Measurements of Antisaccades Parameters Can Improve the Prediction of Parkinson's Disease Progression

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Abstract. In this text we present the results of oculometric experiment consisting the registration of anitsaccades of patients with Parkinson's Disease (PD) in relation to their neurological data. PD is an important and incurable neurodegenerative disease and we are looking for methods optimizing the treatment. In our previous works we used Reflexive Saccades (RS) and Pursuit Ocular Movements (POM) to check what it can tell us about the disease's progression expressed in the Unified Parkinson's Disease Rating Scale (UPDRS). The UPDRS is the most commonly used scale in the clinical studies of Parkinson's disease. In this experiment we examined antisaccades (AS) of 11 PD patients who performed eye movement tests in controlled conditions. We correlated neurological measurements of patient's motoric abilities and data describing their treatment with values of AS parameters. We used RSES and for prediction of the UPDRS scoring groups and Weka methods for presentation of the results. We achieved good results with accuracy of 91% and coverage of 100%. The AS test is a relatively easy and non-invasive method that can be used in the telemedicine in the future.

Keywords: Parkinson's disease · Antisaccades · Eye tracking · Data mining · Machine learning

1 Introduction

Antisaccade is a voluntary eye move in the opposite direction of appearing target [8]. Subject have to suppress a glance towards a suddenly presented peripheral stimulus and look away from it to the mirror location [13]. The eye move schema is presented in Fig. 1. Antisaccades are generally more difficult than eye move towards the stimuli (prosaccades) for some PD patients even impossible to perform. The performance of antisaccades is influenced by parameters interacting with the fixation and/or attention system of oculomotor control [9]. Olk and Kingstone [10] assumed in their research, that prosaccades to new objects are

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made reflexively and for antisaccades, this reflexive eye movement have to be inhibited thus antisaccades are generated volitionally. This oculomotor inhibition is the main factor leading to long antisaccade latency causing that antisaccades are generally slower than prosaccades. Inhibition is being produced by the reallocation of covert attention from the target location towards the opposite antisaccade location [10]. The prefrontal cortex (PFC) is being found to be crucial for control of reflexive behavior allowing for voluntary reaction [13]. Brain imaging studies showed that cortical and subcortical network is widely active during the generation of antisaccades [15]. The interesting finding has been made by Fischer and Weber [9] who observed that parameters supporting the disengagement of fixation at the time of stimulus onset provoke a reduction of the antisaccadic reaction times and that certain state of disengagement seems to facilitate the occurrence of reflex-like errors.

The ability to suppress reflexive responses in favor of voluntary motor acts is very important for everyday life and variety of neurological diseases result in dysfunctions and errors of this mechanism, what can be observed in the voluntary eye move tasks [15]. In terms of PD disease, various studies have shown that patients have impaired executive function, including deficits in attention, movement initiation, motor planning and decision making leading to impairments in controlling involuntary behavior [12,17]. Such dysfunctions plays important role during execution of voluntary eye movements and resulting in difficulties, as antisaccade requires suppression of an automatic eye movement to a visual stimulus and execute a voluntary eye movement in the opposite direction [17]. Antisaccade deficits in PD have been attributed to fronto-basal ganglia (BG) dysfunction and are similar to those seen in the task switching, whereby one is required to change a response after performing a different behavior [17]. Crevits et al. [11] observed that the degree of advancement of Parkinson's disease significantly increases mean latencies and error rate in the antisaccade tasks. Antisaccades in PD has been described as abnormal, multiple-step and hypometric and associated with a significant decrease in the velocity [14]. PD patients are treated medically or by stimulation of the Subthalamic Nucleus (STN) with an electrode (Deep Brain Stimulation - DBS). In terms of medical treatment, Hood et al. [12] found that Levodopa (L-Dopa) commonly used to improve the symptoms of Parkinson's disease significantly reduces error rate for antisaccades and suggests that L-Dopa improves function of the voluntary frontostriatal system, which is deficient in PD. It has been also observed that PD patients in the medicated state are better able to plan and execute antisaccades [12]. In contrast to L-Dopa, electrical stimulation of the STN, the alternative method to the medical treatment, has been found to have no effect on the antisaccade task. According to Rivaud-Péchoux, et al. [16] STN stimulation improves only the accuracy of the memory guided saccades.

The UPDRS becomes common rating scale of the progression of a Parkinson's disease among neurologists and researchers who want to carry out measurements with objective instruments [5]. It consists of 42 items divided into 4 sections [6]. First 2 sections consist scoring of personal behavior, mood, mental activity and

activities of daily living. Next 2 sections consist examination of patient's motor fitness and difficulties during the treatment. In our experiment we decided to compare the results of Sects. 3 and 4 of UPDRS examination with the results of the oculomotor study. The UPDRS III includes clinician-scored monitored motor evaluation and evaluation of complications during the therapy (UPDRS IV) [7]. The UPDRS III refers directly to motor results an UPDRS IV to motor fluctuations, both might have direct correlation with the patient's oculomotor abilities.

The problem in evaluating the scale of Parkinson's disease progression lies in the very individual symptoms of this disease. Every patient diverge substantially in his combinations of symptoms, rates of progression, and reactions to treatment [4]. In the experiment we wanted to check the effectiveness of predictions of neurological evaluations, represented by Sects. 3 and 4. We tried to find out whether there are correlations between the antisaccade parameters collected from oculometric tests and data from the neurological classifications. We used combined results of neurological diagnoses as decision attributes along with oculometric measurements as conditions expressed in the parameters. With such approach we researched correlations between both sources of the data. The aim of this experiment was to test algorithms, allowing for machine-learning evaluation of the UPDRS III and IV, based on type of the treatment and results of the anitsaccade trials. We believe that methods of predictions like presented in this article might extend available data of patient, if patients could perform oculomotor tests using their personal devices in different conditions, not only in the clinical settings. Data evaluation presented in this article could be automated by open-access software running on personal device like PC, tablet or a smart-phone.

2 Methods of the Experiment

We examined 11 patients in the clinical conditions. Patients underwent experimental trials under the supervision of a doctor. Results of patients were collected and divided according to their treatment. Our data distinguished patients who undergo pharmacological (BMT - Best Medical Treatment) treatment basing on the medication of the L-Dopa and the DBS (Deep Brain Stimulation). Patients qualified for DBS surgery are mainly characterized by low sensitivity to L-Dopa [4].

Possible variants of those two parameters described types of different sessions in which the results of patients were considered:

- S1: No treatment - (BMT Off, DBS Off)
- S2: Patients undergo only non-pharmacological treatment (BMT Off, DBS On)
- S3: Patients undergo only pharmacological treatment (BMT On, DBS Off)
- S4: Patients undergo both types of treatment (BMT On, DBS On)

We compared correlations between types of the sessions and UPDRS results. In total our data contained 28 registrations with relevant data from neurological

tests including the results of the UPDRS classifications. Not every patients were treated with both pharmacological and surgical treatment, so it was impossible to examine each patient in the four different sessions. The eye moves of the patient were recorded by the eye tracker. We used head-mounted eye-tracker JAZZ-Novo with frequency of 1000 Hz. Patient head was positioned on the chin-rest at a distance of 60–70 cm from the monitor in order to minimize the head movements.

During each experimental trial patients task was to follow horizontal moves of the light spot generated by the eye tracker. At the beginning of each one patients were viewing the fixation point and it was the primary position of the gaze in each antisaccade trial (0°). When trial started fixation point disappeared and at the same moment target of the antisaccade appeared randomly on its left or the right side (10° to the left or right of the fixation point) in arbitrary times between 500–1500 ms. The antisaccade target remained for 100 ms before another trial started. Patient task was to move eyes in opposite direction to the appearing targets with best accuracy and smallest delay. The experiment was conducted in "no-gap" model in contrast to the model introduced by Saslow [21]. Schema on Fig. 1 presents the model of the anisaccade trial.

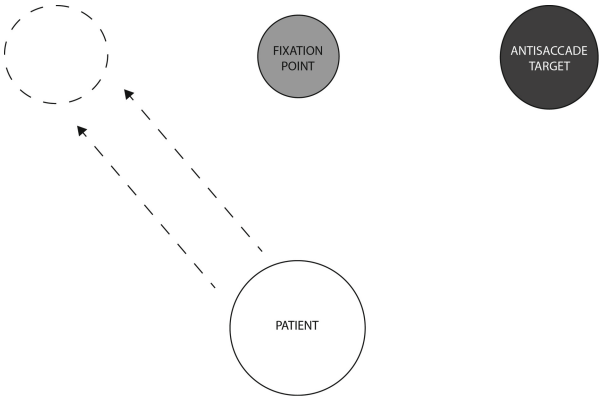

Fig. 1. Model of the antisaccade trial.

All experimental trials were conducted in the same lighting conditions. The data was analyzed by software detecting antisaccades in the eye move signal and calculating its Delay, Duration and Speed parameters. The algorithm searched the oculometric data composed from the time stamps and x-coordinates of the stimuli and patient eyes. The start point of each search window was the moment of appearance of the antisaccade target. The algorithm expected straight-aimed move from fixation point to the opposite direction of the appearing target below the delay threshold of 500 ms. The latency parameter have proved to be a valuable source of detailed and quantitative information in a wide range of neurological conditions [19]. Parameter Latency can also give the information of

the impairments of the decision mechanisms described in the section "Introduction". Any record which hadn't passed criteria of move direction (patient performed prosaccade) in the defined window below the maximum acceptable latency were removed from the original data. The record was also rejected if there was non-response or mis-recording (blinks, head movements, etc.) [19]. Calculated statistics of successful antisaccades gave the mean of 6.53 (SD 2.5). This fairly weak indicator may be explained by the fact, that for many PD patients the antisaccade can be a quite difficult task. For particular cases even impossible to perform.

3 Computational Basis

The eye move parameters, mean latency, mean duration and max speed were calculated on the basis of registered appearances of fixation point and the target in correlation with patient's eye moves. Duration (time) and speed (velocity) are base parameters describing the eye move. We choose max speed (peak velocity) because we believe that this parameter is better in showing the oculomotoric capabilities of the patient than the average speed.

We used the following approach for parameters calculations. The latency was measured as a period between appearance of the target (and fixation point disappearance) and start of the eye move in the right direction. Start of the antisaccade (start point of the duration) has been fixed to the moment when gaze speed exceeded the threshold of speed determined for particular trial. The speed threshold was calculated from all subsequent frames of the record by dividing the maximum speed and the average speed. The Duration of the antisaccade was determined as the period when gaze direction has began to follow the opposite direction of the target and when simultaneously the eye speed has started to rise from the starting point of change of the move direction. The means of Delay and Duration parameters were calculated arithmetically for a particular patient. The Max Speed was counted as the maximum from all values collected and calculated for every eye-tracked frame in the period of the antisaccade duration.

After carrying out the oculometric tests we created the dataset from parameters of the anticassade trials (numeric values) and the neurological data. The neurological data contained parameters describing type of the treatment expressed in the symbolic attribute "Session" (S1, S2, S3, S4) and the results of UPDRS classifications (numeric values). In the next phase, the dataset has been used as the input decision table for Rough Set Exploration System (RSES) we used for further analysis. RSES is a data-mining software written at Warsaw University and it has been previously found that RSES deals very good with predicates based on small data [3]. RSES contains a tool set of methods coming from the Rough Set Theory (RST) [1]. RST is founded on the assumption that every object associate some information which are characterized by the same information in view of the available information about them [3]. This approach is related to the granular computing paradigm where every particular granule contains all attributes are related to "and" logic, and where interactions between granules

are related to "or" logic [4]. The relation of indiscernibility is the mathematical basis of this theory stating that a set of similar objects forms a basic granule of knowledge and any union of those elementary sets formulates a precise set [1]. In contrast to the precise set, the rough set (RS) cannot be characterized in terms of information about its elements. Each RS has boundary-line of objects which cannot be certainly classified. Each RS contains also associated pair of precise sets (the lower and high approximations). The lower consists of all objects certainty belong to the set and the upper one containing objects which possible belong to the set and difference between the upper and the lower precise sets constitutes the boundary region of the RS [1]. Such approximations are basic operations used in this data-mining methodology [3].

We used decision table as input data for RSES (as proposed by Pawlak [1]) constructed from columns where two last are the condition attributes measured by the neurologist (UPDRS III and IV) and all preceding columns are the decision attributes. Each row of the table describes the rules, by which each patient can be described. Therefore, rules can have many specific conditions, as number of rules equals number of rows. Using this approach, we can describe different UPDRS values in different patients. This approach should also simulate the way in which neurologists might interact with patients, perceiving various patient's symptoms at various levels of granularity. There are large inconsistencies between PD progression, symptoms, between individual patients and also in effects of similar treatments and the task of neurologists is to abstract and consider only those symptoms that are universally significant and serve to determine a specific treatment [4]. For visualization of the results obtained from RSES we used the WEKA data-mining software written at University of Waikato with J48 algorithm generating a pruned or unpruned C4.5 decision tree [2]. C4.5 is an algorithm building decision trees from a set of data using the concept of the information entropy and is probably one of most widely used machine learning tool in the current practice [20].

4 Results

Initial dataset contained 16 attributes and 28 experimental measurements (observations), representing calculated parameters from the antisaccade records mapped to the records from neurological database of particular patients. The example of initial dataset is presented in Table 1. Attributes it the Table 1 were defined as follow:

- Patient ID (ID) - the id of particular patient.
- Session - parameter describing the session type.
- Delay Mean - calculated eye mean delay relative to the movement of the spot.
- Duration Mean - calculated parameter describing duration of particular antisaccade.
- Max Speed - calculated maximum eye speed during particular antisaccade.
- UPDRS III - numeric result of patient's UPDRS III classification.
- UPDRS IV - numeric result of patient's UPDRS IV classification.

The example from combined dataset with mostly numeric data is presented in Table 1. In the first step of analysis we separated the UPDRS III and IV parameters placing it in two different tables. Then we used RSES for reduction of attributes and data discretization using the local method with symbolic attributes, allowing for nominal values analysis. In some cases it give better outputs in terms of sensitivity of discretization, as it is generating much more cuts and it is also slightly faster than the global method [18].

Table 1. Sample of the initial dataset

ID	Session	DelayMean	DurationMean	MaxSpeed	UPDRS-III	UPDRS-IV
13	S4	0.26	1.95	5.05	8	6
14	S1	0.5	4.4	5.05	43	0
14	S2	0.35	4.15	5.08	14	0
14	S3	0.42	4.01	5.24	5	8
14	S4	0.33	2.86	5.29	9	0

The final dataset containing decision important and discretized attributes representing ranges of values after the classified selection is presented in examples of data in Tables 2 and 3 accordingly to different UPDRS scale parameters.

Table 2. Sample of the reduced and discretized dataset with attribute UPDRS III

PatientID	Session	DelayMean	DurationMean	MaxSpeed	UPDRS-III
"13"	"S4"	(−inf–0.335)	(1.85–inf)	(−inf–5.075)	(3–13)
"14"	"S1"	(0.445–inf)	(1.85–inf)	(−inf–5.075)	(25–59)
"14"	"S2"	(0.335–0.445)	(1.85–inf)	(5.075–5.6)	(13–25)
"14"	"S3"	(0.335–0.445)	(1.85–inf)	(5.075–5.6)	(3–13)
"14"	"S4"	(−inf–0.335)	(1.85–inf)	(5.075–5.6)	(3–13)

In the next phase we wanted to find correlations between UPDRS values and the rest of the attributes. We compared different RSES classifiers performing the same cross-validation prediction of attribute UPDRS III and UPDRS IV on the discreatized datasets. The values of the UPDRS has been estimated with various accuracy and coverage depending on used algorithm. The classification has been performed in the method of global 5 Folds cross-validation. We tested different variants of classifications and 5 Folds gave the best predictive results for our dataset.

Table 3. Sample of the reduced and discretized dataset with attribute UPDRS IV

PatientID	Session	DelayMean	DurationMean	MaxSpeed	UPDRS-IV
13	S4	(−inf–0.335)	(1.94–2.725)	(−inf–5.105)	(3–9)
14	S1	(0.375–inf)	(3.885–inf)	(−inf–5.105)	(0–1)
14	S2	(0.335–0.375)	(3.885–inf)	(−inf–5.105)	(0–1)
14	S3	(0.375–inf)	(3.885–inf)	(5.105–inf)	(3–9)
14	S4	(−inf–0.335)	(2.725–3.885)	(5.105–inf)	(0–1)

We compared two different classifiers available in the RSES - the Decision Rules and the Decomposition Tree. The Decision Rules is based on decision table approach where columns are labeled by attributes, rows by objects of interest and entries of the table are attribute values [1]. Rows of a decision table are referred to "if/then" decision rules which give conditions necessary to make decisions specified by the decision attributes [1]. The Decomposition Tree splits dataset into fragments represented as a tree's leafs. Those subsets of data are used for calculation of decision rules and are supposed to be more uniform and easier to cope with decision-wise [17]. The RSES expresses the results of classifications in two main attributes: Total Accuracy (TA) and Total Coverage (TC). The TA represents the ratio of number of correctly classified cases (sum of values on diagonal in confusion matrix) to the number of all tested cases (number of test objects used to obtain this result) [18]. The TC represents ratio of classified objects from the class to the number of all objects in the class (percentage of test objects that were recognized by classifier) [18]. The best results were achieved with the RSES Decomposition Tree. For attribute UPDRS III classification results indicated 0.85 of TA with TC of 0.48. The value of the UPDRS IV has been estimated with TA of 0.91 and TC of 0.39. Other classifiers i.e. Decision Rules gave worse TA of 0.7 but with much better TC of 1. Tables 4 and 5 are showing the results for best classification where columns represent predicted values and rows represent actual values.

In order to better understand and visualize correlations provided by results we derived the decision trees using WEKA J48 classifier [2]. Analysis of visualization of the obtained trees brought interesting observations. When viewing

Table 4. Result of Decomposion Tree classification with 5 Folds Cross Validation for attribute UPDRS III.

UPDRS III	(3, 13)	(13, 25)	(25, 59)	No. of obj.	Accuracy	Coverage
(3, 13)	0.8	0	0	1.6	0.4	0.333
(13, 25)	0.2	0.2	0	1.6	0.1	0.133
(25, 59)	0.2	0	1	1.8	0.7	0.68
Total accuracy:	0.85				Total coverage:	0.48

Table 5. Result of Decomposion Tree classification with 5 Folds Cross Validation for attribute UPDRS IV.

UPDRS IV	(3, 9)	(0, 1)	(1, 3)	No. of obj.	Accuracy	Coverage
(3, 9)	1.75	0	0.25	2.75	0.938	0.708
(0, 1)	0.25	0.25	0	1.75	0.125	0.25
(1, 3)	0	0	0.25	2.5	0.25	0.083
Total accuracy:	0.91				Total coverage:	0.39

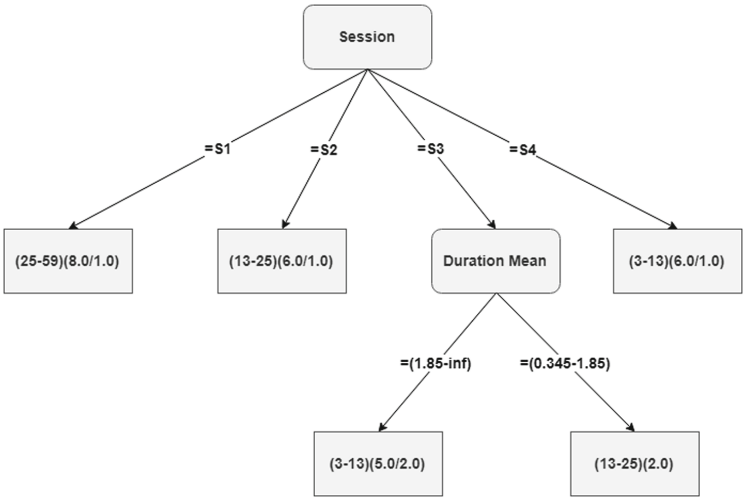

Fig. 2. Decision tree visualization for decision attribute UPDRS III and discretized dataset.

tree describing the UPDRS III attribute (Fig. 2) we can see that it is characterized by strong correlations with method of treatments represented by attribute Session obscuring the oculometric parameters. However quite strong interplay can be seen between the type of pharmacological treatment of examined patient (S3) and mean duration parameter (Duration Mean). To see direct correlations between UPDRS score and the antisaccade parameters we removed the Session attribute. With unified methods of treatments, the results showed correlations between group of the highest results of the UPDRS III (25–59) and groups of the highest duration (1.85–inf) and delay (0.445–inf) and the group of lowest the speed (−inf–5.075). In Fig. 3 we can see that Duration Mean is the main attribute describing the UPDRS III score group and how values of other oculometric parameters are being distributed. A quite different view emerged from the analysis of the decision tree containing attribute UPDRS IV (Fig. 4). Duration Mean applied as the main decision attribute. What seems to be interesting the attribute Session created own branch connected to the group located exactly in middle of Duration Mean values. Additionally attribute Max Speed correlated with the group of highest Mean Duration values.

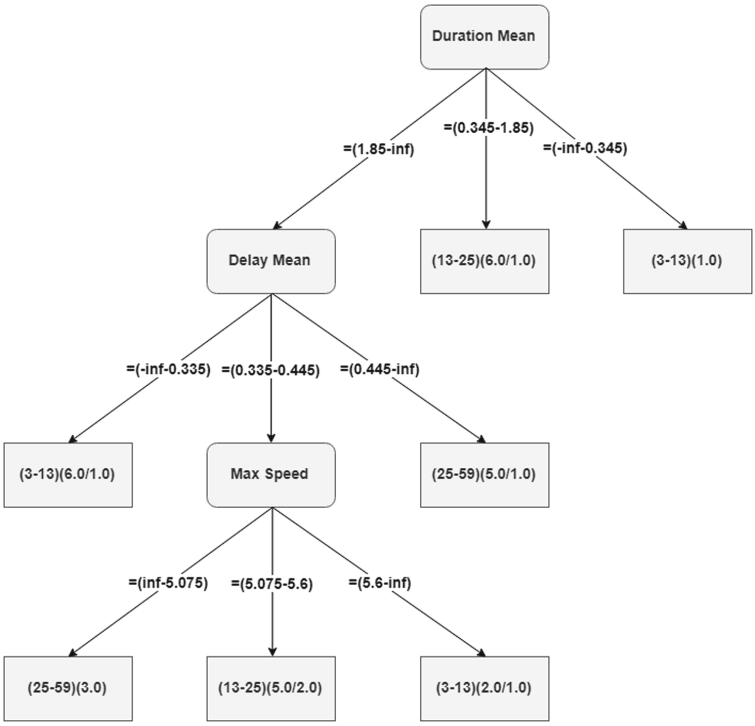

Fig. 3. Decision tree visualization for decision attribute UPDRS III and discretized dataset with attribute Session removed.

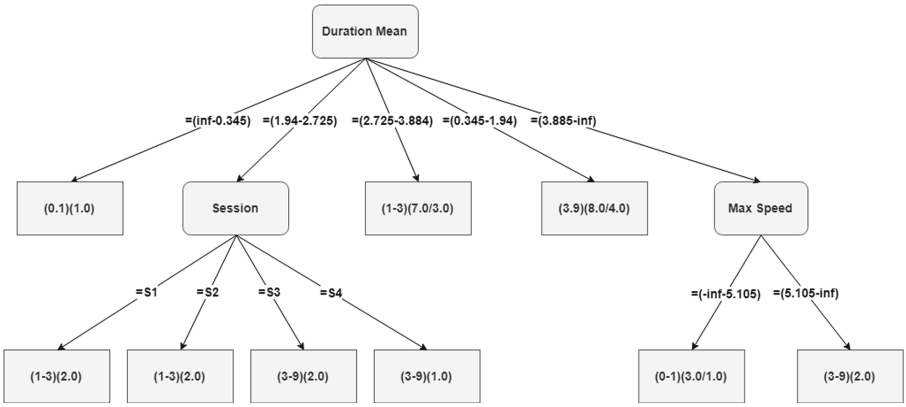

Fig. 4. Decision tree visualization for decision attribute UPDRS IV and discretized dataset.

5 Discussion and Conclusions

As can be seen in the results the attribute Session (describing methods of patients treatment) and attribute Duration Mean (antisaccade parameter) were most sensitive in predicting scoring group of UPDRS III and IV. When comparing results for both UPDRS III an IV, analysis showed greater correlation between UPDRS IV scoring and anitisaccade parameters obtained during oculometric examination. Attribute UPDRS IV also showed better accuracy during predictions (0.91). The results obtained using our dataset suggests that UPDRS IV scale is more sensitive in predictions to anitsaccade parameters than the UPDRS III. In our dataset the Delay Mean also presents as the most important decision attribute. Results of classification for this attribute also shows that we may increase UPDRS predictions by adding antisaccade parameters to neurological dataset of the patient.

We found results of this classification as very indicative taking into account such small group of records and quite high prediction with TA varying from 0.85 to 0.91. It proves sense of further experiments in presented area of correlations, between parameters of patient's oculometric results and the UPDRS motor evaluations. It is hoped that further development of methodology described in this text and similar approaches may help in determining the Parkinson Disease progression. We believe that in the upcoming future, applied algorithms can be used in applications installed on personal devices. Patients then could be free from clinical conditions and could perform oculometric tests under different environments and circumstances enlarging the amount of information describing the disease. Such a widespread availability of diagnostic tools, by increasing the quantity of patients data, should also increase the precision of patient's diagnosis.

6 Ethic Statement

This study was carried out in accordance with the recommendations of Bioethics Committee of Warsaw Medical University with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Bioethics Committee of Warsaw Medical University.

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