Quantitative EEG Normative Databases: Validation and Clinical Correlation

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SENSITIVITY AND SPECIFICITY OF AN EEG NORMATIVE DATABASE: Validation and Clinical Correlation

(see also J. Neurotherapy 7(3/4): 87-121, 2003)

R.W. Thatcher, Ph.D., R.A. Walker, B.A. C.J. Biver, Ph.D., D. M. North, M.A. and R. Curtin, B.A.

We each had different contributions as a team to compute and test these databases. Robert Thatcher was the program director and P.I., Rebecca Walker, Richard Curtin, Duane North and Dr. Carl Biver were the database managers and analysists and colleague scientists who spent years analyzing these data (Walker and Thatcher = 22 years and no one for less than 5 years). Dr. Biver was responsible for writing of IDL and C programs for the Interpolations, sliding averages, digital signal processing and, with Duane North, for the cross-validation procedures. Rebecca Walker computed the means and standard deviations of EEG values in the database and grouped and tabulated subjects, and oversaw the organization of the clinical database and Richard Curtin helped edit and archive data and organize the databases. Duane North, Rebecca Walker and Richard Curtin were the data analyzers for the computation of sliding averages and for writing Excel programs to compute and tabulate the Skewness and Kurtosis and the parametric and non-parametric sensitivity and specificity statistics in the cross-validation studies as well as the clinical correlations.

Abstract

The digital Electroencephalogram (EEG) was recorded from19 scalp locations from 625 screened and evaluated normal individuals ranging in age from 2 months to 82 years. After editing to remove artifact; one year to 5 year groupings were selected to produce different average age groups.. Estimates of Gaussian distributions and logarithmic transforms of the digital EEG were used to establish approximate Gaussian distributions when necessary for different variables and age groupings. The sensitivity of the lifespan database was determined by Gaussian Cross-Validation for any selection of age range in which the average percentage of Z scores ± 2 st. dev. equals approximately 2.3% and the average percentage for ± 3 st. dev. equals approximately .13%. It was hypothesized that measures of Gaussian cross-validation of Z scores is a common metric by which the statistical sensitivity of any normative database for any age grouping can be calculated. This notion was tested by computing eyes closed and eyes open Average Reference and Current Source Density norms and independently cross-validating and comparing to the Linked Ears norms. The results indicate that age dependent Digital EEG normative databases are reliable and stable and behave like different Gaussian lenses that spatially focus the Electroencephalogram. Clinical correlations of a normative database are determined by content validation and correlation with neuropsychological test scores and discriminate accuracy. Non-parametric statistics were presented as an important aid to establish the alpha level necessary to reject a hypothesis and to estimate Type I and Type II errors, especially when there are multiple comparisons of an individual's EEG to any normative EEG database.

Key Words: EEG Normative Databases, Gaussian Distributions, Error Estimates

1.0- Introduction

There are many potential uses of a normative EEG database among the most important being a statistical "guess" as to the "error rate" or to the probability of finding a particular patient's EEG measure within a reference normal population. [1] Most other uses of a reference EEG database also involve statistics and the same statistics that all of modern clinical medicine relies upon. For example, null hypothesis testing, measures of reliability, sensitivity, power, predictive validity, content validity, etc. all depend on specific assumptions and statistical procedures.

Predictive accuracy and error rates depend on the data that make up a given EEG database and the statistics of the database. The statistical foundations of the scientific method were visited by the Supreme Court in *Daubert*, 1993 regarding admissibility of scientific evidence. The Four *Daubert Factors* for scientific standards of admissibility in Federal Courts were: 1- hypothesis testing, 2- error estimates of reliability and validity, 3- peer reviewed publications and 4- general acceptance (Mahle, 2001) [2]. These four *Daubert* factors for several EEG normative database have already been met. The minimal standards are publication of: 1- inclusion/exclusion criteria, 2- methods to remove artifact and adequate sample sizes per age groups, 3- demographic representativeness (e.g., balanced gender, ethnicity, socioeconomic status, etc.), 4- means and standard deviations as being normally distributed or "Gaussian" including Gaussian Cross-Validation and, 5- Content validity by correlations with Neuropsychological test scores and school achievement scores, etc. as validation. Predictive validity is determined by regression and classification statistics. Predictive validity relates to the classification accuracy, clinical severity, clinical outcome, etc. estimates. The sensitivity and specificity of any EEG database is directly proportional to its adherence to the established statistical principals in the history of statistics (Hayes, 1973).

[1] The phrase 'reference normal' is used to emphasize: that the term "normative" when used alone tends to obscure or mask the fundamental fact that only a "sample" of subjects drawn from a much larger population are contained in any data base.

[2] The court benefited by input from the American Academy of Science and 13 Nobel Laureates.

1.1 – General Method to Produce a Valid Normative EEG Database

Figure 1 is an illustration of a step by step procedure by which any normative EEG database can be 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.

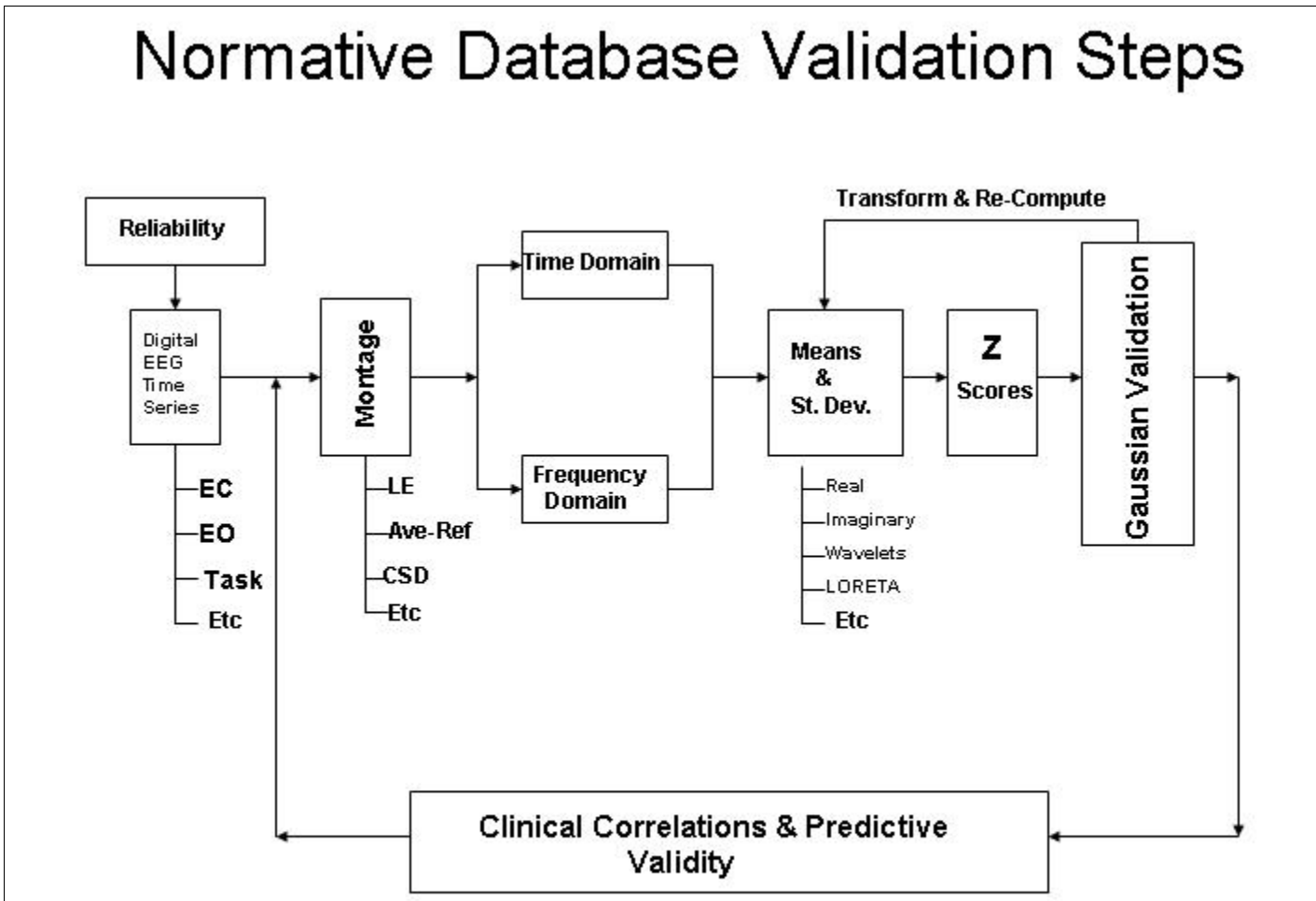

Fig. 1 - Illustration of the step by step procedure to Gaussian cross-validate and then validate by correlations with clinical measures in order to estimate the predictive and content validity of any EEG normative database. The feedback connections between Gaussian Cross Validation and the means and standard deviations refers t transforms to approximate Gaussian if the non-transformed data is less Gaussian (see section 6). The Clinic

Correlation and Validation arrow to the Montage stage represents repetition of clinical validation to a differe montage or reference or condition such as eyes open, active tasks, eyes closed, etc. to the adjustments and understanding of the experimental design(s) (see sections 6 to 8).

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[3] 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..

1.2- Example of a Normative EEG Database and the Procedure in Section 1.1

An example of the step-by-step procedure in Figure 1 to produce a validated normative digital EEG database will be provided to show how any normative reference

[3] The leave-one-out is a bit over sold, because the fact is that leave-one-out is self-referential with respect to the particular population that was selected and it is the nearly the same as simply computing the Z scores

database can be constructed to meet measurable standards of reliability and validity. The Steps in Figure 1 can be repeated for different selections of subjects

2.0 - Subject and Variable Selection

Nineteen (19) channels of EEG and a EOG (Electro-Oculogram) channel, a two hour battery of evoked potential tests and active challenges, psychometric tests, dietary evaluations, anthrometric measurements, demographic and trace element measurements from a population of 1,015 rural and urban children were collected (Thatcher et al, 1983; 1987; Thatcher, 1997). The principal goal of this project was to evaluate the effects of environmental toxins on child development and to determine the extent to which good or poor diets may ameliorate or exacerbate the deleterious effects of environmental toxins. Two data acquisition centers were established, one at the rural University of Maryland Eastern Shore campus and one at the urban campus of the University of Maryland School of Medicine in Baltimore, Maryland. Identical data acquisition systems were built and calibrated, a staff was trained using uniform procedures and a clinical and psychometric protocol were utilized in the recruitment of normal subjects. The total of 1,015 subjects ranging in age from 2 months to 82 years were tested during the period from 1979 to 1987. Of these subjects, 564 met the criteria of normalcy and were included in the normative reference database (Thatcher et al, 1987; Thatcher 1997). In 2000 the original digital EEG was revisited and a different selection of individuals was selected that also spanned the same interval from 2 months to 82 years and included 61 additional adult subjects to give rise to a total sample size of 625 subjects. The expanded selection

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without replacement. Multiple independent validations are impractical, therefore, reliance on the clinical correlations are more important, whether or not leave-one-out procedures were used.

contained more individuals between the ages of 25 and 55 years of age.

Figure 2 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

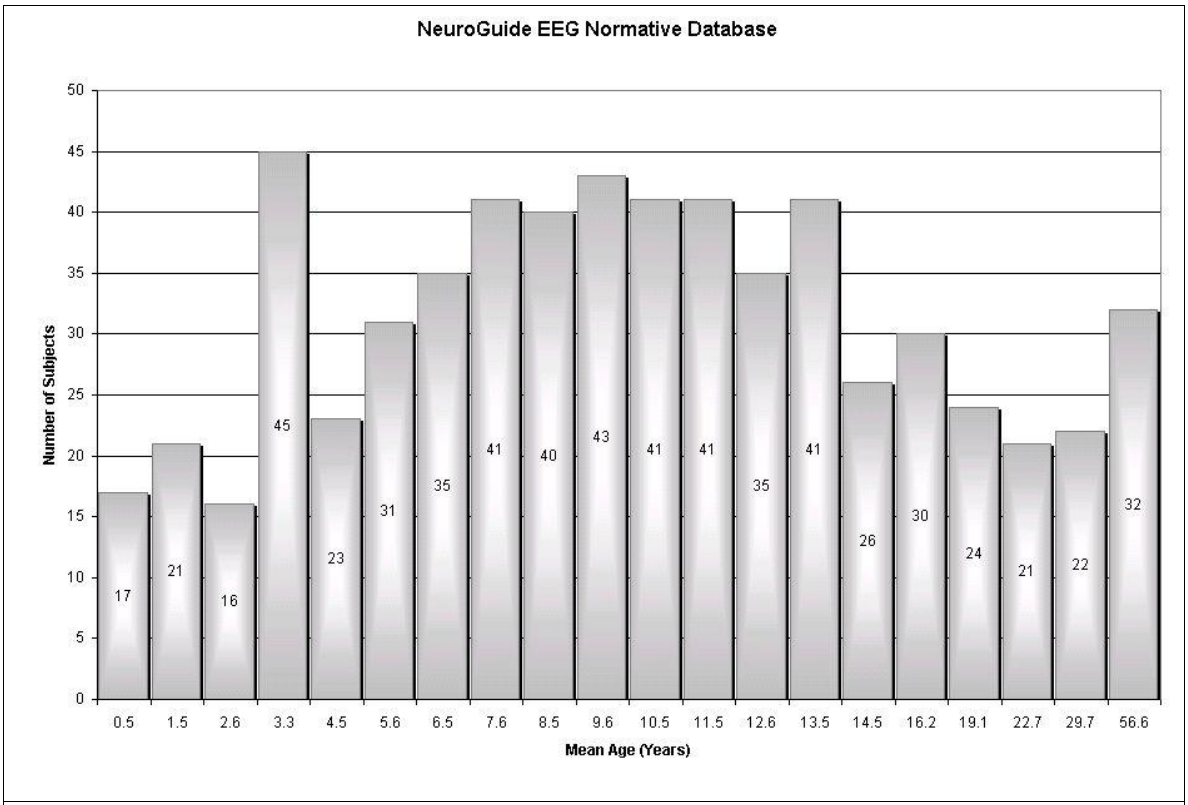

Fig. 2 - The number of subjects per year in the Lifespan EEG reference normative database. The database is a "life-span" database with the 2 months of age being the youngest subject and 82.3 years of age being the oldest subject. This figure shows the number of subjects constituting mean values which range from a mean of .5 years to 62.6 years of age and constituting a total number of subjects = 625.

previously, a proportionately smaller number of subjects represents the adult age range from 14 to 83 years (N = 155). Fifteen one-year groupings of subjects were computed with reasonable sample sizes from birth to 15 years of age. Thirteen out of the 15 one year age groups have N > 20 with the largest sample size at age 3 to 4 years, N = 45. The smallest one year sample size was between age 2 and 3 when N = 16.

For each subject, original selections of the original digital EEG occurred by different artifact procedures involving the use of NeuroGuide editing selections in 2001. Original arrangements of coherence, phase, amplitude asymmetry and relative power also occurred when comparing the database to previous publications and the 1988 copyright (Thatcher et al, 1987; Thatcher, 1988; Thatcher, 1997). Although different selections of digital EEG values and different arrangements of the original digital EEG have occurred since 1987, nonetheless, the Gaussian validations and sensitivities of the previous databases and the current 2001-2002 database were all similar and equally valid and Gaussian distributed within a 90% to 99% range depending on the measure. The original digital EEG and subjects and neuropsychological test scores that were measured from 1979 to 1987 are the same.

3.0- Inclusion/Exclusion Criteria, Demographics and Gender

Details of the neuropsychological testing, demographic and sampling of the normative 1987 EEG database were previously published in Thatcher et al (1983; 1986; 1987) and Thatcher (1997). Some but not all of the 61 adults added in 2000 - 2001 were given neuropsychological tests and other evaluations to help determine "normalcy", however, all of the subjects were interviewed and filled out a history and neurological questionnaire. All of the 61 added adults were gainfully employed as professors, graduate students, and other successfully employed adults without a history of neurological problems. Normalcy for the age range from 2 months to 18 years was determined by one or more exclusion/inclusion criteria: 1- a neurological history questionnaire given to the child's parents and/or filled out by each subject, 2- psychometric evaluation of I.Q., and/or school achievement, 3- for children the teacher

and class room performance as determined by school grades and teacher reports and presence of environmental toxins such as lead or cadmium. A Neurological questionnaire was obtained from all of the adult subjects >18 years of age and those in which information was available about a history of problems as an adult were excluded. .

3.1- Intelligence and School Achievement Criteria:

Psychometric, demographic and socioeconomic status measures were obtained from each child, adolescent and for some of the adults. Different psychometric tests were administered depending upon the age of the child. There is little reliability in the I.Q. tests of infants, however, when possible the infant's Apgar Score was obtained and the Vineland Social Maturity Scale test was administered (age birth to 2 years, 4 months). From age 2 years to 3.99 years, the McCarthy Intelligence Scale Test was administered, from age 4.0 years to 5.99 years the Weschler Pre-school and Primary Scale of Intelligence (WIPPSI) test was administered, from age 6.0 years to 16.99 years the Wechsler Intelligence Scale for Children (WISC-R, 1972) was administered and from age 17.0 years to adulthood the Wechsler Adult Intelligence Scale test (WAIS) was administered. In addition to Intelligence Tests, the Wide Range School Achievement test (WRAT) was administered to the school age children and grade cards were obtained from the public school systems. Finally, a variety of neuropsychological tests were administered including the pegboard test of skilled motor movements, the Stott, Moyes and Henderson Test of Motor Impairment (MIT) and a eight item laterality test (see Thatcher et al, 1982; 1983 for further details).

The criteria for entry into the normative database for those subjects given I.Q. tests

and school achievement tests were:

1- A Full Scale I.Q. > 70.

2- WRAT School Achievement Scores > 89 on at least two subtests (i.e., reading, spelling, arithmetic) or demonstrated success in these subjects.

3- A grade point average of 'C' or better in the major academic classes (e.g., English, mathematics, science, social studies and history).

3.2- Demographic Characteristics:

It is important that the demographic mixture of males and females, different ethnic groups and socioeconomic status be reasonably representative of expected North American clientele. The normative EEG database is made up of 58.9% males, 41.1% females, 71.4% whites, 24.2% blacks and 3.2% oriental. Socioeconomic status (SES) was measured by the Hollingshead four factor scale (Hollingshead, Four factor Index of Social Status, 1975). (see Thatcher et al, 1983 for details).

3.3 - Time of Day and Other Miscellaneous Factors

There are many uncontrollable factors that influence the frequency spectrum of the EEG. In general these factors are all confounded, and it would require an enormously expensive and large sample size to control each factor individually. Even if one could control each factor, such experimental control would preclude the practical use of a database since each patient's EEG would have to be acquired in a precisely matching manner. Statistical randomization is one of the best methods to deal with these uncontrollable and miscellaneous factors. Statistical randomization of a database involves randomly varying time of day of EEG acquisition, time between food intake and

EEG acquisition, food content and EEG acquisition, etc. across ages, sex and demographics. Because these factors are confounded with each other, randomization with a sufficient sample size will result in increased variance but, nonetheless, convergence toward a gaussian distribution. Such convergence, even in the face of increased variance, still allows quantitative comparisons to be made and false positive and false negative error rates (i.e., sensitivity) to be calculated. The method of statistical randomization of miscellaneous factors was used in the Matousek & Petersen, Thatcher, John and Duffy EEG normative databases (John et al, 1988; Thatcher et al, 1989; Duffy et al, 1994).

4.0 – Digital Electroencephalographic Recording Procedures

EEG was recorded and digitized at a rate of 100 Hz from the 19 leads of the International 10/20 system of electrode placement referenced to linked ear lobes and one bipolar EOG lead (Electrooculogram) (i.e., a total of 20 channels). (Thatcher et al, 1983; 1986; 1987, Thatcher 1997). When head size was amenable, the data were acquired using a stretchable electrode cap (Electrocap International, Inc.). When head sizes were either too small or too large for the electrocap, then the electrophysiological data were acquired by applying standard silver disk Grass electrodes. Amplifiers were calibrated using sine wave calibration signals and standardized procedures and a permanent record made before and after each test session. The frequency response of the amplifiers was approximately 3db down at 0.5 Hz and 30 Hz. Impedance was measured and recorded for each electrode and efforts were made to obtain impedance measures less than 10K ohms (most of the impedance's were < 5k ohms) for all subjects.

4.1 – Artifact Removal and Quality Control Procedures

EEG recording lengths varied from 58.6 seconds to 40 minutes. Artifact rejection involved using the NeuroGuide editing procedures in which a 1 to 2 second template of "clean" or "artifact free" EEG was selected. This template was then used to compute matching amplitudes of EEG using a flexible criteria of equal amplitudes to amplitudes that are 1.25 or 1.5 times larger in amplitude. The decision as to which clean EEG sample multiplier to use was determined by the length of the sample 58.6 seconds as a minimum, visual inspection of the digital EEG and when split-half reliability > 0.97. After multiple visual inspections and selection of "clean" EEG samples the edited samples varied in length from 58.6 seconds to 142.4 seconds. Average split-half reliability = 0.982 for the selected EEG in the database. Care was taken to inspect the EEG from each subject in order to eliminate "drowsiness" or other state changes in the EEG which may have been present in the longer EEG recording sessions. No evidence of sharp waves or epileptogenic events were present in any of the EEG records.

4.2- Re-Montage to the Surface Laplacian and Average Reference

The average reference involved summing the voltages across all 19 leads for each time point and dividing this value into the microvolt digital value from each lead at each time point. This procedure produced a digital EEG time series that was then submitted to the same age groupings and Power Spectral analyses and the same Gaussian normative evaluations as for Linked ears. See Figure 1.

The reference free surface Laplacian or current source density (CSD) was

computed using the spherical harmonic Fourier expansion of the EEG scalp potentials to estimate the current source density (CSD) directed at right angles to the surface of the scalp in the vicinity of each scalp location (Pascual-Marqui et al., 1988). The CSD is the second spatial derivative or Laplacian of the scalp electrical potentials which is independent of the linked ear reference itself. The Laplacian is reference free in that it is only dependent upon the electrical potential gradients surrounding each electrode. The Laplacian transform also produces a new digital EEG time series of estimates of current source density in microamperes, that were also submitted to the same age groupings Spectral Analyses (see Figure 1).

4.3 - Complex Demodulation Computations

The mathematical details of both the FFT and complex demodulation are adequately described in Otnes and Enochson, (1977); Bendat and Piersol, (1981). The EEG norms use both the complex demodulation and the FFT so that users can compare and contrast both methods in the same subject or application. 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 even integers of the power of 2 as does the FFT. The FFT integrates frequency over the entire epoch length and requires windowing functions which can dramatically affect the power values whereas complex demodulation does not require

windowing (Otnes and Enochson, 1972; 1978). Complex demodulation was computed for the linked ears and eyes closed condition. Future analyses are being considered for the computation of complex demodulation for average reference and the Laplacian estimate of current source density for eyes open and closed conditions. However, due to the large amount of data and the large number of computations, the FFT may be the preferred method to conduct these analyses.

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4.4 – FFT Linked Ears, Average Reference and Laplacian

The 100 samples per second digital EEG were cubic-spline interpolated to 128 samples per second using standard procedures (Press, 1994). The second step was to high pass filter the EEG at 40 Hz to eliminate any possible splice artifact that may have been produced by the short segment NeuroGuide editing method described in section 4.1. The third step was to compute the FFT Power Spectral Density. Four second epochs were used to compute the FFT Power Spectral Density thus producing 0.5 Hz resolution and a Hanning window was used for each 4 second epoch computation. The 75% sliding window method of Kaiser and Sterman (2001) was used to compute the FFT normative database for linked ears, average reference and Laplacian estimator of current source density (CSD) in which successive four second epochs were advanced by 500 millisecond steps in order to minimize the effects of the FFT windowing procedure. The FFT Power Spectral Density and the 256 point and 2 second epochs produced a total of 61 frequency values in uv^2 /Hz from 0 to 30 Hz in 0.5 Hz increments.

This procedure was repeated for linked ears, average reference and Laplacian digital values for both the eyes closed and eyes open conditions, thus producing for a

given subject a total of six different 61 point FFT power spectral density values. These values were then used to compute means and standard deviations for different age groups as described in the next section (5.0)

5.0 – Amplifier and Digital Matching

The frequency characteristics of all amplifiers differ to some extent, especially in the < 3 Hz and > 20 Hz frequency range and there are no universal standards that all EEG amplifier manufacturers must abide by. Therefore, amplifier filter and gain characteristics must be equilibrated to the amplifier gains and frequency characteristics of the normative EEG amplifiers that acquired the EEG in the first place. A simple method to accomplish this is to inject into each amplifier system microvolt sine waves from 0 to 40 Hz in 1 Hz steps and at three different amplitudes. The ratio of the frequency response characteristics between the normative EEG amplifiers and the amplifier characteristics by which EEG was measured from a patient can be used as equilibration factors to approximately match the norms. There are some frequencies that are so severely attenuated by the amplifier filters that equilibration to the normative database amplifiers will not be able to recover the signal. For example, rations of > 5.0 will significantly amplify the noise of the amplifiers where little or no EEG signal is present and render the Z scores invalid.

It should be kept in mind, that even with matching of amplifier characteristics within 3 to 5% error the enormous variability in skull thickness effects the amplitude and frequency characteristics of the EEG itself far more than slight differences in amplifier characteristics. For example, the human skull is on the average 80 times less conductive than the brain and scalp. Therefore, an individual with a 10% thinner skull may be result

in a 800% change in EEG amplitude across all frequencies.

6.0- Statistical Foundations: Gaussian Distributions

The Gaussian or Normal distribution is a non-linear function that looks like a ideal bell shaped curve and provides a probability distribution which is symmetrical about its mean. Skewness and kurtosis are measures of the symmetry and peakedness, respectively of the gaussian distribution. In the ideal case of the Gaussian distribution skewness and kurtosis = 0. In the real world of data sampling distributions skewness and kurtosis = 0 is never achieved and, therefore, some reasonable standard of deviation from the ideal is needed in order to determine the approximation of a distribution to Gaussian. In the case of the Lifespan EEG Database we used the criteria of approximation as a reasonable measure of Gaussian distribution. The most serious type of deviation from normality is "Skewness" or a unsymmetrical distribution about the mean (e.g., a tail to the left or right of the mean), while the second form of deviation from normality "Kurtosis" is the amount of peakedness in the distribution, which is not as serious an offense since the variance is symmetrical about the mean (mean = median). However, it is preferable to attempt to achieve normality as best as one can to insure unbiased estimates of error. The primary reason to achieve "Normality" is that the sensitivity of any normative database is determined directly by the shape of the sampling distribution. In a normal distribution, for example, one would expect that 5% of the samples will be equal to or greater than ± 2 standard deviations and approximately .13 % ± 3 SD.

It is important to note that automatic and blindly applied transformations of EEG measures does not insure improved normality of the sampling distribution. For example,

it is simple to demonstrate that while some transformations may improve the normality of distributions, these same transforms can also degrade the normality of the distributions. For example, table I shows the effects of transforms on the distributions of the various EEG variables in the Lifespan EEG reference normative database. The "No Transform" column shows the deviation from Gaussian for the untransformed or raw

Table I: Gaussian Distribution of the EEG Normative Database

EEG Measure	Skewness		Kurtosis	
	No Transform	**Transformed**	**No Transform**	**Transformed**
Coherence:	**0.1%**	**---**	**3.8%**	**---**
Delta	0%	---	3.3%	---
Theta	0%	---	2.9%	---
Alpha	0%	---	3.2%	---
Beta	0.2%	---	5.7%	---
Phase (Absolute)**:**	**3.2%**	**0.9%***	**27.2%**	**5.2%***
Delta	2.3%	0.4%*	26.0%	3.6%*
Theta	3.6%	0.5%*	28.9%	3.2%*
Alpha	2.0%	2.1%*	23.0%	8.5%*
Beta	5.0%	0.4%*	31.0%	5.4%*
Amplitude Asym:	**0%**	**---**	**2.6%**	**---**
Delta	0%	**---**	2.0%	**---**
Theta	0%	**---**	1.7%	**---**
Alpha	0%	**---**	3.7%	**---**
Beta	0%	**---**	3.0%	**---**
Relative Power	**0 %**	**---**	**4.5%**	**2.3% ***
Total Power	**4.2%**	**0%***	**25.4%**	**1.8% ***
Absolute Power	**3.8%**	**0%***	**30.6**	**1.8% ***

* Transformed variables

EEG values and the "Transform" column shows the deviation from Gaussian for the transformed EEG values. Table I shows that overall the EEG values are well behaved, even without transforms. The only exceptions to this is in EEG phase, total power and absolute power. Transforms of coherence and amplitude asymmetry actually increased

skewness or kurtosis, thus blind transformations is not recommended. The asterisks in Table I identify which transformed variables are used in the Lifespan EEG normative database. It can be seen that only the transformed EEG phase and the power variables are contained in the database. Table I provides the statistics of Gaussian distribution of the database. The user of the normative database should take into account the different degrees of Gaussian fits of the different variables to understand which variables deviate from normality and to what extent. This information should be used when making clinical evaluations based on the database.

6.1- Statistical Foundations: Cross-Validation

As mentioned in section 5.0 the statistical accuracy or sensitivity of a normative database is judged, directly, by the Gaussian distribution of the database. The Supreme Court's *Dalbert* Factor One is met because the Gaussian is the null-hypothesis which was tested and Factor Two will be met by any database because the error estimate was tested and adjusted to approximate a Gaussian distribution. *Daubert* factors one and two are expressed as the Gaussian sensitivity and accuracy of a database as provided by cross-validation (see Figure 1). There are many different ways to cross-validate a database. One is to obtain independent samples and another is to compute Z scores for each individual subject in the database. The former is generally not possible because it requires sampling large numbers of additional subjects who have been carefully screened for clinical normality without a history of problems in school, etc. The second method is certainly possible for any database. Cross-validation of the Lifespan EEG database was accomplished by the latter method in which Z scores were computed using a leave-one-

out procedure for all variables from each individual subject based on his/her respective age matched mean and SD in the normative database. A distribution of Z scores for each of the 924 variables for each subject was then tabulated. Table II shows the results of the cross-validation of the 625 subjects in the normative EEG database.

A perfect Gaussian cross-validation would be 2.3% at + 2 S.D., 2.3% at – 2 S.D., 0.13% at + 3 S.D. and 0.13 % at – 3 S.D. Table II shows a cross-validation grand average of 2.58% to 1.98% ± 2 S.D. and 0.18% to 0.14 % ± 3 S.D. The Z score cross-validation results in Table II shows that the database is statistically accurate and sensitive

Table II: Gaussian Cross Validation of the EEG Normative Database

Measure	% >2 SD	% <2 SD	% >3 SD	% <3 SD
Delta Amplitude Asym.	2.58	3.08	0.21	0.19
Theta Amplitude Asym.	2.29	2.62	0.15	0.13
Alpha Amplitude Asym.	2.71	2.72	0.18	0.19
Beta Amplitude Asym.	2.68	2.65	0.15	0.15
Delta Coherence	1.99	2.14	0.14	0.22
Theta Coherence	2.22	1.88	0.22	0.16
Alpha Coherence	2.55	1.62	0.18	0.18
Beta Coherence	2.20	1.38	0.18	0.10
Delta Phase †	0.89	3.52	0	0.23
Theta Phase †	1.61	1.87	0.04	0.13
Alpha Phase †	1.61	1.66	0.04	0.24
Beta Phase †	2.83	0.72	0.27	0.03
Absolute Power †	4.15	1.67	0.23	0.12
Relative Power	4.09	0.52	0.68	0
Total Power †	4.23	1.60	0.08	0.04
Average	2.58	1.98	0.18	0.14

† Data was logged transformed

with slight differences between variables. For example, the power and EEG phase measures showed a small deviation from normality with a tendency toward skewness and kurtosis which is consistent with the values in Table I.

Figure 3 are the complex demodulation approximate Gaussian distributions in which the transforms or non-transforms in Table I were used and the sensitivity

calculated as illustrated in Figure 4. Table III is an example of a standard Table of Sensitivities for one of the FFT databases.

Figure 4 is an illustrative bell shaped curve showing the ideal Gaussian and the average cross-validation values of the database by which estimates of statistical sensitivity can be derived. True positives (TP) = the percentage of Z scores that lay within the tails of the

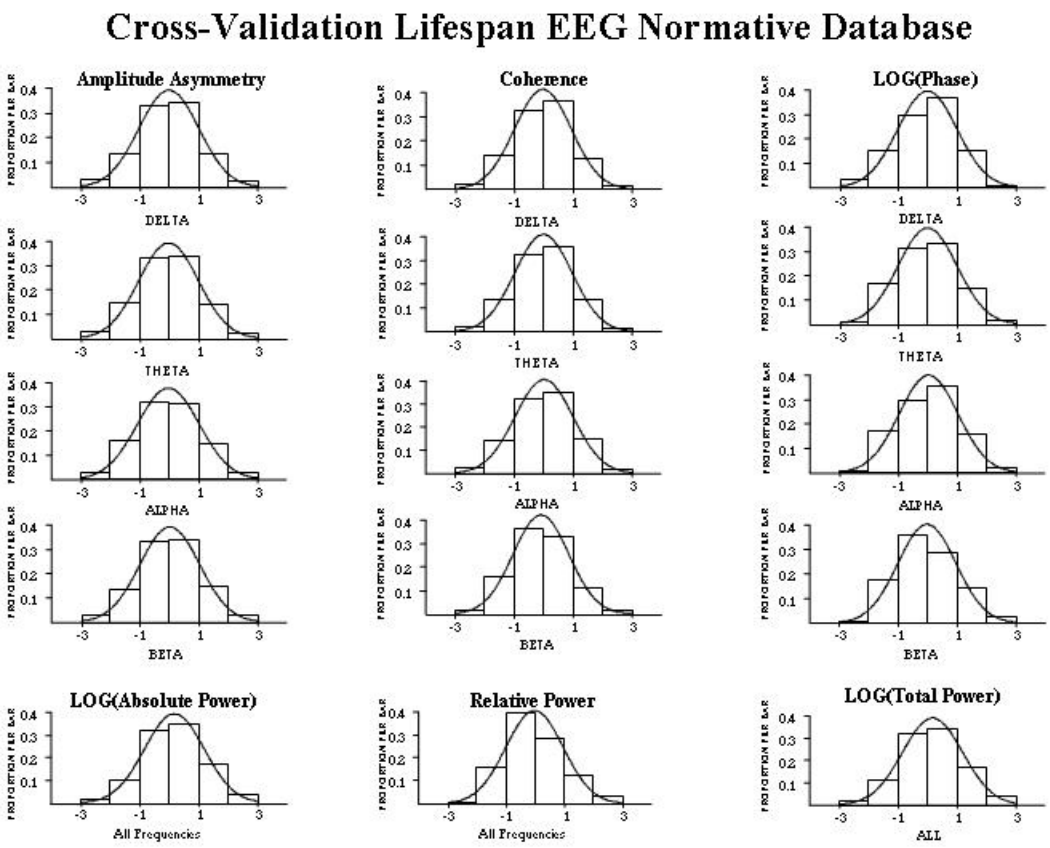


Fig. 3 - Histograms of the complex demodulation Z Score Cross-Validation for all ages.

Gaussian distribution, False negatives (FN) = the percentage of Z scores that fall outside of the tails of the Gaussian distribution. The error rates or the statistical sensitivity of a QEEG normative database are directly related to the deviation from a Gaussian

distribution. Figure 4 depicts a mathematical method of estimating the statistical sensitivity of a normative EEG database in terms of the deviation from Gaussian.

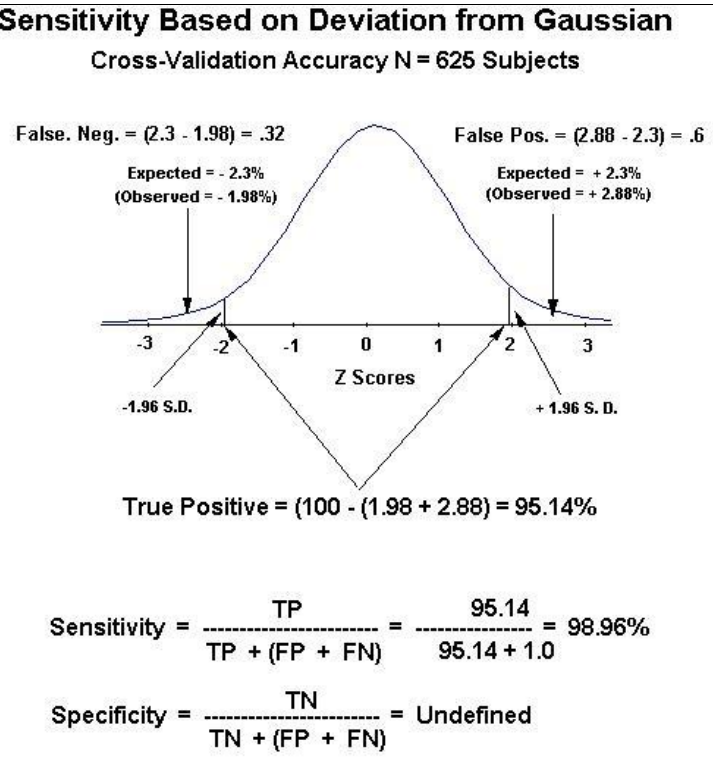


Fig. 4 - A normal curve showing values of Z (±1.96), which includes the proportion which is .95 of the total area. The left and right tails of the distribution show probability values of .025 (one-tailed). The results of the cross-validation of 625 subjects showed a classification accuracy that was normally distributed with 2.28% of the Z scores > ± 2 standard deviations and 0.16% of the Z scores > ± 3 SD. The clinical evaluation of EEG measures rely upon such a normal distribution by estimating the probability of finding an observed EEG value in a given range of a normal population and then empirically testing the sensitivity of the database by cross-validation.

Table III is an example of the calculated sensitivity of a EEG normative database for different age groups. This same table of

FFT Normative Database Sensitivities

2 STDEVs	CALC SENSITIVITY: FP=TP/(TP+FP) or FN=TP/(TP+FN)			
AGES	(+/- 2 SD)	(>= 2 SD)	(<= -2 SD)	
0-5.99	0.95448265	0.9771774	0.97730526	
6-9.99	0.95440363	0.9772031	0.97720054	+/- **2 Std. Dev.**
10-12.99	0.9543997	0.97724346	0.97715624	
13-15.99	0.95440512	0.97723601	0.97716911	
16-ADULT	0.9543945	0.97718143	0.97721307	
ALL	0.95442375	0.97720714	0.97721661	

3 STDEVs	CALC SENSITIVITY: FP=TP/(TP+FP) or FN=TP/(TP+FN)			
AGES	(+/- 3 SD)	(>= 3 SD)	(<= -3 SD)	
0-5.99	0.99743898	0.99871123	0.99872774	
6-9.99	0.99744112	0.99871611	0.99872501	+/- **3 Std. Dev.**
10-12.99	0.99744688	0.99873171	0.99871518	
13-15.99	0.99743186	0.99871951	0.99871234	
16-ADULT	0.99743835	0.99870216	0.99873619	
ALL	0.99744002	0.99871716	0.99872286	

Table III – Example of Normative EEG database sensitivities for different age groups at +/- 2 standard deviations and +/- 3 standard deviations. Linked Ears, Eyes Closed Condition.

sensitivity scores were calculated for the eyes open, eyes closed, absolute and relative power in current source density, average reference and linked ears. The percentage of Z scores in the tails of the Gaussian Distribution at +/- 2 SD for the various databases (LE = Lined Ears, AVE = Average Reference and CSD = Current Source Density are shown in figures 5 and 6 for the FFT eyes open and eyes closed normative databases.

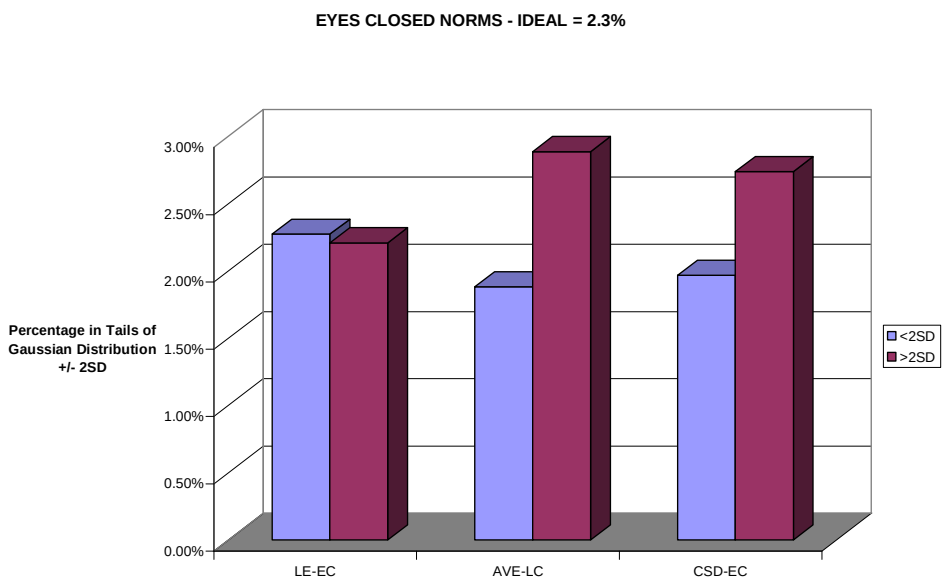


Fig. 5 - Bar graphs of percentage deviation of Z scores from the ideal Gaussian cross-validation in eyes closed Linked Ears, Average Reference and Current Source Density norms.

The reliability of different Gaussian databases can be measured directly by their deviation from Gaussian because the same normative individual subjects are used to validate the different EEG normative databases. For example, Average reference norms and Current

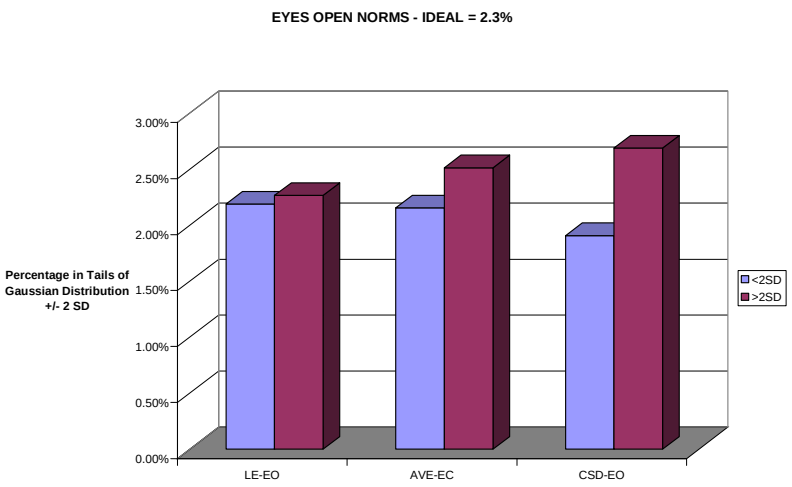


Fig. 6. - Bar graphs of the percentage deviation from the ideal Gaussian cross-validation in the eyes open condition Linked Ears, Average Reference and Current Source Density norms.

Source Density norms, when cross-validated using the same subjects as for the Linked Ears norms gives rise to a reliability coefficient and a statistical reliability reference. The null hypothesis , reliability = 0 can be directly tested using seven different norms in NeuroGuide.

Figure 7 is an example of visually verifiable reliability and repeatability of the spectra of Z scores using three different montages (Linked ears, Average Reference & Current Source Density) derived from the same edited samples of EEG in a traumatic brain injured patient (TBI)

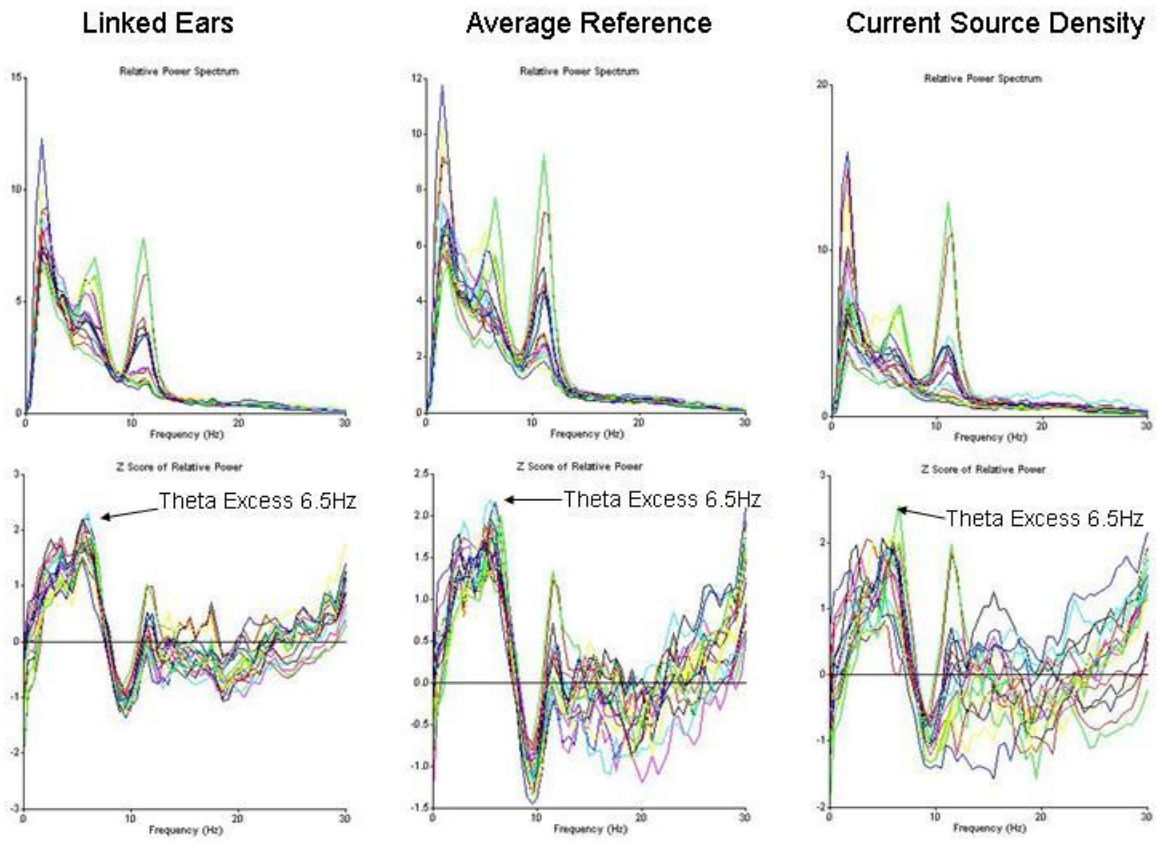


Fig. 7 - Example of reliability between different normative databases and montages in a TBI patient. The general spectral shape is consistently present while the magnitude of deviation from normal and the spatial localization of the deviation increased from Linked Ears to Average Reference to CSD. CSD (i.e., the second spatial derivative) is also more "noisy" as expected.

7.0 – Statistical Foundations: Validation by Clinical Correlations

Validity concerns the relationship between what is being measured and the natureand use to which the measurement is being applied. Another way to put it is that validity is defined as the extent to which any measuring instrument measures what it is intended to measure. Just as reliability is a matter of degree, so also is validity. Hypothesis formation and hypothesis testing as emphasized in *Daubert* (1993) is an important part of determining the validity of a scientific measure.

7.1 –Predictive Validity of Normative Databases

Predictive (or criterion) validity has a close relationship to hypothesis testing by subjecting the measure to a discriminant analysis or cluster analysis to some statistical analysis in order to separate a clinical sub-type from a normal reference database. Nunnally (1978) gives a useful definition of predictive validity as: "when the purpose is to use an instrument to estimate some important form of behavior that is external to the measuring instrument itself, the latter being referred to as criterion [predictive] validity." For example, science "validates" the clinical usefulness of a measure by its false positive and false negative rates and by the extent to which there are statistically significant correlations to other clinical measures and, especially, to clinical outcomes.

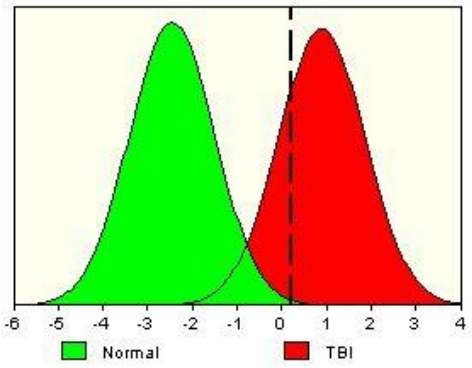
An example of predictive validity of the Linked Ears qEEG normative database is shown in figure 8 in which normative database was used to discriminate traumatic brain injured patients from age matched normal control subjects at a classification accuracy = 96.2% (Thatcher et al, 1989). Another example of predictive validity is the ability of qEEG normative values to predict cognitive functioning. Figure 9 shows correlations to Full Scale I.Q. as an example of predictive validity and content validity . A more

Traumatic Brain Injury Discriminant Analysis*

TBI DISCRIMINANT SCORE = 0.18

TBI PROBABILITY INDEX = 97.5%

The TBI Probability Index is the subject's probability of membership in the mild traumatic brain injury population. (see Thatcher et al, EEG and Clin. Neurophysiol., 73: 93-106, 1989.)



			RAW	Z
FP1-F3	COH	Theta	80.04	0.05
T3-T5	COH	Beta	72.31	1.71
C3-P3	COH	Beta	81.97	1.24
FP2-F4	PHA	Beta	0.27	-0.76
F3-F4	PHA	Beta	0.02	-1.55
F4-T6	AMP	Alpha	-7.28	0.97
F8-T6	AMP	Alpha	-57.97	1.18
F4-T6	AMP	Beta	37.23	1.13
F8-T6	AMP	Beta	10.49	1.84
F3-O1	AMP	Alpha	-76.60	0.25
F4-O2	AMP	Alpha	-98.94	-0.11
F7-O1	AMP	Alpha	116.15	-0.35
F4-O2	AMP	Beta	-37.23	0.07
P3	RP	Alpha	30.25	-1.37
P4	RP	Alpha	32.90	-1.15
O1	RP	Alpha	41.12	-1.03
O2	RP	Alpha	46.62	-0.75
T4	RP	Alpha	22.89	-1.11
T5	RP	Alpha	30.00	-1.27
T6	RP	Alpha	34.90	-1.10

Fig. 8 - Example of a typical scattergram in the content and predictive validation step in Figure 1. The y-axis is Full Scale I.Q. and other neuropsychological tests and the X-Axis is amplitude asymmetry ([(R+L/R-L) x 200], see Thatcher et al, 1983 for further details). The correlation between I.Q. and amplitude asymmetry in this example was $r = 0.460$, $N = 466$ and $P < .0001$)

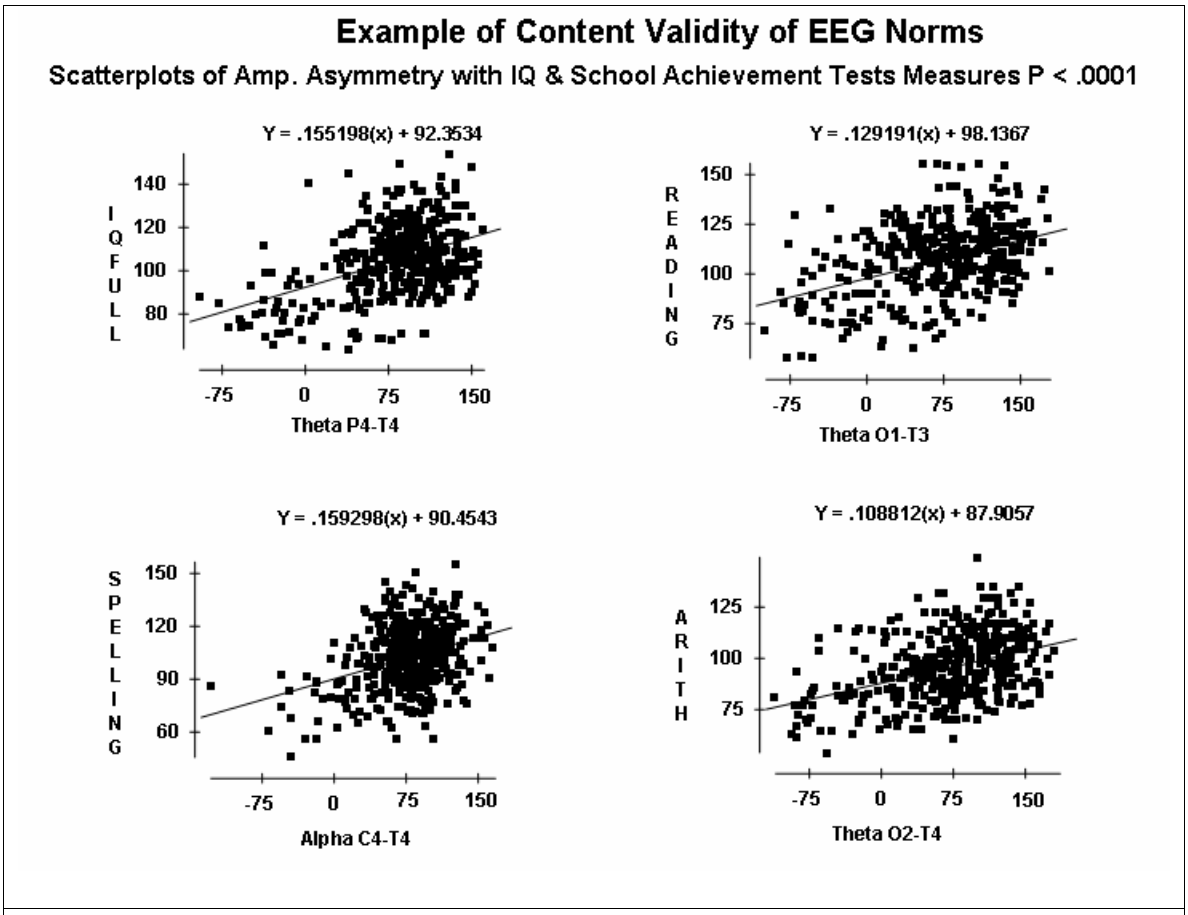


Fig. 9 - Example of a typical scattergram in the content and predictive validation step in Figure 1. The y-axis is Full Scale I.Q. and other neuropsychological tests and the X-Axis is amplitude asymmetry ([(R+L/R-L) x 200], see Thatcher et al, 1983 for further details). The correlation between I.Q. and amplitude asymmetry in this example was r = 0.460, N = 466 and P < .0001)

complete analysis of the predictive validity of the normative EEG database is shown in Table IV. In this table the percentage of statistically significant correlations at P < .01. between qEEG normative EEG and WRAT School Achievement scores and measures of intelligence.

EFFECT SIZE P < .01: qEEG Correlations with School Achievement & IQ Measures						
Percent Significant Correlations @ P < .01, N = 466						
Amplitude Asymmetry						
P <= .01	READING	SPELLING	ARITH	IQFULL	IQVERB	IQPERF
DELTA	**64%**	**61%**	**55%**	**64%**	**61%**	**61%**
THETA	**78%**	**70%**	**70%**	**70%**	**67%**	**59%**
ALPHA	**63%**	**63%**	**53%**	**64%**	**63%**	**52%**
BETA	**56%**	**56%**	**34%**	**58%**	**61%**	**47%**
Coherence						
P <= .01	READING	SPELLING	ARITH	IQFULL	IQVERB	IQPERF
DELTA	**27%**	**14%**	**41%**	**38%**	**22%**	**38%**
THETA	**27%**	**6%**	**36%**	**30%**	**27%**	**23%**
ALPHA	**9%**	**6%**	**45%**	**11%**	**14%**	**5%**
BETA	**11%**	**5%**	**38%**	**22%**	**17%**	**6%**
Absolute Phase						
P <= .01	READING	SPELLING	ARITH	IQFULL	IQVERB	IQPERF
DELTA	**11%**	**8%**	**8%**	**16%**	**6%**	**17%**
THETA	**9%**	**5%**	**8%**	**13%**	**9%**	**17%**
ALPHA	**9%**	**3%**	**33%**	**14%**	**19%**	**6%**
BETA	**9%**	**5%**	**30%**	**6%**	**9%**	**3%**
Relative Power						
P <= .01	READING	SPELLING	ARITH	IQFULL	IQVERB	IQPERF
DELTA	**13%**	**0%**	**31%**	**0%**	**6%**	**0%**
THETA	**56%**	**44%**	**94%**	**6%**	**6%**	**0%**
ALPHA	**19%**	**0%**	**75%**	**0%**	**0%**	**0%**
BETA	**13%**	**6%**	**44%**	**19%**	**13%**	**13%**
Relative Power Ratios						
P <= .01	READING	SPELLING	ARITH	IQFULL	IQVERB	IQPERF
Theta/Beta	**50%**	**44%**	**63%**	**56%**	**56%**	**50%**
Theta/Alpha	**13%**	**0%**	**69%**	**0%**	**0%**	**0%**
Alpha/Beta	**50%**	**31%**	**50%**	**38%**	**38%**	**25%**
Delta/Theta	**19%**	**25%**	**56%**	**19%**	**13%**	**25%**

Table IV – Percentage of statistically significant correlations with Intelligence and School Achievement from Linked Ears, Eyes Closed Condition.

7.2 –Examples of Content Validity of Normative Databases

Content validity is defined by the extent to which an empirical measurement reflects a specific domain of content. For example, a test in arithmetic operations would not be content valid if the test problems focused only on addition, thus neglecting

subtraction, multiplication and division. By the same token, a content-valid measure of cognitive decline following a stroke should include measures of memory capacity, attention and executive function, etc.

There are many examples of the clinical content validity of qEEG and normative databases in ADD, ADHD, Schizophrenia, Compulsive disorders, Depression, Epilepsy, TBI and a wide number of clinical groupings of patients as reviewed by Hughes and John, (1999). There are over 280 citations in the review by Hughes and John (1999) and there are approximately twenty three citations to peer reviewed journal articles in which a normal reference database was used. A year 2003 Internet search of the National Library of Medicine will give citations to many more qEEG and content validity peer reviewed studies using a reference normal group than were included in the Hughes and John (1999) review.

8.0 – Non-Parametric Statistics to Measure Content Validity of a qEEG Normative Database

Non-parametric statistics such as the Binomial Probability and for small sample sizes the Poisson Probability are simple non-parametric tests that are distribution free and automatically adjust for multiple comparisons. The catch is that the non-parametric statistics must define an hypothesis by a specific statistical probability alpha level, otherwise they do not work. . The Binomial Distribution which is defined as $P(X) = \binom{N}{x} p^x (1-p)^{N-x}$ of successful outcomes at a specific probability, for example, P < .01 for a specific hypothesis. N = the number of Z-tests, p is the 'success rate' and 1 – p the 'failure rate' for the test of the null hypothesis, x = the number of observed Z scores at a given probability level, e.g., P < .01. For example, the null hypothesis is that by chance there will be 1 event per 64 observations at P < .01. The experiment is run and there were 5 observations at P < .01. The exact probability as computed by the Binomial Equation = P < .000421394.

Figure 10 is an example of the statistical significance of some of the clinical correlations of the EEG database, i.e., Wide Range Achievement Test for Reading, Spelling, Arithmetic and Full Scale I.Q. E(X) is the expected number of correlations at P < .01, X = the number of observed correlations at P < .01 and P(X) = the Binomial Probability to reject the null-hypothesis. Table IV shows the observed percentage of correlations at P < .01 by which the X value in figure 10 corresponds..

BINOMIAL PROBABILITIES of Expected Significant Correlations @ P <=.01

Amplitude Asymmetry			Reading		Spelling		Arithmetic		IQFULL	
P <= .01	N	E(X)	X	P(X)	X	P(X)	X	P(X)	X	P(X)
DELTA	64	1	41	0.0000	39	0.0000	35	0.0000	41	0.0000
THETA	64	1	50	0.0000	45	0.0000	45	0.0000	45	0.0000
ALPHA	64	1	40	0.0000	40	0.0000	34	0.0000	41	0.0000
BETA	64	1	36	0.0000	36	0.0000	22	0.0000	37	0.0000

Coherence			Reading		Spelling		Arithmetic		IQFULL	
P <= .01	N	E(X)	X	P(X)	X	P(X)	X	P(X)	X	P(X)
DELTA	64	1	17	0.0000	9	0.0000	26	0.0000	24	0.0000
THETA	64	1	17	0.0000	4	0.0005	23	0.0000	19	0.0000
ALPHA	64	1	6	0.0000	4	0.0005	29	0.0000	7	0.0000
BETA	64	1	7	0.0000	3	0.0039	24	0.0000	14	0.0000

Absolute Phase			Reading		Spelling		Arithmetic		IQFULL	
P <= .01	N	E(X)	X	P(X)	X	P(X)	X	P(X)	X	P(X)
DELTA	64	1	7	0.0000	5	0.0000	5	0.0000	10	0.0000
THETA	64	1	6	0.0000	3	0.0039	5	0.0000	8	0.0000
ALPHA	64	1	6	0.0000	2	0.0265	21	0.0000	9	0.0000
BETA	64	1	6	0.0000	3	0.0039	19	0.0000	4	0.0005

Relative Power			Reading		Spelling		Arithmetic		IQFULL	
P <= .01	N	E(X)	X	P(X)	X	P(X)	X	P(X)	X	P(X)
DELTA	16	0	2	0.0005	0	0.1485	5	0.0000	0	0.1485
THETA	16	0	9	0.0000	7	0.0000	15	0.0000	1	0.0109
ALPHA	16	0	3	0.0000	0	0.1485	12	0.0000	0	0.1485
BETA	16	0	2	0.0005	1	0.0109	7	0.0000	3	0.0000

Relative Power Ratios			Reading		Spelling		Arithmetic		IQFULL	
P <= .01	N	E(X)	X	P(X)	X	P(X)	X	P(X)	X	P(X)
Theta/Beta	16	0	8	0.0000	7	0.0000	10	0.0000	9	0.0000
Theta/Alpha	16	0	2	0.0005	0	0.1485	11	0.0000	0	0.1485
Alpha/Beta	16	0	8	0.0000	5	0.0000	8	0.0000	6	0.0000
Delta/Theta	16	0	3	0.0000	4	0.0000	9	0.0000	3	0.0000

Fig. 10 - An example of the use of the non-Parametric statistic of the Binomial Probability Distribution to calculate the alpha level for the content validation of clinical

measures with the qEEG normative database. The Binomial Distribution which is defined as $P(X) = \binom{N}{x} p^x (1-p)^{N-x}$ of successful outcomes at a specific probability, for example, P < .01 for a specific hypothesis. N = the number of Z-tests, p is the 'success rate' and 1 – p the 'failure rate' for the test of the null hypothesis, x = the number of observed Z scores at a given probability level, e.g., P < .01. P(X) = the distribution free Binomial Probabilities. The percentage of statistically significant correlations at P < .01 is shown in Table IV.

9.0 – Effect Size of a Normative EEG Database

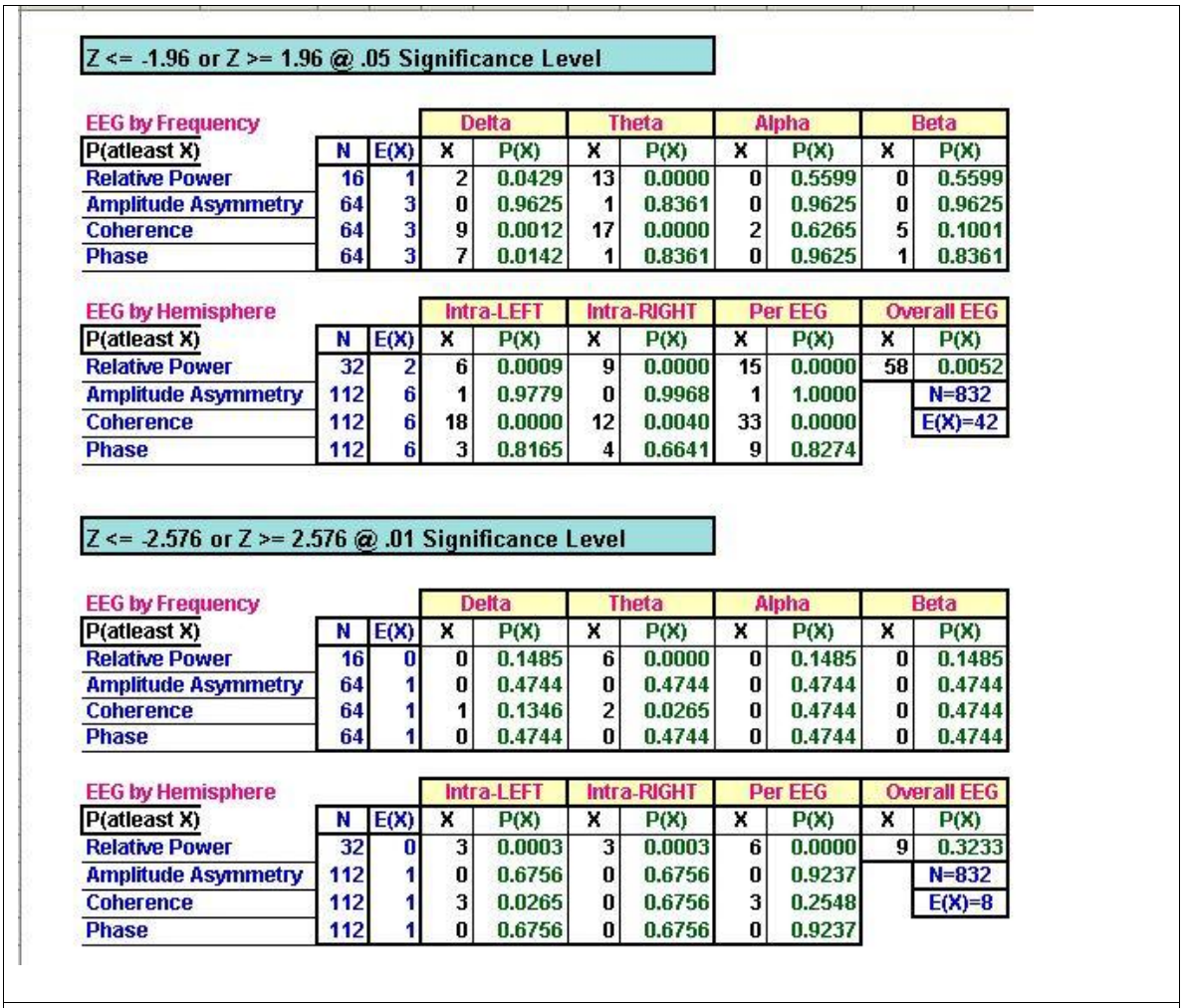
The Effect Size of a normative database for any set of clinical measures can be estimated from the percentage of statistically significant correlations (Cohen, 1977). Table IV are effect sizes based on the percentage of statistically significant observations at alpha set at P < .01. Based on the percentage in Table IV, one can translate the number in the column X in figure 9 as the number observed out of a total universe of correlations. It can be seen that amplitude asymmetry and ratios of power have the strongest effect size, especially in arithmetic and I.Q. The peer reviewed literature clearly demonstrates that qEEG is clinically valid with varying effect sizes (Hughes and John, 1999). Estimates of effect size are relative clinical validation measures that a clinician or scientist takes into consideration when rendering a clinical or scientific judgment. Effect size is also useful in counseling graduate students to calculate the sample size that they will need in their thesis by Power Analysis.

10.0 – Non-Parametric Statistics, Estimates of Alpha Levels and the Issue of Multiple Comparisons in a Single Subject Comparison to a EEG Normative Database

The use of many t-tests or Z tests in EEG applications requires some adjustment for the total number of tests in order to accurately estimate levels of alpha or the

probability of a Type I error (i.e., saying something is statistically significant when it is not). As explained by Hayes (1973) Multiple comparisons refers to multiple group comparisons and not to the adjustment of the total number of t-tests or Z-tests, where as, non-parametric statistics is one of the best methods to adjust for both Type I and Type II error rates.

Figure 11 shows an example of the use of the Binomial Probability Distribution to determine the alpha level for a single subject's comparison to the complex demodulation normative database. The number of Z tests is represented as 'N', E(X) = the number expected by chance alone at $P < .05$ (Top of Figure 10) or at $P < .01$ (Bottom of Figure 11), X = the number of successful Z tests observed and P(X) = the Binomial Probability.



Z <= -1.96 or Z >= 1.96 @ .05 Significance Level

EEG by Frequency			Delta		Theta		Alpha		Beta	
P(atleast X)	N	E(X)	X	P(X)	X	P(X)	X	P(X)	X	P(X)
Relative Power	16	1	2	0.0429	13	0.0000	0	0.5599	0	0.5599
Amplitude Asymmetry	64	3	0	0.9625	1	0.8361	0	0.9625	0	0.9625
Coherence	64	3	9	0.0012	17	0.0000	2	0.6265	5	0.1001
Phase	64	3	7	0.0142	1	0.8361	0	0.9625	1	0.8361

EEG by Hemisphere			Intra-LEFT		Intra-RIGHT		Per EEG		Overall EEG	
P(atleast X)	N	E(X)	X	P(X)	X	P(X)	X	P(X)	X	P(X)
Relative Power	32	2	6	0.0009	9	0.0000	15	0.0000	58	0.0052
Amplitude Asymmetry	112	6	1	0.9779	0	0.9968	1	1.0000		N=832
Coherence	112	6	18	0.0000	12	0.0040	33	0.0000		E(X)=42
Phase	112	6	3	0.8165	4	0.6641	9	0.8274		

Z <= -2.576 or Z >= 2.576 @ .01 Significance Level

EEG by Frequency			Delta		Theta		Alpha		Beta	
P(atleast X)	N	E(X)	X	P(X)	X	P(X)	X	P(X)	X	P(X)
Relative Power	16	0	0	0.1485	6	0.0000	0	0.1485	0	0.1485
Amplitude Asymmetry	64	1	0	0.4744	0	0.4744	0	0.4744	0	0.4744
Coherence	64	1	1	0.1346	2	0.0265	0	0.4744	0	0.4744
Phase	64	1	0	0.4744	0	0.4744	0	0.4744	0	0.4744

EEG by Hemisphere			Intra-LEFT		Intra-RIGHT		Per EEG		Overall EEG	
P(atleast X)	N	E(X)	X	P(X)	X	P(X)	X	P(X)	X	P(X)
Relative Power	32	0	3	0.0003	3	0.0003	6	0.0000	9	0.3233
Amplitude Asymmetry	112	1	0	0.6756	0	0.6756	0	0.9237		N=832
Coherence	112	1	3	0.0265	0	0.6756	3	0.2548		E(X)=8
Phase	112	1	0	0.6756	0	0.6756	0	0.9237		

Fig. 11 - An example of the use of the non-Parametric statistic of the Binomial Probability Distribution to calculate the alpha level for the complex demodulation norms for a given patient. N = the total number of Z scores in the measure set, (X) = the number of observed Z scores at P < .05 and P .01; E(X) = the probability of the number of expected Z scores at P < .05 or at the probability P < .01.

Figure 11 is only one example of how non-parametric statistics can be used to eliminate multiple comparison problems.

11.0 – Peer Reviewed Publications and Independent Replications

The Lifespan EEG database presented in this paper is unique and represents a sample or a "snap shot" of electrical events in a medium size population. The oldest person in the database was age 82 but the sample size from 50 to age 100 needs to be

lexpanded as the population grows older. Each normative EEG database is necessarily unique by virtue of subject selection, number of subjects, age span and arrangement of the subjects and the digital methods. Also, each EEG database uses different methods to acquire the EEG and to edit and analyze the EEG and, therefore, replication and comparisons across EEG databases are often difficult. In order to use any EEG normative database matching of amplifiers and analytic methods must first be accomplished. It should be kept in mind, that even with matching of amplifier characteristics within 3 to 5% error the enormous variability in skull thickness effects the amplitude and frequency characteristics of the EEG itself far more than slight differences in amplifier characteristics. For example, the human skull is on the average 80 times less conductive than the brain and scalp. Therefore, an individual with a 10% thinner skull may be result in a 800% change in EEG amplitude across all frequencies.

Although precise replication is difficult for any of the existing EEG databases, nevertheless, independent replication of certain aspects of the Lifespan EEG Database have been published. Also, most of the acquisition methods, analysis methods and results of experiments using the Lifespan EEG database have been published in refereed journals which are cited below. Aspects of the development of relative power of the Lifespan EEG norms have been replicated in studies by Matousek and Petersen (1973) as analyzed by John et al (1977); Fischer (1987); Thatcher (1980), Epstein (1981), and van Baal (1995) Aspects of the EEG coherence development in the database presented in this paper have been replicated by Gasser et al (1988) and by van Baal and others in genetic analyses (van Baal, 1997; van Beijsterveldt CE, et al, 1998; van Baal GC, et al, 1998).

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