Neurometrics: Computer-Assisted Differential Diagnosis of Brain Dysfunctions

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Normative developmental equations provide reliable descriptors of brain electrical activity in people 6 to 90 years old. Healthy persons display only chance deviations beyond predicted ranges. Patients with neurological impairment, subtle cognitive dysfunctions, or psychiatric disorders (including dementia and primary depression) show a high incidence of abnormal values. The magnitude of the deviations increases with clinical severity. Different disorders are characterized by distinctive profiles of abnormal values of brain electrical features. Computerized differential classification of some of these disorders can be achieved with high accuracy. Such classification, providing objective corroboration of brain dysfunctions, may be a useful adjunct to psychiatric diagnosis, which relies primarily on subjective clinical impressions. These methods may provide independent criteria for diagnostic validity, evaluations of treatment efficacy, and more individualized therapy.

IN 1977, IT WAS PROPOSED THAT STATISTICAL ANALYSIS OF standardized, quantitative electrophysiological features relative to a body of normative data (Neurometrics) might aid in the differential diagnosis of a variety of subtle brain dysfunctions (*1*). Subsequently, a set of developmental equations was reported that described the electroencephalogram (EEG) features that could be observed in healthy children in the United States and Sweden, aged 6 to 16 years (*2*). A high proportion of children with learning disabilities or neurological dysfunctions showed marked deviations of certain features from the predicted normal range (*3*). Large numbers of normal subjects aged 17 to 90 years have now been studied. The set of features that can be considered normal from age 6 to 90 has been greatly expanded and described by normalized age-regression equations. These features include univariate and multivariate descriptors of absolute power, relative power, mean frequency, and coherence and asymmetry between homologous leads for both monopolar and bipolar derivations (*4*). All features are extracted from a 60-second sample of artifact-free EEG, automatically recorded and analyzed by a mobile microprocessor system, collected from scalp electrodes or a helmet placed on a subject resting comfortably with eyes closed in a quiet, dimly lit room.

In eight countries, including the United States, investigators have found that normal persons display few values outside the predicted range, indicating that these features are independent of cultural or ethnic background (*3, 5–11*). When these features were evaluated in large groups of patients with a variety of cognitive, psychiatric, and neurological dysfunctions, a high proportion of abnormal values were found (*6, 8, 9, 11–13*). The patterns of abnormal values appeared to be distinctive for different disorders and made it possible to perform computer-assisted differential classification with high accuracy (*9, 12, 13*).

These findings are of particular importance in psychiatry, where current diagnostic methods rely almost exclusively on subjective impressions obtained by clinical interviews and rating scales. Objective evidence of specific abnormalities in brain electrical activity provides independent corroboration of clinical judgment and permits validation of the physiological homogeneity of clinical psychiatric classifications. Such adjuncts to psychiatric diagnosis are presently lacking. Since the magnitude of many abnormal neurometric values increases with clinical severity, longitudinal tracking may provide criteria for describing the natural course of different disorders and for the evaluation of treatments. Such sequential measurements should lead to more individualized therapeutic management and better outcomes of treatment.

Topographic head maps depict in Fig. 1 the average deviations from the values predicted by the developmental equations, for one subset of relative power features in large groups of normal persons (*14*) and of patients with mild cognitive impairment (*15*), primary degenerative dementia (*15*), schizophrenia (*16*), alcoholism (*17*), unipolar depression (*18*), and bipolar depression (*18*).

The color coding on these maps is scaled to reflect the *probability* that the observed findings are within the normal range. First, for each of the 19 electrodes of the International 10/20 System, the values of relative power X in the delta, theta, alpha, and beta

Fig. 1. Average topographic head maps for Z scores of relative power (percentage) in delta, theta, alpha, and beta frequency bands, computed across groups of individuals classified as stated. These maps represent the mean relative power difference between each group and the reference group, expressed in standard deviation of the reference (normal) group not shown on the figure. Color coding is proportional to the mean Z score for each group, in steps corresponding to those shown on the Z scale. The scale from $+1.5$ to -1.5 applies to the first six rows. The scale $+0.7$ to -0.7 applies only to the last row. The significance of Z-scale values can be estimated by taking the square root of sample size and the standard deviation of each group into account and ranges from 0.002 to <0.001. For example, for $n = 60$, the probability associated with an average Z value of 0.7 is that corresponding to a standard normal deviate of 5.4, that is, a probability considerably less than 0.0001.

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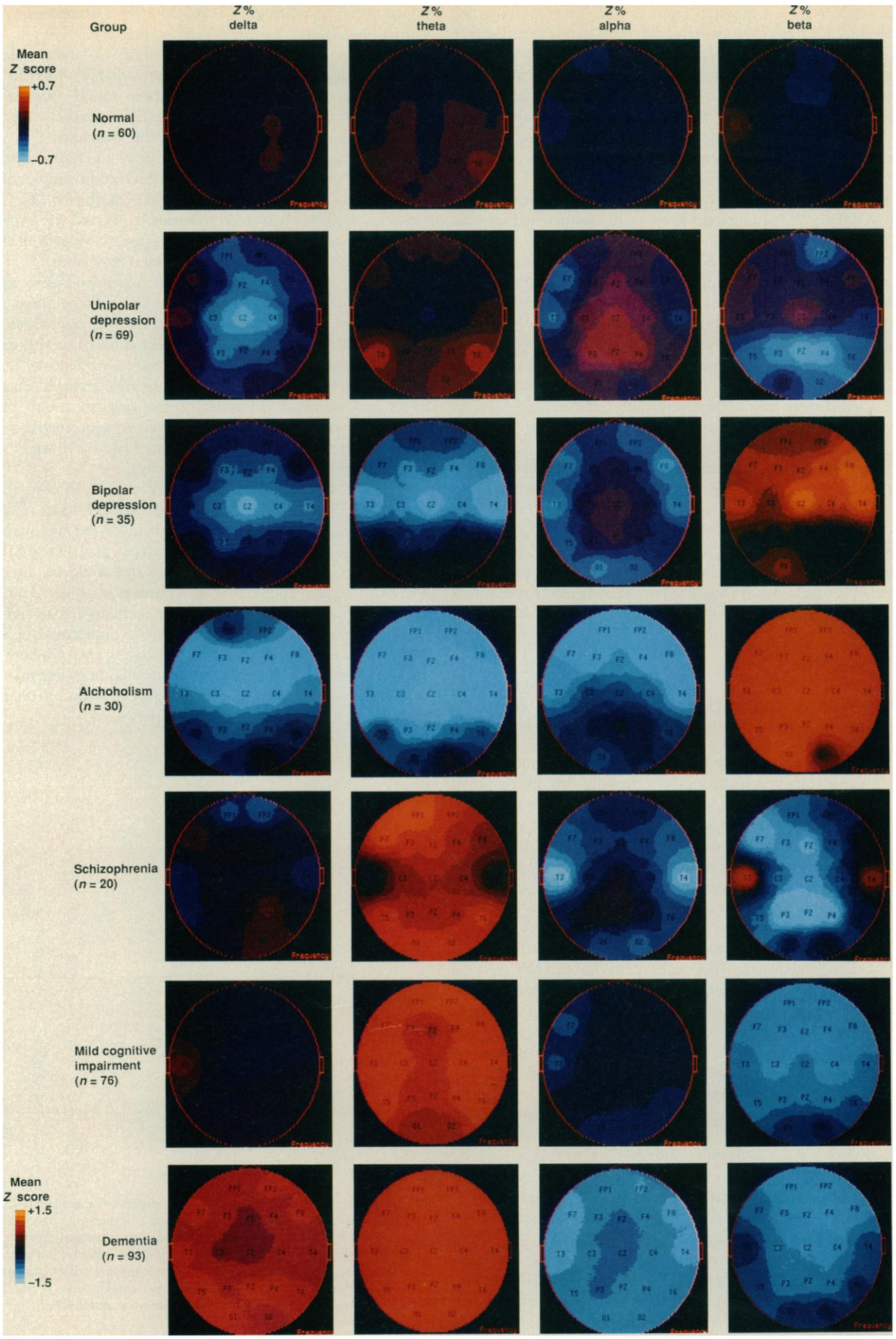
Group
Z% delta
Z% theta
Z% alpha
Z% beta
Mean Z score
+0.7
−0.7
Normal (n = 60)
Unipolar depression (n = 69)
Bipolar depression (n = 35)
Alchoholism (n = 30)
Schizophrenia (n = 20)
Mild cognitive impairment (n = 76)
Dementia (n = 93)
Mean Z score
+1.5
−1.5

frequency bands were computed from the EEG sample recorded from every subject (*19*). Second, the individual data were subjected to the transform $Y = \log[X/(1.0 - X)]$ which achieves Gaussian distributions for these features (*2, 4, 5*). Third, the significance of the obtained individual values of Y was assessed by computing the standard score or Z score (*4, 20*). Finally, the individual Z scores were averaged for each electrode position separately for each group of patients, and the group means were displayed as the color-coded topographic maps shown in Fig. 1.

A sufficiently high proportion of individuals within each of these groups of 20 to 93 patients deviated from normal in the same direction for particular features so that the mean value of Z was often greater than 1.0. This is evidence that many features for each group are significantly different from normal, which was corroborated by multiple t tests. Many patients with the same disorder have some abnormal features in common. Marked differences are visible in the average profiles of abnormality among these disorders. Consistent patterns of weak differences across large numbers of features, even if individual feature differences do not reach significance, can yield extremely high multivariate significance.

However, individual variability within each group is appreciable. As a result, patients with the same disorder often show differences so marked that accurate classification by visual inspection of topographic maps of individual features alone is not possible. It is therefore necessary to use multivariate statistical analysis of composite descriptors of relations among brain regions, as well as of local features, in order to accomplish computer classification of the individual patients. Here, we briefly review the development and basic principles of this neurometric approach and present results that demonstrate the accuracy achieved with this method, especially in classification of psychiatric patients.

Developmental Equations for the EEG of Children

In 1973, Matoušek and Petersén (*10*) published normative data for 16 features extracted from EEGs of healthy Swedish children from 1 to 21 years old. These features were the absolute power (in squared microvolts) in four frequency bands (delta, theta, alpha, and beta) in each of eight bipolar derivations, averaged across homologous pairs on the two hemispheres (*21*). Computer analysis of these features in EEGs from healthy, normally functioning, black U.S. 9-year-olds showed that they corresponded very closely to 9-year-old Swedish children (*1*).

In view of this correspondence, 60 seconds of artifact-free EEGs were collected from healthy, normally functioning, U.S. children aged 6 to 16, with a microprocessor-controlled digital data acquisition and analysis system with an on-line artifact rejection algorithm (*1*). After visual editing to remove residual contamination not excluded by this algorithm, the same features were quantitatively extracted from these data, separately for each hemisphere. The resulting 32 absolute power features were normalized as relative (in percent) power within each derivation, because such normalization yielded high test-retest reliability. Logarithmic transformations were devised to approximate a Gaussian distribution, so that parametric statistical procedures could be validly applied. Age-regression equations were then calculated for the means and standard deviations of these distributions. Age-regression equations for the same features were also calculated from the previously published data from Swedish children, after transformation to relative power. Comparison of the equations describing the U.S. and Swedish samples revealed that they were almost identical (*2*). These equations were subsequently used to express features as Z scores [(observed value minus mean value)/standard deviation] for comparison with the normal distribution for the corresponding age.

A number of investigators have obtained similar results. The transformations of neurometric features that we used to approximate a Gaussian distribution have been found accurate (*5, 11*). Spectral features extracted from short EEG samples were found to be replicable characteristic traits of the individual (*12, 22*). The range of values predicted by the normative equations corresponded well with distributions subsequently observed in samples of healthy, normally functioning children studied in Barbados (*3*), Cuba (*8*), Germany (*12*), Mexico (*6, 9*), Venezuela (*9*), and the United States (*7*). The incidence of values outside the normative distributions (false positives) was at the level expected by chance.

Sensitivity and specificity. Whereas an independent sample of normal children showed a chance incidence of false positives (about 5%), groups of children with specific learning disabilities, children with multiple learning disabilities, and children at risk for a wide variety of neurological disorders showed an incidence of "hits" (true positives) as high as 56% on some individual features relative to the mean and standard deviation of the original group of normal subjects (*3, 4*). It was concluded that these neurometric descriptors were sensitive to cognitive dysfunctions as well as to well-recognized neurological disorders.

Gasser *et al.* (*12*) similarly compared samples of normal, learning disabled (LD), and mentally retarded (MR) children. The features of the normal children were predominantly in the range expected for normal subjects, while a high proportion of the LD and MR groups showed significantly abnormal values and could be discriminated well from the normal individuals. Alvarez *et al.* (*8*) and Harmony (*9*) studied samples of normal and mildly retarded Cuban and Mexican schoolchildren and found that the two groups could be separated neurometrically with high accuracy. Yingling *et al.* (*7*) have reported a low incidence of abnormal neurometric findings in a neurologically screened sample of children with "pure dyslexia," in contrast with

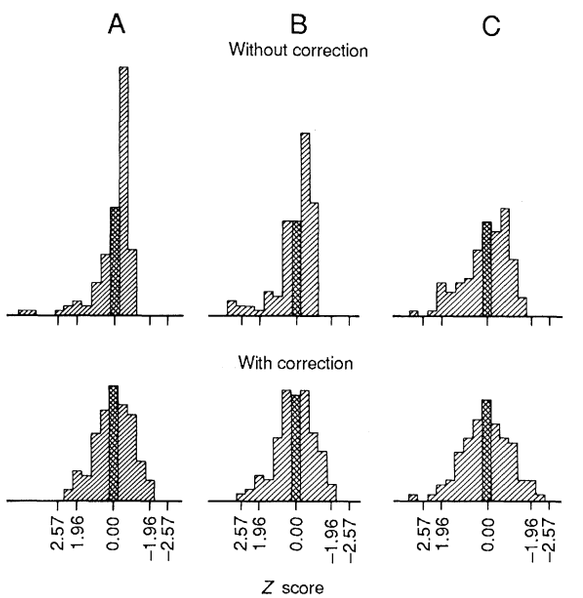

Fig. 2. Histograms of Z values for three different neurometric features (**A**) absolute power α F_1 (from frontal electrode 1 in the alpha band), (**B**) relative power Δ RFT (from right frontotemporal derivation in the delta band), and (**C**) total power T_3 (from left anterior temporal electrode) without (top row) and with (bottom row) transformations to approximate a Gaussian distribution. The transformation for absolute and total power is log X and for relative power is $\log[X/(1.0 - X)]$. Note that distributions are markedly skewed before correction.

the relatively high incidence observed by us in our reading-disabled children. Most of our reading-disabled children were in a special education facility. Many had mild neurological signs, such as impulsive behavior, brief attention span, clumsy performance of fine motor tasks, or awkward gait. Since our subjects do not meet the rigorous criteria for pure dyslexia, we cannot comment on this finding.

Extension to Adults

The approach used in children was then extended to adults. Five groups of subjects were studied: normal adults and patients with depression, alcoholism, dementia, and schizophrenia.

1) The normal adults (n = 120; 77 males, 43 females) were aged 17 to 90 years. The normative data were collected from projects at New York University Medical Center and six other sites (*14*). Normal subjects were selected on the basis of extensive psychiatric and neuropsychological test batteries, a psychiatric as well as neurological examination, achievement tests, and determination of eye, hand, and foot dominance. All intelligence quotients (IQs) were within normal range. Medical and psychosocial histories, pre- and perinatal data, and current and past school or work records were also evaluated. The subset of instruments used varied with age. Subjects with significant abnormal findings or events in their history that placed them at risk were excluded. Additional exclusion criteria included current use of prescription drugs, a history of head injury or loss of consciousness, any previous EEG or neurological examination, or febrile convulsions.

2) The depressed patients (n = 103; 61 females, 42 males; mean age, 53 years) were selected on the basis of Research Diagnostic Criteria (RDC) for the diagnosis of primary depression and were divided into unipolar (n = 68) and bipolar (n = 35) subtypes. All had symptomatic affective illness severe enough to interfere with daily functioning, and included both voluntary admissions to an inpatient evaluation unit and outpatients (*18*). Psychiatric, medical, and family histories, mental status evaluation, and physical examination were obtained. A score on the Hamilton Psychiatric Rating Scale for Depression greater than 18 (or its equivalent on the Carroll self-rating scale) was required for entry into the study.

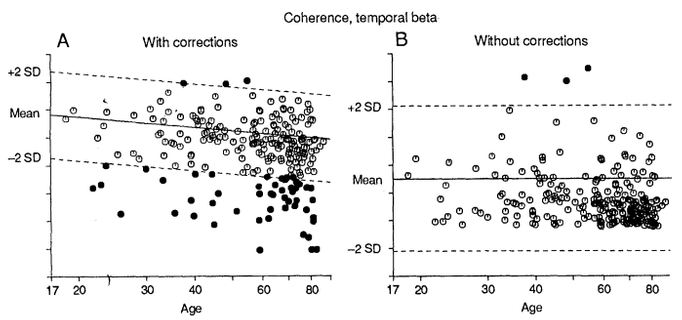

Fig. 3. Scatterplots for coherence in the beta band between derivations T_3T_5 and T_4T_6, shown with both age regression and log transformation to approximate a Gaussian distribution (**A**) and without either (**B**). Dotted lines represent ± 2 SD from mean of the normative reference group (solid line). Solid circles indicate cases displaying significantly abnormal values. Note the far greater sensitivity achieved when features are corrected for biases.

	n	Percent abnormal	
		(A) with correction	(B) without correction
Depression	103	17	0
Alcoholism	30	27	10
Dementia	93	26	0

3) The alcoholic patients (n = 30; all males; mean age, 41 years) were in early stages of withdrawal and had been referred for testing from an alcohol inpatient treatment program (*17*). These patients were consecutive admissions not balanced for severity of problem, degree of deterioration of function, or other clinical variables, and ranging in age from 21 to 60. Since they comprise a heterogeneous group at various stages of disease progression, abnormal neurometric features shared by this group are likely to reflect alcoholism per se rather than chronicity or complications of the disease.

4) The dementia patients (n = 125; 73 females, 52 males; mean age, 70 years) were selected from several hundred patients who were tested as a part of a large ongoing multidisciplinary study of dementia (*15*). All of them had a DSM III (*23*) diagnosis of dementia [primary degenerative dementia (n = 93) or multi-infarct dementia (n = 32)]. The diagnosis had the concurrence of both a psychiatrist and a psychologist and was based on clinical history, psychiatric and medical (including neurological) examinations, and psychological test performance. All patients showed measurable cognitive decline reflected by a global deterioration scale (GDS) score of 3 or greater. An additional group of elderly patients with a GDS score of 2 will be referred to as having "mild cognitive impairment" (n = 76).

5) The schizophrenic patients (n = 20; all male; mean age, 40 years) had all received extensive clinical evaluation and met DSM III criteria for diagnosis of schizophrenia (*16*).

All patients were evaluated a minimum of 10 days after discontinuation of all psychotropic medication. Informed consent was obtained for all subjects.

Methods for Data Collection and Analysis

The data acquisition procedures and feature extraction methods have been described previously (*1, 2, 4*). Recordings were monopolar and used all 19 electrodes of the International 10/20 Electrode Placement System referenced to linked earlobes. Eight bipolar derivations were then constructed by computation. Univariate and multivariate features were computed for absolute and relative power, mean frequency, and coherence and symmetry in the four frequency bands for the 19 monopolar derivations, as well as for the 8 bipolar derivations. Transforms for approximating a Gaussian distribution were devised and tested for all of these features and age-regression equations computed for the full expanded feature set. Z scores expressed the deviation of the disparate neurometric features from the predicted normative values in the common metric of relative probability.

Once these univariate features were similarly scaled, multivariate or composite features could be computed. Composite features of two sorts were computed: (i) within each derivation across frequency bands for absolute power, relative power, coherence, or symmetry; (ii) across derivations in the anterior or posterior regions of each hemisphere, across the whole left and right hemispheres, and across the whole brain for every feature. Correction for intercorrelations among the features combined in each composite was accomplished by computing the Mahalanobis distance across the set of features. By procedures analogous to those used for univariate features, normative data were used to permit Z transformation of these new composite features (*4*).

Split-half samples were constructed for every group, counterbalanced to control for possible differences in recording conditions or diagnostic criteria among sites. In every discriminant computation reported herein, one of these split-half samples was used for the initial "training" discriminant and the other as a test set for the independent replication of the initial discriminant. Z values were

based on the mean and standard deviation of the first split-half normal sample, to which all other samples, including the second split-half normal sample, were then referred.

Statistical Issues and Sensitivity

There is a current upsurge of interest in "functional imaging" of brain electrical activity in neurology and psychiatry, reflected in numerous recent international symposia on this topic and the appearance of a large number of commercial instruments for this purpose. Increasingly, topographic mapping devices use statistical methods to compare quantitative features extracted from an individual recording to reference data from a normative database. There is a general tendency in current applications of this neurometric technology to neglect certain statistical issues that greatly affect the sensitivity of the method, such as biased distributions, correlations with age, and correlations among features. Failure to consider these issues properly can lead both to increased false positive and false negative findings, which greatly diminish the clinical usefulness of this method.

1) *Biased distributions.* Histograms were made of the distribution of every feature in the normal and abnormal groups, with and without transforms to approximate a Gaussian distribution. Numerous features displayed distributions that were skewed in such a manner that appreciable incidence of both false positive and false negative errors would ensue unless corrections were applied before parametric statistical methods were applied. Examples of uncorrected and corrected distributions are shown in Fig. 2.

2) *Correlations with age.* Scatterplots were made of the distribution of every feature as a function of age, for all groups. Numerous features displayed a significant correlation with age. Were the values of these features used to compute an overall mean value and standard deviation across the entire age range, the resulting "normative data" would embody several errors. First, the variance would be greater than with age regression, causing a bias against positive findings. Second, Z transforms from individuals below the mean of the age range would be biased in one direction, whereas those from individuals above the mean age would be biased in the opposite direction. These effects can be significant. Figure 3 shows that more patients lie outside the normal confidence interval (dotted lines) when these biases are corrected.

3) *Intercorrelations among features.* Many features of brain electrical activity are highly intercorrelated. On the one hand, this introduces a high degree of redundancy into the measure set, which must be taken into consideration when estimates of overall abnormality are desired. On the other hand, this provides an additional source of valuable information, because pathology often causes changes in brain relations that increase or decrease these intercorrelations.

A composite feature combines the information from several univariate measures, and its value will be overestimated if there are intercorrelations among those measures. The accuracy with which a composite feature estimates the significance of deviations from normal values depends on how adequately such relations are taken into account.

If the variables were assumed to be independent, the determination of significance would depend on the variances. In Fig. 4, A and B, the area inside the circle is the 95% confidence region, if one assumes that the two variables were independent. Although few points for normal subjects (Fig. 4A) fall outside the circle (false positives), many points for abnormal subjects (Fig. 4B) lie inside the circle (false negatives). If the intercorrelations among the variables were taken into account, the composite significance would be equivalent to the Mahalanobis distance. In Fig. 4, A and B, the area inside the ellipse is the 95% confidence region based on the Mahalanobis distance. Although the area of the ellipse is much smaller than the circle, the majority of the normal subjects are encompassed with even fewer false positives (Fig. 4A). Conversely, a much higher proportion of the points for abnormal subjects fall outside the ellipse (Fig. 4B). Thus, false positives decrease and true positives increase. These results are due to the fact that the two variables display a strong negative correlation. Therefore, deviations in the same direction are much more significant than those in opposite directions.

Detection of Dysfunctions in Adults

Mean incidence of abnormal findings. The mean incidence of false positives in an independent sample of 60 normal healthy adults and of true positives in 354 patients representing seven dysfunctional categories were calculated separately for each of 274 univariate and 431 multivariate features from both monopolar and bipolar derivations (*21*) with and without correction for biases due to age effects and lack of conformation to a Gaussian distribution. On the average, multivariate features had 34% higher sensitivity and 41% higher specificity (true positives/false positives) than univariate, and corrected features had 19% higher sensitivity and 47% higher specificity than uncorrected ones.

For the 705 properly corrected features, the mean sensitivity per feature across the seven groups of patients was 21.9% (at the $P \leq 0.05$ level), whereas the mean incidence of false positive findings was 3.9%. Figure 5 compares the average incidence of positive findings in 95 univariate and 121 multivariate monopolar absolute power features for normal subjects and patients in seven dysfunctional categories. The same tendencies were true for other sets of features, including monopolar relative power and bipolar relative power, coherence, and symmetry data.

Sensitivity of multivariate features in cerebrovascular disease. In a recent collaborative study performed in Holland (*11*), the sensitivity

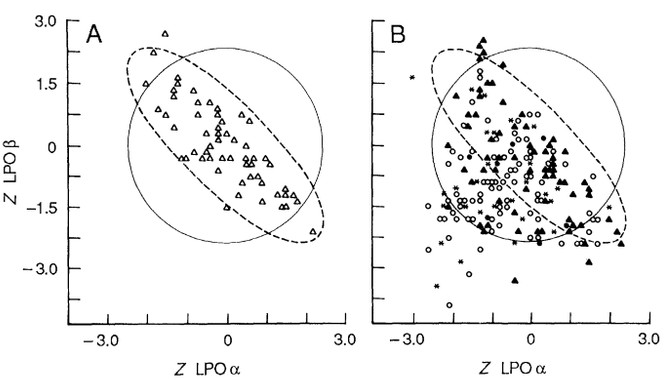

Fig. 4. Scatterplot for Z values of relative power (percentage) in alpha and beta bands in derivation P_3O_1 for 60 normal subjects (**A**) and for 202 patients in three categories (**B**). In each graph, the 95% confidence region is represented within the circle, if the multivariate compression is computed as the square root of the sum of the squared Z values of these two features (for which one assumes independence), and within the ellipse, if the multivariate compression is computed as the Mahalanobis distance (which corrects for intercorrelation between the two features). Note the far superior sensitivity achieved by taking the intercorrelations among features into account. The percentage abnormal for points outside the circle and outside the ellipse, respectively, were as follows: normal subjects (△, n = 60) 6.7 and 3.3; subjects with mild cognitive impairment (▲, n = 76) 15.8 and 31.6; patients with dementia (○, n = 93) 19.3 and 52.7; patients with vascular dementia (*, n = 33) 24.2 and 54.5.

of neurometric analysis and xenon-133 measures of regional cerebral blood flow (rCBF) were compared in the evaluation of patients with known cerebrovascular disease. Three groups of patients were assessed with both methods: 11 patients with completed strokes and 43 patients with partial nonprogressive strokes (symptomatic), 15 patients with reversed ischemic neurological deficit and 24 patients with transient ischemic attacks (asymptomatic), and a group of 64 healthy volunteers (normal subjects).

In the group with completed strokes or partial nonprogressive strokes, with neurological symptoms present at the time of examination, both methods detected a high proportion of abnormalities, although the neurometric method was superior (see Table 1). In the asymptomatic group with reversed ischemic neurological deficit or transient ischemic attacks, the ^{133}Xe rCBF detection dropped far below the neurometric detection of abnormalities, which remained high. Multivariate neurometric analysis detected abnormalities in 91% of all the patients, compared with 62% for ^{133}Xe and 54% for skilled electroencephalographers visually evaluating the same recordings. The incidence of false positive findings in the matched control group of healthy Dutch volunteers was 3%.

A noteworthy aspect of this study was the absence of abnormal univariate findings in the majority of the asymptomatic patients. Most of these patients were extremely abnormal on the composite feature "overall frequency abnormality." This feature compresses the full set of relative power features from the eight bipolar derivations used in this study. These results suggest that such highly compressed features can be of great utility for dichotomous decisions about normal versus abnormal profiles, although they can be logically expected to have less utility for differential diagnosis. Although these patients had no detectable localized abnormality, the relations among electrical events in different brain regions were markedly disturbed, perhaps reflecting a hemodynamic alteration. It may be feasible to use these indications of cerebral reorganization to identify asymptomatic individuals at risk for strokes, a possibility that is under study.

Discrimination between normal and abnormal individuals. The utility of these methods for the detection of subtle cognitive dysfunctions was evaluated by computing a discriminant function between normal persons and patients with a variety of psychiatric disorders. The data in Table 2 reveal an accuracy of about 80% for this discrimination, based solely on the overall composite neurometric feature "whole head abnormality." Performance of the discriminant is impaired somewhat by the high variability of the profiles of abnormal features represented within this mixed sample of patients. This discriminant function must construct a rule for dichotomous classification, for example, normal or abnormal, in spite of the great inhomogeneity of the abnormal group.

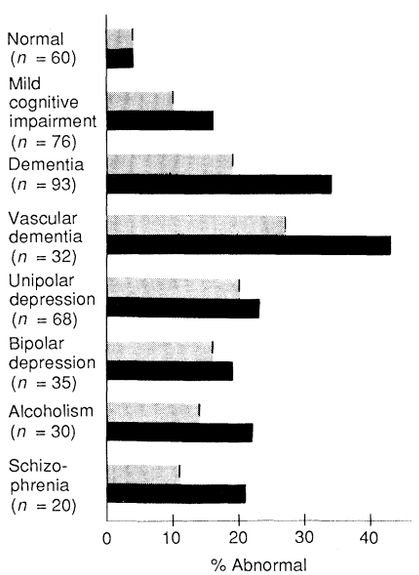

Fig. 5. Percentage of abnormal findings for the average of 95 univariate (shaded bars) and 121 multivariate (black bars) monopolar absolute power features for eight different groups. Note the incidence of false positives at the chance level (5% in the normal group), the relatively high incidence of abnormal findings among patients with a variety of disorders, and the consistently higher sensitivity of multivariate indices.

Differential Diagnosis in Patients with Various Psychiatric Disorders

Multiple discrimination among a variety of disorders. A multiple discriminant function was computed among a group of normal persons and separate groups of patients with dementia, alcoholism, or depression. As shown in Table 3, the overall accuracy of classification by this four-way multiple discriminant with 11 variables was 76% (79% on independent replication), far superior to the 25% accuracy expected by chance. It is unusual that the accuracy of the independent replication actually exceeded that of the initial discrimination. This may be attributed to fluctuations in composition of the patient groups. The subset of neurometric variables which accounted for most of the variance in this discrimination were: central theta, frontotemporal alpha, and the composite variables theta all regions, anterior power, total slow-wave asymmetry, and total delta coherence (*4*). Note that the accuracy of differential diagnosis was comparable to that achieved for the apparently simpler task of separating normal and abnormal individuals, because their distinctive profiles facilitated differentiation between relatively homogeneous groups of patients each with a different disorder. The number of "misclassifications" was low and distributed evenly across all groups. Results with the schizophrenic patients similarly indicated high classification accuracy, but even though the results of "leave-one-out" replication were excellent, the data are not presented here because the sample was not large enough for independent replication.

Table 1. Percentages of abnormal findings in symptomatic and asymptomatic patients with cerebrovascular disease using ^{133}Xe measures of regional cerebral blood flow (rCBF) or neurometric evaluation (Nx). Only the composite neurometric feature "overall frequency abnormality" was used.

Subject description	*n*	% Abnormal	
		rCBF	Nx
Symptomatic			
Completed strokes (n = 11) and partial nonprogressive strokes (n = 43)	54	69	91
Asymptomatic			
Reversible ischemic neurological deficits (n = 15) and transient ischemic attacks (n = 25)	40	53	90
Normal subjects	64		3

Table 2. Computer classifications of normal (I) and mixed abnormal groups (II) using neurometric variables. Only the composite neurometric feature "whole head abnormality" was used.

Actual group	*n*	Classification (%) as	
		I	II
	Initial discriminant		
I Normal	60	83	7
II Abnormal	145	20	80
	Independent replication		
I Normal	60	85	15
II Abnormal	128	25	75

Correlation between neurometric and clinical severity. The profile of abnormal features described the pattern of deviations characteristic of a particular disorder; the magnitude of the deviation correlated with the severity.

Histograms of the distributions of abnormal values of the composite neurometric feature, "relative power theta (all regions)," are shown (Fig. 6) in groups of patients with increasing severity of senile dementia assessed by a clinically derived GDS (*14*) based on an extensive multidisciplinary evaluation. The deviation of this feature from the normal range increased with increasing clinical impairment, with a significance of $P < 0.0001$ with analysis of variance (ANOVA). This scaling of cognitive dysfunction may provide an independent method for evaluating the effectiveness of different treatments, leading to more individualized therapy.

Discrimination among subgroups with similar symptoms. It is also important to be able to distinguish subgroups of patients with different pathophysiology within a population with similar clinical symptoms. Members of different subgroups may display similar symptoms for different physiological reasons and may respond very differently to particular treatments. Table 4 shows the results of a discriminant function separating unipolar from bipolar depressed patients with (left side) and without (right side) correction for bias of age and for approximation to a Gaussian distribution. Unipolar and bipolar patients in a clinically depressed state were differentiated with accuracy of almost 85% with six variables that were log-transformed and age-regressed, but only 70% without such corrections. The subset of variables that accounted for most of the variance in this discriminant were the composites left medial alpha (across F_3, C_3, P_3, and O_1), central and occipital slow-wave asymmetry, and overall beta relative power (*4*).

Depressed patients constitute a significant percentage of the psychiatric patient population. The ability to differentiate between these two subtypes electrophysiologically would significantly shorten the period required for confident diagnosis, effective treatment, and prophylaxis.

Table 3. Computer classification of normal (I), primary depression (II), alcoholism (III), and dementia (IV) groups using neurometric variables.

Actual group	*n*	Classification (%) as			
		I	II	III	IV
	Initial discriminant				
I Normal	60	77	11	7	5
II Primary depression	69	9	72	10	9
III Alcoholism	20	20	0	80	0
IV Dementia	63	9	6	6	79
	Independent replication				
I Normal	60	75	10	3	12
II Primary depression	34	6	85	6	3
III Alcoholism	10	5	5	90	0
IV Dementia	62	13	8	2	77

Table 4. Computer classification of unipolar (I) versus bipolar (II) depression using neurometric variables with [or without] age regression and log transformation.

Actual group	*n*	Classification (%) as	
		I	II
	Initial discriminant		
I Unipolar	34	85[67]*	15[33]
II Bipolar	18	15[25]	85[75]
	Independent replication		
I Unipolar	34	85[65]	15[35]
II Bipolar	17	13[13]	87[87]

*Brackets are around values without age regression and without log transformation.

Discussion

The evolution of brain electrical activity across the human life span follows a predictable course that has been described by simple equations for each of a large number of quantitative features. Presumably, these features reflect the interaction of neuroanatomical and neurochemical processes within the central nervous system that are largely genetically determined. Healthy, normally functioning individuals with a wide diversity of cultural and ethnic backgrounds display brain electrical activity consonant with the same set of quantitative descriptors. This supports the proposition that the organ responsible for cognition is fundamentally similar for all healthy members of the human species. Should systematic deviations from these proposed universal rules of human brain development eventually be found, it seems reasonable to expect that they will follow "local" rules reflecting the influence of nutrition, altitude, or other systematic environmental influences.

Individuals with overt neurological diseases, subtle affective disorders, "thought" disorders, or cognitive dysfunctions usually deviate from these rules of normal development. The developmental equations that have been derived reflect the organization of brain relations whose integrity is essential for the normal performance of higher nervous system functions. Such quantitative indices should facilitate the identification of subgroups of patients with different underlying neurophysiological and neurochemical factors that produce a final common path of apparently similar clinical symptoms. By recognizing the different underlying pathologies and creating more homogeneous groups, it will be possible ultimately to identify the different pathophysiologies. This in turn can lead to individualized treatment and provide the means to evaluate the relative efficacy of different therapeutic approaches. It should also become possible to identify premorbid "trait" markers of vulnerability to stroke, dementia, depression, and schizophrenia. Preliminary assessments indicate that some patients can be classified correctly, whether they are actively symptomatic before treatment or in remission. With some disorders, we have been able to distinguish between mildly symptomatic patients who subsequently deteriorate and those whose clinical condition remains stable over several years.

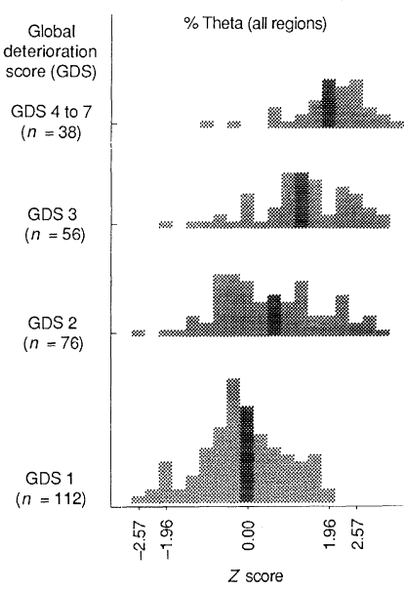

Fig. 6. Distributions of Z scores for multivariate feature "relative power (percentage) in theta across all regions" for groups of elderly individuals showing a GDS of 1 (normal), 2 (mild impairment), 3 (moderate impairment), and 4 or above (severe impairment). Note that the mean Z score increases with greater impairment.

The standard for psychiatric diagnosis and categorization in the United States and Canada is now DSM-III and soon will be DSM-IIIR. The categories defined therein have often been criticized as nothing more than a compilation of symptoms. The results obtained with neurometrics have shown that at least the categories studied are much more than arbitrary groupings of symptoms. These results are the first independent validation of clinical nosology and, of greater importance, the validation utilizes neurophysiological measures. While the agreement between neurophysiology and description is not perfect, it is exceptionally robust. Validity—the great deficiency of psychiatric nosology—is beginning to emerge and, thus far, to reveal an impressive concordance with biology.

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14. The neurometric normative data base was derived from over 750 subjects between 6 and 90 years old. Data were collected from seven acquisition sites with standardized methods and criteria: Board of Cooperative Education Services, Dix Hills, NY; Menninger Clinic, Topeka, KS; New York University Medical Center, New York, NY; Rusk Hospital, Chicago, IL; St. Francis Hospital, Miami, FL; Stony Brook Medical School, Stony Brook, NY; and University of Rhode Island Medical Center, Providence, RI. In addition, normal subjects were acquired in two collaborative studies: a positron-emission tomography normative study (in collaboration with J. Brodie under grant NS 15638), and a study of the neurometric characteristics of demented and normal elderly patients (in collaboration with S. Ferris under grant MH 32577). Identical equipment, recording parameters, and standardized conditions were used in all recording sites, with calibrations performed before and after all recording sessions. Digital recordings on floppy disks were sent to the Brain Research Laboratories, New York University, where final visual editing and all quantitative analyses were performed.
15. In collaboration with S. Ferris under grant MH 32577.
16. In collaboration with B. Angrist, E. Peselow, and J. Rotrosen, Psychiatry Service, Manhattan V. A. Medical Center and Department of Psychiatry, New York University Medical Center.
17. In collaboration with C. Rohrs, New York University Medical Center and Manhattan V. A. Medical Center.
18. In collaboration with A. Lieber, Department of Neuroscience, St. Francis Hospital, Miami, FL, and F. Mas, Department of Psychiatry, New York University Medical Center, New York, NY.
19. The frequency bands were as follows: delta (1.5 to 3.5 Hz), theta (3.5 to 7.5 Hz), alpha (7.5 to 12.5 Hz), and beta (12.5 to 25 Hz).
20. $Z_i = [Y_i - \overline{Y}]/\sigma$, where Y_i is individual feature value X_i after transform to approximate a Gaussian distribution, $\overline{Y}$ is the mean value predicted for normal individual same age as patient by normative developmental equation, σ is the standard deviation of normative distribution, and Z_i reflects the probability that the observed value of the features X_i lies within the normal range.
21. The bipolar derivations were F_7T_3/F_8T_4 (frontotemporal), T_3T_5/T_4T_6, (temporal), C_3C_z/C_4C_z, (central), and P_3O_1/P_4O_2 (parieto-occipital). These computations were not performed for monopolar coherence and symmetry features.
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