Theory of Mind Helps to Predict Neurodegenerative Processes in Parkinson's Disease

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Abstract. Normally, it takes many years of theoretical and clinical training for a physician to be the movement disorder specialist. It takes additional multiple years of the clinical practice to handle various “non-typical” cases. The purpose of our study was to predict neurodegenerative disease development by abstract rules learned from experienced neurologists. Theory of mind (ToM) is human's ability to represent mental states such as emotions, intensions or knowledge of others. ToM is crucial not only in human social interactions but also is used by neurologists to find an optimal treatment for patients with neurodegenerative pathologies such as Parkinson's disease (PD). On the basis of doctors' expertise, we have used supervised learning to build AI system that consists of abstract granules representing ToM of several movement disorders neurologists (their knowledge and intuitions). We were looking for similarities between granules of patients in different disease stages to granules of more advanced PD patients. We have compared group of 23 PD with attributes measured three times every half of the year (G1V1, G1V2, G1V3) to other group of 24 more advanced PD (G2V1). By means of the supervised learning and rough set theory we have found rules describing symptoms of G2V1 and applied them to G1V1, G1V2, and G1V3. We have obtained the following accuracies for all/speed/emotion/cognition attributes: G1V1: 68/59/53/72%; G1V2: 72/70/79/79%; G1V3: 82/92/71/74%. These results support our hypothesis that divergent sets of granules were characteristic for different brain's parts that might degenerate in non-uniform ways with Parkinson's disease progression.

Keywords: Granular Computing, Rough Set, Rules, Cognition.

1 Introduction

We are interested in the mechanisms related to the neural death with related compensation and reorganization mechanisms in different brain's neural circuits.
The majority of the reorganization mechanisms are related to human's learning and adaptation inspired by our rich environment, and they are the biological basis of our intelligence. In the consequence, the most patients are not able to notice significant cognitive, emotional and behavioral changes related to their brain neurodegeneration processes for over 20 years before their first noticed symptoms.
Another side of this long period of individual compensatory learning processes is that "there is no two PDs with exactly same symptoms". It is not effective and possible to observe every single neuron (there is about $8.6*10^{10}$ neurons and just as many nonneuronal cells, which actively participate in the neurodegeneration, in the human brain) and its connections (about 10^4 for each neuron) during neurodegenerative process, so we will observe meta-learning by recording attributes related to changes in the different brain structures. These processes are related to many different neuronal changes that are principally compensated by two major kinds of learning. The first one

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DOI: 10.1007/978-3-030-77967-2_45

is the supervised learning based on the "teacher's feedback" (beginning with our Mothers), and the second kind of compensation is related to the reinforced learning (RL) [1]. The RL is based on the selection of such activity (behavior) that gives reward. As the reward is associated with the pleasure and release of the neurotransmitter - dopamine, the RL mechanisms might change in Parkinson's disease (PD). PD is primary caused by dopamine depletion related to the neurodegeneration of the substantia nigra. PD has characteristic dominating motor symptoms (bradykinesia) with emotional and cognitive dysfunctions. There are also related subtle adaptation (RL) problems e.g., responses to sudden changes in patient's environment, as one PD patient said: "*when my husband went to hospital for three days, I became crazy*". The reliable (supportive) part of the environment has changed; therefore, patient has problems to adapt that caused emotional instabilities (another role of the dopamine).

In order to understand the complex interactions between different mechanisms related to the neurodegeneration (loss of neurons) and also to the compensatory learning, we have introduced the Theory of Mind (ToM). Generally, in the literature the ToM was used in the domain of cognitive and motor related (verbal fluency) social cognition [2]. There are also findings related to deficits of the cognitive components of ToM in early stages, and affective parts of ToM in the late stages of PD patients [3]. But in order to find patients' ToM abilities we need to follow neurologists' ToM to "get inside" of the patient's changes in the brain. For example, the social emotional thinking is based on the mirroring [4] of movements and emotions introduced by others' facial expressions (movements) [5] that might be formalized by rough set theory [6].

In summary, our purpose was twofold, not only to look into the ToM ability in different PD patients, but also to propose the machine's ToM that will mirror neurologists reasoning and make it more universal by introducing the *abstract rules*. We wanted to check the following hypothesis: if our abstract rules related to the disease progression of different patients are appropriate, then they should be more similar to rules describing disease symptoms of the more advanced patients. This postulate is evident for the most neurologists but notice that each patient has different mechanisms and rates of the disease progression. It follows by another more detailed question: are different structures, such as related predominantly to the movement, cognition, and emotion have similar rates of the disease progression or not?

The structure of our paper is the following: in the Methods section we have described four different tests that involve: all parameters (general test), movements related parameters (movements test), emotion related parameters (emotional test), and cognition related parameters (cognition test), in addition we have review our method based on rough set theory (RST). In the Result section we have performed statistical evaluation of all our parameters and in the following paragraphs we have evaluated four different tests mentioned above. For each set of tests, the discretization and parameters reduction were performed with help of the RSES software. The RST rules for the more advanced patient's group were found and applied to other groups. The prediction accuracy and coverage for each group and each test were found and compared between different groups and different tests. In the Discussion and Conclusion sections the meaning of our findings and the practical consequences were discussed, as well as our future plans.

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DOI: 10.1007/978-3-030-77967-2_45

2 Methods

2.1 Review Stage

All 47 PD patients were divided into two groups: the first group of 23 patients was tested three times every half of the year (visits were numbered as G1V1, G1V2, G1V3), and the second group (G2V1) of more advanced 24 patients was a reference model of disease progression to the first group. All patients were tested in two sessions: with-Ses=2 or without-medication Ses=1. The neurologists in Brodno Hospital, Department of Neurology, Faculty of Health Science, Medical University Warsaw, Poland performed all tests [7]. In the present work, in addition to standard neurological tests, we have measured the fast eye movements: reflexive saccades (RS) by means of saccadometer (Ober Consulting) using methodology as described in [8]. In short, 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. Patient has to follow movements of the light spot during 20 trails. The following parameters were measured: the latency - *RSLat* as time difference between beginning of spot and eyes movements, the saccade duration - *RSDur;* the saccade amplitude - *RSAmp* and the saccade velocity - *RSVel*.

In addition to the general test (**General ToM**) where all 12 attributes were used, all PD patients have three distinct groups of tests related to functions of different systems in the brain:

1. **Movements ToM - Speed and accuracy of movements**: reflexive eye movements parameters, *Epworth* (quality of sleep) and *Trail A* (speed and precision of connecting circled numbers) results

2. **Emotional ToM - Emotional stage** of patients estimated by the *PDQ 39* (quality of life), *Beck* depression tests, and eye movements parameters.

3. **Cognitive ToM - Cognitive processes** tested by *FAS* test (test od language fluency) and *Epworth* (sleep quality test that is related to memory consolidation) *Trail B* (speed and precision of connecting circled numbers and letters), and eye movements measures.

We have analyzed all attributes together or alternatively in three separated mentioned above tests in order to predict developments of the diseases progression that is estimated by the standard PD test: the UPDRS (Unified Parkinson's Disease Rating Scale) that has parts related to behavior and mood, activities of daily living, motor symptoms and estimation of patient's stage of the disease; or by the UPDRS III that is a part of the UPDRS limited to only motor symptoms. The UPDRS scale has 42 items and it is a ‘golden standard’ for estimation of the progression in Parkinson’s disease.

2.2 Rough Set Theory

Our data mining analysis follows rough set theory (RST) discovered by Prof. Zdzislaw Pawlak [9]. He has considered the problem of the boundaries after the philosophical

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DOI: 10.1007/978-3-030-77967-2_45

approach of Frege that “concepts must have sharp boundaries”. Prof. Pawlak solution of the vague concept of boundaries is to approximate them by sharp sets of the upper and lower approximations (Fig. 1).
It was demonstrated previously that RST gave the best results in the PD symptoms classifications in comparison to other methodologies [10]. Our data are represented as a decision table where rows represented different measurements (from the same or different patients) and columns were related to different attributes. An information system [9] is as a pair $S = (U, A)$, where U, A are nonempty, finite sets: U is the universe of objects; and A is the set of attributes. The value $a(u)$ is a unique element of V (where V is a value set) for $a \in A$ and $u \in U$. The RST *indiscernibility relation* is defined as: $(x, y) \in IND(B)$ or $xI(B)y$ iff $a(x) = a(y)$ for every $a \in B$ where the value of $a(x) \in V$. It is an equivalence relation $[u]_B$ that we understand as a *B-elementary granule*.

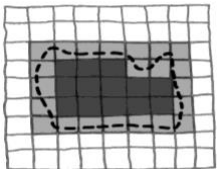

Figure 1 Rough set concept explanation. Interrupted curve represents properties of the complex object S. Squares represent elementary granules (atoms); squares in black are related to the lower approximation of S, grey and black squares represent the upper approximation of S, and white squares are placed outside of S.

A *lower approximation* of set $X \subseteq U$ in relation to an attribute B is defined as:

$$\underline{B}X = \{u \in U: [u]_B \subseteq X\}.$$

The *upper approximation* of X *is* defined as:

$$\overline{B}X = \{u \in U: [u]_B \cap X \neq \emptyset\}.$$

The difference of $\overline{B}X$ *and* $\underline{B}X$ is the boundary region of X that we denote as $BN_B(X)$. If $BN_B(X)$ is empty then set than X is *exact* with respect to B; otherwise, if $BN_B(X)$ is not empty and X is not *rough* with respect to B [9, 11]. A decision table for S is the triplet: $S = (U, C, D)$ where: C, D are condition and decision attributes. Each row of the information table gives a particular rule that connects condition and decision attributes for a single measurement of a particular patient. As there are many rows related to different patients and sessions, they gave many particular rules. Rough set approach allows generalizing these rules into universal hypotheses that may determine optimal treatment options for an individual PD patient. However, an important difference to other classification system is that RST by using rules (with explicit meanings) is easy understand, also gives better accuracies than most AI but does not cover all cases (coverage is smaller than 1). Fuzzy RST gives coverage =1 but has lower accuracies for the same data e.g. [12].

We have used Rough Set Exploration System RSES 2.2 as a toolset for analyzing data with rough set methods [13].

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DOI: 10.1007/978-3-030-77967-2_45

3 Results

3.1 Statistics

For the first group of PD patients we have performed three tests, every half-year, whereas the second group of more advanced PD we have measured only one time. The mean age of the first group (G1) was 57.8+/- 13 (SD) years with disease duration 7.1+/-3.5 years. It is very strong and significant influence of medication, but only UPDRS and eye movements parameters are measured in without/with medication (MedOff/On). UPDRS MedOff/On was 48.3+/-17.9 and 23.6+/-10.3 for the first visit (V1); 57.3+/-16.8 and 27.8+/-10.8 for the second visit (V2), 62.2+/-18.2 and 25+/-11.6 for the third visit (V3). The second group (G2) of patients was more advanced with mean age 53.7+/- 9.3 years, and disease duration 10.25+/- 3.9 years; UPDRS MedOff/On was 62.1+/-16.1 and 29.9+/-13.3 measured one time only. In all cases influences of medications on UPDRS were stat. sig. ($p<0.001$).

The eye movements parameters were the following for G1V1 MedOff/On: RSLat 257+/-78ms / 220+/-112ms; RSDur: 50.3+/-5.1ms / 46+/-16ms; RSAmp: 10.5+/-2.4 / 8.6+/-7.0; RSVel 409+/-104 / 471+/-354.
For G2V1 MedOff/On: RSLat 247+/-69ms / 250+/-60ms; RSDur: 49.3+/-5.7ms / 48+/-5ms; RSAmp: 9.6+/-2.4 / 7.6+/-3.9; RSVel 402+/-104 / 453+/-101.

The quality of sleep measured by the Epworth score was the following for G1V1/G2V1: 7.9+/-4.9 / 9.1+/-5.5; for Trail A: 55.5+/-29.7 / 50.0+/-13.0; for Trail B: 141+/-99 / 108.7+/-68.5; FAS: 43.9+/-12.9 / 39.9+/-14.5; the Beck depression inventory (Beck test): 14.2+/-9.8 / 14.8+/-10.1; the quality-of-life score (PDQ 39): 48.3+/-29.3 / 56.5+/-22.8.

As states above mean values between groups are different, but because large variabilities between patients not all parameters are stat. different.

There were several stat. sig. differences between G1 and G2 patients: UPDRS III (characteristic for Parkinson's movement disorders); MedOff G1V1: 29.4 +/-16.1; G2: 35.8+/-9.9 ($p<0.04$), AIMS (abnormal involuntary movements score) G1V1: 2.3 +/-4.0; G2: 9.1 +/-5.7; ($p<0.0001$), and significantly different for all G1 visits.

The learning Slope (CVLT – California Verbal Learning Test) G1V1: 2.9 +/-1.36; G2: 2.0+/- 0.8 ($p<0.016$), and significantly different for all G1visits. There were other significantly different parameters between both groups like the means time of dyskinesia and mean OFF time [7], also many other cognitive parameters were recently statistically analyzed [14].

Data were placed in four information tables: G1V1, G1V2, G1V3, and G2V1.

3.2 General ToM

We have used rough set theory [9] in order to obtain rules connecting decision and condition attributes for the advanced group of PD patients: G2V1. We have placed all data in the information table (as described above) that had 48 rows: 24 patients measured in two sessions (see above) each. Columns of this table were related to different 12 attributes and rows to results of different patients testing.

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DOI: 10.1007/978-3-030-77967-2_45

There were 12 columns related to the condition attributes: patient number id: *#P*, *Ses:* session number, *dur:* disease duration, *PDQ39* – quality of life, *Epworth* – quality of sleep, *Beck* depression test, RS (reflexive saccade): *RSLat, RSDur, RSAmp, RSVel* (as explained above), *Trail A* and *B* (as described above). The last column was related to the decision attribute: *UPDRS* (Unified Parkinson's Disease Rating Scale) (as above). In the next step, by using RST algorithms (RSES 2.2) we *have discretized (found optimal bin width) and reduced number of attributes*. As the results of the reduction the following attributes: RSDur, RSAmp, RSVel, Trail A, B were discarded. UPDRS was optimally divided by RSES into 4 ranges: *"(-Inf, 18.5)", "(18.5, 43.0)", "(43.0, 54.0)", "(54.0, Inf)"*. We have divided G2V1 data (48 objects) into 6 groups and predictions were performed by rules learned from 5 groups in order to predict UPDRS of 5th group then it was performed 6 times for different groups (5-fold). We have used LEM 2 [15] algorithm with its parameters: *coverage 0.8 and with a simple voting*. These tests with different algorithms and parameters were performed in this and other cases in order to find maximum prediction accuracy.
From above data we have obtained 71 rules from which after filtering for removing single matches we have got the following 7 rules:

(Ses=1)&(Beck="(12.5,Inf)")&(dur="(8.5,Inf)")=>(UPDRS="(54,Inf)"[8]) (1)

(Ses=1)&(Beck="(12.5,Inf)")&(RSLat="(219,Inf)")=>(UPDRS="(54,Inf)"[6]) (2)

(Ses=1)&(PDQ39="(58.5,Inf)")&(dur="(8.5,Inf)")=>(UPDRS="(54,Inf)"[5]) (3)

(Ses=2)&(Beck="(12.5,Inf)")&(PDQ39="(58.5,Inf)")&RSLat="(-Inf,219)")=>
(UPDRS="(18.5,43)" [5]) (4)

(dur="(8.5,Inf)")&(PDQ39="(58.5,Inf)")&(RSLat="(Inf,219)")=>
(UPDRS="(18.5,43)" [3]) (5)

(Ses=2)&(Beck="(12.5,Inf)")&(dur="(8.5,Inf)")&(RSLat="(219,Inf)")=>
(UPDRS="(18.5,43)"[2]) (6)

(Ses=2)&(Beck="(12.5,Inf)")&(dur="(-Inf,8.5)")&RSLat="(-Inf,219)")=>
(UPDRS="(18.5,43)"[2]) (7)

Equations (1-3) were for the *Ses=1* (patient without medication) and they were fulfilled by 8 (1), 6 (2) and 5 (3) cases, whereas equations (4, 6, 7) were for the *Ses=2* (patients on medication) and they were fulfilled by 5 (4), and by 2 (6, 7) cases. Equation (5) was session independent. We read eq. (1) as **if** the patient is without medication (*Ses=1*) and has the *Beck* depression score larger than 12.5 and with the *disease duration* longer than 8.5 years **then** his/her UPDRS will be above 54.
On the basis of above rules, we have estimated similarities between the UPDRS values obtained during three visits (every half-year) of G1 patients (less advanced group of patients) to symptoms of more advanced group of patients (G2). If the effect of the disease progression is that granules from group G2V1 become more similar to granules from PD group, it would suggest that G2V1 is a good model *M* of the disease

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DOI: 10.1007/978-3-030-77967-2_45

progression. On the basis of above rules, we have predicted that UPDRS values of G1V1 group can be predicted from above rules (1-7) with global accuracy 0.68, and global coverage 0.48. Whereas G1V2 UPDRS, on the basis of the same rules, can be predicted with the global accuracy 0.72 and coverage 0.39; G1V3 UPDRS with the global accuracy 0.82 and coverage 0.37.

In summary, application of G2V1 rules to less advanced PD patients have demonstrated that all used significant attributes predicted disease progression as accuracy of the UPDRS estimation was increasing, in agreement with doctors' expectations, from 0.68 (G1V1), to 0.72 (G1V2), and 0.82 (G1V3).

In the next step, we were looking for the more elementary granules that were associated with the disease progression related to different parts of the brain. We have analyzed three sets of attributes related to properties of movements, emotions and cognitive changes of patients. The first what neurologists specialized in Parkinson's disease (doctors ToM) are looking for is the slowness of patients' movements. On this basis they normally estimate disease stage.

3.3 Movements ToM

Deficits in movements such as speed or precision are primary PD symptoms; they are like light spots in the visual system.

We took the following six condition attributes as patient number id: *P#, Ses*: session number, *dur* – disease duration, *RSLat* - reflexive saccade latency, and *Trail A*: speed of circled numbers connection, *Epworth* score (quality of sleep). The decision attribute was the *UPDRS.* The *UPDRS* was optimally divided by RSES into 4 ranges: *"(-Inf, 33.5)", "(33.5, 43.0)", "(43.0, 63.0)", "(63.0, Inf)". A*s above, we have divided G2V1 data (48 objects) into 4 groups and predictions were performed by rules learned from 3 groups in order to predict *UPDRS* of 4th group then it was performed 4 time for different groups (4-fold).

We have obtained the following three rules:

(Ses=2)&(TrailA="(-Inf,42)") => (UPDRS="(-Inf,33.5)" [5]) (8)

(Ses=1)&(RSLat="(264.0,Inf)")&(Eworth="(Inf,14.0)")=>UPDRS="(63.0,Inf)"[3]) (9)

(Ses=2)&(dur="5.695,Inf)")&((RSLat="(-Inf,264.0)"))&(Epworth="(14.0,Inf)") => (UPDRS= "(63.0,Inf)" [2] (10)

Equation (8) is relatively simple and describe UPDRS predictions as a function of the session number (*MedOn)* and *Trail A* tests only. Equations (9,10) are more complex as they depend on the *Ses* number, *RSLat* and *Epworth* (quality of the sleep) and also eq. (10) depends on the *dur* – disease duration.

It is interesting that there are only 3 relatively simple equations, but disadvantage is that they are only estimation of two ranges of the UPDRS. All other ranges are patients specific so there are no universal rules for their estimation.

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DOI: 10.1007/978-3-030-77967-2_45

On the basis of above rules, we have estimated similarities between G1V1, G1V2, G1V3 and G2V1 groups. We have used LEM 2 [15] algorithm with a simple voting and with 4-fold that gave the highest accuracy.

We have applied above rules to speed-related attributes of G1V1 group and obtained TPR: True positive rates for decision classes were *{(0.29, 0.0, 0.0, 0.8)}*, ACC: Accuracy for decision classes were *{(1.0, 0.0, 0.0, 0.89)}*, the global accuracy was 0.59 and global coverage was 0.37. As you may notice only the 1st and the 4th rages of UPDRS were predicted with the high accuracy.

We have estimated similarities between G1V2 and G2V1 groups:

We have applied above rules to speed-related attributes of G1V2 group and obtained TPR: True positive rates for decision classes were *{(0.43, 0.0, 0.0, 1.0)}*, ACC: Accuracy for decision classes were *{(1.0, 0.0, 0.0, 0.843)}*, the global accuracy was 0.70 and global coverage was 0.435.

We have estimated similarities between G1V3 and G2V1 groups:

We have applied above rules to speed-related attributes of G1V3 group and obtained TPR: True positive rates for decision classes were *{(1.0, 0.0, 0.0, 0.9)}*, ACC: Accuracy for decision classes were *{(1.0, 0.0, 0.0 ,1.0)}*, the global accuracy was 0.923 (great) and global coverage was only 0.3.

In summary, application of the G2V1 rules to less advanced PD patients' groups have demonstrated that such elementary attribute as speed of eyes and hands movements can predict disease progression at accuracy of the UPDRS estimation was increasing from 0.59 (PDV1), to 0.7 (PDV2), and 0.92 (PDV3). These results, with the high accuracy of 4 UPDRS ranges, confirm doctors' ToM intuitions.

3.4 Emotional ToM

As in PD is lack of the dopamine; there are related emotional self-problems that projects to the social interactions (one of the major social problem of PD leading to the isolation). Emotions are like higher visual areas integrating all parts together. Movements evoke the pleasure and emotions are also visible in movements.

We took the following five condition attributes: patient number id: *P#, Ses*: session number, *PDQ39* (quality of life test), *Beck* (depression test), and *RSLat*: saccade latency. As the decision attribute was the *UPDRS.* The *UPDRS* was optimally divided by RSES into 3 ranges: *"(-Inf; 43.0)"*, *"(43.0; 63.0)"*, *"(63.0; Inf)"*. We have divided G2V1 data (48 objects) into 5 groups and predictions were performed by rules learned from 4 groups in order to predict UPDRS of 5th group then it was performed 5 time for different groups (5-fold). We have used LEM 2 algorithm [15] with coverage 0.8 and with a standard voting. TPR: True positive rates for decision classes were (0.6, 0.8, 0.0), ACC: Accuracy for decision classes were (0.6, 0.75, 0.0), the global accuracy was 0.7 and global coverage was 0.29 As you may notice only the first and the second rages of UPDRS were predicted with the high accuracy. We have obtained the following six rules:

(Ses = 2)&(RSLat = "(208.0, 244,5"))=> (UPDRS = "(-Inf, 43.0)"[7]) (11)

(Ses = 2)&(RSLat ="(194.5,20.0)")&(Bec="(9.5,Inf)")=>(UPDRS = "(-Inf; 43.0)"[4])

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DOI: 10.1007/978-3-030-77967-2_45

(12)

(Ses = 1)&(RSLat = "(244.5,342.0)") => (UPDRS = "(63.0,Inf)"[4]) (13)

(Ses = 2)&(RSLat = "(342.0, Inf)")) => (UPDRS = "(-Inf, 43.0)"[3]) (14)

(Ses=1)&(RSLat="(194.5,208.0)")&(Beck="(9.5,Inf)"))=>(UPDRS="(43.0,63.0)" [2]) (15)

(Ses = 1)&(RSLat = "(34.0, Inf)")&(Beck = "(9.5; Inf)"))=>(UPDRS= "(63.0, Inf)"[2]) (16)

Equations (11-16) describe precisely UPDRS changes as dependent on emotional progressions. Notice that the parameters of eye movements play here a significant role as they are in all equations (see in the Discussion section). In three equations (12, 15, 16) there is the attribute related to the depression (Beck test score), but only with higher values that indicats the emotional problems.

On their basis we have estimated similarities between G1V1 and G2V1 groups:

We have applied above rules to emotion-related attributes of G1V1 group and obtained TPR: True positive rates for decision classes were (0.2, 0.9, 0,0), ACC: Accuracy for decision classes were (1.0, 0.8, 0.0), the global accuracy was 0.53 and global coverage was 0.41. As you may notice only the first and the second rages of UPDRS were predicted with the high accuracy.

We have estimated similarities between G1V2 and G2V1 groups:

We have applied above rules to emotion-related attributes of G1V2 group and obtained TPR: True positive rates for decision classes were (0.56, 0.9, 1.0), ACC: Accuracy for decision classes were (1.0, 0.9, 0.2), the global accuracy was 0.74 and global coverage was 0.41. As you may notice in this case all three rages of UPDRS were predicted and two of them very high accuracy.

We have estimated similarities between G1V3 and G2V1 groups:

We have applied above rules to emotion-related attributes of G1V3 group and obtained TPR: True positive rates for decision classes were (0.5, 0.9, 0.5), ACC: Accuracy for decision classes were (0.7, 1.0, 25), the global accuracy was 0.71 and global coverage was 0.30. As you may notice in this case all three rages of UPDRS were predicted and two of them very high accuracy.

It is the first surprising result that emotions were not progressing with the disease development. In the early phase progressions were more significant and later they have stabilized: accuracy for G1V1 was 0.53, for G1V2 was 0.79, but later for G1V3 went down to 0.71.

3.5 Cognitive ToM

Cognitive processes play the role of the integrator of different neurological systems. There are related to the consciousness of self: influencing movements like e.g., equilibrium makes us aware of subliminal emotions, as well as related emotions.

We took the following seven condition attributes: patient number id: *P#; Ses*: session number; results of *FAS* test (it is related to the speech fluency); *Epworth* score (quality of sleep test related to memory consolidation); *Trail B* results (speed and precision of connecting circled numbers and letters), and parameters of the eye movements: *RSLat*, *RSDur*. As the decision attribute was the *UPDRS*. After discretization and parameter

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DOI: 10.1007/978-3-030-77967-2_45

reduction by RSES, the *UPDRS* was optimally divided by RSES into 4 ranges: *a="(-Inf; 43,0)", b="(43,0; 47,5)", c="(47.5, 63.0)", d="(63,0; Inf)".* Only four condition attributes are left: *Ses* number *(MedOff/On), FAS* (speech fluency), parameters of saccadic eye movements: *delay (RSLat)* and *saccade duration (RSDur).*

From G2V1 group, we have obtained 25 rules that gave seven rules after removing rules fullfield in single cases, below are all seven rules as a basis for prediction of the possible longitudinal cognitive problems in G1 group:

(Ses=2)&(RSLat="(213.5,Inf)")&(RSDur="(-Inf,48.5)")=>(UPDRS_T="(-Inf,43.0)" [7]) (17)

(Ses=2)&(FAS="(-Inf,46.5)")&(RSDur="(48.5,Inf)")&(RSLat="(Inf,213.5)")=> (UPDRS="(-Inf,43.0)"[5]) (18)

(Ses=1)&(RSLat="(-Inf,213.5)")&(RSDur="(48.5,Inf)")&(FAS="(Inf,46.5)")=> (UPDRS="(47.5,63.0)"[3]) (19)

(Ses=1)&(FAS="(-Inf,46.5)")&(RSDur="(-Inf,48.5)")&(RSLat="(Inf,213.5)")=> (UPDRS ="(63.0,Inf)"[2]) (20)

(Ses=2)&(RSLat="(-Inf,213.5)")&(RSDur="(-Inf,48.5)")=>(UPDRS="(-Inf,43.0)" [2]) (21)

(FAS="(46.5,Inf)")&(RSLat="(-Inf,213.5)")&(Pat=76)=>(UPDRS="(Inf,43.0)"[2]) (22)

(Ses=1))&(RSDur="(48.5,Inf")&(RSLat="(-Inf,213.5)")&(FAS="(46.5,Inf")=> (UPDRS="(43.0,47.5)"[2]) (23)

Equations (17-20) describe the *UPDRS* changes as function of cognitive changes in 7, 5, 3, 2 cases. From statistics: the *UPDRS* range *(-Inf,43.0)* was used in four rules, other ranges were used each one in one rule. Parameters of the eye movements (EM) are in all rules, so the EM plays an important role in the cognition. Only one rules eq. (22) is not depend on medication, but it is the patient's dependent. Also, only two rules are not dependent on (speed fluency) attribute.

We have divided G2V1 data (48 objects) into 10 groups (10-fold) as described above. We have used the Exhaustive algorithm [11] with standard voting (RSES). For G2V1 population we have obtained global accuracy of 0.73 with coverage 0.67.
On basis of above rules (17-13) we have estimated similarities between G1V1, G1V2, G1V3 and G2V1 groups.

Predicted

Actual	"(63.0, Inf)"	"(-Inf, 43.0)"	"(47.5, 63.0)"	"(43.0, 47.5)"	ACC
"(63.0, Inf)"	0. 0	0.0	1.0	0.0	0.0

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"(-Inf, 43.0)"	0.0	12.0	1.0	0.0	0.86
"(47.5, 63.0)"	2.0	0.0	0.0	1.0	0.0
"(43.0, 47.5)"	0.0	0.0	1.0	1.0	0.5
TPR	0.0	1.0	0.0	0.5	

Table 1. Confusion matrix for UPDRS of G2V1 patients base on rules (17-23), TPR: True positive rates for decision classes; ACC: Accuracy for decision classes; Coverage for decision classes: (0.33, 0.47, 0.125, 0.4); the global accuracy was 0.72 and global coverage was 0.39.

Predicted

Actual	"(63.0, Inf)"	"(-Inf, 43.0)"	"(47.5, 63.0)"	"(43.0, 47.5)"	ACC
"(63.0, Inf)"	0. 0	0.0	0.0	1.0	0.0
"(-Inf, 43.0)"	1.0	11.0	0.0	0.0	0.92
"(47.5, 63.0)"	1.0	0.0	0.0	1.0	0.5
"(43.0, 47.5)"	0.0	0.0	1.0	2.0	1.0
TPR	0.0	1.0	0.0	0.5	

Table 2. Confusion matrix for UPDRS of G2V2 patients base on rules (17-23), TPR: True positive rates for decision classes; ACC: Accuracy for decision classes: Coverage for decision classes: (0.14, 0.5, 0.36, 0.5); the global accuracy was 0.79 and global coverage was 0.41.

Tables 1 to 3 demonstrate changes of cognitive symptoms with the disease progression in comparison to the more advanced PD group (G2V1). The cognitive accuracy is not changing so dramatically like the movements or even less than the emotional symptoms. The values of this attribute are significant different between Alzheimer's and Parkinson's diseases that also means that neurodegeneration processes with many similarities are basically different, mainly related to the different structures. There are PD patients with cognitive problems but their influence in these group of 47 patients is not dominant.

In our longitudinal study, comparison of the cognition with more advanced patients did not show large changes with time. The accuracy for G1V1 was 0.72, for G1V2 was 0.79, but later for G1V3 went down to 0.74.

Predicted

Actual	"(63.0, Inf)"	"(-Inf, 43.0)"	"(47.5, 63.0)"	"(43.0, 47.5)"	ACC
"(63.0, Inf)"	1. 0	0.0	1.0	2.0	0.25

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DOI: 10.1007/978-3-030-77967-2_45

"(-Inf, 43.0)"	0.0	13.0	0.0	0.0	1.0
"(47.5, 63.0)"	0.0	1.0	2.0	2.0	0.4
"(43.0, 47.5)"	0.0	0.0	0.0	1.0	1.0
TPR	1.0	0.93	0.67	0.2	

Table 3. Confusion matrix for UPDRS of G2V3 patients base on rules (17-23), TPR: True positive rates for decision classes; ACC: Accuracy for decision classes: Coverage for decision classes: (0.33, 0.47, 0.125, 0.4); the global accuracy was 0.74 and global coverage was 0.5.

What is interesting that the coverage with time was increasing, from 0.39, 0.41 to 0.50. It means that with the time patients from G1 group become more similar to cases in G2 group but not necessarily that their cognitions are significantly deteriorating.

4 Discussion

We have used the granular computing to estimate disease progression in our longitudinal study of patients with Parkinson's disease (PD). We've applied granular computing with RST (rough set theory [9]) that looks into "crisp" granules (in the contrast to Fuzzy RST [12]) and estimate objects/symptoms by upper and lower approximations that determine precision of the description as dependent from properties of granules [9]. As we are able to precisely classify a complex, unknown objects as we are tuning and comparing their particular attributes in many different levels (with help of rough set theory).
This approach has similarities to other works using intelligent classification methods in order to test influences of different systems (like dissimilar object's properties – [16]) e.g., elementary granules related to the speed, cognition or depression [17] in their variable influences on the PD progression (object recognition).
Our results generally support intuitions of the neurologists that even if every patient is different, the most of PD patients' attributes become, with time development, similar to symptoms of more advanced group (G2V1) of patients. These intuitions are probably based on patients' movement changes that were confirmed in our study. However, we found that disease progression is not directly related to the emotional changes (even if depression might be advanced before PD [17]) and cognitive changes are decaying very slowly.
There is a significant number of papers that studied ToM in Parkinson's disease, e.g., see review in [3]. Generally, they assumed that the abilities to understand, and recognize mental state and intends of others are deteriorated during the course of Parkinson's disease [18]. They suggested that the cognitive impact may influence affective ToM in PD, and it is related to the involvement of the visual spatial abilities (VSA) [18]. It is in agreement with our findings that the saccade latencies are important to estimate movements and cognition ToM and saccade latencies and durations are important in the cognitive ToM. As ToM is the basic skill for development of the social relationships, PD patients showed impairments in ToM connected to the working

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DOI: 10.1007/978-3-030-77967-2_45

memory and executive functions that were related to the white volume matter and grey matter decreases. These changes are mainly related to the frontal cortex and inferior frontal gyrus [19] and are associated largely with the cognitive changes. Another cause of PD patient's poor performance on tests of ToM, might be explained by the deficits in the inhibitory mechanisms [20]. Inhibitory mechanisms are important in the executive functions such as Trial B that was a significant parameter in our Cognitive ToM.

In summary, we have demonstrated that there are many mechanisms related to the Social Brain that are affected in Parkinson's disease (PD) patients, and they can also estimate PD progression. The first practical meaning for neurologists is to pay attention not only to movements deficits, but also to emotional and cognitive changes. In our work, we have estimated changes in different deficits (brain structures) related to neurodegenerations in Parkinson's disease progression by our abstract rules, and we found that they are not changing uniform with the disease progression (the second practical meaning). The third practical consequence of our study is that the eye movements (EM) parameters is the very important attribute that helps to estimate not only the peripheral movements symptoms, but also emotional and cognitive related disorders and their progressions.

5 Conclusions

Our different Machine's ToM follows changes in the human brain, and they use abstract rules based on the visual brain mechanisms. We have used the principle of object recognition as a comparison of the actual sensory input with the Model of the object saved in the higher visual areas [16]. Our 'Model' is related to attributes of advanced PD patients and object 'recognition' is related to similarities between attributes of PD patients progressing in time and the Model. We have demonstrated that PD disease progression is generally not uniform in relationship to the movements, emotions and cognitions changes, even if an individual patient may be more or less affected by depression or cognitive problems. Our rules gave very good prediction accuracy, but not very good coverage. It is mostly related to small groups of patients. Therefore, in order to get more subjects, our future projects will be related on on-line testing that should significantly increase the number of subjects. As an automatic evaluation of different test results is relatively easy, but it is a problem with precise and automatic estimation of the EM. We are actually working on it by using the OpenCV approach with the real-time computer vision and their hardware implemented AI libraries.

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DOI: 10.1007/978-3-030-77967-2_45

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DOI: 10.1007/978-3-030-77967-2_45