Granular Computing to Forecast Alzheimer's Disease Distinctive Individual Development

Andrzej W. Przybyszewski[1,2(✉)], Jerzy P. Nowacki[1], Aldona Drabik[1], and the BIOCARD Study Team

[1] Polish-Japanese Academy of Information Technology, 02-008 Warszawa, Poland
{przy,jerzy.nowacki,drabik}@pjwstk.edu.pl
[2] Department of Neurology, UMass Medical School, Worcester, MA 01655, USA

Abstract. Our study aimed to test if clinically tested normal subjects might have patterns in the results of their cognitive tests that have some similarities to suits obtained from patients in different AD stages.

Due to the aging population, the prevalence of Alzheimer's Disease (AD) related dementia is fast increasing. That is already a worldwide problem. AD-related neurodegeneration starts several decades before the first symptoms and AD biomarkers were identified in recent years. The purpose of our study was to find AD-related biomarkers in healthy subjects. We have estimated such changes based on the Model consisting of subjects in different AD stages from normal to patients with dementia from Biocard data. By using the granular computing method, we found reducts (sets of attributes) related to different stages of the disease. By applying this classification to psychophysical test results of normal subjects, we have demonstrated if some of them might show some similarities to the first symptoms related to AD. As such psychophysical tests can be easily implemented in computers connected to the internet, our method has the potential to be used as a new AD preventive method. We have analyzed Biocard data by comparing a group of 150 subjects in different AD stages with normal subjects. we have found granules that classify cognitive attributes with disease stages (CDRSUM). By applying these rules to normal (CDRSUM = 0) 21 subjects we have predicted that one subject might get mild dementia (CDRSUM > 4.5), one very mild dementia (CDRSUM > 2.25), and five others might get questionable impairment (CDRSUM > 0.75). AI methods can find, invisible for neuropsychologists, patterns in cognitive attributes of normal subjects that might indicate their pre-dementia stage.

Keywords: Neurodegeneration · multi-granular computing · feedbacks

N. T. Nguyen et al. (Eds.): ACIIDS 2023, LNAI 13995, pp. 70–81, 2023.
https://doi.org/10.1007/978-981-99-5834-4_6

1 Introduction

The prevalence of Alzheimer's Disease (AD) related dementia is fast increasing due to our aging population. The prevalence worldwide is estimated to be as high as 24 million, by 2050, AD number could potentially rise to 139 million worldwide. There is no cure for AD, as during the first clinical symptoms and neurological diagnosis many parts of the brain are already affected without the possibility to recovery. As the neurodegenerations begin two to three decades before observed symptoms, the best chance to fight AD is to estimate the beginning period of the AD-related brain changes.

The BIOCARD* study was initiated in 1995 by NIH with 354 normal individuals interrupted in 2005 and continued from 2009 as Johns Hopkins (JHU) study. At JHU, patients have yearly cognitive and clinical visits that measured total of over 500 attributes with 96 cognitive parameters [1, 2]. Albert [2] has successfully predicted conversion from normal to MCI (Mild Cognitive Impairment) due to AD, 5 years after baseline, for 224 subjects by using the following parameters: beta-amyloid (b-Symbol format), MRI hippocampal and entorhinal cortex volumes, cognitive tests scores, and APOE genotype. Even if their predictions were for all tested patients, they found important biomarkers that we are using in our study.

But our approach is different, as we have performed classification by using granular computing (GrC) [3] connecting cognitive test results with genetic data (related to the apolipoprotein E ApoE genotype) and AD-related clinical symptoms in the group of different subjects from normal to AD. We took this group as our Model for the supervised training of different granules related to various stages of the disease, from normal subjects to MCI (Mild Cognitive Impairment) and subjects with AD-related dementia. In the next step, we applied these granules to individual, normal subjects to predict in every individual tested subject, a possibility of the beginning of the neurodegeneration (AD-related brain changes). To confirm our method, we have also applied it to the early stages in patients that were diagnosed with AD if we can predict their future Alzheimer's disease stage.

As AD-related dementia is so fast increasing, we need an easy and accessible internet method for the preclinical classification of all potential patients, otherwise, we will soon live in a different world.

Our granular computing method and its implementation with a rough set are well established in neurodegeneration disease, especially used in many publications related to Parkinson's disease patients [4].

- Data used in preparation of this article were derived from BIOCARD study, supported by grant U19 – AG033655 from the National Institute on Aging. The BIOCARD study team did not participate in the analysis or writing of this report, however, they contributed to the design and implementation of the study. A listing of BIOCARD investigators can be found on the BIOCARD website (on the 'BIOCARD Data Access Procedures' page, 'Acknowledgement Agreement' document)

2 Methods

It is a continuation of our previous study [5] therefore methods are similar, but in this part, we are looking into longitudinal changes in our subjects. We have analyzed predominantly cognitive of several different groups of subjects. The first group consists of 150 subjects with 40 normal subjects, 70 MCI (Mild Cognitive Impairment), and 40 subjects with dementias (AD). It was chosen this way as in the whole population of 354 normal subjects followed from 1995, only 40 subjects became demented. Therefore, we have added 40 normal subjects and 70 MCI as they are in between AD and normal subjects. The second group was 40 AD subjects, and the last group was 21 subjects, clinically classified as normal.

In all subjects with recorded their age, had the following neuropsychological tests formed every year:

1. Logical Memory Immediate (LOGMEM1A) - participants are read a logically organized story and asked to recall the story immediately after its presentation
2. Logical Memory Delayed (LOGMEM2A) - approximately 20 min later, the participants are again asked to recall the story from memory
3. Trail Making, Part A (TrailA - connecting time in a sec of randomly placed numbers),
4. Trail Making Part B (TrailB - connecting time in a sec of randomly placed numbers and letters),
5. Digit Symbol Substitution Test (DSST) from the Wechsler Adult Intelligence Scale - requires a subject to match symbols to numbers according to a key located on the top of the page (associative learning).
6. Verbal Fluency Letter F (FCORR) requires the generation of words from the initial letters F under 60 s of time constraints.
7. Rey Figure Recall (REYRECAL), in which examinees are asked to reproduce a complicated line drawing from memory (visual memory test).
8. Paired Associate Immediate (PAIRED1), from the Wechsler Memory Scale – subjects are asked to learn unrelated word pairs (e.g., stove-letter).
9. Paired Associate Delayed (PAIRED2), from the Wechsler Memory Scale – as above but delayed matching-to-sample tasks (testing hippocampus function).
10. Boston Naming Test (BOSTON) determining confrontational picture-naming abilities in patients.
11. CVLT (California Verbal Learning Test) - an examinee listens to series of words and is then asked to recall the terms and the category to which they belong (test of verbal learning and memory).

In addition, we have registered APOE genotype; individuals who are *ApoE4* carriers vs. non-carriers (digitized as 1 vs. 0).

The decision attributes were CDRSUM (sum of boxes) as precise and quantitative general index of the Clinical Dementia Rating [6]. There are the following CDRSUM values related to different AD stages:

1. (0.0) – normal; 2. (0.5–4.0) – questionable cognitive impairment: 2a. (0.5–2.5) – questionable impairment; 2b. (3.0–4.0) – very mild dementia,

3. (4.5–9.0) – mild dementia [6].

2.1 Rough Set Implementation of GrC

Our data mining granular computing (GrC) analysis was implemented by rough set theory (RST) discovered by Zdzislaw Pawlak [7] whose solutions of the vague concept of boundaries were approximated by sharp sets of the upper and lower approximations [7]. In the first step, our data were inserted in the decision table with rows stand out the actual attributes' values for the different or for the same subject and columns were linked to diverse attributes with the decision attribute CDRSUM. Following Pawlak [7] an *information system* is a pair $S = (U, A)$, where U, A are nonempty finite sets. The set U is the universe of objects, and A is the set of attributes. If $a \in A$ and $u \in U$, the value $a(u)$ is a unique element of V (where V is a value set).

Based on our classification, we have estimated CDRSUM, compared with CDRSUM obtained by neurologists and determined the predicted stage of individual patient.

The *indiscernibility relation IND(B)* of any subset B of A is defined after Pawlak (1991): $(x, y) \in IND(B)$ *iff* $a(x) = a(y)$ for every $a \in B$ where the value $a(x) \in V$. This relation divides U into *elementary granules* and it is the basis of the rough set theory. The most important rough set properties are the *lower approximation* of set $X \subseteq U$ in relation to an attribute B defined as: $\underline{B}X = \{u \in U : [u]_B \subseteq X\}$, and the *upper approximation* of set X defined as $\overline{B}X = \{u \in U : [u]_B \cap X \neq \phi\}$.

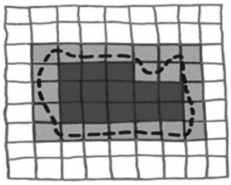

Fig. 1. Interrupted curve symbolizes properties of the set X. Squares represent elementary granules $[u]_B$ those in the black are associated with the *lower approximation* of X, grey and black squares are associated with the *upper approximation* of X, and white squares are outside of the set X.

The difference between the upper and lower approximation sets is the boundary region (BR). As it is visible on Fig. 1, squares marked in grey (boundary region) are related to imprecision of our classification. If BR is empty then set X is classified in an exact way, if not is rough classified with respect to $[u]_B$.

Therefore, we can divide U into three parts: the positive region *POS(X)* (black in Fig. 1), the boundary region *BR(X)* (gray in Fig. 1), and the negative region *NEG(X)* (white in Fig. 1). These three regions generate, on the RST basis, different type of decision rules: the certain rules are generated by the positive region, the uncertain rules by the boundary region, and the incorrect rules by the negative region.

We can also extend the decision table to a triplet: $S = (U, C, D)$ where the set of attributes A is divided into C *as* condition and D as decision attributes [8, 9]. In a single row there are many conditions and only one decision attribute, all related to a specific test of the individual subject. Names and values of conditions attributes related to the value of the decision attribute give a unique rule. One hard problem, especially in the medical

field, is related to the inconsistent results, leading to contradictory rules. In this situation, doctors often are using averaging techniques. In the case of the inconsistent (conflicting) data, it means that the same attributes values are classified as different concepts. In general, it means that in the data set some attributes are missing. We will show an important example in our data when we wrongly have classified symptoms of one subject because missing values of attributes, or because missing attributes. LERS (Learning from example based on Rough Sets) [10] computes lower and upper approximation of all concepts. Conflicting data are not removed from the data set. Instead, concepts are approximated by new sets of the lower and upper approximations. Rough Set Theory generalizes individual measurements (rules) to universal principles (knowledge) but rules have different confidence. There are always true rules related to the *lower approximation set* and rules that are only partly true associated with the *upper approximation set*. If the border set (Fig. 1) is nonempty it is related to the uncertain rules.

In this work we have used different intelligent algorithms implemented in RSES 2.2 software such as: exhaustive algorithm, genetic algorithm [9, 11] covering algorithm, or LEM2 algorithm [10].

We have based our approach on the mechanisms in the visual brain related to advanced processes of the complex objects' recognition [12]. The processes in the higher visual brain areas that are related to different objects classification are using GrC to find upper and lower approximations of the retinal image [12]. These approximations are compared with the different objects' models (images) saved in the visual cortex (as the Model).

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

3 Results

3.1 Statistics

In Table 1 * means stat.sig.difference of means, if in all three columns all combinations are significant, if in two columns * or # mean values in these columns are significantly different.

Table 1 presents the statistical calculations for Group1 (40 normal subjects, 70 MCI subjects, and 40 (AD patients), Group2 (40 AD patients same as in Group1), and GroupN (40 normal subjects different to Group1 normal subjects) as mean $\pm$ SD. The age of subjects in different groups is similar, but other parameters show differences: Lgm1A (LOGMEM1A) is smallest for AD patients and largest for N, Lgm2A (LOGMEM2A) has similar changes as Lgm1A, execution functions: TrailA and TrailB are growing from N to AD, DSST is decreasing from N to AD in a similar way as Fcorr (FCORR). We did not show other parameters because of lack of the space. The changes of the CDRSUM are obvious as in normal subjects its values are 0 and significantly larger for AD patients. There are large differences between the values of individual subjects, so the mean values (except CDRSUM) were not all statistically significant, but we are not looking for means here, but for similarities in patterns.

Table 1. Statistic calculations of tested data

	Group1 n = 150	Group2 n = 40	GroupN n = 21
age	76 ±9.1	78.5 ±12	76.6 ± 8.4
LOGMEM1A	16.1 ±4.6	12.2 ±4.4	18.0 ± 3.0
LOGMEM2A	15.2 ±5.3	10.1 ±5.2	17.5 ± 3.9
TrailA	39.6 ±20	50.6 ±30	30.7 ± 12
TrailB	99.9 ±59	151 ±78	64.2 ± 21
DSST	46.5 ±14	37.3 ±13	57 ±13
FCORR	15.4 ±5*	12.6 ±6*	18.2 ±5 *
REYRECAL	19.7 ±8*	14.6 ±7*	24.2 ±6*
PAIRED1	18.4 ±8*	15.5 ±4*#	19.9 ±3#
PAIRED2	6.9 ±1*	6.2 ±1.5*#	7.2 ±1#
BOSTON	27.7 ±3*	25.3 ±4*	29.1 ±1*
CVLT	53 ±14*	41 ±13*	64.4 ±10*
APOE	0.35 ±0.5	0.3 ±0.5	0.3 ±0.5
CDRSUM	1.3 ±1.8	3.5 ±2.5#	0 ±0#

3.2 Granular Computing for Reference of Group1 Group

Previously [5], we have used all **14 attributes** to find with help of RSES which attributes are significant, and after discretization which rules can describe patients from Group1.

Comparing with all 14 condition attributes [5], there were the following 3 ranges of the decision attribute *CDRSUM: "(-Inf, 0.75)", "(0.75, 2.25)", "(2.25, Inf)"* for patients in Group1.

From 324 rules we have found *several rules* with a small number of attributes (used in actual study):

$$(TRAILB = ''(153.0, Inf)'')\&(REYRECAL = ''(-Inf, 15.75)'')\&(APOE = 1) \\ => (CDRSUM = ''(2.25, Inf)''[6])6 \quad (1)$$

$$(TRAILB = ''(74.5, 153.0)'')\&(FCORR = ''(16.5, Inf)'')\&(REYRECAL = ''(15.75, 25.25)'') \\ \&(age = ''(-Inf, 76.5)'') => (CDRSUM = ''(0.75, 2.25)''[2])2 \quad (2)$$

There is the following interpretation of above equations: Eq. 1 claims for 6 cases that if *TrailB* has bad time above 153s, and *REYRECALL* (visual memory) is also bad then *CDRSUM* is also above 2.25 that means the questionable impairment [6]. In Eq. 2, *TrailB* is better than in Eq. 1 but still has a relatively long time, and *FCORR* (speech fluency) is good (above 15), *REYRECALL* is about medium then *CDRSUM* is below 2.25 which suggests questionable cognitive impairment.

We have used 324 general rules from Group1 to predict CDRSUM of the normal patients (GroupN), we found that three patients might have a potential impairment:

$$(Pat = 164087)\&(LOGMEM1A = ''(-Inf, 15.5)'')\&(LOGMEM2A = ''(-Inf, 16.5)'')\& (TRAILA = ''(35.5, Inf)'')\&(TRAILB = ''(74.5, 153.0)'')\&(FCORR = '' (-Inf, 16.5)'')\& (REYRECAL = ''(15.75, 25.25)'')\&(PAIRD2 = '' (-Inf, 6.5)'')\&(age = ''(-Inf, 76.5)'')\& (APOE = 1) => (CDRSUM = ''(2.25, Inf)'') \quad (3)$$

$$(Pat = 401297)\&(LOGMEM1A = ''(-Inf, 15.5)'')\&(LOGMEM2A = ''(-Inf, 16.5)'')\& (TRAILA = ''(-Inf, 23.5)'')\&(TRAILB = ''(-Inf, 74.5)'')\&(FCORR = ''(-Inf, 16.5)'')\& (REYRECAL = ''(-Inf, 15.75)'')\&(PAIRD2 = ''(6.5, Inf)'')\&(age = ''(-Inf, 76.5)'')\& (APOE = 1) => (CDRSUM = ''(2.25, Inf)'') \quad (4)$$

$$(Pat = 808698)\&(LOGMEM1A = ''(15.5, 20.5)'')\&(LOGMEM2A = ''(16.5, Inf)'')\& (TRAILA = ''(-Inf, 23.5)'')\&(TRAILB = ''(-Inf, 74.5)'')\&(FCORR = ''(-Inf, 16.5)'')\& (REYRECAL = ''(15.75, 25.25)'')\&(PAIRD2 = ''(6.5, Inf)'')\&(age = ''(-Inf, 76.5)'')\& (APOE = 1) => (CDRSUM = ''(0.75, 2.25)'') \quad (5)$$

The first patient *(Pat = 164087)* Eq. 3 has affected logical memories: immediate and delayed, executive functions (*TrialA&B*), (especially *TrialB* longer execution time) executive functions, bad *FCORR*, low *REYRECALL,* and in addition bad APOE genotype (*ApoE4* carrier) that determines that *CDRSUM* is larger than 2.25 (questionable impairment to very mild dementia [6]). The second patient *(Pat = 401297)* Eq. 4 is like the first one, affected logical memories: immediate and delayed, but good executive functions (*TrialA&B*), and bad *FCORR* and *REYRECALL* and in addition bad APOE genotype that determines *CDRSUM* above 2.25. The third patient is *(Pat = 808698)* in better shape with good logical memories, and executive functions, but bad *FCORR* and *APOE* genotype then with *CDRSUM* below 2.25 (questionable impairment [6]).

Therefore, in this study, at first, we reduced number of attributes from 14 to the following **five**: *APOE, FCORR, DDST, TrailB,* and as the decision attribute was *CDRSUM*. These condition attributes are significant as the early predictors of AD.

The APOE genotype; individuals who are *ApoE4* is important genetic factor, which influence probability of AD. One of the early predictors of AD is the poor language performance that is quantify by FCORR test. Another early indication are difficulties in reasoning that may be estimated by DDST test. Slowing processing speed is also observed as an early AD indicator that can be quantified by Trail B tests.

We put all data in the decision table (as described in the Methods section), and with RSES help, after discretization we found that because large data set and small number of parameters, the decision attribute has 7 ranges: "(-Inf,0.25)", "(0.25,0.75)", "(0.75,1.25)", "(1.25,2.25)", "(2.25,3.25)", "(3.25,4.25)", "(4.25,Inf)". After generalization, there were 82 rules, below are some examples:

$$(APOE = 0)\&(DSST = ''(66.5, Inf)'') => (CDRSUM = ''(-Inf, 0.25)''[4])\ 4 \quad (6)$$

$$(APOE = 1)\&(DSST = ''(43.5, 45.5)'') => (CDRSUM = ''(0.25, 0.75)''[4])4 \quad (7)$$

$$(APOE = 1)\&(DSST = ''(46.5, 49.5)'')\&(TRAILB = ''(72.5, 128.5)'') => (CDSUM = ''(2.25, 3.25)''[2])2 \quad (8)$$

$$(APOE = 1)\&(TRAILB = ''(128.5, Inf)'')\&(FCORR = ''(6.5, 10.5)'') => (CDSUM = ''(4.25, Inf)''[2])2 \quad (9)$$

As one may notice above, a small number of the condition attributes are used in the above rules. One significant attribute in the genetic *APOE* genotype, and in these

approximate rules lack of *ApoE4* carriers ($APOE = 0$) is related to health (very low *CDRSUM*). Another attribute *DSST* - digit symbol substitution test is related to associative learning, and higher numbers are better. In Eq. 6 is the best result, in Eq. 7 lower value of *DSST* and $APOE = 1$ (higher genetic chance to get AD) gives a small increase of *CDRSUM*. In Eq. 8 *DSST* looks better, but the execution function attribute *TrailB* is on the slower side with $APOE = 1$ influence *CDRSUM*. In Eq. 9 execution (*TrailB*) is very slow and, $APOE = 1$ and language fluency problems (low value of *FCORR*) are the main factors that such patients have indications of mild dementia (*CDRSUM* is larger than 4.5).

By applying all 82 rules to the healthy patients (GroupN) with clinically confirmed $CDRSUM = 0$, we found one patient with *CDRSUM* significantly larger than 0 in the following classification:

$$(Pat = 164087)\&(APOE = 1))\&(DSST =''(46.5, 49.5)'')\&(FCORR =''(10.5, 13.5)'')\& \\ (TRAILB =''(72.5, 128.5)'' => (CDRSUM =''(2.25, 3.25)'' \tag{10}$$

The Eq. 10 indicates based on 4 condition attributes that patient *164087* might have *CDRSUM* = *"(2.25,3.25)"* that suggests very mild dementia [6].

In the next step, we have increased number of attributes to **seven**: *APOE, BOSTON, FCORR, DDST, TrailB, REYRECAL,* and *CDRSUM* as the decision attribute. These additional attributes are also related to the early AD symptoms, like forgetting names of objects (BOSTON), or problems with remember place and environment where you are (as visual memory of the complex figure).

We have obtained 104 rules from Group1 patients and applied them to GroupN normal subjects, and got the following classifications (two examples):

$$(Pat = 558865)\&(APOE = 1)\&(FCORR = ''(10.5, 13.5)''))\&(REYRECAL = ''(15.75, 25.25 \\ )'')\&(TRAILB = ''(75.0, 114.5)'')\&(DSST = ''(33.5, 41.5)'')\&(BOSTON = ''(26.5, 27.5)'') \\ => (CDRSUM = ''(0.75, 1.25)) \tag{11}$$

$$(Pat = 164087)\&(APOE = 1))\&(FCORR = ''(10.5, 13.5)''))\&(REYRCAL = ''(15.75, 25.25) \\ '')\&(TRAILB = ''(75.0, 114.5)'')\&(DSST = ''(47.5, 53.5)'')\&(BOSTON = ''(25.5, 26.5)'') => \\ (CDRSUM = ''(2.0, 3.25)) \tag{12}$$

It is interesting that for $Pat = 164087$ more condition attributes are in Eq. 12 in comparison to Eq. 10 give almost identical results for *CDRSUM*, as the main factors are related to bad speech fluency (*FCORR*) and the *APOE* genome. These differences are subtle and are probably difficult to be noticed by clinical researchers.

3.3 Granular Computing for Reference of Group2 Patients

In this part, we have reduced the number of attributes from 14 to the following, same as above, **five** condition attributes: *APOE, DDST, FCORR, TrailB,* and as the decision attribute was *CDRSUM*. We put all data in the decision table (as described in the Methods section), and with RSES help, after discretization, we found that the decision attribute has 3 following ranges: *"(-Inf,0.75)", "(0.75,3.25)",* and *"(3.25, Inf)"*. After generalization, there were 4 rules, and 2 rules were shown below:

$$(APOE = 1)\&(FCORR = ''(-Inf, 15.5)'') => (CDRSUM = ''(3.25, Inf)''[6])6 \quad (13)$$

$$(DSST = '' (37.5, 45.0)'')\&(APOE = 0)\&(FCORR = '' (-Inf, 15.5)'') => (CDSUM = ''(0.75, 3.25)''[5])5 \quad (14)$$

What is unusual is that there is there no rule with decision attribute *CDRSUM = "(-Inf,0.75)"*. It is the consequence of a small number of condition attributes for the group of only 40 patients with Alzheimer's disease. We applied the above rules obtained from Group1 to predict the CDRSUM of GroupN.

Table 2. Confusion matrix for CDRSUM of GroupN by rules obtained from Group1 Predicted

Actual	"(3.25, Inf)"	"(0.75, 3.25)"	"(-Inf, 0.75)"	ACC
"(3.25, Inf)"	0.0	0.0	0.0	0.0
"(0.75,3.25)"	0.0	0.0	0.0	0.0
"(-Inf, 0.75)"	4.0	1.0	0.0	0.0
TPR	0.0	0.0	0.0	

TPR: True positive rates for decision classes; ACC: Accuracy for decision classes: the global coverage was 0.24 and the global accuracy was 0.0, the coverage for decision classes was 0.0, 0.0, 0.24.

In Table 2 for healthy patients, we got on our rule's basis, *CDRSUM > 0*. In one patient *Pat = 377216 CDRSUM* was between 0.75, and 3.25, but in four patients *Pat = 164087, Pat = 242874, Pat = 40129, Pat = 808698* above 3.25. Below are two examples, on this basis we have identified subjects with the possible impairments:

$$(Pat = 164087)\&(APOE = 1))\&(DSST = '' (45.0, 56.0)'')\&(FCORR = '' (-Inf, 15.5)'')\& (TRAILB = '' (-Inf, 128.5)'' => (CDRSUM = '' (3.25, Inf)'') \quad (15)$$

$$(Pat = 242874)\&(APOE = 1))\&(DSST = '' (45.0, 56.0)'')\&(FCORR = '' (-Inf, 15.5)'')\& (TRAILB = '' (-Inf, 128.5)'' => (CDRSUM = '' (3.25, Inf)'') \quad (16)$$

In the two above equations, speech fluency (*FCORR*) is affected. The executive function *TrialB* is below 128.5s, but this classification is rather crude and does not give us the lower value (from other equations (e.g., Eq. 11), we know that for *Pat = 164087* is above 72s which is a good value, but almost one minute more is not so good). In two last Eqs. 15 and 16 DSST is very good, but it seems that it does not have a strong influence on our results.

In our previous study [5] with 14 attributes, we obtained 58 rules for Group2 subjects, and as an example, we present below two rules with only 3 attributes each:

$$(DSST = ''(39.5, Inf)'')\&(FCORR = ''(20.5, Inf)'') => (CDRSUM = ''(-Inf, 4.5)''[2])2 \quad (17)$$

$$(LOGMEM\,1A = ''(13.5, 15.5)'')\&(FCORR = ''(-Inf, 12.5)'') => (CDRSUM = ''(4.5, 6.5)''[2])2 \quad (18)$$

Interpretation: Eq. 17, if *DSST* is above 39.5 and *FCORR* above 20.5 then *CDRSUM* is below 4.5; Eq. 18, if Logical Memory Immediate (LOGMEM1A) is above between 13.5 and 15.1 and the Verbal Fluency (Letter F -FCORR), is poor (below 12.5) then CDRSUM is between 4.5 and 6.5, which means mild dementia [6]. However, notice that this rule was fulfilled in principle in only one case in our 40 AD patients.

$$(Pat = 164087)\&\big(LOGMEM\,1A = ''(13.5, 15.5)''\big)\&\big(DSST = ''(39.5, Inf)''\big)\&(FCOR = ''(-Inf, 12.5)''\big)\&\big(BOSTON = ''(24.5, Inf)''\big)\&(APOE = 1) => (CDRSUM = ''(4.5, 6.5)'') \quad (19)$$

$$(Pat = 164087)\&\big(TRAILA = ''(-Inf, 73.5)''\big)\&\big(TRAILB = '' (52.5, Inf)''\big))\&(FCOR = ''(-Inf, 17.0)''\big)\&(PAIRD1 = '' (14.5, Inf)''\big)\&(PAIRD2 = '' (-Inf, 5.5)''))\&(BOSTON = ''(-Inf, 27.5)''\big)\&\big(CVLT = ''(33.5, Inf)''\big)\&(APOE = 1) => (CDRSUM = '' (5.75, 6.5)'') \quad (20)$$

However, two subjects had *CDRSUM* between 4.5 and 6, which means that they might have mild dementia [6]. The one our patient *Pat* = *164087*, with his/her results described in Eq. 19 seems to be easier to interpret with poor logical memory intermate and poor verbal fluency also with sensitive genetics with APOE = 1. To confirm this result, we have repeated the same subject classification using an additional attribute *CVLT* as a more universal test of verbal learning and memory. The result is in Eq. 20 not only confirms our previous results (Eqs. 15, 19), but also gives a narrower *CDRSUM* range between 5.75 and 6.5 which means mild dementia.

4 Discussion

Alzheimer's disease has about 20–30 years long prodromal phase, with brain changes before the first symptoms onset. This makes it a challenge to find biomarkers related to this period as when the first symptoms are clinically confirmed, there is no cure. Brain plasticity and adaptation processes may explain why patients do not notice several decades of extensive neurodegeneration. We proposed novel AI-related tools to increase the precision, sensitivity, and accuracy in monitoring ongoing neurodegenerations by looking not only into individual results in a clinical way but into patterns of many different cognitive test results and by comparing them with results of more advanced AD patients

We have studied these patterns with a granular computing approach and by comparing different sets of attributes (granules) to find possible patterns in normal subjects (n = 21) that might have similarities to granules observed in AD patients. We have used data from the BIOCARD study and analyzed all their AD patients (n = 40), part of their MCI patients (n = 70), and verified their normal, healthy patients (n = 20), as the reference groups. We were looking for different granules in all reference groups together as Group1, and in only the AD group Group2. In this study, we have increased the number of different granules by changing the number of used attributes. As in the previous study [5] we have always used 14 attributes, in this part we have changed from 5 to 7 attributes and compared results with 14 attributes. The other new and important part was the interpretability of obtained rules.

We have tried to estimate what is the meaning of individual granules, as we have performed similar estimations for Parkinson's disease patients [14]. We have used two groups: Group1 has granules related to normal subjects, MCI, and AD patients. On this

basis, we have obtained a large set of rules that have represented subjects' different stages of the disease from normal to dementia. We have tested several of such models mostly changing normal subjects and getting different rules, which we have applied to other normal subjects to get in the reference group 'pure' normal. Also, rules can be created with different granularity and algorithms that might give different classifications. Therefore, we were looking for classifications that are complete e.g., they give similar results with different sets of rules. Groupl1 has given us rules that are subtle and determine the beginning of possible symptoms. In addition to our previous classifications of 14 attributes [5], we have added classifications with 5 or 7 attributes. These new granules gave us rules supporting our previous classifications like Eq. 10 or gave new rules Eqs. 11–12.

In the next step, we used a more advanced model – Group2 that gave rules based on AD patients. We got higher values of the CRDSUM that gave us only classifications of the possible subjects with mild dementia.

Using only 5 attributes, we obtained 5 new rules that partly confirmed our previous classifications and were easier to interpret. We have also performed classifications with 15 attributes that gave us conformation and better precision of the patient with mild dementia (Eq. 19, 20). As it is the first, to our knowledge, work that estimates a singular complex pattern of the individual patient's symptoms, our rules are taken from one population and applied to different subjects, so they are not certain. Therefore, the next step is to find different methods for their conformation.

References

1. Albert, M., et al.: The BIOCARD research team, cognitive changes preceding clinical symptom onset of mild cognitive impairment and relationship to *ApoE* genotype. Curr Alzheimer Res. **11**(8), 773–784 (2014)
2. Albert, M., Zhu, Y., Moghekar, A., Mori, S., Miller, M.I., Soldan, A. et al.: Predicting Progression from Normal Cognition to Mild Cognitive Impairment for Individuals at 5years Brain. **141**(3): 877–887 (2018)
3. Pedrycz, W. (ed.): Granular Computing: an Emerging Paradigm. Physica Verlag, Heidelberg, New York (2001)
4. 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
5. Przybyszewski A.W., Bojakowska, K., Nowacki, J.P., Drabik, A.: Rough set rules (RSR) predominantly based on cognitive tests can predict Alzheimer's related dementia. Nguyen, N.T., et al. (eds.): ACIIDS 2022, LNAI 13757, pp. 129–141 (2022)
6. O'Bryant, S.E., Waring, S.C., Cullum, C.M., et al.: Staging dementia using clinical dementia rating scale sum of boxes scores: a Texas Alzheimer's research consortium study. Arch Neurol. **65**(8), 1091–1095 (2008)
7. Pawlak, Z.: Rough Sets: Theoretical Aspects of Reasoning About Data. Kluwer, Dordrecht (1991)
8. Bazan, J., Nguyen, S.H., et al.: Desion rules synthesis for object classification. In: Orłowska, E. (ed.), Incomplete Information: Rough Set Analysis, Physica – Verlag, Heidelberg, pp. 23–57 (1998)

9. Bazan, J., Nguyen, H.S., Nguyen, et al.: Rough set algorithms in classification problem. In: Polkowski, L., Tsumoto, S., Lin, T. (eds.), Rough Set Methods and Applications, Physica-Verlag, Heidelberg New York, pp. 49–88 (2000)
10. Grzymała-Busse, J.: A New Version of the Rule Induction System LERS Fundamenta Informaticae, **31**(1), 27–39 (1997)
11. Bazan, J., Szczuka, M.: The Rough Set Exploration System. Peters, J.F., Skowron, A. (Eds.): Transactions on Rough Sets III, LNCS 3400, pp. 37–56 (2005)
12. Przybyszewski, A.W.: The neurophysiological bases of cognitive computation using rough set theory. Peters, J.F., et al. (eds.): *Transactions on Rough Sets IX*, LNCS 5390, pp. 287–317 (2008)
13. Bazan, J., Szczuka, M.: RSES and RSESlib - a collection of tools for rough set computations. Ziarko, W., Yao, Y. (eds.): RSCTC 2000, LNAI 2005, pp. 106−113 (2001)
14. Przybyszewski, A.W.: Parkinson's disease development prediction by C-granule computing. Nguyen, N.T., et al. (eds.): ICCCI 2019, LNAI 11683, pp. 1–11 (2019)