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Angaben zur Veröffentlichung / Publication details:

Muthuraman, Muthuraman, Abdulnasir Hossen, Ulrich Heute, Günther Deuschl, and Jan Raethjen. 2011. "A new diagnostic test to distinguish tremulous Parkinson's disease from advanced essential tremor." *Movement Disorders* 26 (8): 1548–52. https://doi.org/10.1002/mds.23672.

A New Diagnostic Test to Distinguish Tremulous Parkinson's Disease from Advanced Essential Tremor

Muthuraman Muthuraman, PhD,[1] Abdulnasir Hossen, PhD,[2] Ulrich Heute, PhD,[3] Günther Deuschl, MD,[1] and Jan Raethjen, MD[1]*

[1]Department of Neurology, University of Kiel, Kiel, Germany; [2]Department of Electrical and Computer Engineering, Sultan Qaboos University, Muscat, Oman; [3]Institute for Circuit and System Theory, Faculty of Engineering, University of Kiel, Kiel, Germany

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

***Correspondence to:** Dr. Jan Raethjen, Department of Neurology, University of Kiel, Schittenhelmstrasse 10, 24105 Kiel, Germany; j.raethjen@neurologie.uni-kiel.de

Relevant conflicts of interest/financial disclosures: Nothing to report. Muthuraman Muthuraman, Günther Deuschl, and Jan Raethjen received research support from the German Research Council (Deutsche Forschungsgemeinschaft [DFG]: SFB 855) Project D2. Abdulnasir Hossen received research support from the DAAD (German Academic Exchange Service) through a research scholarship. Ulrich Heute received support from the German Research Council (DFG: SFB 855) Project C3. Full financial disclosures and author roles may be found in the online version of this article.

Table 1. Age, sex, and disease duration distribution of PD, ET, and MT patients

	PD	ET	MT
Number of patients	39	41	12
Age (y), mean (range)	66.38 (40–90)	63.38 (27–94)	68.2 (50–88)
Sex (male/female)	23/16	23/18	7/5
Disease duration (y), mean	15.85	31.5	3.4

Misdiagnoses between essential tremor (ET) and tremulous Parkinson's disease (PD) are relatively common,[1] one reason being that advanced ET may show a continuation into the resting condition,[2] and early tremor-dominant PD can present as monosymptomatic tremor without significant akinetic rigid features.[3,4] But the relevant difference in prognosis and emerging neuroprotective disease-modifying agents for PD make an early and accurate diagnosis highly desirable. Thus, technical aids are necessary in these unclear cases. Dopamine transporter imaging (DATScan) picks up the asymmetric loss of dopaminergic neurons in early PD and has been proven to differentiate it accurately from atypical ET cases.[5] However, it entails the injection of radioactive tracers, is time consuming, and requires single-photon emission computed tomography technology, the availability of which is limited to specialty centers. Electrophysiological hand tremor recordings with accelerometry are easily applicable and widely available, but the currently applied analyses of such short-term recordings in the clinical neurophysiological laboratory setting alone cannot reliably distinguish between the 2 diseases.[6,7] Recent evidence suggests that the additional frequency peaks at integer multiples (harmonics) of the tremor frequency play a special role in Parkinsonian tremor.[8,9] Furthermore, in a recent technical study the band at double the tremor frequency was shown to be one of the most informative bands with respect to the differentiation of PD from ET.[10] Here we present a new analysis of such recordings quantifying the power at such harmonic peaks.

Patients and Methods

Patients

Thirty-nine PD and 41 ET patients were studied (Table 1). All patients were selected in a blinded manner from a data base of 100 ET and 100 tremulous PD patients on the basis of the printed power spectra of the accelerometrically recorded tremor on the more affected side. One person who was blind to the diagnosis was given the power spectra from each group separately and asked to find as many pairs from both groups as possible in which the spectra were virtually indistinguishable with respect to the basic peak frequency, peak power, and presence/absence or number of peaks at higher harmonic frequencies (for details, see Supporting Information).

Twelve additional patients with clinically unclear monosymptomatic rest and postural tremor (MT) were analyzed. Ten of them later turned out to have PD, and 2 could subsequently be diagnosed with atypical ET (Table 2 and Supporting Information).

Tremor Recordings and Analysis

Postural tremor was recorded accelerometrically in all patients for 30 seconds. Power spectra were calculated using the Welch-periodogram method.[11] Tremor frequency, peak power at the basic frequency, and all harmonic peaks were calculated. Asymmetry of the decay of the autocorrelation function was computed.[12] Cutoff values for the differentiation between ET and PD were determined by receiver operating characteristics

Table 2. Patients with unclear tremor at time of recording

			Tremor activation						
Patient no.	Age (y)	Sex	Rest	Post.	Intent.	DAT	F-dopa	Time to akin./rigid from tremor onset (y)	Final Diagnosis
1	66	f	+	+	−	na	+	3	PD
2	76	m	+	+	−	na	+	2.5	PD
3	60	f	+	+	−	na	+	3	PD
4	79	f	+	+	−	na	+	2	PD
5	71	f	+	+	−	na	+	2.5	PD
6	70	m	+	+	−	+	na	3	PD
7	74	f	+	+	−	+	na	2.5	PD
8	59	f	+	+	−	+	na	3	PD
9	62	m	+	+	−	na	na	2.5	PD
10	88	m	+	+	−	na	na	2.5	PD
11	54	m	+	+	−	−	na	None after 4 y	ET
12	65	m	+	+	−	−	na	None after 4 y	ET

f, Female; m, male; +, present/positive; −, absent/negative; na, not available; DAT, FP-CIT-SPECT; F-dopa, fluorodopa-PET; PD, Parkinson's disease; ET, essential tremor.

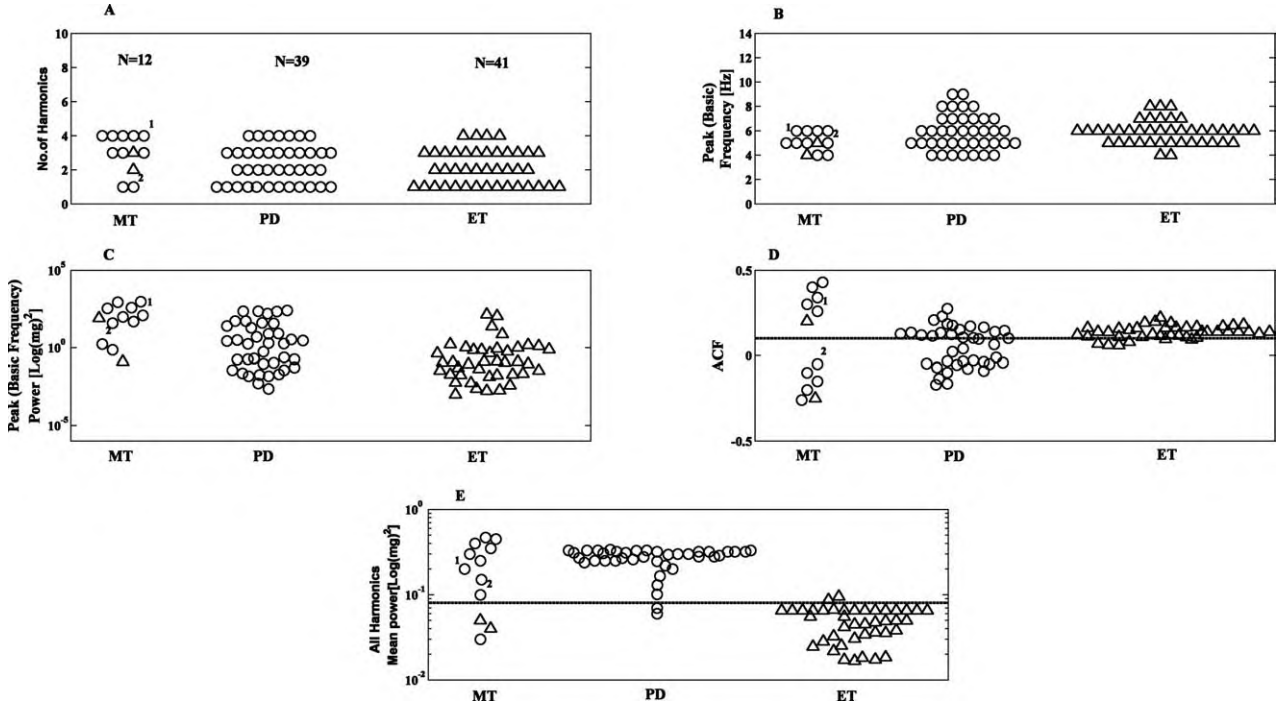

FIG. 1. Summary of the results for all the tremor measures **A:** Number of harmonics is plotted for the 39 patients with Parkinson's disease (PD, open circles), 41 patients with essential tremor (ET, triangles), 12 patients with monosymptomatic tremor (MT, circles or triangles according to the final diagnosis, see Table 2). The 2 patients who did have DAT or F-dopa scan are marked by 1 and 2. **B:** Tremor frequency (basic frequency) for all the patients is shown. **C:** Peak power (basic frequency) in log scale is depicted for all the patients. **D:** Auto-correlation function values for the patients; dotted line, threshold value taken from the ROC curves where sensitivity and specificity were maximal. **E:** All harmonics mean power values in the log scale; dotted line, threshold value to differentiate ET (Δ) and tremulous PD (○) patients.

(ROC). Sensitivity, specificity, and diagnostic accuracy of the different measures were analyzed (supplementary material).

Results

Most measures explored in the present study showed a considerable overlap between the tremulous PD and ET patients. Tremor frequency, amplitude as measured by the peak power at the basic frequency, and number of harmonic peaks were within the same range (Fig. 1), as determined by the selection process (see the Patients and Methods section). The asymmetry of the autocorrelation function (ACF) showed clear differences between ET and PD, but only the distributions of the mean power of the peaks at the harmonic frequencies were almost completely separated for the 2 groups (Fig. 1). The ROC curves (Fig. 2) deviated from the diagonal only for the asymmetry of the ACF and the mean harmonic power, indicating some diagnostic yield. Therefore the best cutoff values were only displayed as horizontal lines for these 2 measures in Figure 1D,E. As can been seen from Supplementary Table 1, the peak (basic) frequency was only able to classify with an accuracy of 42.8%. The peak power at the basic frequency leads only to 52.8% classification accuracy. The degree of asymmetry of the decay of the autocorrelation function in this study allowed correct discrimination between PD and ET in 64% of all cases. The mere number of harmonic peaks only had a correct classification rate of 39%.

However, when looking at the peak power at these harmonic frequencies, this rate increased to diagnostically relevant values (Supporting Information Table 2). The power at the first harmonic peak alone gave a separation accuracy of 82.8%. The second, third, and fourth harmonic peak powers alone also yielded a

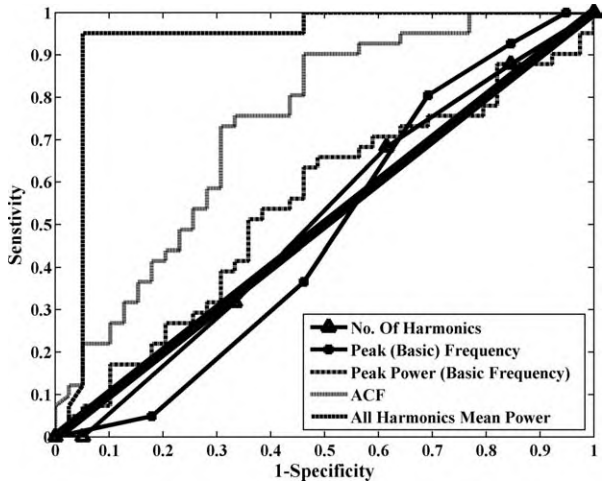

FIG. 2. The receiver operating characteristic (ROC) curves are depicted. Solid line with triangles, number of harmonics; solid line with squares, the peak (basic) frequency; dashed-dotted line, peak power (basic frequency); dotted line, values of the asymmetry of the auto correlation function (ACF); dashed line, all harmonics mean power.

reasonable separation of 74%–81%. But the mean power of all the harmonic peaks greatly increased the classification accuracy to 94%, with a similarly high specificity and sensitivity (see Supporting Information Table 2).

The diagnostic accuracy was similarly high in the clinically unclear cases (Fig. 1E). Only 1 PD patient was misclassified as ET; the remaining 10 cases were allocated correctly. Thus, the classification accuracy was 11 of 12 (91.7%). Using the basic peak frequency, only 40% were classified correctly; 55% would have been detected correctly when only looking at the peak power, 50% by the asymmetry of the ACF, and 39% by the number of harmonic peaks.

Discussion

In the present article we show that the cumulative power of all the peaks at integer multiples of the basic tremor frequency allowed us to distinguish between clinically definite ET and tremulous PD in a large sample with high accuracy (94%). Furthermore, 11 of 12 patients with initially unclear monosymptomatic tremor were assigned the correct diagnosis.

Differential Diagnostic Value

In the present study we used clinically definite cases to find the cutoff value between the 2 diseases, but we selected the 41 and 39 cases each from a much larger cohort on the basis of the accelerometric power spectra balancing out for tremor amplitude (total power), tremor frequency, and number of additional peaks at integer multiples of the basic tremor frequency, ensuring that the 2 groups could not be separated by the standard spectral measures already. This was confirmed by the lack of significant difference in total power, basic frequency, and number of additional peaks. We only looked at the accelerometric recordings on the more affected side and only at the postural condition. Therefore, the present analysis was blind to differences between the activation conditions (rest, posture), asymmetries, and EMG-synchronization, both of which are important hints in clinical assessment or conventional tremor analyses.[7,13,14] In this setting a clinical differentiation by only looking at the postural/reemergent tremor of the more affected side would not be possible, indicating that our analysis clearly goes beyond clinically detectable features.

This was confirmed by its good performance in 12 clinically unclear cases (11 of 12 classified correctly), in which a definitive diagnoses was achieved only later by DATScan, fluorodopa-positron emission tomography, or clinical course. The cutoff value detected in our study cannot be used by other laboratories as such.[15] We therefore suggest using a cutoff value normalized by the mean total power of a small normal population analyzed in the individual laboratory.[16] See supplementary material (supplementary text and Supplementary Fig. 1).

Comparison with Previous Approaches

Standard power spectral analysis of accelerometrically and electromyographically recorded tremor time series alone is inferior to clinical examination in assigning the correct diagnosis. Only in combination with the clinical picture or by accompanying measurements of clinical test maneuvers does it have an additional diagnostic yield.[6,14]

In one attempt to find a differentiating measure in such recordings, the asymmetry of the waveform, which is reflected in the asymmetric decay of the autocorrelation function of the accelerometer curves, was analyzed.[12] In this previous cohort of patients, this approach showed good classification accuracy. In the presently examined group of patients, we looked at this analysis and found that it was clearly inferior to the new one.

Others have extended the recording time to several hours and combined a number of features in a complex score that had a classification accuracy for ET and tremulous PD in a similar range as the analysis presented here.[17] However, this approach needs to be tested on clinically unclear cases as it includes measures like symmetry and activation times of tremor partly overlapping with the clinical diagnostic criteria.[18] It is time consuming and requires high patient compliance, and the analysis is more complicated.

Pathophysiological Implications

The additional peaks at integer multiples of the tremor frequency have previously been addressed as higher harmonic frequencies arising from the asymmetry of the tremor waveforms.[12] We confirmed that this asymmetry, as indicated by the asymmetric decay of the autocorrelation function being more common in PD tremor than in ET. However, in our selected groups of patients, this measure only separated 60%–70% of the PD patients from ET patients, whereas the cumulative power of the peaks at these harmonic frequencies classified 94% of the PD patients correctly. This is in keeping with emerging evidence suggesting that these peaks in PD tremor represent distinct oscillatory activity rather than pure harmonic frequencies due to waveform characteristics.[8] And the present data suggest that the pathophysiological mechanism of these higher-frequency peaks is different in ET. On the basis of accelerometric data, this clearly remains very speculative, but further studies including EMG and EEG analyses are warranted and currently under way.

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