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An Algorithmic Approach for Quantitative Evaluation of Parkinson's Disease Symptoms and Medical Treatment Utilizing Wearables and Multi-Criteria Symptoms Assessment

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ABSTRACT The paper presents a novel sensor-based disease symptoms evaluation method which can be applied in the domain of neurological treatment monitoring and efficiency analysis. The main purpose of the method is to provide a quantitative approach for symptoms recognition and their intensity, which can be used for efficient medicine intake planning for Parkinson's Disease patients. This work presents an innovative method, which enables to objectify the process of clinical trials. The developed solution implements sensor data fusion method, which analyses time correlated wearable sensor biomedical data and symptoms survey. We have merged two separate methods of recognizing and assessing the intensity of Parkinson's Disease (PD) symptoms using time-constrained survey as well as sensor and interaction-based algorithms, which enable to objectively assess the intensity of disease symptoms. Based on process-based analysis and clinical trials observations, a set of requirements for validating symptoms of neurological diseases have been formulated. Proposed solution concentrates on PD indicators connected with arms movement and mental reaction delays, which can be registered using wearable sensors. Since 2017 the tool has been tested by a group of four selected neurologists and 10 users, 3 of which are PD patients. To meet the project's supplementary (efficiency, security) requirements, a test clinical trial has been performed involving 3 patients executing trials which lasted two weeks and was supported by the continuous application usage. After successful deployment the method and software tools has been presented for commercial use and further development in order to adjust its usage for other neurological disorders.

INDEX TERMS Machine learning, biomedical signal processing, computer aided diagnosis, Parkinson's disease, medicine intake prediction.

I. INTRODUCTION

One of the crucial problems for people suffering from Parkinson's disease is the difficulty to precisely adjust and tune pharmaceutical treatment involving both dosage and intake frequency [19]. From patient's point of view, the support for monitoring the PD symptoms in order to minimise the treatment bias is extremely important. It delivers lower costs for the patient but also prolongs available usage of the assigned treatment designed in form of mono or polytherapy, lowering the risk of drug tolerance. In order to optimize the dosage and composition of the pharmaceuticals, neurologist apply commonly effective treatment strategies, which may be inefficient, for many reasons among which major role plays the drug composition and dosage. It can be observed that in the earlier stages of the treatment the lower amounts are effective, but the conventional methods rely only on neurological consultations, thus making the adjustment process very inert. The introduction of handheld, personal devices in form of configured smartphones integrated with wearable sensor, can offer new means of quantitative disease symptoms assessments. The tool presented in the paper is aimed at evaluating symptoms of the disease therefore indirectly supporting the evaluation of drug dosage and usage. The clinical

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trials [25] and their methodology have been constructed as a process of testing new drugs in comparison to reference pharmaceuticals and placebo products, however, the main problem is the subjective evaluation of the drug effects made by patients. Ordinarily patients report the daily treatment effects and health events at the end of day, making the process inaccurate and remembering in which state they have been during the day, making the assessment process inaccurate and biased.

The major, original findings of presented research provide three correlating aspects of pharmaceutical therapy evaluation: subjective health state evaluation - based on the patient survey reports; tremor and movement disorders recognition and evaluation of their intensity – based on the inertial and biomedical sensor signals; reflex and mental perception assessment - based on dedicated exercises requiring interaction with the touch screen (not discussed in this paper).

The developed method and sensor data processing algorithms provide all three aspects in correlation with the prescribed therapy (mono or poly - therapy) assigned to patient in conducted clinical trial. IQPharma Clinical Trials Assistant can also be used by medical institutions to assess efficiency of treatment providing alternative usage scenario. The constructed tool and its methodology utilizes conventional surveying supplemented with biomedical sensor signal recording for neurological symptoms recognition and intensity evaluation, making testing more time-constrained and compliant with prescribed treatment [1]. Developed mobile system is using wearable sensors and exercises to assist clinical trials in order to supplement used assessments with quantitative approach evaluating registered symptoms. Such approach is a supplement for patient's subjective evaluation of health state. Existing on the market methodology relies often on patient's health state evaluation based on iteratively answered diagnostics questions, which can be easily postponed thus biasing accurate patient's health state evaluation and consequently treatment efficiency. The paper proposes a method for planning the medicine intake schedule; beginning with sensor data acquisition, through biomedical signal processing (for state evaluation), finishing with an optimization problem solving adjusted and personalised pharmaceuticals daily schedule. This work main purpose is to describe software tool supplemented with method for data validation and functionality testing. Presented data have been collected and further extended as test sets in order to check the consistency of the system and implemented methods.

II. RESEARCH BACKGROUND

Parkinson's disease is a neurodegenerative disorder affecting the central nervous system. It is caused by neuronal loss in the substantia nigra which leads to lower dopamine level and accumulation of alpha-synuclein – a protein that forms Lewy bodies [5]. However, the diagnosis does not rely on the cause but on visible symptoms including bradykinesia, tremor, rigidity, postural instability and asymmetry of motor symptoms. To rule out other diseases blood tests are conducted and in order to confirm the diagnosis a positive response to levodopa is expected. Levodopa is one of the medication used in treatment, it is a precursor of dopamine that is able to cross the blood-brain barrier and is later metabolized to dopamine in the brain, leading to the increase in concentration of dopamine decreasing the intensity of symptoms [18]. Wrong administration of medication in Parkinson's disease can lead to severe side effects, overdosing may lead to hypotension, dyskinesia, arrythmias, freezing during movement and dopamine dysregulation, but the doses must be big enough to restrict the symptoms. During treatment clinicians try to limit the dosage of this drug as much as possible. This is why it is necessary to predict the dosage and interval of medication intake accurately. The implemented system provides a solution to predicting both the size of the dosage and the intake time to keep the dopamine level optimal for patients with diagnosed Parkinson's disease. The solution presented in this paper bases on the profile of a patient – his medical history provided at the beginning and the evaluation of his state using subjective data (provided by the patient) and objective indicators (data acquired from sensors).

For the purpose of the research presented in the paper sensor data has been collected from 3 selected template patients (P1, P2 and P3 on Fig. 3) experiencing the Parkinson's tremor of the Medical Center Pratia in Warsaw based on informed consent. Using acquired data and knowledge additional 11 patients have been generated (P4-P14). An example of an examination has been presented on Fig. 1.

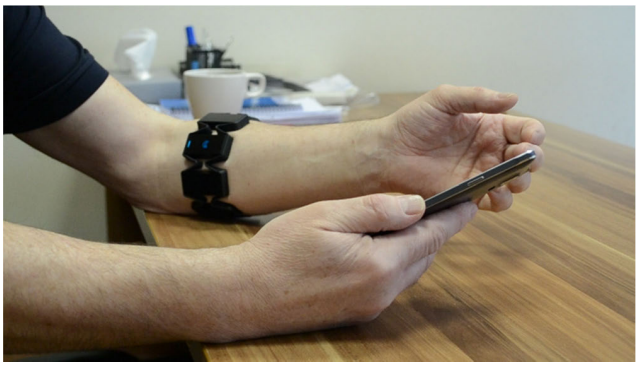

FIGURE 1. Test trials with multi-sensor examination conducted by a patient using Myo armband during project's testing and calibration phase.

III. TOOL REQUIREMENTS AND PROCESS COMPOSITION

The described solution consists of two applications, the mobile application designed to serve the patient with his daily examinations and a web application which is mostly used by the clinical trials supervisor e.g. a medical doctor. The activity of the patient is tracked by external as well as internals sensors of the mobile device. All the data is transmitted to the web application, where the supervisor can view and manually adjust the treatment. The structure of the system is presented on Fig 2.

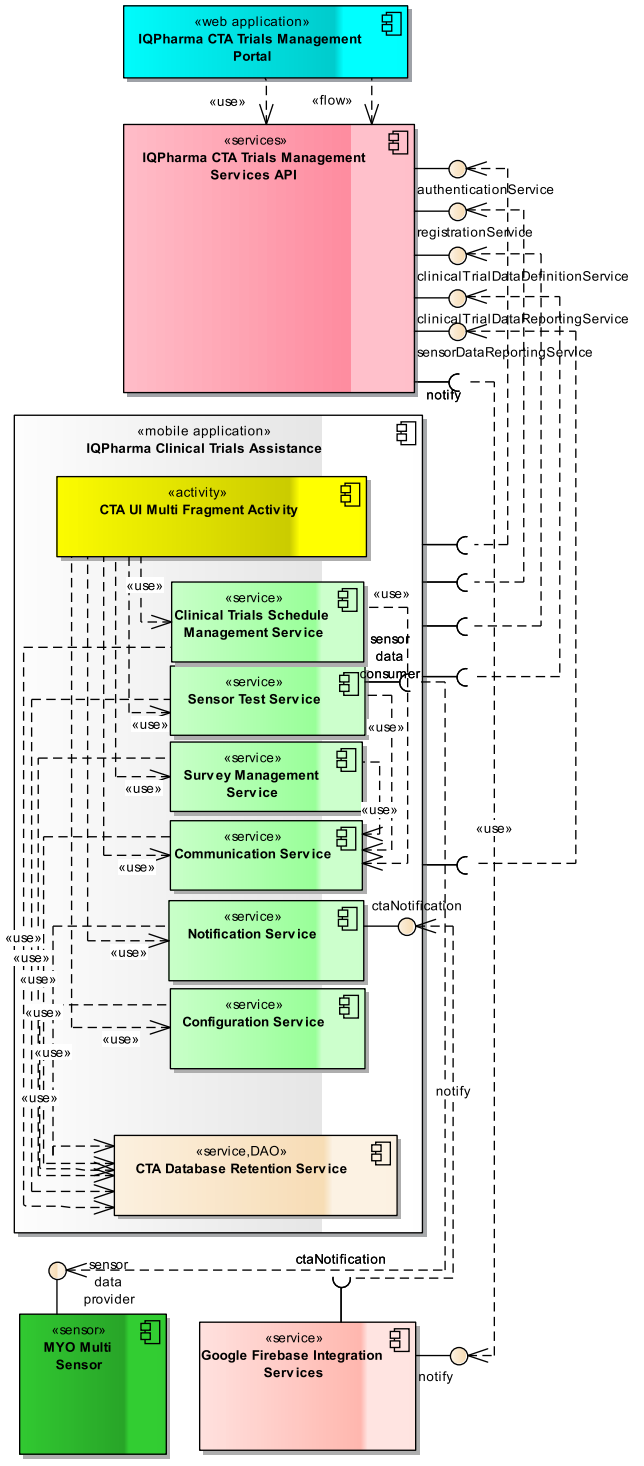

FIGURE 2. The architecture and main logical components of the CTA system mobile application and server services integrated with MYO multi-sensor wearable. Diagram represents subsystems, functional components and service providers-consumers.

Upon registration every user is required to provide data about his condition: age, sex, coexisting diseases, length of treatment, taken medication, addictions, weight, height, average sleeping hours and blood type. Provided information will be used to indicate an appropriate treatment most accurately.

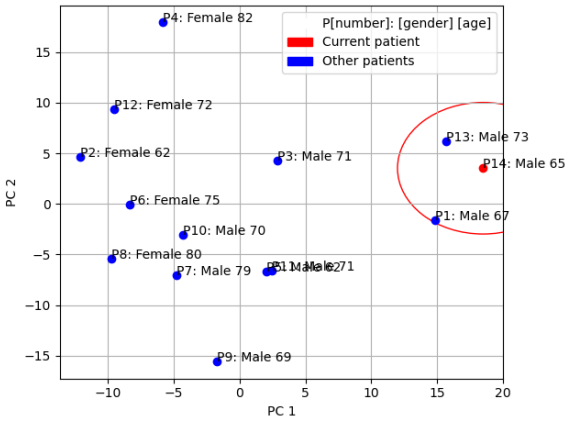

FIGURE 3. Newly added patient in relation to other patients regarding first two principal components.

Patients that are already in treatment, pose as a base to the nearest neighbors algorithm that is used to find patients in similar conditions and their current and most successful treatment. The nearest neighbor algorithm finds patients that are the closest to the analyzed node in the multidimensional space using specific metrics to calculate distance between the nodes. Most commonly used metrics include Euclidean, Manhattan, Minkowski and Mahalanobis [22].

To define a point in the space for each patient, the provided attributes will be treated as coordinates along specific axis. Continuous attributes (age, length of treatment, weight, height, sleeping time) of the patient are used directly, coexisting diseases, taken medication and addictions are aggregated and afterwards represented by binary values, e.g. the addictions are aggregated to the following values: none, alcohol, drugs, nicotine and others. Each of the addiction type is represented by a binary value indicating whether it occurs. The coexisting diseases are aggregated according to the ICD-10 [4] resulting in 21 binary features and the taken medication in additional 20 (14 regarding basic classification and 6 regarding Parkinson's disease). The resulting vector consist of many features what results in bad time performance (when there are many patients) in case of nearest neighbors algorithms. Principal component analysis (PCA) [29] has been used to reduce the number of features dimensions to 4, delivering satisfactory calculation time and classification accuracy. PCA is a statistical method often used for dimension reduction, it computes principal components making sure that every next component accounts for the largest remaining variance. There can be as many principal components as there are variables, but every newly introduced component is less significant and depending on the level of required accuracy (usability in the method) only the first few are considered. PCA can decrease the required computation time, at the cost of accuracy and interpretation of newly defined variables (each of them is a combination of primary variables that are easy to understand and interpret).

Fig. 3 presents finding closest, most similar patients to the newly registered user. Treatment schedule for a new

patient will be based on schedules of his nearest neighbors. In this example Euclidean metrics was used because it has proven to give the best results in this situation. Specific variable values for current patient and his nearest neighbors are shown in Table 1, a feature vector for the new patient (P14) is (65,0,1,182,82,8,6,22,0,1,0,0,0,0,0,0,0,0,0,1,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,1,0,0,0,0,0,0,0,0,0,0,0,1,0,0,0,0,0).

TABLE 1. Features of newly added patient and his nearest neighbors.

	Patient 1	Patient 13	Patient 14
Age	67	73	65
Sex	Male	Male	Male
Blood type	0+	0+	0+
Height	178	182	182
Weight	86	81	82
Length of treatment	8 months	10 months	8 months
End sleep time	7:00	6:00	6:00
Sleep start time	22:00	22:00	22:00
Addictions	-	Nicotine	Nicotine
Coexisting diseases	Cardiovascular disease	-	Cardiovascular disease
Taken medication	Levodopa, Cardiovascular system related	Levodopa	Levodopa, Cardiovascular system related

After the registration process is complete the supervisor, based on similar cases (k-Nearest Neighbors algorithm), assigns a new schedule to the patient. Once the schedule is made available, the mobile device is notified, schedules events and notifies the user about all of them according to the provided schedule. The whole process, since the registration to completion of first examination is presented using a sequence diagram on Fig. 4.

IV. PROCES OF DATA ACQUSITION

The application captures signals registered by sensors built into the mobile device as well as data from external sensors e.g. Thalmic Labs Myo armband, Shimmer + ECG/EMG units. The data from external devices is transmitted via Bluetooth to the mobile device. The signal data is saved to the device and is persisted to the global database via Internet connection.

The process of data acquisition can be carried out in two modes: continuous and on-demand – as remotely scheduled by the neurologist.

The on-demand mode focuses on the calendar with planned events that require user interaction. These events include examination, survey and medicine intake. Each examination has an assigned duration and sensors that will be providing data. The patient can also evaluate his state as one of the following: ON, OFF, ON-OFF – meaning in between states.

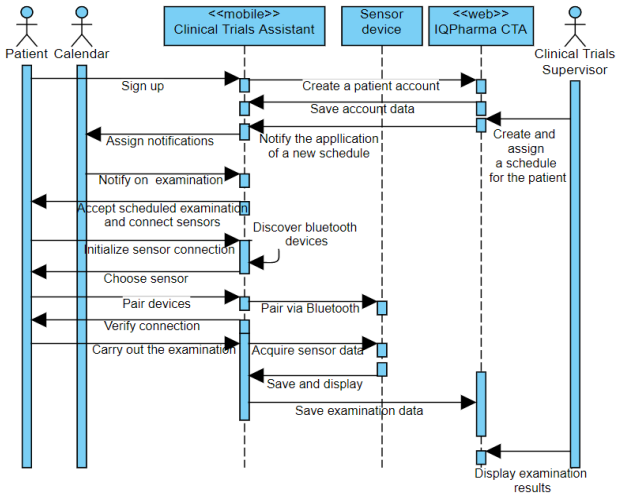

FIGURE 4. Sequence diagram presenting basic patient interaction with the system.

Before the examination, it is required to put on all of the sensors and to limit movement for the duration of examination. During the examination the user is provided with live view of collected data. The survey is a short questionnaire about the current condition of the patient. It allows to receive a subjective evaluation of his condition. The survey usually consists of four question, with the last one asking the user to grade his current state in scale of 0 (no symptoms) to 4 (hard to bear symptoms), but any kind of questionnaire can be used including UPDRS [20], as long as it is defined by the supervisor in the management portal. At the time of answering, the sensors of the mobile device collect data to persist it later to the server. The medicine intake event is just a simple remainder, forcing the user to either accept it or dismiss it, the information about the intake time is also saved and sent to the server. All of the presented events can be delayed by the patient by 5 minutes.

In the continuous mode data from the sensors is received and saved with no interaction from the user needed. The only requirement is a prior sensor pairing. The drawback of this approach is a faster battery discharge, but it allows to capture more data regarding the patient. In continuous mode the data from built-in sensors is only collected when the screen is on (it is assumed that only then the users is using and holding the device). In case of external sensors, that can be worn non-stop, data is saved if two conditions are met: the amplitude of signal is above a certain threshold (signal specific) and the frequency of signal is within expected range.

To discover the time of activity two methods are used, the fast wavelet transform and the fast Fourier transform, they are applied to the magnitude of the accelerometer signal of the wearable device. The wavelet transform [3], [9] is used to process real-time data in order to discover the exact time, the component with a frequency within the interesting range (0.7 – 15 Hz) appears. Fig 5. presents a wavelet transform for filtered accelerometer signal with frequency on y axis and

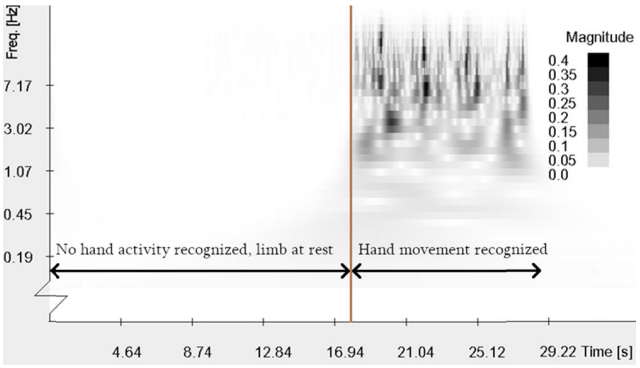

FIGURE 5. Wavelet transform (Morlet) evaluated for inertial data (accelerometer) indicating the algorithmically identified and recognized starting moment of limb activity.

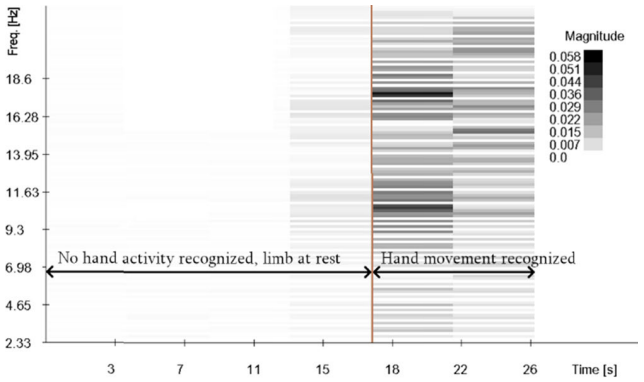

FIGURE 6. Fourier transform with 5 seconds intervals evaluated for inertial data (accelerometer) indicating the starting moment of activity.

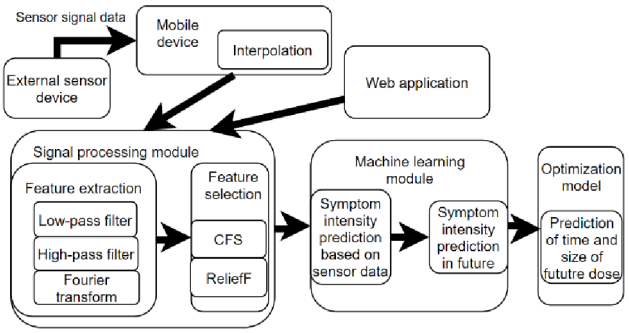

FIGURE 7. The process of predicting the intake time and size of future doses using sensor data.

time on x axis, The starting time of activity (hand movement) is easy to read from the chart (high magnitude for frequencies within range).

Fourier transform does not provide any information about the time of event (change in frequencies of signal), just information about frequency components. To be able to estimate the time of an event (user activity) the signal is split into smaller parts (5 seconds long) and for every piece the transformation is calculated. This solution makes it possible to track events with accuracy to 5 seconds. It is not as accurate as Continuous wavelet transform (CWT) but is computed faster. The visualization for the Fourier transform of the same signal is presented on Fig. 6, the magnitude changes every 5 seconds, with the highest value around the same time as in previous example.

Both modes can operate simultaneously, but it is advised to use the 'on-demand' mode at the beginning of trials with a new patient, because it allows to learn more precise information about the patient (their subjective state evaluation through surveys).

After each examination is saved to the web application, the signals from all of the sensors are processed in order to predict future doses, what has been presented on Fig. 7. All of the steps are further described in following chapters.

V. BIOMEDICAL DATA SOURCES

The mobile devices that were used in the trials presented in this paper are Samsung Galaxy S10+ and Samsung Galaxy Note 4. The application consumes accelerometer, gyroscope, magnetometer and touch data.

The accelerometer and gyroscope signals are registered by LSM6DSO inertial module [26]. It is stable in temperatures from $-40°$ to $+85°$ C with sensitivity ± 0.01 %. The accelerometer signal is captured within ± 2, ± 4, ± 8, ± 16 g with sensitivity accordingly 0.061, 0.122, 0.244, 0.488, mg/LSB (1 g $\approx$ 9.81 m/s^2). The angular velocity module also provides data with sensitivity depending on the range, it is 0,0244% of the range (± 125, ± 250, ± 500, ± 1000, ± 2000 dps – degrees per second). The output data rate of the sensor can be one of the following: 12.5, 26, 52, 104, 208, 416, 833, 1666, 3332, 6664 Hz for both accelerometer and gyroscope data. The Android interface provides accelerometer data as three float values describing the acceleration along three axes x, y, z, the result unit is m/s^2, for the gyroscope also three float values are returned that indicate the rotation around each of the axis in rad/s.

The magnetometer signal is provided by AK09918C [27] magnetic field sensor that can operate in temperatures from $-30°$ C to $+85°$ C, its sensitivity at 25° C is 0.15 μT/LSB with the measurement range ± 4912 μT. It is capable of transmitting measurements at one of the following frequencies: 10, 20, 50 or 100 Hz, the ambient magnetic field measured along three axes.

Unfortunately the Android interface does not allow setting the exact frequency at which data from any of the sensors will be received. It only allows to provide a hint about the frequency, but the events may be received faster or slower. For signal processing algorithms it is necessary to have a constant sampling rate, to 'stabilize' the output frequency an interpolation is performed as the signal is received by the application. All of the measurements are received with a timestamp, what simplifies the alteration of the signal to a constant frequency of 50 Hz. This sampling rate will allow to discover frequencies up to 25 Hz what is above the typical frequency for Parkinson tremor [12].

FIGURE 8. Sensor placement details with EMG segments tuned to specific muscle activity recognition.

FIGURE 9. Sensor-based examination with built-in sensors and MYO armband for patient P2 holding another object in the other hand to distract her from suppressing the tremor.

The external sensor used in the trials is an armband – Thalmic Labs – Myo armband [15]. The device was designed for gesture recognition, but it is also capable of transmitting sensor data via Bluetooth Low Energy [13], intended to reduce power consumption. The signals captured by the application are electromyogram (electromyograph), linear acceleration (accelerometer) and angular acceleration (gyroscope). The device does not provide any timestamp associated with the measurement, what might be a problem considering data transmission with high frequencies, in situations where it is essential to have the timestamp, the arrival time at mobile device is used. The electromyography (EMG) signal is described to be transmitted with a frequency of 200 Hz and inertial sensor data (gyroscope and accelerometer) at 50 Hz [16]. During trials it was noticed that the frequency of EMG data was far from 200 Hz. A series of 200 test was conducted and the mean measured frequency was 159.5 Hz with standard deviation of 4.4 Hz. Interpolation has been used to keep the data samples at constant intervals. The Myo armband has 8 EMG segments, their positioning has been presented on Fig 8., every EMG data package consists of two measurements for each of the sensors. During trials it is necessary to always put on the armband the same way (to make sure that each segment always touches the same muscles), the desired positioning is presented on Fig 8.

Fig. 8 shows that the armband and the mobile device are collecting sensor data from only one arm. This is because of the asymmetric nature of the disease [5]. For every examination it is required to indicate which hand was holding the sensors (by the supervisor or patient). In most cases the examinations are carried out only for one arm, chosen by the supervisor as the one more affected by the disease. During first trials it was noticed that whenever the patients knew that the examination was in progress, they were able to partially suppress the tremor. Giving them something to hold in the other hand, to focus on, has reduced this adverse behavior (Fig. 9).

VI. SIGNAL CHARACTERISTICS

The data collected from sensors is disrupted by noise, in order to rectify the signal, filtering has been applied. The inertial sensor data from accelerometer, gyroscope and magnetometer (mobile device and Myo armband) have been all filtered using a low-pass filter with a cut-off frequency of 20 Hz. For accelerometer signal a high-pass filter has been applied with a cut-off frequency of 1 Hz to remove the gravity component. For EMG signal no additional filtering has been applied because the signal provided by the sensor is already filtered.

Inertial sensor data is evaluated based on the aggregated features described in [2], [6], [9], [14], [17], [24] and composed into homogenous data vectors for each sensor channel (accelerometer, gyroscope, magnetometer, each electromyograph out of 8 sensing segments). All of the selected features (Table 2) are calculated for every component separately (e.g. x, y, z) and also for magnitude, as the data at this stage of development, will be used to determine all possible variants of limbs movement characteristics:

$$Magnitude = \sqrt{x^2 + y^2 + z^2} \tag{1}$$

The time domain features presented in the first section of the table are all normalized to the length of the signal, the values of the rest might be proportional to the duration. It is essential to compare only feature values from the signals of the same length, to solve the problem of different lengths of measurements all of these parameters will be calculated for 2 seconds windows. The frequency domain features are calculated using the Fourier transform [23].

For EMG the set of features is extended by 3 additional: Integral of EMG, Myopulse percentage rate and Log detector, which provides an estimate of muscle contraction force.

Capturing the touch in mobile devices is different than previously described signals. It is not a signal with measurable frequency or amplitude, it is an action. Unfortunately in Android devices it is not possible to capture touch events from the background, which restricts registering these events in the continuous mode. However, all touch events that take place within the application can be registered. Whenever a user answers questions in the survey or confirms medicine intake as well as performs other clicks, the attributes of the actions are saved. Since this is not a continuous signal there

TABLE 2. Features extracted from inertial sensor signals.

	Sym.	Feature name	Interpretation
Time domain	MIN	Minimum value	The minimum value of the signal, usually a negative number.
	MAX	Maximum value	The maximum value of the signal, usually a positive number.
	ENA	Approximate entropy	Measure of repeatability to quantify levels of complexity within a time series. High regularity leads to low entropy value.
	ENS	Sample entropy	Measure of complexity, does not include self-similar patterns.
	MN	Mean	Arithmetic sample mean.
	SD	Standard deviation	Measure of dispersion of values in the dataset.
	MD	Median	The "middle value", separation of the lower and higher half.
	SKW	Skewness	Measure of asymmetry of the signal distribution about its mean. The sign of the value indicates whether the maximum value is on the left or right of the mean.
	KRT	Kurtosis	Quantification of the distribution shape of a signal relative to Gaussian distribution. A transient signal produces a positive value, a fixed signal a negative.
	MAD	Median absolute deviation	Median value of absolute deviations from signal median.
	MAV	Mean absolute value	Arithmetic sample mean of absolute signal values.
	MAV1, MAV2	Modified mean absolute value	Arithmetic sample mean of absolute values amplified (if are in the middle half) or diminished (otherwise).
	DASDV	Difference absolute standard deviation value	Standard of the difference between the adjacent samples.
	P	Power	Amount of energy (sum of squared signal values) consumed per unit time.
	MPD	Mean peak distance	Arithmetic mean of time between peaks.
	IQR	Interquartile range	Measure of statistical dispersion, difference between the upper and lower quartiles.
	RMS	Root mean square	Sum of squared signal values divided by sample count.
	AAC	Average amplitude change	Absolute gain value per unit time.
	ZC	Zero crossing	Number of crossings of the time axis by the signal (above a certain threshold).
	SSC	Sign slope change	Number of slope changes.
	WL	Waveform length	Length of signal along the magnitude axis.
	E	Energy	The sum of squared values of the signal.
	PC	Peak count	Number of peaks in the signal.
	SSI	Simple square integral	Sum of squared signal values.
	WAMP	Wilson amplitude	Number of value changes above a threshold.
Frequen	MNF	Mean frequency	Weighted arithmetic frequency mean.
	MDF	Median frequency	Frequency with median power.
	TP	Total power	Sum of power for every frequency.
	PKF	Peak frequency	Frequency with maximum power.
	R1, R2	Range	Cutoff frequency range.
	MNP	Mean power	Arithmetic mean power of the power spectrum.

is no need for signal processing all of the features are passed to the event callback. The following features/attributes are collected from every touch:

Registered touch events usually do not occur with a constant frequency, mostly they appear in series. To minimalize the data redundancy and improve the accuracy, similar actions, that are taking place with little intervals (within 2 minutes) are aggregated and all of the continuous considered features are represented by their mean and standard deviation.

VII. FEATURE SELECTION AND MACHINE LEARNING

The features extracted from the signals are to be used for predicting the future medication doses, but directly they can be used for predicting the intensity of Parkinson's disease symptoms: in comparison with other patients or in comparison with previous measurements of the patient. This paper does not focus on comparing the symptoms (their intensity based on sensor data) between patients, the aim is to keep the predictions as accurate as possible and after the initial period only measurements of the patient are taken into account. The characteristics of symptoms and sense of their disruptiveness can differ among patients and this is why this approach has been selected.

The considered target value for symptom intensity prediction (in the beginning of treatment) will be the symptom severity provided by the user in the survey. Every patient while completing the survey will evaluate his current momentary state on a scale of 0-4, 0 – no symptoms, 4 – very severe symptoms. The answer provided has a discrete value. The problem of predicting the intensity of symptoms can be solved with many regression machine learning algorithms, but first, the number of features must be reduced. Since the characteristics of tremor can differ between patients it was decided that the feature reduction process will be carried out separately for every patient.

The number of extracted features for each of the measurement types is too large (e.g. 324 features for EMG signal). To make the prediction process faster and to reduce overfitting it was decided to reduce the number of variables. Feature selection was carried out in two steps. First step was performed using only features values, the relationship with target values was not considered. At this step the CFS (Correlation-based feature selection) algorithm [10] was used to exclude features that are highly correlated with another within the tested subset of measurements. To achieve this a correlation matrix was built. All of the values were between -1 and 1 and the closer they were to 0, the weaker the correlation. For each pair of variables with a high Pearson correlation coefficient one of them was removed from the list. The system uses a threshold of 0.75, which in case of inertial and EMG signals allows to remove a large part of features that could be correlated due to their mathematical formula or

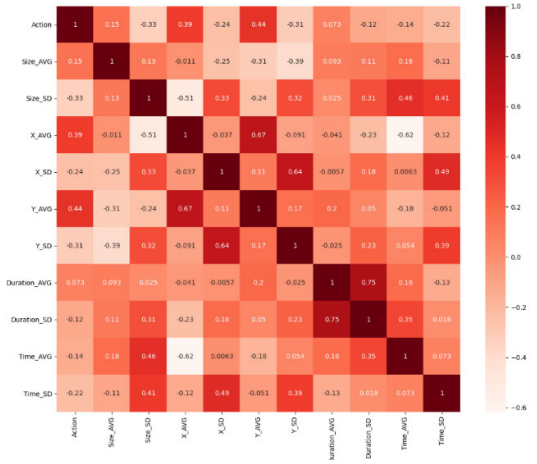

FIGURE 10. The correlation matrix for selected features of the touch action.

are correlated just in case of this specific patient, because the symptoms vary in their intensity and characteristics between cases.

Fig. 10 shows the correlation matrix of features for touch actions, due to no redundancies, none of them had correlation above the threshold. SD stands for Standard deviation and AVG for arithmetic mean.

CFS is carried out for each sensor separately. Evaluating the state of a patient during examination is executed based on data from all of the selected sensors, what requires another feature selection to reduce overfitting. After merging the data, the RreliefF [11] algorithm is executed. This algorithm evaluates the quality of attributes in reference to the predicted value (evaluation of the state provided in the survey), it is a modification of the ReliefF algorithm [10] (dedicated for classification problems) to support regression problems. Feature selection can be done by choosing a number of features with highest quality or choosing features with quality above a certain threshold. In this case only 20 with the highest quality are chosen. The features that turn up in the final vector used by machine learning algorithms depend strictly on the patient. The most commonly chosen features are placed in Table 5.

In the beginning of treatment, when there are not enough examinations carried out by the patient, the measurements from similar patients (k-NN) are treated as training data, after 7 days of treatment foreign examinations will be no longer used – only if the patient has earnestly completed assigned examinations and surveys.

For predicting the current state, machine learning methods [14] from the *scikit-learn* library have been used. The system has defined a number of methods with set parameters that are compared using cross validation (10 fold) and the one resulting with highest score is assigned to the patient. Currently used methods include: Bayesian ridge, Logistic regression, Support vector machines, Decision tree, Random forest, Multilayer perceptron, Gradient boosting (decision tree), Ada boost (decision tree). The score value for

TABLE 3. Features selected for state evaluation from touch actions of the patient.

Name	Description
Timestamp	Time and date of the event.
Size	Size of fingertip touching the screen corresponds to the pressure applied by the finger.
Duration	Time in milliseconds since the user touched the screen to the occurrence of action.
Orientation	Orientation of the finger performing the action.
X	Distance from the center of the component to the touch point along the X axis.
Y	Distance from the center of the component to the touch point along the Y axis.
Action type	Type of action the user was performing.

TABLE 4. Results of feature selection with CFS.

Sensor	Number of features	Removed features number	Remaining features percentage
EMG	342	267	21,9%
Accelerometer	128	100	21,9%
Gyroscope	128	96	25,0%
Magnetometer	128	98	23,4%

TABLE 5. 20 most commonly chosen features with RreliefF algorithm out of features extracted from mobile device and myo armband sensors.

Device	Sensor	X	Y	Z	Mag
Mobile device	Gyroscope	PKF, MAV1	KRT, PKF	PKF, SD	MNP, PC, ENS
	Accelerometer	MAV1	MAV1, PKF		MNP, MDF
Myo armband	Gyroscope			PKF	
	EMG	4: AAC,	7: PKF,SSC		PKF, MD

regression is calculated the following way:

$$R^2 = 1 - \frac{\sum \left(y_{true} - y_{pred}\right)^2}{\sum \left(\overline{y_{true}} - y_{true}\right)^2} \tag{2}$$

y_{true} - target value, $\overline{y_{true}}$ - target value mean,
y_{pred} - predicted value.

The closer the score to 1, the better the regressor. Score equal to 0 indicates a model that predicts always the target mean value disregarding the input features.

The score mean and standard deviation presented in Table 6 indicate that, in this case, the Ada boost and Multilayer perceptron were performing the best. None of the scores for the regressors are close to the perfect regressor (score equal to 1), this is due to the fact that the target values used are subjective, provided by the patient. The values are granulated, the patient has to classify his state to one of the 5 levels of

TABLE 6. Score for ML algorithms used for symptom intensity regression based on measurements carried out during examinations.

ML algorithm	Parameters	A	σ
SVM	RBF, C: 1, γ: scaled	0.541	0.112
Decision tree	criterion: mse, split: best	0.497	0.283
Random forest	100 trees, criterion: mse	0.672	0.140
Ada boost	50 trees, l. rate: 1	0.731	0.145
Gradient boosting	100 trees, LS, l. rate: 0.1	0.648	0.218
Bayesian ridge	300 iterations	0.579	0.176
Multilayer perceptron	hidden layers: (200, 100, 100)	0.701	0.218
Logistic regression	250 iterations	0.52	0.169

TABLE 7. Score for ML algorithms used for symptom intensity regression based on touch events from completing the survey.

ML algorithm	Parameters	A	σ
Random forest	60 trees, criterion: mse	0.764	0.062
Ada boost	50 trees, l. rate: 1	0.822	0.069
Gradient boosting	100 trees, LS, l. rate: 0.1	0.817	0.054
Bayesian ridge	300 iterations	0.634	0.177

intensity, what can sometimes be inaccurate also the survey completing does not take place at the exact same time as used sensor measurements.

The touch actions are aggregated separately what causes a separate state prediction. Based on experimentation the following regressors were selected: Bayesian ridge, Random forest, Gradient boosting and Ada boost.

VIII. MEDICAL TREATMENT MODELS

Every medication to be used with the system must be provided with a set of necessary data that is essential for future dosage prediction to avoid suggesting unsuitable doses. The necessary features are listed in Table 8 [7], [8], [19].

The medication intake for some of the PD medicine (e.g. Levodopa) is divided into morning bolus dose and maintenance doses throughout the day. The morning dose is called an effective dose (ED), its aim is to increase the level of dopamine to an effective level after the night [21]. The maintenance doses are applied to make sure the medicine concentration does not drop below the threshold. Maintenance doses are meant to keep the level of dopamine steady with little fluctuations [19].

The prediction of future dosage bases on the following: currently assigned schedule, realization of schedule, current and previous states (symptom intensity), patient profile and drug profile. No modification of the schedule is performed without the verification of Clinical trials supervisor.

Fig. 11 demonstrates symptoms measurements (their intensity) in relation to treatment schedule and answers provided by the patient in the survey. In the beginning, after the patient wakes up, the symptoms are very severe, after taking the morning dose the symptoms decrease until they fully disappear. After some time the level of levodopa gets reduced, and

TABLE 8. Features required for every medication used with the system.

Name	Description	Example value
Drug name		---
Active ingredients	Ingredients that influence the weakening of the symptoms	Levodopa with carbidopa
Active ingredients content	Dose of active ingredients in one pill	Levodopa: 250 mg, carbidopa: 25 mg
Intake frequency	Number of daily doses	2-8 doses
Maximum daily dose	Maximum daily intake	8 pills
Maximum dose	Maximum dose to be administered at one time.	4 pills
Half-life	After this time only half of the taken dosage will be left.	1h
Absorption rate	The percentage of dosage that can be absorbed, cross the blood-brain barrier.	60%
Absorption speed	The percentage of dosage that is absorbed in one time unit	30%
Peak	After that time the medication has reached its peak value in the system	2h
Threshold dose	Minimum dosage to be administered at one time.	0,5 pill

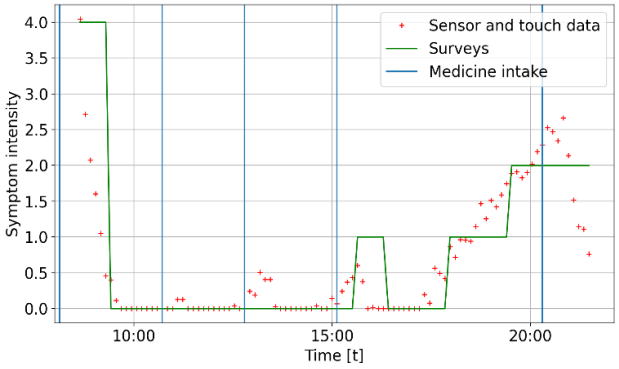

FIGURE 11. Symptoms intensity assessment based on data gathered in the CTA mobile application fusing sensor data and surveys in relation to medicine intake for patient P1.

in order to prevent the return of the symptoms a maintenance dose must be taken. The fifth dose (Fig. 11) has been taken with a long delay what led to an increase in the symptom intensity. To predict the time and size of the doses a threshold value for the symptom intensity must be defined - θ, every dose will be planned to make sure the intensity never exceeds it and the minimum time interval between doses - t_{min}. The rest of variables in the Table 9, except the estimated decision variables d_i and t_i are extracted from medicine information, patient profile and acquired signals:

Finding the dosage requires solving the following optimization task with decision variables t_i and d_i, minimizing

TABLE 9. Definition of variables and functions used in the optimization task in order to predict the size and time of future doses.

t_d	fall asleep time	R_+
t_u	wake up time	$[0, t_d)$
θ	threshold symptom intensity	[0,4]
$st(t)$	patient's state at time t based on sensor data	$R_+ \rightarrow [0,4]$
$s(t, T, D)$	predicted patient's state at time t for daily medicine intake schedule defined by T – intake times and D – intake doses	
N	number of doses during the day	N_0
n_c	number of last doses considered for prediction of symptom intensity	N_0
I	dose number during the day	{1,…,n}
t_i	time of i-th dose	$[t_u, t_d]$
T	set of n dose intake times	$\{t_i : i \in \{1,...,n\}\}$
t_{min}	minimum time interval between doses	R_+
d_i	size of i-th dose	N_0
D	set of n dose intake sizes	$\{d_i : i \in \{1,...,n\}\}$
d_{max}	maximum single dose	R_+
d_{min}	minimum single dose	$[0, d_{max}]$
D_{max}	maximum daily dose	R_+
t_p	time to reach peak medicine concentration after intake	R_+
Δt	time step used for prediction and constraint verification	R_+

the amount of medicine taken during the day – in order to reduce side effects:

Objective Function:

$$\min \sum_{i=1}^{n} d_i \tag{3}$$

Constraints:

$$t_i - t_{i-1} > t_{min}, \quad for\ i = 2, \ldots, n \tag{4}$$

$$d_i < d_{max}, \quad for\ i = 1, \ldots, n \tag{5}$$

$$d_i > d_{min}, \quad for\ i = 1, \ldots, n \tag{6}$$

$$t_1 \geq t_u \tag{7}$$

$$t_n \leq t_d \tag{8}$$

$$\sum_{i=1}^{n} d_i \leq D_{max} \tag{9}$$

$$s\,(t, T, D) \leq \theta, \quad for\ t_1 + t_p < t < t_d \tag{10}$$

The values of *s(t,T,D)* function, required for finding the solution, are known only for sets of arguments that have appeared in the past – Fig. 12., to predict the values of the function for various set of arguments regression methods were used, fitted using datasets from the past. The data needed for the algorithm includes previous medication intake times and their doses, the values of previous symptom intensity, time passed since the wake up and current symptom intensity as the target value. These form a vector (11) used for machine learning of length dependent on n_c – number of last doses considered for prediction (when there are not enough previous doses in the day the vector is filled with 0 values).

$$v = (s\,(t - \Delta t, T, D)\,, (T\,[l_d - i])_{i=1,...n_c}, \times (D\,[l_d - i])_{i=1,...n_c}, t - t_u) \tag{11}$$

where l_d is the index of the last dose before t.

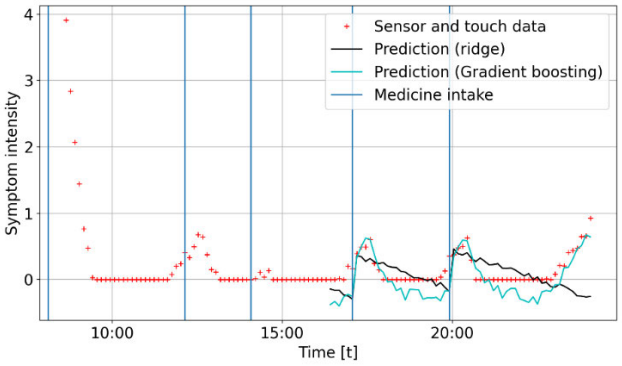

FIGURE 12. Comparison of symptom intensity values predicted with ridge and gradient boosting regressors to values based on sensor data for patient P1.

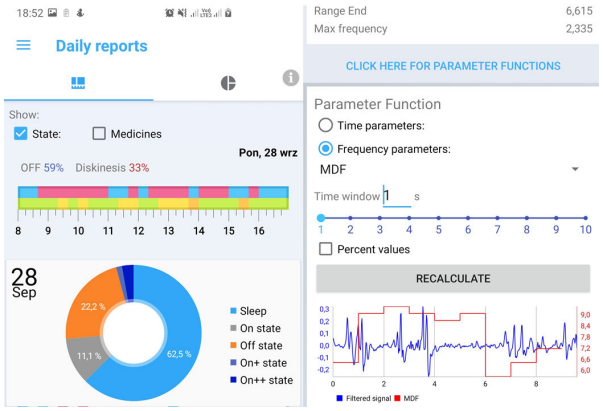

FIGURE 13. IQPharma CTA application views presenting the patient health state identified on the basis of sensor data and surveys (left), view of the gyroscope signal from the application (right).

An example vector definition for the past, when $n_c = 3$ and $t > t_3$ is $(st(t-\Delta t), t - t_3, t - t_2, t - t_1, d_3, d_2, d_1, t - t_u)$ with a target value of *st(t)*. Based on experimentation ridge and gradient boosting regressors were chosen for predicting future values of symptom intensity. The results of their prediction are presented on Fig. 12. The used methods provided good results considering predicting the symptom intensity until the next intake.

The *s(t, T, D)* function is a black box, to check constraint (10) for a schedule (represented by T and D), a simplified method is used, which verifies the inequality only for some values of the function using a time step - Δt. The solutions of the optimization task are discovered using simulation-based optimization methods [28]. The proposed model is currently applied in the Clinical Trials Application and the suggestions are provided to both: the user through the mobile application (if permissions are assigned) and to the supervisor through the web application.

IX. CONCLUSION

The developed quantitative assessment method and implemented mobile tool set have proven that remotely planned and executed symptom intensity evaluation can optimize treatment and help to organize complex time constrained therapy.

Based on the results collected during the IQPharma CTA application testing phase it was possible to compare and correlate patient's health state reported in conventional surveys with the results of reasoning, based on wearable sensor captured movement and muscle activity. The accuracy of the health state classification depends on the quality of gathered sensor data and calibrated threshold used for classification and recognition of ON/OFF states and their intensity, which at this stage of development have not been validated on real clinically tested data. This work promotes specific approach to acquire quantitative data for medical reasoning processes allowing to correlate outcomes of patient's self-assessment and recorded inertial and biomedical data. The estimation of patient's health state is based on the sensing process evaluating limbs movement and activity data in reference to the answers taken from medical questionnaires. Often medical survey results are subjective and strictly depend on the patient awareness and sensibility. Provided in the paper quantitative assessment method objectifies the survey results and can be treated as supplementary data source for clinical trials effectiveness assessment. Measuring the tremor, rigidness of arms movement or the other motion based symptoms (bradykinesias) can be efficiently performed using proposed set of sensors and algorithms. The tool has been subjected to functional testing by IT team but also PD patients (3) which provided several important adjustment for the algorithms and software behavior.

The described in the paper methodology, research results and tool itself deliver means for medication efficiency assessment and planning of medicine intake based on measurable characteristics of movement and muscle activity. Provided 3 level evaluation (survey, sensor, interactions) supplement each other and provide wide spectrum of quantitative tools for assisting therapy. Elaborated analytical method and obtained conclusions demonstrate the applicability of smartphones with dedicated, highly integrated with the system software, controlling and guiding the patient through efficient health state and events reporting. Many observations and requirements for the tool come from analogue clinical trials observations. In result a set of requirements for validating symptoms of neurological diseases have been formulated, concentrating on the ones which can be registered using wearable sensors. The IQPharma CTA delivers extended, configurable scheduling options, for trials managers to adjust specific treatment process parameters – schedule, intake, therapy composition. A calibration of algorithms supports patient personalization, which enables more accurate recognition of significant health states but also supports symptom's intensity evaluation and prediction of medication dosage. Proposed solution constantly aggregates gathered survey reports and time correlated biomedical data. Such approach supplements patient's subjective evaluation of health state, what makes this method attractive for neurologists who seek for treatment adjustment methods, but most of all monitoring of patient's compliance. Currently we have gathered a set of few preliminary PD patient data sets (∼ 2 GB sensor and survey datasets with video recordings). To extend the base for reasoning, we have chosen a simulation as a data generation engine, which has been able to provide the test data sets in correspondence with significant health events and their specificity.

The paper demonstrates successful application of clinical assistance tool for assessment of complex treatment processes, based on effectiveness and usefulness of selected sensor signals – functionally validated and prepared for clinical trials execution process. Presented in the paper innovative techniques can be used to supplement remote medical examinations with specific physical exercises as well as reflex evaluations in order to improve the accuracy of treatment composition and configuration. To achieve that goal the tool is currently extended to record a wider spectrum of sensor data as well as deliver more tuned classification and regression methods in order to develop recognition of more complex neurological symptoms e.g. rigidness, bradykinesia, impaired posture and balance, or even loss of automatic movements, disturbed handwriting and speech.

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