|}{R_t^2 R_t'^2} \equiv 1 \tag{10}$$

The instantaneous phase-difference is $\varphi_t - \varphi'_t$. That is, the instantaneous phase difference is computed by estimating the instantaneous phase for each time series separately and then taking the difference. Instantaneous phase difference is also the arctangent of the imaginary part of V_t divided by the real part (or the instantaneous quadspectrum divided by the instantaneous cospectrum) at each time point.