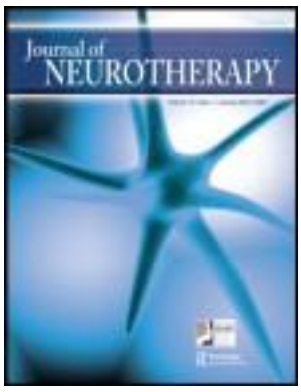

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Parametric and Non-Parametric Analysis of QEEG: Normative Database Comparisons in Electroencephalography, a Simulation Study on Accuracy

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SCIENTIFIC ARTICLES

Parametric and Non-Parametric Analysis of QEEG: Normative Database Comparisons in Electroencephalography, a Simulation Study on Accuracy

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SUMMARY. Quantitative electroencephalography (QEEG) as a tool for the diagnosis of neurological and psychiatric disorders is receiving

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increased interest. While QEEG analysis is restricted to the scalp, the recent development of electromagnetic tomography (ET) allows the study of the electrical activity of all cortical structures. Electrical measures from a patient can be compared with a normative database derived from a large sample of healthy individuals. The deviance from the database norms provides a measure of the likelihood that the patient's electrical activity reflects abnormal brain functioning. The focus of this article is a method for estimating such deviance. The traditional method based on z-scores (parametric) is reviewed and a new method based on percentiles (non-parametric) is proposed. The parametric and the non-parametric methods are compared using simulated data. The accuracy of both methods is assessed as a function of normative sample size and gaussianity for three different alpha levels. Results suggest that the performance of the parametric method is unaffected by sample size, given that the sample size is large enough (N > 100), but that non-gaussianity jeopardizes accuracy even if the normative distribution is close to gaussianity. In contrast, the performance of the non-parametric method is unaffected by non-gaussianity, but is a function of sample size only. It is shown that with N > 160, the non-parametric method is always preferable. Results will be discussed taking into consideration technical issues related to the nature of QEEG and ET data. It will be suggested that the sample size is the only constant across EEG frequency bands, measurement locations, and kind of quantitative measures. As a consequence, for a given database, the error rate of the non-parametric database is homogeneous; however, the same is not true for the parametric method.

KEYWORDS. EEG, QEEG, quantitative electroencephalography, normative database, norms, non-parametric

INTRODUCTION

Comparison to quantitative electroencephalography (QEEG) norms is a valuable tool in both electrophysiological research and clinical practice. Typically, the individual's electroencephalogram is analyzed in the frequency domain by means of time series analysis techniques such as the Fast Fourier Transform, also called FFT (Beauchamp, 1973; Brillinger, 1975; Lynn & Fuerst, 1989). A certain number of features are extracted from the Fourier cross-spectral matrix, each one describing a particular feature of the brainwaves in a specified frequency range.

These may include univariate and multivariate measures of absolute power, relative power and mean frequency for each electrode location in addition to coherence, phase and asymmetry for each electrode pair. Each individual's quantitative feature is called a *descriptor*. Descriptors are compared to norms derived under the same conditions from a sample of healthy "normal" subjects, allowing the statistical estimation of the deviance from the population norms. A recent trend in the electrophysiological literature is the derivation of norms for electromagnetic tomographic data (Bosch-Bayard et al., 2001). Electromagnetic tomographies (ET) make use of the EEG potential difference recording on the scalp to estimate the current density within the brain. Functional images of the current density distribution are then superimposed onto MRI standard atlas anatomical images (Talairach & Tournoux, 1988), providing true neuroimaging of electromagnetic brain activity either in the time or in the frequency domain. The most popular ET is the Low Resolution Electromagnetic Tomography, better known as LORETA (Fuchs, Wagner, Kohler, & Wischmann, 1999; Pascual-Marqui, 1995, 1999; Pascual-Marqui, Michel, & Lehmann, 1994). The derivation of norms for current density data is analogous to the derivation of norms for QEEG. In the former, electrical activity is not measured on the scalp at the electrode level, but estimated within the brain in discrete cubic regions of arbitrary size called voxels. Since, typically, one defines thousands of voxels, but makes use of only 19 to 128 electrodes, the comparison to ET norms poses more stringent statistical problems than the comparison to the QEEG norms. In both cases the deviance from each norm is usually expressed in terms of z-scores. The method assumes gaussianity of the sampling distribution and hereafter will be referred to as "parametric." The assumption of gaussianity is not always matched with real data. The aim of this article is to propose an equivalent "non-parametric" method based on percentiles for the estimation of the deviance from the norms. Furthermore, by means of a simulation we compared the two methods in terms of accuracy. The non-parametric method applies equally well to QEEG and to ET data.

The Nature of EEG

It is clear that in utilizing EEG norms we make several assumptions regarding the nature of human EEG. Essentially we assume that the human EEG is a stationary process with relatively high intra-subjects and inter-subjects reliability. Those assumptions are critical for the validity of the comparison process. Most of the initial work in this respect has been done by E. Roy John and his associates (Ahn et al., 1980; John et

al., 1977, 1980a, 1980b; John, Prichep, Fridman, & Easton, 1988). First, it was shown that quantitative EEG measures follow developmental equations, meaning that the frequency composition of the EEG reflects the age and the functional status of the brain. In other words, in a normal condition, normal values depend on and can be predicted by age (Ahn et al., 1980; John et al., 1980a, 1980b; Gasser, Verleger, Bacher, & Stroka, 1988; Matthis, Scheffner, Benninger, Lipinsky, & Stolzis, 1980). For example, the relationship may be quadratic on the log of the age. This is the case of the dominant frequency power of the normal EEG, which increases during brain development and declines slowly after age thirty or so (Bosch-Bayard et al., 2001; John, Prichep, & Easton, 1987; Szava et al., 1994). As a result, data from a wide age-range database is modeled by means of polynomial regression equations in order to take into account the age differences (John et al., 1980a, 1980b). There is little evidence suggesting that EEG norms may vary significantly as a function of sex and hemispheric dominance (Matthis et al., 1980; Veldhuizen, Jonkman, & Poortvliet, 1993). If such effects are found in the data, corrections for these two factors should be applied as well. Second, it is well known that the intra-subject spectral descriptors of the EEG are consistent over short periods of time, probably as a result of stable homeostatic regulations of the neurotransmitters (Hughes & John, 1999). This is particularly true for the EEG recorded during a resting state where the subjects have their eyes closed, and for relative power measures (John et al., 1987). Another advantage of relative measures is that they are independent of factors such as skin and skull thickness, being invariant in respect to a global scale power factor that increases inter-subjects variability (Hernández et al., 1994). For these reasons QEEG normative databases are usually generated for the eyes-closed resting state only, and relative power measures are preferred. Third, normative QEEG descriptors were found to be independent from cultural and ethnic factors. High reliability was found in studies from Barbados, China, Cuba, Germany, Holland, Japan, Korea, Mexico, Netherlands, Sweden, the United States, and Venezuela (quoted and referenced in Hughes & John, 1999).

The independence of the EEG spectrum from cultural and ethnic factors is a remarkable characteristic of the EEG. It has been suggested that it reflects the common genetic heritage of mankind (Hughes & John, 1999). A study on a large sample of 16-year-old twins found that the variance of EEG power (76% to 89% depending on the frequency band) is mostly explained by heritability (van Beijsterveldt, Molenaar, de Gaus, & Boosma, 1996). The authors conclude that the EEG frequency pattern is one of the most heritable characteristics in humans. Fourth,

QEEG norms proved to have high specificity and sensitivity. When subjects with no neurological or psychiatric dysfunction are compared with norms, only a few descriptors show significant deviance (high specificity). On the contrary, when subjects with neurological or psychiatric dysfunctions are compared to norms, the number of significant deviant descriptors greatly exceeds the number expected by chance alone (high sensitivity; John, Prichep, Fridman, & Easton, 1988).

Comparisons to QEEG norms has proven useful in the diagnosis of the attention deficit disorder with and without hyperactivity, learning disabilities, dementia, schizophrenia, unipolar and bipolar depression, anxiety disorders, obsessive-compulsive disorder, alcohol and substance abuse, head injury, lesions, tumors, epilepsy, and cerebrovascular diseases. (For a review see Hughes & John, 1999; Nuwer, 1988.) For many other disorders and diseases, QEEG signatures have been found, but additional research is needed to establish usefulness for diagnostic purposes. The four characteristics of the EEG power spectrum mentioned previously can be considered the fundamental properties of QEEG since they enable objective assessment of brain integrity in persons of any age, origin or background.

Signal Detection Theory and Diagnostic Systems

In this section we briefly review some important concepts in the literature on signal detection theory. These concepts will provide us with a workable framework to compare the parametric and non-parametric methods. Normative databases are essentially diagnostic systems. The general task of diagnostic systems is to discriminate among possible states of the object under study, and to decide which one actually exists. In the case of normative databases, the task is to label the descriptor of the new individual as "normal" or "abnormal," or, using a more appropriate terminology, as "non-deviant" or "deviant." No diagnostic system is perfectly accurate. Modern detection theory treats the decision in probabilistic terms, according to which there are two statistical hypotheses. In the following discussion we will refer to a particular descriptor only. The arguments readily extend to an indeterminate number of descriptors.

The study of the accuracy of diagnostic systems sprang from signal detection theory and is a common subject in the biomedical literature (Swets, 1988; Swets & Pickett, 1982). In comparing to norms the system receives an input, the value of the descriptor, and makes one of two possible decisions. We will refer to the input, or actual status of the new individual, as the "event" (E). E can take on two mutually exclusive values. Let us label them as positive (+) or negative (−) which we will use

hereafter instead of "deviant" and "non-deviant," respectively. E+ is the event corresponding to a true deviance from the norms, and E− is the event corresponding to a true non-deviance from the norms. Notice that the status of the subject is given and not observed. The system output is the decision taken. We will refer to this output based on the decision of the database and call it "diagnosis" (D). D can also take on two mutually exclusive values. Following the same notation we will have D+ in the case of a positive decision (the new individual is decided to be deviant) and D− in the case of a negative decision (the new individual is decided to be non-deviant). With two alternative events and two corresponding diagnosis, the data of a test of accuracy is conveniently summarized in a two-by-two contingency table (Table 1). We wish to obtain perfect correspondence between the events and the diagnosis. That is, we wish that the value of the descriptor for a new subject is labeled as deviant if it is in reality deviant and non-deviant if it is in reality non-deviant. These two outcomes correspond to the agreement (or concordance) between the input and the output of the diagnostic system, referred to in Table 1 as true positive (TP) and true negative (TN). When there is no agreement then we have an error, which can be of two types: false positive (FP) and false negative (FN). If we consider proportions instead of raw frequencies of the four outcomes, then just two proportions contain all of the information about the observed outcomes (Swets, 1988). For instance we normalize each raw frequency in a cell by the column total. We have now:

$$TP = TP/(TP + FN);\ FN = FN/(TP + FN);\ FP = FP/(FP + TN);\ TN = TN/(FP + TN)$$

In this way we obtain proportion estimations (analogous to probability values) bounded between zero and one and the following properties hold:

$$TP + FN = 1;\ FP + N = 1$$

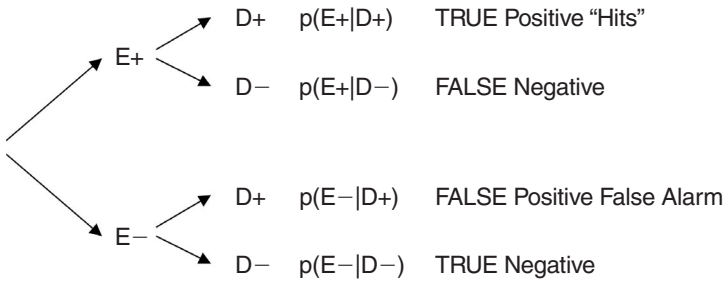
In other words, the elements of the couples TP-FN and FP-TN are complements of each other and all the information about the observed outcomes can be obtained considering only one element for each couple. Furthermore, by normalizing the raw frequencies we obtain measures *independent of the prior probability of the event*, meaning that the estimation of errors will be independent of the proportions of positive events (E+) and negative events (E−) entered in the system (Swets, 1988). This is a fundamental property of any accuracy measure of diag-

nostic system. Figure 1 shows these normalized measures in a different, albeit equivalent, perspective. Organizing the same data in a probability tree diagram we see that what we are computing, equivalently, are the probabilities to have positive or negative diagnosis (D+ and D−) *conditional* on the probability that the event was positive or negative (E+ and E−). For example, the rate of normalized true positives is the probability to have a positive diagnosis given (conditional on the fact) that the event was positive. In notation we write p(E+|D+). This quantity (normalized TP) is also referred to as 'sensitivity' (SN) and is usually reported together with the normalized TN, or p(E−|D−), which is referred to as "specificity" (SP). SN is a measure of the ability of the system to take a positive decision when it is indeed the case. Its complement is the normalized FN proportion. The SP is a measure of the ability of the system to take a negative decision when it is indeed the case. Its complement is the normalized FP proportion. According to what we have said before, SN and SP summarize the contingency table exhaustively.

TABLE 1

		Event (E) [Input]	
		Positive	Negative
Diagnosis (D)	Positive	TRUE POSITIVE	FALSE POSITIVE
[Output]	Negative	FALSE NEGATIVE	TRUE NEGATIVE

FIGURE 1. Probability Tree. The same data summarized in Table 1 can be arranged, after normalization, in a probability tree. The tree shows the resulting conditional probabilities. See text for details.



However, for the purpose of our simulation, a more complete depiction of the errors committed by a normative database is achieved considering two additional measures. These are the *inverse probability* of a true positive response and the inverse probability of a true negative response (Guggenmoos-Holzmann & Houwelingen, 2000; Swets & Pickett, 1982).

Practically, what we want to know is the probability that a deviance exists when the system says it does, and the probability that a deviance does not exist when the system says it does not. These definitions are not just a play on the words (see previous definitions of SN and SP). We seek p(E+|D+) and p(E−|D−), respectively, the *inverse* probability of SN and SP (to obtain those you need to invert the position of E and D). These probabilities are easily computed arranging the data as in Figure 1 and using the formula defining the conditional probability or the Bayes' formula (Lipschutz & Lipson, 2000). The agreement E+D+ corresponds to the true acceptance of the alternative hypotheses "the new individual is deviant on that descriptor," while the agreement E−D− corresponds to the true rejection of this alternative hypotheses. Accordingly, we will refer to the quantity p(E+|D+) as "true acceptance" (TA) and to the quantity p(E−|D−) as "true rejection" (TR). For reasons that will be clear later, only considering together SN, SP, TA, and TR, will enable us to perform a complete and fair estimation of the systematic error rate for the parametric and non-parametric methods.

The Parametric Method Based on Z-Scores

We are now ready to turn to the issue of deviance estimation. The steps required in order to build a normative database according to the parametric method (PM) and to the non-parametric method (nPM) are listed in Table 2. The focus of this article is steps 5 and 7 in Table 2, and in fact, these are the only two steps where the procedures for the PM and the nPM differ. We are concerned here with the way in which the significance of the deviance is estimated. We will not discuss the sampling of the normative subjects (which determine the homogeneity and representativeness of the normative sample) or the issue of multiple comparisons (which is essential to avoid false positives). Based on our review of the literature, all published normative EEG and QEEG databases estimated the significance of the deviance according to a parametric method based on z-scores (e.g., Bosch-Bayard et al., 2001; John et al., 1987; Thatcher, 1999; Veldhuizen et al., 1993). The work of John and his colleagues was decisive for the development and assessment of this statistical methodology (John et al., 1977). When z-scores at each electrode

location are interpolated to construct brain topographical maps, the result is called "Significance Probability Mapping," or SPM (Duffy, Bartels, & Burchfiel, 1981). In step 3 of Table 2 we defined the descriptors of our own LORETA database. According to the notation used in Table 2, there are d = L × F descriptors for each normative subject (i.e., for each subject there is a descriptor) for each combination of location (electrode for QEEG and voxel for ET) and feature (quantitative measure in a specified frequency range). For example, a descriptor is the relative power in the alpha range, and another descriptor is the relative power in the theta range. Thus, each descriptor can be conceived as a vector comprised of N values, where N is the number of subjects in the database. Let us call x_d the vectors of the descriptor d. For each feature, the appropriate log-transformation is applied to all subjects (John et al., 1987). The resulting data distribution of the vectors x_d is approximately normal with mean y_d and standard deviation σ_d. In step 6 we considered the L × F matrix of descriptors referring to a new individual to be compared to the database. Notice that the L × F matrix for the normative database is a matrix of vectors (i.e., a 3-D matrix). Instead for any new individual the L × F matrix is a 2-D matrix of individual entries. Identical log-transformations are applied to this matrix as well. Let us call $\hat{y}_d$ each entry of the descriptor matrix for the new individual. The task is to obtain an estimation of the deviance, from the mean of the x_d, for each $\hat{y}_d$. Given gaussianity of the normative sample distribution, the deviance of the new individual for each descriptor d is estimated as

$$z_d = (\hat{y}_d - y_d)/\sigma_d \quad [1.0]$$

The mean of the normative sample is subtracted from the new individual's descriptor and the result is divided by the standard deviation of the normative sample. The z-scores computed with 1.0 are accurate if the normative sample distribution is normal (gaussian). The more the normative sample distribution deviates from normality, the less the z-scores will be accurate, leading to more and more false negatives and false positives as a function of the distribution skewness and kurtosis. Skewness refers to the third moment around the mean of a distribution and is a measure of asymmetry. For example, a chi-square distribution with one degree of freedom is said to be right-skewed. Kurtosis is the fourth moment around the mean and is a measure of the peakedness of the distribution. A "flat" distribution has higher kurtosis than a "peaked" one. A theoretical standard normal distribution has skewness = 0 and

TABLE 2

Steps	Parametric Method	Non-Parametric Method
1	A reference Population (usually normal) is defined and a sample of **N** subjects is selected. Each subject is screened in order to match inclusion criteria previously chosen. The **N** subjects constitute the database.	A reference Population (usually normal) is defined and a sample of **N** subjects is selected. Each subject is screened in order to match inclusion criteria previously chosen. The **N** subjects constitute the database.
2	The set of **F** features is defined. Each feature refers to a quantitative measure for a particular frequency range. For example, a feature could be "Delta Relative Power" or "Alpha Coherence."	The set of **F** features is defined. Each feature refers to a quantitative measure for a particular frequency range. For example, a feature could be "Delta Relative Power" or "Alpha Coherence."
3	For each of the **N** subjects constituting the database, for each location (electrode or voxel) or pair of locations (electrodes or voxels), **L** measures for each of the chosen set of **F** features are derived. Each combination of measure and feature is called **Descriptor**.	For each of the **N** subjects constituting the database, for each location (electrode or voxel) or pair of locations (electrodes or voxels), **L** measures for each of the chosen set of **F** features are derived. Each combination of measure and feature is called **Descriptor**.
4	Database Data form a **L** $\times$ **F** $\times$ **N** matrix.	Database Data form a **L** $\times$ **F** $\times$ **N** matrix.
5	For each feature, an appropriate transformation (based on log) is applied to all locations and subjects in order to approximate gaussianity.	For each feature and location the **N** data of the database subjects is sorted.
6	For each new individual to be compared to the database, a corresponding data matrix of descriptors (**L** $\times$ **F**) is derived.	For each new individual to be compared to the database, a corresponding data matrix of descriptors (**L** $\times$ **F**) is derived.
7	For each location (**L**) and feature (**F**), i.e., for each descriptor, the deviation from normality is expressed in terms of z-scores, using the mean and standard deviation of the descriptor computed for all database subjects.	For each location (**L**) and feature (**F**), i.e., for each descriptor, the deviation from normality is expressed in terms of discrete random variable sp (sample proportion) expressing the proportion of the subjects in the database falling above (right-handed test) or below (left-handed test) the new individual.
8	Additional statistics are performed in order to correct for multiple comparisons.	Additional statistics are performed in order to correct for multiple comparisons.

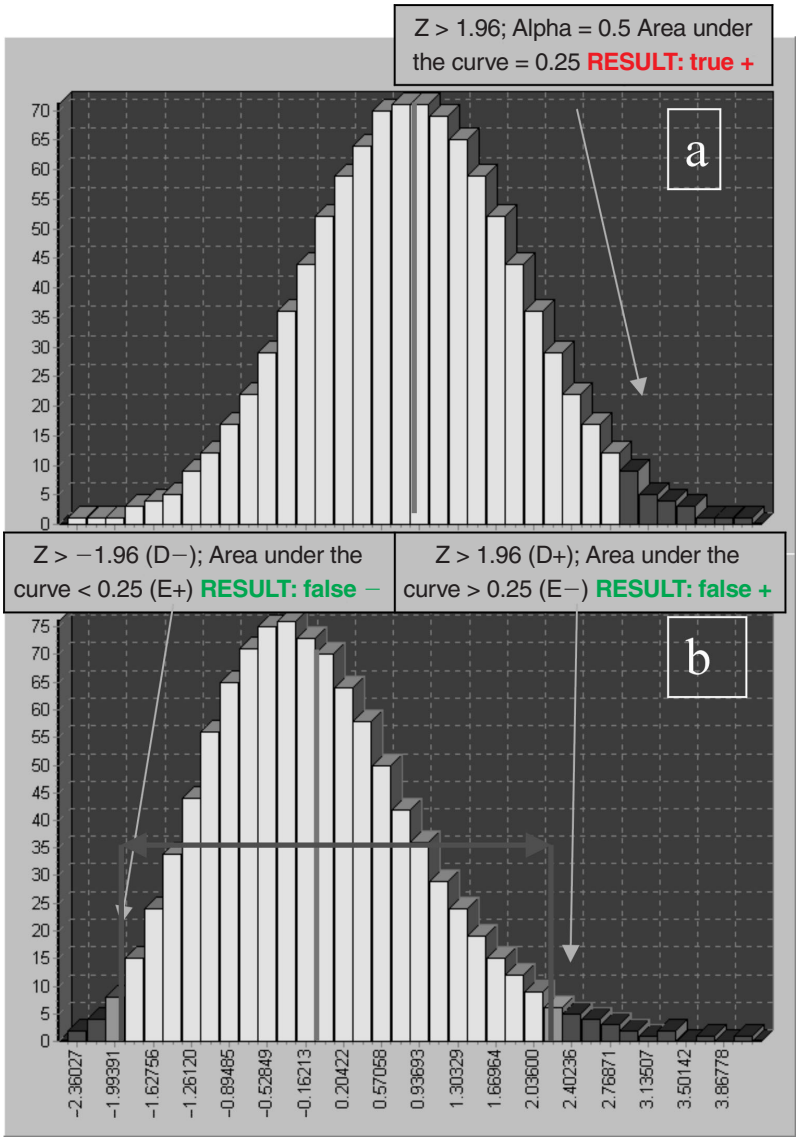
kurtosis = 3. Given an approximate gaussian distribution, the more these two values deviate from the theoretical values, the more the distribution deviates from gaussianity. The problem with the rate of false positives and false negatives in the case of non-gaussian distributions is a subtle one. With estimation [1.0] we obtain different rates of false

positives and false negatives depending on the side of skewness (left-skewed or right-skewed distribution) and the side of the test (left-handed or right-handed test). Similar arguments apply to the amount of kurtosis.

The effects of skewness and kurtosis on the rate of false positives and false negatives are easily captured in a graphical fashion (Figure 2). This figure is crucial for the interpretation of the results of this study and should be analyzed carefully by the reader. Figure 2a depicts a normative sampling distribution very close to the theoretical gaussian. Suppose that distribution is indeed gaussian. With an alpha level of 0.05, the decision criterion of the database is to label as "deviant" all new observations with z-score > 1.96 or < -1.96 (the area under the curve for $z > 1.96$ or $z < -1.96$ equals 0.025, so their sum is 0.05). Let us consider the right-handed test first. A z-score exceeding 1.96 leaves on its right a proportion of the area under the curve less than 0.025. So the diagnosis will be positive (D+). By definition, a new individual's score with $p < 0.025$ is positive (E+). The result is a concordance between the event and the diagnosis (true positive).

Because of simmetricity, for a left-handed test the result will be the same. For all z-scores comprised between -1.96 and 1.96 both the event and the diagnosis will be negative (E− and D−), and we will have concordance again (true negative). Thus if the normative sampling distribution is truly gaussian, the normative database will virtually commit no error. Figure 2b depicts a normative sampling distribution right skewed. Notice that the mean of the distribution (blue line) is no longer at the peak of the distribution since the density on the right side of the distribution is bigger than the density on the left side. The two violet vertical lines delimitate the interval including 95% of the density (area under the curve). On the right of the right violet line the density is 0.025%, and so it is on the left of the left violet line. Let us consider the right-handed test first. Because of skewness for a value of z slightly bigger than 1.96 (D+), the area under the curve on the right of the z-value is greater than 0.025 (E−). The diagnosis is positive ($z > 1.96$), but the event was not (area > 0.025). We have a false positive. In the hypothetical distribution of Figure 2b, the right-sided z-interval for which a false positive will happen is indicated in green. For the left-sided test the situation is opposite. Here for some $z > -1.96$ (D−) the area under the curve is already less than 0.025 (E+). The diagnosis is not positive, but the event was indeed positive. We obtain a false negative. In Figure 2b, the left-sided z interval for which a false negative will happen is, again, indicated in green. If the distribution is left-skewed, we would have obtained "mirror results" (i.e., false negatives on the right side of the dis-

FIGURE 2. Depiction of gaussian and non-gaussian distributions and the outcome of the parametric method. (a): The normality case. If the sample is truly gaussian then the outcome of the parametric normative database leads to true positives and true negatives only. (b) The non-normality case. The sample distribution is right skewed. On the right side of the distribution we have false positives, while on the left-side of the distribution we have false negative.



tributions and false positives on the left side). It is clear that with skewed normative sample distributions we obtain different types of errors on the two sides of the distribution. This means that what in reality are equivalent, but opposite, magnitude of deviances, are interpreted by the diagnostic system differently, according to the sign of the z-score. If the amount of error generated is not negligible, this property of the parametric method would constitute a serious problem. Therefore we need to estimate it. This will be accomplished in the simulation we are going to present. Before that, let us introduce an alternative method for the estimation of the deviance, a non-parametric method based on proportions.

The Non-Parametric Method Based on Proportions

In the previous section we have seen that the parametric method relies on the assumption of normality of the distribution. As a practical example, in a one-sided (right) testing framework, a z-score = 1.645 means that on the theoretical normal distribution 95% of the population falls below that value. In other words, only 5% of the population exhibits a value equal or greater. The corresponding value on the other side of the distribution (left-sided test) is -1.645, for which only 5% of the population exhibits a value equal or smaller. A non-parametric method, to obtain a similar result, is by use of the sample proportion (sp; Lunneborg, 1999). Sample proportions are analogous to percentiles and, like them, are obtained by sorting the sampling distribution values. The method is easily illustrated with an example. Refer first to a *right-handed test* with alpha = 0.05. In this case we label a new individual as deviant if his/her value is large as compared to the normative database. For example, if the descriptor under analysis is the alpha relative power at the electrode O2, then a deviant subject will show a large power value as compared to the norm. Suppose our normative sample is comprised of 20 subjects (N = 20). Let us sort the normative values referring to any descriptor d in ascending order to obtain the sorted x_d vector:

$$x_d : \{2, 2.5, 2.8, 3.5, 3.6, 3.7, 4, 4.9, 5.2, 5.7, 8.4, 8.5, 11.1, 12.3, 14.8, 16.4, 18.9, 20 ,21, 25.4\}$$

The 95th percentile is the value below which 95% of the subjects fall. Values comprised between 21 and 25.4, leave on the right-side 5% of the observations (5% of 20 = 1). A value bigger than 21 is associated

with a p-value < 0.05. We obtain a p-value with a counting random variable (e.g., Holmes, Blair, Watson & Ford, 1996). Let us define the discrete random variable (RV), sample proportion (Φ) as the *proportion of values in the x_d vector falling above the new individual's value*. Then Φ is indeed a p-value, although it is discrete and not continuous. By definition, if no value in the x_d vector exceeds the new individual's value, then Φ = 0. In this case in fact the new individual shows the most extreme value and this is as significant (unlike) as it can possibly be. With this definition the discrete RV Φ can take on N+1 values ranging from 0 to 1 and decreasing by multiples of 1/n. Φ = 1 (20/20 = 1) means that all normative subjects exceed the new individual's value. In this case the new individual's value is the smallest and there is no evidence at all that the new individual's value is significant (keep in mind that if our test is right-handed we have to ignore the extreme values on the left of the distribution, no matter how extreme they are). Φ = 0 means that the new individual exhibits the most extreme value.

Suppose our new individual's value for the descriptor *d* is 22.3. Comparing this value to the sorted vector above we see that 5% of the observations fall above this value, thus Φ is 0.05 (there is only 1 observation falling above the value 22.3; 1/20 = 0.05). Suppose the value is 1.8; Φ is 1 (20/20 = 1). Suppose it is 5.4; Φ is 0.55 (11/20). Φ = 0.05 can be considered deviant just like a z-score = 1.645. Both correspond to a probability of 0.05, with the difference that in a non-parametric fashion the p-value is computed on the actual data and not as a result of the integrals of the theoretical normal distribution.

The same method, reversed, is applied in the case of a *left-handed test*. In this case the discrete random variable (RV) sample proportion (Φ) is defined as the *proportion of values in the x_d vector falling below the new individual's value*. By definition, if all values in the x_d vector are bigger than the new individual's value, then Φ = 0. In this case the new individual's value is the smallest and this provides the strongest evidence for his/her deviance on the left side of the distribution. With this reversed definition the discrete RV Φ still can take on N+1 values ranging form 0 to 1 and increasing by multiples of 1/n. Φ = 0 means that all normative subjects exceed the new individual's value. Φ = 1 means that the new individual's value exceed all normative subjects. Suppose again our new individual's value for the descriptor *d* is 22.3. For a left-handed test, comparing this value to the sorted vector above we see that 95% of the observations fall below this value, thus Φ is 0.95 (there

are 19 observation falling below the value 22.3; 19/20 = 0.95). Suppose the value is 1.8; Φ is, by definition, 0. Suppose it is 5.4; Φ is 0.45 (9/20).

If a two-tailed test is wished, then the median of the distribution is computed. If the new individual's value is on the right of the median then a right-handed test as described is performed. On the other hand, if the new individual's value is on the left of the median then a left-handed test is performed. Of course, for a two-tailed test we need to halve the alpha level at the two sides of the distribution, so that the total alpha level equals indeed alpha. The performance of the non-parametric method here described is not affected by non-gaussianity of the sampling distribution. However its performance is a function of the sample size. Considering sample proportions we define a discrete RV, but the underlying phenomenon is continuous, hence we lose "resolution." In the following simulation we assess the amount of errors generated because of this loss of resolution and we compare it with the amount of error generated by the parametric method because of non-gaussianity.

METHOD

Simulation Study

In order to perform a simulation aiming to evaluate the performance of a normative database we need to define uniquely positive events (E+) and negative events (E−) (i.e., we need to delineate conditions under which a simulation entry is by definition deviant or non-deviant). Any particular method to make a decision about the deviance of the event will provide a diagnosis, either positive (D+) or negative (D−) according to its own procedure, and being unaware of the real status of the event. The agreement, or concordance, between the event and the diagnosis can then be estimated. By allowing a large number of events to enter the system we obtain reliable estimations of concordance and discordance. In order to define unambiguous positive and negative events we need to refer to theoretical distributions for which the "true" acceptance interval of the null hypothesis is known. For instance, let us set the type I error (alpha) as 0.05. For a random variable z distributed as a standard normal we accept the null hypothesis for $-1.96 < z < 1.96$. In other words, if z is comprised between −1.96 and 1.96, we accept the null hypothesis. In terms of a normative database this means that the new individual is considered to be normal. In our simulations the normative

sample of reference was emulated by means of normal distributions. New individuals were emulated as individual points generated with the same density function as the normative reference. For all practical purposes they constitute events for which the status (E+ or E−) is known a priori on the basis of the distribution of the normative reference.

In the discussion that follows we will call each event submitted to diagnosis a *simulation entry*. As an example of the procedure followed to define simulation entries consider the following: given a normative reference sample distributed as a random normal, alpha = 0.05, and a right handed test, we know a priori that any simulation entry with $p(z) < 0.025$ is positive. For each simulation entry, we computed the database outcome (D+ or D−) with both the parametric and non-parametric method, independently one from the other. According to what is seen above, the parametric diagnosis is based on equation [1.0], and the non-parametric diagnosis is based on the RV sample proportion. For each simulation entry there will be a concordant or discordant outcome and this will add a raw frequency in a table just like Table 1. This constitutes an outcome among four possibilities (Table 1).

We submitted 100,000 simulation entries, under identical conditions, for each normative reference sample considered. This allowed reliable estimations of sensitivity (SN), specificity (SP), true acceptance (TA) and true rejection (TR). The evaluation of concordance was repeated varying sample size and gaussianity of the normative reference sample. This way we could assess the error rate of the parametric and non-parametric methods. In addition, we repeated the simulations for three alpha levels (decision criterion of the system). The latter variable must be included because all of the four measures of accuracy we chose depend on the decision criterion used (Swets & Pickett, 1982). Therefore we need to monitor the error rate as a function of alpha. Finally, two simulations for all the above conditions are needed with one evaluating the right-handed test, and the other evaluating the left-handed test. The reason for this further splitting is that, as we have shown above in the case of skewed distributions, the parametric method generates two different types of error at the two sides of the distribution and we do not want to confuse them considering the outcomes of a two-sided test.

A total of 486 ($9 \times 9 \times 3 \times 2$) simulations were performed, each one evaluating 100,000 simulation entries. The simulations were performed by a computer program written in Delphi Pascal (Borland Corporation). All together they required approximately four hours computation time on a Dell personal computer equipped with a 1.8 GHz Pentium 4 pro-

cessor and 512 Mb of RAM. Normative samples, the x_d vector described above, were emulated by means of a gaussian random number generator function embedded in Delphi Pascal. The function (called randG) generates random samples gaussian-distributed with a specified mean and standard deviation. For all simulations we used mean = 10 and variance = 1. In this way all random samples were non-negative. This was required by the skewness manipulation we chose (performed by means of a power transformation as seen below). Each distribution actually employed in the simulation was computed as the (sorted sample-by-sample) average of 10,000 gaussian distributions generated with the randG function. This ensured that correspondent distributions were very similar across different conditions of the simulation.

Alpha Level Manipulation

The alpha level is the decision criterion employed in the normative database. It quantifies the amount of evidence requested by the system before a positive outcome is issued. Three alpha levels were considered: 0.05, 0.025, and 0.0125. Since all tests were one-tailed, these three levels correspond to the two-tailed test alpha levels 0.01, 0.05, 0.025. Published databases considered in our review (e.g., Bosch-Bayard et al., 2001; John et al., 1987; Thatcher, 1999; Veldhuizen et al., 1993) use the fixed alpha level 0.05. In our simulations this corresponds to alpha = 0.025. In addition to this alpha level we considered a more stringent criterion (alpha = 0.0125), and a more lenient criterion (alpha = 0.05). The reason is that the measures of accuracy we used are independent of the prior probabilities of positive or negative events, but are not independent of the decision criterion (Swets & Pickett, 1982). Since we expect different error rates solely because the decision criterion is changed, we might want to monitor the behavior of our system as a function of the decision criterion.

Sample Size Manipulation

Nine sample sizes were considered, ranging from 80 to 720 with an increment of 80 (80, 160, 240, 320, 400, 480, 560, 640, 720). The choice for the increment was contingent. It can be shown that the accuracy of the non-parametric method for the minimum alpha level we considered (alpha = 0.0125) increases discretely in steps of 80 (sample size). The reason is intuitive. We show that the RV sample proportion (Φ) can take

on only discrete values ranging between 0 and 1 increasing by a factor of 1/N. Consider the alpha level alpha = 0.0125. With N = 80, the possible values that the RV Φ can take, sorting them in ascending order, are 0, 0.0125, . . . 1. With N = 160, they will be 0, 0.00625, 0.0125, . . . 1. As soon as N reaches 160, the random variable Φ gains resolution, having the ability to take on three possible values less than the alpha level ($p <$ alpha).

Gaussianity Manipulation

Gaussianity was manipulated transforming the normal averaged distribution with a power function. For each level of gaussianity considered each sample of the normative distribution was raised to a fixed power. This resulted in a skewed distribution respecting the order of the original samples. Nine levels of gaussianity were considered, corresponding to nine different powers ranging from 1 to 3 with an increment of 0.25 (1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3). The first distribution always remained unchanged after transformation (power of 1) and constituted a true empirical random gaussian distribution. In this case the performance of the parametric method was expected to be excellent. Table 3 reports the mean and standard deviations of the skewness and kurtosis of the empirical distributions actually used in the left-handed test and right-handed test simulations. Mean and standard deviations were computed across the different sample sizes used in the simulations for each level of the variable manipulating the gaussianity of the distribution. From Table 3 we can see that because of the averaging procedure, the gaussian random distributions all had very similar skewness and kurtosis for all the levels of sample size (small standard deviation), yielding almost identical distributions to be used in the left-handed test and right-handed test simulations. Table 3 also shows how skewness deteriorates with higher powers.

RESULTS

To capture the essence of our results we need to consider again Figure 2b. Let us anticipate the results for the parametric method. For a right-handed test, since the distribution has positive skewness, we expect three possible outcomes: E+|D+ (red area on the right of the distribution), E−|D+ (green area on the right of the distribution), and E−|D−

TABLE 3

Distribution	Mean Sk	Sd Sk	Mean Kt	Sd Kt
Pw of 1.00	0.000	0.002	2.869	0.085
Pw of 1.25	0.070	0.004	2.870	0.082
Pw of 1.50	0.140	0.006	2.884	0.084
Pw of 1.75	0.209	0.009	2.916	0.091
Pw of 2.00	0.279	0.010	2.962	0.093
Pw of 2.25	0.347	0.015	3.022	0.103
Pw of 2.50	0.417	0.017	3.100	0.113
Pw of 2.75	0.486	0.021	3.192	0.124
Pw of 3.00	0.556	0.024	3.299	0.137

Right-handed test

Distribution	Mean Sk	Sd Sk	Mean Kt	Sd Kt
Pw of 1.00	0.000	0.001	2.869	0.085
Pw of 1.25	0.070	0.004	2.870	0.083
Pw of 1.50	0.140	0.006	2.886	0.086
Pw of 1.75	0.210	0.008	2.916	0.089
Pw of 2.00	0.279	0.012	2.962	0.095
Pw of 2.25	0.348	0.015	3.026	0.102
Pw of 2.50	0.418	0.017	3.104	0.111
Pw of 2.75	0.486	0.021	3.193	0.125
Pw of 3.00	0.555	0.025	3.298	0.141

Left-handed test

(all the area left). The only discordant outcome (error) is the E−|D+ pairing. These are false positives. The error is due to the fact that although the area on the left of the observation is bigger than alpha (E−), the z-score computed with [1.0] is bigger than 1.96, leading to a p-value less than alpha (D+). Since this error happens on the right side we wish to compare it to the TP proportion. In other words (referring to Figure 2b), we wish to compare the green area (error) with the red area on its right. We will show that the specificity measure (SP) does not give us this information, but the true acceptance measure (TA) does. Remember that SP has been defined as TN/(FP+TN). Remember also that TN = p(E−|D−) and FP = p(E−|D+). In our simulations most entries are negative events. In fact the simulation entries were always random samples of the normative sample distribution. Hence (1-alpha)% of them is by definition a negative event and will fall in the E−|D− (TN) category. The remaining will include E+|D+ and E−|D+ outcomes. Even if the FP

proportion is large as compared to the TP proportion (the green area is big as compared to the red area) the specificity will be excellent, since it does not compare FP with TP, but FP with TN. On the other hand TA, defined as p(E+|D+), has as complement p(E−|D+). Its value is the right estimation of errors for this simulation (i.e., it compares the FP proportion to the TP proportion). This is the information we need. It is telling us among the events with positive diagnosis (green area + red area), how many, in proportion, were in reality positive (TP: red area) as compared to negative (FP: green area).

Consider next the left-handed test. Refer again to Figure 2b. Here we expect three different possible outcomes: E+|D+ (red area on the left of the distribution), E+|D− (green area on the left of the distribution), and E−|D− (all the area left). The only discordant outcome (error) is the E+|D− pairing (false negative), which is different from the type of error found on the right side. Here the error arises because although the area on the left of the observation is less than alpha (E+), the z-score computed with equation [1.0] is bigger than −1.96 (non-significant), leading to a p-value less than alpha (D−). We obtain some false negatives. Again, we wish to compare them to the TP proportion, and not to the TN proportion. In this case the sensitivity measure (SN) will give us this information. Remember that SN has been defined as TP/(TP+FN). Remember also that FN = p(E+|D−) and TP = p(E+|D+). For a left-handed text, (1-alpha)% of the outcomes will fall in the E−|D− category (notice that on this side of the distribution errors [FN] come at the expense of the TP proportion and the TN proportion is exactly [1-alpha]%). The remaining 5% will include E+|D+ and E+|D− outcomes. SN compares indeed TP to FN. This result is telling us that among the positive diagnosis how many, in proportion, were in reality positive events (TP) as compared with negative events (FN).

Errors with the non-parametric method follow a different pattern. For this method the appropriate measure of accuracy turns out to be the true acceptance (TA) for tests on both sides of the distribution. This means that for both the right-handed and left-handed test, the non-parametric method results in only three outcome pairings: the two concordant pairs E+|D+, E−|D−, and the discordant pair E−|D+. In other words, the non-parametric method tends to issue positive diagnosis when it is not the case.

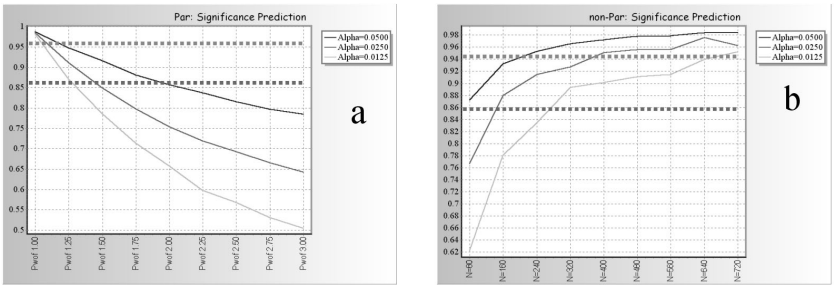
In summary, considering that real normative distributions can be both left and right skewed, with the parametric method we expect both FP and FN errors depending on the side of the test and on the side of the

skewness. With the non-parametric method we expect FP only, regardless the side of the test and the side of the skewness. We now show quantitative results of these errors. As expected, the accuracy of the parametric method was found to be the same (with little random error) at different sample sizes ($N > 100$) for all levels of non-gaussianity and alpha. Thus it will be shown as a function of non-gaussianity and alpha levels only. The accuracy of the non-parametric method was found to be the same (with little random error) at different non-gaussianity levels for all levels of sample size and alpha. Thus it will be shown as a function of sample size and alpha levels only. In every simulation performed, two out of the four measures of accuracy employed in this study always displayed a value of 1.0 (perfect accuracy) for all levels of the manipulated variable (i.e., they do not constitute a valuable test). The reason why this is the case has just been discussed. For example, for a right-handed test we do not expect false negatives for either method regardless the gaussianity, sample size, and alpha. Of the remaining two measures only the critical measure is reported. We have just seen that this is either the SN or the TA for the parametric method, and the TA for the non-parametric method. The critical measure always displayed values of accuracy less then or equal to 1.0 and changed monotonically across the levels of the manipulated variables.

Right-Handed Test

Results for the right-handed test are reported in Figure 3. Figure 3a refers to the parametric method (PM), while Figure 3b refers to the non-parametric method (nPM). The blue lines indicate the 0.95 level of a measure of accuracy. This level of accuracy can be considered excellent for any diagnostic system. The red lines indicate the 0.85 level of a measure of accuracy. This level of accuracy can be considered the minimum required for a normative database. Figure 3a reports the PM true acceptance (TA) proportion as a function of gaussianity of the normative reference sample (x-axis) for the three alpha levels employed. As explained in the above discussion, this is the critical test for the parametric method for a right-handed test when the reference distribution is right skewed. The TA is excellent in the case of normality of the reference distribution (power of 1) and deteriorates rapidly as the power increases; for power > 1.5 the TA proportion for the usual alpha level (0.025) is unacceptable (< 0.85). The critical test of the nPM method under identical conditions is shown in Figure 3b. This graph plots the TA proportion as a function of the sample size. As expected, the perfor-

FIGURE 3. Results of the simulations for the RIGHT-HANDED test. Reported on the vertical axis are the true acceptance (a) for the parametric method, and the true acceptance (b) for the non-parametric method. For the parametric method results are shown as a function of non-gaussianity (horizontal axis) of the normative reference distribution and alpha level (a). For the non-parametric method results are shown as a function of sample size (horizontal axis) and alpha level (b). The green line indicates where the measure of accuracy is equal to 0.95 (very good level of accuracy). The red line indicates where the measure of accuracy is equal to 0.85 (acceptable level of accuracy).



E+|D+ Concordance
(complement: E−|D+)

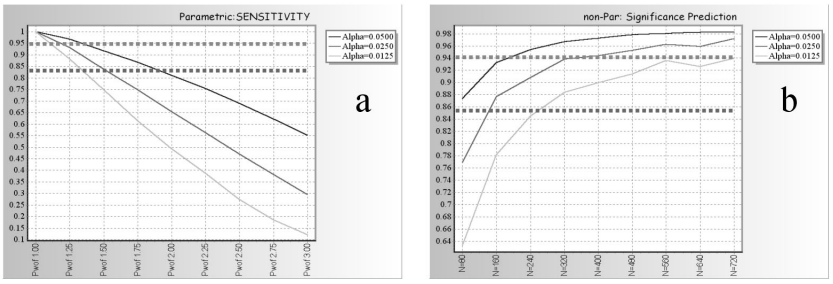
E+|D+ Concordance
(complement: E−|D+)

mance of the nPM increases monotonically with N. For the usual alpha level (0.025), the performance is acceptable (TA > 0.85) for N = 160, and excellent (TA > 0.95) for N = 400 or more.

Left-Handed Test

Results for the right-handed test are reported in Figure 4. Figure 4a refers to the parametric method (PM), while Figure 4b refers to the non-parametric method (nPM). The blue lines indicate the 0.95 level of a measure of accuracy. This level of accuracy would be considered excellent for any diagnostic system. The red lines indicate the 0.85 level of a measure of accuracy. This level of accuracy can be considered the minimum required for a normative database. Figure 4a reports the PM Sensitivity (SN) proportion as a function of gaussianity of the normative reference sample (x-axis) for the three alpha levels employed. As explained in the above discussion this is the critical test for the parametric method for a left-handed test, when the reference distribution is right skewed. The SN is excellent in the case of normality of the reference distribution (power of 1) but deteriorates rapidly as the power increases.

FIGURE 4. Results of the simulations for the LEFT-HANDED test. Reported on the vertical axis are the sensitivity (a) for the parametric method, and the proportion of true acceptance (b) for the non-parametric method. For the parametric method results are shown as a function of non-gaussianity (horizontal axis) of the normative reference distribution and alpha level (a). For the non-parametric method results are shown as a function of sample size (horizontal axis) and alpha level (b). The green line indicates where the measure of accuracy is equal to 0.95 (very good level of accuracy). The red line indicates where the measure of accuracy is equal to 0.85 (acceptable level of accuracy).



E+|D+ Concordance
(complement: E+|D−)

E+|D+ Concordance
(complement: E−|D+)

The decline is faster for the left-handed test than for the right-handed test (compare with Figure 3a). This phenomenon can easily be captured inspecting the two tails of the distribution in Figure 2b and considering the definition of SN and TA. On the left side errors (green area) grow at the expense of the true positive proportion (red area), while on the right side errors (green area) grow at the expense of the true negative proportion (all the area remaining on the left of the green area). The true positive proportion (red area) remains unchanged. For power > 1.25 the SN proportion for the usual alpha level (0.025) is already unacceptable (< 0.85). The critical test of the nPM method under identical conditions is shown in Figure 4b. This graph plots the TA proportion as a function of the sample size. As for the right-handed test, the performance of the nPM increases monotonically with N. For the usual alpha level (0.025), the performance is acceptable (TA > 0.85) for N = 160, and excellent (TA > 0.95) for N = 480 or above. Allowing few random errors, these results for the nPM are comparable to those obtained for the right-handed test. In fact the nPM performs equally at both sides of the distribution, no matter what the skewness is.

CONCLUSIONS

A total of 486 simulations were performed in order to compare two methods for the comparisons to EEG norms. The parametric method is based on z-scores and has been employed so far. The non-parametric method is based on sample proportions or, equivalently, percentiles and has been proposed in this paper to overcome some problems related with the use of the parametric method. Each simulation estimated the error rate in the diagnostic predictability of the two methods for both left-handed and right-handed tests. Variables manipulated included the decision criterion of the normative database (alpha level), sample size, and non-gaussianity of the normative reference sample. For each combination of the side of the test and the method employed, the critical test was individuated. This was one of the four accuracy measures considered in this study [sensitivity (SN), specificity (SP), true acceptance (TA), and true rejection (TR)]. The performance on the critical tests provided a framework for comparing the two methods. The performance of the parametric method (PM) was found to be unrelated to the sample size, given that N is not too small. With $N < 80$ the performance of the method starts deteriorating, therefore we conclude that this independence is true for approximately $N > 100$. The performance of the parametric method was found related to the non-gaussianity of the normative sample distribution. Empirical distributions for which the parametric performance can be considered acceptable have to be very close to a true theoretical gaussian distribution.

The performance of the non-parametric method was unaffected by the non-gaussianity of the normative reference distribution but was affected by the sample size. Acceptable (> 0.85) accuracy (enough resolution) can be attained with $N = 160$. Excellent accuracy (> 0.95) can be attained with no less than around 440 subjects. This result contradicts the common notion that non-parametric statistics "should be used with a small sample size." For both methods and for both the right-handed and left-handed tests, the critical tests result in less accuracy the smaller the decision criterion (alpha level). This important result contradicts the intuitive notion that reducing the alpha level would lead to a smaller rate of false positives. This is definitely not the case. Indeed alpha affects positively all measures of accuracy proportionally to its value; the bigger the alpha level, the better the accuracy. This result is explained with a specific example. The reasoning extends readily to all possible situations. Consider the left-handed test for the parametric test. The critical test for this situation is the sensitivity (SN). Remember the SN is de-

fined as TP/(TP+FN) and that under these circumstances the database is going to issue only TP, FN and TN outcomes. SN increases proportionally as TP increases and as FN decreases. Refer to Figure 2b and look at the left tail of the distribution. This figure refers to a one-handed alpha level equal to 0.025. Imagine we halve the alpha level. Both the green area under the curve (FN) and the red area under the curve (TP) will decrease (they will be displaced on the left and here the height of the curve is smaller). However the red area will decrease more than the green area, the reason being that the curve is shorter at the left extremity. As a result, the ratio TP(TP+FN) will be smaller (i.e., sensitivity will be smaller). Doubling the alpha level, on the contrary, will result in a sensitivity increase.

Implications of Our Simulations for Database Development

We have been shown by means of simulations that the performance of the parametric test is impaired as a function of skewness. Non-gaussianity due to high or low kurtosis is known to affect the test even more (Pollock, Schneider, & Lyness, 1990). These results are not a surprise. The problem is to assess how good the approximation to gaussianity for QEEG and ET the data is, and to evaluate the advantages acquired by using an alternative method. Regarding the approximation to gaussianity the literature is scattered and inconsistent. Only a few studies have been done investigating specifically the gaussiantity approximation for QEEG data and none, to our knowledge, have investigated the gaussianity approximation for electromagnetic tomographic (LORETA) data. Nonetheless the same transformations applied for QEEG measures have recently been applied to this kind of data to generate a normative database (Bosch-Bayard et al., 2001).

Electroencephalographic data in the frequency domain is markedly non-gaussian. Each measure is distributed in a particular way and the theoretical studies on their distribution are not exhaustive. For example, the power spectrum (absolute power) is distributed approximately as a chi-square (Beauchamp, 1973; Brillinger, 1975). The degrees of freedom (df) are a function of the EEG recording length (number of epochs), the FFT frequency resolution, wideness of the frequency bands considered, the time-domain tapering employed, and other technical factors. One should take into consideration all these factors in estimating the df associated with a power spectrum chi-square distribution. At the time when the databases were first developed (1970s) a simpler approach was employed. For each measure a suitable data transformation

(based on log transformations) was used to approximate gaussianity. The idea was to allow a general method for the assessment of the deviance from the norms and also to allow parametric statistics to be employed in research comparing different groups. A few specific studies provided evidence of the appropriateness of these transformations (Gasser et al., 1982; Oken & Chiappa, 1988; Pollock et al., 1990). Other evidence has been provided in papers describing the construction of normative databases, but they are not as stringent from a statistical point of view (e.g., John et al., 1988).

A review of the literature and a close analysis of a large normative database convinced us that the gaussian approximation is not good enough to allow the use of parametric statistics. All specific studies found that the log-based transformations approximate gaussianity fairly well, but all of them found exceptions. Gasser et al. (1982) found exceptions in delta, theta, beta 1 and beta 2 for the absolute power measures. Oaken and Chiappa (1988) found that approximately one-eighth of the descriptors for absolute power remain non-gaussian after transformation. Relative power behaved a little better. Pollock et al. (1990) found the transformation of amplitude (square root of absolute power) to be excellent in all frequency bands but in theta. While John and his colleagues (1987, 1988) insist on data transformation, Thatcher (1998) found that for all measures, with the exception of phase, the untransformed data approximated gaussianity better than the transformed data, contradicting all previous results. It is worth noting that the sample size used in the John and Thatcher studies was similar, so the unreliability of results cannot be explained by means of "deus ex machina" such as the central limit theorem. Furthermore, all of these studies used different montages, electrode reference, age range of subjects and even different measures. Finally, if in the case of QEEG a few proportions of departure from gaussianity can be ignored, for electromagnetic tomography (LORETA) data it cannot be done capriciously.

Before compiling a parametric database one has to check that the distribution for all descriptors is approximately gaussian. In the case of ET data this involves tens of thousands of checks. With such a large number and all the variability of EEG data, many of them will not pass the tests. The question is how should one deal with them? Should the non-gaussian descriptors be excluded from the database? Even ignoring this problem, we will be left with a normative database in which accuracy is different for each descriptor. In fact, we have shown that the accuracy is a function of skewness and each approximation to gaussianity will lead to different skewness levels. Furthermore, the outcome of the

normative database will be different on the two sides of the distribution. These are not desirable characteristics for a normative database. One may overcome all of these problems by using a non-parametric approach, given that the sample size is large enough. It is fortunate that normative databases of clinical usefulness are constructed on the basis of large samples. Actually the sample sizes commonly employed are so large (500-600) that they would lead to more than 96% accuracy if the non-parametric method described in this article was employed. Furthermore, the validity of results would be the same for the right-handed and the left-handed test, for all electrodes, frequency bands and for whatever measure is employed regardless of its distribution. In fact the sample size is the only true constant across descriptors. We have shown in this article that the accuracy of the non-parametric method, given a fixed alpha level, depends solely on sample size. This is the distinct advantage of the non-parametric method. The extension of the non-parametric method to ET data and to new electroencephalographic measures is straightforward. We also contend that developmental equations and other kinds of between-subject differences can be taken into account while compiling a non-parametric normative database. For instance, polynomial regression equations based on age can be computed. Each descriptor value can be normalized over its predicted value to remove any unwanted trend in the data. In the 1970s it was not easy to perform a non-parametric test. Computers were slow and the computations required could took hours. Today they would take minutes. Another possible reason why non-parametric methods have not been employed is that they require more intense computer programming. However one does not have to check data gaussianity, nor struggle to find appropriate data transformation, nor be concerned about the distribution of new measures any longer. By using a non-parametric method one would actually maximize resources and the prediction of clinical versus non-clinical membership would be improved.

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