Parametric vs. Non-Parametric Statistics of Low Resolution Electromagnetic Tomography (LORETA)

R. W. Thatcher, D. North and C. Biver

Key Words
EEG Inverse Solutions
LORETA Parametric Statistics
Non-parametric Statistics

ABSTRACT

This study compared the relative statistical sensitivity of non-parametric and parametric statistics of 3-dimensional current sources as estimated by the EEG inverse solution Low Resolution Electromagnetic Tomography (LORETA). One would expect approximately 5% false positives (classification of a normal as abnormal) at the $P < .025$ level of probability (two tailed test) and approximately 1% false positives at the $P < .005$ level.

EEG digital samples (2 second intervals sampled 128 Hz, 1 to 2 minutes eyes closed) from 43 normal adult subjects were imported into the Key Institute's LORETA program and then used the Key Institute's cross-spectrum and the Key Institute's LORETA output files (*.lor) as the 2,394 gray matter pixel representation of 3-dimensional currents at different frequencies. The mean and standard deviation *.lor files were computed for each of the 2,394 gray matter pixels for each of the 43 subjects. Tests of Gaussianity and different transforms were computed in order to best approximate a normal distribution for each frequency and gray matter pixel. The relative sensitivity of parametric vs. non-parametric statistics were compared using a "leave-one-out" cross validation method in which individual normal subjects were withdrawn and then statistically classified as being either normal or abnormal based on the remaining subjects.

Log_{10} transforms approximated Gaussian in the range of 95% to 99% accuracy. Parametric Z score tests at $P < .05$ cross-validation demonstrated an average misclassification rate of approximately 4.25%, and range over the 2,394 gray matter pixels was 27.66% to 0.11%. At $P < .01$ parametric Z score cross-validation false positives were 0.26% and ranged from 6.65% to 0% false positives. The non-parametric Key Institute's t-max statistic at $P < .05$ had an average misclassification error rate of 7.64% and ranged from 43.37% to 0.04% false positives. The non-parametric t-max at $P < .01$ had an average misclassification rate of 6.67% and ranged from 41.34% to 0% false positives of the 2,394 gray matter pixels for any cross-validated normal subject.

In conclusion, adequate approximation to Gaussian and high cross-validation can be achieved by the Key Institute's LORETA programs by using a $\log_{10}$ transform and parametric statistics, and parametric normative comparisons had lower false positive rates than the non-parametric tests.

INTRODUCTION

Both non-parametric[1,2] and parametric[3-10] statistics have been used in studies of Low Resolution Electromagnetic Tomography or LORETA,[11,12] however, the relative sensitivity of parametric vs. non-parametric statistics has not been systematically evaluated. Non-parametric statistics have the advantage of being distribution independent as well as insensitive to extreme values or outliers. The disadvantage of non-parametric statistics is the complexity, lower power and time required for computation. In contrast, parametric statistics are simple and easy to compute but rely upon the assumption of a "Gaussian" distribution. Parametric statistics are known to be generally robust even when the assumption of Gaussian distribution is violated,[13-16] nonetheless, an objective evaluation of the assumption of Gaussian distribution of LORETA current sources is helpful when deciding what statistic to use.

The purpose of the present study is: (1) to determine the extent to which LORETA 3-dimensional current sources are Gaussian distributed with and without transforms, and (2) to compare and contrast parametric vs. non-parametric statistics of LORETA 3-dimensional current sources using a leave-one-out cross validation procedure.

METHODS

Subjects

A total of 43 normal adults ranging in age from 16 to 25 years (male = 40) were included in this study. The subjects

From the NeuroImaging Laboratory, Bay Pines VA Medical Center, St. Petersburg, Florida, and the Department of Neurology, University of South Florida College of Medicine, Tampa, Florida (R. W. Thatcher).

Address requests for reprints to Robert W. Thatcher, PhD, NeuroImaging Laboratory, Research and Development Service-151, Veterans Administration Medical Center, Bay Pines, Florida 33744, USA. Email: robert@appliedneuroscience.com

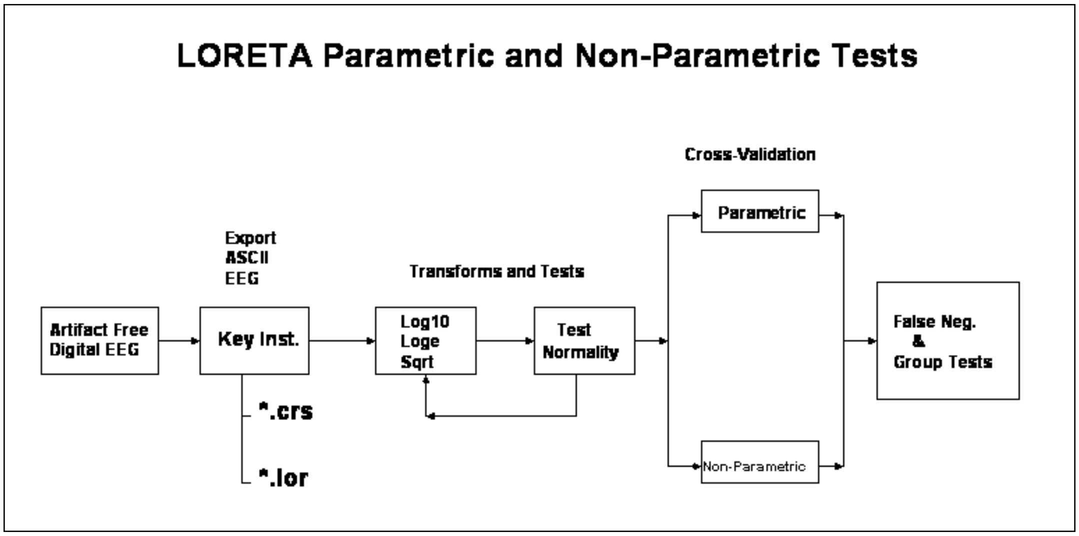

Figure 1.
A diagram of the experimental design. Digital EEG samples were analyzed by the Key Institute LORETA software, and mean and standard deviations of the current sources for each of the 2,394 gray matter pixels were computed for purposes of parametric statistical analyses. Non-parametric tests utilized the same individual data files but used the t-max statistic. Leave-one-out cross validation was used to compare the statistical sensitivity of parametric vs. non-parametric statistics on the same set of test subjects.

were students and professionals without a history of neurological disorders such as no epilepsy, no head injuries, normal development and successful school performance.

The EEG was also recorded from a patient with a CT scan confirmed hematoma of the right hemisphere, for comparative purposes. The same recording conditions and analyses were performed for the normal control subjects. The purpose of the single patient recording was to validate the specificity of LORETA using a clinical case, as well as to examine the statistical stability of parametric statistics.

EEG Recording

The EEG was recorded from 19 scalp locations based on the International 10/20 System of Electrode Placement, using linked ears as a reference. Bipolar eye movement electrodes were applied to the canthus and cheek bone to monitor eye movement artifact. Each EEG record was plotted and visually examined and then edited to remove artifact using the Neuroguide software program (NeuroGuide, 1.7.3). The amplifier bandwidths were nominally 0.5 to 30 Hz, the outputs being 3 db down at these frequencies, and the EEG was digitized at 128 Hz. Split-half reliability tests were conducted on the edited EEG segments, and only records with > 95% reliability were entered into the spectral analyses. The EEG was acquired in the eyes-closed condition, and recording lengths varied from 58.6 seconds to 120 seconds. An average reference time series was computed for each EEG record. The average reference involved summing the voltages across all 19 leads for each time point and dividing this value into the microvolt digital value from each lead at each time point.

Export of EEG Time Series to the Key Institute LORETA Programs

Figure 1 is a diagram of the experimental design. The edited EEG was organized into a format compatible with the Key Institute software,[17] which is 256 blocks of ASCII data (2 seconds x 128 samples/sec) in which the 19 channels were columns and the 256 time points were rows. In order to minimize windowing effects, 75% overlapping 256 point segments were produced according to the procedure described by Kaiser and Sterman.[18] This series of overlapping 256 time points of digitized EEG were then exported to the Key Institute "EEG Cross Spectral Maker" using the "All EEGs Spec[Aut]" option to spectrally analyze the digital EEG samples using the Key Institute cross-spectral FFT. The frequency bands were the standard seven LORETA Key Institute settings: delta = 1-3 Hz; theta = 4-7 Hz; alpha = 8-12 Hz; beta-1 = 13-18 Hz; beta-2 = 19-21 Hz; beta-3 = 22-30 Hz; omega = 1-30Hz. This procedure produced a cross-spectral matrix with the seven different frequency bands for each of the 2,394 gray matter pixels. The LORETA current source values are defined as the square root of the sum of squares of the x, y, z cross-spectral values for each of the 2,394 gray matter pixels.

Parametric Statistical Analyses

1- Means and standard deviations were computed across the 43 subjects for each of the 2,394 variables. Estimates of Gaussianity were computed for each variable using measures of skewness, kurtosis and normal probability plots and Z scores. A $\log_{10}$ transform was applied to each of the 2,394 current source values, and then the skewness

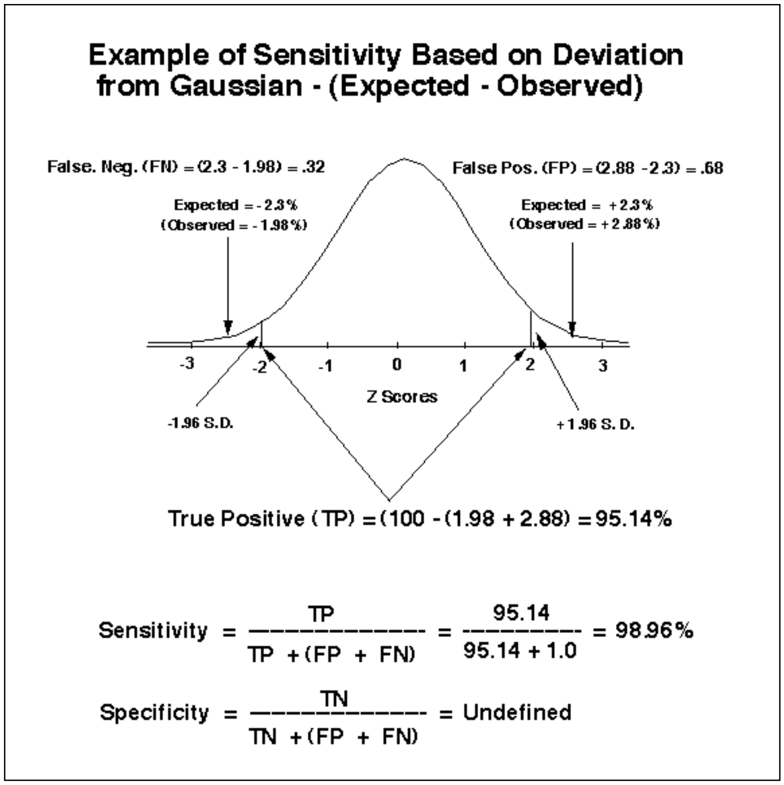

Figure 2.
An example of a normal or Gaussian curve showing values of Z (±1.96), that includes the proportion which is .95 of the total area. The left and right tails of the distribution show probability values of .025 (one-tailed). The classification accuracy of any sample of subjects is based on the assumption of a normal distribution. The probability of finding an observed EEG value in a given range of any population can be determined, and then the sensitivity of the sample can be tested by cross-validation (adapted from Thatcher et al.[16]

and kurtosis and normal probability plots were recomputed to evaluate the degree of Gaussianity of the distributions before and after transforms. The equation to compute

$$\text{skewness} = \frac{1}{N}\sum_{j=1}^{N}\left[\frac{x-\bar{x}}{\sigma}\right]^3 \quad \text{and}$$

$$\text{kurtosis} = \left\{\frac{1}{N}\sum_{j=1}^{N}\left[\frac{x-\bar{x}}{\sigma}\right]^4\right\}-3$$

where N is the number of current density values and σ is the standard deviation.

2- A leave-one-out cross-validation procedure was conducted on the $\log_{10}$ transformed variables in which a single subject was removed from the total population, and means and standard deviations were recomputed for the remaining 2,394 current source values. Z scores were computed for the 2,394 values of the subject that was left out, then this subject was re-entered and a second subject was removed. The means and standard deviations of the remaining population were recomputed and the Z scores of the removed subject's 2,394 current source values were computed, and this step was repeated for each of the 43 subjects.

3- Sensitivity was defined by the percentage of current source variables that were in the tails of the distribution. A perfect Gaussian cross-validation would be 2.3% at +2 SD, 2.3% at –2 SD, 0.13% at +3 SD and 0.13% at –3 SD. The computation of sensitivity based on deviation from an expected Gaussian distribution was used to cross-validate the LORETA current source values as illustrated in Figure 2.

True positives equal the percentage of Z scores that lay within the tails of the Gaussian distribution. False negatives (FN) equal the percentage of Z scores that fall outside of the tails of the Gaussian distribution. The error rates or the statistical sensitivity are directly related to the deviation from a Gaussian distribution. The sensitivity was also computed based on the percentage of the 2,394 current sources at $P < .05$ and at $P < .005$.

Non-Parametric Statistical Analyses

The Key Institute's t-max parametric statistic[16] was computed by using the Key Institute "Statistical Info FileMaker" program[13] to create group A of 42 subjects and group B the single leave-one-out cross-validation subject. Non-parametric independent t-tests (2-tailed) were computed with no normalization using no log transform for each subject. This step was repeated using log transformed data. The removed subject was replaced and a different subject was removed, and the t-max statistic was recomputed until all 43 subjects had been analyzed. The estimate of the sensitivity of the non-parametric statistics was the same as for the parametric statistics, i.e., the percentage of the current sources that were at $P < .05$ and $P < .005$.

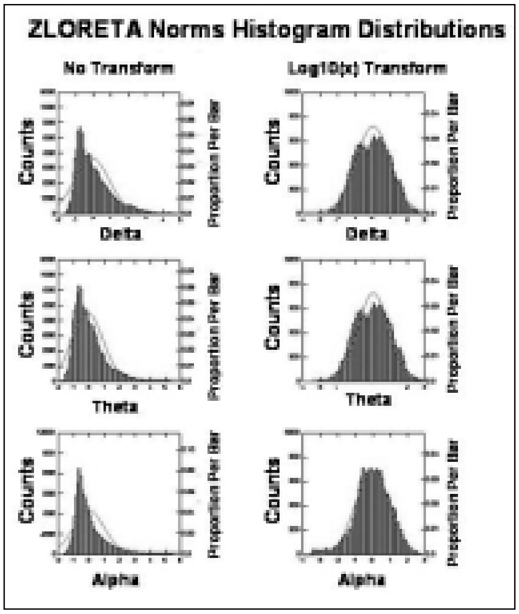

Figure 3.
The distribution of the Z scores of the current source density LORETA values (sqrt. Root of the sum of the squares of x, y and z using the Key Institute software.[17] The y-axis is the number or count and the x-axis is the Z Score, defined as the mean – each value divided by the standard deviation. The left column is the Z score distribution before transform and the right column is the Z score distribution after $\log_{10}$ transform of the current source values. The rows are the first three frequency bands using the option 5 frequency settings[17]: delta = 1-3 Hz; theta = 4-7 Hz; alpha = 8-12 Hz.

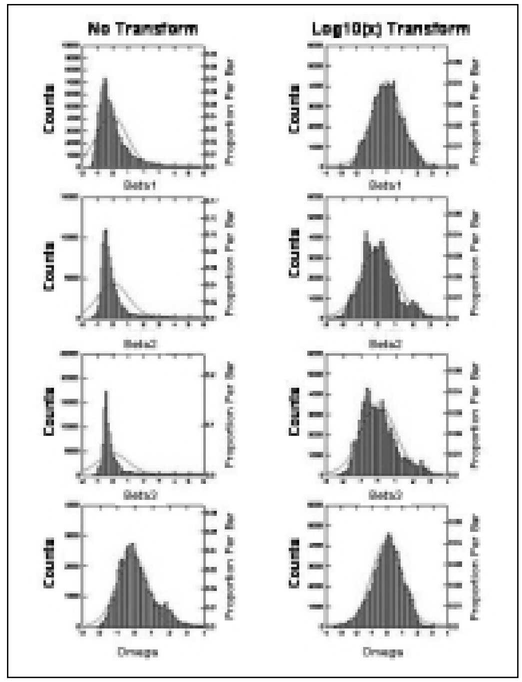

Figure 4.
The distribution of the Z scores of the current source density LORETA values (sqrt. Root of the sum of the squares of x, y and z using the Key Institute software.[17] The y-axis is the number or count and the x-axis is the Z Score, defined as the mean – each value divided by the standard deviation. The left column is the Z score distribution before transform and the right column is the Z score distribution after $\log_{10}$ transform of the current source values. The rows are the last four frequency bands using the option 5 frequency settings[17]: beta-1 = 13-18 Hz; beta-2 = 19-21 Hz; beta-3 = 22 to 30 Hz; omega = 1-30Hz.[17]

RESULTS

Transforms and Gaussian Distributions

Figure 3 shows the distribution of current source densities before (Figure 3 left) and after (Figure 3 right) $\log_{10}$ transform for the delta, theta and alpha frequencies.

Figure 4 shows the distribution of current source densities before (Figure 4 left) and after (Figure 4 right) $\log_{10}$ transform for the beta-1, beta-2 and beta-3 frequencies. It can be seen that reasonable approximation to Gaussian was achieved by the $\log_{10}$ transform, especially for the delta, theta and alpha frequencies. The distribution was slightly less Gaussian for the beta frequencies, as seen in Figure 4.

Cross-Validation Sensitivities of the Parametric Z Statistic

Table 1 shows the skewness and kurtosis of the $\log_{10}$ transformed data and the results of the leave-one-out cross validation Z score statistic for the eyes-closed condition, for linked ears (LE) reference, and the average (AVE) reference montages.

The sensitivities ranged from 95.63% at 2 standard deviations to 99.74% at 3 standard deviations.

Cross-Validations Comparisons Between the Non-parametric t-Max Statistics and the Parametric Z score Statistics

Figure 5 shows the comparative results of the cross-validation tests for the parametric Z scores vs. the non-parametric t-max statistic at $P < .025$. The y-axis is the percentage of the 2,394 pixels with P values greater than 0.025, and on the x-axis are the frequency bands (delta, theta, alpha, beta-1, beta-2, beta-3, omega and all frequencies). The white columns are non-parametric test results and the black columns are the Z parametric statistic results. It can be seen that the parametric analyses result in fewer current source values at $P < .025$ than does the non-parametric test. Very similar results were obtained for the average reference data as seen in Table 1.

Figure 6 shows the comparative results of the cross-validation tests for the parametric Z scores vs. the non-parametric t-max statistic at $P < .005$. The y-axis is the

Table 1

LORETA zcross-validation zlog10(x)

LE Summary	Skew	Kurt	< -1 SD	> 1 SD	<-2 SD	> 2 SD	< -3 SD	> 3 SD	Sen 2 SD	Sen 3 SD
Delta	0.03	-0.46	17.37%	16.84%	1.45%	1.59%	0.03%	0.00%	95.63%	99.74%
Theta	-0.06	-0.08	15.93%	15.77%	2.30%	1.70%	0.12%	0.08%	95.64%	99.74%
Alpha	-0.37	0.71	13.26%	15.55%	3.12%	1.40%	0.80%	0.00%	95.64%	99.75%
Beta1	0.15	-0.12	15.68%	16.24%	1.23%	2.50%	0.03%	0.14%	95.63%	99.74%
Beta2	0.48	0.35	13.74%	14.50%	0.82%	4.57%	0.00%	0.16%	95.65%	99.74%
Beta3	0.73	0.40	13.77%	14.90%	0.23%	4.89%	0.00%	0.15%	95.65%	99.74%
Omega	-0.35	0.21	15.31%	15.48%	3.12%	0.83%	0.34%	0.00%	95.64%	99.74%
AVE										
Delta	-0.09	-0.46	18.56%	16.19%	1.77%	1.26%	0.06%	0.00%	95.63%	99.74%
Theta	-0.26	0.19	15.86%	14.92%	3.21%	1.58%	0.16%	0.01%	95.64%	99.74%
Alpha	-0.62	1.34	12.31%	14.78%	3.74%	1.12%	1.09%	0.00%	95.64%	99.75%
Beta1	-0.07	-0.06	15.25%	16.10%	2.38%	1.71%	0.10%	0.00%	95.64%	99.74%
Beta2	0.25	0.32	13.94%	14.36%	1.74%	3.65%	0.00%	0.10%	95.65%	99.74%
Beta3	0.54	0.23	15.76%	15.12%	0.50%	4.37%	0.00%	0.09%	95.64%	99.74%
Omega	-0.64	0.65	14.98%	14.24%	4.37%	0.60%	0.56%	0.00%	95.65%	99.75%

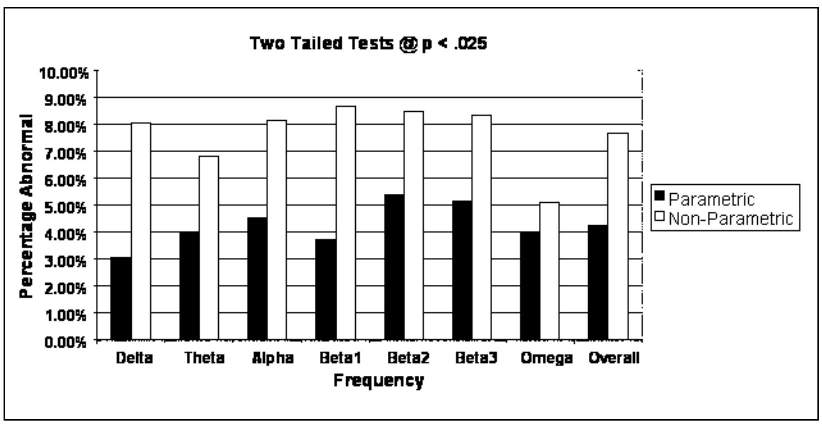

Figure 5. The comparative results of the cross-validation tests for the parametric Z scores vs. the non-parametric t-max statistic at P < .025 for the linked ears, eyes closed condition. The y-axis is the percentage of the 2,394 pixels with P values greater than 0.025, and the x-axis are the frequency bands (delta, theta, alpha, beta-1, beta-2, beta-3, omega and all frequencies). The white columns are non-parametric test results and the black columns are the Z parametric statistic results.

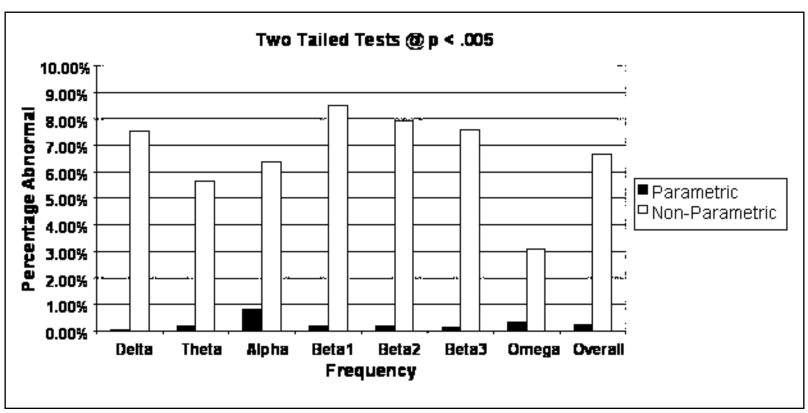

Figure 6. The comparative results of the cross-validation tests for the parametric Z scores vs. the non-parametric t-max statistic at P < .005 for the linked ears, eyes closed condition. The y-axis is the percentage of the 2,394 pixels with P values greater than 0.005, and the x-axis are the frequency bands (delta, theta, alpha, beta-1, beta-2, beta-3, omega and all frequencies). The white columns are non-parametric test results and the black columns are the Z parametric statistic results.

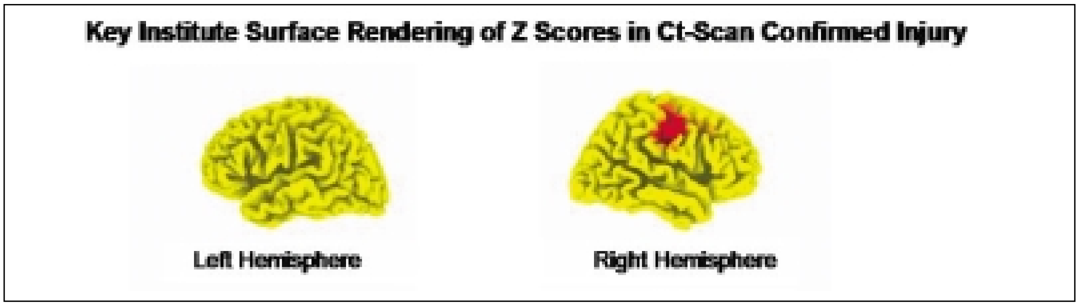

Figure 7.
Surface rendering of the Z scores at 4 Hz using the Key Institute 3DSurf program.

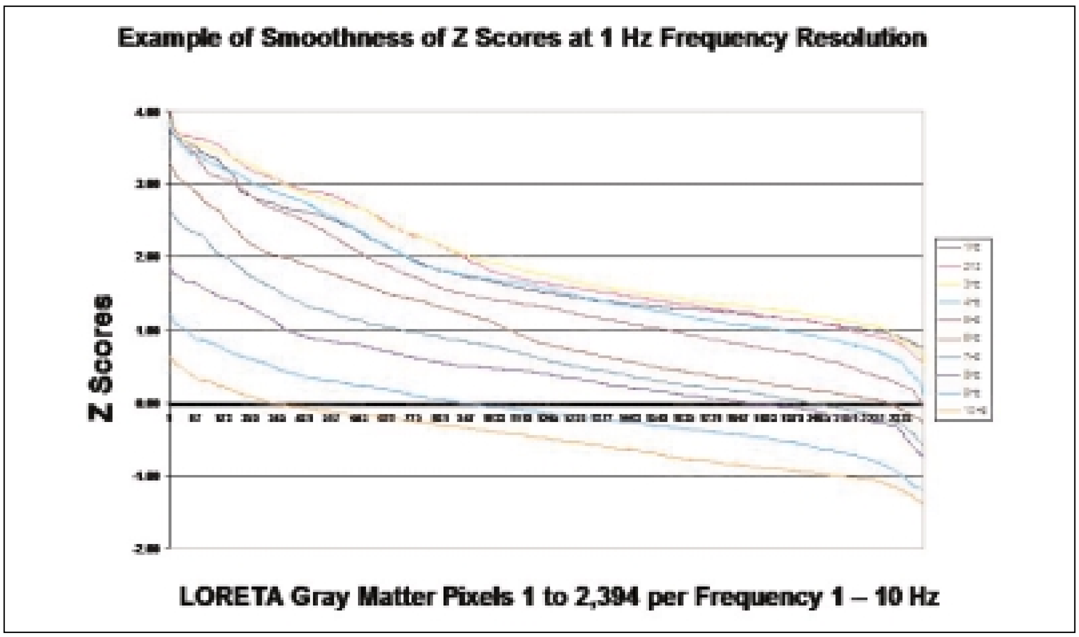

Figure 8.
Evaluation of the smoothness of the Z scores at 4 Hz for frequencies 1 to 10 Hz. The .lor current source values were ranked ordered for each single hertz frequency. The y-axis is Z scores and the x-axis is the number of gray matter pixels from 1 to 2,394.

percentage of the 2,394 pixels with P values greater than 0.005 and on the x-axis are the frequency bands (delta, theta, alpha, beta-1, beta-2, beta-3, omega and all frequencies). The white columns are non-parametric test results and the black columns are the Z parametric statistic results. It can be seen that the non-parametric tests consistently produced a larger number of false positives than did the parametric tests. An exact comparison is an average of 7.65% for non-parametric vs. 4.24% for parametric.

Figure 6 shows that the parametric analyses result in fewer current source values at $P < .005$ than does the non-parametric test. Also, the non-parametric statistics did not change much between $P < .025$ vs. $P < .005$ in comparison to the results of the parametric analyses. For example, the average false positive rate for non-parametric is 0.25% at $P < .005$ and 4.24% at $P < .025$. This is in contrast to the parametric tests where the average false positive rate was 6.65% at $P < .005$ and 7.65% at $P < .025$. The change of parametric statistical false positives is close to what is expected assuming a Gaussian distribution, and the constant hit rate of non-parametric statistics reflects the distribution independence of this statistic.

Smoothness at 1 Hz Resolution and Regions of Interest (ROI)

Individual slices and single frequency analyses were computed for a single patient in order to study the normality and validity of smaller numbers of gray matter current source density values. The patient was injured in the right parietal lobe as confirmed by CT scan and other clinical information. A smooth distribution of Z scores with maxima near to the location of the confirmed injury is expected if parametric statistics using LORETA are valid. The results of a parametric Z score analysis using LORETA in the CT scan revealed that the maximum Z scores were present in the same location that the CT scans showed maximum injury.

Figure 7 is the surface rendering of the Z scores in the CT scan confirmed patient, which shows the region of interest of significant Z score current source values that register to the spatial location of the patient's injury.

Figure 8 is a graph of the rank order of Z scores for different 1 Hz frequency bands from 1 to 10 Hz for the 2,394 current source values. It can be seen that the rank ordering of the Z scores is smooth and well behaved at each 1 Hz frequency analysis with maximum Z score deviation at 2-6 Hz, which is the same frequency band in which the surface EEG was most deviant from normal. A smooth rank ordering of Z scores is expected if parametric statistical analysis is valid.

DISCUSSION

The results of this analysis support the general conclusion that parametric and non-parametric statistical tests are valid when applied to LORETA. The results of the parametric analyses are consistent with studies that have used parametric statistics to evaluate EEG inverse solutions in general[17-20] and LORETA and VARETA in particular.[3-6,9,10,21]

The advantage of parametric statistics is its ease of use and flexibility. However, it is important to emphasize that an approximation to Gaussian requires the use of a transform such as a $\log_{10}$ transform, and that without a transform the statistical accuracy of parametric statistics may diminish. It is recommended that cross-validation procedures be used no matter what statistical method is employed so that the relative accuracy, power and specificity of the statistics can be estimated. The non-parametric tests tended to show higher error rates than the parametric analyses. However, both statistical methods are valid and their application is a matter of preference. The advantage of the non-parametric is its insensitivity to extreme values.[14] A safeguard against extreme values when using parametric tests is to evaluate the smoothness of the Z scores or parametric t-tests in order to identify and remove outliers or extreme values.

Smoothness of Regions of Interest (ROI)

In this study the summation of current density values was over the entire 2,394 LORETA gray matter pixels, which provided a general statement about the relatively Gaussian distribution of current values. More limited and specific analyses showed that much smaller samples of LORETA current source density values at 1 Hz resolution also approximated a Gaussian distribution, thus supporting the more general statement about Gaussianity.[21] The fact that the distribution of Z scores in a single patient were smooth and maximal in a location of confirmed pathology is evidence that the general Gaussian nature of LORETA current source density values also applies to regions of interest and smaller sample sizes.

CONCLUSIONS

Both parametric and non-parametric statistics are valid and useful when analyzing LORETA current sources. The relative sensitivity and specificity of parametric vs. non-parametric statistics is likely to vary depending upon the experimental design. However, no matter which statistic is used some form of validation either by tests of Gaussian such as skewness and kurtosis or by cross-validation of non-parametric statistics is recommended.

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