Quantitative Methods for Evaluating the Efficacy of Thalamic Deep Brain Stimulation in Patients with Essential Tremor

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Abstract

Background: Deep brain stimulation (DBS) of the thalamus is a safe and efficient method for treatment of disabling tremor in patient with essential tremor (ET). However, successful tremor suppression after surgery requires careful selection of stimulus parameters. Our aim was to examine the possible use of certain quantitative methods for evaluating the efficacy of thalamic DBS in ET patients in clinical practice, and to compare these methods with traditional clinical tests.

Methods: We examined 22 patients using the Essential Tremor Rating Scale (ETRS) and quantitative assessment of tremor with the stimulator both activated and deactivated. We used an accelerometer (CATSYS tremor Pen) for quantitative measurement of postural tremor, and an eurythmokinesimeter (EKM) to evaluate kinetic tremor in a rapid pointing task.

Results: The efficacy of DBS on tremor suppression was prominent irrespective of the method used. The agreement between clinical rating of postural tremor and tremor intensity as measured by the CATSYS tremor pen was relatively high ($r_s = 0.74$). The agreement between kinetic tremor as assessed by the ETRS and the main outcome variable from the EKM test was low ($r_s = 0.34$). The lack of agreement indicates that the EKM test is not comparable with the clinical test.

Discussion: Quantitative methods, such as the CATSYS tremor pen, could be a useful complement to clinical tremor assessment in evaluating the efficacy of DBS in clinical practice. Future studies should evaluate the precision of these methods and long-term impact on tremor suppression, activities of daily living (ADL) function and quality of life.

Keywords: Quantitative methods, tremor assessment, essential tremor, thalamic deep brain stimulation


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Introduction

Essential tremor (ET) is the most common tremor disease. The prevalence of ET varies from 0.4% to 3.9% in population-based studies and increases with age, as does its incidence.1 In typical cases, the upper limbs are affected by postural and/or kinetic tremor.2 ET is progressive in nature, and with longer disease duration the tremor amplitude increases and other body parts may be affected, most often the head.1 Patients with more severe ET may show an intentional tremor component in voluntary movements, as well as other motor signs such as difficulty with tandem gait, indicating involvement of the cerebellum.3 The treatment primarily entails pharmacotherapy with propranolol or primidone.3 However, pharmacotherapy is successful in only about 50% of ET patients.2 For those patients who do not respond to or tolerate medication, neurosurgery might be an alternative.

Continuous deep brain stimulation (DBS) of the nucleus ventralis intermedius (Vim) of the thalamus is the preferred surgical approach for ET patients with disabling medication-resistant tremor.2,3 DBS has been shown to be effective in reducing hand tremor by 50–91% in several studies with follow-up times varying from 1 to 7 years.4 However, some patients in whom DBS is initially effective could have stimulation failure over time. Data from long-term studies revealed worsening of tremor among 13–40% of ET patients treated with DBS at follow-ups beyond the first year.5 It is not clear why long-term
stimulation efficacy of DBS fails in some ET patients, but possible reasons include suboptimal lead position in combination with disease progression or tolerance. Selection of optimal stimulus parameters is necessary for successful tremor suppression with a minimum of side effects, and may prolong battery life. Evaluations must assess both the postural and the kinetic components of tremor. Even if some general guiding principles can be given, the selection of stimulus parameters is usually performed ad hoc, often a difficult and time-consuming process. In clinical practice, the effects of different combinations of stimulation parameters on tremor suppression are evaluated using common clinical tests.

Tremor rating scales are commonly used for assessment of tremor severity in ET. In this manner, the examiner evaluates rest, postural, and kinetic tremor in the hands and other body parts according to a 4- or 5-point grading scale. The motor tasks used are similar to the clinical tests performed in a standard neurological examination. Most rating scales have quite good reproducibility, but the sensitivity is usually insufficient to detect small changes in tremor amplitude. However, there are several quantitative methods, including accelerometry, electromyography, and digitizer tablets, which can be used to measure tremor in ET patients.

Our aim was to find quantitative methods that can be used in daily clinical practice for tremor evaluation in ET patients treated with DBS. The CATSYS Tremor Pen is a portable, computerized system containing a lightweight microaccelerometer for measuring postural tremor. The equipment is commercially available and simple to use. It has been standardized, and normative data are available. The tremor recordings are visualized in real time on the computer screen, and the measures calculated by the system’s software are shown immediately. Tremor recording using the CATSYS system during DBS surgery for ET has been described in a case report. The eurythmokinesimeter (EKM) is supposed to be similar to the finger–nose test. Kinetic tremor is the most disabling for the ET patient, and the EKM system is a new method that gives the opportunity to investigate different characteristics of this tremor component, for example speed, precision, and multiple contacts with the target, and evaluate how these are affected by DBS treatment. The device is simple to use, as is the CATSYS system.

The aim of this study was to investigate the possible use of these methods in evaluating the efficacy of DBS on hand tremor in patients with ET, and to compare them with traditional qualitative methods, such as clinical rating scales.

### Methods

#### Study participants

The study participants were recruited among patients who had undergone DBS surgery for ET at Sahlgrenska University Hospital, Sweden, in the past 10 years. Before surgery, these patients had been evaluated and diagnosed with ET by a neurologist with experience in movement disorders.

In all, 22 patients (11 males and 11 females) aged from 33 to 78 years were included in the study. Of these, 16 patients (73%) had a family history of tremor. All patients had unilateral implants in the ventrolateral thalamus, contralateral to the dominant hand, and had been treated with DBS for at least 6 months. The mean duration of treatment with DBS was 5.9 years. One patient had undergone DBS surgery twice: 14 and 5 years before the present study, respectively. Twenty participants were right-handed, and two (one male and one female) were left-handed. Eight patients (36%) had current treatment with propranolol. All participants gave written informed consent. The study was approved by the Ethics Committee of the University of Gothenburg. The background characteristics of the 22 patients are summarized in Table 1.

#### Evaluation procedures and tests

The patients were asked to have their stimulator activated, to bring appropriate visual correction, and not to use tobacco during the hour prior to testing. They were evaluated in two conditions: with the

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, in years, mean (range)</td>
<td>64 (33–78)</td>
</tr>
<tr>
<td>Sex, no. of females/males</td>
<td>11F/11M</td>
</tr>
<tr>
<td>Right-handedness, % (n)</td>
<td>91 (20)</td>
</tr>
<tr>
<td>Heredity for tremor, % (n)</td>
<td>73 (16)</td>
</tr>
<tr>
<td>Smokers, % (n)</td>
<td>18 (4)</td>
</tr>
<tr>
<td>All tobacco use, % (n)</td>
<td>45 (10)</td>
</tr>
<tr>
<td>Alcohol consumption in g/week, median (range)</td>
<td>21 (0–100)</td>
</tr>
<tr>
<td>Use of β-blockers, % (n)</td>
<td>36 (8)</td>
</tr>
<tr>
<td>Duration of treatment with deep brain stimulation in years, mean (range)</td>
<td>5.9 (2–14)</td>
</tr>
</tbody>
</table>
stimulator activated (“on”) and with it deactivated (“off”). The order of the two conditions was randomized, with 50% of the patients beginning evaluations with the stimulator “on” and the other 50% with the stimulator “off.” Only one examiner (G.W.), who switched the stimulator, knew whether the stimulator was activated or deactivated. After switching the stimulator, there was a 5-minute pause before the evaluations began.

The clinical tremor assessment using the Essential Tremor Rating Scale (ETRS) (see below) was conducted by a neurologist specialized in movement disorders (B.J.), assisted by a specially trained nurse. The neurologist, nurse, and patient were all blinded to the current stimulation condition. The clinical evaluation was followed by quantitative tests of tremor and of the ability to perform rapid pointing movements. These tests, which were performed by one of the authors (G.W.), were always administered in the same order, for both conditions and all patients. Finally, when all evaluations were finished, the stimulator was switched to the “on” condition.

The ETRS was used for clinical assessment of tremor. The assessor evaluated the severity of tremor (rest, postural, and kinetic), as well as the patient’s performance in line and spiral drawing.

Postural tremor in the forearms was assessed using the CATSYS Tremor Pen®. The patient was asked to sit in a chair, with the elbow bent at an angle of 90°, the forearm in front of the abdomen, and free from body contact or any obstacles. The light stylus was held in the same way as an ordinary pen, horizontally and approximately 10 cm in front of the navel, parallel to the abdomen. Tremor was recorded successively in each hand over 16.4 s; the patient was asked to look at the tip of the stylus and breathe normally during recording. The stylus (12 × 0.8 cm) contains a biaxial microaccelerometer, sensitive when perpendicular to the central axis of the stylus and individually calibrated with a calibration file.

Fourier transformation was used to determine the power distribution across a frequency band varying from 0.9 Hz to 15 Hz. We used four measures calculated by the CATSYS software: Tremor intensity (m/s²) is the root mean square of accelerations recorded in the 0.9–15 Hz band. Center frequency (Hz) is the mean frequency of the accelerations in the 0.9–15 Hz band. Frequency dispersion (Hz) is the standard deviation of the center frequency, and indicates the degree of irregularity of the tremor (a regular tremor has a small frequency dispersion). Harmonic index compares the tremor frequency pattern with the pattern of a single harmonic oscillation, which has a value of 1.0. Tremors with homogeneous patterns, such as ET, have values close to 1.0.

The EKM measures rapid and precise proximo-distal movements in a pointing task. The apparatus is composed of one distal and one proximal target, each divided into three electrically isolated concentric areas, and a pointer. The areas are labeled A, B, C, and D from center to outer square. The centers of the target were kept at a fixed distance of 25 cm. The patient was asked to sit down in front of the apparatus and hold the pointer like a pen, and alternately touch the center of each target, as precisely and quickly as possible, beginning with the proximal target. Each recording period lasted 30 s and was repeated twice, with both hands alternating, and with a 15-s pause between each recording.

The recordings were transformed to nine calculated measures used to characterize the performance: 1) Speed: the number of events on target divided by the sum of the times taken to reach the target before each event (in events per second). 2) Precision: the proportion of events involving a strike on target A. 3) Imprecision: the proportion of events involving a strike on target B, C, or D. 4) Unsureness: the average number of contacts per event. Smaller scores indicate lower disposition to sideslip across target areas or multiple contacts in one target area. 5) Tremor: the number of contacts, less the number of target areas contacted (averaged over events). The number of extra contacts after the initial contact when there are multiple contacts on a target area. 6) Transit duration: the average duration of transportation of the hand from one target to another. 7) Contact duration: the average total duration of contacts on the target. 8) Fitts’ Law constant: The constant, k, is calculated as the average over events of $k = t / \log(2A/W)$, where $t$ is the transit time to the target, $A$ is the distance between the two target centers (=25 cm) and $W$ is the approximate distance between the location of the contact(s) and the target center. This constant k should be a measure of inherent ability, independent of the subject’s choice in the speed/accuracy tradeoff. The lower the k value, the better the performance. 9) Irregularity: the standard deviation of intervals between events. Events from both targets and trials were used together to calculate a single standard deviation. Smaller scores indicate more regular performance. For the statistical analyses, four values (two trials and two targets) were obtained for each characteristic and averaged to a mean for each hand.

### Data analyses

The efficacy of DBS was evaluated by comparing the “on” and “off” condition using the Wilcoxon signed rank test for all data from the ETRS, CATSYS tremor pen, and EKM assessments. The associations between measures of performance were calculated using Spearman’s rank correlation coefficient ($r_s$). The reliability of single EKM measures was analyzed using the coefficient of variation (CV) and the intraclass correlation coefficients (ICCs). p-Values of <0.05 (for two-tailed tests) were considered statistically significant. Version 9.1 of the SAS statistical software package was used for the statistical analyses. Since the variability of the tests used was unknown in ET patients, a priori sample size calculations could not be performed.

### Results

#### Clinical evaluation with ETRS

Only a few patients had rest tremor (score >0): five patients displayed this type of tremor in the “off” condition and only one patient in the “on” condition. In the clinical evaluation of postural tremor, 14 patients improved when the stimulator was activated, three patients showed no change between conditions, and three patients had no detectable postural tremor (score =0) in either condition (Figure 1A). Two patients had a higher tremor score in the “on” condition than in the “off” condition. In the finger–nose test for clinical evaluation of kinetic tremor, most patients (n=16) had less tremor in the “on” condition, whereas the remaining six patients were unchanged (Figure 1B).
Improvement in spiral drawing and line drawing was seen in 18 patients when the stimulator was activated. Significantly lower scores for postural and kinetic tremors were found in the “on” condition than in the “off” condition using the Wilcoxon signed rank test (Table 2). The effect of DBS was most pronounced regarding kinetic tremor (finger–nose test), and spiral and line drawing.

**CATSYS tremor pen**

Tremor intensity was significantly lower when the stimulator was activated (Table 3). The tremor registrations from one of the ET patients are shown in Figure 2. The median ratio of tremor intensity in the “on” vs. “off” condition (n=22) was 0.11 (Wilcoxon signed ranked test, p<0.0001). Nearly all (20/22) patients showed improvement (lower intensity) when the stimulator was activated; the remaining two patients showed higher tremor intensity (Figure 3A). The frequency dispersion was significantly higher and the harmonic index was significantly lower in the “on” condition. However, no significant change was seen in center frequency between conditions (Table 3).

**Eurythmokinesimetry**

We compared the performance in the EKM test between the “off” and “on” conditions. Three patients were unable to touch any target in the “off” condition owing to severe tremor. We replaced the missing values for these patients with the value for worst performance in the other 19 patients. Significant changes in the expected direction (better performance in the “on” condition) were found for most outcome variables (Table 3). The median on/off ratio of the Fitts' Law constant,

![Figure 1](image-url)

**Figure 1.** A. Postural tremor, dominant hand. B. Kinetic tremor, dominant hand. Clinical tremor score (0–4) evaluated by the Essential Tremor Rating Scale in 22 patients with essential tremor, treated with deep brain stimulation. Stimulator in the “off” and “on” conditions.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>OFF (n=22)</th>
<th>ON (n=22)</th>
<th>Median difference</th>
<th>p-Value¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest tremor</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0.13</td>
</tr>
<tr>
<td>Postural tremor</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>0.002</td>
</tr>
<tr>
<td>Kinetic tremor</td>
<td>2</td>
<td>1</td>
<td>4</td>
<td>1.5</td>
</tr>
<tr>
<td>Spiral drawing</td>
<td>4</td>
<td>1</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Line drawing</td>
<td>3</td>
<td>1</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>

¹Wilcoxon signed rank test.

Table 2. Results (scores 0–4) from Assessment of Clinical Tremor in the Dominant Hand Using the Essential Tremor Rating Scale.
Table 3. Results from Measurement of Postural Tremor with the CATSYS System, and Rapid Pointing Movements Using a Eurythmokinesimeter, in the Dominant Hand

| Characteristic                          | Off (n=22) | On (n=22) | Median ratio on/off | p-Value
|-----------------------------------------|------------|-----------|--------------------|---------
| **The CATSYS system**                  |            |           |                    |         |
| ↓ Tremor intensity (m/s²)               | 2.95       | 0.09      | 25.4               | 0.255   | 0.10 | 18.9 | 0.11 (0.01–1.22) | <0.0001 |
| ↑ Center frequency (Hz)                 | 4.50       | 3.40      | 6.90               | 4.45    | 3.10 | 7.2  | 0.98 (0.81–1.62) | 0.76   |
| ↑ Frequency dispersion (Hz)             | 0.20       | 0.10      | 3.0                | 1.15    | 0.10 | 3.60 | 3.75 (0.20–20.0) | 0.006  |
| ↓ Harmonic index                        | 0.99       | 0.91      | 0.99               | 0.96    | 0.87 | 0.99 | 0.98 (0.90–1.01) | 0.0004 |
| **The eurythmokinesimeter**            |            |           |                    |         |
| ↑ Speed (mm/s)                          | 0.871      | <0.281    | 1.52               | 0.918   | 0.539 | 1.68 | 1.17 (0.75–3.05) | 0.01   |
| ↑ Precision                             | 0.0758     | 0.0       | 0.540              | 0.115   | 0.0   | 0.660 | 1.22 (0–2.66) | 0.03   |
| ↓ Imprecision                           | 0.970      | 0.527     | 1.0                | 0.908   | 0.368 | 1.0  | 0.93 (0.70–1.07) | 0.001  |
| ↓ Unsureness                            | 1.35       | 1.0       | >2.22              | 1.19    | 1.02 | 2.55 | 0.91 (0.54–1.27) | 0.08   |
| ↓ Transit duration                      | 0.367      | 0.0875    | >0.857             | 0.278   | 0.0480 | 1.07 | 0.69 (0.11–2.44) | 0.17   |
| ↓ Contact duration                      | 1.05       | 0.581     | >3.80              | 0.991   | 0.538 | 1.61 | 0.82 (0.26–1.29) | 0.0002 |
| ↓ Contact duration                      | 0.0870     | 0.0308    | >0.222             | 0.147   | 0.0563 | 0.486 | 1.57 (0.34–4.11) | 0.0008 |
| ↓ Fitts’ Law constant                   | 0.241      | 0.134     | >0.929             | 0.185   | 0.112 | 0.308 | 0.77 (0.27–1.30) | <.0001 |
| ↑ Irregularity                          | 0.232      | 0.0630    | >1.75              | 0.130   | 0.0460 | 0.454 | 0.63 (0.08–2.13) | <0.0001 |

The arrows indicate the expected direction of improvement.

1Wilcoxon signed rank test.
2Three patients were unable to touch any target in the “off” condition. The missing values are replaced with the value for worst performance in the other 19 patients.
which is an overall measurement of a patient’s performance in the EKM test, was 0.77 (Wilcoxon signed ranked test, \(p<0.0001\)). In total, 19 patients had lower values of the Fitts’ Law constant when the stimulator was activated (Figure 3B).

**Comparisons of clinical and quantitative tremor assessment**

**Postural tremor.** All patients who improved their performance in the postural tremor test as evaluated by the ETRS \((n=14)\) were included among those patients \((n=20)\) who had a decrease in tremor intensity as

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**Figure 2.** Tremor registrations from one of the essential tremor patients performed with a biaxial accelerometer (CATSYS tremor pen) in the dominant hand. Measurements in the “off” condition are shown to the left, and in the "on" condition are shown to the right.

**Figure 3.** A. The CATSYS tremor pen  B. The eurythmokinesimeter. Tremor intensity measured by the CATSYS tremor pen, and Fitts’ Law constant measured by a eurythmokinesimeter in the dominant hand, in 22 patients with essential tremor, treated with deep brain stimulation. Stimulator in the “off” and “on” conditions.
measured by the CATSYS system. The median on/off ratio in tremor intensity was 0.09 (0.007–0.49) in the 14 patients who improved in the clinical tremor assessment, and 0.86 (0.07–1.21) among six patients who showed no change between conditions in the clinical tremor score. In contrast, two patients who showed more tremor in the “on” condition as assessed with the ETRS showed lower tremor intensity (ratios 0.79 and 0.07) as measured by the CATSYS system.

Agreement between postural tremor as assessed by the ETRS and tremor intensity as measured by the CATSYS system was relatively high in the “off” condition (Spearman, rs = 0.74, p < 0.0001). However, the association was low and insignificant in the “on” condition (Spearman, rs = 0.18, p = 0.44). To evaluate which method best detects a “true” improvement in the “on” condition, we had to classify the patients in this respect. Either a lower score in clinical assessment of postural tremor in the “on” than in the “off” condition, or an unchanged clinical score but substantial improvement in the CATSYS test was considered a “true” improvement. A substantial improvement in the CATSYS test was defined as an on/off ratio of <0.5 in tremor intensity, or a change in tremor intensity between conditions from abnormal to normal, i.e. a value below the upper reference limit of the general population.10 Using these criteria, 15 of the 22 patients were classified as having a “true” improvement, while this could not be shown for seven patients. Fourteen of these 15 patients improved according to the clinical assessment. All 15 patients improved when the strict criteria for improvement in the CATSYS test mentioned above was applied.

**Kinetic tremor.** We compared the results from the finger–nose test with the Fitts’ Law constant. The median on/off ratio for the Fitts’ Law constant was 0.77 (0.27–1.30) in the 16 patients who improved in the clinical test of kinetic tremor, and 15 of these 16 improved in the Fitts’ Law constant. Six patients showed no change between conditions in the clinical assessment; among these, the median on/off ratio in the Fitts’ Law constant was 0.78 (0.27–1.11).

The association between kinetic tremor as assessed by the ETRS and the main outcome variable from the EKM test (Fitts’ Law constant) was low to moderate in the “off” condition (Spearman, rs = 0.34, p = 0.12), and was low in the “on” condition (Spearman, rs = 0.23, p = 0.31). Either a lower score in clinical assessment of kinetic tremor in the “on” than in the “off” condition and no substantial impairment in the Fitts’ Law constant, or an unchanged clinical score and an on/off median ratio of <0.75 for the Fitts’ Law constant as measured by the EKM system was considered a “true” improvement. Seventeen patients fulfilled these criteria, 15 of whom improved according to the clinical assessment of kinetic tremor. Using these criteria above for an improved Fitts’ Law constant resulted in “true” improvement in 17 patients.

**Discussion**

**Efficacy of DBS**

The effect of DBS on tremor suppression was prominent irrespective of the method used, and in agreement with earlier studies.4 The median score for kinetic tremor as evaluated by the ETRS was higher than the median score for postural tremor in the “off” condition, in accordance with findings in other studies.17 Kinetic tremor is most disabling for the ET patient, and is often accompanied by an intentional component in more advanced cases.2 Thalamic DBS affects postural as well as kinetic tremor, but the reduction is believed to be greater for postural tremor.10 However, according to the clinical rating, the effect of DBS was most pronounced on the kinetic tremor component in our patients.

Five patients (23%) had rest tremor in the “off” condition, which may be present in ET patients with severe disease and long disease duration.19 However, postural tremor with incomplete muscle relaxation may look like rest tremor.2 The five patients with rest tremor had visible postural tremor in the “off” condition, whereas all but one of them scored 0 for both rest and postural tremor in the “on” condition.

The typical postural tremor pattern in ET (high narrow peak, regular oscillations)20 was prominent in the “off” condition as measured by the CATSYS system, but changed toward a more “normal” pattern in the “on” condition. The effect of DBS on tremor intensity was pronounced, showing an improvement of 89% in the entire group. The tremor frequency in ET decreases over time and is inversely related to age,21,22 and so the relatively low tremor frequency we observed (median 4.5 Hz) was probably due to the high average age among our patients. Tremor frequency did not change when the stimulator was activated, which is in accordance with a previous study.10

We chose the EKM test because it is supposed to be similar to the clinical finger–nose test. As expected, our patients were faster and had greater precision in the EKM test when the stimulator was activated. Thus the Fitts’ Law constant, an overall measure of performance that is independent of the patients’ choice in the speed/accuracy trade-off, improved 23% between conditions. The patients had a more regular performance when the stimulator was activated, as reflected by a 37% improvement in irregularity. Recent studies have shown that difficulties in eye–hand coordination in ET are due not only to intention tremor in the target phase, but also to a defective regulation in the early phase of hand movement, probably as a result of cerebellar dysfunction.23 Moreover, impaired rhythm generation has been shown in ET patients.24,25

**Comparisons of ETRS and quantitative tests**

The association between clinical rating of postural tremor as assessed by the ETRS and tremor intensity as measured by the CATSYS system was relatively high (Spearman, rs = 0.74, p < 0.0001) in the “off” condition. There may be several reasons for the agreement between the methods not being perfect. First, tremor is known to change over time, and there was a short delay of about 5 minutes between the two examinations. Second, the examiner is evaluating displacement in the clinical tremor assessment, rather than acceleration, which is measured by the CATSYS system. Therefore, we estimated displacement of tremor amplitude by dividing the
acceleration by the squared tremor frequency (radians/s), and compared agreement with postural tremor assessed by the ETRS in the “off” (Spearman, \( r_s = 0.76 \), \( p < 0.0001 \)) and “on” (Spearman, \( r_s = 0.09 \), \( p = 0.70 \)) conditions. Thus, the association between amplitude of tremor as measured by the CATSYS system and clinical rating of tremor, seems to be similar irrespective of the use of displacement or acceleration data. Third, the CATSYS system gives a value averaged over a time period, while the clinician may take certain qualitative acceleration data. Third, the CATSYS system gives a value averaged over a time period, while the clinician may take certain qualitative aspects of tremor into account. Finally, different hand positions may exacerbate or decrease tremor.

The complete lack of association in the “on” condition (Spearman, \( r_s = 0.18 \), \( p = 0.44 \)) indicates that the clinical tremor scoring is not sufficiently discriminative at low tremor amplitudes. The poor correlation could also be due to the narrow range of ratings and high intraindividual variability in CATSYS tremor measures in ET patients. The logarithmic relationship between 5-point (0–4) rating scales and tremor amplitude\(^{26}\) has to be taken into account when clinical assessment is compared with quantitative measurements of tremor. However, the rank correlation (\( r_s \)) we used also adequately captures the association when the distribution of tremor amplitude is skewed.

We considered a >50% reduction in tremor intensity to be a clinically significant improvement. All patients who improved in clinical score between conditions (n=14) also had >50% reduction in tremor intensity; therefore, our choice of cut-off point seems reasonable. Even though we used somewhat conservative criteria, the CATSYS system identified all ET patients with a “true” improvement.

The association between kinetic tremor as assessed by the ETRS, and the Fitts’ Law constant was low to moderate in the “off” condition, \( r_s = 0.34 \), \( p = 0.12 \), which is in accordance with other studies.\(^{12}\) Possible explanations may be the time-delay between the tests (about 10 minutes), and that the clinical test (finger–nose test) and the EKM test are not entirely comparable. The finger–nose test is performed with the eyes closed, whereas the EKM test involves the visual pathways. The EKM test measures several aspects of the performance, such as speed, precision, tendency to sideslip, and regularity, in contrast to the clinical test which is focused on tremor severity and dysmetria. The Fitts’ Law constant, which is independent of the patients’ choice in the speed/accuracy trade-off, seems not to be in agreement with the criteria used in the clinical examination.

### Aspects of validity

All ET patients had been evaluated by a neurologist specialized in movement disorders before surgery, and the diagnosis had not been changed later. Patients with concurrent neurological diseases were not included. The patients were asked to continue their medication as usual. Eight patients were treated with propranolol, which may have reduced tremor amplitude among these patients. Smoking increases tremor amplitude in humans,\(^{27–29}\) and this increase has been reported to remain significant for at least half an hour after smoking has ceased.\(^{30}\) Hence, we asked the ET patients to avoid smoking or using other forms of tobacco within 1 hour before testing. In order to minimize bias in the assessments, the order of conditions was randomized, and the ETRS evaluators, as well as the patients, were blinded to whether the stimulator was activated or deactivated. Another reason for randomizing the order of conditions was to balance out any learning effect between the first and second evaluation sessions.

Tremor rating scales are used in clinical studies and in daily clinical practice. However, the method demands trained examiners, and there may be differences in evaluation between examiners when repeated examinations are performed, especially when assessing tremor in writing and drawing.\(^{13}\) Moreover, the method is quite crude and has a “floor and ceiling” effect: for example, a patient with no tremor and a patient with very slight tremor will both score 0, while a patient with severe tremor cannot score >4. The CATSYS tremor pen is supposed to be independent of the examiner and has been proven to have a high degree of reproducibility in previous studies.\(^{15,31}\) However, patients with ET were not included in these study populations, and test–retest variability varies with tremor severity.\(^{32}\) In the present study, postural tremor was recorded once in each hand; consequently, it is not possible to calculate test–retest reliability from our data. The lack of knowledge about test–retest reliability for the CATSYS system in ET patients may be a limitation for our study. An advantage is that all patients in the present study could perform the test, even those with severe postural tremor.

The test–retest reliability of the EKM (presented as correlation coefficients) has been shown to be above 0.8 for most outcome variables,\(^{12}\) and the intraindividual variability expressed as a CV ranges between 9% and 31% for all outcome variables except tremor and irregularity.\(^{16}\) We calculated the CV for each of the nine EKM measures using data from our study of ET patients. The test–retest reliability was acceptable for most EKM measures, the CV ranging between 11% and 33% in the “off” condition and between 7% and 24% in the “on” condition, but poor for three of them: precision, tremor, and irregularity. In addition, we calculated the intraclass correlation (from the within- and between-subject variability). The ICC ranged between 54% and 87% for most measures in the “off” condition and between 65% and 92% for most measures in the “on” condition, except tremor and irregularity in both conditions. One disadvantage of the test is that three of our ET patients were unable to reach any target in the “off” condition, which limits its use among patients with severe tremor.

### Clinical implications

Thalamic DBS is a well-established, safe, and effective treatment of tremor suppression in ET patients. However, the optimal combination of stimulus parameters must be chosen, and possible side effects and the patients’ preference have to be taken into account. The process may be difficult and time consuming, putting high demands on the evaluator. In this process, quantitative methods such as the CATSYS tremor pen could complement clinical assessment. The results are immediately shown on the data screen and can be used to give feedback to the patient. In addition, the CATSYS tremor pen could be
used to follow up the ET patient over time, as it is supposed to be independent of the evaluator, and repeated CATSYS results can be easily stored in the patient’s file. However, the test–retest variability of the CATSYS system in ET patients should be explored in larger studies, and longitudinal studies of ET patents with DBS comparing the use of the CATSYS system to clinical tests in follow-up, with respect to tremor suppression, ADL function, and quality of life are required. The EKM test needs further exploration with respect to validity and test–retest reliability in larger study populations before its introduction into clinical practice can be considered. An alternative might be to use the CATSYS tremor pen for evaluating kinetic tremor; in that case the instrument must be validated and standardized for that condition.

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