Published in final edited form as:
Mov Disord. 2011 September ; 26(11): 2073–2080. doi:10.1002/mds.23808.

Validation of Digital Spiral Analysis as Outcome Parameter for Clinical Trials in Essential Tremor

Dietrich Haubenberger, MD[1,2,*], **Daniel Kalowitz**[3], **Fatta B. Nahab, MD**[4], **Camilo Toro, MD**[5], **Dominic Ippolito**[6], **David A. Luckenbaugh, MA**[7], **Loretta Wittevrongel, MA**[1], and **Mark Hallett, MD**[1]

[1]Human Motor Control Section, Medical Neurology Branch, NINDS/NIH, Bethesda, Maryland, USA

[2]Department of Neurology, Medical University of Vienna, Austria

[3]Albert Einstein College of Medicine, Bronx, New York, USA

[4]Department of Neurology, University of Miami Miller School of Medicine, Miami, Florida, USA

[5]Undiagnosed Diseases Program, Office of the Clinical Director, NHGRI/NIH, Bethesda, Maryland, USA

[6]Duke University, Durham, North Carolina, USA

[7]National Institutes of Mental Health (NIH), Bethesda, Maryland, USA

Abstract

Essential tremor, one of the most prevalent movement disorders, is characterized by kinetic and postural tremor affecting activities of daily living. Spiral drawing is commonly used to visually rate tremor intensity, as part of the routine clinical assessment of tremor and as a tool in clinical trials. We present a strategy to quantify tremor severity from spirals drawn on a digitizing tablet. We validate our method against a well-established visual spiral rating method and compare both methods on their capacity to capture a therapeutic effect, as defined by the change in clinical essential tremor rating scale after an ethanol challenge. Fifty-four Archimedes spirals were drawn using a digitizing tablet by nine ethanol-responsive patients with essential tremor before and at five consecutive time points after the administration of ethanol in a standardized treatment intervention. Quantitative spiral tremor severity was estimated from the velocity tremor peak amplitude after numerical derivation and Fourier transformation of pen-tip positions. In randomly ordered sets, spirals were scored by seven trained raters, using Bain and Findley's 0 to 10 rating scale. Computerized scores correlated with visual ratings ($P < 0.0001$). The correlation was significant at each time point before and after ethanol ($P < 0.005$). Quantitative ratings provided

[*]**Correspondence to:** Dr. Dietrich Haubenberger, Human Motor Control Section, Medical Neurology Branch, National Institutes of Neurological Disorders and Stroke, National Institutes of Health, 10 Center Drive MSC 1428, Building 10, Room 7D37, Bethesda, MD 20892, USA; haubenbergerd@ninds.nih.gov.

Additional Supporting Information may be found in the online version of this article.

Relevant conflicts of interest/financial disclosures: Nothing to report. Dr. Toro is the developer and intellectual owner of Neuroglyphics, a freely available software, with no financial interests involved.
Full financial disclosures and author roles may be found in the online version of this article.

better sensitivity than visual rating to capture the effects of an ethanol challenge ($P < 0.05$). Using a standardized treatment approach, we were able to demonstrate that spirography time-series analysis is a valid, reliable method to document tremor intensity and a more sensitive measure for small effects than currently available visual spiral rating methods.

Keywords

essential tremor; spirography; spiral analysis; digitizing tablet; ethanol

With a prevalence of up to 5%, essential tremor (ET) is one of the most common movement disorders in adulthood.[1–3] Characteristic features include postural and kinetic tremor, affecting the hands in the majority of patients.[4] Data suggest that up to 75% of ET patients experience impairment in their activities of daily living, such as eating, drinking, and handwriting.[5]

ET therapy is, therefore, geared toward reduction of tremor symptoms to reach an improvement in these functional domains. Current treatment recommendations also suggest future research on development and standardization of outcome measures assessing tremor and to determine the magnitude of treatment effect.[6] In fact, it has been suggested that tremor-amplitude changes measured by tremor accelerometry, typically collected during an isometric posture position, often do not reflect task-related kinetic tremor intensities, such as tremor during writing, which have more impact on patients' perception in their daily life and the disability caused by tremor. Although the objective nature of quantifying postural tremor reflects the main advantage of accelerometry, ratings of Archimedes spirals help to document kinetic tremor during a task more reflective of activities of daily living. Drawing of spirals has been an integral part of the routine examination of tremor patients and was integrated into clinical rating scales.[7,8] Visual rating of spirals was proposed by Bain et al.[9] This scale has been widely used as a screening instrument and outcome measure in clinical trials of ET.[10–13]

Collecting spirals using a digitizing tablet offers the advantage not only to graphically store the image of a spiral, but also allows a time-series generation of data points for further quantification through numerical methods, such as spectral analysis of derived velocity or acceleration that describe features of tremor power (i.e., severity) and frequency.[14,15] Similar objective methods of spirographic tremor assessment have been validated in parkinsonian tremor[16] and have been used to document tremor in patients with Niemann-Pick disease type C and ET.[17,18] A semidigitized method of measuring tremor amplitudes from scanned spirals originally drawn on paper was suggested to correlate well with spiral ratings.[19]

To our knowledge, no study has formally investigated the validity of spirography time-series analysis to document tremor intensities in a prospective treatment design. Here, we present a digitizing-tablet–based method for quantifying ET spirals and report data on validity, reliability, and sensitivity to reflect tremor-intensity changes before and after a standardized treatment intervention.

Patients and Methods

Patients

Nine subjects (4 female, mean age, 66.4 ± 7.4), diagnosed with ET according to standard clinical criteria,[4] who participated in a clinical trial examining the bioavailability of 1-octanol, were included in the study (NCT00102596; approved by NINDS Combined Neurosciences Institutional Review Board). Mean tremor duration at time of examination was 27.2 ± 19.6 years. Tremor was the only allowed abnormality in the neurological examination, performed by a movement disorders specialist. All patients were right-handed and reported a beneficial effect of ethanol in reducing tremor intensity. Patients under pharmacotherapy were off antitremor medication for at least four plasma half-lives and were instructed to abstain from ethanol and/or caffeine for 48 hours prior to the experiment. Patients on primidone were excluded because of the long half-life of its metabolites. Other exclusion criteria were as follows: active or past alcohol abuse; women who were pregnant or lactating; age less than 21; and patients of East Asian or Native American descent who may possess variant alleles influencing alcohol metabolism, resulting in higher sensitivity to toxic effects of alcohol.

Treatment Intervention

As part of the screening visit for the clinical trial, an ethanol challenge was performed. After documenting the history, physical examination, and baseline tremor severity using the proposed methods and a clinical tremor rating scale, subjects received 2 oral servings of 50 mL of ethanol (40%, by volume), 30 minutes apart, which could be diluted at the subject's request. The aim was to document ethanol response on tremor amplitude over time, including the time of peak effect, which was expected to occur at approximately 40 to 60 minutes after administration.[20] The selection of time points after administration was based on the experience of our group gained from previous studies. [20,21] To cover the expected peak effect of ethanol and to have enough measures to capture interindividual variations in the time to peak effect, we chose time points 15 minutes apart up to 75 minutes after administration of the first serving.

Spiral Collection and Analysis

Fifty-four spirals, drawn with the right hand, were completed by the study subjects immediately before and at 15, 30, 45, 60, and 75 minutes after the first ethanol serving—one spiral per time point (n = 6) for each patient (n = 9). The spirals were drawn on paper (U.S. letter format), which contained a preprinted spiral in the clockwise direction with five loops and was centered on a digitizing tablet (Wacom Intuos 3 Model PTZ-930; Wacom Technology Corporation, Vancouver, WA), connected to a laptop. The spiral maximum radius was 7.5 cm, with an interloop distance of 1.5 cm. Patients were instructed to draw the spiral between the printed loops using a Wacom inking stylus, from the inside to the outside with the drawing arm unsupported. A previous study on spirography stated that spiral drawings between given loops showed good interrater reliability, compared with drawings over the lines and freehand drawings, as used in the original study by Bain et al.[22] We chose to have patients to draw between lines to ensure spatial consistency across spirals.

Spiral recordings were collected and analyzed using a MS Windows-based software package (*Neuroglyphics*, developed by Camilo Toro, MD; available at: http://www.neuroglyphics.org. Accessed June 22, 2011). As defined by the tablet firmware, the pen-tip position was sampled at a rate of 200 Hz with a spatial resolution of 2,000 values for 1 cm of displacement. The digitized spirals included air points, *x*, *y* coordinates of the pen-tip position within 6 mm of the tablet surface. The entire stream of position points during spiral execution was stored in binary format for off-line analysis.

As subjects had no time constraint to draw the spiral, individual spirals had different numbers of data points. To normalize the spiral for subsequent analysis and ensure comparability across spirals, we explored two different methods of data selection for subsequent spectral analysis to be tested for validity (Fig. 1). A first approach (i.e., fixed *space*) was defined as the selection of 3.75 spiral turns, regardless of the number of data points. As each raw spiral had slightly different actual start and end points, by selecting 3.75 turns, every selected spiral portion included a similar stretch of the original spiral path. The collection of points was window-tapered and zero-padded to the next power-of-two size.

In a second approach (i.e., fixed *time*), a fixed number of data points was acquired from each original spiral segment. In total, 2,048 data points, reflecting 10.24 seconds at a sampling rate of 200 Hz centered on the midpoint of the spiral time series, were selected for further analysis.

Selected data segments were numerically differentiated and pen-tip velocity spectra calculated, using a fast Fourier transformation (FFT). Spectral tremor peak frequency (i.e., Hz) was determined at baseline for each subject, using the velocity spectra. Amplitude measures for baseline and subsequent spirals were obtained at baseline tremor frequency, calculating the area under the curve of a window ±1 Hz around the spectral peak. Because method *space* and *time* differed in the number of data points, the values were normalized by the number of bins in the spectral ±1-Hz window.

Clinical Rating Scales

At baseline, subjects were rated using the Fahn-Tolosa-Marin (FTM) tremor rating scale.[7] Spirals were rated post hoc, according to a rating scale by Bain et al.[9] Seven independent raters, who were not involved in the study otherwise, where chosen for visual spiral rating. Four raters were board-certified neurologists and movement disorder specialists experienced in the collection of Archimedes spirals. Three additional raters were chosen among participants of the National Institutes of Health summer internship program, without professional experience in movement disorders. All raters underwent training using the examples of spirals for each grade, as given in the original booklet by Bain and Findley. We intentionally selected both professional and nonprofessional raters to investigate whether consistency of ratings might be influenced by previous experience interpreting Archimedes spirals.

Raters were presented with a random, blinded compilation of the 54 spirals, to ensure that raters could not associate a sequence of spirals to a given individual or the time with respect

to the intervention. Raters were asked to rate each spiral from 0 (*no tremor*) to 10 (*tremor too severe for spiral to be recognizable as such*), in increments of 1.

Data Analysis

Visual spiral ratings were compared across raters to investigate interrater reliability using the intraclass correlation coefficient, and a mean rating per spiral was calculated.

For evaluating validity, digital spiral scores, using the two methods, *space* and *time*, were compared to the mean visual spiral ratings. To calculate reliability, digital scores were compared to visual ratings at each time point before and after ethanol. Correlation analyses between methods were performed using Pearson's statistics.

Because the sensitivity of the digital spiral analysis at detecting tremor is unknown, we modeled increasing amplitudes of sinusoidal signal (5–7 Hz) and introduced them into spirals drawn by 10 healthy volunteers without pathological tremor to determine the minimal amplitude required for reliable detection (see Supporting Information online).

As for sensitivity to change after ethanol, computerized spiral scores and visual ratings were normalized to baseline. Before normalization, visual ratings were converted into an amplitude measure by applying the algorithm suggested by Elble et al (using $\alpha = 0.2436$; see below).[23] A repeated-measures two-factorial ANOVA design was calculated using the factors, time point (15, 30, 45, 60, and 75 minutes) and method (*space*, *time*, mean converted visual rating). Post-hoc comparisons were made using Student's *t* tests with Bonferroni correction for multiple comparisons. The level of significance was defined as $P = 0.05$, corrected.

For test-retest analysis to determine the reproducibility of each measure, two approaches were taken. First, because test-retest analysis of two spirals by the same subject contains natural variability of the biological signal, we calculated the test-retest ability of each method using the same given spirals, therefore eliminating any confounding underlying change of the spiral themselves. For the visual ratings (converted to amplitude measures as described above), we used the score of the seven blinded raters as a variability measure. For the two computerized methods, potential variability is primarily the result of operator-dependent factors, such as the placement of clip-marks of the time-series selection for analysis. We, therefore, modeled the potential human error underlying the computerized methods. For *space* and *time*, we computed seven iterations for each individual spiral, modeling up to a maximum jitter of one quarter loop for *space* and 0.375 seconds around the spiral midpoint for *time*. Coefficients of variations (SD/average × 100) were calculated for each method.

Second, using our ethanol administration paradigm, we calculated relative changes and effect sizes for each individual visual rater and each iteration per computerized method, based on the change of tremor between baseline and 15 minutes after administration.

Results

Visual ratings were highly correlated among raters. All individual ratings were within 2 rating points of the mean across all seven raters for each spiral. The intraclass correlation coefficient across the seven raters for the total set of 54 spirals was 0.930 (to single measures, absolute agreement, CI 95%; $P < 0.0001$) and showed equally high correlations when computed for each time point separately (ranging from 0.903 to 0.947; $P < 0.0001$).

All subjects completed the required task and generated a total of 54 gap-free time series containing *x*, *y* coordinates at a sampling rate of 200 Hz. Mean spirography scores using both algorithms correlated significantly with mean visual ratings (Pearson's *r* for method *time*: 0.866, $P = 2.81 \times 10^{-17}$; *space*: 0.870, $P = 1.37 \times 10^{-17}$). Correlations between each computerized method and visual ratings followed a logarithmic relationship (Fig. 2). As a consequence of our observation of a nonlinear relationship between spiral scores and visual ratings, we applied Fechner's law of psychophysics, which predicts a proportional relationship between perceived magnitude (e.g., clinical tremor rating scale; TRS) and the log of the measured tremor amplitude (*T*), and was demonstrated for comparisons between rating scales and objective measures of tremor amplitudes[23]:

$$\log T = \alpha \cdot \mathrm{TRS} + \beta$$

Using regression analysis, the slope of the fit line (α) was 0.1913 (*time*) and 0.2436 (*space*). For the constant, β, we computed 0.0401 (*time*) and −0.2379 (*space*). By applying this regression model to each method, over 90% of the variance of the actual data was explained.

To assess reliability, spiral scores at each time point during the ethanol challenge were analyzed by correlation with visual ratings. At each time point, correlation coefficients were between 0.852 and 0.922 ($P < 0.005$).

Each method demonstrated a significant reduction of tremor scores within 15 minutes ($P < 0.05$), with the maximum reduction at 45 minutes after administration, compared to baseline ($P < 0.01$; Fig. 3).

Mean clinical tremor score (FTM) at baseline was 39.56 ± 15.96. Comparison of computerized spiral scores with the FTM ratings at baseline revealed a significant correlation (*r*: *time*: 0.922, $P < 0.0005$; *space*: 0.829, $P < 0.05$; Fig. 4).

Modeled analysis of an artificially embedded tremor signal into spirals from control nontremor subjects revealed that the threshold for detecting a spectral peak in the frequency band of interest, using our analysis platform and strategy, was below the level of pen accuracy of the graphics tablet system (0.25 mm; see Supporting Information online).

Sensitivity to change analysis was performed by comparing the measured effect between computerized scores and mean visual ratings across the ethanol challenge. Repeated-measures ANOVA revealed a significant effect of factor time point ($P = 0.005$), whereas the factor method and interaction time point × method showed no significant effect.

Test-retest analysis for each spiral revealed that visual ratings, after being converted to amplitude measures as described above, showed a coefficient of variation of 35.9% ± 14.2% (Fig. 5A). The coefficient of variation for *time* was 1.0% ± 0.9% and for *space* was 1.0% ± 1.1%. Compared with the variation of the visual ratings, each computerized method showed a significantly lower variation across iteration (*t* test; $P < 0.0001$), whereas there was no difference between the *time* and *space* methods ($P = 0.9$).

The mean reduction of tremor from baseline to time point 15 minutes after administration was 51.9% ± 9.8% for visual ratings, 49.0% ± 0.2% for *time*, and 48.7% ± 0.8% for *space*. Effect sizes, using individual raters with the visual rating scale, showed a range of 0.71 to 2.87 (mean, 1.67 ± 0.75); for the iterations of *time*, the range of effect sizes was 1.40 to 1.42 (mean, 1.41 ± 0.01); and the range for *space* was 1.42 to 1.61 (mean, 1.50 ± 0.08; Fig. 5B).

Discussion

The development of an objective, reliable measure of ET severity provides benefits for both routine clinical assessment and as an outcome measure in ET clinical trials. Spirography is a commonly used task in clinical practice for documenting tremor. The use of digital spirography promises to provide an objective, user-independent method to quantify kinetic tremor severity. Spirography time-series analysis has not been validated previously in a prospective, interventional design, with the aim of assessing validity, reliability, and sensitivity to change, which is a key factor for calculating effect sizes to ensure adequately powered trials.

Our methodology is geared toward standardization and simplicity of spiral acquisition, using readily available equipment and an off-line analysis method to obtain our tremor metric. We examined two approaches of data analysis, spatial and temporal sample selection, and compared these outcomes to a visual rating scale. In comparing the results of seven raters, we found high interrater reliability along with significant correlations with both proposed spirography methods, regardless of their expertise, and attribute this to the training session all raters underwent before rating.

Correlations between digital scores and visual ratings, as well the total FTM score, was found to be logarithmic, following the Weber-Fechner law of psychophysics, which is in line with previous observations.[23]

When compared across time points throughout the ethanol challenge and, therefore, different tremor intensities, this significant correlation remains present at each time point with correlation coefficients of ≥0.8, demonstrating the reliability of both proposed digital methods.

All three methods (i.e., *time*, *space*, and visual ratings) showed significant improvement after ethanol, with a maximum effect 45 minutes after the first ethanol dose. Therefore, all three methods are suitable to document ethanol-induced changes. The sensitivity of a scale is determined by its granularity (i.e., resolution) and its test-retest reproducibility. Although raters were highly correlated in our study, each individual visual rating showed certain variability around a calculated mean across raters. This inevitable variability was

disproportionately larger for visual ratings (35.9%), compared with the variability of the digital methods (1%). In other words, whereas visual ratings underlie a certain interrater variability, the computer-generated scores are highly consistent, with no significant influence of operator-dependent factors on the result.

At 15 minutes after ethanol administration, tremor intensities were reduced by roughly 50%. This change was documented with the computerized methods and average visual ratings. Although the digitized methods showed highly reproducible effect sizes of 1.4 (*time*) and 1.5 (*space*), the effect sizes of the individual visual raters varied significantly. If a sample size calculation is conducted for a clinical trial using spiral analysis as an outcome measure, a consistent effect size is necessary to avoid an underpowered study because of variability of the measure. When using a single visual rater, our data suggest that up to 28 patients would be required to document a 50% reduction in tremor amplitude, whereas 9 patients would be sufficient using a computerized method (power, 95%; alpha, 0.05).

We also showed that the digital spiral platform is highly sensitive for detecting very low levels of tremor (<1 mm displacement), which is limited by the accuracy of the pen of the graphics-tablet hardware. On the opposite end of the severity spectrum, any digital spirography is limited to subjects who are able to hold a pen and produce a digital time series by keeping the pen on the tablet or within the range of detection capabilities of the system.

The high variability of effect sizes across raters might be overcome by using a large number of raters, resulting in the interrater variabilities averaging out. However, the reproducibility of both proposed digital methods suggest that the immediately available computer-generated spiral score might give a similar answer, making it a potential application not only in an outpatient clinical setting or during clinical trials, but also as a bedside test or during field studies, such as those of ET pedigrees.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding agencies: This research was conducted through funding from the NINDS Intramural Research Program, the Austrian Science Fund, FWF (Erwin Schrödinger Fellowship, project no.: J2783-B09; to D.W.), and Ariston Pharmaceuticals (to L.W.).

Visual spiral ratings were performed by Aviva Ellenstein, MD, Sarah Kranick, MD, Brian Berman, MD, Codrin Lungu, MD, Joshua Aizen, Jessica Walthall, and Jessica Zhang.

References

1. Benito-Leon J, Bermejo-Pareja F, Morales JM, Vega S, Molina JA. Prevalence of essential tremor in three elderly populations of central Spain. Mov Disord. 2003; 18:389–394. [PubMed: 12671944]
2. Dogu O, Sevim S, Camdeviren H, et al. Prevalence of essential tremor: door-to-door neurologic exams in Mersin Province, Turkey. Neurology. 2003; 61:1804–1806. [PubMed: 14694055]

3. Wenning G, Kiechl S, Seppi K, et al. Prevalence of movement disorders in men and women aged 50-89 years (Bruneck Study cohort): a population-based study. Lancet Neurol. 2005; 4:815–820. [PubMed: 16297839]
4. Deuschl G, Bain P, Brin M. Consensus statement of the Movement Disorder Society on Tremor. Ad Hoc Scientific Committee. Mov Disord. 1998; 13(Suppl 3):2–23. [PubMed: 9827589]
5. Louis ED, Barnes L, Albert SM, et al. Correlates of functional disability in essential tremor. Mov Disord. 2001; 16:914–920. [PubMed: 11746622]
6. Zesiewicz TA. Practice parameter: therapies for essential tremor: report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2005; 64:2008–2020. [PubMed: 15972843]
7. Fahn, S.; Tolosa, E.; Marin, C. Clinical Rating Scale for Tremor. In: Jankovic, J.; Tolosa, E., editors. Parkinson's Disease and Movement Disorders. Munich, Germany: Urban und Schwarzenberg; 1988. p. 271-280.
8. Elble R. The Essential Tremor Rating Assessment Scale (TETRAS). Tremor Research Group (TRG). 2008
9. Bain PG, Findley LJ, Atchison P, et al. Assessing tremor severity. J Neurol Neurosurg Psychiatry. 1993; 56:868–873. [PubMed: 8350102]
10. Lorenz D. No benefit of 3,4-diaminopyridine in essential tremor: a placebo-controlled crossover study. Neurology. 2006; 66:1753–1755. [PubMed: 16769957]
11. Lorenz D, Papengut F, Frederiksen H, et al. Evaluation of a screening instrument for essential tremor. Mov Disord. 2008; 23:1006–1012. [PubMed: 18381648]
12. Ondo W, Hunter C, Vuong KD, Schwartz K, Jankovic J. Gabapentin for essential tremor: a multiple-dose, double-blind, placebo-controlled trial. Mov Disord. 2000; 15:678–682. [PubMed: 10928578]
13. Shill HA, Bushara KO, Mari Z, Reich M, Hallett M. Open-label dose-escalation study of oral 1-octanol in patients with essential tremor. Neurology. 2004; 62:2320–2322. [PubMed: 15210907]
14. Elble RJ, Sinha R, Higgins C. Quantification of tremor with a digitizing tablet. J Neurosci Meth. 1990; 32:193–198.
15. Pullman SL. Spiral analysis: a new technique for measuring tremor with a digitizing tablet. Mov Disord. 1998; 13(Suppl 3):85–89. [PubMed: 9827601]
16. Saunders-Pullman R, Derby C, Stanley K, et al. Validity of spiral analysis in early Parkinson's disease. Mov Disord. 2008; 23:531–537. [PubMed: 18074362]
17. Elble RJ, Lyons KE, Pahwa R. Levetiracetam is not effective for essential tremor. Clin Neuropharmacol. 2007; 30:350–356. [PubMed: 18090460]
18. Hsu A, Piboolnurak P, Floyd A, et al. Spiral analysis in Niemann- Pick disease type C. Mov Disord. 2009; 24:1984–1990. [PubMed: 19672994]
19. Kraus PH, Hoffmann A. Spiralometry: computerized assessment of tremor amplitude on the basis of spiral drawing. Mov Disord. 2010; 25:2164–2170. [PubMed: 20572156]
20. Zeuner KE, Molloy FM, Shoge RO, Goldstein SR, Wesley R, Hallett M. Effect of ethanol on the central oscillator in essential tremor. Mov Disord. 2003; 18:1280–1285. [PubMed: 14639668]
21. Bushara KO, Goldstein SR, Grimes GJ, Burstein AH, Hallett M. Pilot trial of 1-octanol in essential tremor. Neurology. 2004; 62:122–124. [PubMed: 14718713]
22. Ondo W, Wang A, Thomas M, Vuong K. Evaluating factors that can influence spirography ratings in patients with essential tremor. Parkinsonism Relat Disord. 2005; 11:45–48. [PubMed: 15619462]
23. Elble RJ, Pullman SL, Matsumoto JY, et al. Tremor amplitude is logarithmically related to 4- and 5-point tremor rating scales. Brain. 2006; 129:2660–2666. [PubMed: 16891320]

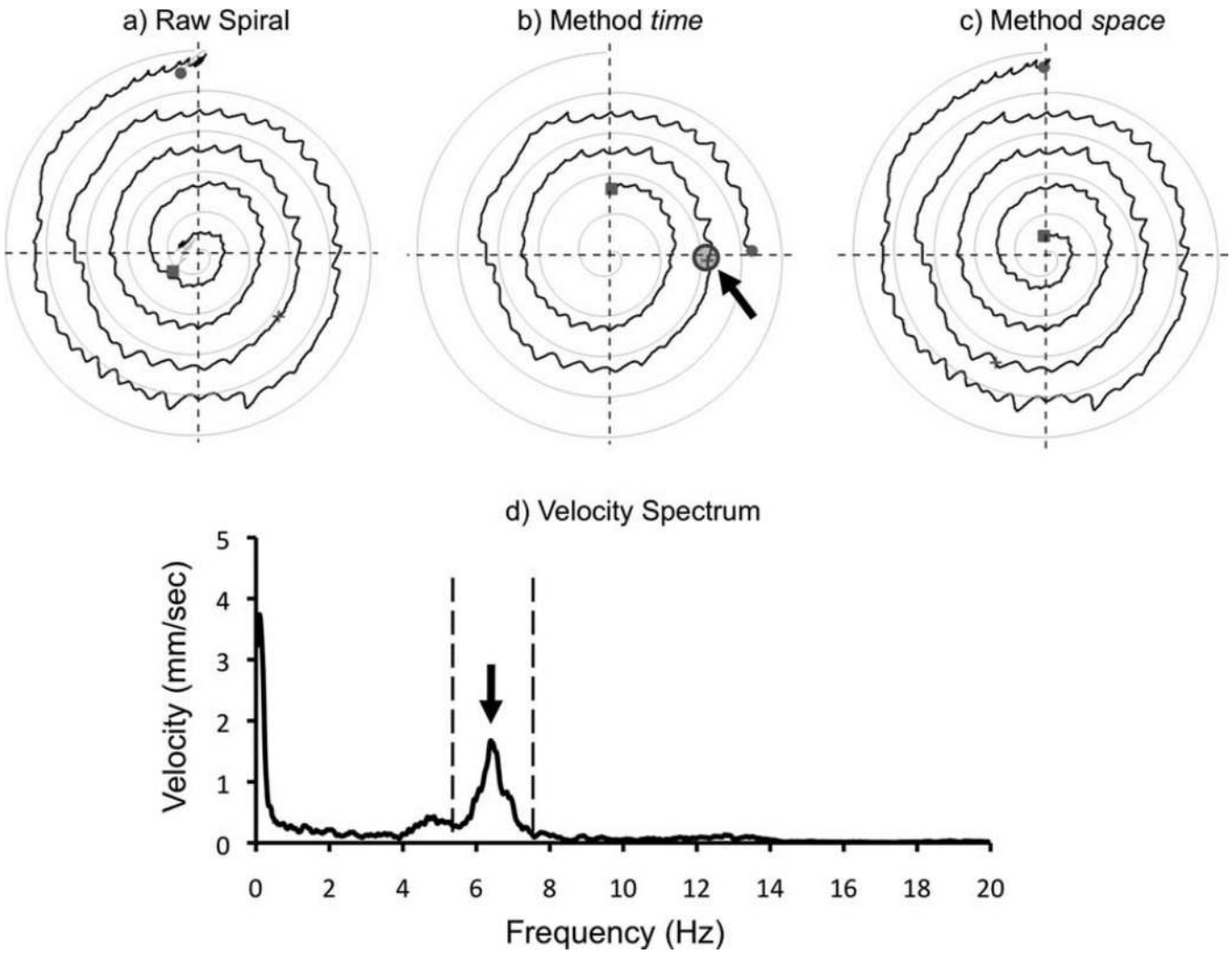

FIG. 1.

Data selection: a) raw spiral as collected, b) method *time*, and c) method *space*. After numerical differentiation of pen-tip velocity, FFT-derived spectra (d) permits the identification of the tremor peak (arrow). Spiral scores reflect the area-under-the-curve bounded by a 2-Hz window (dashed lines) centered at the tremor peak.

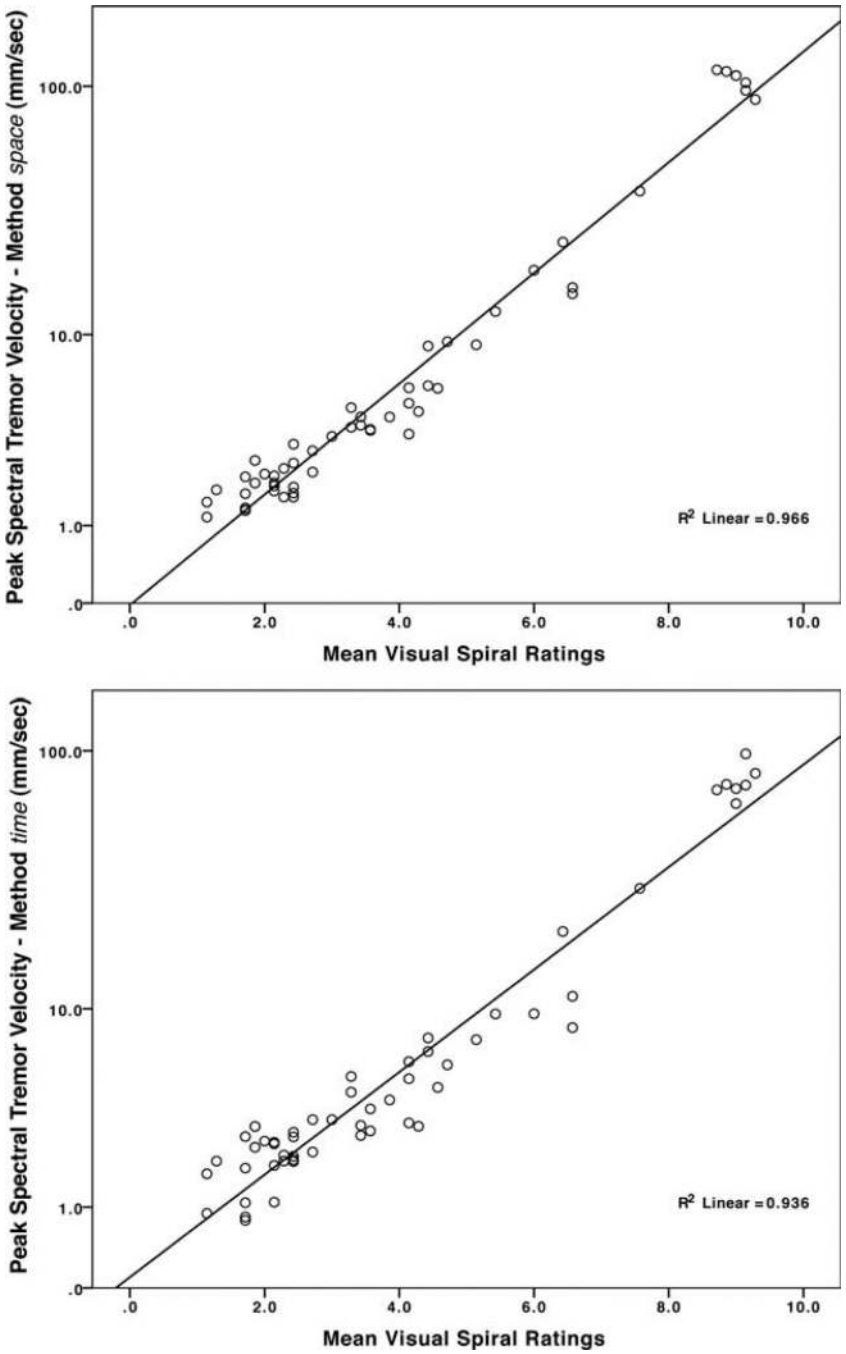

FIG. 2.

Correlation between computerized spiral scores generated with method *space* or *time* and mean visual spiral ratings (scale 0 to 10, higher scores indicate more severe spiral tremor). Correlations are highly significant (each $P < 0.0001$). Note the logarithmic scale of the y-axis.

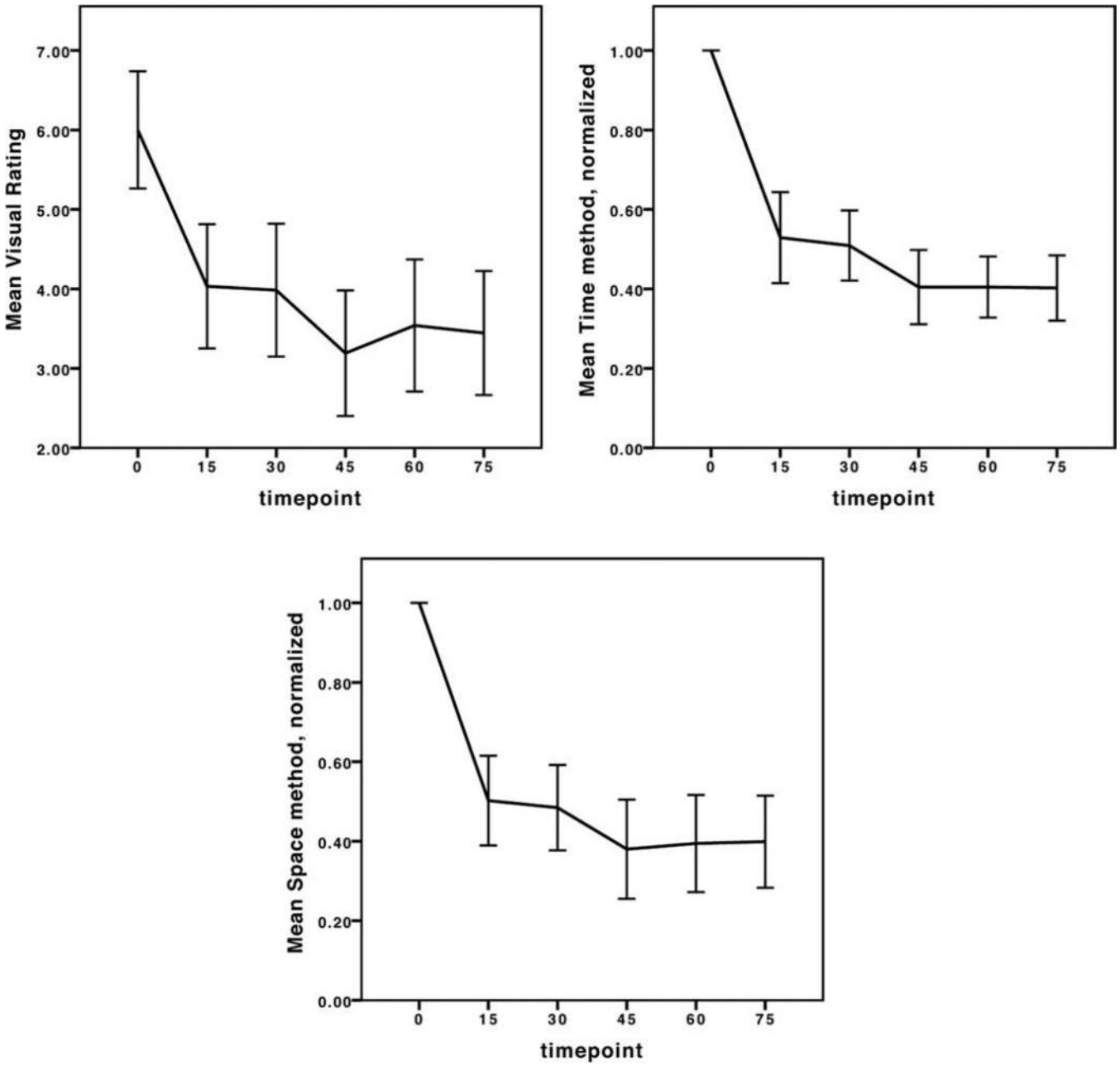

FIG. 3.

Tremor scores and ratings for each method over time after ethanol administration at time point 0 (mean±1SE). Computerized scores were normalized to baseline, and visual ratings are given in the scale by Bain and Findley.

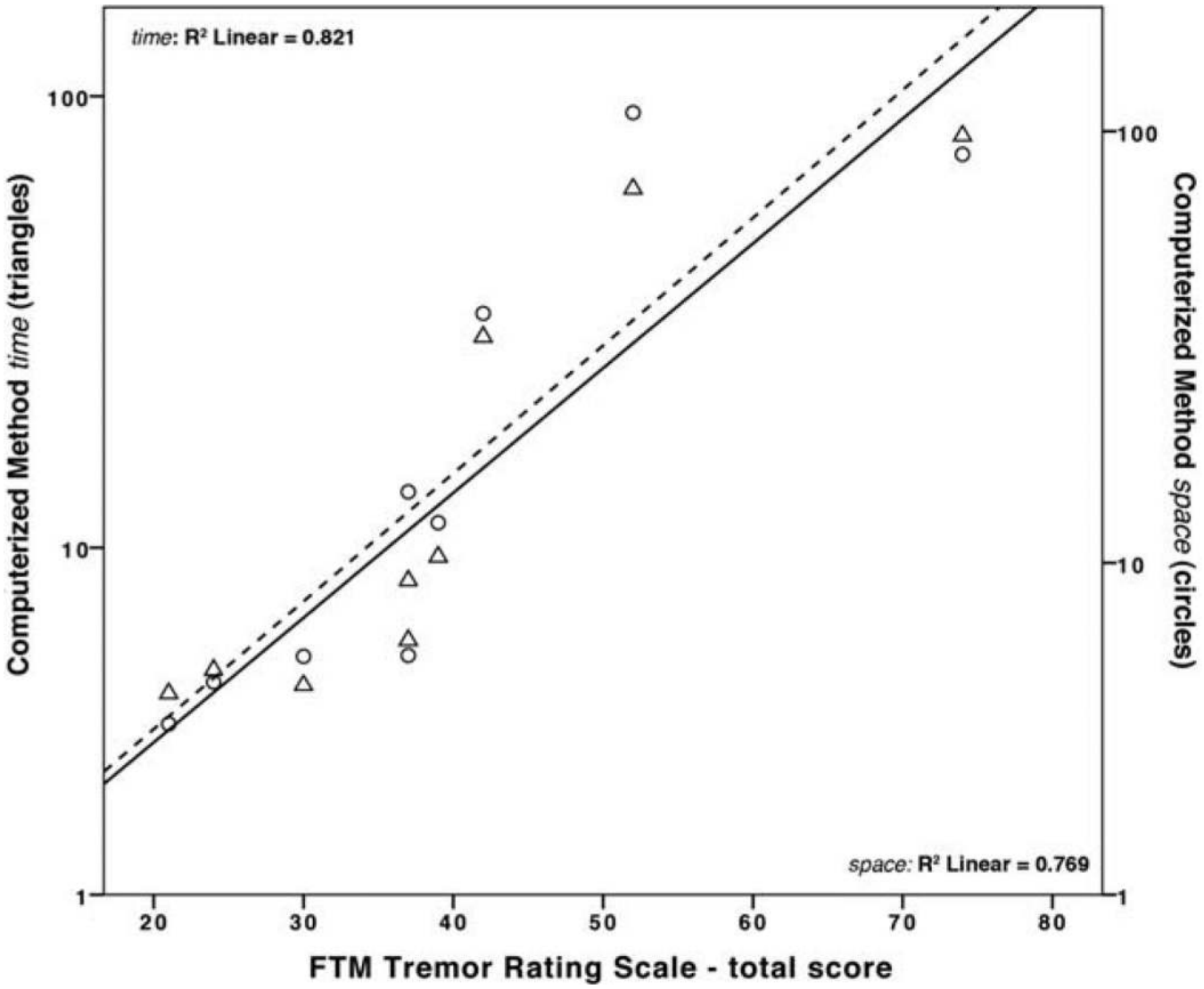

FIG. 4.

Significant logarithmic correlation between spiral methods *time* (triangles) and *space* (circles) with the total score of the Fahn-Tolosa-Marin Tremor Rating Scale at baseline (note the log-scale of the y-axes). Regression lines are shown (*time*: continuous; *space*: dashed line).

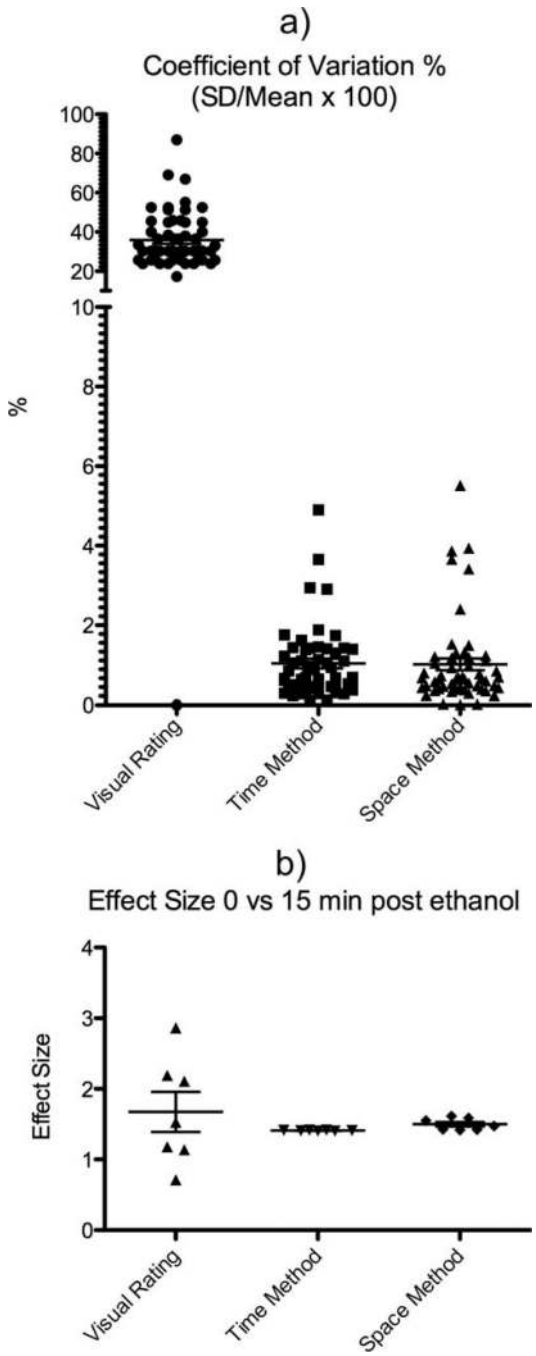

FIG. 5.

a) Coefficient of variation between methods. Each dot represents one coefficient of variation of one spiral. b) Effect size (baseline to 15 minutes post ethanol) distribution across 7 individual raters and computerized iterations for each method. In both plots, horizontal lines represent mean±1SE.