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ORIGINAL ARTICLE

A novel device for continuous monitoring of tremor and other motor symptoms

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Abstract

The clinical assessment of Parkinson's disease (PD) symptoms is typically performed with neurological examinations and simple motor tests. However, this only takes into account the severity of motor symptoms during the length of the recording and fails to capture variations in a patient's motor state, which change continuously during the day. Most of the current methods for long-term monitoring of extrapyramidal symptoms are based on the use of a wearable magneto-inertial device that evaluates the frequential content of signals in the range of movement disorders. However, the typical daily motor activities performed by patients may have a power spectrum into the same range of motor symptoms, and habitual activity may be indistinguishable from that due to movement disorders. In this work, we report a new device and method for the continuous and long-term monitoring of tremor due to PD and other movement disorders to reduce the probability of mistaking the discrimination between extrapyramidal symptoms and normal daily activity. The method is based on the evaluation of frequential data content from multi-axial sensors and on the identification of specific movement patterns that Parkinsonian and extrapyramidal symptoms are typically associated with. In this study, 16 patients with movement disorders were recruited. While results need to be extended with further studies and clinical trials, the proposed device appears promising and suitable for the use as part of clinical trials and routine clinical practice for supporting the evaluation of motor symptoms, disease progression, and the quantification of therapeutic effects

Keywords Parkinson's disease · Accelerometer · Wearable technology · Neurophysiology · Movement disorders

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder, with an estimated ten million people worldwide living with this affliction; approximately 1.2 million of those live in Europe and about 250,000 in Italy [1–4]. The usual symptoms of PD are rigidity, bradykinesia, and tremor [5, 6]. There are various treatments for the motor symptoms caused by PD [7–11], and, usually, treatment with levodopa is initially effective, but after 5 and 10 years, around 50% of patients with PD experience levodopa-induced dyskinesia (LID) [12].

Both the diagnosis of PD and the assessment of its progression are essentially clinical and are typically based on performing neurological examinations and simple motor tests [2]. However, these examinations assess the state of the Parkinsonian patient's health only throughout the duration of the testing and so are limited in time and fail to detect fluctuations in motor symptoms, which can vary considerably throughout the day and from 1 day to the next [13]. Moreover, rating scales are typically subjective [14], as are reports and information provided by the patient and so are not always reliable [15].

In order to reduce these shortcomings, several devices and methods have been proposed for the objective and quantitative assessment of movement disorders and tremor due to PD [16–30]. However, some proposed methods and clinical trials using inertial sensors to provide such measurements require the presence of a clinician. Moreover, usually they do not allow monitoring of tremor and movement disorders during

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the day or, in particular, during daily typical activity, and therefore might fail to capture variations in a patient's continuously changing motor state. Other studies have been proposed for the continuous monitoring of movement disorders and are typically based on wearable systems containing magneto-inertial sensors. Data measured by means of these sensors are usually used to perform signal processing in order to evaluate the frequential content of signals in the range in which motor symptoms due to PD typically occur (i.e., mainly up to about 12 Hz) [6, 31–33].

However, most typical habitual motor activities performed by patients may have a power spectrum up to 20 Hz [34] and, therefore, may have a frequential content in the same range in which motor symptoms typically occur. Therefore, evaluating only the frequential content of data measured by sensors typically is not enough to reasonably distinguish movement disorders from normal daily motor activity and one kind of motor symptoms from another.

Here, we present a new device and method for the continuous and long-term monitoring of tremor due to PD and other motor symptoms. The method is based on the evaluation of frequential content of data coming from multi-axial sensors and on the identification of specific movement patterns with which motor symptoms are typically associated [35, 36]. Indeed, hand tremor in PD usually occurs between 3 and 7 Hz with a supination–pronation characteristic, while tremor in patients affected by essential tremor (ET) typically occurs between 5 and 10 Hz with a flexion–extension pattern [4]; moreover, patients' individual dyskinesia phenomenology tends not to change with time [33] and may take place mainly between 1 and 3 Hz and, secondary, between 3 and 8 Hz [12, 33]. Therefore, this proposed device and method are based on the combination of the frequential analysis of the measured data and the detection of specific movement patterns, in order to support physicians in their clinical evaluation of motor symptoms and to support physicians in refining distinguishing motor activity due to movement disorders from that due to patients' normal daily activities.

Indeed, a typical hand tremor due to PD with a pronation–supination movements and a spectrum within 3 and 7 Hz may determine, in specific configurations, a distribution of spectral energy among the various axes of the measurement system characterized by an overall spectral energy (between 3 and 7 Hz) on an axis (e.g., *x*-axis) greater than the spectral energy (between 3 and 7 Hz) on the other axes (e.g., *y*-axis and *z*-axis). Therefore, a typical hand tremor due to PD usually determines a specific distribution of spectral energy among the various axes, which is different from the distribution typically associated with hand tremor in patients affected by ET or with a voluntary movement occurring with a power spectrum between 3 and 7 Hz (e.g., clapping hands).

Materials and methods

In this study, 16 patients with movement disorders were recruited from the Neurology Unit of the Hospital of Potenza "San Carlo," Italy; 14 patients were affected by PD and two patients were affected by ET. Patients provided informed consent prior to participation in the study. The study protocol was approved by the Ethics Committee.

After neurological examination, patients were asked to wear at their own wrist a portable wearable system, configured as a wrist-watch (e.g., "Parkinson's Disease Watch, PD-Watch") (Fig. 1a and Supplementary Material), for continuous measurements of motor activity in each patient's normal environment. This wearable system

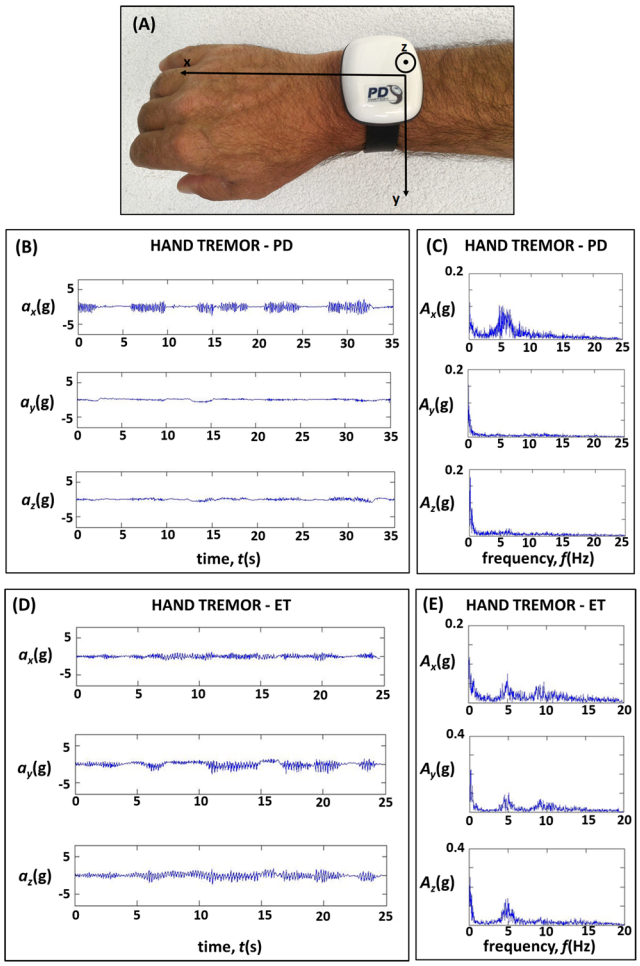

Fig. 1 Wearable device and data acquisition. **a** Scheme of the wearable device with the axes' orientation of the internal tri-axial accelerometer. PD patient experiencing hand tremor. **b** Temporal data pattern measured during a 35-s acquisition with a PD patient experiencing hand tremor by accelerometer. **c** Frequential analysis performed with FFT of acceleration signals reported in (b). ET patient experiencing hand tremor. **d** Temporal data pattern measured during a 35-s acquisition with a patient with ET experiencing hand tremor by accelerometer; **e** Frequential analysis performed with FFT of acceleration signals reported in (d)

comprised a tri-axial accelerometer (measurement range: from −8 to 8 g; accuracy: lower than 3% of full scale range), a battery, a memory support, and a microcontroller unit. Data from the tri-axial accelerometer was sampled with a frequency of 100 Hz per channel, obtaining acceleration signals for each axis: $a_x(t)$ for x-axis, $a_y(t)$ for y-axis, and $a_z(t)$ for z-axis, where t is the time. The duration T of data acquisition was set to 24 h. Detected data were processed to perform the offset compensation of accelerometric data and to compute the Fast Fourier Transform (FFT)—,i.e., A_x for x-axis, A_y for y-axis, and A_z for z-axis.

The proposed method was based on the execution of a frequential analysis conducted through the FFT and on the execution of two different steps:

(a) the qualitative analysis of the obtained spectrograms and frequential data;
(b) the computation of concise indexes for the various motor symptoms on the basis of the conducted spectral analysis.

In particular, a preliminary spectral analysis was conducted through FFT on the entire 24-h acquisition with reference to the three axes of the accelerometer to verify the presence of significant spectral content in the frequency range of movement disorders. However, such information concerns the entire acquisition period from a global point of view, so to analyze every moment of the day and to ascertain the moments of acquisition containing likely motor symptom events, the 24-h recording were divided into equal time portions of the entire acquisition. For each time portion, the power spectral density of accelerometric signal was determined to obtain a spectrogram and time-frequency analysis.

The qualitative analysis of such frequential data and spectrograms was conducted to obtain an indication of the overall monitoring with simple visual examinations of the images containing such time-frequency analysis. For example, the visual inspection of 3D surface spectrograms may be used to evaluate the distribution of spectral energy for various temporal instants of the entire acquisition, the distribution of spectral energy on the various axes of the measuring system, the frequency of occurrence, and the intensity of motor activity within a certain frequency range.

In order to obtain the concise indexes, the following quantities were considered for each axis and for each portion, i, of the entire 24-h acquisition:

$$\left(E_{i,x}\right)_k = \int_{f_1}^{f_2} S_{\mathrm{ix}}\mathrm{df} \tag{1a}$$

$$\left(E_{i,y}\right)_k = \int_{f_1}^{f_2} S_{\mathrm{iy}}\mathrm{df} \tag{1b}$$

$$\left(E_{i,z}\right)_k = \int_{f_1}^{f_2} S_{\mathrm{iz}}\mathrm{df} \tag{1c}$$

$$E_{k,i} = \frac{\left(E_{i,x}\right)_k + \left(E_{i,y}\right)_k + \left(E_{i,z}\right)_k}{E_{k,\mathrm{REF}}} \tag{1d}$$

where f was the frequency, and the integral was computed from the frequency value, f_1, to the frequency value, f_2; S_{ix} was the power spectral density of the a_x signal for the time portion, i (the power spectrum S_{ix} of the time series, $i(t)$, described the distribution of power into frequency components, f, composing the signal a_x); S_{iy} is power spectral density of the a_y signal for the time portion, i; S_{iz} is the power spectral density of the a_z signal for the time portion i; the subscript k was used for distinguishing various movement disorders ("P" refers to hand tremor due to PD, "ET" refers to hand tremor due to essential tremor, "D" to LID in patient with PD and "B" to bradykinesia); $E_{k,\mathrm{REF}}$ was a reference value of spectral energy; $E_{k,i}$ was a normalized value of the sum of the spectral energy values detected on each axis.

The above parameters were used to perform an inter-axes comparison and to quantify the mode by which the detected frequential content was distributed over the various axes of the measurement system, thus allowing the detection of a specific movement pattern typically associated with PD and other motor symptoms.

For example, in order to evaluate the concise indexes associated with hand tremor in PD (k = "P"), the numerical integration of Eq. (1) was carried out by considering $f_1 = 3$ Hz and $f_2 = 7$ obtaining, for each temporal portion i, the following quantities: $(E_{i,x})_P$, $(E_{i,y})_P$, and $(E_{i,z})_P$. These parameters were related to the spectral energy, within 3 and 7 Hz, distributed during a specific temporal portion, i, on the x, y, and z-axis, respectively. However, such spectral energy may be due to movement disorders or typical daily motor activity. Therefore, to evaluate the occurrence of possible hand tremors due to PD, a differential comparison between the axial spectral energy parameters $(E_{i,x})_P$, $(E_{i,y})_P$, and $(E_{i,z})_P$ was performed (inter-axes evaluation).

Figure 1b shows the temporal and frequential pattern for each axis of the acceleration signal acquired from a patient with PD during a hand tremor event with pronation–supination characteristics. As reported in Fig. 1c, the frequential content within 3 and 7 Hz for the x-axis was greater than the frequential content within 3 and 7 Hz for the y-axis and z-axis; finally, from computation of the parameters in Eq. (1), it emerged that the frequential content within 3 and 7 Hz for the z-axis was greater than the frequential content within 3 and 7 Hz for the y-axis. Therefore, in this proposed method, the detection of a possible hand tremor event due to PD occurred if a specific spectral energy distribution due to pronation–supination was found. Hence, for a temporal portion i, a possible hand

tremor event due to PD was detected if the following conditions were simultaneously verified:

$$\begin{cases} (E_{i,x})_P > (E_{i,z})_P + \sigma_{xz} \\ (E_{i,x})_P > (E_{i,y})_P + \sigma_{xy} \\ (E_{i,z})_P > (E_{i,y})_P + \sigma_{zy} \end{cases} \quad (2)$$

where σ_{xz}, σ_{xy}, and σ_{zy} were threshold values to be set according to the desired selectivity.

On the basis of such a discriminating method, some concise indexes were defined in order to quantify the severity of tremor due to PD.

For each time portion i, the $B_{P,i}$ index was defined; for the time portions, i, in which possible hand tremor events due to PD were not detected (i.e., the conditions (2) are not simultaneously verified), the value of the $B_{P,i}$ index equaled zero, whereas the value of $E_{P,i}$ might be different from zero; for the time portions, i, in which possible hand tremor events due to PD are detected (i.e., the conditions (2) are simultaneously verified), the value of the $B_{P,i}$ index was equal to $E_{P,i}$ and was related to the severity and the intensity of movement occurring during the time portion, i.

Moreover, for the entire duration of acquisition, the following concise indexes were found:

- the B_P index (bustle intensity index) was defined as the sum of the $B_{P,i}$ indexes detected during the acquisition period and summarized the total movement severity and intensity related to the entire duration of monitoring (e.g., 24 h);
- the $\overline{B_P}$ index (mean bustle intensity index) was defined as the mean of the $B_{P,i}$ indexes as different from zero;
- the L_P index (lasting index) was related to the number of detected events (according to conditions in (2)) and, as a consequence, was related to the cumulative duration of the various possible hand tremor events detected during the entire duration of monitoring period (e.g., 24 h) or another reference duration. The L_P index was reported in a time unit (e.g., $L_{P,\min}$ for minutes, $L_{P,h}$ for hours) or as the ratio between the cumulative duration of symptoms and the duration T of the acquisition, e.g., $L_{P\%} = L_{P,h}/T$;
- the BL_P index was defined as the product between L_P index and B_P index and summarized both severity and duration of movement disorders detected during the entire duration of monitoring time. Another index considering both severity and duration is the $\overline{\mathrm{BL}_P}$ index, which was defined as the product between L_P index and $\overline{B_P}$ index.

Similarly, other B, $\overline{B}$, L, $\overline{\mathrm{BL}_P}$, and BL indexes may be defined for the other movement disorders.

For the hand tremor in patients affected by essential tremor (Fig. 1d), the distribution of spectral energy among the various axes of the measurement system was typically characterized by a spectral energy (between 5 and 10 Hz) on the z-axis being greater than the spectral energy (between 5 and 10 Hz) on the x-axis (Fig. 1e). Therefore, in patients with ET, the detection of a possible event of tremor with flexion–extension pattern was achieved by considering $f_1 = 5$ Hz, $f_2 = 10$ Hz, $k =$ "ET" in (1) and the condition:

$$(E_{i,z})_{\mathrm{ET}} > (E_{i,x})_{\mathrm{ET}} + \delta_{zx} \quad (3)$$

where δ_{zx} was a threshold value to be set according to the desired selectivity. Similarly to the argumentation on tremor due to PD, the following indexes for tremor in patients with ET were defined: $\overline{B_{\mathrm{ET}}}$, L_{ET}, $\mathrm{BL}_{\mathrm{ET}}$, $\overline{\mathrm{BL}_{\mathrm{ET}}}$, $B_{\mathrm{ET},i}$ and B_{ET}.

With reference to LID, dyskinesia typically may happen between 1 and 8 Hz, and patients' individual dyskinesia phenomenology tends not to change with time [33].

Therefore, it is likely not possible to define an absolute pattern associated with dyskinesia. In this proposed method, the detection of possible dyskinesia events was carried out mainly with an in-depth investigation into the obtained spectrograms and frequential data (qualitative analysis). This analysis should take into account that patients with LID are infrequently motionless, and their movements are typically characterized by a higher spectral energy and a higher intensity than a normal person. Therefore, as reported in greater detail in the following section, qualitative analysis may be used to evaluate the distribution of power spectra between 1 and 8 Hz in the various temporal instants of the entire acquisition process, the distribution of spectral energy on the various axes of the measuring system, the frequency of occurrence of motor activity between 1 and 8 Hz, and the intensity of motor activity events between 1 and 8 Hz and compared with the typical intensity values found in normal subjects and in patients with hand tremors due to PD.

For patients with dyskinesia, the parameters in (1) were computed by considering that $f_1 = 1$ Hz, $f_2 = 8$ Hz, and $k =$ "D," to obtain $E_{D,i}$. Then, the computed $E_{D,i}$ values were compared to μ_D, which is a threshold value to be set according to the desired selectivity. Therefore, for each time portion i, the $B_{D,i}$ index was defined; for the time portions, i, if $E_{D,i}$ was equal to or lower than μ_D, the value of the $B_{D,i}$ index was equal to zero; for the time portions, i in which $E_{D,i} > \mu_D$, the value of the $B_{D,i}$ index was equal to $E_{D,i}$. Similarly to the previous argument, the following indexes for dyskinesia were defined: $\overline{B_D}$, L_D, $\overline{\mathrm{BL}_D}$, BL_D, and B_D.

Finally, it is likely not possible to define an absolute movement pattern associated with bradykinesia. Thus, similar to the argument for dyskinesia, the study on bradykinesia was conducted mainly by means of qualitative analysis with an in-depth investigation into spectrograms and looking for events in the range between 0.2 and 3 Hz. Similarly to the definition

of indexes and to the dissertation on dyskinesia, the following indexes for bradykinesia were defined: $\overline{B_B}$, L_B, $\overline{\mathrm{BL}_B}$, BL_B, $B_{B,i}$, and B_B. The $B_{B,i}$ index was evaluated considering that: if $(E_{B,i})^{-1}$ was greater than a certain threshold value, $B_{B,i}$ index was equal to $(E_{B,i})^{-1}$, otherwise $B_{B,i}$ was equal to zero.

Results

A preliminary evaluation of the proposed method is reported in the Supplementary Material with experimental trials carried out with both normal patients (controls) and patients with movement disorders (cases), together with a preliminary and exemplifying assessment of the performances on sensitivity, specificity, and accuracy [37] of the proposed method.

Results with the proposed concise indexes are reported in Table 1. As an example, a right-handed patient (male, 66 years) with hand tremor due to PD was instructed to wear the device on his left wrist (most affected wrist) for 24 h with the possibility of removing it in particular conditions (e.g., during showering). Data acquisition began at about 8:30 a.m. and data measured during the monitoring period are reported in Fig. 2a, whereas the correspondent FFTs of such accelerometric signals are reported in Fig. 2b. Figure 2c shows the 3D surface representation of the power spectrum detected on the *x*-axis (see Supplementary Material for the other axis). As in the previous section, the power spectrum, S_{ix} of the time series, $i(t)$ describes the distribution of power into frequency components, f, composing the signal, a_x; in this representation, the time t was reported according to the format hh:mm (ISO 8601). From the visual inspection of such time-frequency analysis, the presence of various motor events within the frequential range between 3 and 7 Hz was observed, particularly during the first half of the acquisition. Moreover, some events were also noticed during the night, e.g., at about 4:00 a.m. Figure 2d, e show the temporal patterns of the root mean square, a_{RMS} of acceleration, the $B_{P,i}$ index, and the quantity $E_{P,i}$; according to the proposed processing method, most of the motor events in the first part of recording were discriminated as possible hand tremor events due to PD occurring in the pronation–supination direction. Other motor events (e.g., between about 17:00 and 19:00, and between about 21:00

Table 1 Results on the concise indexes detected during various 24-h acquisitions performed with patients with movement disorders. ID is the identifier of the 24-h acquisition. IDs from (a) to (m) refer to indexes on hand tremor due PD which were computed in patients with hand tremor due to PD; IDs from (o) to (q) refer to indexes on LID which were computed during acquisitions performed with patients affected by PD and with LID; IDs from (r) to (s) refer to indexes on hand tremor due to ET which were computed during acquisitions performed with patients affected by ET

ID	Patient	B-index	L-index			LB-index
			$L_{\min}$ (min)	L_h (h)	$L_{\%}$	
ID (P)	Detail on patient with hand tremor due to PD	B_P	$L_{P,\min}$ (min)	$L_{P,h}$ (h)	$L_{P\%}$	LB_P ($L_{P\%} \times B_P$)
(a)	Female, 60 years	59.16	374.73	6.25	0.26	15.39
(b)	Male, 66 years	27.17	318.33	5.31	0.22	6.01
(c)	Female, 64 years	31.05	234.33	3.91	0.16	5.05
(d)	Male, 84 years	25.50	272.87	4.55	0.19	4.83
(e)	Male, 61 years	24.14	167.60	2.79	0.12	2.81
(f)	Male, 73 years	38.59	84.80	1.41	0.06	2.27
(g)	Male, 66 years	16.61	188.13	3.14	0.13	2.17
(h)	Male, 80 years	43.50	70.20	1.17	0.05	2.12
(i)	Male, 80 years	13.41	123.33	2.06	0.09	1.15
(l)	Male, 59 years	3.86	63.73	1.06	0.04	0.17
(m)	Female, 71 years	4.70	39.60	0.66	0.03	0.13
ID (D)	Detail on patient affected by PD and with LID	B_D	$L_{D,\min}$ (min)	$L_{D,h}$ (h)	$L_{D\%}$	LB_D ($L_{D\%} \times B_D$)
(o)	Male, 80 years	296.85	919.13	15.32	0.64	189.47
(p)	Male, 80 years	197.59	689.53	11.49	0.48	94.61
(q)	Male, 73 years	102.29	267.13	4.45	0.18	18.98
ID (ET)	Detail on patient affected by ET	B_{ET}	$L_{\mathrm{ET},\min}$ (min)	$L_{\mathrm{ET},h}$ (h)	$L_{\mathrm{ET}\%}$	$\mathrm{LB}_{\mathrm{ET}}$ ($L_{\mathrm{ET}\%} \times B_{\mathrm{ET}}$)
(r)	Male, 78 years	42.82	255.33	4.26	0.18	7.59
(s)	Female, 73 years	4.70	737.87	12.30	0.51	2.41

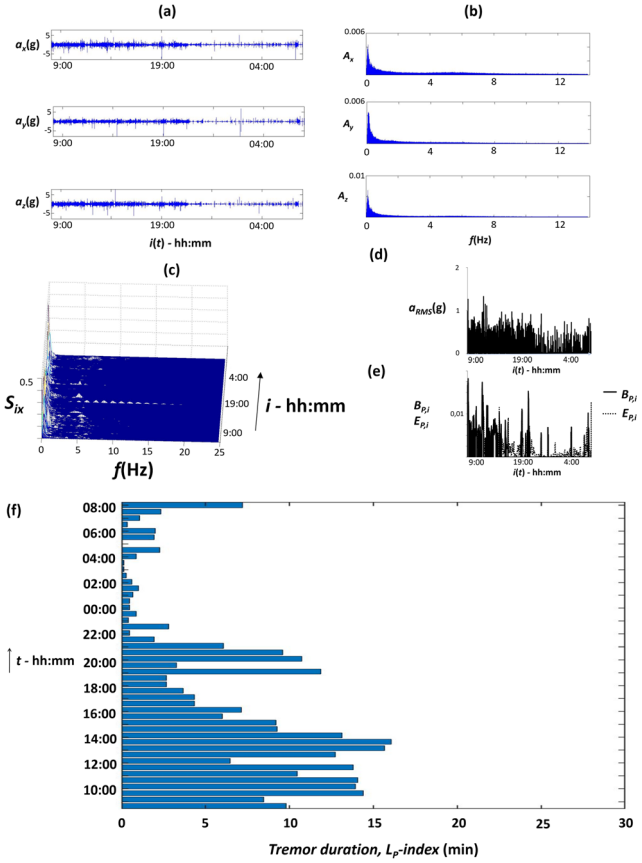

Fig. 2 24-h acquisition for patient with hand tremor due to PD. **a** Temporal pattern of acceleration signals. **b** FFT of acceleration signals. **c** Time-frequency analysis. Temporal patterns of the: **d** root mean square a_{RMS} of acceleration, **e** $B_{P,i}$-index, and $EP_{,i}$-index. **f**. Tremor duration detected by the device during the trial in time intervals of 30 min

and 4:00 a.m.) were not detected as possible hand tremors due to PD (in Fig. 2e, the $B_{P,i}$ index is equal to zero, whereas the parameter $E_{P,i}$ is different from zero). Indeed, for such events, even if the frequential content was within 3 and 7 Hz, the characteristic pattern of pronation–supination due to tremor in PD was not detected. Finally, Fig. 2f summarizes the tremor duration detected by the device during the trial in time intervals of 30 min.

The above results may be used both to evaluate a single data acquisition and to compare more data acquisitions for the same patient to assess the temporal progression of the illness and the effectiveness of the therapeutic intervention in place. For example, Fig. 3a, b show the comparison between two different 24-h monitoring periods conducted on the same patient in two different days by means of the 3D surface representations of the power spectrum detected on the *x*-axis. During the first day of monitoring (Fig. 3a), the patient was untreated; after considering the results of monitoring and an in-depth neurological examination, a treatment based on the use of a dopamine agonist was prescribed to the patient from the neurologist. Then, a second 24-h period of monitoring was performed with the same patient after treatment with the dopamine agonist (Fig. 3b). The visual inspection of both 3D surface representations of the power spectrum reported in Fig. 3a, b shows that the frequency of occurrence of motor activity events within 3 and 7 Hz in the first 24-h of monitoring was lower than the same in the second 24-h monitoring period; Figure 3c, d shows the comparison between the tremor duration detected by the device during the different days, confirming that the cumulative duration of tremor in the first monitoring (untreated patient) is greater than the duration related to the second monitoring (treated patient). Moreover, Fig. 3e, f shows the comparison between the values of the $B_{P,i}$ index detected during the different monitorings; in Fig. 3e, the values of the $B_{P,i}$ index computed for each 24-h of monitoring were sorted and plotted from the lowest to the highest value of $B_{P,i}$ with respect to the total duration of the monitoring. In this plot, it is possible to find a graphical relationship with the indexes of the proposed method; indeed, the L_P index corresponds to the first time value along the abscissa axis where the value of the $B_{P,i}$ index is different from zero; finally, the $\overline{\mathrm{BL}_P}$ index ($\overline{\mathrm{BL}_P} = L_P \times \overline{B_P}$), summarizing both severity and duration of movement disorders detected during the entire 24-h of monitoring, is related to the area under the curve.

Therefore, from a visual inspection of Fig. 3e, it emerges that the indexes related to the first 24-h of monitoring (untreated patient, dashed line in the graph) are greater than those related to the second 24-h of monitoring (patient treated with dopamine agonist, solid line in the graph). Indeed, the cumulative duration of tremor in the first monitoring is about 5 h compared to the second monitoring of about 3 h ($L_{P,1} > L_{P,2}$), as reported also in Fig. 3c, d. Moreover, the area under the curve for the first monitoring seems greater than that in the second monitoring ($\mathrm{BL}_{P,1} > \mathrm{BL}_{P,2}$). From a numerical point of view, $\mathrm{BL}_{P,1}$ was equal to 6.01 and $\mathrm{BL}_{P,2}$ was equal to 2.17 with a reduction of about 64% of the BL_P-index from the first monitoring (untreated patient) to the second monitoring (treated patient). This seems to confirm that the considered therapeutic treatment reduced the motor symptoms.

An alternative graphical representation of the computed $B_{P,i}$ indexes was based on the cumulative distribution function of $B_{P,i}$ (Fig. 3f) or on the normalized cumulative distribution function of $B_{P,i}$. In this representation, the B_P index was the maximum value found on the ordinate axis. The graphical representation shown in Fig. 3e, f may be adopted for each motor symptom.

As an example dealing with a patient affected by PD and with severe LID, Fig. 4a reports data measured in a right-handed patient (male, 80 years). The correspondent computed FFTs showed the presence of an important frequential content around 4 Hz on every axis (Fig. 4b). From the visual inspection of the 3D power spectrum detected on the *x*-axis (see Supplementary Material for the other axis), it emerged that

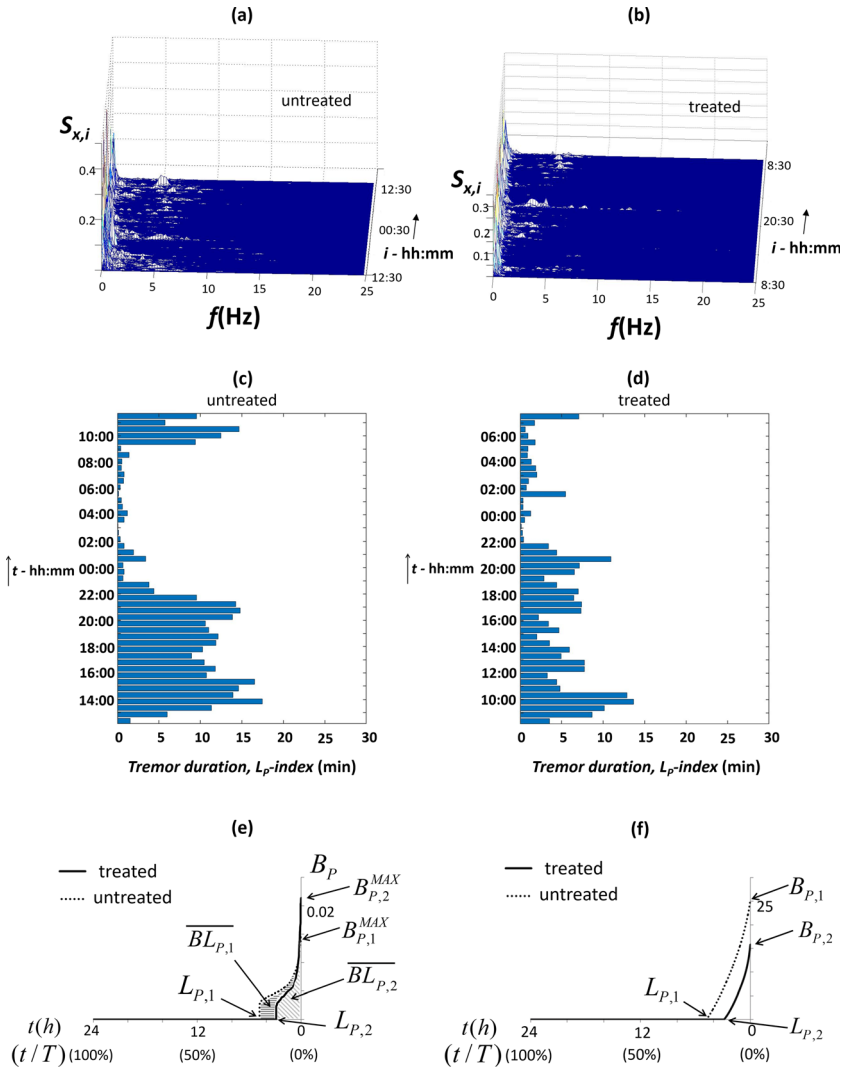

Fig. 3 Comparison between two different 24-h acquisitions. Power spectrum detected when patient was: **a** untreated and **b** treated. Tremor duration detected by the device during the trial in time intervals of 30 min when patient was: **c** untreated and **d** treated. Representation of the $B_{P,i}$ indexes detected during each 24-h acquisition: **e** after the operation of sorting and **f** by cumulative distribution function

most of the entire duration of 24-h acquisition was characterized by motor activity mainly comprised between 3 and 10 Hz, with a peak mainly around 4 Hz (Fig. 4c). Qualitative analysis of this data confirmed that there were typical features of a Parkinsonian patient with severe dyskinesia. In particular, it is possible to confirm that the patient was rarely motionless during the day, and the contribution of frequency between 0.5 and 3 Hz was very low with respect to the higher spectral density between 3 and 6 Hz. Figure 4d, e shows the temporal patterns of the root mean square a_{RMS} of acceleration and the $B_{D,i}$ indexes computed for data reported in Fig. 4a, confirming that the patient with dyskinesia was rarely motionless during the day ($L_{D,h}$ was about 15 h and $L_{D\%}$ was equal to about 63%). Finally, Fig. 4f recaps the tremor and dyskinesia duration detected by the device during the trial in time intervals of 30 min.

Figure 5 reports data measured during a 24-h acquisition with a patient (male, 73 years) affected by PD and with a dyskinesia less severe than that in the previous patient whose results are shown in Fig. 4 (from data shown in the Fig. 5, $L_{D,h}$ was about 4 h and $L_{D\%}$ was equal to about 18%). Fig. 5e reports the plot with $B_{D,i}$ indexes which are representative of the pattern of patient's motor fluctuations during the day.

Results of a 24-h acquisition with the patterns of the various movement disorders considered here are reported in Supplementary Material.

Discussion

Several methods have been proposed to assess motor symptoms in patients with PD. However, most systems available to date still do not allow continuous monitoring of movement disorders during the day; other systems for continuous monitoring are based on signal processing to evaluate the frequential content of signals in the spectral range in which movement disorders due to PD typically occur. However, as most typical daily motor activities performed by patients may have a power spectrum in the same range as those due to motor symptoms, the mere evaluation of the frequential

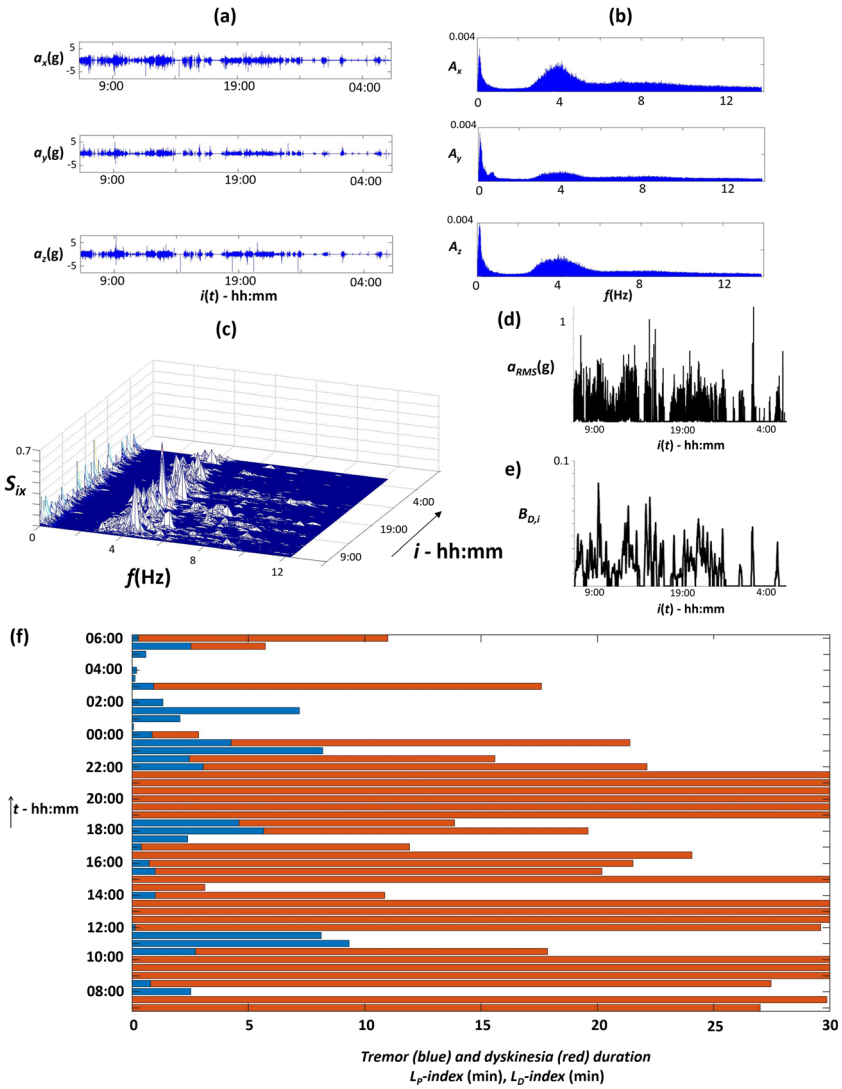

Fig. 4 24-h acquisition for patient affected by PD with severe dyskinesia. **a** Temporal pattern of acceleration signals. **b** FFT of acceleration signals. **c** Time-frequency analysis. Temporal patterns of: **d** the root mean square a_{RMS} of acceleration, **e** the $B_{D,i}$ index. **f** Tremor and dyskinesia duration detected by the device during the trial in time intervals of 30 min

content usually does not allow a distinction between movement disorders and normal daily motor activity.

Here, we have reported the results obtained by means of a new device for the continuous and long-term monitoring of movement disorders. This also reduces the probability of being mislead in the discrimination between extrapyramidal symptoms and normal daily activity. The preliminary illustrative evaluation confirms that performances on sensitivity, specificity, and accuracy of the proposed method are very promising.

The proposed system differs from other studies, and magneto-inertial systems as it is not only based on the evaluation of frequential content of data from multi-axial sensors, but also on the identification of specific movement patterns typically associated with Parkinsonian and extrapyramidal symptoms (e.g., a supination–pronation movement of the hand between 3 and 7 Hz) is typically encountered during hand tremor events in patients with hand tremor due to PD; a flexion–extension pattern of the hand between 3 and 12 Hz is typically encountered during hand tremor events in patients with hand tremor due to ET). We report the results of this proposed approach by considering one possible processing method for the discrimination of such patterns based on the use of a multi-axial measuring system and on the quantification of the mode by which the detected frequential content is distributed over the various axes of the measurement system. Although most of the current systems and methods are based on the use of a multi-axial measuring device (e.g., tri-axial accelerometer), they typically do not evaluate the distribution of spectral power and energy among the various axes; indeed, they usually only refer to the root mean square (RMS) or to the quadratic mean of the signals of the various axes, without any intra-axis and inter-axis comparison. Evidently, the root mean square value condenses the information of all axes, so, the use of this parameter and other similar summary parameters usually does not allow an extraction of the information on single

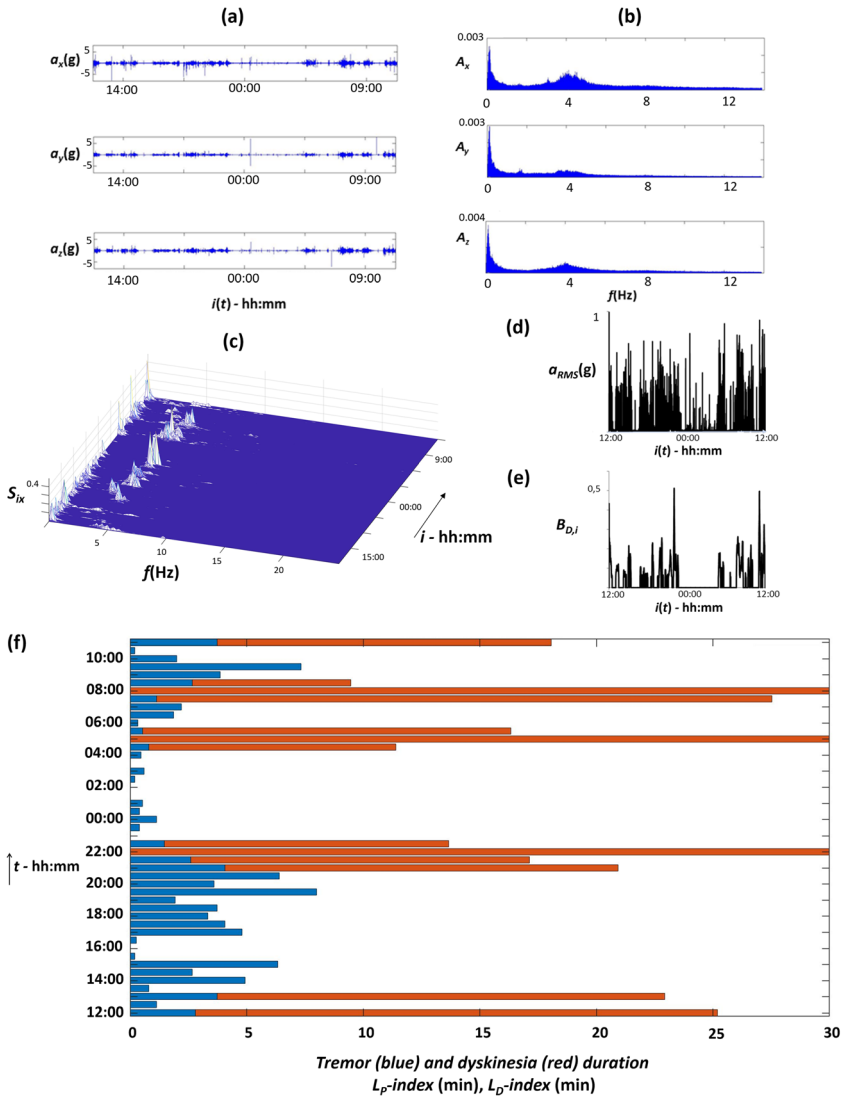

Fig. 5 24-h acquisition for patient affected by PD with dyskinesia. **a** Temporal pattern of acceleration signals. **b** FFT of acceleration signals. **c** Time-frequency analysis. Temporal patterns of: **d** the root mean square a_{RMS} of acceleration and **e** the $B_{D,i}$ index. **f** Tremor and dyskinesia duration detected by the device during the trial in time intervals of 30 min

axes and on the movement pattern occurring. However, the execution of the proposed method might need a computational efforts slightly greater than ones required by other processing methods, due to the need of performing frequential analysis for each axis.

Moreover, the proposed method is based on the qualitative analysis of the obtained frequential data and on the computation of concise indexes for the various motor symptoms (i.e., tremor, essential tremor, dyskinesia, and bradykinesia).

The qualitative analysis of the frequential data and power spectrograms was conducted to obtain an indication of the overall monitoring by means of a simple visual examination of the images containing such time-frequency analysis.

The computation of concise indexes with the here proposed method (the so-called "BL-method") for the various motor symptoms allows information to be obtained both for every moment of the day (the B_i-index is evaluated for each time portion, i, of the acquisition) and the entire monitoring duration (24 h or other). In fact, the entire acquisition can be summarized, for each symptom, with the L-index (related to the cumulative duration of the detected symptom), the B-index (related to the cumulative severity of the detected symptom), the $\overline{B}$ -index (related to the mean of the values of B_i-index different from zero), the $\overline{\mathrm{BL}}$ -index and the BL-index (related to the combination of both cumulative duration and cumulative severity of the detected symptom).

Both qualitative analysis and computation of impairment indexes can be used to compare various monitoring acquisitions for the same patient to assess the temporal progression of the illness and to evaluate the effectiveness of the therapeutic intervention in place. Moreover, they can be used to perform a statistical analysis on a patient's sample and to have a graphical representation of the proposed indexes.

Evidently, results on the proposed method need to be extended with further studies and more clinical trials involving

other patients with various kinds and severity of symptoms. Nevertheless, the proposed system and method appear promising and suitable for use as part of clinical trials and routine clinical practice for supporting the evaluation of motor symptoms, the progression of the disease, the quantification of the effects of the therapeutic action, and as a comparison between several acquisitions.

Other studies are going to be carried out in order to compare the proposed concise indexes to the current rating scales (e.g., Unified Parkinson's Disease Rating Scale) and to improve performances of the proposed method (e.g., analyzing distinction between different kinds of tremor due to PD).

Authors' contribution LB conceived the device and the method. AR is the principal investigator of the clinical trial. All authors discussed results.

Compliance with ethical standards

Conflict of interest Eng. Luigi Battista is the inventor and, to date, holds intellectual property rights of an Italian patent and has filed for a patent related to a wearable system for Parkinson's disease. Dr. Antonietta Romaniello has nothing to disclose.

Informed consent Informed consent was obtained from all individual participants included in the study.

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