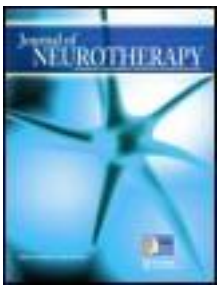

Journal of Neurotherapy: Investigations in Neuromodulation, Neurofeedback and Applied Neuroscience

Normative EEG Databases and EEG Biofeedback

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Published online: 20 Oct 2008.

To cite this article: Robert W. Thatcher Ph.D. (1998) NORMATIVE EEG DATABASES AND EEG BIOFEEDBACK, Journal of Neurotherapy: Investigations in Neuromodulation, Neurofeedback and Applied Neuroscience, 2:4, 8-39

To link to this article: http://dx.doi.org/10.1300/J184v02n04_02

NORMATIVE EEG DATABASES AND EEG BIOFEEDBACK

Robert W. Thatcher, Ph.D.

Reference EEG Databases and Neurotherapy

Electroencephalograhic (EEG) biofeedback is an operant conditioning procedure where by an individual modifies the amplitude, frequency or coherency of the neurophysiological dynamics of their own brain (Cohen, 1975; Blanchard and Epstein, 1978; Rosenfeld, 1990). The exact physiological foundations of this process are not well understood, however, the practical ability of humans and animals to directly modify their EEG through feedback is a well established fact (Fox and Rudell, 1968; Rosenfeld et al, 1969; Hetzler et al, 1977; Sterman, 1996). The ease by which direct modifications of EEG can be accomplished is partly responsible for the rapid, almost explosive rise in the use of EEG biofeedback for the purposes of therapeutic amelioration of a wide range of psychological and neurological disorders (see reviews by Cohen, 1975; Rosenfeld, 1990; Lubar, 1997).

The therapeutic application of EEG biofeedback is often referred to as "Neurotherapy" and, most importantly, the therapeutic efficacy and success of Neurotherapy is a force that is driving the development and clinical application of EEG biofeedback (Lubar, 1997).

As pointed out by several studies (Johnson, 1997; Lubar, 1997; Striefel, 1995; Schwartz, 1995), EEG biofeedback is not a "kids toy" because in the hands of a professional it is a strong and effective methodology and must be treated with great respect and competence. The reader must be reminded that modifications of one's own EEG is a very serious undertaking because it involves direct manipulations of neuronal excitabilities and neural connections in the brain. Although no ill effects of EEG Biofeedback have been noted to date, nonetheless caution, professionalism and knowledge are the prerequisite requirements for the application of this technique. It is in this spirit that the present paper reviews electrophysiological analyses as they pertain to EEG biofeedback and discusses the use of a "Normative EEG Database" (NDB) to aid the professional Neurotherapist in evaluating the neurological status of their patients prior to therapy, to evaluate the course of their therapy and to provide a guide for the development of therapeutic strategies using EEG biofeedback. It is assumed that knowledge about the electrophysiology and anatomy of the brain, which are being modified by the patient under the guide of the Neurotherapist, is important and that deeper knowledge can only benefit the patient, the therapist and the field of Neurotherapy.

It is likely that in the future, a reference[1] "Normative EEG Database" (NDB) will be commonly used for purposes of EEG biofeedback and that Normative EEG Databases (NDBs) will play an increasingly important role in the clinical evaluation and treatment of patients. As discussed in more detail in section 5.0 there are three primary uses of a NDB: 1- to assess the neurological status of the patient and to determine to what extent there is a neurological basis of the patient's complaints (i.e., the issue of Organicity), 2- to identify possible strengths and weaknesses in the organization and

electrophsiological status of the patient's brainin order to aid in the efficient and optimal design of Neurotherapy (i.e., the issue of Therapy Design) and, 3- to increase efficiency and to objectively evaluate the efficacy of treatment by comparing the patient's EEG before, during and after treatment (i.e., the issue of Treatment Evaluation). Currently, there are only a small number of EEG normative reference databases that seem adequate to meet the minimal standards necessary for responsible and ethical uses of a NDB in the field of EEG Biofeedback. A growth in the number of normative or reference EEG databases is expected to grow over time.

Active Tasks vs Eyes Closed and Eyes Open QEEG Databases

An active task refers to the recording of EEG and/or evoked potentials (EPs) while a subject performs some kind of perceptual or cognitive task. Many EEG and EP studies have reported reproducible changes in brain dynamics which are task dependent. Such studies are important for understanding normal and pathological brain processes responsible for perceptual and cognitive function. In contrast, an eyes closed or eyes open EEG state involves an alert subject simply sitting quietly and not moving. The eyes closed and/or eyes open conditions are commonly used as reference normative EEG databases, Because of the simplicity and relative uniformity of EEG recording conditions. Such databases can be compared across laboratories and populations with relatively high reliability. Active tasks, on the other hand, are dependent on the intensity of stimuli, the back ground noise of the room, the distance between the subject and the stimuli, the subject's understanding of the task instructions, the subject's motivation, etc. These are very difficult to control across experimenters or across clinics for the purposes of constructing a "reference" normative EEG database. It is for this reason that there are few if any active task reference normative EEG databases, whereas there are at least three normative eyes closed lifespan EEG normative databases (e.g., E. Roy John (John, et al, 1977; 1988); Frank Duffy (Duffy et al, 1994) and Robert Thatcher (Thatcher 1987).

It should be kept in mind that the alert eyes closed EEG state is very much an active state, e.g., there is still about 20% glucose metabolism of the whole body occurring in the brain of an eyes closed subject (Herscovitch, 1994). During the eyes closed state, there is dynamic circulation of neural activity in connected cortical, reticular and thalamo-cortical loops (Thatcher and John, 1977; Nunez, 1981). The allocation of neural resource is simply different from when the subject is directing his/her attention to an experimentally controlled situation. Active tasks are very important because they reflect the switching and dynamic allocation of neural resource and they do have clinical importance. However, in the present paper only the alert and resting EEG have been used for the purposes of a reference EEG normative database and, therefore, this paper will only concern the EEG recorded from during conditions. This emphasis occurs only from a practical point of view and comparisons between resting EEG conditions and active EEG conditions should be encouraged. A good and stable resting EEG normative database can enhance and facilitate the understanding of the underlying neural dynamics and clinical condition of a patient during an active task.

Therefore, one purpose of the present paper is to discuss the minimal standards for the creation and use of a resting EEG normative database. This discussion will emphasize the Thatcher normative EEG database or NDB (Thatcher

et al, 1983; 1986; 1987; 1989; Thatcher, 1992; 1994a) which has been in use throughout much of the EEG Biofeedback community since 1992. Between 1987 and 1994 a raw mean and standard deviation version of the Thatcher NDB was in use. The raw means and standard deviations exhibited discontinuities at some ages and, therefore, in order to improve the statistical stability a 5-point Savisky and Golay (1964) smoothing of the Thatcher NDB is now used (see Thatcher, 1991a; 1992 for smoothing details). The reader should note, however, that databases other than the Thatcher NDB are available for clinical and research purposes and each of these databases contain their own strengths and weaknesses. It is not the goal of the present paper is to examine and compare each currently available EEG database. While some comments will be made regarding some of the databases, these comments are primarily in the general context of discussion of a given topic. The emphasis on the Thatcher NDB in the present paper is only because this is the NDB that this author is most familiar with and it should not be construed that this database is necessarily better or the only NDB available.

Full Disclosure of the Content of EEG Normative Databases

Currently there are several available normative resting EEG databases which may have relevance for clinical diagnoses and evaluation of therapy. However, the extent to which these databases are useful is largely determined by the degree of open disclosure of the contents of the databases themselves. Specifically, there sould be open disclosure of the number of subjects per age group, gender, the demographics of the sample, the geographic location of the samples, quality control measures, and acquisition and technical procedures (e.g., artifact rejection, filter and gain settings, digitization rates, spectral procedures, etc.). The reader and/or users of these databases must demand full disclosure of the make up of a database so the relative merits and applicability of the database for their particular needs can be assessed. Especially important is the establishment of the relative sensitivity and specificity of the normative database, which depends on knowledge of the population and statistical details of the database.

In the following pages clinical and statistical criteria for "normative" and/or "reference" EEG databases will be presented. The goal is to understand the concepts and value of parametric statistics for the determination of diagnostic sensitivity and specificity. Next will be a review of some of the most crucial EEG analyses with an attempt to highlight the clinical and physiological bases of each one. Finally, a practical discussion of the diagnostic and therapeutic applications of EEG databases will be presented. Special emphasis will be placed on the uses of "reference" normative EEG databases to determine the "organic" basis of a patient's complaints, and then to design and evaluate neurotherapy.

Criteria for the Development and Use of EEG Databases

In contrast to a "conventional" visual reading of an EEG printout or display, I will refer to the exact quantification of the electroencephalogram as QEEG. The essential criteria for a clinically useful quantitative EEG (i.e., QEEG) database are the same as for all clinical normative databases: 1- representative demographic sampling and certainty that only "normal" or non-clinically compromised subjects are included, 2- large enough sample sizes at different ages to cover both early childhood and adulthood, 3- Non-artifact or "clean" EEG samples and, 4-Correct statis-

Figure 1

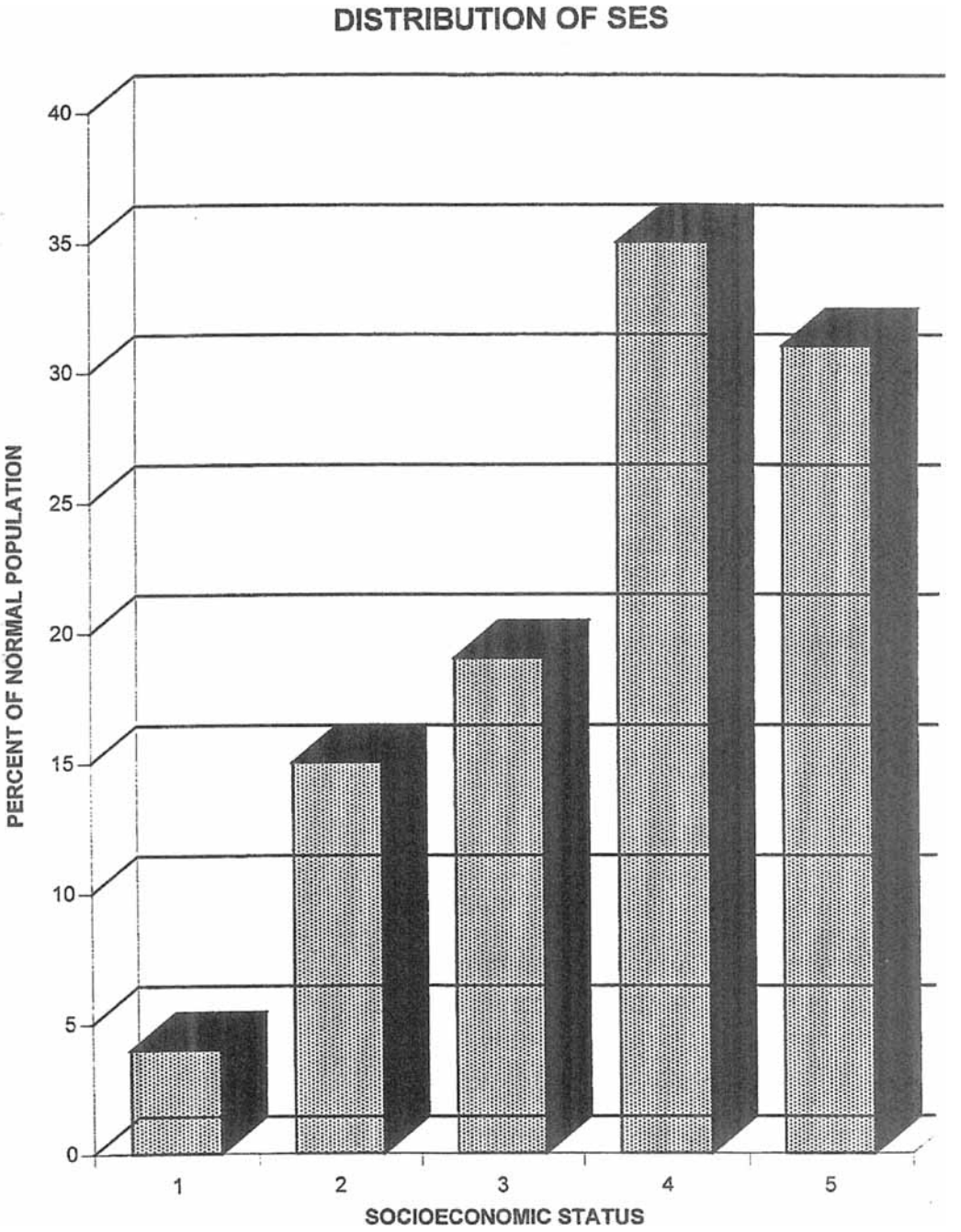
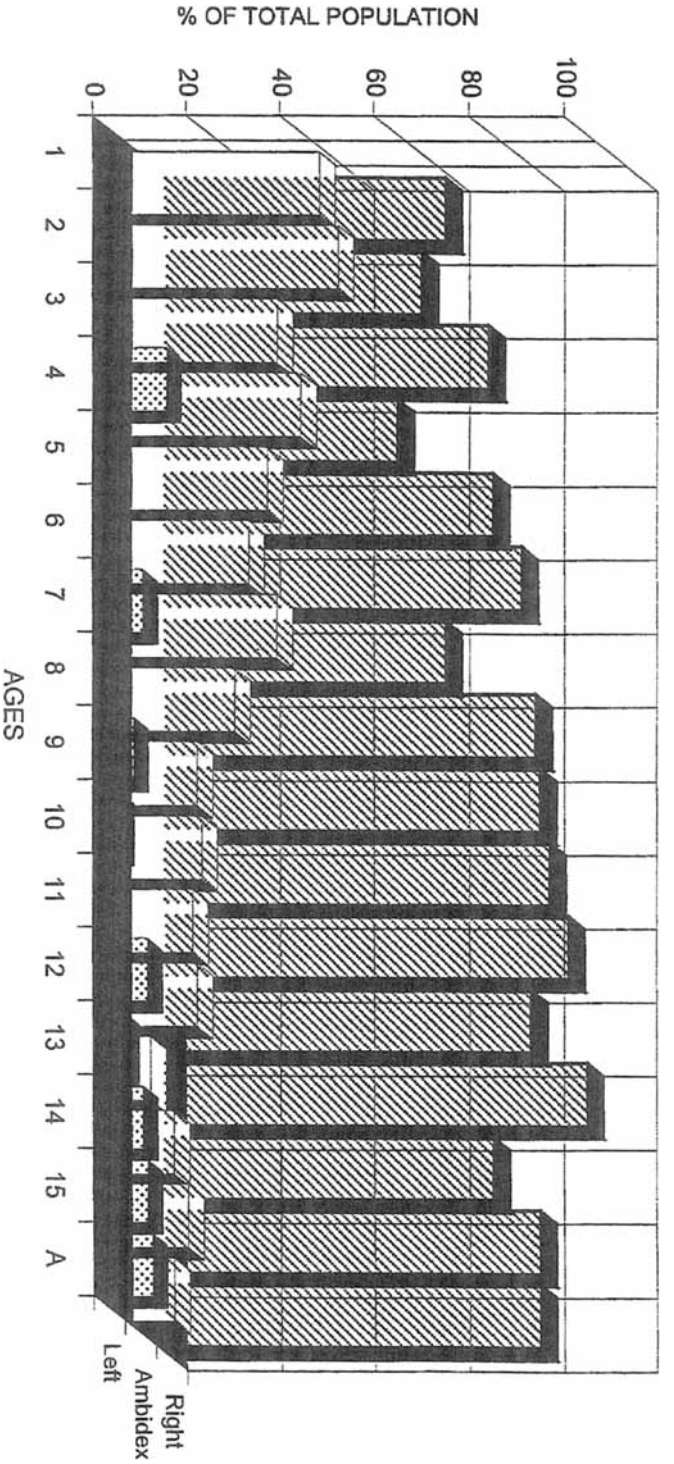

DISTRIBUTION OF SES
PERCENT OF NORMAL POPULATION
40
35
30
25
20
15
10
5
0
1
2
3
4
5
SOCIOECONOMIC STATUS

Figure 2



HANDEDNESS DISTRIBUTION OF NORMALS

ical properties of the database samples to insure interpretable parametric statistical analyses.

Demographics and Gender Criteria for Normality and Subject Selection

In the remainder of this chapter the term "normative database" will be used only in the sense of a "reference normative database". 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 database. Mathematically, the practical utility of a database is measured only to the extent that the database constitutes a representative sample of the general population of Neurologically and clinically normal individuals. Therefore, the concepts of normalcy and demographic representation are crucial to the creation of a "reference" EEG database of normal individuals. The "reference normative" population must be drawn from a representative sample of people whose ethnic and cultural backgrounds are as diverse as the clinical populations that will be studied. There are many demographic populations analyses of the United States that are broken down into individual states. In general, the U.S. ethnic population is comprised of approximately 18% Afro-Americans, 3% oriental, 12% Hispanic and 63% Caucasian. Socio-economic status and handedness are also important factors when evaluating a normative reference database. Figure 1 and 2 show the distribution of socio-economic status (SES) and handedness, respectively, in the Thatcher (1987) database.

Stringent normalcy criteria for membership in a normative QEEG database must also be followed. One of the first reference normative QEEG databases was created by Matousek and Petersen in 1973 (Matousek and Petersen, 1973). An independent replication of specific ages in the Matousek and Petersen NDB established the reliability and clinical value of quantitative methods in EEG (John et al, In addition to these nominal clinical criteria for exclusion, additional objective criteria should also be applied if available. For example, measures of intelligence, neuropsychological functioning, school achievement, successful life work, etc. should also be considered when individuals are selected for inclusion in a "reference normative" database.

Statistical Standards of QEEG Databases

A fundamental rule of parametric statistics is the rule of independent gaussian distributions where each measurement is independent of all other measures and each one exhibits a histogram shape referred to as a "bell shaped" curve. Mathematically the bell shaped curve or gaussian distribution is defined as:

$$Y = \frac{N}{\sigma\sqrt{2\pi}} e^{-(X-\mu)^2/2\sigma^2},$$

where Y = height of the curve for particular values of X, π= 3.1416, e = 2.7183, N = number of cases, which means that the total area under the curve is N, μ and σ = mean and standard deviation of thedistribution, respectively. This equation can be simplified by writing it in standard-score form with a mean of 0 and a standard deviation of 1. When we substitute 0 and 1 for the mean and standard deviation then we may write:

$$Y = \frac{1}{\sqrt{2\pi}} e^{-z^2/2}.$$

Table 1

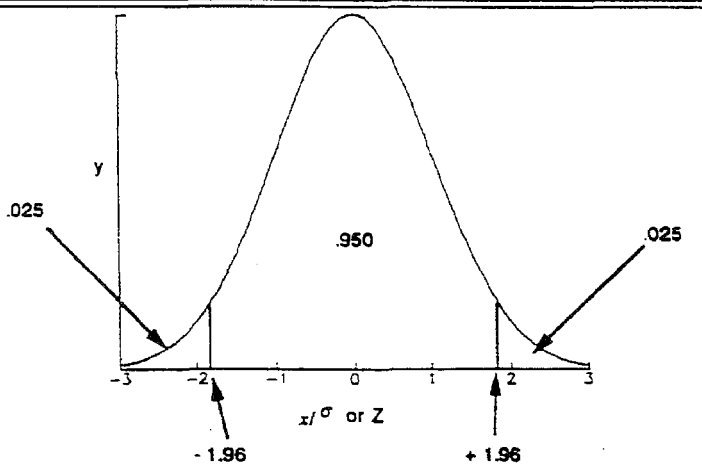
Neurological Normalcy Critera

A neurological questionnaire and interview with the subjects and/or, parents and guardians were conducted. Entry into the normative data base required:

1- An uneventful prenatal, perinatal and postnatal period.
2- No disorders of consciousness.
3- No head injury with cerebral symptoms.
4- No history of central nervous diseases.
5- No convulsions of emotion, febrile, or other nature.
6- No abnormal deviation with regard to mental and physical development.

Here Z is a standard score on X and is equal to$(X-\mu)/\sigma$. The score Z is a deviation in standard deviation units measured along the base line of the curve from a mean of 0, deviations to the right of the mean being positive and those to the left negative. By substituting different values of Z in the above formula, different values of Y may be calculated. For example, when Z = 0, Y = $1/\sqrt{2\pi}$ = .3989 or, in other words, the height of the of the curve at the mean of the normal distribution in standard-score form is given by the number .3989. For Z = +1, Y = .2420, and for Z = +2, Y = .0540. For purposes of assessing deviation from a NDB, the values of Z above and below the mean which include a proportion .95 of the area of the Gaussian is commonly used as a level of confidence (i.e., to minimize Type I and Type II errors, or the probability of saying something is present when in fact it is not, or saying something is not present when in fact it is, respectively). As shown in Figure three, the proportion .95 or 95% of the area of the Gaussian curve falls within the limits Z = ±1.96 with the proportion of .05 or 5% falling outside of these limits. Similarly, 99% of the area of the curve falls within, and 1 % outside, the limits Z = ±2.58.

Figure 3



The Gaussian or Normal distribution, especially when used in a multivariate statistical test, provides methods to insure independence of measures or zero correlation between different measures as they relate to statistical inferences. However, it should be noted that the gaussian distribution is a hypothetical distribution that, in sampling procedures, is never actually achieved. That is, the ideal of the gaussian equation can only be obtained mathematically but, in real life sampling procedures, one can never exactly reproduce a gaussian distribution. Therefore, in the real world of sampling statistics, efforts must be taken to minimize departures from a gaussian distribution. The most serious type of deviation from normality is *Skewness* or an 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 a problem 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 many different frequency distributions can be reduced to one common distribution and that for this distribution "there is an exact and known relationship between z-score and percentile rank" (Ferguson, 1976). In this way comparisons between "Apples and Oranges" such as evoked potentials and EEG or relative power and coherence, etc., can be made with accuracy (see Fig. 1).

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, John et al (1988) state that specific logarithmic and ratio transforms must be applied to all EEG power, EEG coherence, EEG phase and EEG amplitude asymmetries in order to best approximate a normal distribution. However, 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 II shows the effects of transforms on the distributions of the various EEG variables in the Thatcher (1987) reference normative database. It should be noted that, with the exception of absolute phase (which tends to be Chi Square distributed because of the absolute transform), the EEG variables were relatively well behaved and normally distributed without using any transforms. Actually one would expect, that EEG variables would approximate a normal distribution as the sample size increases, assuming no artifact or experimenter bias.

Statistical Inferences and Reliability

Two crucial and interacting concepts to determine valid statistical inference are: 1- Multiple statistical comparisons and, 2- Reliability. Because a large number of statistical comparisons are typically conducted in QEEG analyses one must be careful to not bias judgments that unduly favor Type I or Type II statistical errors. A general rule to determine the number of expected statistically significant differences is to multiply the total number of statistical tests by the probability value or alpha value, e.g., if there were 100 statistical tests then 100 x .05 = 5 or one would expect 5 statistically significant effects by chance alone. A second method is to use a "multiple comparison" adjustment procedure such as the Schafe, Bonferroni or Tukey adjustment. The latter adjustments for multiple comparisons tend to bias the statistical tests toward reduced Type I errors and increased Type II errors (Hays,

Table 2

Gaussian Distributions (<3.0) of Normative EEG Measures From the Thatcher NDB (1987)

	Untransformed (<3)		Transformed[1] (<3)	
	Skewness	Kurtosis	Skewness	Kurtosis
Rel. Power (64)[2]	100%	100%	100%	100%
Tot. Power (16)	100%	100%	100%	94%
Amp. Asymmetry				
Inter (32)	100%	94%	99%	85%
Left (112)	100%	98%	100%	91%
Right (112)	100%	99%	100%	70%
Coherence				
Inter (32)	97%	91%	91%	82%
Left (112)	98%	93%	100%	93%
Right (112)	99%	87%	100%	94%
Phase				
Inter (32)	77%	56%	100%	91%
Left (112)	87%	57%	99%	94%
Right (112)	79%	58%	93%	88%

[1]Mathematical details of the transformations in the Thatcher et al (1983;1986).

[2]Number of variables for each QEEG category are in parentheses.

1973; Ferguson, 1976) and thus must be used with caution. Another method to minimize inferential errors is to compute a Multivariate Analysis of Variance (MANOVA) test which provides a measure of the overall F value of statistical significance after adjusting for the intercorrelations between all of the variables. When comparisons to a NDB are being made, the null hypothesis for the MANOVA is that Z = 0 and that there is an equal number of negative Z values as there are positive Z values with the overall mean Z = 0. If a statistically significant overall F (e.g., P < .05) is present then adjustments for multiple comparisons are not necessary (Hays, 1973).

The second statistical concept to minimize inferential errors is the concept of reliability. Reliability can be measured using the reliability coefficient defined as:

$$r_{xx} = \frac{s_1^2}{s_2^2},\ s_1^2$$

where S_1^2 is the sample estimate of variance of the QEEG test at time one and S_2^2 is the estimate of the sample variance of the QEEG from the same patient at test time two. The reliability coefficient is the proportion of obtained variance that is true (i.e., reliable) and thus it represents the reproducible aspects of the QEEG test. For example, if $S_2^2 = 400$ and $S_1^2 = 360$, then the reliability coefficient $r_{xx} = .90$. This means that 90 percent of the variation in the QEEG measurement is attributable to variation in true score, with the remaining 10 percent being attributable to error. Two practical methods of estimating QEEG reliability are the "Test-Retest Method" and the "Split-Half Method". The former is where a beginning session sample of EEG is compared to an end of session sample of EEG and the latter is where a testing session is randomly divided into two samples of EEG (assuming the size of each sample is of adequate length, e.g., > 60 seconds). Reliability measures are important because they minimize both Type I and Type II errors and eliminate the need for multiple comparisons because "by definition chance findings do not replicate" (Duffy et al, 1994, p. XI).

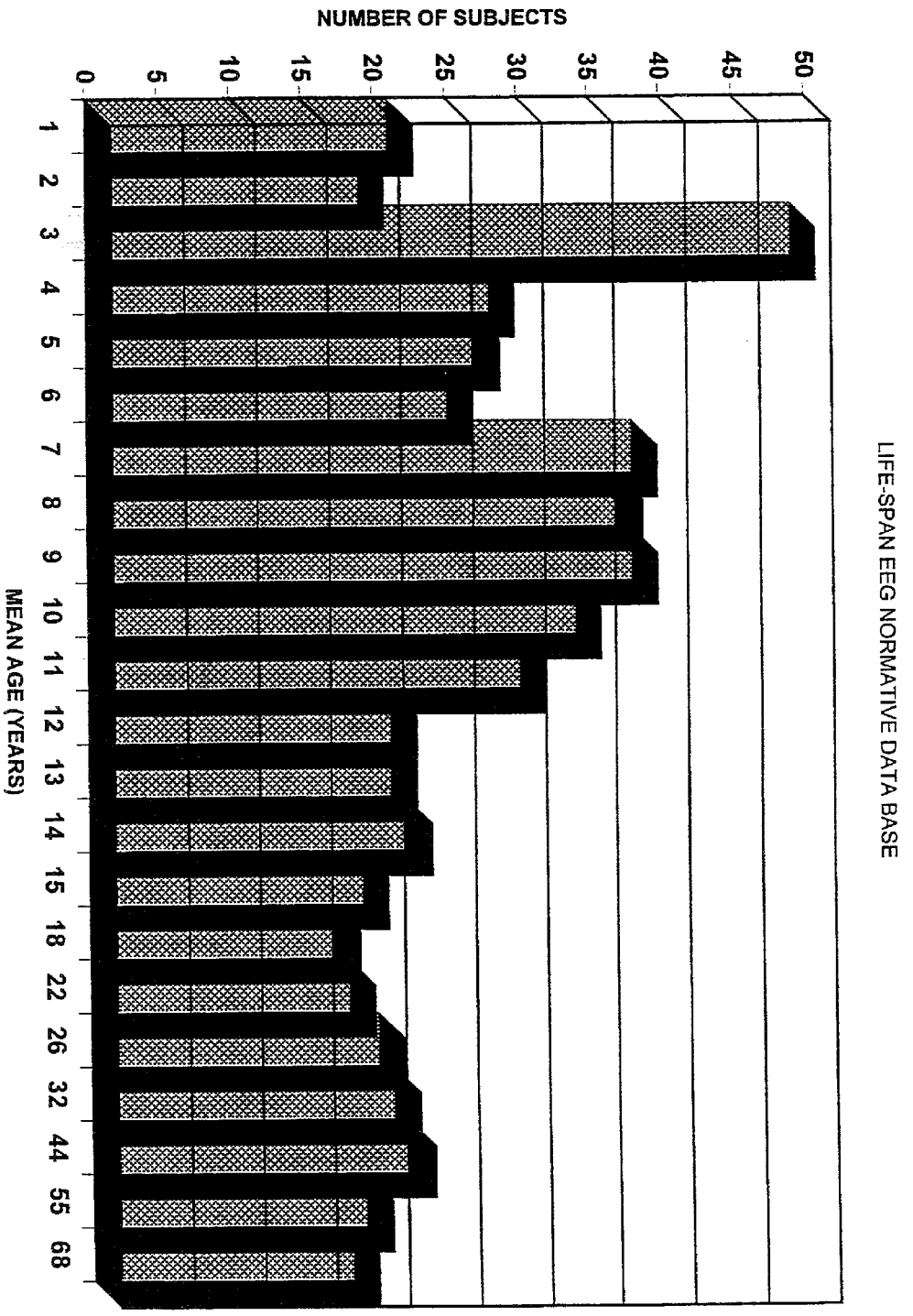
Uniform Data Acquisition Procedures and Quality Control

Quality control is essential for the creation of a useful reference QEEG database. That is, the EEG amplifiers must be carefully calibrated with daily checks to insure their stability andprecisely the same acquisition parameters and procedures must be employed on all individuals included in the database. In addition, all artifact must be eliminated prior to subsequent spectral analyses. Furthermore, comparisons of an individual to a given NDB must be made using the exact same procedures and settings that were used for the creation of the NDB.

Artifact Rejection

An especially important aspect of quality control is the elimination of EEG artifact due to eye movements, blinking, scalp sweating, movement, EKG and other non-brain sources of electrical activity. The importance of this aspect of EEG data acquisition cannot be overstated. In the Thatcher normative QEEG database, the artifact rejection procedures were contained within two general categories of EEG artifact rejection: 1- on-line artifact rejection and 2- off-line artifact rejection. The "On-Line" method used representative samples of artifact free EEG as templates to reject subsequent EEG samples that significantly deviated from the template. The on-line method also used diagonal eye electrodes to detect eye movement as well as eye blinks. EEG technicians were trained to minimize artifact during the acquisition procedure by monitoring the subject's EEG and helping maintain the subject's comfort and alertness. In the "Off-Line" category of artifact rejection, considerable and diligent efforts must be made to edit out any evidence of artifact after the EEG has been digitized. Care must be taken to insure that "real" electrophysiological events are not deleted or misinterpreted as artifact, such as high amplitude alpha or beta bursts or mu rhythms, etc. Properly trained individuals are necessary for this phase of quality control. As mentioned previously, in the Thatcher reference QEEG database, both on-line and off-line procedures were followed, and trained Ph.D.s visually edited the data from each and every subject who was included in the database. Only when there was agreement between two independent QEEG readers were the final sections of EEG passed on for the purposes of power spectral analysis.

Figure 4


NUMBER OF SUBJECTS
0
5
10
15
20
25
30
35
40
45
50
MEAN AGE (YEARS)
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
18
22
26
32
44
55
68
LIFE-SPAN EEG NORMATIVE DATA BASE

In addition to non-brain types of artifact (e.g., eye movements, blinking, sweating, EMG, EKG) brain state types of artifacts such as drowsiness or medication effects must also be either removed or controlled for. Drowsiness is a physiological state that the produces slowing of the alpha rhythm and diffuse delta (& associated eye movements). Fortunately, the effects of drowsiness and sleep on the EEG has been extensively studied and such states are easily recognized by a competent EEG technician or clinician. In the case of medication effects, when ever possible patients should be taken off of medication at least 48 hours prior to testing. When this is not possible, then the clinician must take into consideration the published effects of a given medication or class of medications on the EEG when comparing a patient to a NDB.

QEEG Reference Database Age Distribution

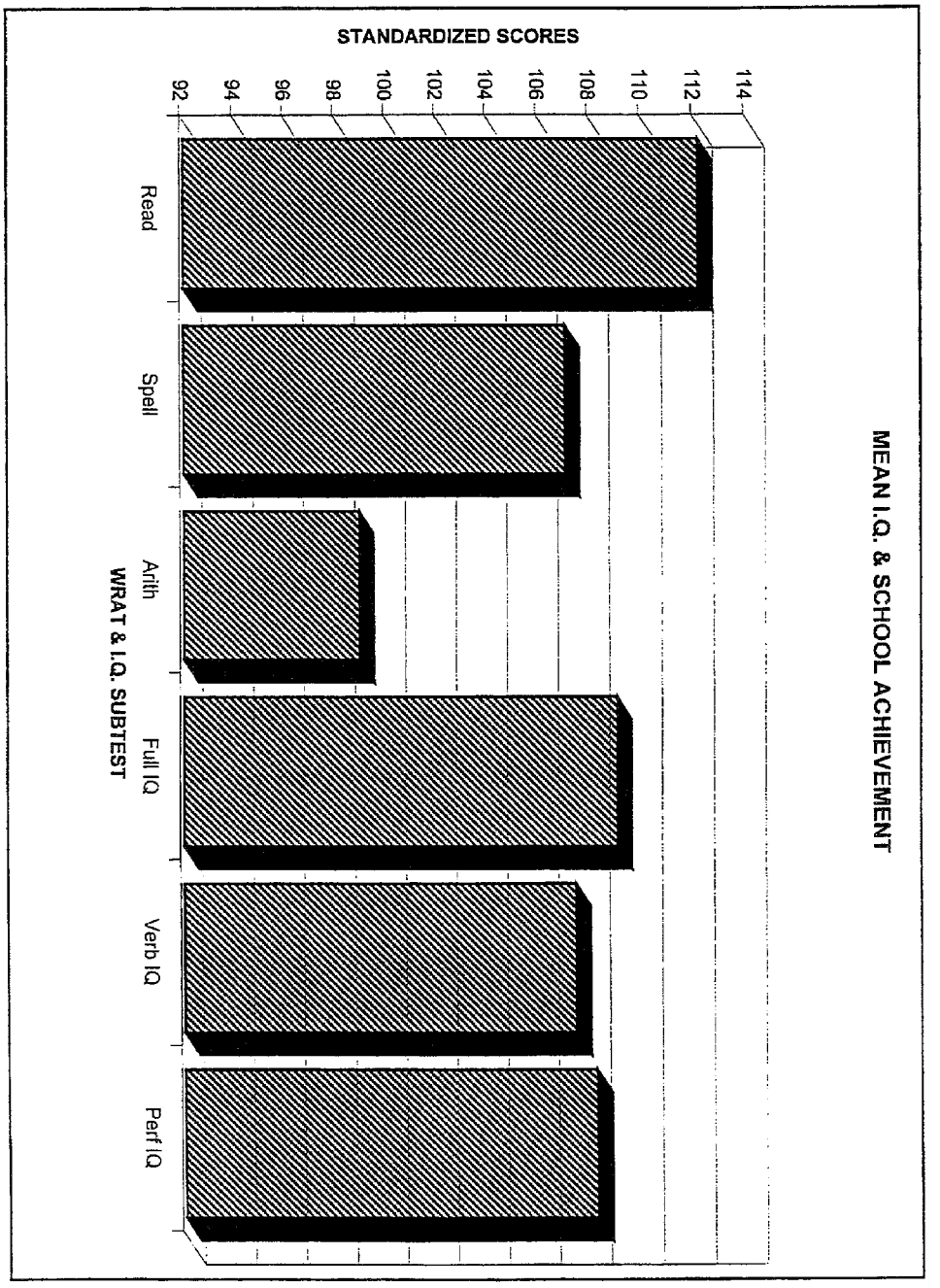
It is important that a reference normative database contain an adequate sample size per age group, and that it span the age range from birth to adulthood. Of course the adequacy of the sample size will vary depending upon the age under investigation. For example, development is most rapid in young children and consequently, the sample size should be large enough to resolve EEG changes related to brain development (see section 4.1 and fig. 6). The importance of spanning the period from birth to adulthood stems from the fact that growth spurts and rapid sequences of change in brain development must be understood in the context of the entire human life-span (Thatcher, 1991a; 1992; 1994a; 1996).

Figure 4 shows the number of subjects per year in the Thatcher reference normative database which spans the human developmental period from 2 months to 82 years of age. It can be seen that the largest number of subjects are in the younger ages (e.g., 1 to 6 years) when the EEG is changing most rapidly. Figure 5 shows the distribution of WRAT (Wide range Achievement Test) reading, spelling and arithmetic scores as well as full-scale I.Q., verbal I.Q. and performance I.Q. in the Thatcher reference normative database (Thatcher, 1987). Figure 5 shows that the average I.Q. is consistently greater than 100 and that there is consistency in mean values on the three sub-categories of the I.Q. test as well as the WRAT.

Time of Day and Other Miscellaneous Factors

There are many uncontrollable factors that influence the frequency spectrum of the EEG. For example, time between EEG acquisition and food intake (Hudspeth et al, 1981; Fishbein et al, 1990), the content of food intake (Cantor et al, 1986; Fishbein et al, 1990), the amount of previous night's sleep, the time of day on a circadian basis and motivational interest and involvement of the subject, etc. 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, suchexperimental control would preclude the practical use of a NDB 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 NDB involves randomly varying time of day of EEG acquisition, time between food intake and EEG acquisition, food content and EEG acquisition, etc. across ages, gender 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.

Figure 5


MEAN I.Q. & SCHOOL ACHIEVEMENT
STANDARDIZED SCORES
92
94
96
98
100
102
104
106
108
110
112
114
WRAT & I.Q. SUBTEST
Read
Spell
Arith
Full IQ
Verb IQ
Perf IQ

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 and specificity) to be calculated. The method of statistical randomization of miscellaneous factors was used in the Matousek & Petersen, Thatcher, John and Duffy EEG normative databases, and the sensitivity and specificity of these databases range from approximately 80% to 97% (John et al, 1988; Thatcher et al, 1989; Duffy et al, 1994)[2].

Power Spectral Measures of a QEEG Database

Because of the inherent complexity of EEG, some form of time series analysis must be employed in order to derive quantifiable measures. The spectral analysis is an efficient method to transform a time series into frequency (Blackman and Tukey, 1958). The power spectral analysis is only one, albeit, a very powerful method of time series quantification. In general, all spectral analyses decompose a complex wave form into a linear sum of more elemental wave-like components, or in other words, they transform a time series into the frequency domain. In the case of Fourier analyses, the elemental waves are sine waves, in the case of wavelet analyses the elemental components are wavelets[3], etc. The elemental wave like components of spectral analyses are often referred to as basis functions with the important mathematical property of "orthonormality". The property of orthonormality allows for efficient and linear analyses to be performed in which the independence of the basis functions can be established, and simple translations from the time domain to the frequency domain can occur.

There are many time series methods available to obtain a frequency spectrum (Otnes and Enochson, 1972). These methods have been thoroughly tested and mathematically derived and no further discussion of the mathematical details of these methods will be provided. All that is necessary to state is that given the specific spectral method used to derive a specific reference QEEG database then one must also use, as close as possible, that exact same method to compare individuals to that database.

Most important for the present discussion is determining which derived EEG measures are most critical for the clinical evaluation of a patient, and then insuring that these measures are included in a reference normative QEEG database. The clinical usefulness of derived QEEG measures is largely established by the scientific literature that has evolved over the past 25 years. Much of this literature has been reviewed in various publications and the reader is encouraged to consult these reviews and this literature (John et al, 1997; 1988; John, 1997; Duffy et al, 1994; Harmony, 1983; Thatcher et al, 1989; Nunez, 1981; 1994; Lopes da Silva, 1991). Approximately 98% of the energy of the human EEG lies between 0 and 30 Hz; thus some form of spectral analysis within the delta (e.g., 0.5 to 3.5 Hz), theta (e.g., 3.5 to 7 Hz), alpha (e.g., 7 to 13 Hz) and beta (e.g., 13 to 25 Hz) frequency bands is crucial. The finer the frequency resolution the better (e.g., alpha 1 and 2 or beta 1, 2, 3 etc.), however, there are operational or practical limits. This is because for every single increase in the number of frequency bands, there is a squared increase in the number of statistical comparisons (i.e., for every element in a matrix there are at least two indices). Thus, given the practical limits of data analysis the authors of all current NDBs decided to only emphasize a selected subset of EEG frequencies. The Duffy, John and Thatcher databases share in coverage of the broad spectrum of EEG from 0.5 to 30 Hz, albeit in slightly different ways and with different emphases. Within the

frequency range from approximately 0.5 to 30 Hz, there are in general three categories of EEG spectral variables that are of critical clinical value: 1- Power and/or amplitude, 2- Coherence and/or phase and, 3- Derived ratios of amplitude and/or coherence and/or phase.

Power and/or Amplitude EEG Spectral Measures

Power is defined as uv^2 /cycle/second while amplitude is simply the square root of power or uv/cycle/second. Power and amplitude are related by the square and square root operation and transformations can be easily performed to insure Gaussian normality and, at the same time, to fit ones preference[4]. For the purposes of this paper, I will refer to EEG amplitude with the understanding that a simple squaring or square root operation equates amplitude and power. The crucial issues are: 1- to what extent is amplitude sensitive to non-brain electrical activity, i.e., various non-EEG artifacts such as EKG, EMG, eye movements, etc. and, 2- is EEG amplitude gaussian distributed. It is important to note that both power and amplitude are considered as "absolute amplitude" measures in that they do not only reflect the amplitude of brain-generated EEG, but also non-brain factors such as scalp resistance, skull thickness and various anisotropic conductance properties of the skull, dura and scalp (Nunez, 1981; 1994). A typical method to control for differences in scalp resistance and skull thickness, etc. is to calculate "relative power" and/or "relative amplitude". Relative amplitude is a percentage measure and is defined as amplitude in a frequency band divided by total amplitude (i.e., total amplitude is the sum of amplitude in all frequencies). In other words, relative amplitude is a measure of the proportion of total amplitude within a given frequency band and is thus independent of skull thickness, skin resistance and other, but not all, non-brain sources of electrical activity (e.g., eye movement artifact, EKG artifact, etc.).

The clinical relevance of EEG amplitude is related to the fact that the output of a population of EEG generators is a function of the number of generators, the synchrony of the generators and the geometry of the generators (Thatcher and John, 1977; Nunez, 1981; 1994). Synchrony is especially important because mathematical calculations show a highly disproportionate (e.g., > 8:1) contribution to surface EEG amplitude by small groups of synchronous generators (e.g., Lopes da Silva, 1991; Cooper et al, 1965; Nunez,1981; 1994). It is known that the relative and absolute amplitude of the EEG varies as a function of age and scalp location, and to the extent of clinical pathology. For example, at birth approximately 40% of the amplitude of the EEG is in the delta frequency band and only approximately 10% of EEG amplitude is in the alpha frequency band. In a normal adult, the percent of amplitude in the delta frequency band is typically less than 5%, whereas the percent amplitude in the alpha band is approximately 70% in occipital areas. In normal subjects delta activity arises from the slow, modulated depolarization of large masses of geometrically aligned cortical pyramidal cells such as that which occurs during expectancy and sustained attention (Walter et al, 1965; Karahashi and Goldring, 1966; Tecce and Cattanach, 1995; Toro et al, 1994). Such slow fluctuations in EEG occur within the D.C. (1 to 5 second time constant) to the mid-delta frequency range (1 to 3 Hz). Thus, EEG amplitude in the delta frequency range is not necessarily a sign of pathology or abnormal thalamic hyperpolarization, but rather, it may be a normal part of the EEG spectrum.

The studies of delta activity in normal subjects illustrates why it is critical that the full frequency spectrum from, at

least, 0.5 Hz to 30 Hz be measured and spectrally analyzed (less than 0.5 Hz, e.g., 0.1 Hz or 0.01 Hz is even better). It is a serious error to not measure this full range of EEG frequencies because of the developmental importance of EEG frequency changes and the clinical interpretation which can be derived from the EEG. Caution should be exercised when using a database with restrictive filter settings. Other limitations of a restrictively filtered database are its non-applicability to infants, children, adolescents or geriatric populations and its lack of the coherence and phase EEG measures. Most importantly, however, the filter limitation of delta EEG frequencies significantly reduces the usefulness of the Sterman database. For example, meaningful comparisons of relative power to other existing databases (e.g., Matousek and Petersen, 1973 and the Duffy, John and Thatcher databases) is difficult if not impossible with filter restrictive EEG databases.

Biophysical Linkage Between MRI and EEG Amplitude

The EEG arises from the rapid movement of ions (e.g., Na, K, Cl, etc.) across large areas of neural membrane surface, thus it is not surprising that strong correlations between MRI biophysical measures of the brain and the EEG have been reported (Thatcher et al, 1998a; 1998b). MRI measures of T2 relaxation time are different depending on the relative concentrations of myelin, cytoplasm and extracellular space (Szafer et al, 1995; Kroeker and Henkelman, 1986; Does and Snyder, 1995). Recent MRI and EEG correlation analyses have demonstrated different relationships between the cerebral white matter and gray matter and the EEG in closed head injured patients. For example, a commonly reported clinical EEG correlate of white matter damage is increased delta EEG amplitude (Jasper and van Buren, 1953; Gloor et al, 1968; Gloor et al, 1977). In contrast, decreased EEG amplitude but not increased delta amplitude is a common clinical correlate of gray matter damage (Gloor et al, 1968; 1977; Goldensohn, 1979a; 1979b). Independent confirmation of this relationship between EEG amplitude and white versus gray matter damage was provided in biophysical MRI correlations to the EEG in traumatic brain injured patients (Thatcher et al, 1998a). This further emphasizes the need not to arbitrarily restrict the frequency spectrum of the EEG when compiling EEG normative databases. Concordance between QEEG and MRI and multimodal integration of QEEG with other imaging methods will likely enhance the value of QEEG normative databases and discriminant analyses in the future.

EEG Coherence Measures

Coherence is mathematically analogous to a cross-correlation coefficient in the frequency domain. For example, coherence which varies between 0 and 1, is a measure of the linear association between two variables in the same manner as the square of a correlation coefficient. Mathematically, the correlation coefficient is defined as:

$$r = \frac{\sum xy}{\sqrt{\sum x^2 \sum y^2}},$$

where x and y are deviations from the means and , respectively. The correlation coefficient is a very important mathematical concept because it represents the linear association between two measures, independent of their relative or absolute amplitudes. Amplitude normalization occurs because the numerator of the equation (i.e., cross-products or covariance) is divided by the standard deviation in the

denominator. EEG coherence is similarly defined as:

$$Coh_{xy} = |R_{xy}(f)|^2 = \frac{|S_{xy}(f)|^2}{S_{xx}(f)S_{yy}(f)}$$

where

$$|S_{xy}(f)|^2$$

is the square of the cross power spectral density at a given frequency (f), and

$$S_{xx}(f) \text{ and } S_{yy}(f)$$

is the square of the cross power spectral density at a given frequency $(f)_1$ and $S_{xx}(f)$ and $S_{yy}(f)$ are the respective auto power spectral densities at that same frequency (f) (Otnes and Enochson, 1972; Bendat and Piersol, 1980). Similar to the correlation coefficient coherence is the ratio of covariance divided by the cross products of variance and, thus, coherence is normalized with respect to amplitude. This is important in EEG analysis because it means that coherence evaluates the linear association or correlation between the EEG waveforms recorded from two different scalp locations, independent of the EEG amplitude at either location. Recently, Nunez et al (1997) thoroughly evaluated the electrophysiological bases of coherence, including issues about reference electrodes and Laplacian derivations, etc. and the reader is encouraged to consult this important review. Table III from Nunez et al (1997) illustrates the relationships between normalized and unnormalized EEG measures.[5]

EEG coherence has considerable clinical utility and can directly reflect neural network connectivity and neural network dynamics. Nunez (1981) first pointed out that EEG coherence does not simply decrease as a function of interelectrode distance, but rather, can increase with increased electrode separation. Thatcher et al (1986) systematically investigated this feature of human EEG coherence and experimentally elaborated Nunez's suggestion that EEG coherence reflects the action of cortico-cortical connections and specific cortico-cortical fasciculi by developing a "Two-Compartmental" model of EEG coherence. The two-compartmental model of EEG coherence is based upon Braitenberg's (1978) two-compartment analysis of cortical axonal fiber systems in

Table 3

Relationships between Normalized and Unnormalized Measures (Nunez et al. 1997)

	Time-Domain Tansient EPs	**Frequency-Domain EEG, Steady-State Eps**
Unnormalized	**Covariance**	**Cross-Spectral Density**
Normalized	**Correlation Function and Coefficient**	**Coherence and Coherency**

which compartment 'A' is composed of the basal dendrites that receive input primarily from the axon collaterals from neighboring or 'short distance' pyramidal cells, while compartment 'B' is composed of the apical dendrites of cortical pyramidal cells that receive input primarily from 'long-distance' intracortical connections. The short

distance 'A' system primarily involves local interactions on the order of millimeters to a few centimeters, while the long distance 'B' system involves long-range interactions on the order of several centimeters which represent the majority of white matter fibers. These two systems exhibit two different network properties. System 'B', due to reciprocal connections and invariant apical dendrite terminations, is involved in long distance feedback or loop systems. In contrast, system 'A', due to the variable depths of the basal dendrites, is not involved in reciprocal loop processes but rather in a diffusion type of transmission process (Thatcher et al, 1986; Pascual-Marqui et al, 1988; Braitenberg, 1978; Braitenberg and Schuz, 1991)).

The developmental changes in EEG coherence in a large group of subjects reflects changes in the mean coupling constants between connected neuronal networks (Thatcher et al, 1987; Thatcher, 1992; 1994; 1998b). For example, if we assume that volume conduction has been controlled, then we can postulate a relationship between EEG coherence and two primary factors: 1-the number of cortico-cortical connections between neural assembles, and 2- the synaptic strength of connections between neural assemblies (the terms cortico-cortical connections and intracortical connections are considered synonymous). This relationship is mathematically described as:

$$\text{Coherence} = (N_{ij} \times S_{ij})$$

where N_{ij} is a connection matrix of the number of connections between neural systems i and j, and S_{ij} is the synaptic strength of those connections. This equation provides a logical means by which developmental changes in EEG coherence can be interpreted in terms of changes in the number and strength of connections between assemblies of neurons (Thatcher et al, 1986; 1987; Pascual-Marqui et al, 1988; Thatcher, 1992; 1994). For example, increased coherence is due to either an increase in the number and/or strength of connections and, conversely, decreased coherence is due to a decreased number and/or reduced strength of connections. The neurophysiological mechanisms responsible for the changes in the numbers or strengths of connections include axonal sprouting, synaptogenesis, mylenation, expansion of existing synaptic terminals, pruning of synaptic connections, presynaptic changes in the amount of neurotransmitter and changes in the postsynaptic response to a given neurotransmitter (see discussions by Purves, 1988; and Huttenlocher, 1984; 1990). Currently, measures of EEG coherence can not discern among these various possibilities.

The "Two-Compartmental" model of EEG coherence was subsequently confirmed and extended by Pasqual et al (1988) and many others (Wright, 1997; Nunez, 1981; 1994). Strong support for the existence of a genetically determined short versus long distance "Two-Compartmental" model of EEG coherence was also provided (van Baal; 1997; van Baal; 1998). For example, an extensive EEG study of 209 identical and non-identical twin pairs was conducted in which the heritability of short distance EEG coherence was approximately 48% and the heritability of long distance EEG coherence was approximately 70%. As van Baal (1997) concluded "... the heritability estimates provide support for a two compartmental model [of human EEG coherence]." (p. 110) and that "The fact that heritability was sensitive to the direction of cortico-cortical connectivity supports Thatcher's claim that individual differences in coherence reflect axonal connectivity of the brain..". (p. 111).

As mentioned previously, EEG coherence has been shown to exhibit clear

and important clinical utility. For example, EEG coherence is often one of the strongest and most sensitive of all QEEG measures in studies of schizophrenia (Ford et al, 1986; Nagase et al, 1992; Shaw et al, 1979), obsessive compulsive disorders (Prichep et al, 1993), depression (Prichep et al, 1990), mild traumatic brain injury (Thatcher et al, 1989), prediction of outcome following head injury (Thatcher et al, 1991b), Alzheimer's Disease and Infarct Dementia (Leuchter et al, 1987; 1992) and ADHD (John et al, 1988; Marosi et al, 1992). In addition, a growing number of studies have also demonstrated relationships involving EEG coherence during normal cognitive function (Petch, 1996; Thatcher et al, 1983; 1987; Thatcher, 1992; Lubar, 1997). Given the anatomical and physiological relevance of EEG coherence plus its clinical utility it would be remiss for any normative reference EEG database to omit either intrahemispheric or interhemispheric EEG coherence.

Biophysical Linkage Between MRI and EEG Coherence

As mentioned previously (section 3.2) the EEG arises from the rapid movement of ions (e.g., Na, K, Cl, etc.) across large areas of neural membrane surface and correlations between MRI biophysical measures of the brain and the EEG amplitude have been reported (Thatcher et al, 1998a). Biophysical correlations between MRI measures of T2 relaxation time and EEG coherence have also been reported (Thatcher et al, 1998b). The biophysical analyses showed that lengthened 1H T2 relaxation times of the cortical gray and white matter were related to: 1- decreased EEG coherence between short interelectrode distances (e.g., 7cm), 2- increased EEG coherence between long interelectrode distances (e.g., 28 cm) and, 3- differences in EEG frequency in which T2 relaxation time was most strongly related to the gray matter in the delta and theta frequencies in CHI patients. The results were interpreted in terms of reduced integrity of protein/lipid neural membranes and the efficiency and effectiveness of short and long distance EEG coherence compartments following traumatic brain injury.

EEG Phase Measures

EEG phase is usually computed at the same time as is EEG coherence. EEG phase is operationally defined by the amount of time shift of one time series with respect to another in order to obtain maximum coherence. The phase of the coherence function is the phase angle or time delay in milliseconds for S_{xy} where x and y are the EEG times series recorded from channel x and channel y. The EEG phase delay between two channels is measured when ever EEG coherence is measured because they are intrinsically related. As mentioned previously (section 3.3), EEG phase is defined as that time delay between two channels in which coherence is at a maximum. Studies by Thatcher et al (1986) have shown that EEG phase delays increase as a function of interelectrode distances and can be used to estimate axonal conduction velocities (Nunez, 1981; 1994). EEG phase has also been shown to be related to the underlying cortico-cortical connectivity of the human brain and it has also been demonstrated to carry considerable clinical utility (Thatcher et al, 1989; 1991b). Unlike EEG coherence, however, EEG phase is more variable and less stable and must be evaluated with even more caution than EEG coherence. The instability of EEG phase results from the fact that complex numbers exhibit a fundamental discontinuity in their computation of phase angle. That is, 0^0 and 36^{00} are adjacent to each other thus resulting in large variability. In order to minimize this inherent variability Thatcher et al (1986; 1987) computed absolute phase

(i.e., no negative numbers). However, even with this transformation and additional logarithmic transformations EEG phase is more variable and less stable than EEG coherence. Nonetheless, EEG phase is an important measure since it can be related to the intrinsic integrity of the gray and white matter as well as the conduction velocities of the cortico-cortical white matter (Nunez, 1981; 1994; 1989; Thatcher et al, 1986). Also, whenever EEG phase is significantly greater than 0 milliseconds (e.g., > 5 milliseconds) then EEG coherence, by definition, does not reflect volume conduction.

In the studies of mild to severe traumatic brain injury by Thatcher et al (1989; 1991b), EEG phase was among the most predictive and sensitive of all of the EEG measures. Again, given the anatomical and physiological relevance of EEG phase plus its clinical utility it would be remiss for any normative reference EEG database to omit EEG phase. However, the reader must be cautioned in the use of EEG phase and urged to rely upon EEG experts who have experience in the clinical interpretations and use of EEG phase before making clinical judgments based exclusively on EEG phase.

EEG Amplitude Differences and Ratios

Differences in the absolute amplitude between EEG recorded at different electrode sites has also been shown to be of clinical utility (John et al, 1977; John, 1977). In normal subjects the greater the amplitude differences then the higher the mean I.Q. (Thatcher et al, 1983). These amplitude differences appear to be within a "normal range" and reflect the amount of functional differentiation in the brain. When pathology is present or neurologically sub-optimal conditions persist, then there may be significantly increased or decreased amplitude differences. For example, a focal lesion may result in increased delta activity or reduced beta activity which may manifest itself through a change in amplitude differences between two or more electrode sites. A problem with amplitude differences is that they, by themselves, do not reveal the source of the differences. For example, increased F3-C3 amplitude difference may be due to reduced amplitude at F3 or C3 or increased amplitude at F3 or C3 (i.e., one electrode relative to the other). Examination of the Z score referenced amplitudes may reveal which electrode location is increasing or decreasing and thus contributing most to the amplitude differences.

Other ratios such as theta/beta ratios, or alpha/beta ratios or theta/alpha ratios, etc. have also been shown to be of clinical use (Matousek and Petersen, 1973; Lubar, 1997). Again, however, in order to understand more about the source of these ratio differences examination of the EEG frequencies from individual leads is necessary.

Univariate Statistics Versus Multivariate Statistics

Most QEEG databases use both parametric univariate statistics and parametric multivariate statistics to compare an individual to a NDB. The Z score or T score are commonly used statistics to express the deviation from the normative reference EEG values in standard deviations. While univariate and multivariate Z scores or Wilks lambda scores are useful statistics, the reader must use caution in order to understand the Type I (saying something is true when it is actually false) and Type II (saying something is false when it is actually true) statistical errors that are inherent in any inferential statistical procedure. In addition to adherence to univariate and multivariate normal distributions,

inferential "inflation" through the use of too many Z or t tests can occur (i.e., increased Type I errors due to multiple comparisons). Various statistical adjustments are available to minimize the problem of multiple comparisons. As a rule of thumb, all one has to do is count the total number of statistical tests within a specific EEG category (e.g., power, coherence, phase, etc.) and then multiply by .05 to determine the number of expected statistically significant comparisons at the probability of $P < .05$ which will occur by chance alone. For example, if 112 univariate EEG coherence Z tests were performed then, one would expect 5.6 significant (i.e., $P < .05$) to occur by chance alone. Bonferroni or Scheffe or Tukey statistical adjustments for multiple comparisons assume sampling distribution independence and are often overly conservative (i.e., increase Type II errors). As described in section 2.3 one can simply eliminate the need for multiple comparisons by calculating reliability in a test-retest or split-half sampling procedure (Duffy et al, 1994, Ferguson, 1976).

Important univariate statistical analyses virtues are their simplicity and both frequency and anatomical localization strengths. For example, a 4 standard deviation Z score in excess delta activity from the left parietal region (P3) points the clinician to a possible focal abnormality that is located near to the left parietal area of the brain. With univariate statistics as a guide then, Biofeedback or Neurotherapy can be focused on a particular region(s) and/or EEG frequency with some confidence as to the location of the deviation from expected values. A similar argument pertains to EEG coherence in which both short and long distance EEG coherence Z score deviations from the NDB may carry specific clinical meaning and help target Neurotherapy. In contrast, multivariate statistics are complicated and reduce the ability to localize the possible regions of the brain that are deviating from normal frequency and/or amplitude. Multivariate statistics involve the summation and correlation correction among a set of variables. This necessarily results in a type of anatomical and frequency smearing in which large collections of variables are averaged together. As a consequence multivariate statistics may or may not improve the sensitivity and specificity of QEEG and certainly reduce one's ability to devise Neurotherapy strategies. For example, if one obtains a multivariate discriminant score of -1.85 involving twenty or more EEG measure, how does this help one plan Neurotherapy sessions in order to address this multivariate deviation from normal? In the case of univariate statistics the answer is to identify the most deviant and clinically significant EEG feature and/or location and then use Neurotherapy to move this deviant area toward the normal distribution. In the case of multivariate statistics, literally scores of EEG measures in combination may be giving rise to the multivariate Wilks Lambda or discriminant values and individual univariate statistics may actually be normal (Cohen and Cohen, 1983).

In general it is best to restrict the use of multivariate statistics by making specific hypotheses and posing specific clinical questions. A good use of multivariate statistics is in the development of discriminant functions when a large number of variables are combined into a single equation designed to classify members of two or more populations, followed by independent validation of the discriminant function (John et al, 1977; Thatcher et al, 1989; John et al, 1988). However the univariate examination of the individual variables that are entered into the discriminant function is important in understanding the physiological and clinical meaning of the analyses. It is for this

reason that publications of discriminant functions should contain a list of the variables that are used in the discriminant function (Thatcher et al, 1989). Factor analyses are useful to reduce redundancy and the size of measure sets, however, the ability of factor analyses to predict outcome or provide inferential statistics is limited (Cohen and Cohen, 1983). Multivariate analyses of variance (MANOVA) are useful in determining group differences after adjusting for intercorrelations, however, MANOVA is limited in its predictive and clinical application. A similar argument holds for other multivariate statistics such as Mahalanobis distances (Cohen and Cohen, 1983).

QEEG Discriminant Functions

The use of QEEG discriminant functions for the purposes of diagnosis is an important and complicated topic. QEEG discriminant functions must only be used in conjunction with other medical or clinical evaluations and diagnoses should never be made simply based on a given QEEG discriminant score (Duffy et al, 1994). A QEEG discriminant function should not be used blindly or without explicit publication of the internal details of the discriminant function in a refereed journal, e.g., exact descriptions of the variables that are contained in the discriminant function, exact description of the subjects in the study, the number of false positives, the number of false negatives, the sensitivity and specificity, and one or more independent cross-validations. Publication of these details is necessary and required before a discriminant function can be used, especially the independent cross-validation(s) of the discriminant function. All of these criteria were met in the Thatcher et al (1989) mild head injury discriminant function which has been used in various settings since its publication.

The Thatcher et al (1989) QEEG discriminant function is sometimes confused with a "normative EEG database" (i.e., NDB). A discriminant function is not a "database" but rather it is a set of derived measures that act as a type of "pattern recognition" procedure. A discriminant function examines a limited number of variables to determine whether the multivariate combination or pattern of the variables is sufficient to classify an individual as a member of a clinical group or an age matched normal control group. The discriminant function merely states that such an EEG pattern is present or absent and provides a statistical estimate of classification accuracy. The clinical merit of a discriminant function is partly measured by the extent that the variables co-vary with the predicted pathology, e.g., increased coherence in the frontal lobes, decreased high frequency amplitude in the case of mild head injury (Thatcher et al, 1989). All of these factors must be considered when one uses a QEEG discriminant function.

Importantly, a discriminant function is a multivariate statistical test and it suffers from all of the problems mentioned in sections 4.0 and 5.2 in regards to its use for Neurotherapy. Univariate NDB comparisons are the best choice for tailoring Neurotherapy with the evaluation of the EEG discriminant function being used as a diagnostic monitor and not as a variable to be used in the biofeedback procedure itself (at least not until a paper is published showing that this is possible).

Growth Spurts in EEG Development:

Human cerebral development does not occur as a smooth linear function of age, but rather it is non-linear with abrupt changes and oscillations (Thatcher et al, 1987; Thatcher, 1991a; 1992; 1994a; Hudspeth and Pribram, 1990; Van Baal,

1997; Chugani, 1996). One advantage of a "Life-Span" database, extending from birth to adulthood, is that it provides the ability to evaluate the rate and time course of human cerebral development. Two issues of major importance in understanding child development are: 1- determining the extent to which the left and right cerebral hemispheres develop at different rates and at different ages and, 2- determining whether human cerebral development occurs as a smooth function of age or in discrete steps or stages. If human cerebral development occurs in steps or stages, then it is important to quantify which cortical regions develop at what ages. The clinical relevance of this information concerns: 1- the early detection of deviation from normal development in individual children, 2- the use of EEG to evaluate remediation strategies and treatment and, 3- the distinction between an "psychological" versus an "organic" basis for a childhood disorder.

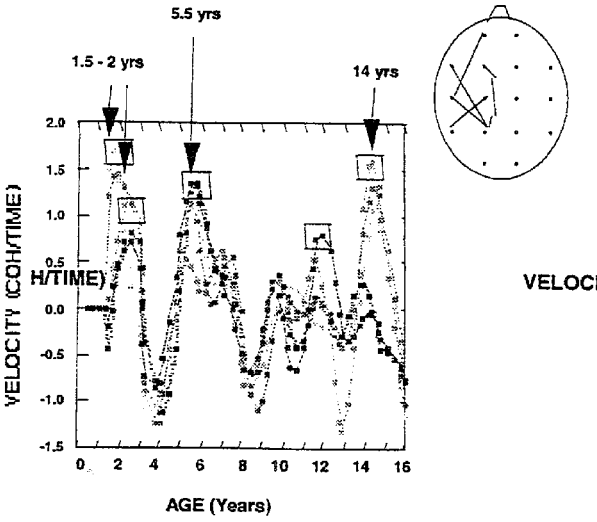
The presence of specific cerebral growth spurts at particular ages are clearly revealed in the Thatcher EEG normative reference database (Thatcher et al, 1987; Thatcher, 1994a). Figure 6 shows the velocity curves or the first derivatives (i.e., rate of change of EEG Coherence) of the developmental trajectories of mean EEG coherence from the sub-groupings of electrode pairs that had the highest factor loadings (e.g., > .80) (Thatcher, 1991a). Growth spurts were defined by a positive peak in the first derivative (i.e., a postnatal time of maximum growth) in multiple interelectrode combinations. These data provide evidence of differential cerebral development and stages of Corticocortical connectivity. The data also emphasize the non-linearity of cerebral development and, thus, the need for large sample sizes especially during the early childhood and adolescent periods of development.

The non-linearity of EEG development was also demonstrated in analyses of Matousek and Petersen's (1973) NDB using relative power (Thatcher, 1980; Epstein, 1986; Hudspeth and Pribram, 1990). Thus, caution should be exercised when using NDBs that are based upon a linear analysis of EEG development or NDB's that use linear regression equations to adjust for age (John et al, 1980). For example, in the John et al (1987) studies linear regression analysis of the Matousek and Petersen (1973) NDB as well as the N.Y.U. Medical Center NDB were conducted. Examination of the figures shows that a relatively small amount of variance was explained by the linear regression equations (e.g., < 70%, personal analyses), thus considerable error is inherently present when such linear analysis are used for normative EEG database comparisons. Because of the inherent non-linearity in human life-span EEG development, the Thatcher NDB does not use age regression and, instead, uses sliding averages with approximately a 3 month age resolution (see Figure 4 and Thatcher, 1992; 1994a; 1994b).

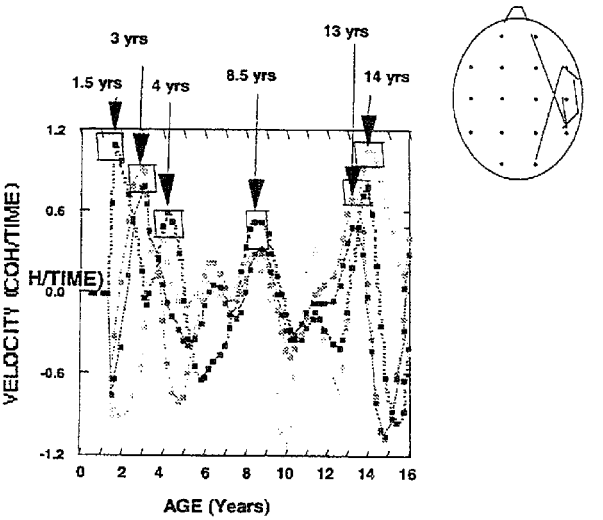
Individualization of Neurofeedback based on reference QEEG Evaluation

To my knowledge, the first use of a lifespan NDB for the purpose of Neurotherapy was devised by Thatcher and Lexicor, Inc. in 1992. Prior to 1992, Neurotherapy protocols were widely different, with differing rationalizations and were essentially arbitrary protocols. That is, a given Neurotherapist discovered by practice that a certain protocol, e.g., increased Alpha power at C3, seemed to help his or her patients. Over time, this protocol became favored and was sometimes promoted as an "effective " protocol for Neurotherapy. Also, prior to 1992, the

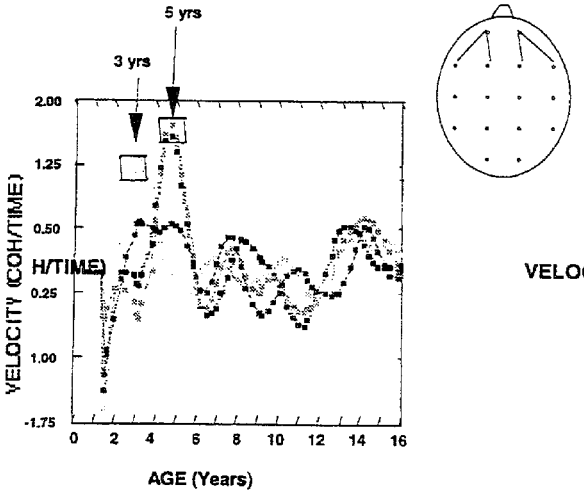
FACTOR 1 - GROWTH SPURTS



FACTOR 2 - GROWTH SPURTS



FACTOR 3 - GROWTH SPURTS



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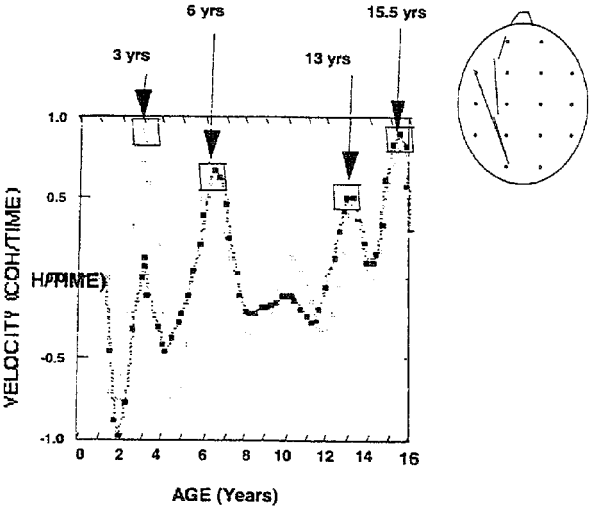

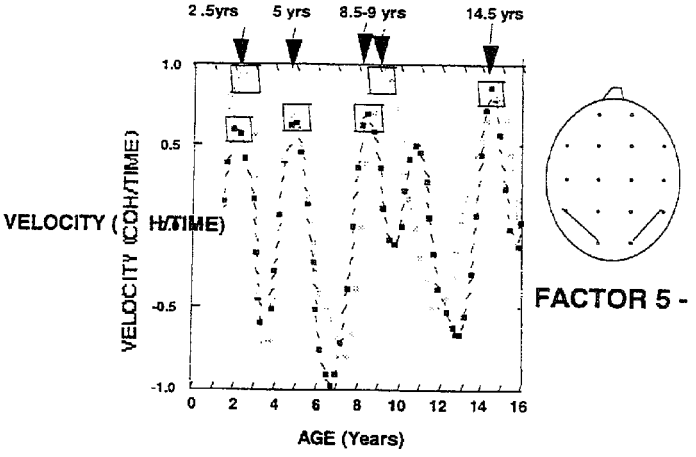

FACTOR 5 - GROWTH SPURTS

objective assessment of the strengths and weakness of the neural organization in a given patient was not used. Also, the ability to use EEG to determine whether there was an "organic" basis for a patient's complaints was not used, and Neurotherpy protocols were not individualized based upon the EEG features and anatomy most deviant from normal. It was the recognition of this 'gap" in clinical assessment that inspired the first applications of a NDB to the field of Neurotherapy.

As mentioned in the introduction, there are at least three primary reasons to use a NDB for the purposes of Neurotherapy: 1- to assess the neurological status of the patient and to determine to what extent there is a neurological basis of the patient's complaints (i.e., the issue of Organicity), 2- to identify possible strengths and weaknesses in the organization and electrophysiological status of the patient's brain so as to aid in the efficient and optimal design or choice of Neurotherapy (i.e., the issue of *Therapy Design*) and, 3- to objectively evaluate the efficacy of treatment by comparing the patient's EEG before and after treatment (i.e., the issue of Treatment Evaluation). A fourth and long-term reason, is that the use of a standardized and objective EEG test may help promote scientific publications in refereed journals to evaluate the efficacy of Neurotherapy as it applies to different patient populations.

The Issue of Organicity

As a clinical practitioner one is often faced with the problem of determining whether or to what extent purely psychological factors such as divorce, emotional trauma or malingering, etc. are contributing to the symptoms presented by the patient. Conversely, the clinical practitioner needs to understand whether and to what extent there is a neurological or organic basis for the patient's complaints. Quite different therapeutic strategies follow depending on the extent to which neurological and/or psychological factors are contributing to the patient's problems. The use of QEEG evaluations using a NDB may aid in this basic clinical assessment by disclosing a *normal* EEG or an *abnormal* EEG. For example, the presence of large amplitude *spike and waves* may indicate the presence of epilepsy for which a conventional neurological evaluation and treatment may be recommended. The presence of large amplitude delta activity may indicate an infarct or other lesion for which an MRI and other neurological evaluations would be recommended. Less dramatic and more subtle neurological problems may also be present such as significant deviation from normal in short and/or long distance EEG coherence or in the scalp distribution of EEG power. In the latter case, Neurotherapy may be highly recommended. At this point it is important to re-emphasize, however, that the clinical practitioner must always be aware of the statistical issues involved in the use of a NDB (see sections 2 - 4) and, thus, must ultimately rely upon his or her clinical judgment. Such reliance is not unique to QEEG since any clinical diagnostic test only provides partial information that is taken into consideration in the context to the total patient evaluation when rendering a clinical judgment.

The Issue of Therapy Design

The use of a NDB allows for individualization of EEG Biofeedback or Neurotherapy based upon the EEG features and anatomical locations that are most deviant from normal. Individualization of Neurotherapy should be contrasted to the standard pre-1992 methods whereby a relatively rigid and arbitrary set of pre-designed protocols were administered

without awareness of an individual's EEG profile. NDB analysis allows for more standardization of Neurotherapy across patients and clinics, as well as for potentially more efficient Neurotherapy by focusing on the most statistically deviant EEG features and anatomy. It is important to recognize that Neurotherapy is a young and growing discipline, and NDB should not be considered as the only diagnostic method or to be used at the exclusion of biofeedback protocols that a given clinician has found useful. However, NDB based Neurotherapy can help facilitate the optimal or most efficient biofeedback approach and help quantify the efficacy of any given protocol, in comparison to other protocols. Finally, univariate and not multivariate analyses are the most straight forward and interpretable QEEG measures to be used for therapy design. Caution should be exercised in the design of neurotherapy based solely on multivariate analyses, including discriminant analyses and Mahalanobis statistics.

The Issue of Treatment Evaluation

There are at least two categories of treatment evaluation where NDB's play a role: 1- Improved efficiency or optimization of treatment protocols and, 2- evaluation of the outcome of treatment. Both of these categories benefit from a quantitative and objective evaluation of methods used for treatment as well as the efficacy of treatment. For example, the extent to which brain EEG measures *normalize* , i.e., exhibit reduced Z scores following treatment can be assessed using a NDB (Hoffman et al, 1996a; 1996b). The test-retest reliability and the sensitivity and specificity of treatment can also be evaluated using an EEG NDB. The number of sessions may be minimized by evaluating the progress of 'normalization' of the EEG with respect to an NDB. These means optimization reduced time and cost to patients and third party insurers plus improved therapeutic outcome may be derived.

The use of a NDB for the purposes of Neurotherapy is relatively recent and the full benefits of such an approach are yet to be realized. However, it is believed that increasing knowledge about anatomy and the genesis of EEG coupled with the objective evaluation of a patient's EEG with respect to a normative database will facilitate the application of Neurotherapy and eventually improve its efficacy as well as its scientific foundations.

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FIGURE LEGENDS

Figure one: The distribution of socio-economic status in the Thatcher 1987 EEG reference normative database (NDB) as measured by the Hollingshead four factor criteria (Hollingshead, 1975).

Figure two: The distribution of handedness as a function of age in the Thatcher 1987 EEG reference normative database (NDB) as measured by an eight item "laterality" test consisting of three tasks to determine eye dominance, two tasks to determine foot dominance and three tasks to determine hand dominance. Scores ranged from -8 (representing strong sinistral or left hand preference) to +8 (representing strong dextral or right hand preference). Ambidextrous subjects were defined by a laterality score between plus and minus 2.

Figure three: A normal curve showing values of Z (), 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 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

Figure four: The number of subjects per year in the Thatcher 1987 EEG reference normative database (NDB). The database is a "life-span" database with 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 68 years of age and constituting a total number of subjects = 564. The Thatcher NDB also uses Savitzky and Golay (1964) smoothed sliding averages with approximately .25 year (i.e., 3 month) age increments.

Figure five: The distribution of mean WRAT (Wide range Achievement Test) reading, spelling and arithmetic scores as well as the mean full-scale I.Q., verbal I.Q. and performance I.Q. in the Thatcher 1987 EEG reference normative database (NDB).

Figure six: The velocity curves or the first derivatives (Mean Coherence/Time) of the developmental trajectories of mean EEG coherence from the sub-groupings of electrode pairs that had the highest factor loadings (e.g.,

> .80) (Thatcher, 1991a). Growth spurts were defined by a positive peak in the first derivative (i.e., a postnatal time of maximum growth) in multiple interelectrode combinations (from Thatcher, R.W. Cyclic cortical reorganization: Origins of Cognitive Development, In: G. Dawson & K. Fischer (Eds.), Human Behavior and the Developing Brain, New York, Guilford Publications, Inc., 1994b).

1 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 database. The practical utility of all clinical databases exusts only to the extent that the database constitutes a representative sample of the general population of neurologically and clinically normal individuals.

2 Recently Kaiser and Sterman (1994) have stated that they have observed circadium periods in the EEG spectrum in a cross-sectional study. However, because they conducted a cross-sectional study and not a repeated measures study their conclusions are not supportable. For example, the Kaiser and Sterman (1994) study was confounded with time between food intake and EEG acquisition, food content and EEG acquisition and amount of sleep deprivation experienced the night before EEG acquistion. These and other factors can only be controlled in a counter-balanced or randomized repeated measures design.

3 A wavelet is a symmetrical and smoothly increasing and decreasing oscillation which forms a "basis" function for orthonormal mathematical formulations. What makes wavelet bases especially interesting is their property of self-similarity , i.e., every function in a wavelet basis is a dilated and translated version of one (or possibly a few) mother functions. Once one knows about the mother function, one knows everthing about the basis functions.

4 The term "Power" was historically used by engineer's during the early applications of spectral analysis. As explained by Blackman and Tukey (1958) power is defined as the square of the autocovariance function in which the time measure was voltage across (or current through) a pure resistance of one ohm, and the time average power dissipated in the resistance is strictly proprtional to the variance of the voltage or current. This important special case is the historical reason for the adjective "power".

5 There may be confusion about the terms 'coherency' versus 'coherence'. Coherency is defined as the complex number representation where the real or x-axis is magnitude and the imaginary or y-axis is phase (Bendat and Piersol, 1980). Coherence is defined as the absolute length of the resultant vector or hypotenuse in the complex plane (i.e., the coherency complex number representation). Thus, mathematically, coherence is defined as:

$$coh = \sqrt{x^2 + y^2}$$

where x and y are the coherency measures of magnitude and phase.

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