Granular Computing (GC) Demonstrates Interactions Between Depression and Symptoms Development in Parkinson's Disease Patients

Andrzej W. Przybyszewski[1(✉)], Jerzy Paweł Nowacki[1], Aldona Drabik[1], Stanislaw Szlufik[2], Piotr Habela[1], and Dariusz M. Koziorowski[2]

[1] Polish-Japanese Academy of Information Technology, 02-008 Warsaw, Poland
{przy, jerzy.nowacki, adrabik, piotr.habela}@pjwstk.edu.pl
[2] Neurology, Faculty of Health Science, Medical University Warsaw, Warsaw, Poland
stanislaw.szlufik@gmail.com, dkoziorowski@esculap.pl

Abstract. There is high frequency incidence of depressive symptoms in neurodegenerative diseases (ND) but reasons for it is not well understood. Parkinson's disease (PD) is often evoked by strong emotional event and related to reduced level of dopamine (reward hormone). Similarly to PD, in older (over 65 year of age) subjects with late onset Alzheimer's disease (LOAD) have first symptoms related to depression (95%). Present work is devoted to the question if evaluation of depression can help to predict PD symptoms? We have gathered results of: neurological (disease duration, values of Unified Parkinson's Disease Rating Scale (UPDRS)), neuropsychological (depression – Beck test, PDQ39 (life quality), Epworth (sleep problems)) and eye movement (RS – reflexive saccadic) tests. We have tested 24 PD patients only with medical treatment (BMT-group), and 23 PD with medical and recent DBS (deep brain stimulation DBS-group), and 15 older DBS (POP-group) treatments during one and half year with testing every six months (W1, W2, W3). From rules found with help of GC (RST-rough set theory) in BMTW1 (patients BMT during first visit W1) we have predicted UPDRS in BMTW2 and BMTW3 with accuracies (acc.) 0.765 (0.7 without Beck result) and 0.8 (0.7 without Beck result). By using BMTW1 rules we could predict disease progression (UPDRS) of another group of patients – DBSW1 group with accuracy of 0.765 but not DBSW2/W3 patients. By using DBSW2 rules we could predict UPDRS of DBSW3 (acc. = 0.625), POPW1 (acc. = 0.77), POPW2 (acc. = 0.5), POPW3 (acc. = 0.33). By adding depression attribute and by using GC we could make better predictions of disease progressions in many different groups of patients than without it.

Keywords: Neurodegeneration · Rough set theory · KDD · Granular computing

N. T. Nguyen et al. (Eds.): ACIIDS 2019, LNAI 11432, pp. 591–601, 2019.
https://doi.org/10.1007/978-3-030-14802-7_51

1 Introduction

It is commonly accepted that clinically important depressive disorders occur in 40–50% of patients with PD and they influence many other clinical aspects of the disease. In addition to triggering innate emotional suffering, depressive disorders harmfully impact quality of life, motor and cognitive deficits, and also functional disability [1].

The significance of depression is mentioned in the Parkinson's Outcomes Project http://parkinson.org/research/Parkinsons-Outcomes-Project is the largest-ever clinical study of Parkinson's disease with over 12,000 participants in five countries. In their outcomes states that Depression and anxiety are the number one factors impacting the overall health of people with Parkinson's.

Depression is also prediagnostic. Depressive symptoms were observed many years before Parkinson's diagnosis in patients in neurological clinics in large studies in different countries [2, 3]. In UK [2] was found that in about 5000 patients 7% was depressed whereas in above 25000 controls only 4% had depression in 5 years before diagnosis. In Rotterdam study [3] they have tested motor and non-motor features over a time period of up 23 years before diagnosis. The early symptoms were related to motor and equilibrium, but about 5 years before diagnosis anxiety and depression was observed.

Depression and anxiety in PD might be physiologically related to a specific loss of dopamine and noradrenaline innervation of cortical and subcortical components of the limbic system [4].

A worldwide study of over 1,000 patients with PD found that more than 50% of the subjects testified clinically substantial depressive symptoms based on Beck depression scores [5]. In majority of PD studies, depressive symptom gravity is mild to moderate. In studies examining the occurrence of PD depression indicate that depressive disorders can advance at any phase in the development of PD [5]. Often, affective disorders precede - 4–6 years before the PD diagnosis - the beginning of motor symptoms [6]. Parkinson's disease (PD) starts from the degeneration of dopamine neurons in the substantia nigra (SN), and later to the neuron death in many other brain's structures.

As SN is one of the main sources of the dopamine (Dopa), its lack causes instabilities in the movement's control, as well as in some patients, depression (Dopa is reward transmitter) in addition to emotional and cognitive problems. As each patient has different neurodegeneration development and compensation in consequence has different disease progression and symptoms that has to be estimated by experienced neurologist in order to find an optimal therapy. This depends on results of tests, neurologist's experience and doctor's time. The knowledge of neurologist is based not only on his/her experience but also intuition to predict results of different therapies for a particular patient.

We have estimated disease progression in different groups of patients that were under different therapies and they were tested during three every half-year visits. We hope that our method will lead to introduce more precise and more automatic follow ups in the perspective possibilities of the remote diagnosis and treatments.

This study is expansion of our previous works by using additional to our granular computing method: rough set theory, a new attribute – the depression that as we will

demonstrate plays a significant role in prediction of PD progression in dissimilar groups of patients with various treatments such as medication and/or DBS (deep brain stimulation) procedures.

2 Methods

We have analyzed tests from Parkinson Disease (PD) patients divided into three groups:

- **BMT-group** (the Best Medical Treatment) consists of 23 patients that were only on medication. The major medication in this group was L-Dopa that increases concentration of the transmitter dopamine in the brain as it that is lacking in Parkinson's patients. In most cases PD starts with neurodegeneration in substantia nigra that is response for the release of the dopamine.
- **DBS-group** (Deep Brain Stimulation) consists of 24 patients on medications and with implanted electrodes in the subthalamic nucleus during our study. These patients were more advanced in the disease than patients from BMT-group. Their first visit DBSW1 was before the DBS surgery, and second DBSW2 and third DBSW3 were with implanted stimulating electrodes in the subthalamic nucleus.
- **POP-group** (Post Operative Patients) consists of 15 patients with stimulating electrodes implanted before the beginning of our study. There were the most advanced patients as they have DBS surgery several years before the beginning of our study. Question was how long electrical stimulation is changing brain mechanisms and if we can approximate disease progression in these patients by other less advanced PD?

All together we have four different sessions: #1 to #4 that are all related to combinations of medication (MedOFF/ON) and brain stimulation (DBSOFF/ON). As in BMT-group patient are without stimulating electrodes so they were tested only in two sessions. Similar situation was in DBS-group before surgery (DBSW1 – visit W1 – the first visit).

We have performed the following testing for all patients:

(a) MedOFF (session #1 without - medication) and MedON (session #3 patients on medications).
(b) DBSOFF (DBS stimulation switched OFF in: session #1 without – medication; and session #3 with – medication) and DBSON (DBS stimulation switched ON in: session #2 without – medication; and session #4 with – medication). It was possible only in patients with implanted electrodes: DBS-group or POP-groups.

In addition all patients have to keep on with the following procedures: several neuropsychological tests (a new depression – Beck test, and used before PDQ39 (quality of life), and Epworth sleepiness test) and eye movement (RS – reflexive saccadic) and many neurological tests involved in the UPDRS (Unified Parkinson's Disease Rating Scale). All tests were performed in Brodno Hospital, department of Neurology, Faculty of Health Science, Medical University Warsaw, Poland. In the present work, we have tested and measured reflexive fast eye movements (saccades) as

described in our previous publications [9]. In summary, every subject was sitting in a stable position without head movements and watching a computer screen before him/her. At the beginning he/she has to fixate in the center of the screen, and to keep on moving light spot. This spot was jumping randomly, ten degrees to the right or ten degrees to the left.

We have recorded simultaneously movements of the light spot and both eyes by means of professionally tested head-mounted saccadometer (Ober Consulting, Poland). On the basis of both signals we have calculated parameters of the saccades: the latency as a delay measured the start of the light spot movement to the beginning of the eye movement; the amplitude of the saccadic, and its max.

All above described procedures were repeated for each session (as mentioned above).

2.1 Theoretical Basis

Our KDD (knowledge discovery database) analysis is based on granular computing implemented in RST (rough set theory proposed by Pawlak [10]).

Our results were converted into the decision table with rows related to different measurements in different or the same subject and columns were related to different attributes. An information system [10] and the *indiscernibility relation,* as well as *lower approximation* and *upper approximation* were described in details before [10, 11].

On the basis of the reduct we have generated rules using four different ML methods (RSES 2.2): exhaustive algorithm, genetic algorithm [12], covering algorithm, or LEM2 algorithm [13].

One can also see the decision table as a triplet: $S = (U, C, D)$ where: C is condition, and D is decision attribute [14]. Each row of the decision table is in a natural way interpreted as a specific rule that links condition and decision attributes for a single measurement of the individual subject. As there are results (rows) related to diverse sessions and patients, they in an automatic way give rules - each one specific for one row. They can be very often contradictory. RS granular computing is approximating human way of thinking. Neurologist is always approximating patient's conditions with certain approximation as patient has some symptoms certainly but other only partly. RS theory implies generalizing all particular rules into general propositions that are always true (lower approximation) and partly true (upper approximation). This is related to discovery of the specific directions in the database (KDD) and determines optimal treatments for different PD patients. The decision attribute D can be interpreted as a single measure of patient's condition estimated by an expert (doctor). One can interpret classification of the data by the information table with the decision attribute submitted by doctor as the *supervised learning (ML)* process with neurologist as the teacher.

It is well recognized that neurodegenerative processes start about 20 years before primary noticeable symptoms in PD and they might be various in diverse patients. It is a famous expression: "no two PDs are the same" so finding optimal treatment is very difficult. Also effects of comparable treatments might give different effects in individual patients. Our algorithms have certain granular properties to cover all individual differences but with certain approximation (RST). The purpose of our computation is to follow interactions: doctor and patients. Significant advantage of our granular

computations is abstraction and generalization in various levels that mimics approach of the very experienced doctor. Granular computing follows complex objects classifications as we have found in the visual brain [7, 8]. Our brains make object classification on the basis of inborn mechanisms and individual experience. We want to find enough flexible rules that will determine disease progressions of PD with diverse treatments, and in distinctive disease stages.

We have applied as KDD the RSES 2.2 (based on RST) [15] in order to find RS rules to process different patients. We have verified in our previous publication that the RS method gives better estimations than other classical methods [9].

3 Results

As described in the Methods section our patients were divided into three different groups: 23 BMT patients that were merely on medication, and 24 DBS patients were in addition to medication had electric stimulation of DBS-STN (subthalamic nucleus) with surgery completed during our study, and 15 POP patients with DBS procedure performed earlier.

Comparison of Longitudinal Changes in Tests Results

In BMT-group of patients in visit 1 (W1) had the mean age of 57.8 ± 13 (SD) years. Their confirmed disease duration was 7.1 ± 3.5 years, PDQ39 = 48.3 ± 29 (SD); Epworth 8 ± 5, Beck 14.2 ± 9.7, UPDRS session 1 was 48.3 ± 17.9 statistically ($p < 0.0001$) different than UPDRS equal 23.6 ± 10.3 in the session 3.

PatBMTW2 PDQ39 = 55.6 ± 34.5 (SD); Epworth 8 ± 5, Beck 16.3 ± 12.1; UPDRS in session 1 was 57.3 ± 16.8 ($p < 0.0005$ significantly different than in visit W1); whereas in session 3 it was 27.8 ± 10.8;

PatBMTW3 PDQ39 = 50.6 ± 28 (SD); Epworth 7.3 ± 4, Beck 14.1 ± 9.7; UPDRS in session 1 was 62.2 ± 18.2 ($p < 0.05$ significantly different than in visit W2); in session 3 was 25 ± 11.6.

It was no statistically significant difference in UPDRS between visits for session 3.

In DBS - group, the mean age of patients was 53.7 ± 9.3 years, and disease duration was 10.25 ± 3.9 years. In visit W1 UPDRS was 62.1 ± 16.1 (statistically different $p < 0.0001$ than in BMT-group, visit W1), PDQ39 = 56.5 ± 22.6 (SD); Epworth 9.1 ± 5.4, Beck 14.8 ± 10.0.

In DBS – group, visit W2 that was directly the surgery, in session 1 UPRDS equal 65.3 ± 17.6 became larger than before the surgery (see above) but there were not statistically significant difference; PDQ39 = 44.0 ± 22.1 (SD); Epworth 9.0 ± 4.8, Beck 11.0 ± 8.8.

In DBS – group, visit W3 session 1 UPDRS was 68.7 ± 17.7 and statistically different ($p < 0.03$) than in visit W2; PDQ39 = 46.1 ± 23.0 (SD); Epworth 9.2 ± 4.3, Beck 10.0 ± 8.4.

In POP-group UPDRS in session 1 for visit W1 was: 63.1 ± 18.2; for visit W2 was: 68.9 ± 20.3 to for visit it was W3: 74,2 ± 18.4. In session 4 (session with medication and DBS procedures) in visit W1 was 21 ± 11.3, in visit W2 was

23.3 ± 9.5, and in visit W3 was 23,8 ± 10.7. There are some similarities between groups DBS and POP.

3.1 KDD Findings Depression for BMT Group

In the BMT group were patients on only medication treatment with two sessions (no medication - MedOff session #1 and on medication MedOn session #3). They were measured three times every half of the year (W1, W2 and W3).

We have used RSES for the discretization and UPDRS were divided into the following ranges: "(−Inf, 24.0)", "(24.0, 36.0)", "(36.0, 45.0)", "(45.0, Inf)".

We had initially 72 rules for BMTW1 patients, but by generalization and filtering we have reduced them to 7 rules that are presented below without one rule that was specific for only one patient.

Table 1 is a discretized table for three patients: 4, 5, and 7 in two sessions: MedOFF (#1), MedON (#3) with parameters related to Beck depression scale and quality of sleep (Epworth scale), saccades latency values (SccLat), and the decision attribute was UPDRS (last column). Notice that Table 1 above is similar to Table 1 in [14] with an exception that in the previous table we did not use Beck score and PDQ39 has replaced present depression score (now PDQ39 is skipped).

Table 1. Discretized-table extract for BMT patients

P#	tdur	Ses	Beck	Epworth	PDQ39	RSLat	RSDur	RSAmp	RSVel	UPDRS
4	"(-Inf,9.75)"	1	"(-Inf,14.0)"	"(-Inf,3.0)"	*	"(-Inf,181.5)"	*	*	*	"(36.0,45.0)"
4	"(-Inf,9.75)"	3	"(-Inf,14.0)"	"(-Inf,3.0)"	*	"(-Inf,181.5)"	*	*	*	"(-Inf,24.0)"
5	"(9.75,Inf)"	1	"(-Inf,14.0)"	"(3.0,Inf)"	*	"(181.5,395.0)"	*	*	*	"(36.0,45.0)"
5	"(9.75,Inf)"	3	"(-Inf,14.0)"	"(3.0,Inf)"	*	"(181.5,395.0)"	*	*	*	"(24.0,36.0)"
7	"(-Inf,9.75)"	1	"(14.0,Inf)"	"(3.0,Inf)"	*	"(181.5,395.0)"	*	*	*	"(36.0,45.0)"
7	"(-Inf,9.75)"	3	"(14.0,Inf)"	"(3.0,Inf)"	*	"(181.5,395.0)"	*	*	*	"(-Inf,24.0)"

Each row can be written as a rule that will give 23 (number of BMT patients) * 2 (OFF and ON) = 46 very specific rules like that for the first row:

(P#4)&(dur="(-Inf,9.75)")&(Ses=1)&(Beck="(-Inf,14.0)")&(Epworth="(-Inf,3.0)") & (RSLat="(-Inf,181.5)") => (UPDRS="(36.0,45.0)") (1)

It means that if the for Pat#4, saccade duration is smaller than 9.7 ms, session is #1, Beck is smaller than 14, Epworth score smaller than 3.0 and saccade latency smaller than 181.5 ms then UPDRS will be between 36 and 45.

By using RST we can generalize rules from above table to the following rules:

$$(dur="(9.75,Inf)")\&(Beck="(14.0,Inf)")\&(Ses=1)\&(Epworth="(3.0,Inf)") \Rightarrow (UPDRS="(45.0,Inf)"[6]) \quad (2)$$

$$(Ses=3)\&(Epworth="(-Inf,3.0)") \Rightarrow (UPDRS="(-Inf,24.0)"[4]) \quad (3)$$

$$(Beck="(-Inf,14.0)")\&(Ses=3)\&(RSLat="(-Inf,181.5)") \Rightarrow (UPDRS="(-Inf,24.0)"[4]) \quad (4)$$

$$(dur="(-Inf,9.75)")\&(Ses=3)\&(RSLat="(-Inf,181.5)") \Rightarrow (UPDRS="(-Inf,24.0)"[3]) \quad (5)$$

$$(dur="(-Inf,9.75)")\&(Ses=1)\&(Epworth="(3.0,Inf)")\&(RSLat="(Inf,181.5)") \Rightarrow (UPDRS="(24.0,36.0)"[3]) \quad (6)$$

$$(dur="(Inf,9.75)")\&(Beck="(-Inf,14.0)")\&(Ses=1)\&(RSLat="(181.5,395.0)") \Rightarrow (UPDRS= "(45.0,Inf)"[2]) \quad (7)$$

In the second formula (2) states that for the session 1 and saccade duration longer than 9.75 ms and Beck depression score larger than 14 and Epworth larger than 3.0 then UPDRS will be larger than 45.0. Eq. 2 was true in 6 cases.

Table 2. Confusion matrix for UPDRS of BMTW2 group by rules obtained from BMTW1-group

Actual	Predicted				
	"(36.0, 45.0)"	"(−Inf, 24.0)"	"(24.0, 36.0)"	"(45.0, Inf)"	ACC
"(36.0, 45.0)"	0. 0	0.0	0.0	0.0	0.0
"(−Inf, 24.0)"	0.0	8.0	0.0	0.0	1.0
"(24.0, 36.0)"	0.0	1.0	0.0	0.0	0.0
"(45.0, Inf)"	0.0	0.0	3.0	5.0	0.625
TPR	0.0	0.9	0.0	1.0	

TPR: True positive rates for decision classes; ACC: Accuracy for decision classes: the global coverage was 0.37 and the global accuracy was 0.765, the coverage for decision classes was 0.0, 0.73, 0.11, 0.4.

In addition, we have used BMTW1 rules to predict UPDRS in the next two visits: BMTW2 and BMTW3 in patients on medication only, with global accuracies of 0.765 (Table 2) and 0.8, and with the global coverage 0.37 and 0.33. It looks that accuracy are better than without Beck scale (0.7 for both visits), but global coverage with PDQ39 was 1 for both visits W2 and W3. Notice that in Eq. (2) fulfilled for 6 cases, the Beck score is high (above 14) and UPDRS is large (above 45), and in Eq. (4) satisfied

in 4 cases the Beck score is low (below 14) and UPDRS is below 24. However, in Eq. 7 in two cases the Beck score is low (below 14) and UPDRS is large (above 45). It means that the depression score is *rough* – is not 100% discriminatory.

3.2 KDD for DBS Group

We have excluded DBSW1 group as these patients do not have implanted electrodes, but we made predictions UPDRS of DBSW3 by rules from DBSW2 (only sessions with DBSON and MedOFF – session 2, MedON – session 4), and we have obtained the global accuracy 0.67 (0.56 without Beck depression score) and global coverage 0.625 (1 without Beck inventory results).

But in DBSW2 decision classes were different than in BMTW1 "(36.5, Inf)" "(28.0, 36.5)" "(19.5, 28.0)" "(−Inf, 19.5)". We have obtained 6 rules with LEM algorithm [10] after filtering one-case rules. There are interesting differences to rules from BMTW1 group e.g.:

(RSLat="(-Inf,310.0)")&(PDQ39="(-Inf,69.5)")&(Ses=3)&(Beck="(4.5,23.0)")=> (UPDRS="(-Inf,19.5)"[10])

(8)

(Epworth="(-Inf,7.5)")&(RSLat="(-Inf,310.0)")&(dur="(8.0,12.58)")&(PDQ39="(-Inf,69.5)")&(Beck="(-Inf,4.5)")=>(UPDRS="(-Inf,19.5)"[4])

(9)

(PDQ39="(-Inf,69.5)")&(Beck="(4.5,23.0)")&(Ses=1)&(RSLat="(-Inf,310.0)")& (dur="(8.0,12.58)")&(Epworth="(-Inf,7.5)")=>(UPDRS="(28.0,36.5)"[2])

(10)

Notice that these rules Eqs. 8–10 have not only Beck scores (depression), but in contrast to BMTW1 rules, also PDQ39 quality of life scale. By adding depression score we have obtained better accuracy (Table 3) than without it [16].

Table 3. Confusion matrix for UPDRS of DBSW3 group by rules obtained from DBSW2-group

Actual	Predicted				
	"(36.0, Inf)"	"(28.0, 36.5)"	"(19.5, 28.0)"	"(−Inf, 19.5)"	ACC
"(36.5, Inf)"	2. 0	1.0	0.0	2.0	0.4
"(28.0, 36.5)"	0.0	3.0	1.0	2.0	0.5
"(19.5, 28.0)"	0.0	0.0	4.0	5.0	0.44
"(−Inf, 19.5)"	0.0	0.0	3.0	11.0	0.92
TPR	1.0	0.75	0.67	0.55	

TPR: True positive rates for decision classes; ACC: Accuracy for decision classes: the global coverage was 0.67 and the global accuracy was 0.625, the coverage for decision classes was 0.5, 0.55, 0.75, 0.75.

3.3 KDD for DBS Group Based on BMT Patients

In the next step, we have applied BMTW1 rules (Eqs. 2–7) to all visits of patients from the DBS group. As before [16] we were successful only for DBSW1 group (patients still before implementation of the stimulating electrodes). Therefore, these patients had only two sessions but with the higher dosage of medication as they were in more advance disease stage in comparison to BMT-group. We have obtained the global accuracy 0.765 (it was 0.64 without Beck [16]) with the global coverage 0.354 (0.5 without Beck [16]), for DBSW2 we got accuracy of 0.85, coverage of 0.3 (0.77 and 0.37 with Beck), for DBSW2 accuracy and coverage were 0.74 and 0.56 (0.8 and 0.33 with Beck depression score).

3.4 KDD for POP Group Based on DBSW2 Patients

Similarly to the previous study [16], we have divided DBSW2 PD into two subgroups: the first one with electric stimulation switched off (DBSOFF), and the second subgroup with electric stimulation switched on – DBSON. The reason was that POP patients were in more advanced stage of the disease and DBS makes POP and DBS patients more similar. Therefore, we made predictions only for UPDRS in POP groups with DBSON and for two sessions: MedOFF and MedON.

We have used rules from the DBSW2 group (see above). Previously [16] using rules without depression inventory (Beck score) we were not able to predict UPDRS of POP patients, as we have found that POP in comparison to DBS rules were contradictory.

Table 4. Confusion matrix for UPDRS of POPW1 group by rules obtained from DBSW2-group

Actual	Predicted				
	"(36.0, Inf)"	"(28.0, 36.5)"	"(19.5,2 8.0)"	"(−Inf, 19.5)"	ACC
"(36.5, Inf)"	1. 0	0.0	1.0	0.0	0.5
"(28.0, 36.5)"	2.0	0.0	1.0	1.0	0.0
"(19.5, 28.0)"	2.0	1.0	3.0	2.0	0.375
"(−Inf, 19.5)"	0.0	1.0	0.0	8.0	0.89
TPR	0.2	0.0	0.6	0.73	

TPR: True positive rates for four decision classes; ACC: Accuracy for decision classes: the global coverage was 0.77 and the global accuracy was 0.52, the coverage for decision classes was 0.4, 0.57, 1.0, 0.9.

Adding depression is important as we could predict disease progression of POPW1 group with accuracy 0.5, coverage 0.77 (Table 4). For POPW2 group we have obtained global accuracy 0.4 and global coverage 0.17. For POPW3 we had global accuracy 0.25 and global coverage 0.33. It means that there are still other long-term effects of brain stimulation that we cannot effectively predict.

4 Discussion

There is permanent problem in handling patients with neurodegenerative diseases: how to find and test if an actual treatment is optimal or even 'near' optimal? It is very important question as the right, optimal therapy may improve patient's quality of life, help caregiver, and prolong patient's activity and his/her life expectancy. Technology made important progress in medical science and introduced new procedures improving patient's handlings. The main problem is the long lasting (about 20 years) neurodegeneration processes with the specific for each person compensatory mechanism happening before the first disease symptoms. As plastic mechanisms are influenced by many factors as such as: daily activity – physical and intellectual, profession as cognitive training, so-called social brain, diet and physical training. In the consequence, each patient must be handled in an individual, unique way. In order to fulfill it, we have used KDD approach looking for hidden rules with help of data mining and machine learning methods (RST granular computations) that propose universal rules with enough generalization and specificity that determine treatments of individuals from different groups of patients. These general rules are related to the knowledge and experience of the neurologist but are also related to individual patients. Our long-term plans are to expand this granular computing approach not only to study patients with many different treatments, but also to compare many different groups of patients various centers using not exactly the same approach in diagnosis and medications. If we obtain rules that are different for different medical centers we can easy compare them in order to find granules determining more optimal set of treatments for each individual patient.

In this study, we have examined three groups of PD patients in the different disease stages and procedures: BMT, DBS, and POP groups and tried to find common mechanisms between them. Previously we have made effective prediction of the disease progression for BMT and DBS groups of patients. However, we were not successful to predict disease progression in the patients with long brain electric stimulation (POP group). In this analysis, we have improved our results by adding depression attribute (Beck score). Depression was sufficient in BMT group but for DBS and POP groups the quality of life (PDQ39), with sleepless (Epworth), and eye movement were major attributes that helped to predict UPDRS. **Therefore depression plays a significant role in the disease progression of PD patients.**

Ethics 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 Bioethics Committee of Warsaw Medical University approved the protocol.

References

1. Reijnders, J.S., Ehrt, U., Weber, W.E., et al.: A systematic review of prevalence studies of depression in Parkinson's disease. Mov. Disord. **23**, 183–189 (2008)
2. Schrag, A., Horsfall, L., Walters, K., Noyce, A.: Petersen I prediagnotic presentations of Parkinson's disease in primary care: a case-control study. Lancet Neurol. **14**(1), 57–64 (2015)
3. Darweesh, S.K.L., et al.: Trajectories of prediagnostic functioning in Parkinson's disease. Brain **140**, 429–441 (2017)
4. Remy, P., Doder, M., Lees, A., Turjanski, N., Brook, D.: Depression in Parkinson's disease: loss of dopamine and noradrenaline innervation in the limbic system. Brain **128**(Pt 6), 1314–1322 (2005)
5. GPDS Steering Committee: Factors impacting on quality of life in Parkinson's disease: results from an international survey. Mov. Disord. **17**, 60–67 (2002)
6. Ishihara, L., Brayne, C.: A systematic review of depression and mental illness preceding Parkinson's disease. Acta Neurol. Scand. **113**, 211–220 (2006)
7. Przybyszewski, A.W.: Logical rules of visual brain: from anatomy through neurophysiology to cognition. Cognit. Syst. Res. **11**, 53–66 (2010)
8. Przybyszewski, A.W.: The neurophysiological bases of cognitive computation using rough set theory. In: Peters, J.F., Skowron, A., Rybiński, H. (eds.) Transactions on Rough Sets IX. LNCS, vol. 5390, pp. 287–317. Springer, Heidelberg (2008). https://doi.org/10.1007/978-3-540-89876-4_16
9. Przybyszewski, A.W., Kon, M., Szlufik, S., Szymanski, A., Koziorowski, D.M.: Multimodal learning and intelligent prediction of symptom development in individual parkinson's patients. Sensors **16**(9), 1498 (2016). https://doi.org/10.3390/s16091498
10. Pawlak, Z.: Rough Sets: Theoretical Aspects of Reasoning About Data. Kluwer, Dordrecht (1991)
11. Bazan, J., Nguyen, S.H., Nguyen, T.T., Skowron, A., Stepaniuk, J.: Decision rules synthesis for object classification. In: Orłowska, E. (ed.) Incomplete Information: Rough Set Analysis, pp. 23–57. Physica–Verlag, Heidelberg (1998)
12. Bazan, J., Nguyen, H.S., Nguyen, S.H., Synak, P., Wróblewski, J.: Rough set algorithms in classification problem. In: Polkowski, L., Tsumoto, S., Lin, T. (eds.) Rough Set Methods and Applications, pp. 49–88. Physica-Verlag, Heidelberg (2000)
13. Grzymała-Busse, J.: A new version of the rule induction system LERS. Fundamenta Informaticae **31**(1), 27–39 (1997)
14. Bazan, J.G., Szczuka, M.: The rough set exploration system. In: Peters, J.F., Skowron, A. (eds.) Transactions on Rough Sets III. LNCS, vol. 3400, pp. 37–56. Springer, Heidelberg (2005). https://doi.org/10.1007/11427834_2
15. Bazan, J.G., Szczuka, M.: RSES and RSESlib - a collection of tools for rough set computations. In: Ziarko, W., Yao, Y. (eds.) RSCTC 2000. LNCS (LNAI), vol. 2005, pp. 106–113. Springer, Heidelberg (2001). https://doi.org/10.1007/3-540-45554-X_12
16. Przybyszewski, A.W., Szlufik, S., Habela, P., Koziorowski, D.M.: Rules determine therapy-dependent relationship in symptoms development of Parkinson's disease patients. In: Nguyen, N.T., Hoang, D.H., Hong, T.-P., Pham, H., Trawiński, B. (eds.) ACIIDS 2018. LNCS (LNAI), vol. 10752, pp. 436–445. Springer, Cham (2018). https://doi.org/10.1007/978-3-319-75420-8_42