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Quantitative assessment of Parkinsonian tremor by using biosensor device

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Abstract

Parkinson disease (PD) is the second most common neurodegenerative disease which affects population older than 65 years. Tremor represents one of the main symptomatic triads in PD, particularly in rest state.

We enrolled 41 idiopathic PD patients, to validate the assessment of tremor symptoms.

To be enrolled in the study, patients had to fulfill the movement disorder society clinical diagnostic criteria for PD.

We used an innovative home-made, low-cost device, able to quantify the frequency and amplitude of rest tremor and stress condition

Our results confirmed the presence of tremor during muscular effort in a significant number of patients and the influence of emotional stress.

We suppose that this new device should be validated in clinical practice as a support of differential diagnosis and therapeutic management of PD patients.

Abbreviations: MMSE = mini-mental state examination, PD = Parkinson disease, UPDRS = unified Parkinson disease rating scale.

Keywords: biosensor device, Parkinson disease, tremor

1. Introduction

Parkinson disease (PD) is a progressive neurodegenerative disorder characterized by bradykinesia, rest tremor, rigidity, and postural instability.[1,2,3,4,5,6] Parkinsonian tremor (oscillatory movement) is the central symptom of PD, presenting in about 70% of PD patients. It can be located at patient's hands, feet, and head with a particular frequency (3.5–7.5 Hz) and amplitude (speed and range).[7] In particular, tremor is produce when there are alternate and synchronous contractions of reciprocally innervated agonistic an antagonistic muscle that cause a symmetrical displacement about the midpoint of the movement in both directions.[8] Parkinsonian tremor manifests under different types: rest, postural, and action tremor. Rest tremor, is the most characteristic of PD and appears, when a body part is relaxed. The postural tremor occurs while a body part is held straight out from the body in a stable position against gravity. The action tremor (kinetic tremor) is present when a voluntary contraction of a muscle follows a certain action—for example, holding a cup.[6] In a PD patient, postural or action tremors appear together with rest tremor, but with different frequencies. Rest tremor may be combined with postural tremor, but disappears during an action tremor task. However, the tremor severity is not always associated with age or disease duration.[8] The unified Parkinson disease rating scale (UPDRS), is the clinical standard for Parkinsonian tremor assessment.

In literature, some authors have used infrared cameras, video tracking, digital drawing tablets, laser-based displacement transducers, and electromyography (EMG) to assess tremors objectively.[1–11] Sensors were placed on the body, feet or arms of the patient. Most of these sensor-based systems could detect the change between "OFF" and "ON" therapy states. However, due to their dimensions or uncomfortable wearing, these systems have limited usability in clinical applications.[10]

Advanced technologies created more precise transducers, affordable, portable, and capable of long-term recording. The most common transducer-based methods are: accelerometry, EMG, gyroscopy, vocal acoustic analysis, and digitizing tablet-based measures.

The kinematic characteristics of tremor and motor task must be considered, and the transducer needs to have sufficient sensitivity, amplitude range, and frequency range to record

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tremor with good fidelity. The transducer should also be small, and light.[12]

Several tremor recording methods have been used: from mobile applications (Android and Apple),[13] to smart watches and wrist-worn activity.[14]

Several studies focused their attention on rest tremor, but some studies have shown that PD patients showed postural tremor that may cause more disability than typical rest tremor, in particular during stress-state conditions.[15]

The aim of our study was to evaluate tremor symptom in idiopathic unilateral tremorigen PD patients using an innovative home-made, low cost and easy device, able to quantify the frequency and amplitude in the 3 axes (x, y, z) and to support the clinical practice and the evaluation of disease progression.

2. Materials and methods

2.1. Patients

We studied 41 consecutive idiopathic unilateral right-handed tremorigen PD patients without dementia Neurolesi (19 females and 22 males, mean age = 70 ± 11.3 years; Hohen & Yahr stage, mean = 1.5 ± 1; UPDRS motor subscore, mean = 21.1 ± 8.9), All patients were admitted to Disorder Movement Unit of IRCCS Centro. Patients included had mini-mental state examination (MMSE) basal score >24: they had not cognitive impairment or attention deficit.

All patients were taking levodopa alone (20 patients) or combined with dopamine agonist (15 with ropinirolo and 6 with pramipexolo). In addition, 3 patients were taking also entacapone.

Each assess was carried out by the same investigator (GDL, CS, and SM for clinical and neuropsychological testing, EC for tremor evaluation). The evaluation included the following assessments: MMSE, UPDRS motor sub-score, and tremor severity.

Data of PD patients were compared to those of 36 demographically age-sex matched healthy controls (HC) (14 females and 22 males, mean age = 60.2 ± 7.2 years).

The study was approved by the Local Ethics Committee and informed consent was obtained from all subjects.

2.2. Tremor device

This device is able to record tremor of each single hand's finger, by computers connection (via Wi-Fi or Bluetooth). It is able to perform an instant and complete analysis giving the values of frequency and amplitude. We also compared our obtained results with literature studies, to validate the device for future use in daily tremor monitoring.

We analyzed the presence or absence of rest tremor and in a stress condition with muscular effort to evaluate the differences and quantify the influence of emotional and muscular stress.

Each patient was subjected to tremor level measurement in 2 positions for each side: 1 at rest state (arm on the bed) and 1 under muscular effort (arm suspended in the air). Each measurement had a minimum duration of 1 minute. Accelerometers were placed on hand's fingers (Fig. 1). All subjects were asked to wear the system keeping own hand, without any further weight, and the tremor was then evaluated. Finally, all subjects were asked to hold a pen with the same hand, and the measurement procedure was performed again. Data were recorded and displayed by mean of the multithread interface developed in Java.

Figure 1. Device positioning: accelerometers were placed on hand's fingers.

The system used in this study for tremor recording was a card Linkit ONE and an array of 4 3-axis accelerometers ADXL345 (Analog Devices). The ADXL 345 is a small, thin, ultra-low power, 3 axis accelerometer with high resolution (13-bit) measurement at up to ±16 g. Digital output data is formatted as 16 bit two's complement and is accessible through either a SPI (3 or 4 wire) or I2C digital serial interface. The platform is equipped with a GPS positioning system, able to geo-reference data from the accelerometer and send them via Bluetooth.

The core of the system is based on the MediaTek MT2502 system-on-chip; with a processor ARM7 EJ-S 260 MHz and a memory of 4MB RAM and 16 MB Flash, equipped with long battery life (3.8 V 5100 mAh).

The system has the size of a cigarette packet and the enclosure is assembled in a 3D printed polylactic acid version, the design of

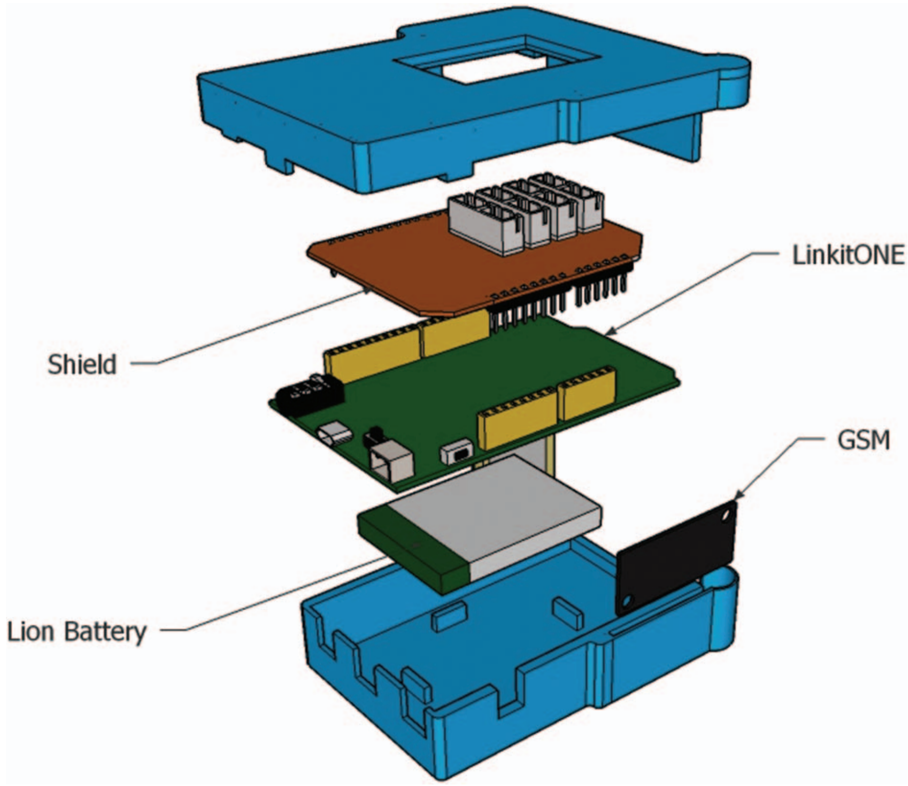

Figure 2. Three-dimensional enclosure design.

the version with the array of 4 accelerometers and its realization is shown in Figures 2 and 3, respectively.

The configuration with an array of 4 accelerometers is able to monitor movement quality. A circuit board was designed to connect the accelerometer array with the Linkit ONE board.

The graphical user interface for personal computer, developed in Java environment, thanking to its multithread features, it is able to handle the data coming from accelerometer array via Bluetooth a low energy. It is possible to set the sampling time and the activation of each sensor to evaluate several parts of the body of the subject wearing the system. A digital low pass filter was employed to perform a better evaluation of the measurement data.

Figure 3. Three-dimensional printed enclosure with 4-accelerometer array.

2.3. Statistical analysis

The software used for tremor analysis was GNU Octave (https://www.gnu.org/software/octave/). GNU Octave is a high-level language, primarily intended for numerical computations. It provides a convenient command line interface for solving linear and nonlinear problems numerically, and for performing other numerical experiments using a language that is mostly compatible with Matlab. It may also be used as a batch-oriented language. The analysis software provided images of the tremor frequency in 3 axes (x, y, z) roll and pitch in the 3 axes, and the analysis of each single accelerometer. Normal distribution of data was evaluated using the Shapiro–Wilk normality test. Correlations among clinical variables (UPDRS-III) and tremor frequency was computed by the Spearman coefficient. The analyses were performed using an open source R3.0 software package (R Foundation for Statistical Computer, Vienna, Austria). A 95% of confidence level was set with a 5% alpha error. Statistical significance was set at $P < .05$.

3. Results

We found that all HC group showed a frequency range under 1 Hz. Twenty-six patients (63%) presented tremor with a frequency between 4 and 6 Hz (a single case at 7 Hz) in both conditions while 15 patients (37%) had mild or no tremor (frequency range between 1 and 2 Hz).

In 26 patients with tremor during stress condition, 13 (50%) had tremor bilaterally, 6 (26%) had tremor at left hand, 4 (15%) had tremor at right hand, 1 (4%) had tremor at right hand in rest state, 1 (4%) had tremor bilaterally in both conditions, and 1

(4%) had tremor left in both states. All patients showed a significant correlation between UPDRS score and tremor frequency ($P < .01$).

4. Discussion

PD is the second most common neurodegenerative disease after Alzheimer disease. Several risk factors and many protective factors have been suggested, sometimes in relation to theories concerning possible mechanisms of the disease, but no 1 has been definitively identified.

There are several studies, that by using conventional and not conventional neuroimaging methods and neurophysiological techniques, identify early markers of PD. Specially nonconventional magnetic resonance imaging (MRI) techniques, such as magnetic resonance spectroscopy, diffusion tensor imaging, and functional MRI, may allow the detection of structural, functional, and metabolic changes useful not only to differential diagnosis between PD and atypical syndromes, but also for early diagnosis, outcome, and treatment monitoring in PD.[16,17,18] The studies of olfactory[19] and nociceptive[20] system, reported alterations of early manifestation disease.

Tremor is one of the most common movement disorder encountered in clinical practice.

Tremor parameters (amplitude and frequency) provide useful clinical information for diagnosis and monitoring. Tremor represents one of the cardinal symptoms in the PD and it can be used to distinguish Parkinson tremor by other movement disorders. However, the study of clinical features of tremor in PD is not sample and a superficial analysis could induce a misdiagnosis, although, the rest tremor at range frequency between 4 and 6 Hz is considered typically characteristic of PD.[9] Several studies show that many PD patients have postural tremor that may cause more disability of rest tremor. Moreover, clinical tremor characteristics are affected by patient condition such as emotional and muscular stress.

Usually in the clinic practice, tremor is diagnosed during a time-limited process in which the patients are observed and the characteristics of tremor are visually assessed to better differentiate tremor conditions. Different techniques available for an objective quantification of tremor were developed in the last years.[21–22] The transducers used to tremor evaluation provide objective and precise linear measurements such as amplitude, frequency, and occurrence, without the potential bias introduced by patient perceptions and clinical rates. To date, most transducers for tremor evaluation were not developed to specific disorders, and the applicability of each device depends in the target signal for which it was developed.[11]

Several type of transducers are now readily available at reasonable cost, and can provide valid measures of tremor. In this study we introduce an innovative device for tremor assessment with the purpose of evaluate quantitative tremor characteristics in 41 PD patients, in rest and in stress condition. Our findings about the rest tremor features confirmed the literature data and the clinic evaluation. Moreover, we confirmed the presence of tremor during muscular effort in a significant number of patients[23–24] and the influence of emotional stress on the tremor characteristics, consistent with previous literature studies. Furthermore, the analysis of tremor parameters of Parkinson patients could be useful in pharmacological management of symptoms. The new device is characterized by availability, low cost, portability, easiness, and repeatability of use. Our previously data validated our device. In fact it should be used in clinical practice as a support of clinical evaluation to identification, differentiate, and diagnosis of tremor. In addition, the transducers are developed to be used by patient at home as a tool for daily tremor monitoring and investigation of therapy responsiveness.

Finally, we suppose that our device should be employed for a systemically standardization of tremor characteristics in different stage of PD to obtain a better clinical management.

Author contributions

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