Rest and action tremor in Parkinson's disease – effects of Deep Brain Stimulation

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Abstract— **One of the cardinal symptoms of Parkinson's disease is rest tremor. While rest tremor generally disappears during sleep and voluntary movement, action tremor may be triggered by voluntary movement, and may even be more disabling than rest tremor. Deep brain stimulation (DBS) in the subthalamic nucleus (STN) has been shown to be efficacious in the treatment of tremor. However, in most studies tremor is quantified using clinical scales such as the Unified Parkinson Disease Rating Scale (UPDRS). In this paper a pilot study is described in which the effect of DBS on rest and action tremor was investigated using inertial sensors for the quantification of tremor.**

Keywords— **Parkinson's disease, rest tremor, action tremor, Deep Brain Stimulation**

I. Introduction

Deep brain stimulation (DBS) is nowadays a widely used clinical therapy for Parkinson's disease (PD), even though its functional mechanisms remain unknown. The cardinal symptoms of the disease, (rest) tremor, rigidity, and bradykinesia are improved by applying continuous stimulation in the subthalamic nucleus (STN) at stimulation frequencies of around 130 Hz even at low stimulus amplitudes. Stimulation of the globus pallidus internus (GPi) in general has shown to be equally effective in symptom reduction, however, often a higher stimulation amplitude is required while the level of dopaminergic medication cannot be significantly reduced [1]. Stimulation of the ventralis intermedius nucleus of the thalamus (Vim) mainly reduces tremor without improving bradykinesia and rigidity.

Rest tremor, having a frequency between 4 to 6 Hz, is hypothesized to result from synchronized oscillatory activity in STN, GPe (globus pallidus externus) and GPi which is intimately related to rhythmic cortical activity [2]. Rest tremor tends to disappear during voluntary movement. During movement PD patients may show action tremor, which may cause the slowing of repetitive voluntary alternating movements [3]. The basis of action tremor is not clear. One hypothesis is that it results from oscillatory behavior in an internal feedback circuit that is triggered by voluntary movement. Another hypothesis is that it represents an exaggeration of normal physiological tremor, which might explain the higher tremor frequency (6-12 Hz) that is generally detected [4,5]. However, physiological tremor does not consist of one dominant frequency but has a broad spectrum. Action tremor can be present without rest tremor, but may be even more troublesome for the patient. Most tremor studies, however, focus on rest tremor as a typical parkinsonian symptom; relatively little attention is paid to parkinsonian action tremor. In this pilot study the effect of DBS on rest tremor and action tremor in both hands of two Parkinson patients was quantified using inertial sensors.

II. Methods

A. Measurement set up and protocol

Two parkinsonian patients participated in the study, both receiving bilateral DBS (Medtronic 3389 electrode lead) in the STN; surgery took place at least three months prior to the test, and the patients satisfied the following criteria:

- Good and fast (within 5 min.) response to stimulation;
- No major fluctuations in the symptoms due to medication;
- Good physical condition and able to fully cooperate during the experiments;
- No dementia and/or dyskinesia diagnosed.

All procedures conformed to the Declaration of Helsinki for experiments on humans and were approved by the Medical Ethical Committee of the Medisch Spectrum Twente in Enschede, the Netherlands. Both subjects signed informed consent before participation in the study.

Inertial sensors (MT9®, Xsens Technologies BV, Enschede, the Netherlands) that measure 3D angular velocity and acceleration were taped on both hands. The x-axis of the sensor was placed along the longitudinal axis of the hand; the y-axis transverse to the hand; and the z-axis perpendicular to the hand. Sensors were connected to the Xbus master that recorded acceleration and gyroscope data at a sample frequency of 50 Hz. The analog signals were filtered with a pre-sampling filter with a cut off frequency of 20 Hz prior to sampling. The data was sent to a laptop via Bluetooth.

Two tests were performed:

Test 1 – detection and quantification of rest tremor: while sitting at a table with the arms resting on the legs the patient was reading a text aloud for 30 seconds.

Test 2 – detection of action tremor: a tapping movement was performed with one hand on a table as fast as possible for 30 seconds; during tapping the wrist was resting on the table.

The study consisted of three series of the above mentioned tests; for each series different settings of the stimulator were applied:

S1: Settings currently used by the patient;

S2: The stimulation amplitude was reduced to 80% of the original setting;

S3: Stimulation was switched off.

In between the series patients were allowed 5 minutes of rest to adjust to the new DBS setting. The order of the tests was randomized for each series and the order of the series was randomized for each patient.

B. Signal analysis

For the analysis of the tremor data use was made of the method developed by Salarian et al. [6] for both types of tremor. The angular velocity (gyroscope) data from the inertial sensors was high-pass filtered with a cut off frequency of 0.25 Hz to remove drift (6^{th} order non-causal Butterworth filter). The signal was divided into 3-s windows for which the spectrum was estimated using an all-pole sixth-degree AR model using the Burg method. The pole with highest amplitude within the frequency range of 3.5-7 Hz, was selected as the dominant pole. For the window to be classified as containing tremor the dominant pole of one of the rotation axes (pitch, roll, yaw) had to exceed a threshold ranging between 0.85 and 0.92, depending on the type of tremor and the patient. The windows containing tremor were used for tremor analysis. For each tremor window the power spectral density (PSD) was calculated as well as the average PSD over all tremor windows when multiple tremor windows were detected. For each window the peak frequency and peak power were determined. In addition, the power spectrum for the total duration of the signal was determined using Welch's method, i.e. determining the average PSD using a Hann window and window lengths of 3 s and 0% overlap, conform the tremor windows. From the windows classified as containing tremor the percentage of time tremor was present during the tests was determined. The root-mean-square (RMS) value of the angular velocity of the tremor was calculated for each axes of rotation and for the norm of the three axes, expressed in deg/s.

The tapping movement was quantified by first filtering the angular velocity data with a low-pass filter with a cut off frequency of 3.2 Hz; tapping rates above 3.2 Hz were not expected and tremor frequencies were expected to be found above 3.5 Hz. The RMS value of the velocity of the tapping movement, the tapping frequency and the PSD of the movement were determined.

III. Results

A. Rest tremor

Fig. 1 shows the PSD of each tremor window as well as the average over all tremor windows of the right hand of patient 1 for the three settings of the stimulator. The DBS setting normally used by patient 1 reduces rest tremor considerably. At reduced stimulation amplitude (S2) tremor amplitude decreased. For S2 and S3 tremor was present during the total duration of the measurement. For the left hand of this patient DBS at S1 was not as efficient in reducing rest tremor. While at S2 for the left hand no rest tremor was detected, at S1 and S3 tremor windows were found. Table 1 gives the quantitative data with respect to rest and action tremor of patient 1.

Table 1 Quantification of rest and action tremor of patient 1.

Tremor parameters	S1	S2	S3
Left hand			
RMS rest tremor (deg/s)	2.41±0.45	0.0	12.32±3.76
rest tremor freq. (Hz)	4.79±0.96		4.66±0.19
%time rest tremor (%)	77.78	0.0	100.0
RMS action tremor (deg/s)	37.43±25.47	41.45±8.66	72.18±43.84
action tremor freq. (Hz)	4.33±0.39	4.17±0.50	4.64±0.53
%time action tremor (%)	87.50	66.67	100.0
Right hand			
RMS rest tremor (deg/s)	0.0	12.97±7.05	22.82±5.21
rest tremor freq. (Hz)		5.02±0.36	4.50±0.25
%time rest tremor (%)	0.0	100.0	100.0
RMS action tremor (deg/s)	59.20±32.14	64.31±13.94	128.10±11.13
action tremor freq. (Hz)	4.01±0.65	4.06±0.54	4.66±0.13
%time action tremor (%)	55.56	100.0	100.0

Patient 2 did not show rest tremor at S1 and S3 for both hands. For setting S2, however, a 'tremor' with large amplitude and low frequency, around 1.5 Hz, which is normally not associated with parkinsonian rest tremor, was found for both hands (see the upper graph of Fig. 2).

B. Action tremor

For all three stimulator settings patient 1 showed action tremor. At setting 2 the tapping movement could be performed with largest amplitude (the RMS of the angular velocity was 37.2 ^{o}/s) and highest frequency (2.4 Hz) with the left hand. However, as shown in Fig. 3, during the periods that action tremor was most severe the tapping

amplitude was significantly reduced. The average frequency of action tremor was about 4.8 Hz for the left hand, and 4.4 Hz for the right hand. The ratio of 2 for the frequency of action tremor and tapping frequency might indicate that action tremor plays a role in pacing the speed of tapping, as was also observed by Berardelli et al. [7].

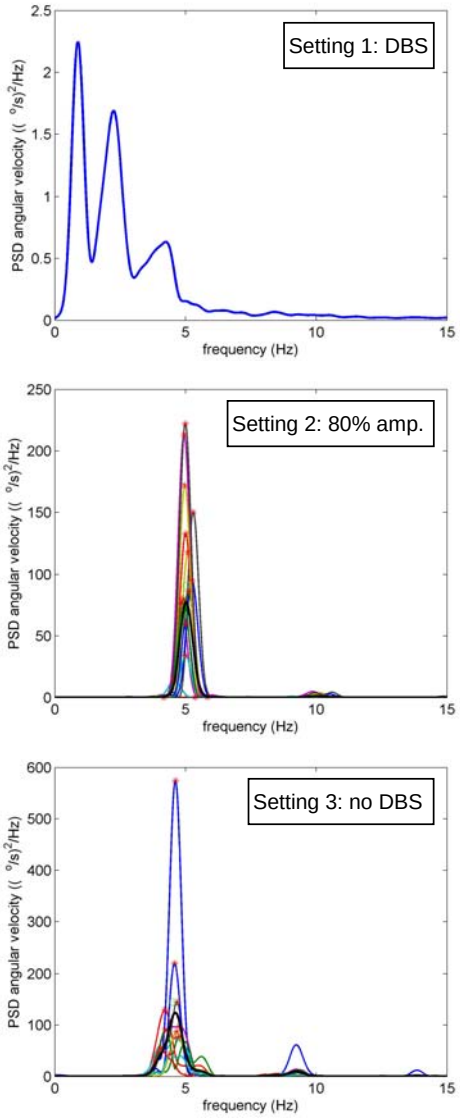

Fig. 1 Power spectra (PSD) of rest tremor for patient 1, S3 (stimulation off) - upper graph; S2 (80% amplitude) - middle graph; S1 (DBS) - lower graph. Each curve represents a 3s tremor window with * indicating the tremor frequency of each window and o the mean tremor frequency; the black curve in the lower two graphs presents the mean PSD of the tremor windows. Since for S1 no rest tremor was detected the PSD of the total signal is given in the upper graph.

Patient 2 showed severe action tremor except for the left hand at setting S2 (see Fig. 5). The RMS value of the angular velocity of the tapping movement, however, did not differ much among the three settings; the average RMS value of the angular velocity was 11.71 °/s, with a tapping frequency of 1.39 Hz.

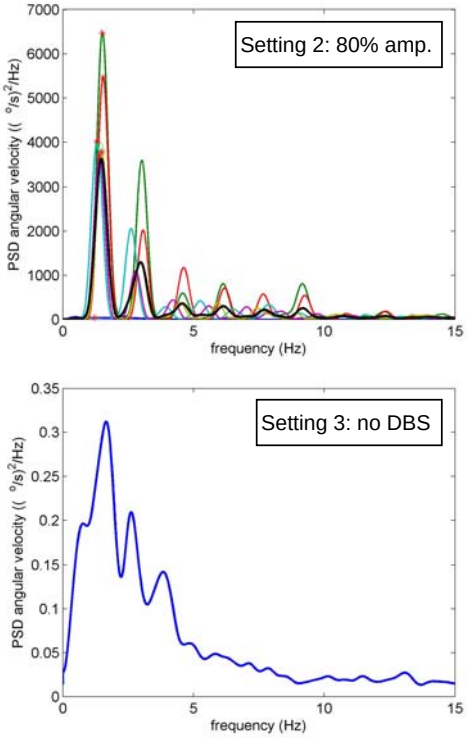

Fig. 2 A high amplitude low frequency 'tremor' was detected for setting S2 of patient 2 – upper graph. This patient did not show rest tremor while the stimulator was off (S3), and for the normal DBS setting (S1) – lower graph.

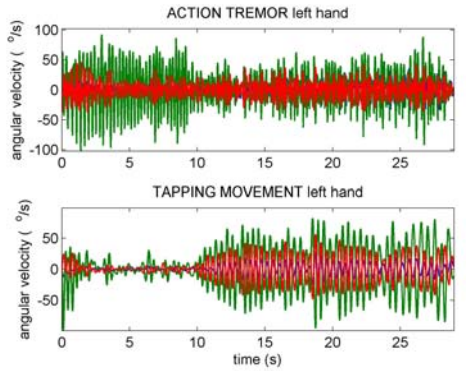

Fig. 3 Angular velocity (pitch, roll, and yaw) showing action tremor and movement during the tapping test performed by patient 1 (S2). Severe action tremor impairs movement performance.

Action tremor thus did not impair movement execution any further in this case. The average frequency of action tremor was about 3.1 Hz for the left hand, and 3.9 Hz for the right hand (see Fig. 6).

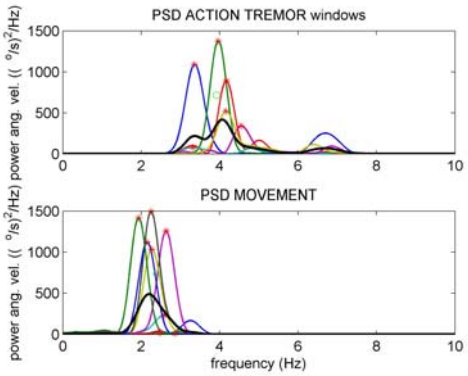

Fig. 4 Power spectral density of the norm of the angular velocity of action tremor (upper graph) and tapping movement (lower graph) for setting S2 of patient 1. The upper graph shows PSD of all windows containing action tremor; the lower graph shows all 3-s windows during the total duration of the test.

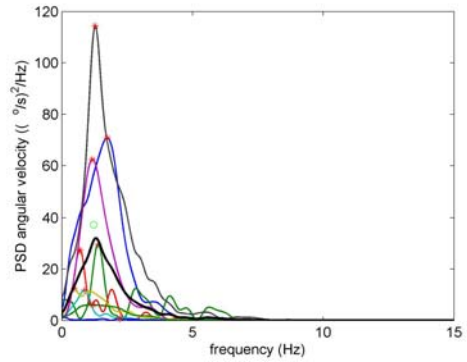

Fig. 5 PSD of the tapping movement performed by patient 2 (left hand) at setting 2.

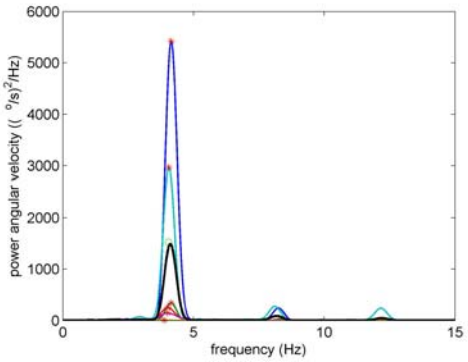

Fig. 6 PSD of the action tremor detected during the performance of the tapping test by patient 2 (right hand) at setting 2.

IV. Discussion

The results of the two tests performed in this pilot study confirm that action tremor may occur independent of the occurrence of rest tremor in a Parkinson's disease patient (patient 2) [8], and that it may impair voluntary motor control and slow down repetitive movements [3]. The frequency of action tremor was found to be comparable to that of rest tremor.

Beuter et al. concluded that DBS decreases rest tremor amplitude irrespective of target stimulated (GPi, STN, Vim) when Group 1 subjects (i.e. subjects with high amplitude tremor) were off medication, but that it did not affect rest tremor significantly when these subjects were on medication. No significant changes were noted for Group 2 subjects (i.e. subjects with small amplitude tremor) [9].

In the present study stimulation was found to be able to generate rest tremor while without stimulation rest tremor may not occur (compare the settings S2 and S3 for patient 2). The effect of stimulation may be different for the right and left hand, indicating that the location of the electrode may be slightly different in right and left STN (compare settings S1 and S2 for the left and right hand of patient 1), and consequently different areas of the STN and/or adjacent fibres may be stimulated. The effect of stimulation also varies for rest and action tremor, implying that different mechanisms of stimulation and/or different pathological oscillators are associated with the two types of tremor.

In summary, the results of the current pilot study shows that DBS has a different impact on rest and action tremor and is sensitive to stimulation amplitude. In a future study more subjects will be included.

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