

Evaluation and Validity of a LORETA Normative EEG Database

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ABSTRACT

Objectives: To evaluate the reliability and validity of a Z-score normative EEG database for Low Resolution Electromagnetic Tomography (LORETA).

Methods: EEG digital samples (2 second intervals sampled 128 Hz, 1 to 2 minutes eyes closed) were acquired from 106 normal subjects and the cross-spectrum was computed and multiplied by the Key Institute's LORETA 2,394 gray matter pixel T Matrix. After a \log_{10} transform or a Box-Cox transform the mean and standard deviation of the *.lor files were computed for each of the 2,394 gray matter pixels for each of the subjects from 1 to 30 Hz. Tests of gaussianity were computed in order to best approximate a normal distribution for each frequency and gray matter pixel. The relative sensitivity of a Z score database was computed by measuring the approximation to a Gaussian distribution. The validity of the LORETA normative database was evaluated by the degree to which confirmed brain pathologies were localized using the LORETA normative database.

Results: \log_{10} and Box-Cox transforms approximated gaussian in the range of 95.64% to 99.75% accuracy. The percentage of normative Z score values at 2 standard deviations ranged from 1.21% to 3.54% and the percentage of Z scores at 3 standard deviations ranged from 0% to 0.83%. Left temporal lobe epilepsy, right sensory motor hematoma and a right hemisphere stroke exhibited maximum Z score deviations in the same locations as the pathologies.

Conclusions: 1- Adequate approximation to a Gaussian distribution can be achieved using LORETA by using a \log_{10} transform or a Box-Cox transform and parametric statistics, 2- a Z-Score normative database is valid with adequate sensitivity when using LORETA and; 3- the Z score LORETA normative database also consistently localized known pathologies to the expected Brodmann areas as an hypothesis test based on the surface EEG before computing LORETA.

Key Words: EEG Inverse Solutions, LORETA Parametric Statistics, LORETA Z Scores

1.0- Introduction

Parametric statistics have been successfully used in studies of Low Resolution Electromagnetic Tomography or LORETA (1 - 6). Valdez et al. (4) created a Z score normative database that exhibited high sensitivity and validity using a variation of LORETA called VARETA. A subsequent study by Machado extended these analyses again using VARETA (5). Thatcher et al. (6) also showed that LORETA current values in wide frequency bands approximate a normal distribution after transforms with reasonable sensitivity. However, there are no studies of the gaussianity and reliability of a normative database using the standard Key Institute LORETA and 1 Hz frequency resolution, including validation studies of known pathologies. Therefore, the purpose of the present study was to evaluate the relative sensitivity and validity of the Key Institute LORETA using Z score parametric statistics at 1 Hz resolution and including evaluation of a LORETA Z score normative database of patients with confirmed pathologies.

2.0 Methods

2.1 Subjects

A total of 106 normal adults ranging in age from 18 to 82 (male = 56) were included in this study. The subjects were without a history of neurological disorders such as epilepsy, head injuries and reported normal development and successful school performance.

The EEG was also recorded from three different patients who had well-localized and confirmed pathologies: 1- left temporal lobe epilepsy, 2- a hematoma of the right hemisphere due to a traumatic brain injury and, 3- a right frontal lobe stroke patient.

2.2 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. Each EEG record was plotted and visually examined and then edited to remove artifact using the Neuroguide software program (NeuroGuide, 1.8.1). The amplifier bandwidths were nominally 0.5 to 30 Hz, the outputs being 3 db down at these frequencies. The 100 samples per second digital EEG of the normal subjects were cubic-spline-interpolated to 128 samples per second using standard procedures (7). The EEG's of the three patients were digitized at 128 Hz. Split-half and test-re-test reliability measures were conducted on the edited

EEG segments and only records with > 95% reliability were entered into the spectral analyses. EEG was acquired in the eyes-closed conditions and record lengths varied from 58.6 seconds to 120 seconds. Details of the normative database collection and analysis have been previously published (8).

2.3 – Cross-Spectral Analysis and Key Institute LORETA programs

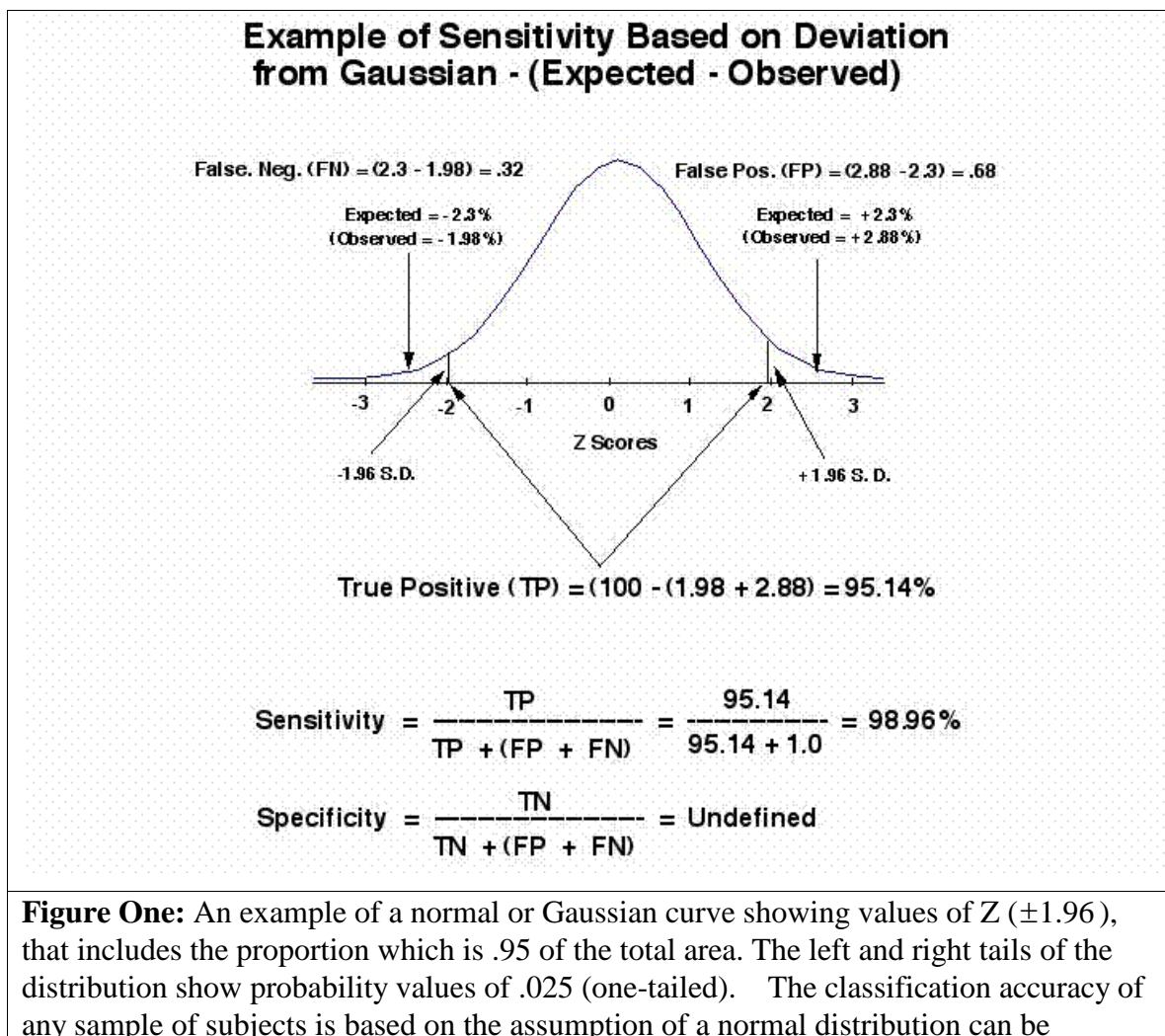
The edited EEG was saved in which the 19 channels were columns and the 256 time points as rows. In order to minimize windowing effects 75% overlapping 256 point segments were produced according to the procedure described by Kaiser and Stermann (9). Cross-spectral analyses using the Hermitian matrix as described by Pascual-Marqui (10 - 12) were computed. A cosine taper windowing was performed using the cross-spectral FFT on each 256 point data sample. The cross-spectra were averaged across the overlapping windows which yielded a total of 61 frequencies from 0.5 Hz to 30 Hz. The spectral resolution was 0.5 Hz, however adjacent frequency bands were averaged to produce a 1 Hz resolution thus yielding a total of 30 frequency bands from 1 to 30 Hz. The Key Institute T-Matrix was computed (10) and the cross-spectral values at each 1 Hz frequency band were multiplied by the T-Matrix and then the square root of the sum of the squares for the x, y & z components was computed as the resultant current source vector for each of the 2,394 gray matter pixels for each 1 Hz frequency band for each subject.

2.4 – Parametric Statistical Analyses:

Means and standard deviations were computed across the normal subjects for each of the 2,394 variables at each 1 Hz frequency. Because of limitations in Excel, only the results from 1 Hz to 27 Hz frequency are presented in this paper. Estimates of Gaussianity were computed for each variable using measures of skewness, kurtosis and normal probability plots or Z scores. A \log_{10} transform was applied to each of the 2,394 current source values and then the skewness and kurtosis and normal probability plots were re-computed to evaluate the degree of gaussianity of the distributions before and after transforms. A second transform, the Box-Cox transform (17) defined as $T(x) = (x^\lambda - 1)\lambda$ where x is the variable being transformed and $\lambda = 0.07$ is the transformation parameter. The value of lambda was determined by an iteration procedure that found the

minimal skewness and kurtosis values. The Box-Cox transform was then compared to the \log_{10} transform.

Sensitivity was defined as the difference between two population distributions, 1- an ideal gaussian distribution and, 2- the observed distribution of Z scores computed from the normal subjects. This method differs from the typical computation of sensitivity in that it does not involve two different subject populations but rather an ideal population and an observed population. For example, the tails of an ideal Gaussian would be 2.3% at + 2 SD, 2.3% at - 2 SD, 0.13% at + 3 SD and 0.13 % at - 3 SD and the difference from this ideal distribution is a measure of the sensitivity of the normal subjects to approximate an ideal gaussian. The computation of sensitivity based on deviation from an expected ideal Gaussian distribution was used to cross-validate the LORETA current source values as illustrated in figure 1.



compared. 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 (8)).

True positives were defined as the percentage of Z-scores that lay within the tails of the Gaussian distribution. False negatives (FN) were defined as 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 $P < .005$. This measure of sensitivity uses the ideal gaussian distribution to represent the expected values of one population versus the observed values of the normative population. Although there are two population values (i.e., ideal gaussian vs. normals) it is not possible to compute specificity without a comparison between two different groups of patients or a normal vs. a clinic group, therefore specificity is undefined as noted in figure one.

3.0 – Results

3.1- Transforms and Gaussian Distributions

Table I shows the skewness and kurtosis of the \log_{10} transformed data and the percentages of Z scores at ± 2 standard deviations and ± 3 standard deviations for each of the 1 Hz frequency bands for the eyes closed condition for linked ears reference. The sensitivities ranged from 95.64% at 2 standard deviations to 99.75% at 3 standard deviations. Average skewness = 0.29 and average kurtosis = 0.68 Thus, gaussianity can be approximated at a frequency resolution of 1 Hz.

TABLE I - LORETA CROSS-VALIDATION: Log10 Transform_n=106

			1 STANDARD DEVIATIONS		2 STANDARD DEVIATIONS		3 STANDARD DEVIATIONS			
Frequency	SKEWNESS	KURTOSIS	z < -1 SD	z > 1 SD	z < -2 SD	z > 2 SD	z < -3 SD	z > 3 SD	SEN 2SD	SEN 3SD
FREQ_1	0.08	0.84	13.76%	14.60%	2.22%	2.52%	0.51%	0.45%	95.64%	99.75%
FREQ_2	0.19	0.39	14.47%	15.20%	1.79%	2.44%	0.21%	0.46%	95.64%	99.75%
FREQ_3	0.24	0.14	15.79%	15.62%	1.66%	2.54%	0.03%	0.35%	95.64%	99.74%
FREQ_4	0.29	0.16	15.73%	15.83%	1.21%	2.63%	0.02%	0.42%	95.64%	99.74%
FREQ_5	0.27	0.17	15.79%	15.13%	1.44%	2.85%	0.00%	0.41%	95.64%	99.74%
FREQ_6	0.33	0.32	15.39%	14.77%	1.62%	3.11%	0.01%	0.54%	95.64%	99.75%
FREQ_7	0.33	0.30	15.25%	15.44%	1.79%	2.99%	0.00%	0.50%	95.64%	99.75%
FREQ_8	0.38	0.47	15.90%	14.69%	1.72%	3.19%	0.00%	0.44%	95.65%	99.75%
FREQ_9	0.21	0.29	15.66%	15.22%	2.20%	2.88%	0.00%	0.32%	95.65%	99.74%
FREQ_10	0.17	0.23	14.52%	16.43%	2.18%	2.38%	0.00%	0.30%	95.64%	99.74%
FREQ_11	0.64	1.51	12.62%	15.23%	1.65%	3.21%	0.00%	0.87%	95.64%	99.75%
FREQ_12	0.29	0.80	13.91%	15.06%	1.88%	3.17%	0.23%	0.44%	95.65%	99.75%
FREQ_13	0.22	0.82	13.97%	15.20%	1.83%	2.93%	0.44%	0.45%	95.64%	99.75%
FREQ_14	0.25	0.82	14.08%	14.75%	1.79%	3.05%	0.34%	0.46%	95.64%	99.75%
FREQ_15	0.20	0.78	13.97%	15.10%	2.03%	2.86%	0.41%	0.46%	95.65%	99.75%
FREQ_16	0.21	0.82	14.05%	14.93%	2.02%	2.88%	0.37%	0.43%	95.65%	99.75%
FREQ_17	0.27	0.97	14.02%	14.41%	1.84%	2.92%	0.31%	0.61%	95.64%	99.75%
FREQ_18	0.27	0.94	13.85%	13.86%	1.75%	3.56%	0.38%	0.52%	95.65%	99.75%
FREQ_19	0.30	0.90	13.20%	14.21%	1.79%	3.54%	0.31%	0.54%	95.65%	99.75%
FREQ_20	0.27	0.75	13.26%	15.16%	1.74%	3.26%	0.43%	0.33%	95.65%	99.75%
FREQ_21	0.34	0.73	13.38%	15.47%	1.71%	3.14%	0.19%	0.54%	95.64%	99.75%
FREQ_22	0.33	0.73	13.93%	14.90%	1.62%	3.33%	0.24%	0.57%	95.65%	99.75%
FREQ_23	0.25	0.68	13.34%	15.09%	1.98%	3.34%	0.31%	0.52%	95.65%	99.75%
FREQ_24	0.30	0.75	13.71%	14.62%	1.81%	3.40%	0.34%	0.59%	95.65%	99.75%
FREQ_25	0.43	0.93	13.11%	14.77%	1.78%	3.39%	0.08%	0.77%	95.65%	99.75%
FREQ_26	0.42	0.94	12.78%	14.70%	1.74%	3.32%	0.14%	0.80%	95.65%	99.75%
FREQ_27	0.47	1.04	12.29%	14.51%	1.76%	3.30%	0.15%	0.83%	95.65%	99.75%
OVERALL	0.29	0.68	14.14%	15.00%	1.80%	3.04%	0.20%	0.51%	95.64%	99.75%

Table II shows the skewness and kurtosis of the Box-Cox (17) transformed data and the percentages of Z scores at ± 2 standard deviations and ± 3 standard deviations for each of the 1 Hz frequency bands for the eyes closed condition for linked ears reference. The sensitivities ranged from 95.60% at 2 standard deviations to 99.74% at 3 standard deviations. Average skewness = 0.06 and average kurtosis = 0.53 which is a slight improvement in comparison to the log₁₀.

TABLE II - LORETA CROSS-VALIDATION: Box-Cox Transform_n=106

Frequency	SKEWNESS	KURTOSIS	1 STANDARD DEVIATIONS		2 STANDARD DEVIATIONS		3 STANDARD DEVIATIONS		SEN 2SD	SEN 3SD
			z < -1 SD	z > 1 SD	z < -2 SD	z > 2 SD	z < -3 SD	z > 3 SD		
FREQ_1	-0.16	0.88	13.86%	14.59%	2.53%	2.10%	0.77%	0.32%	95.60%	99.74%
FREQ_2	-0.02	0.34	14.69%	15.26%	2.13%	2.09%	0.42%	0.22%	95.60%	99.74%
FREQ_3	0.05	0.01	15.98%	15.77%	2.13%	2.21%	0.12%	0.19%	95.60%	99.74%
FREQ_4	0.11	-0.04	15.97%	15.98%	1.76%	2.29%	0.05%	0.24%	95.60%	99.74%
FREQ_5	0.09	-0.01	15.93%	15.29%	1.97%	2.50%	0.03%	0.28%	95.60%	99.74%
FREQ_6	0.12	0.10	15.63%	14.93%	2.10%	2.72%	0.04%	0.36%	95.60%	99.74%
FREQ_7	0.11	0.08	15.53%	15.57%	2.48%	2.53%	0.00%	0.32%	95.60%	99.74%
FREQ_8	0.11	0.20	16.20%	14.84%	2.56%	2.69%	0.01%	0.30%	95.60%	99.74%
FREQ_9	-0.07	0.17	15.73%	15.23%	2.88%	2.34%	0.06%	0.15%	95.60%	99.74%
FREQ_10	-0.11	0.27	14.59%	16.41%	2.47%	1.71%	0.42%	0.16%	95.60%	99.74%
FREQ_11	0.31	0.95	13.23%	15.57%	2.07%	2.89%	0.13%	0.53%	95.60%	99.74%
FREQ_12	0.05	0.70	14.08%	15.15%	2.14%	2.72%	0.49%	0.34%	95.60%	99.74%
FREQ_13	-0.01	0.84	14.05%	15.27%	2.05%	2.45%	0.70%	0.38%	95.60%	99.74%
FREQ_14	0.02	0.80	14.21%	14.80%	2.16%	2.61%	0.59%	0.32%	95.60%	99.74%
FREQ_15	-0.04	0.78	14.06%	15.13%	2.40%	2.42%	0.63%	0.29%	95.60%	99.74%
FREQ_16	-0.04	0.81	14.13%	14.98%	2.41%	2.45%	0.54%	0.30%	95.60%	99.74%
FREQ_17	0.02	0.86	14.13%	14.50%	2.28%	2.55%	0.55%	0.33%	95.60%	99.74%
FREQ_18	0.02	0.91	13.98%	13.93%	2.21%	3.15%	0.65%	0.32%	95.60%	99.74%
FREQ_19	0.11	-0.04	15.97%	15.98%	1.76%	2.29%	0.05%	0.24%	95.60%	99.74%
FREQ_20	0.02	0.77	13.41%	15.25%	2.13%	2.71%	0.68%	0.21%	95.60%	99.74%
FREQ_21	0.10	0.64	13.64%	15.57%	2.04%	2.72%	0.51%	0.37%	95.60%	99.74%
FREQ_22	0.09	0.66	14.16%	15.02%	1.89%	3.03%	0.49%	0.32%	95.60%	99.74%
FREQ_23	0.02	0.67	13.48%	15.17%	2.25%	2.93%	0.55%	0.24%	95.60%	99.74%
FREQ_24	0.06	0.69	13.90%	14.73%	2.18%	2.86%	0.54%	0.32%	95.60%	99.74%
FREQ_25	0.19	0.74	13.39%	15.00%	2.07%	3.02%	0.37%	0.48%	95.60%	99.74%
FREQ_26	0.18	0.77	13.06%	14.90%	2.00%	2.91%	0.37%	0.48%	95.60%	99.74%
FREQ_27	0.22	0.83	12.61%	14.72%	2.01%	3.01%	0.36%	0.54%	95.60%	99.74%
OVERALL	0.06	0.53	14.43%	15.17%	2.19%	2.59%	0.37%	0.32%	95.60%	99.74%

Figure two shows the distribution of current source densities after \log_{10} transform in 1 Hz frequency bands from 1 to 9 Hz. It can be seen that a reasonable approximation to a Gaussian distribution was achieved by the \log_{10} transform. The distribution of current source densities after the Box-Cox transform were essentially the same as for the \log_{10} and therefore are not displayed.

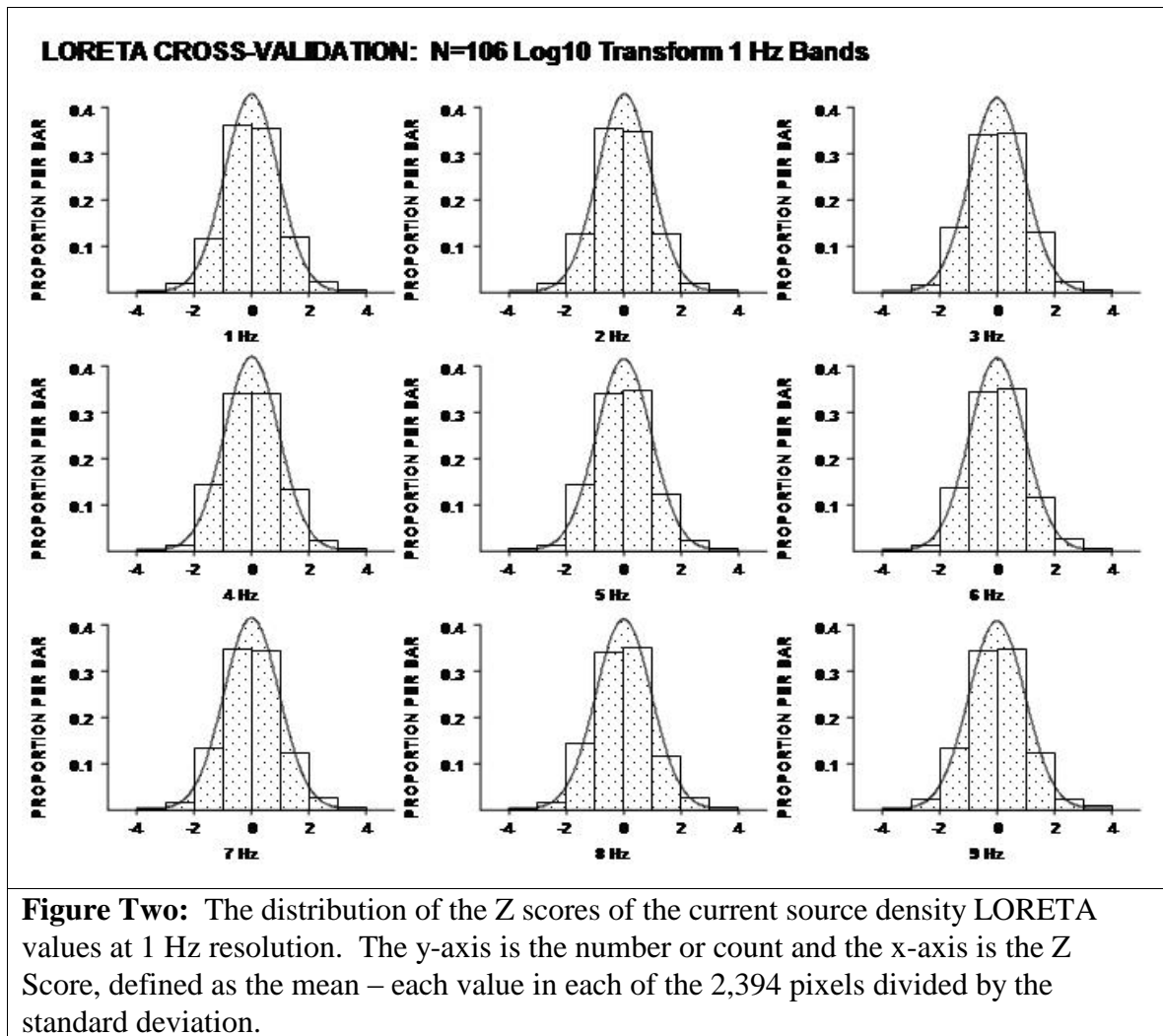
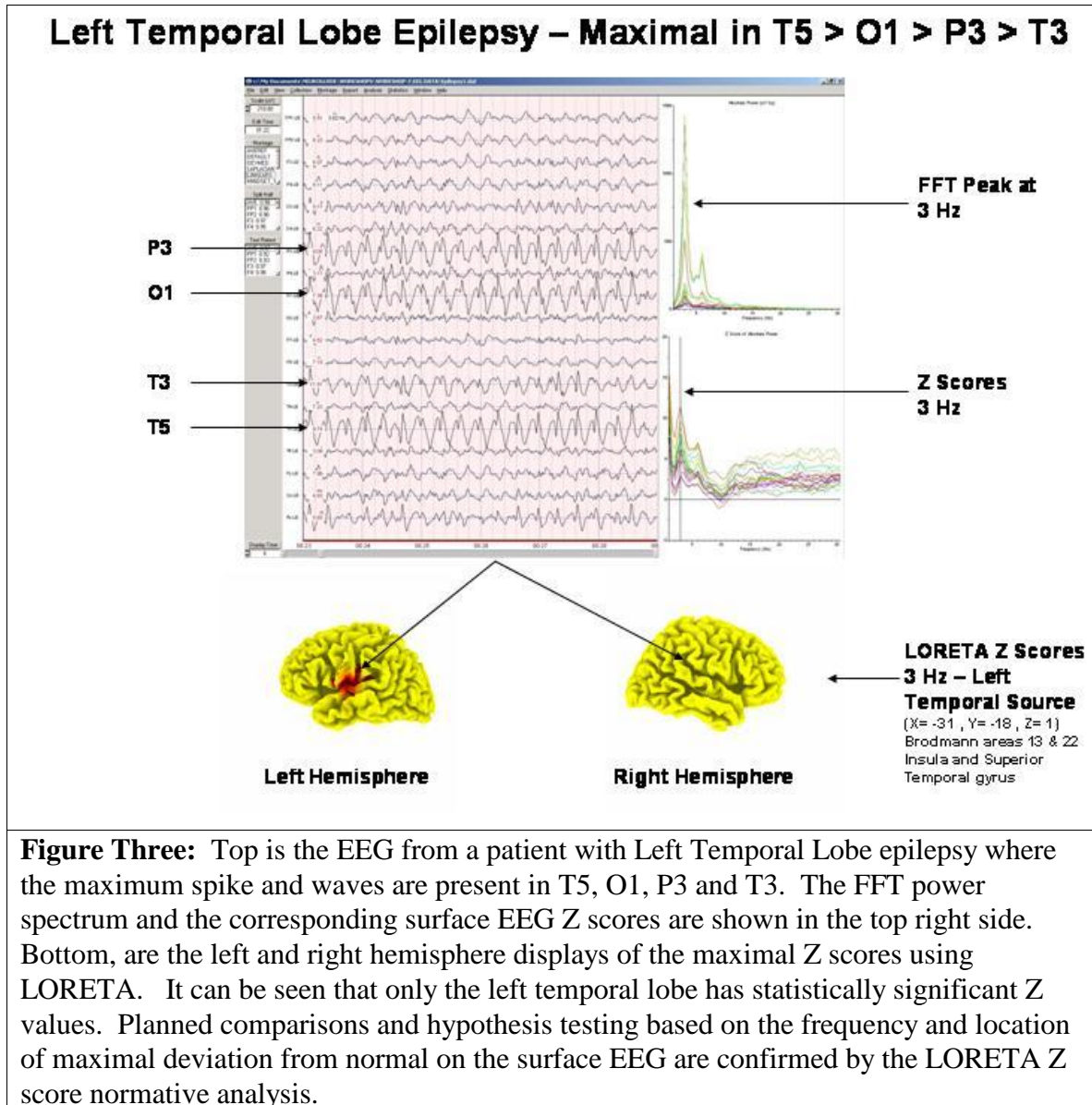


Figure 3 (Top) shows an example of the EEG from the epilepsy patient in which maximal epileptic discharges are present in the left temporal, left parietal and left occipital regions. The maximum amplitude of epilepsy was in the left temporal lobe lead (T5) at 3 Hz as measured by the FFT and the Z scores from the scalp surface.

Figure 3 (Bottom) shows the Z scores in LORETA slices in the left temporal lobe of the epilepsy patient. It can be seen that the maximum Z scores were consistent with the surface EEG by being present in the left temporal lobe at 3 Hz. The sources were localized to Brodmann area 22 superior temporal gyrus and Brodmann area 13 of the insula.



LORETA is low resolution electromagnetic tomography (est. 2 – 4 cm resolution) and precise millimeter localization of epileptic foci is beyond the resolution of LORETA. Nonetheless, verification of the surface EEG with 3-dimensional source currents illustrates the use of hypotheses as to the expected hemisphere and regions based on the surface EEG. In this case the hypothesis from the surface EEG was that there is an expected source in the left temporal regions (Brodmann areas were predicted beforehand) and this hypothesis was confirmed. This is an example of specificity of a Z score

normative database in which 3-dimensional hypotheses are formed (and thus planned comparisons) based on the surface EEG and the hypothesis is then tested using LORETA.

Figure 4 (Top) shows an example of the EEG from a TBI patient with a right hemisphere hematoma. The maximum amplitude of slow waves (1- 6 Hz) was in the right pre-frontal (C4), right parietal (P4) as well as right occipital regions (O2) as measured by the FFT and the Z scores from the scalp surface.

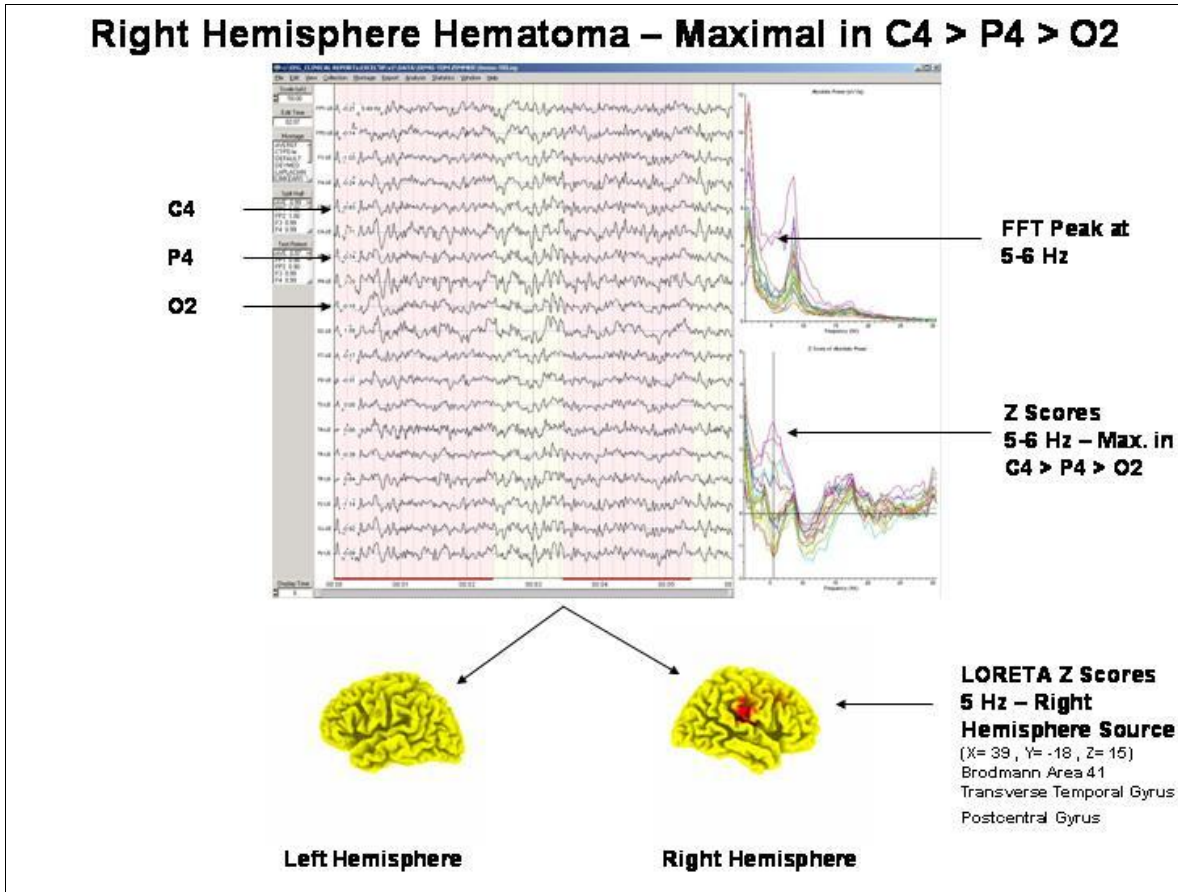


Figure Four: Top is the EEG from a patient with a right hemisphere hematoma where the maximum slows waves are present in C4, P4 and O2. The FFT power spectrum from 1 to 30 Hz and the corresponding Z scores of the surface EEG are shown in the right side of the EEG display. Bottom, are the left and right hemisphere displays of the maximal Z scores using LORETA. It can be seen that only the right hemisphere has statistically significant Z values. Planned comparisons and hypothesis testing based on the frequency and location of maximal deviation from normal on the surface EEG are confirmed by the LORETA Z score normative analysis.

Figure 4 (Bottom) shows the Z scores in LORETA slices in the right hemisphere hematoma patient which were consistent with the surface EEG deviation from normal by

being in the right hemisphere and near to the area of maximal damage. The maximum Z scores were present in the right post-central gyrus at 5 Hz and were localized to Brodmann area 43 right post-central gyrus as well as Brodmann areas 13 insula cortex and 41 transverse temporal gyrus.

Figure 5 (Top) shows an example of the EEG from a right hemisphere stroke patient. The maximum Z scores from the scalp EEG were in the right anterior frontal regions (F4 & Fp2) at 23 Hz.

Figure 5 (Bottom) shows the Z scores in LORETA slices. It can be seen that the maximum Z scores were present in the right frontal regions at 23 Hz and the Key Institute Talairach Atlas were maximally localized to Brodmann area 9 right inferior frontal gyrus as well as Brodmann area 6 right frontal pre-central gyrus. This is another example of validation of a LORETA Z score normative database in which 3-dimensional hypotheses are formed (and thus planned comparisons) based on the surface EEG and the hypothesis is then tested using LORETA.

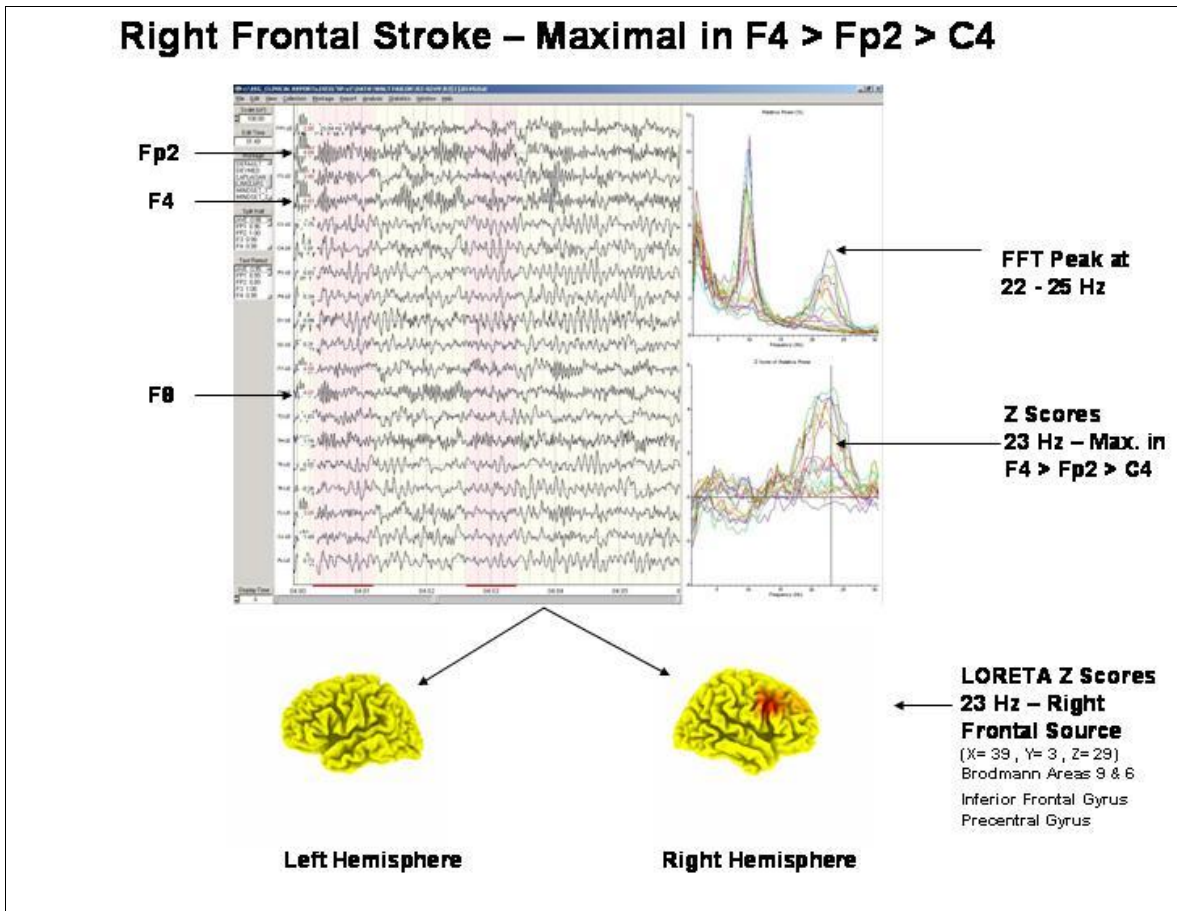


Figure Five: Top is the EEG from a patient with a right frontal lobe stroke where the maximum slows waves are present in F4 and Fp2. The FFT power spectrum from 1 to 30 Hz and the corresponding Z scores of the surface EEG are shown in the right side of the EEG display. Bottom, are the left and right hemisphere displays of the maximal Z scores using LORETA. It can be seen that only the right hemisphere has statistically significant Z values. Planned comparisons and hypothesis testing based on the frequency and location of maximal deviation from normal on the surface EEG are confirmed by the LORETA Z score normative analysis.

3.3- Smoothness at 1 Hz Resolution and Regions of Interest (ROIs)

A smooth distribution of Z scores with maxima near to the location of the confirmed injury is expected if parametric statistics using LORTA are valid. Figure 6 shows the results of a parametric Z score analysis using LORETA in the right hemisphere hematoma patient shown in Figure 4.

Figure 6 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 in the right hemisphere hematoma patient in figure 4. 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 (see Figure 4). A smooth rank ordering of Z scores is expected if parametric statistical analysis is valid.

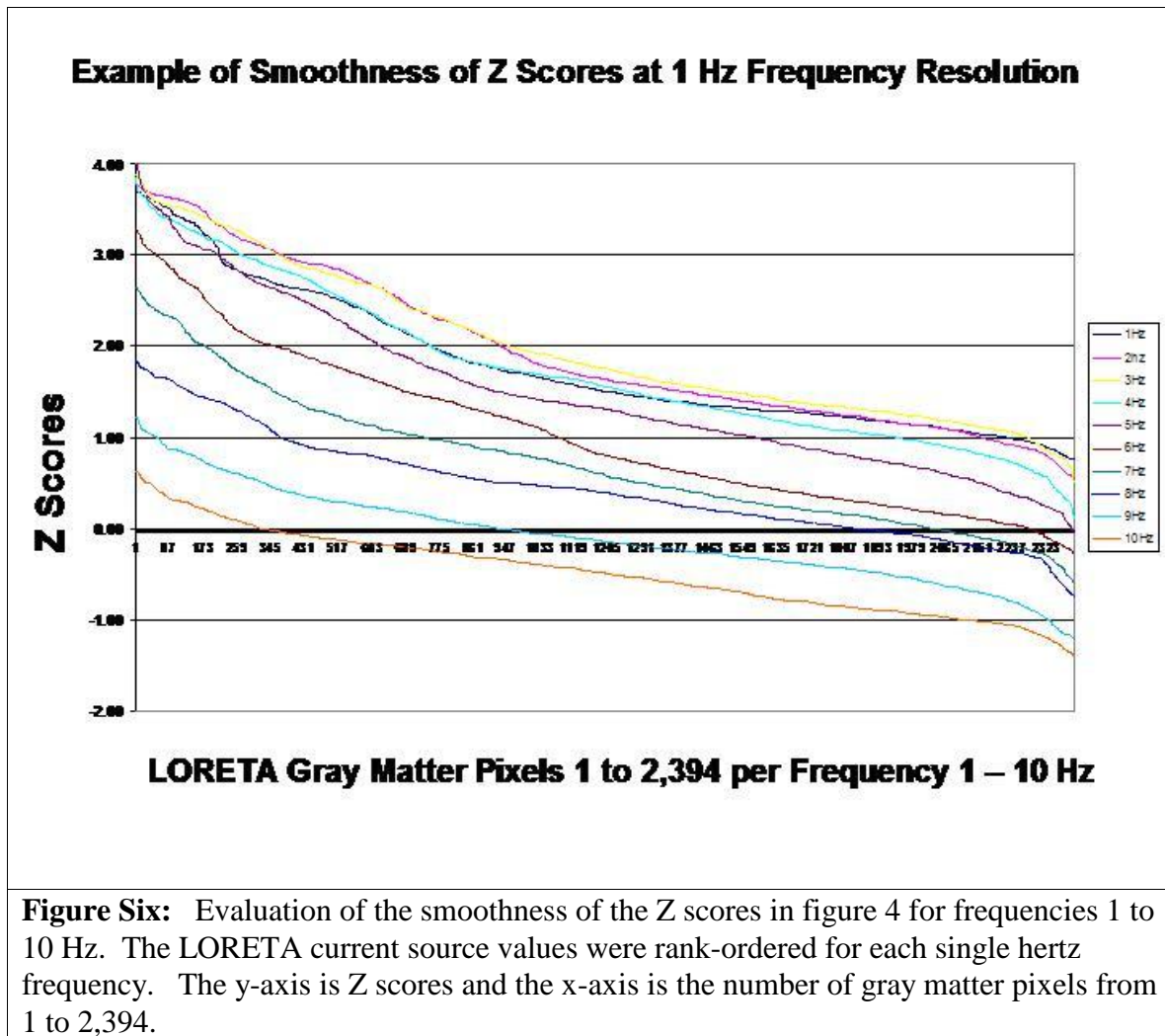


Figure Six: Evaluation of the smoothness of the Z scores in figure 4 for frequencies 1 to 10 Hz. The LORETA current source values were rank-ordered for each single hertz frequency. The y-axis is Z scores and the x-axis is the number of gray matter pixels from 1 to 2,394.

4.0 - Discussion

The results of this study are consistent with Z scores studies by Valdez et al (4), Machado et al (5) and Thatcher et al (6) which show that distributed inverse solutions such as LORETA and VARETA are well-behaved and adequately approximate a Gaussian or normal distribution. The degree of sensitivity observed at 1 Hz frequency resolution is similar to that observed for wider frequency bands in a previous study (6). The sensitivity which ranged from 95.60% to 95.75% was essentially the same as observed for measures of gaussianity of the surface EEG (8). The Box-Cox transform was slightly better than \log_{10} when the appropriate lambda coefficient is selected. The advantage of the \log_{10} transform is that it is a uniform and constant transform whereas the Box-Cox transform differs with each selected lambda value. The validity in terms of

localization accuracy is adequate to the extent that the three patients with confirmed pathologies all exhibited maximal Z score deviation that corresponded to the areas where the pathologies were known to exist. Furthermore, hypotheses about LORETA can be formed before computing LORETA based upon the surface EEG. This is important because planned comparisons preclude or make unnecessary multiple comparison adjustments of the alpha level (14).

Advantages of a Z score LORETA normative database are ease of use and simplicity as well as statistical accuracy. For example, Type I and Type II errors that arise when attempting to adjust for multiple comparisons can be avoided by using planned comparisons based on the frequency and topography of the surface EEG. That is, hypotheses can be formed prior to computing LORETA by examining the location and frequency of the surface EEG and the Z score deviations of the surface EEG. Once a specific frequency band and scalp surface location of maximal Z scores is ascertained, then a set of specific hypotheses can be formed as to which Brodmann areas are expected to have the greatest deviation from normal or the largest Z scores before computing LORETA. The hypotheses can then be subjected to an objective planned comparison analysis and thus, arbitrary statistical adjustments such as Bonferroni or Scheffé methods which result in large Type II errors can be avoided. This is important because verification of LORETA is always important and the use of blind multiple comparison statistics not only inflates Type II errors but also interferes with verification of the localization accuracy of LORETA.

In summary, the results of this study support the conclusion that Z score statistical analyses using a LORETA distributed source solution provides adequate sensitivity and validity even at the frequency resolution of 1 Hz. The use of Z scores for purposes of clinical evaluation of surface EEG distributions is well established (8, 14 - 16). The present findings, when combined with those of Valdez et al. (4), Machado et al. (5) and Thatcher et al. (6) show that a significant level of sensitivity and validity is present in 3-D source space analysis of LORETA when using adequate (> 95%) approximations to Gaussian.

5.0 – References

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