Ambulatory monitoring of tremor and other movements before and after thalamotomy: a new quantitative technique

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Summary

Tremor, e.g. in Parkinson patients, often shows large spontaneous fluctuations in severity over the day, to such an extent that a short observation is usually not sufficient to assess the overall severity or the effect of a treatment. Since momentary impressions of the tremor can thus be misleading, long-term ambulatory recordings would be helpful in the evaluation of severity and treatment effectiveness. As existing methods for long-term tremor registration have several shortcomings, a new method is proposed: an algorithm was designed to discriminate tremor from other movements and to describe the amount (i.e. the proportion of tremor or movements per time unit) as well as the intensity (i.e. average acceleration amplitude) of the two types of movement. In the evaluation of the severity of tremor both the amount and intensity of tremor episodes are of importance. The algorithm was tested on 24-h analog tape recordings of wrist-movement in 10 young and 10 aged controls, as well as in 8 patients with tremor – both before and after a tremor relieving thalamotomy. The algorithm scored movements as ‘tremor’ exclusively in patients prior to the operation. Fluctuations in tremor severity over the day were detected, and tremor could be discriminated from non-pathological movements. Moreover, following thalamotomy, motor slowing (bradykinesia) was detectable using this algorithm. Based on these test results, a miniaturized device in wrist-watch format is now being developed for long-term registrations.

Introduction

Although the mere occurrence of clinically significant tremor, e.g. in Parkinson’s disease, can be diagnosed fairly easily, the amount and intensity of tremor can be highly variable in the course of one day, depending on factors such as alertness and emotional state (Teräväinen and Calne 1980). The variability of the tremor over the day often makes it difficult to establish the right dose and timing of medication. Long-term continuous registration of the tremor can reveal recurring patterns in the fluctuations in tremor severity, and may thus be of help in optimizing and evaluating therapeutical efforts to alleviate tremor.

As most existing methods for short-term objective tremor evaluation, e.g. EMG recordings, give precise but momentary impression, they cannot describe fluctuations in tremor over longer periods and thus can even be misleading with respect to its overall severity. Long-term subjective evaluation might be influenced by the overall state of well-being and the severity of other symptoms, and long-term observation by a clinician is not feasible. Until now, long-term automated registrations have not gained wide application in clinical research, let alone in clinical practice, due to the shortcomings of the methods proposed so far (Cowell et al. 1965; Ackmann et al. 1977; Pimlot et al. 1983; Scholz et al. 1988; Bacher et al. 1989; Gruen 1990). These methods are generally laborious and expensive and require extensive data analysis. Also, the freedom

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of movement and maximum duration of registration are limited, patients are required to keep a meticulous log of activities, and discrimination between tremor and other movements can be problematic. In the present paper a new method for tremor detection and quantification is described. Accelerometer wrist movement signals, recorded on an analog portable recorder, were used to develop and test an algorithm which had to fulfill two criteria: first, it must be able to discriminate between tremor and other movements, and, second, it should be possible to have the procedure performed on-line by fairly simple electronics with low power consumption. The last feature would enable the future development of a device even smaller than a portable analog recorder; our ultimate aim is a miniaturized, 'wrist-watch like' device for long-term tremor quantification.

The new algorithm was tested on 24-h continuous movement registrations made both in healthy subjects and in patients suffering from tremor of various natures, before as well as after stereotactic thalamotomy. The algorithm was able to clearly differentiate healthy subjects from patients with tremor, and also between the pre- and post-operative registrations in the patient group.

Methods

Subjects

Two groups of healthy controls were recorded: a group of 10 ‘young’ subjects (mean age 30 years ± 1.8 SEM) and a group of 10 ‘elderly’ subjects (mean age 61 years ± 1.1). Eight patients (mean age 63 years ± 4.7) with tremor of various origin were recorded before and after a stereotactic thalamotomy aimed at unilateral elimination of the tremor at the most or uniquely affected side. Table 1 gives a description of the patients and their motor symptoms as evaluated with the 5-point (0–4) UPDRS rating scale (Fahn et al. 1987) within 2 weeks before and after the operation. A heterogeneous patient group was chosen to evaluate if the method would work in several tremor types. Pharmacological therapy, although not satisfactory, was given to all but one patient and was not changed after the operation. Before the operation, the average score for the severity of tremor in the registered arm was 3, range 2–4. Shortly after the operation contralateral tremor was rated as absent (0) in all patients. By the time of the post-operative accelerometer recording though, tremor incidentally returned in 2 patients. In 2 other patients tremor was absent in the registered arm, but present in other limbs; moderate to severe in all other limbs in one patient, and moderate in one arm in the other. The hypo/bradykinesia score – combining slowness, hesitance, decreased armswing, small amplitude and poverty of movement in general – was unaffected by the operation and rigidity decreased in one patient. Pre-operative recordings were made between 1 and 14 days before the operation. The operation was aimed at unilaterally lesioning the posterior part of the thalamic nucleus ventralis lateralis. Post-operative registrations were performed after 1 week in 6 patients, after 2.5 weeks in one patient, and after 7 weeks in another patient. The patient group as well as the control groups consisted of equal numbers of males and females.

Movement recordings

An ENDEVCO Picochip model 12 piezoelectric accelerometer, two 1.5-V batteries and a CMOS low power, high input impedance amplifier (A = 54 dB) were built into a small metal box (2.5 × 2.5 × 5.5 cm) weighing approximately 50 g. The output of this system

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<td>CLINICAL DESCRIPTION OF TREMOR PATIENTS</td>
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<td>A = action tremor; R = resting tremor; TC = trauma capitis; CVA = cerebrovascular accident; PD = Parkinson’s disease; E = essential tremor. The last 12 columns show the UPDRS (Fahn et al. 1987) rigidity and hypo/bradykinesia scores as well as tremor scores for left and right arms and legs before and shortly after the thalamotomy. The registered arm is printed in bold italics. A / + mark indicates the return of a clinically unquantified amount of tremor during the ambulatory recording performed after the initial UPDRS-scoring in patients SB en BW.</td>
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<th>Tremor postoperative</th>
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was 1 V at 1 g acceleration. The box was worn on the wrist, under a sweat-band, with a shielded wire connecting it to a portable data recorder (TEAC HR-30 J, frequency range DC to 39 Hz, maximum recording time 24 h) which was worn on a belt. As the dominant hand is most likely to make rhythmic movements, and a conservative estimate of false positive ‘tremor’ classification was preferred, controls were asked to wear the device continuously for 24 h on their dominant wrist. Patients wore it on the wrist contralateral to the side of the operation. Subjects were free to move and perform as usual, with sports and showering being the only exceptions. Controls were asked to keep a log of any motor activity they observed to be rhythmic, to check if such movements would be classified erroneously as tremor. No such log was available in the patient group, though.

Data analysis

The recordings were played back on a TEAC R71, at 32 times the recording speed, amplified 10 times and sampled with a resolution of 12 bits (4096 levels with ±2048 corresponding to ±10 V) and a frequency of 3205 Hz, corresponding to approximately 100 Hz for the original recordings. Fig. 1 shows 5-sec tracings of 3 patients and a control subject. A Period Amplitude Sequence Analysis (PASA) program, running on a personal computer, was developed as described below.

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**Fig. 1.** Examples of posttraumatic tremor (SB), Parkinsonian tremor (JH), essential tremor (DW) and movements in a control subject (ES). The tracings represent 5 sec, and the acceleration axis is ±1 g. Note that tremor is not necessarily a perfect sine wave, e.g. in patient SB due to harmonics the peaks are smaller than the troughs. Furthermore, note that the movements of the control subject differ from tremor more in repetetiveness than in frequency range. All recordings contain some narrow-bandwidth high frequency noise (ca. 46 Hz) that is filtered out before further processing.

General considerations in developing PASA. Following Elble and Koller (1990) tremor was defined as an involuntary, approximately rhythmic, and roughly sinusoidal movement. For Parkinson’s disease the dominant frequency varies between 3 and 5 Hz for a rest tremor, and up to 12 Hz for postural tremor (Elble and Koller 1990). However, tremor cannot be distinguished reliably from normal movements on the basis of frequency alone. As we found in a pilot study, the frequency spectrum of normal arm movements overlapped the 3–12 Hz range. Although this frequency band will hence include both other movements as well as tremors, other movements will not be confined to this frequency range for a long time. Whereas, for example, a few seconds of tremor will consist exclusively of movements confined to the 3–12 Hz range a few seconds of other movements also contains oscillations with periods falling outside of the 3–12 Hz range, or contain interruptions, i.e. periods without movement. Thus, the basic assumption of the PASA program was that tremor differs from other movements in the number of repetitions of waves within a confined frequency band. Tremor was, therefore, defined operationally as a sequence of repetitive movements restricted to the 3–12 Hz range for a certain critical duration. Details are described below.

**Application of PASA.** To illustrate the analytical steps taken by this computer program, and to include
all possible classification options in one picture a drawing of 30 sec of artificial movement signal is shown in Fig. 2.

(1) Recording and playback noise was reduced using digital filtering. High frequency noise was smoothed using a 3 sample moving average, and low frequencies were reduced with a digital highpass IIR filter (−3 dB at 2 Hz, 6 dB/octave) (Press et al. 1986).

(2) A Period Amplitude Analysis (see, e.g., Hoffmann et al. (1979) for a clear description) based on zero-crossings was used to reduce the signal to durations and maximum absolute values between successive zero crossings: half-periods and their amplitudes, i.e. maximum deflection between two zero crossings. This amplitude reflects the maximal acceleration and is interpreted as the intensity of the movement.

(3) After visual inspection of the filtered signal, a threshold was set at 10 (= 48.8 mV) to avoid scoring of minor fluctuations around zero as movement or tremor. Whenever the signal between two or more zero-crossings did not exceed this threshold (e.g. epochs ‘c’ and ‘e’ in Fig. 2) it was discarded as ‘rest’.

(4) Of the remaining signal, only half-periods with a duration between 40 and 170 msec – corresponding to signal containing frequencies in the tremor range of 2.94–12.5 Hz – were selected. Half-periods with a shorter or longer duration (epoch ‘a’ and ‘b’ in Fig. 2, respectively), were discarded as ‘activity 1’. It might be argued that this range could be narrowed in patients with a more or less stable and sine wave like tremor. On the other hand, in patients with a tremor rich in harmonics (e.g. Fig. 1, patient SB) this broad range captures a pattern of alternating half-period lengths.

(5) The next step, based on the repetitive characteristics of tremor and the arrhythmic characteristics of most other movements, was to select – of the remaining signal – only sequences of at least 12 half-periods (6 full waves) uninterrupted by ‘rest’ or ‘activity 1’.

These sequences were classified as ‘tremor’ (epoch ‘f’ in Fig. 2), while shorter sequences were discarded as ‘activity 2’ (epoch ‘d’ in Fig. 2). The criterion of 12 was chosen after a visual inspection of the signal. Depending on the frequency of the tremor, this criterion requires a minimum uninterrupted tremor signal of at least 0.48 sec for a 12.5 Hz tremor, up to at least 2.04 sec for a 2.94 Hz tremor.

(6) The last step was to calculate an hourly total time of epochs scored as ‘tremor’, as well as the average acceleration amplitude of the signal during these epochs and the mean duration of the epochs. Furthermore, ‘activity 1’ and ‘activity 2’ were combined as ‘arrhythmic activity’ and its hourly total time and average acceleration amplitude were calculated as well. The average acceleration amplitudes are given in arbitrary units, based on the 12-bit sampling resolution; for unfiltered signal 1 g acceleration corresponds to 2048 units.

The hourly scores were plotted in 24-h graphs, giving an impression of the fluctuations in amount of tremor and other movements for every subject. Moreover, day time (8:00–23:00) hourly scores were averaged to a single day-time score for every parameter in each subject. Differences between healthy controls and patients on these parameters were evaluated using the Mann-Whitney test. The Wilcoxon signed-rank test was used for the repeated measures (pre- vs. post-operative recordings). A two-tailed significance level of α = 0.05 was used in all tests.

Results

Apart from 2 patients, all subjects wore the recording equipment without problems for 24 h. Two patients, who objected to 24-h recording, were registered for only 8 h (before and after the operation); one from
'arrhythmic activity' and 'tremor' over the day in the same patient. The control subject shows a clear day-night pattern in the amount of 'arrhythmic activity'. A very small proportion of the movements is erroneously scored as 'tremor'. In the patient there is some 'arrhythmic activity' in the early morning, between 4 and 6 h, which is in accordance with her report of restlessness. The hourly amount of 'tremor' fluctuates with a clear decline between 17 and 19 h and during the night. The patient reported that she usually noted an increase in the amount of tremor in the course of the day. Apart from some peaks and falls, the amount of 'tremor' is indeed increasing significantly (Fig. 3, middle panel), as was confirmed using the Spearman rank correlation test ($r = 0.46; P < 0.05$) over her active period (4–24 h). In contrast, it can be seen in the lower panel of Fig. 3 that this increase does not occur in the intensity of movements classified as 'tremor' or 'arrhythmic activity', although some fluctuations were detected.

Fig. 4 shows the distribution of 'arrhythmic activity', 'rest' and 'tremor' for the four groups, averaged per h, as an illustration of the finding that a substantial amount of signal was classified as 'tremor' in pre-operative patients (panel C), whereas very little signal was scored as 'tremor' in young and old controls (panel A and B). In agreement with the clinical observations and with the subjective experience of the patients, 'tremor' was almost absent post-operatively (panel D). Furthermore, it can be seen that during the night not only 'arrhythmic activity' but also 'tremor' time in patients is close to zero. Since, also subjectively, there were no tremors at night, night-time (23:00–08:00 h) values were excluded from subsequent analyses aimed at evaluating the discrimination between tremor and activity. As no effect of sex or age could be detected on any of the variables (MW-test), both age groups were taken together as 'controls'.

Except for one of the healthy controls who had outlying 'tremor' scores, the maximum hourly 'tremor' score found in any of the controls was 5:59 min. The outlying scores were due to knitting for a couple of hours, a repetitive movement which the method did not discern from tremor. Despite the fact that she did not complain of or showed any sign of tremor, her 'tremor' time was up to 19:59 min in the hours she reported to have been busy knitting. However, her outlying values were not excluded from further analyses. Before the operation, patients had hourly 'tremor' scores of up to 53:40 min. After the operation the maximum score was 8:10 min.

Group differences and their significance, on average daytime scores for all variables, are illustrated in Fig. 5. The operation reduced the average 'tremor' amount from $21:21 \pm 4:01$ min/h to $1:21 \pm 0:22$ min/h, comparable ($\alpha = 0.36$) to the level of healthy subjects ($1:31 \pm$
0.18 min/h), while the amount of 'arrhythmic activity', which was lower than in the controls (35:40 ± 1:04 min/h), remained unchanged (α = 0.78) following the operation: 24:31 ± 2:42 min/h before versus 26:01 ± 2:30 min/h after the operation. Consequently, 'rest' time increased after the operation.

For patients, the average duration of epochs classified as 'tremor' was 16.83 ± 1.76 sec before and 5.05 ± 0.56 sec after the operation, which is comparable (α = 0.24) to the control value (5.69 ± 0.38 sec).

Finally, Fig. 5 shows that the intensity, or average acceleration of 'tremor' and 'arrhythmic activity' is reduced post-operatively, which might implicate bradykinesia. The 'arrhythmic activity' intensity significantly decreased from 162 ± 49 before to 91 ± 12 after the operation, with control values of 151 ± 5. The 'tremor' intensity was 242 ± 80 before the operation, which was higher than control values (171 ± 14), and decreased to 114 ± 13 after the operation. This decrease in 'tremor' intensity occurred in 7 out of 8
patients but did not reach significance ($\alpha = 0.07$) due to the considerable increase in one of the patients.

**Discussion**

The large differences in the amount of ‘tremor’ between pre-operative patients and controls and between pre- and post-operative patients (Fig. 5, left panel) shows that the method is successful in discriminating tremor from other movements. Nevertheless, some movements in the controls were classified as ‘tremor’, on average one and a half min. With an average ‘arrhythmic activity’ score of 36 min/h, this yields a false positive error rate of 4%. This error rate can be changed by varying the critical sequence length (see Methods), which was arbitrarily set at 12 half-periods in the present study; increasing the critical series length lowers the error rate but also the amount of ‘tremor’ scored in patients, while decreasing the critical series length has a reverse effect. One of our healthy subjects revealed that specific movements of a rhythmical nature may confound our ‘tremor’ score. In the subject who, during the recording, spent a number of hours knitting, the amount of movement classified as ‘tremor’ was comparable to the amount of tremor scored in patients. Therefore, it will be necessary to be alert to specific kinds of voluntary, rhythmical movements (e.g. knitting, finger tapping, tooth brushing) while recording.

Apart from false positive classification, false negative classification may also have occurred by discarding tremor as rest or activity. However, as the threshold setting (Fig. 2) is very low, any tremor of clinical importance will elicit a signal that exceeds the threshold, thus misclassification as ‘rest’ is highly unlikely. Discarding tremor as ‘activity 1’ (Fig. 2), i.e. movement with low or high frequency characteristics, is also unlikely, as we used a fairly broad frequency range for tremor detection. On the contrary, one of the advantages of the algorithm may be its robustness for small changes in the dominant frequency over time, that occur in many patients and seem to be of minor value in clinical evaluation. Tremor may also have been discarded as ‘activity 2’, i.e. sequences of movements with a frequency within the 2.94–12.5 Hz range, but interrupted by epochs classified as ‘rest’ or ‘activity 1’ before completing 6 full waves. However, depending on its frequency, the tremor-movement should be sustained for only 0.48–2.04 sec (see Methods) in order to classify as ‘tremor’ according to our algorithm, whereas the pre-operative duration of ‘tremor’ epochs was, on average, about 17 sec. Thus, it is unlikely that systematic interruption of tremor by epochs scored as ‘rest’ or ‘activity 1’, erroneously reducing the amount of recorded ‘tremor’ time, will take place very often. The fact that the amount of signal scored as ‘tremor’, but not the amount of signal scored as ‘arrhythmic activity’, is changed after the stereotactic operation supports the idea that only little, if any, tremor is incorrectly classified as activity, because this should also have resulted in a reduction of ‘arrhythmic activity’ time after the operation. Furthermore, in the patients having an action tremor, substantial average day-time amounts of ‘tremor’ were scored preoperatively; 9:21 min/h for the patient (DW) with an exclusive action tremor, and 25:50 and 41:23 min/h for the patients with combined rest and action tremor (BW and PJ). This suggests that tremor during movement can be classified correctly, at least in part, as ‘tremor’. In the near future a study will be undertaken to evaluate how much ‘tremor’ and ‘arrhythmic activity’ is scored when both occur simultaneously. If our method strongly favors ‘tremor’, and an independent ‘arrhythmic activity’ score is wanted, an additional actigraph registration in a non-trembling limb could be needed.

The average duration of epochs scored as ‘tremor’ (Fig. 5, middle panel) is short when there is in fact no, or little, tremor, as in the controls and post-operative patients. This indicates that the false positive ‘tremor’ epochs have a much shorter average duration than the epochs scored as ‘tremor’ in signal that actually does contain tremor.

The intensity of movement, represented by the average acceleration of ‘tremor’ and ‘arrhythmic activity’ (right panel in Fig. 5), is reduced after the operation, although the pre-vs. post-operative comparison for ‘tremor’ intensity does not quite reach statistical significance ($\alpha = 0.07$). Thus, in addition to quantification of the amount of tremor and other movements, our method appears to detect slowing of movements. This finding is not in agreement with the post-operative UPDRS hypo-/bradykinesia score, but it is likely that the present method is more sensitive than the 5-point rating scale. Also, the UPDRS score is based on a momentary impression. Slowness after thalamotomy has been reported before (Selby 1967), and unpublished data from the Academic Medical Centre showed a decreased performance on the finger tapping test after thalamotomy. Another factor in the discrepancy between the UPDRS score and the accelerometer findings could be that the UPDRS combines hypo- and bradykinesia to one score while the present method found changes in the intensity of movements but not in the amount of movements. This fact suggests that the present method could discriminate hypokinesia from bradykinesia, and that thalamotomy resulted in a significant reduction in the intensity but not the amount of movements, at least shortly after the operation.

The sensitivity of the method for fluctuations in the amount and intensity of tremor seems to be adequate for clinical purposes, as appears from several lines of
observations. In the first place, 'tremor' was detected where it was expected: during the day-time in pre-operative patients and not during the night, in control subjects and in post-operative patients. Moreover, a subjective increase in the amount of tremor during the day was recognized by the method (see 'Results' and Fig. 3). Thirdly, the time classified as 'tremor' ranged up to almost 54 min/h, which is 90% of the theoretical maximum amount possible. Furthermore, after the operation, the two patients (SB and BW) that had an occasional recurrence of the tremor, and the patient (PJ) that showed a moderate to severe tremor in all other limbs (see Methods; Subjects), showed higher post-operative average daytime 'tremor' scores (2:03–3:16 min/h) than the 4 patients (0:17–0:55 min/h) without any postoperative tremor. The patient (DW) with a moderate postoperative tremor in one other limb showed a 'tremor' score in the range of the tremor-free patients (0:47 min/h). Finally, in agreement with previous findings on a finger tapping test, the method detected motor slowing after thalamotomy.

The new method meets the requirements for useful long-term registrations of tremor. Although EMG recordings can give a more detailed description of the muscle activity involved in the tremor, it is difficult to make EMG recordings continuously for a long period. An accelerometer can be worn for weeks, and gives useful indices of the severity of the tremor. In contrast to actigraphs the method described in the present paper is able to discriminate normal, common movements from tremor. In contrast with methods using repetitive fast Fourier transforms our algorithm can be performed on-line by relatively simple electronics with low power consumption. This now enables us to miniaturise the recording system to a 'wrist-watch like' device, which can be used to attain our ultimate aim: to assess movement patterns continuously for several weeks in out-patients, and to analyze rhythmicity in the severity of the tremor. Prototypes of such a 'tremor watch' are currently being developed, and will be used for further validation and optimization of the method. Parameters such as threshold, frequency range, and critical sequence length, arbitrarily set in the present study, will be adjustable in this 'tremor watch', which may lead to an even better discrimination between tremor and other movements.

With such long-term tremor registrations, it will become possible to analyze, in a non-restraining way, temporal variations in amount and intensity of tremor in various diseases such as Parkinson's disease or other disorders in which tremor has a paroxysmal character. Registration of tremor fluctuations could be helpful in optimization of the timing and dose of medication. As wearing a 'tremor watch' for several weeks will not be more uncomfortable than wearing a wrist-watch, movement registrations may be introduced in the outpatient and home care of individual patients suffering from tremor. In addition, the method may be used in the development of therapeutic tools for its reduction.

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