Euclidean distance and Kolmogorov-Smirnov analyses of multi-day auditory event-related potentials: a longitudinal stability study

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Abstract. The validity of ERPs as indices of stable neurophysiological traits is partially dependent on their stability over time. Previous studies on ERP stability, however, have reported diverse stability estimates despite using the same component scoring methods. This present study explores a novel approach in investigating the longitudinal stability of average ERPs—that is, by treating the ERP waveform as a time series and then applying Euclidean Distance and Kolmogorov-Smirnov analyses to evaluate the similarity or dissimilarity between the ERP time series of different sessions or run pairs. Nonlinear dynamical analysis show that in the absence of a change in medical condition, the average ERPs of healthy human adults are highly longitudinally stable—as evaluated by both the Euclidean distance and the Kolmogorov-Smirnov test.

1. Introduction
Among numerous adaptive dynamical systems known to humanity, many consider the human brain as the most complex due to its sophisticated neural networks[1] comprising over 100 billion interacting nerve cells or neurons that process and transmit information through electrical signals[2]. Tracking this electrical activity is important in studying brain function, in medical diagnosis, and in monitoring the effectiveness of therapies used to treat neurological or psychiatric disorders[3]. To date, recording event-related potentials (ERPs) from the human scalp is still the best non-invasive and inexpensive method[4] for tracking the rapid changes in the brain’s electrical activity in preparation for, or in response to sensory, affective, or cognitive stimuli[3,5].

Since the first published ERP experiment in 1964, ERPs have remained a useful diagnostic tool in both neuroscience and psychiatry. But if ERPs are to be legitimately used in clinical trials and in clinical diagnosis or screening, it is imperative to first establish that they exhibit good measurement properties, especially test-retest stability[6–8]. Sufficient knowledge regarding ERP stability helps

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evaluate how much of the variance embodied in a given ERP waveform is indicative of the task-
pertinent brain mechanisms that the ERP must encapsulate[8].

1.1. Previous studies on ERP stability
Over the last two decades, however, published ERP stability studies have reported quite diverse
results. Table 1 provides a summary of some earlier findings on the test-retest stability of major
auditory ERP components commonly encountered in psychophysiology and neuroscience research. As
depicted, stabilities vary from as low as .07 to as high as .80 despite using the same component
scoring methods (e.g. peak latency, base-to-peak amplitude) and the same stability measures—
specifically, the Pearson product moment test-retest correlation coefficient, r to index inter-subject
stability, and the intraclass test-retest correlation coefficient, ICC to index score agreement.

| Peak | Study | No. of subjects | Latency | Amplitude |
|------|-------|-----------------|---------|-----------|
|      |       |                 | r       | ICC       | r       | ICC       |
| N1   | [9]   | 19              | 0.48    | 0.27      | 0.09    | 0.09      |
| N1   | [10]  | 10              |         | 0.53      |         | 0.47      |
| N1   | [11]  | 46              | 0.40    | 0.40      | 0.75; 0.75 |
| N1   | [12]  | 29; 30          | 0.35; 0.42 | 0.63; 0.50 |         |           |
| P2   | [9]   | 19              | 0.51    | 0.50      | 0.23    | 0.23      |
| P2   | [11]  | 46              | 0.45; 0.15 |         | 0.80; 0.75 |
| P2   | [12]  | 29; 30          | -0.07; 0.07 |         | 0.63; 0.52 |
| P3   | [9]   | 19              | 0.74    | 0.71      | 0.62    | 0.61      |
| P3   | [10]  | 10              | 0.12 - 0.46 | 0.47     | 0.54 - 0.68 | 0.54    |
| P3   | [11]  | 46              | -0.07; 0.45 |         | 0.75; 0.80 |
| P3   | [12]  | 29; 30          | 0.54; 0.14 | 0.58; 0.66 |         |           |

To some extent, this considerable variation in stability estimates may have been caused by
methodological differences between studies in: (i) the technique or algorithm used to detect, extract,
and quantify specific ERP components[13,14]; (ii) the choice of electrode channels to analyze[14,15];
and (iii) the number of subjects that constitute the averaged results[7]. Given these conflicting
estimates, there is apparently a lack of evidence in current ERP literature to verify whether or not ERP
waveforms exhibit substantial consistency over time.

1.2. Rationale, objective, and research question
This present study explores a novel approach in investigating the test-retest stability of average
ERPs—that is, by treating the ERP waveform as a time series and then applying two nonlinear
dynamical measures, namely, Euclidean Distance (ED) and Kolmogorov-Smirnov Test (KST) to
evaluate the similarity or dissimilarity between the ERP time series of different sessions. Since the
entire ERP waveform will be subjected to analysis, this time series approach overcomes the inherent
difficulty in isolating individual ERP components and in quantifying their respective feature.

ED and KST are established proximity metrics that have been successfully used in numerous
diverse fields of science and engineering research, including the nonlinear analysis of multi-channel
EEG recordings [16]. Nevertheless, despite ERPs being derived from EEG data, there is no published
study as yet that employs any of these two nonlinear metrics to investigate the behavior of ERPs. In
this present study, ED and KST are used to quantify the degree of longitudinal stability of multi-day
auditory ERPs derived from multi-channel scalp EEG recordings of healthy human adults by
comparing pairs of trials across five different experiment sessions. The predominant question
encompassing all aspects of this study is: In the absence of a change in medical condition, will the
average ERPs of healthy human adults be longitudinally stable—as evaluated by a specific measure—or will they exhibit a high degree of day-to-day variability?

2. Methods
The ERP data used in this study are from the laboratory of Prof. Paul Rapp of the Department of Military and Emergency Medicine, Uniformed Services University of the Health Sciences, Bethesda, Maryland. Four male adults participated in five different experiment sessions separated by days. All participants were in good health, as determined from their medical records at the university clinics. More specifically, they had no history of neurological or psychiatric disorders or of drug abuse, had normal hearing, and were not under any medication during the entire course of the experiment.

2.1. ERP stimuli
ERPs were evaluated using two auditory stimulus categories, both presented binaurally to the subjects via headphones, as the subjects were comfortably seated in a dimly lit, electrically and acoustically shielded room. In both categories, the time series began 250 milliseconds prior to stimulus presentation. In the first category (also referred to as Task 1), a single click is delivered at $t = 0$ milliseconds—that is, after 250 baseline samples have been collected. In the second category (also referred to as Task 2), a click is delivered at $t = 0$ milliseconds and then followed by another click at $t = 500$ milliseconds. The inter-stimulus interval in both stimulus categories varied randomly between three and five seconds.

Figure 1. Scalp locations (marked red) of the five electrode channels used in the experiment. In the International 10-20 system, electrode pairs are typically placed in 19 standard positions distributed over the head, with letters to indicate position (F = frontal, C = central, P = parietal) and numbers to identify hemisphere location (odd #s = left, even #s = right).

Figure 2. ERP waveforms of subject 1 (for task 1, electrode site Fz). The $x$-axis is in milliseconds while the $y$-axis is in microvolts. Each of the plots for runs 1 (a), 2 (b), 3 (c), 4 (d), and 5 (e) consists of seven trials. Thus, the superimposed plots of runs 1 to 5 in (f) comprise a total of 35 trials.

2.2. EEG acquisition
EEG signals were simultaneously recorded and analyzed from multiple scalp electrodes—specifically, from three mid-sagittal electrode channels (Fz, Cz, Pz) and two mid-lateral electrode channels (C3, C4). These five electrode channels whose scalp locations are shown in figure 1 were consistently employed across all trials per session and across all five sessions. Aside from these five electrodes measured in reference to linked earlobes, other electrodes were also used to monitor the vertical and horizontal electro-oculogram (EOG). All electrode impedances were kept below 5 kΩ.
The signals were sampled every millisecond and subsequently digitized using a 12-bit digitizer. For each trial, the baseline was derived from the average of the first 250 samples. A single trial was rejected if it violated any of these two cases: (1) the amplitude of the horizontal and vertical EOG was 100 µV greater or less than the baseline; or (2) the amplitude of any of the five EEG channels was 50 µV greater or less than the baseline. The first 80 single trials that satisfy the above requirements were then combined to produce an average signal. Each experiment session consisted of seven average signals, denoted as trials 1,2,....,7, thereby totaling 35 trials for all five sessions (see figure 2).

2.3. Pairwise analysis of ERP waveforms
This study employs two nonlinear measures of similarity, namely EDand KST to detect how closely or distantly related the ERP waveforms of the five different experiment sessions are to each other, despite the apparent complexity in their shapes and behavior. This similarity characterization is accomplished for each subject, task, and electrode channel through rigorous, comprehensive pairwise analysis involving a total of 10 different test-retest pairs derived from all possible combinations of the five experiment sessions. Furthermore, for each test-retest pair, e.g. Run 1 vs. Run 2, each of the seven trials of Run 1 will be paired to all seven trials of Run 2. Therefore, for every test-retest pair associated with a particular task, electrode channel, and subject, there are a total of 49 trial pairs to be analyzed using EDand KST.

Table 2 and table 3 list the 10 test-retest pairs and the 49 trial pairs, respectively, along with their corresponding indices. These indices will be used to refer to any particular test-retest pair or trial pair throughout the rest of this paper. More importantly, results of the analysis will be plotted using these indices as x-coordinates and the ED and KST values as y-coordinates.

**Table 2. Test-retest pairs.**

| N  | Test-retest pair       |
|----|------------------------|
| 1  | Run 1 vs. Run 2        |
| 2  | Run 1 vs. Run 3        |
| 3  | Run 1 vs. Run 4        |
| 4  | Run 1 vs. Run 5        |
| 5  | Run 2 vs. Run 3        |
| 6  | Run 2 vs. Run 4        |
| 7  | Run 2 vs. Run 5        |
| 8  | Run 3 vs. Run 4        |
| 9  | Run 3 vs. Run 5        |
| 10 | Run 4 vs. Run 5        |

**Table 3. Indexed trial pairs for every test-retest pair.**

| m   | Trial pair            |
|-----|-----------------------|
| 1, 2, ..., 7 | Trial 1 vs. Trial x, where x = 1, 2, ..., 7 |
| 8, 7, ..., 14 | Trial 2 vs. Trial x, where x = 1, 2, ..., 7 |
| 15, 16, ..., 21 | Trial 3 vs. Trial x, where x = 1, 2, ..., 7 |
| 22, 23, ..., 28 | Trial 4 vs. Trial x, where x = 1, 2, ..., 7 |
| 29, 30, ..., 35 | Trial 5 vs. Trial x, where x = 1, 2, ..., 7 |
| 36, 37, ..., 42 | Trial 6 vs. Trial x, where x = 1, 2, ..., 7 |
| 43, 44, ..., 49 | Trial 7 vs. Trial x, where x = 1, 2, ..., 7 |

2.4. Euclidean distance
Given two time series, \( X = \{x_1, x_2, ..., x_n\} \) and \( Y = \{y_1, y_2, ..., y_n\} \), the Euclidean distance, \( d_E \) (also referred to as Pythagorean distance) between \( X \) and \( Y \) is given by:

\[
d_E = \sqrt{(x_1 - y_1)^2 + (x_2 - y_2)^2 + \cdots + (x_n - y_n)^2} = \left( \sum_{i=1}^{n} (x_i - y_i)^2 \right)^{1/2}.
\] (1)

This simple measure, which reflects the proximity in space of two time series [17] is one of the most commonly used similarity criteria aimed at assessing how close or how distant the time patterns of two series are [18]. In this study, ERPs are normalized to zero mean and unit variance before calculating EDs in order to minimize the effects of differences in amplification and of amplifier drift.
2.5. Kolmogorov-Smirnov test
The Kolmogorov-Smirnov test is a well-known non-parametric test used to distinguish between distributions [19]. More specifically, it is used to ascertain whether two distributions disagree (two-sample KST), or whether a probability distribution disagrees from a reference distribution (one-sample KST). This test is applicable to continuous, unbinned, one-dimensional data and is sensitive to changes in both location and shape of the empirical cumulative distribution function of two data sets or time series [20, 21]. Particularly, the KST Scilab implementation [22, 23] used in this study outputs the probability that the two ERP waveforms being compared come from the same distribution, i.e., the probability that corresponding time series of the ERPs are statistically similar.

2.6. Schreiber-Schmitz surrogates
The method of surrogate data is normally employed in nonlinear time series analysis to establish scale and context for the measured topological properties of the experimental time series [24]. First introduced by Theiler et al. in 1992, this method has developed into a valuable tool in establishing whether or not the structures and irregularities exhibited by a particular time series are indeed indicative of nonlinear dynamics. If not, then the time series may be considered basically stochastic, whose structures can be due to random inputs to the system or fluctuations in some parameters. In this case, the time series may not be worth analyzing further [25]. There are currently several methods of calculating surrogate data sets. This study uses the Schreiber-Schmitz iterative surrogate which preserves both the power spectrum and the distribution of the original data set or time series [22, 26].

3. Results and discussion
3.1. Euclidean distance analysis
Preliminary ED analysis of the ERP data of subjects 1 to 4 reveals that for any particular subject, task, and electrode site/channel, the average EDs of the 10 test-retest pairs are consistently and significantly lower than the mean EDs of 1000 pairs of Schreiber-Schmitz surrogates derived from 10 sets of randomly chosen trial pairs. This indicates that the ERPs of the five different experiment sessions are more similar to each other than their corresponding surrogates are.

![Figure 3. ED values (left column) and average ED values (right column) of subject 1, task 1, electrode channels Fz ((a), (b)), Cz ((c), (d)), Pz ((e), (f)), C3 ((g), (h)), and C4 ((i), (j)).](image-url)
The $x$-axis of the ED plots correspond to the indexed trial pairs in Table 3, while the $x$-axis of the average ED plots correspond to the indexed test-retest pairs in Table 2. The solid black lines in the upper portion of the ED plots correspond to the EDs of 49 pairs of Schreiber-Schmitz (S-S) surrogates of 10 sets of randomly-chosen trial pairs. For the average ED plots, the solid red lines are the mean EDs of 100 pairs of S-S surrogates of 10 sets of randomly-chosen trial pairs. The dashed black lines are the maximum and the minimum values of the S-S surrogate EDs.

Figure 3 displays the resulting graphs of the ED analysis for subject 1, task 1. The same analysis was performed for task 2 of subject 1, and also for tasks 1 and 2 of subjects 2 to 4. Due to limited space, however, only the graphs for subject 1, task 1 are shown. As evident in the ED plots (left column of figure 3), the Euclidean distances between trials of the same experiment run or session (denoted by a single-colored line) are approximately the same, suggesting good within-session consistency and reliability. On the other hand, the Euclidean distances of different runs show some considerable spread, as manifested in the average ED plots (right column of figure 3). Nevertheless, this spread is almost always less than that of the surrogate EDs—that is, in terms of both the computed
range and standard deviation (stdev) of the ED values for both data and surrogates. This behavior is better exemplified in tables 3 and 4, which depict the data EDs and surrogate EDs corresponding to the graph in figure 3(b) of subject 1, task 1, electrode channel Fz.

### Table 3. Average data EDs for subject 1, task 1, electrode channel Fz.

| n  | Mean |
|----|------|
| 1  | 9.34 |
| 2  | 10.75|
| 3  | 11.69|
| 4  | 10.53|
| 5  | 9.06 |
| 6  | 10.91|
| 7  | 11.41|
| 8  | 10.30|
| 9  | 11.81|
| 10 | 12.08|

The range and the standard deviation of the data EDs of the 10 test-retest pairs in table 3 are 3.02 and 1.02, respectively. These values are significantly lower than the computed average range (10.49) and average standard deviation (3.02) of the total 1000 pairs of Schreiber-Schmitz surrogates involved in the analysis. A similar trend is consistently manifested in the results of the range and standard deviation comparison summarized in figures 4 and 5, in the form of bar graphs.

### Table 4. Surrogate ED statistics for subject 1, task 1, electrode channel Fz.

Surrogate analysis involves 10 random trial pairs (denoted by s), each of which consists of 100 pairs of Schreiber-Schmitz surrogates.

| s  | Mean | Max | Min | Range | Stdev |
|----|------|-----|-----|-------|------|
| 1  | 23.72| 27.96| 18.36| 9.61  | 2.13 |
| 2  | 23.86| 28.02| 15.72| 12.30 | 2.10 |
| 3  | 24.05| 27.56| 16.79| 10.77 | 2.08 |
| 4  | 23.94| 29.01| 15.82| 13.20 | 2.81 |
| 5  | 23.73| 27.23| 19.10| 8.14  | 1.94 |
| 6  | 23.85| 28.71| 17.83| 10.89 | 2.15 |
| 7  | 23.85| 27.61| 19.54| 8.07  | 2.01 |
| 8  | 23.82| 28.15| 17.47| 10.68 | 2.40 |
| 9  | 24.15| 29.88| 19.38| 10.50 | 2.25 |
| 10 | 24.06| 28.13| 17.34| 10.79 | 2.14 |

It is evident from figures 4 and 5 that the variation in the EDs between successive experimental runs separated by days is almost always less than that between surrogates, $S_1(i)$ and $S_2(j), i, j = 1, 2, \ldots, 1000$ for which all the $S_1(i)$ have identical distributions and spectra and all the $S_2(j)$ have identical distributions and spectra, distinct from those of the $S_1(i)$. More specifically, 97.5% of the range of the data EDs are less than the range of the surrogate EDs, while 87.5% of the standard deviation of the data EDs are less than that of the surrogate EDs. These results suggest that, using Euclidean distance as a criterion, the auditory ERPs of subjects 1 to 4 are longitudinally stable.
Figure 5. Standard deviation comparison of the data and surrogate EDs of subjects 1 (a), 2 (b), 3 (c), and 4 (d). For each graph, the y-axis is the standard deviation of the EDs, while the x-axis has identical labels as in figure 4.

Figure 6. Summary of the Z-scores between the range of the data EDs and the range of the surrogate EDs of subjects 1 (a), 2 (b), 3 (c), and 4 (d). The associated confidence intervals (red bars) are shown directly below the Z-scores: subject 1 (e), 2 (f), 3 (g), and 4 (h). The labels along the x-axis are similar to that in figure 4.

Figure 7. Summary of the Z-scores between the standard deviation of the data and the surrogate EDs of subjects 1 (a), 2 (b), 3 (c), and 4 (d). The associated confidence intervals (blue bars) are shown directly below the Z-scores: subject 1 (e), 2 (f), 3 (g), and 4 (h). The labels along the x-axis are similar to that in figure 4.
Another interesting result of the ED analysis concerns the $Z$-score calculations comparing the range and the standard deviation of the data and surrogate EDs. Figure 6 and 7 provide summaries of the $Z$-scores between the ranges and the standard deviations of the data EDs and the surrogate EDs, as determined by the following equations:

\[
Z_{\text{range}} = \frac{\text{range of } ED_{\text{data}} - \langle \text{range of } ED_{\text{surr}} \rangle}{\text{stdev of the range of } ED_{\text{surr}}}. \tag{2}
\]

\[
Z_{\text{stdev}} = \frac{\text{stdev of } ED_{\text{data}} - \langle \text{stdev of } ED_{\text{surr}} \rangle}{\text{stdev of the stdev of } ED_{\text{surr}}}. \tag{3}
\]

In a more descriptive manner, physicists refer to the $Z$-score as the number of sigmas that the original data differs from the surrogates [22]. That is, with the assumption that the ranges and the standard deviations of $ED_{\text{surr}}$ are normally distributed, a $Z$-score of 2 or greater signifies a probability of better than 97% that the original data and the surrogates do not belong to the same class. Inspection of figures 6 and 7 reveals that majority of both the $Z_{\text{range}}$ and the $Z_{\text{stdev}}$ are indeed greater than 2, thereby suggesting that successive measurements of ERPs contain more significant dynamical connections than that expected of random data.

### 3.2. Kolmogorov-Smirnov analysis

Results of the Kolmogorov-Smirnov analysis support the findings of the Euclidean distance analysis discussed previously, i.e., that the individual-subject ERP waveforms are longitudinally stable across all five experiment sessions. More specifically, only 2.75% of the combined total run pairs (of all four subjects, five electrode channels, and two tasks) have KS values that significantly deviate from 1. In other words, 97.25% of all run pairs are statistically similar to each other, indicating stability of auditory ERPs over time. Figure 8 displays the KST results of all the 11 test-retest pairs (out of the total 400 run pairs) that exhibit significant deviation from 1. On the contrary, only the KS results for subject 1, task 1, electrode channel Fz are shown in figure 9 as representative of all the other 389 test-retest pairs with KS values of 1 or approximately equal to 1.
4. Conclusion
Nonlinear dynamical analysis of multi-day, multichannel auditory event-related potentials show that in the absence of a change in medical condition, the average ERPs of healthy human adults are longitudinally stable—as evaluated by both the Euclidean distance and the Kolmogorov-Smirnov test. Given their excellent within-session reliability and test-retest stability, ERPs can therefore be legitimately used in clinical trials, diagnosis or screening and essentially, as biomarkers or as indices of stable neurophysiological traits.

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