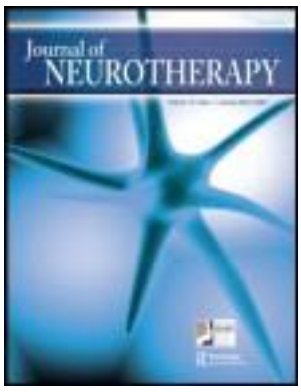

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Quantitative EEG Normative Databases: Validation and Clinical Correlation

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Quantitative EEG Normative Databases: Validation and Clinical Correlation

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SUMMARY. The quantitative digital electroencephalogram (QEEG) was recorded from 19 scalp locations from 625 screened and evaluated normal individuals ranging in age from two months to 82 years. After editing to remove artifact, one-year to five-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

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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 standard deviations (SD) equals approximately 2.3% and the average percentage for ± 3 SD equals approximately 0.13%. 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 theory 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.

KEYWORDS. EEG normative databases, gaussian distributions, error estimates

INTRODUCTION

There are many potential uses of a normative electroencephalogram (EEG) database. Among the most important it is 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. 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

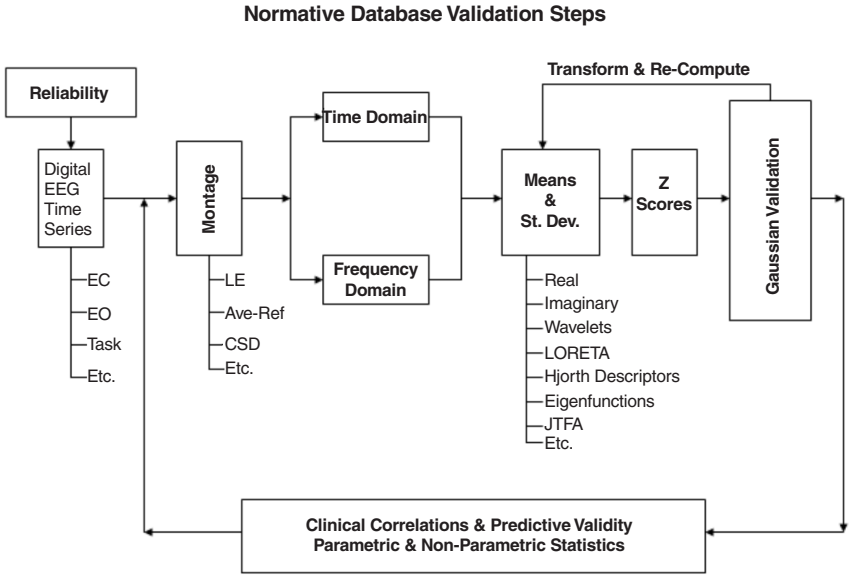
Courts are: (a) hypothesis testing, (b) error estimates of reliability and validity, (c) peer-reviewed publications and (d) general acceptance (Mahle, 2001; Thatcher, Biver, & North, 2003. These four *Daubert* factors have already been met for several EEG normative databases (John, Prichep, & Easton, 1987; Duffy, Hughes, Miranda, Bernad, & Cook, 1994; Thatcher, Walker, & Guidice, 1987; Thatcher et al., 2003). The minimal standards of publication are: (a) inclusion/exclusion criteria, (b) methods to remove artifact and adequate sample sizes per age groups, (c) demographically representative (e.g., balanced gender, ethnicity, socioeconomic status, etc.), (d) means and standard deviations as being normally distributed or gaussian including gaussian cross-validation, and (e) content validity by correlations with clinical measures, neuropsychological test scores and school achievement scores, etc., as validation. Predictive validity is determined by regression and classification statistics. Predictive validity relates to the estimation of classification accuracy, clinical severity, clinical outcome, etc. 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).

The purpose of this paper is to review the current NeuroGuide normative database which uses the University of Maryland EEG normative database in which the methods and clinical validity have been published (Thatcher, McAlaster, Lester, Horst, & Cantor, 1983; Thatcher, Walker, & Guidice, 1987; Thatcher, 1991, 1992, 1994, 1998) and then to illustrate step by step the procedures that NeuroGuide used to meet measurable standards of reliability and validity of clinical correlation using the University of Maryland EEG data as an example of how to construct a normative database. Similar steps to construct a normative EEG database were described for the NYU School of Medicine database by John, Prichep, and Easton (1987). However, important differences in tests of clinical validity and age groupings were used in comparison to the NeuroGuide methods described in this paper. The reader is encouraged to read the John et al. (1987) paper in order to broaden understanding about the foundations of EEG normative databases.

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.

FIGURE 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 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).



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.

The selected normal subjects are grouped by age with a sufficiently large sample size. 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, Z-scores are computed for each subject in the database and leave one out gaussian cross-validation is computed in order to arrive at optimum gaussian cross-validation sensitivity. Finally the gaussian validated norms are subjected to content and predictive valida-

tion 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.

STEPS TO PRODUCE A NORMATIVE EEG DATABASE

The steps in Figure 1 can be repeated for different selections of subjects, different selections of derived measures and different frequency and spatio-temporal transforms for any normative QEEG database. The gaussian distribution is emphasized because most other distributions, such as the chi square distribution, F distribution, t distribution and Kamma distribution can be mathematically transformed into a gaussian distribution (Hayes, 1973). Also, the scientific standards of parametric statistics are best applied when means and standard deviations are gaussian distributed (John et al., 1987; John, Prichep, Fridman, & Easton, 1988; Duffy et al., 1994; Thatcher, 1998; Thatcher, Biver & North, 2003).

SUBJECT AND VARIABLE SELECTION

Nineteen (19) channels of EEG and an Electro-Oculogram (EOG) 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; Thatcher et al., 1987; Thatcher, 1998). 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 clinical and psychometric protocols were utilized in the recruitment of normal subjects. A total of 1,015 subjects ranging in age from two 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, 1998). In 2000 the original digital EEG was revisited and a different selection of individuals was selected that also spanned the same interval from two months to 82 years and included 61 additional adult subjects to increase the total sample size to 625 subjects. The expanded selection contained more individuals between the ages of 25 and 55 years of age.

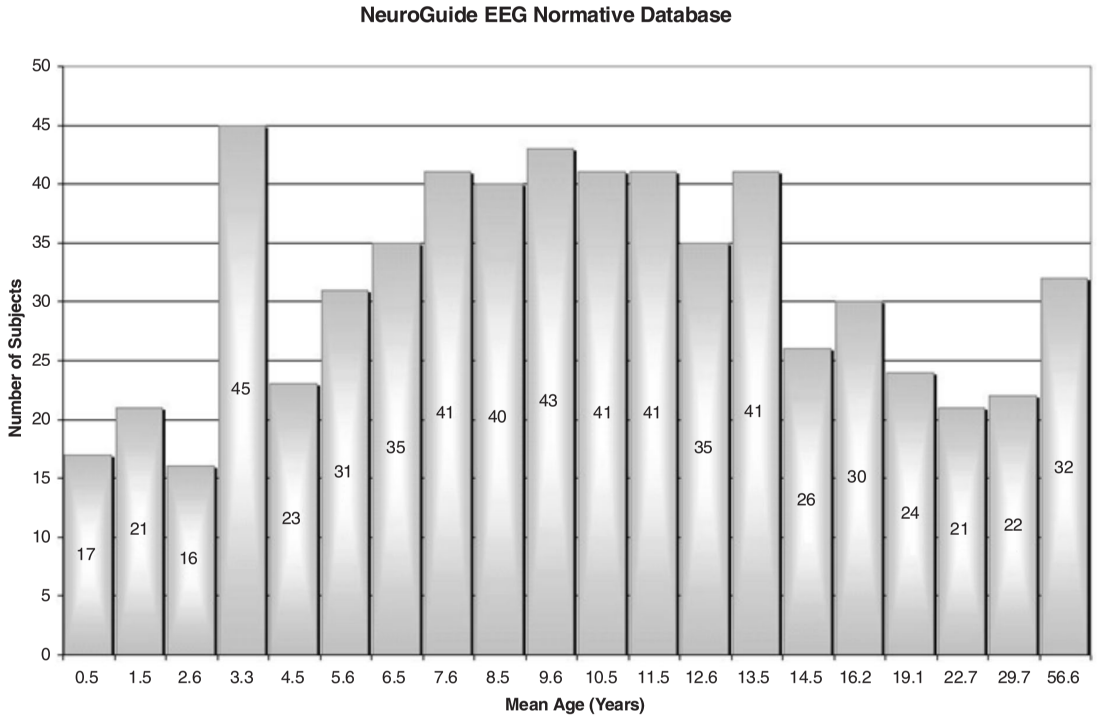
Figure 2 shows the number of subjects per year in the normative EEG lifespan database. It can be seen that the largest number of subjects are in the younger ages (e.g., 1 to 14 years, N = 470) when the EEG is changing most rapidly. As mentioned previously, a proportionately smaller number of subjects represent 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 (N = 16).

For each subject, original selections of the digital EEG occurred by different artifact procedures involving the use of NeuroGuide editing selections (www.appliedneuroscience.com). Original arrangements of coherence, phase, amplitude asymmetry and relative power also occurred when comparing the database to previous publications (Thatcher et al., 1987; Thatcher, 1998). Although different selections of digital EEG values and different arrangements of the original digital EEG have occurred since 1987, the gaussian validations and sensitivities of the previous databases and the current 2003 database are all similar and equally valid and gaussian distributed within a 90 to 99 percent range depending on the measure. The original digital EEG, the subjects and neuropsychological test scores that were measured from 1979 to 1987 are the same.

INCLUSION/EXCLUSION CRITERIA, DEMOGRAPHICS AND GENDER

Details of the neuropsychological testing, demographic and sampling of the normative 1987 EEG database were previously published in

FIGURE 2. The number of subjects per year in the Lifespan EEG reference normative database. The database is a “life-span” database with two 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 0.5 years to 62.6 years of age and constituting a total of 625 subjects.



Thatcher et al. (1983), Thatcher and Krause (1986), Thatcher et al. (1987) and Thatcher (1998). Some but not all of the 61 adults added in 2000 to 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 two months to 18 years was determined by one or more exclusion/inclusion criteria: (a) a neurological history questionnaire given to the child's parents and/or filled out by each subject, (b) psychometric evaluation of IQ and/or school achievement, (c) 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 more than 18 years of age and those in which information was available about a history of problems as an adult were excluded.

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 IQ 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 Wechsler 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, Lester, McAlaster, & Horst, 1982; Thatcher et al., 1983 for further details).

The criteria for entry into the normative database for those subjects given IQ tests and school achievement tests were:

1. A Full Scale IQ > 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).

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 (see Thatcher et al., 1983 for details).

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 and Petersen (1973); Thatcher, Walker, Gerson, and Geisler (1989); John et al. (1988); and Duffy et al. (1994) EEG normative databases.

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 (i.e., a total of 20 channels; Thatcher et al., 1983; Thatcher & Krause, 1986; Thatcher et al., 1987; Thatcher, 1998). 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. A permanent record made before and after each test session. The frequency response of the amplifiers was approximately three decibels 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 10 K ohms (most of the impedances were < 5 K ohms) for all subjects.

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 one- to two-second template of "clean" or "artifact free" EEG was selected. This template was then used to compute matching amplitudes of EEG using 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 in-

spect 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 was present in any of the EEG records.

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 CSD directed at right angles to the surface of the scalp in the vicinity of each scalp location (Pascual-Marqui, Gonzalez-Andino, Valdes-Sosa, & Biscay-Lirio, 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).

COMPLEX DEMODULATION COMPUTATIONS

The mathematical details of both the FFT and complex demodulation are described in Otnes and Enochson (1972), Bendat and Piersol (1980), and Thatcher (1998). The NeuroGuide 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 & Enochson, 1972).

FFT LINKED EARS, AVERAGE REFERENCE AND LAPLACIAN

The 100 samples per second digital EEG were first cubic-spline interpolated to 128 samples per second using standard procedures (Press, Teukolsky, Vettering, & Flannery, 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 appending short segments of EEG using the NeuroGuide editor. The third step was to compute the FFT power spectral density. Two-second epochs were used to compute the FFT power spectral density thus producing 0.5 Hz resolution and a Cosine window was used for each FFT computation. The 25% 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 two-second epochs (i.e., 256 points) were overlapped by 500 millisecond steps (64 points) in order to minimize the effects of the FFT windowing procedure. The FFT power spectral density and the average of the two second overlapping epochs produced a total of 61 frequency values in μv^2/Hz from 0 to 30 Hz at 0.5 Hz resolution.

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. The FFT normative database did not use sliding averages of age in the manner of the complex demodulation database (see Thatcher, 1998). Instead, five sequential age groupings were selected to cover the age range from two months to 82 years. The age groupings were: (a) two months to 5.99 years (N = 122), (b) 6.0 years to 9.99 years (N = 147), (c) 10 to 13 years (N = 72), (d) 13 to 16 years (N = 117) and (e) 16 to 82 years (N = 167).

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 single Hz steps and at three different microvolt 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 frequency characteristics of the norms.

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 result in an 800% change in EEG amplitude across all frequencies. This is one of the reasons that relative measures and ratios are especially important because these measures can naturally correct for amplifier differences and differences in skull thickness.

STATISTICAL FOUNDATIONS: GAUSSIAN DISTRIBUTIONS

The gaussian or normal distribution is a non-linear function that looks like an 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 equal zero. In the real world of data sampling distributions, skewness and kurtosis equal to zero 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 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 five percent of the samples will be equal to or greater than ± 2 standard deviations (SD) and approximately .13% ± 3 SD.

It is important to note that automatic and blindly applied transformations of EEG measures do 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. Table 1 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 EEG values and the "Transform" column shows the deviation from gaussian for the transformed EEG values. Table 1 shows that overall the EEG values are well behaved, even without transforms. The only exceptions to this are in EEG phase, total power and absolute power. Transforms of coherence and amplitude asymmetry actually increased skewness or kurtosis, thus blind transformations are not recommended. The asterisks in Table 1 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 1 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.

STATISTICAL FOUNDATIONS: CROSS-VALIDATION

As mentioned in the section on Amplifier and Digital Matching, the statistical accuracy or sensitivity of a normative database is judged

TABLE 1. 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

directly by the gaussian distribution of the database. The Supreme Court's *Daubert* 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 2 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 SD, 2.3% at −2 SD, 0.13% at +3 SD and 0.13% at −3 SD. Table 2 shows a cross-validation grand average of 2.58% to 1.98% ± 2 SD and 0.18% to 0.14% ± 3 SD. The Z-score cross-validation results in Table 2 show that the database is statistically accurate and sensitive 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 1.

TABLE 2. 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

Figure 3 shows the complex demodulation approximate gaussian distributions in which the transforms or non-transforms in Table 1 were used and the sensitivity calculated as illustrated in Figure 4. Table 3 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 equal the percentage of Z-scores that lay within the tails of the gaussian distribution. False negatives (FN) equal the percentage of Z-scores that fall outside of the tails of the gaussian distribution. The error rates or the statistical sensitivity of a quantitative electroencephalogram 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.

Table 3 is an example of the calculated sensitivity of an EEG normative database for different age groups. This same table of sensitivity scores was 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 $\pm$ 2 SD for the various databases (LE = linked 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.

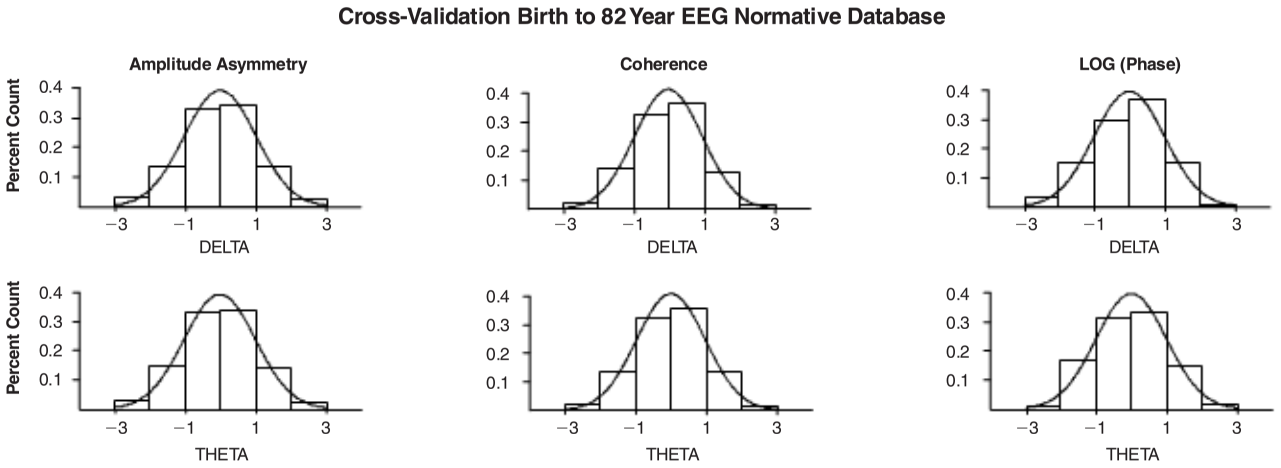
The reliability of different gaussian databases can be measured directly by their deviation from gaussian because the same normative individual subjects are used to validate the different EEG normative databases. For example, average reference norms and current source density norms, when cross-validated 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 equals zero, 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 (LE, AVE and CSD) derived from the same edited samples of EEG in a traumatic brain injured patient (TBI).

STATISTICAL FOUNDATIONS: VALIDATION BY CLINICAL CORRELATIONS

Validity concerns the relationship between what is being measured and the nature and use to which the measurement is being applied. An-

FIGURE 3. Histograms of the complex demodulation Z-score cross-validation for all ages.



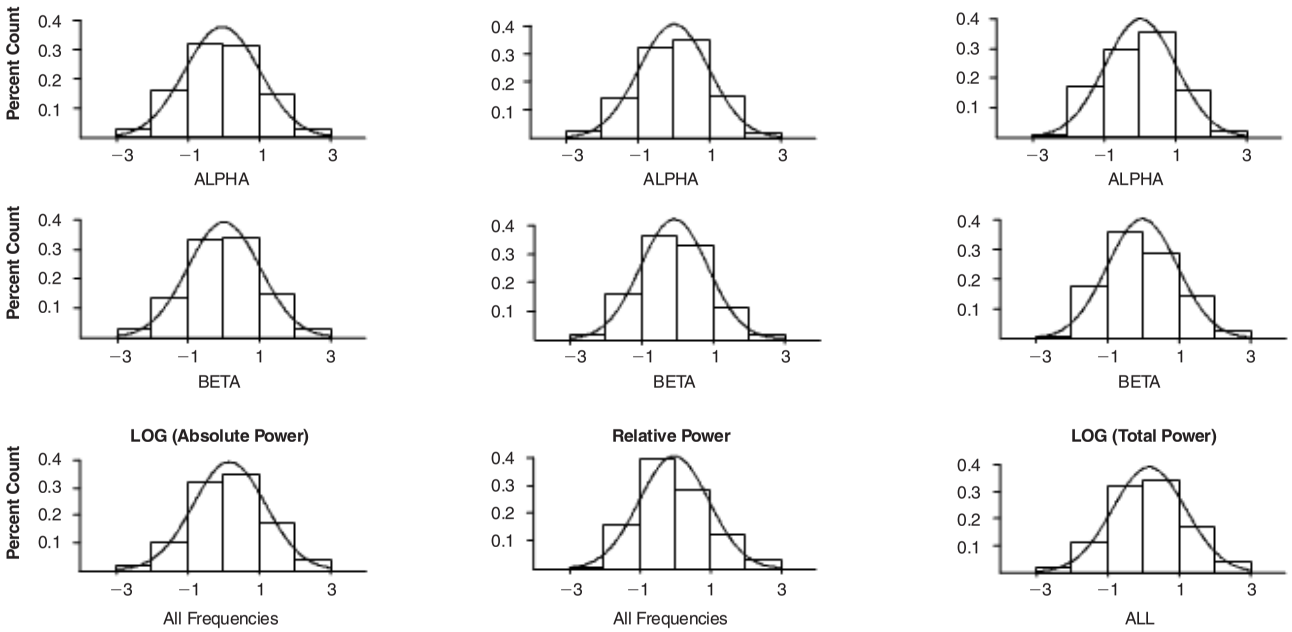
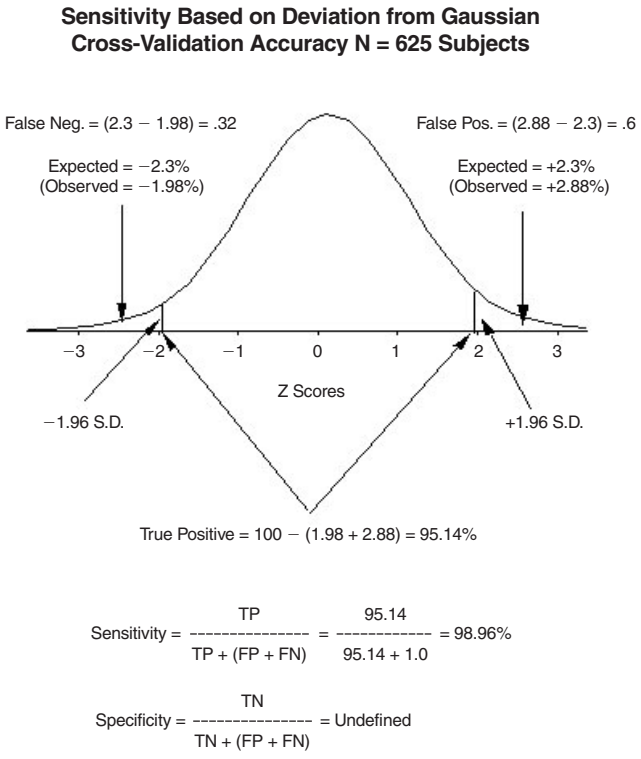

Percent Count
0.4
0.3
0.2
0.1
−3
−1
1
3
ALPHA
BETA
LOG (Absolute Power)
All Frequencies
Relative Power
All Frequencies
LOG (Total Power)
ALL

FIGURE 4. A normal curve showing values of Z (± 1.96), which includes the proportion which is 0.95 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 (SD) 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.



other 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 is validity. Hypothesis formation and hypothesis testing as emphasized in *Daubert* (1993) is an important part of determining the validity of a scientific measure.

TABLE 3. FFT Normative Database Sensitivities

2 STDEVs	CALC SENSITVITY: 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	± **2 Std. Dev.**
6-9.99	0.95440363	0.9772031	0.97720054	
10-12.99	0.9543997	0.97724346	0.97715624	
13-15.99	0.95440512	0.97723601	0.97716911	
16-ADULT	0.9543945	0.97718143	0.97716911	
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	± **3 Std. Dev.**
6-9.99	0.99744112	0.99871611	0.99872501	
10-12.99	0.99744688	0.99873171	0.99871518	
13-15.99	0.99743186	0.99871951	0.99871237	
16-ADULT	0.99743835	0.99870216	0.99873619	
ALL	0.99744002	0.99871716	0.99872286	

PREDICTIVE VALIDITY OF A QEEG NORMATIVE DATABASE

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 the normative database was used to discriminate TBI patients from age-matched normal control subjects at a classification accuracy equal to 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 IQ as an example of predictive validity and content validity. A more complete analysis of the predictive validity of the normative EEG database is shown in Table 4. In Table 4 the percentage

FIGURE 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.

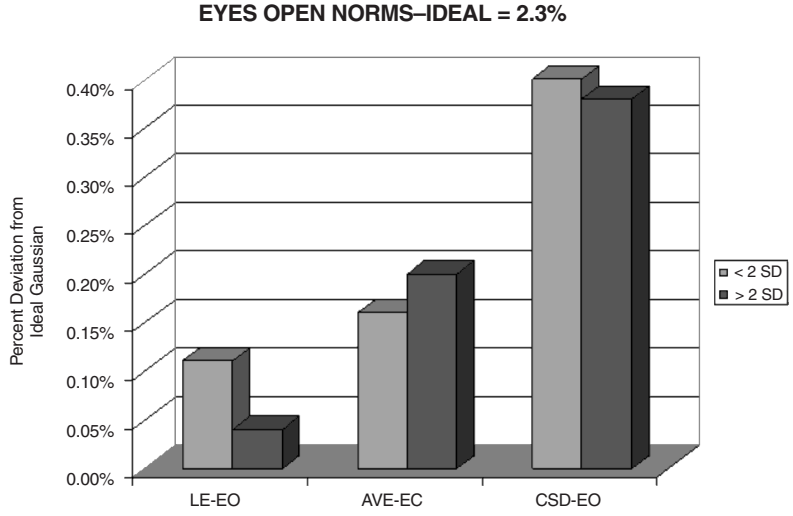


FIGURE 6. Bar graphs of the percentage deviation from the ideal gaussian cross-validation in the eyes-open condition linked ears, average reference and current source density norms.

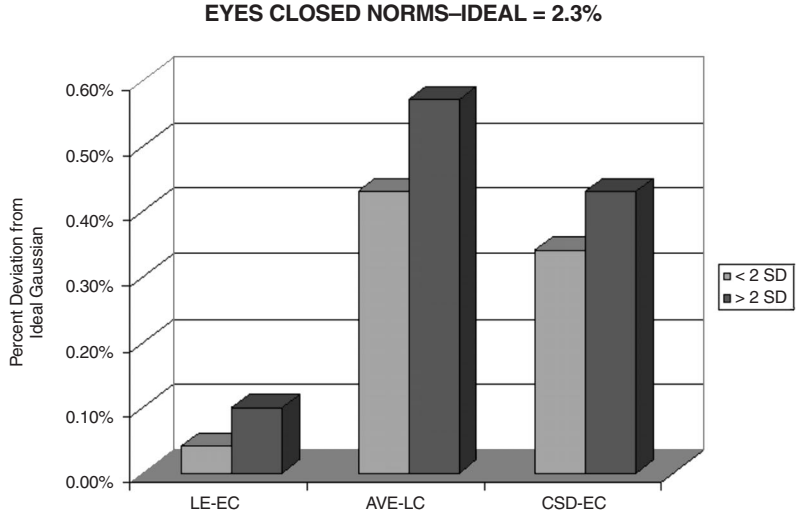


FIGURE 7. Example of reliability between different normative databases and montages in a TBI patient. The general spectral shape is consistently present while the magnitude of deviation from normal and the spatial localization of the deviation increased from linked ears to average reference to current source density (CSD).

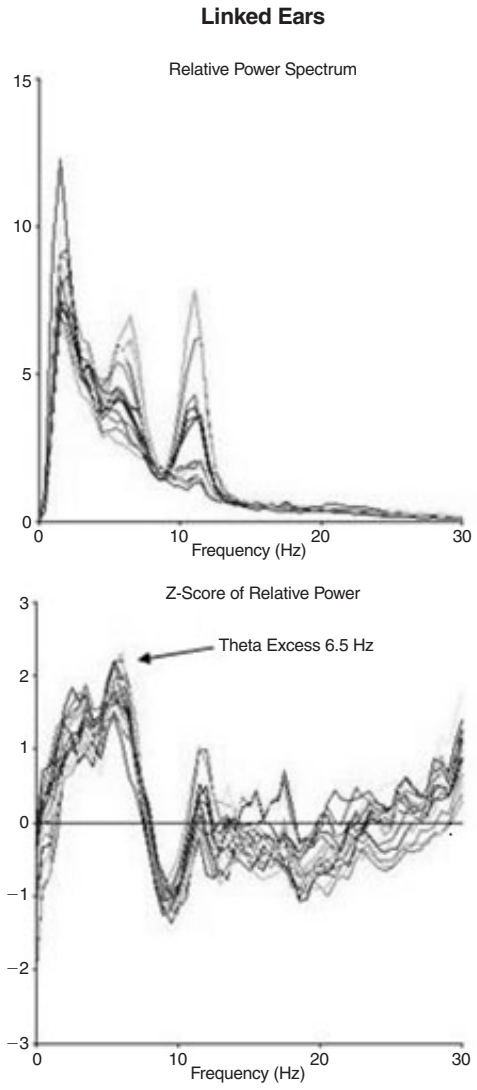
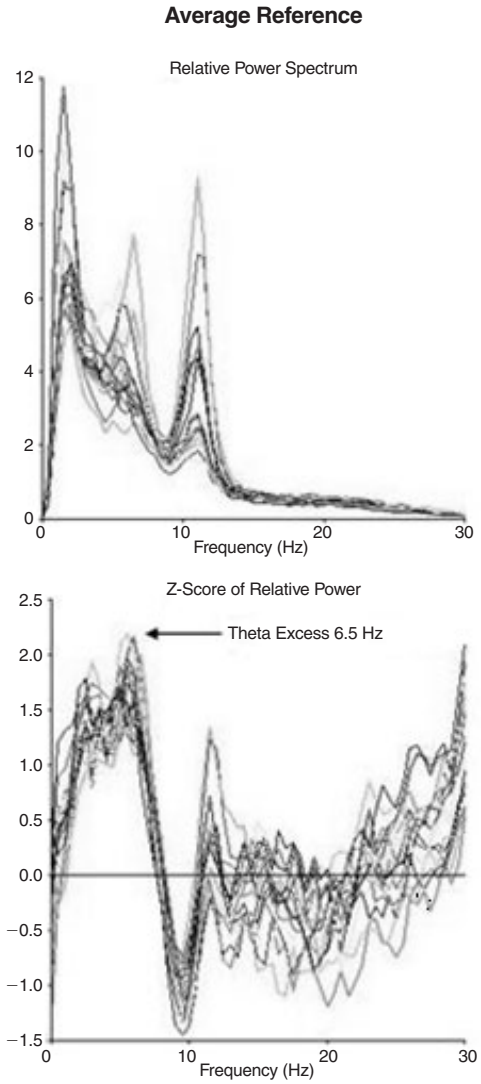


FIGURE 7 (continued)



Current Source Density

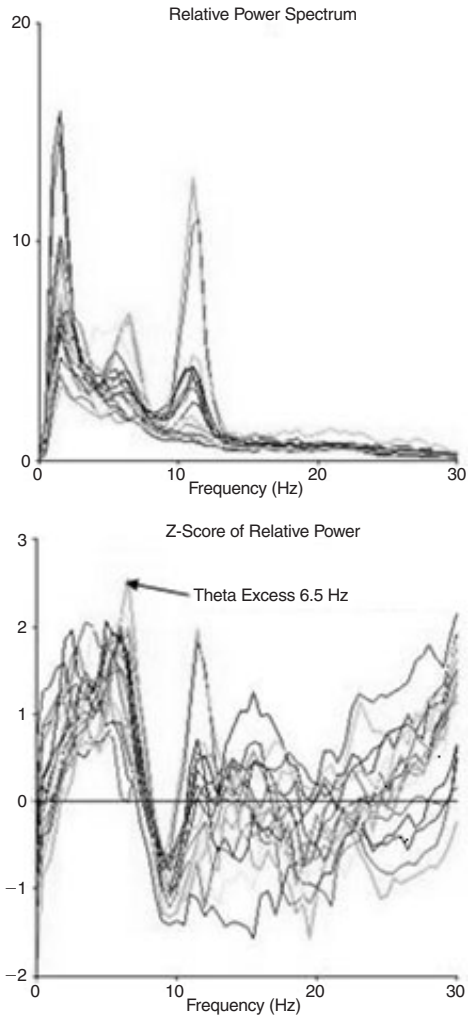
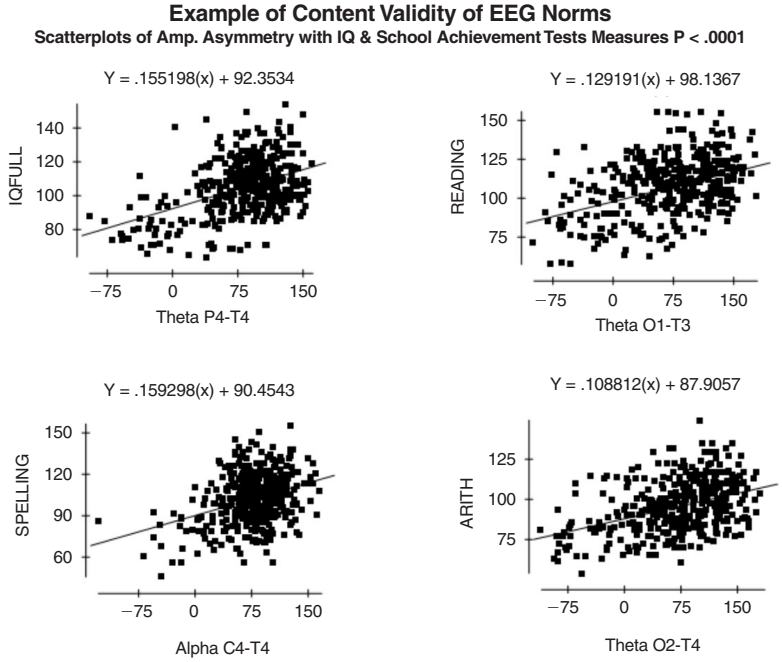


FIGURE 8. Example of a typical scattergram in the content and predictive validation step in Figure 1. The y-axis is full scale IQ and the x-axis is amplitude asymmetry ([(R + L/R − L) × 200], see Thatcher et al., 1983 for further details). The correlation between IQ and amplitude asymmetry in this example was r = 0.460, N = 466 and P < .0001.



of statistically significant correlations at P < .01 between QEEG, normative EEG, and WRAT school achievement scores and measures of intelligence are shown.

EXAMPLES OF CONTENT VALIDITY OF A QEEG NORMATIVE DATABASE

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.

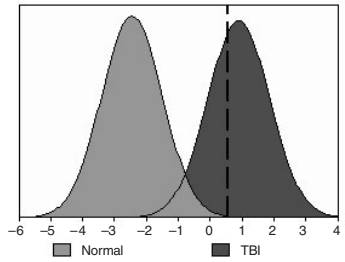
FIGURE 9. An example of the normative database predictive validity as demonstrated in a discriminant analysis of 264 mild traumatic brain injured patients and 108 age-matched normal control subjects (Thatcher et al., 1989). The discriminant accuracy, upon replication, was > 95%.

Montage: LINKEARS EEG ID: Demo1

Traumatic Brain Injury Discriminant Analysis

TBI DISCRIMINANT SCORE = 0.53 TBI PROBABILITY INDEX = 99.0%

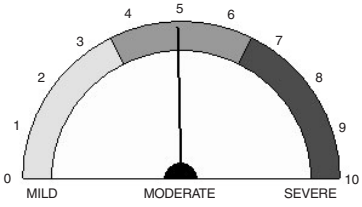
The TBI Probability Index is the subject's probability of membership in the mild traumatic brain injury population (see Thatcher et al., EEG and Clin. Neurophysiol., 73: 93-106, 1989).



			RAW	Z
FP1-F3	COH	Theta	82.41	0.49
T3-T5	COH	Beta	71.81	1.64
C3-P3	COH	Beta	82.19	1.38
FP2-F4	PHA	Beta	0.11	−1.16
F3-F4	PHA	Beta	0.16	−1.26
F4-T6	AMP	Beta	3.67	1.22
F8-T6	AMP	Alpha	−57.85	1.25
F4-T6	AMP	Alpha	35.04	1.02
F8-T6	AMP	Beta	9.93	1.68
F3-O1	AMP	Alpha	−75.59	0.44
F4-O2	AMP	Alpha	−88.52	0.25
F7-O1	AMP	Alpha	120.33	−0.49
F4-02	AMP	Beta	−36.64	0.19
P3	RP	Alpha	29.91	−1.29
P4	RP	Alpha	31.14	−1.16
O1	RP	Alpha	40.26	−1.03
O2	RP	Alpha	43.11	−0.90
T4	RP	Alpha	21.37	−1.19
T5	RP	Alpha	29.34	−1.20
T6	RP	Alpha	31.69	−1.21

TBI SEVERITY INDEX = 4.91

This severity score places the patient in the MODERATE range of severity.



			RAW	Z
FP1-C3	COH	Delta	56.57	0.96
FP1-FP2	COH	Theat	95.12	1.62
O1-F7	COH	Alpha	9.94	−1.14
O2-T6	COH	Alpha	85.79	0.46
P3-O1	COH	Beta	85.04	1.57
FP1-T3	PHA	Theta	−1.63	−0.83
T3-T4	PHA	Theta	3.94	−1.20
O1-F7	PHA	Alpha	7.73	−1.80
F7-F8	PHA	Alpha	1.87	−0.03
T5-T6	PHA	Beta	1.06	−0.88
C3-F7	AMP	Delta	20.73	−1.32
FP2-F4	AMP	Delta	−18.93	0.14
C4F8	AMP	Delta	11.10	−1.55
O1-O2	AMP	Theta	4.12	0.36
P3-F7	AMP	Alpha	79.66	−1.51
FP2-P4	AMP	Alpha	−74.49	0.96

The TBI Severity Index is an estimate of the neurological severity of injury (see Thatcher et al., J Neuropsychiatry and Clinical Neuoscience, 13(1): 77-87, 2001).

TABLE 4. Effect Size: QEEG Measures with School Achievement Tests and IQ Measures Percent Significant Correlations at 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%

There are many examples of the clinical content validity of QEEG and normative databases in ADD, ADHD, schizophrenia, compulsive disorders, depression, epilepsy, TBI (Thatcher, Bivier, McAlaster, & Salazar,1998; Thatcher, Biver, Camacho, McAlaster, & Salazar, 1998) 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 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 review.

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 a hypothesis by a specific statistical probability alpha level; otherwise they do not work. The binomial distribution 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 equals the number of Z-tests, p is the 'yes' and q the 'no' test of the null hypothesis, r is the alpha cut-off for the probability (e.g., P < .01). For example, the null hypothesis is that by chance there will be one event per 64 observations at P < .01. The experiment is run and there were 50 observations at P < .01. The exact probability for the binomial equation in this instance is probability P(X) = .0000060.

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 IQ). E(X) is the expected number of correlations at P < .01. X equals the number of observed correlations at P < .01 and P(X) equals the binomial probability to reject the null hypothesis. Table 4 shows the observed percentage of correlations at P < .01 by which the X value in Figure 10 corresponds.

FIGURE 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 probability is defined as $P(X) = \binom{N}{x} p^x (1-p)^{N-x}$ of successful outcomes defined as a correlation coefficient at the probability of P < .01. N = the total number of correlations for a given QEEG measure, X = the number of observed correlations at P .01; E(X) = the number of expected correlations at P < .01. P(X) = the distribution free binomial probabilities. The percentage of statistically significant correlations at P < .01 is shown in Table 4.

BINOMIAL PROBABILITIES of Expected Significant Correlations

qEEG Measures with School Achievement Tests & IQ Measures, @ 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

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 4 effect sizes are based on the percentage of statistically significant observations at alpha set at $P < .01$. Based on the percentage in Table 4, one can translate the number in 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 IQ. The peer-reviewed literature clearly demonstrates that QEEG is clinically valid with varying effect sizes (Hughes & 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.

NON-PARAMETRIC STATISTICS, ESTIMATES OF ALPHA LEVELS AND THE ISSUE OF MULTIPLE COMPARISONS IN A SINGLE SUBJECT COMPARISON TO AN 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, whereas 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) equals the number expected by chance alone at $P < .05$ (top of Figure 10) or at $P < .01$ (bottom of Figure 11). X equals the number of successful Z-tests observed and P(X) equals the binomial probability.

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

FIGURE 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. The binomial probability is defined as $P(X) = \binom{N}{x} p^x (1 - p)^{N-x}$ of successful outcomes at the probability of P < .05 and P < .01. 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 number of expected Z-scores at P < .05 or at the probability P < .01.

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		

PEER REVIEWED PUBLICATIONS AND INDEPENDENT REPLICATIONS

The University of Maryland NeuroGuide EEG database presented in this paper is unique and represents a sample or a "snapshot" of electrical

events in a medium-size population. The oldest person in the database is age 82, but the sample size from age 50 to 100 needs to be expanded 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. In order to use any EEG normative database matching amplifiers and analytic methods must first be accomplished.

Independent replication of certain aspects of the NeuroGuide University of Maryland EEG Database (Thatcher et al., 1983, 1986, 1987; Thatcher, 1998) have been published and they are consistent with the NYU School of Medicine database (i.e., John et al., 1987) and the Harvard School of Medicine database (i.e., Duffy et al., 1994). Also, most of the acquisition methods, analysis methods and results of experiments using the University of Maryland EEG database in this paper and the NYU and Harvard databases have been published in refereed journals which are cited below. Aspects of the development of relative power of the University of Maryland NeuroGuide EEG norms have been replicated in studies by Matousek and Petersen (1973) as analyzed by John et al. (1977), Fischer (1987), Thatcher (1980), Epstein (1980), van Baal (1997), Hanlon (1996) and Hanlon, Thatcher, and Cline (1999). Aspects of the EEG coherence development in the database presented in this paper have been replicated by Gasser, Verleger, Bacher, and Stroka (1988), Gasser, Jennen-Steinmetz, Stroka, Verleger, and Mocks (1998), Thatcher, Biver, Camacho, McAlaster, and Salazar (1998) and by van Baal and others in genetic analysis (van Beijsterveldt, Molenaar, de Geus, & Boomsma, 1996; van Baal, 1997; van Ball, de Geus, & Boomsma, 1998; van Beijsterveldt, Molenaar, de Geus, & Boomsma, 1998).

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