Pattern Classification Can Detect Prodromal Alzheimer's Neurodegenerations

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Abstract. Alzheimer's disease (AD)-related neurodegeneration can begin several decades before the first symptoms appear, and AD biomarkers have only recently been identified. Our research focused on identifying AD-related biomarkers in healthy subjects. We analyzed Biocard data using a group of 150 subjects in different AD stages, with 40 AD patients compared to normal subjects. Using the granular computing method, we identified sets of attributes related to various stages of the disease. We applied this classification to the psychophysical test results of normal subjects to determine if some cases might show granular pattern similarities to groups with AD. Earlier detection can uncover patterns invisible to neuropsychologists in the cognitive like executive or immediate/delayed memory functions. These patterns may help to determine if a patient is getting amnestic or non-amnestic early symptoms that lead to dementia or not. Our analysis of Biocard data identified granules that classify cognitive attributes with disease stage scores (CDRSUM - Clinical Dementia Rating Scale Sum of Boxes). By applying these rules to 21 normal subjects with a CDRSUM of 0, we predicted that one subject might develop mild dementia (CDRSUM > 4.5) with a mixture of executive and cognitive test results. Another patient might get very mild dementia (CDRSUM > 2.25), but with dominating memory problems which might lead to serious amnestic symptoms. Other patients might develop questionable impairment (CDRSUM > 0.75). Our AI-powered method can identify patterns in cognitive attributes in normal subjects that might indicate their pre-dementia amnestic or non-amnestic stages, which may be invisible to neuropsychologists.

Keywords: Neurodegeneration · Granular Computing · Rough Set Theory · Amnestic MCI · Non-amnestic MCI

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1 Introduction

The number of individuals with Alzheimer's Disease (AD) related dementia is increasing rapidly due to the aging population. Worldwide, the prevalence is estimated to be as high as 24 million, and it could rise to 139 million by 2050 (World Health Organization, Global Dementia Observatory (GDO), 2021). Unfortunately, there is currently no cure for AD, as by the time clinical symptoms are observed and a neurological diagnosis is made, many parts of the brain are already dead. As neurodegenerative changes begin two to three decades before observable symptoms, the best chance to fight AD is to estimate the beginning period of AD-related brain changes. The BIOCARD* study was initiated in 1995 by the NIH and involved 354 normal individuals. The study was interrupted in 2005 but continued from 2009 as a Johns Hopkins (JHU) study. At JHU, patients have yearly cognitive and clinical visits that measure over 500 attributes with 96 cognitive parameters. Albert [1, 2] successfully predicted the conversion from normal to Mild Cognitive Impairment (MCI) due to AD, five years after baseline, for 224 subjects using the following parameters: CSF β-amyloid and p-tau, MRI hippocampal and entorhinal cortex volumes, cognitive test scores, and APOE genotype. Although their predictions were for all tested patients, they found important biomarkers that we are using in our study.

However, in this study, we are looking for patterns related to amnestic (memory) and non-amnestic directions of the disease development. As we are testing normal subjects, we would like to test early cognitive symptoms, Younes et al. [3] demonstrated that four cognitive tests had changepoints 10–15 years before symptom onset: (1) Digit Symbol Substitution Test, (2) Logical Memory – delayed recall, (3) Verbal Paired Associates – Immediate recall, and (4) Boston Naming Test (explained in the Methods section). We are using these tests as related to amnestic symptoms.

Our approach is different as we have performed classification by using granular computing (GrC) to connect cognitive test results with genetic data (ApoE genotype) and AD-related clinical symptoms in a different group of patients from normal to AD. We used this group as a Model for the supervised training of granules (rules) related to various stages of the disease, from normal to MCI and AD subjects. In the next step, we applied these granules to individual normal subjects to (look into similarities) predict the possibility of the beginning of neurodegeneration (AD-related brain changes) in everyone. As AD-related dementia is increasing at such a fast pace, we need an easy and accessible method for the preclinical classification of all potential patients. Otherwise, we will soon face many "disoriented" people. Our granular computing method and its implementation with a rough set are well-established in neurodegenerative disease, especially used in many publications related to Parkinson's disease (PD) patients [4]. In [4], we have compared algorithms using rough set theory (RST), with other classifiers such as Naïve Bayes, Decision Trees/Tables, and Random Forests (implemented in KNIME/WEKA). We have demonstrated that the RST-based algorithms gave the best results and are powerful biomarkers in PD.

2 Methods

This study is a continuation of our previous research see details in [5]. Our data are from the BIOCARD study started in 1995 with normal subjects and continued by JHU till now. We have used data obtained from JHU in 2020. We analyzed the cognitive performance of several groups of subjects. The first one consists of 150 subjects with 40 normal subjects, 70 MCI with Mild Cognitive Impairment (MCI), and 40 subjects with Alzheimer's Disease (AD). We chose this group as, out of the total population of 354 normal subjects who were followed from 1995, in 2020 we found 40 subjects with dementia, which had all needed test results. Therefore, we added 40 normal subjects and 70 MCI as they are in between AD and normal subjects. The second group included 40 AD subjects, and the last group consisted of 21 subjects clinically classified as normal. All subjects had their age recorded, and they underwent the following neuropsychological tests every year:

Memory-related tests:

1. Logical Memory Immediate (LOGMEM1A) - participants are read a logically organized story and asked to recall it immediately after its presentation.
2. Logical Memory Delayed (LOGMEM2A) – as above with recall 20 min. later.
3. Rey Figure Recall (REYRECAL), in which subjects are asked to reproduce a complicated line drawing from memory (visual memory test).
4. Paired Associate Immediate (PAIRED1), from the Wechsler Memory Scale - subjects are asked to learn unrelated word pairs (e.g., stove-letter).
5. Paired Associate Delayed (PAIRED2), from the Wechsler Memory Scale - as above but with delayed matching-to-sample tasks (testing hippocampus function).
6. CVLT (California Verbal Learning Test) - an examinee listens to a series of words and is then asked to recall the terms and the category to which they belong (test of verbal learning and memory).

Associative learning and memory

7. 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
8. Verbal Fluency Letter F (FCORR) requires the creation of words from the initial letters F under 60 s of time constraints.
9. Boston Naming Test (BOSTON) determining confrontational picture-naming abilities in patients.

Executive functions tests:

10. Trail Making, Part A (Trail A) - connecting time in seconds of randomly placed numbers.
11. Trail Making Part B (Trail B) - connecting time in seconds of randomly placed numbers and letters.

In addition, we registered the APOE genotype; individuals who are ApoE4 carriers vs. non-carriers (digitized as 1 vs. 0). The decision attributes were CDRSUM (sum of

boxes) as a precise and quantitative general index of the Clinical Dementia Rating [6]. The CDRSUM (Clinical Dementia Rating Scale Sum of Boxes) is 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 Block Diagram of Method

After preprocessing (removing artifacts and partial patient records), we have selected significant attributes [1–3, 5] (Fig. 1). In the following step, we split the data set into training and testing sets. The training set has two subsets related to Model1 and Model2. Model1 consists of 150 subjects: AD, MCI, and normal. Model2 has only 40 AD patients. The first model gave the Mixed rules, while the Model2 gave the AD rules. Both models determined a possible cognitive problem in normal subjects (GroupN) with different significance (more seriously related to Model2) (Fig. 1).

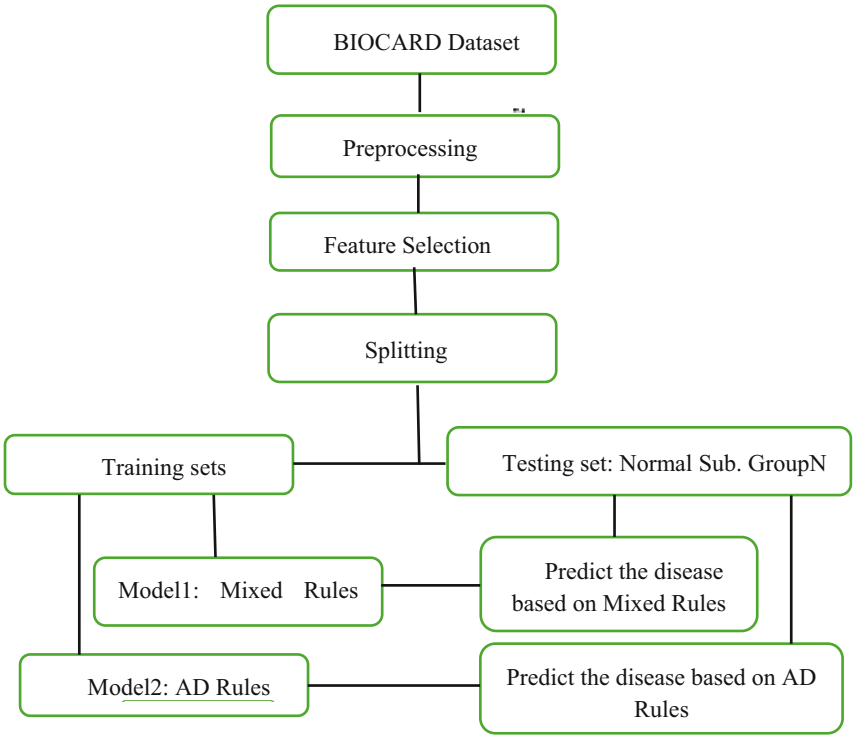


Fig. 1. Block diagram represents a schematic of our method.

2.2 Granular Computing Implemented in Rough Sets

In our study, we used data mining granular computing (GrC) analysis, which was implemented using rough set theory (RST) discovered by Zdzislaw Pawlak [7]. RST is a method for approximating the boundaries of vague concepts by using sharp sets of upper and lower approximations [7], as we described previously [5]. In short, an information system is 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. If $a \in A$ and $u \in U$, the value $a(u)$ is a unique element of V (where V is a value set) as $(x, y) \in IND(B)$ *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 is the basis of rough set theory. Granules are sets of different elements with similarities (with similar values).

One can broaden 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. In a single row, there are many conditions and only one decision attribute, all related to a specific test of the individual subject. Conditions attributes and related decision attributes give unique rules. One tough problem is inconsistent results, leading to contradictory rules, when the same attribute values are classified as different concepts [8]. In general, it means that some attributes are missing from the dataset. LERS (Learning from Examples based on Rough Sets) [10] computes lower and upper approximations of all concepts. Conflicting data is not removed from the dataset. Instead, concepts are approximated by new sets of lower and upper approximations. Rough Set Theory generalizes individual measurements (rules) to universal principles (knowledge), but rules have different confidence. There are true rules related to the lower approximation set and rules that are only partly true associated with the upper approximation set. In the present study, we used different intelligent algorithms implemented in RSES 2.2 software, such as the exhaustive algorithm, genetic algorithm, covering algorithm, or LEM2 algorithm [9, 11]. Our approach is like the visual brain mechanisms of advanced processes of complex object recognition [12]. The processes in the higher visual brain areas related to different object classifications use GrC to find upper and lower approximations of the retinal image [12]. These approximations are compared with various 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

We have divided the Table 1 into two parts: the upper part is mostly related to execution functions, age, and genetics, whereas the lower part to memory-related tests. There are three columns: the first one (GroupM1) consists of 150 subjects (40 normal, 70 MCI, and 40 AD patients; the second column consists of 40 AD patients (GroupM2); and the third column consists of 21 normal subjects (GroupN) that are different subjects from the normal subjects in GroupM1. The age of subjects in different groups is similar, as

Table 1. Statistic calculations of tested data with mean ±SD, * 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.

Execution function tests:

	GroupM1 n=150	GroupM2 n=40	GroupN n=21
age	76 +/- 9.1	78.5 +/- 12	76.6 +/ 8.4
Trail A	39.6 +/- 20	50.6 +/- 30	30.7 +/- 12
Trail B	99.9 +/- 59	151 +/- 78	64.2 +/- 21
FCORR	15.4 +/- 5 *	12.6 +/- 6*	18.2 +/- 5 *
APOE	0.35 +/- 0.5	0.3 +/- 0.5	0.3 +/- 0.5
CDRSUM	1.3 +/- 1.8	3.5 +/- 2.5#	0 +/- 0#

Memory-related tests:

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
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*
DSST	46.5 +/- 14	37.3 +/- 13	57 +/- 13
CVLT	53 +/- 14*	41 +/- 13*	64.4 +/- 10*
REYRECAL	19.7 +/- 8*	14.6 +/- 7*	24.2 +/- 6*

well as the execution functions *TRAILA*, and *TRAILB (TMT A and B*), but there are significant differences in language fluency (*FCORR*).

The changes of the *CDRSUM* are obvious as in normal subjects its values are 0 and significantly larger for AD patients. In memory-related tests: fresh memory test Lgm1A (*LOGMEM1A*) is the smallest for AD patients and largest for N, more importantly, delayed memory test Lgm2A (*LOGMEM2A)* has similar changes as Lgm1A. Paired memory tests, for fresh *(PAIRED1*) and delayed memory test (*PAIRED2)*, have significantly different values for all groups of patients, as well as *BOSTON* naming tests, *DSST* (digit symbol substitution test), is decreasing from N to AD (no stat. differences). The *REYRECAL* complex figure test is used for the evaluation of visuospatial constructional ability, and visual memory, and its values are statistically different for all groups. The *CVLT (*California Verbal Learning Test) is for comprehensive, detailed assessment of verbal learning & memory tests, and it is significantly different for all groups of 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, but for similarities in patterns. The above cognitive tests were chosen based on Albert's group papers [1–3].

3.2 Granular Computing for Reference of GroupM1

We have placed GroupM1 (Model1-150 subjects) data in the table where columns (15 in our case) are related to different attributes, and rows show test results of different patients (150 rows). If in the last column is the decision attribute, we call such a table, the information table. The 13 condition attributes are in the Table 1, the 14th attribute is the patient's number, and the 15th attribute is the decision attribute *CDRSUM*. In the next step, we used RSES 2.2 for GroupM1 discretization with the global cuts (RSES 2.2) [13]. There were the following 3 ranges of the decision attribute values *CDRSUM: "(-Inf, 0.75)", "(0.75, 1.25)", "(1.25, Inf)"*. We used the exhaustive algorithm for the GroupM1 data, and from the obtained after filtering, rules we chose two below with a small number of attributes, which are easy to interpret:

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

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

The interpretations are important. Equation 1 claims for 6 cases that if *TRAILB* has a bad time above 153s (normal time is 75s) and *REYRECALL* (visual memory) less than 16 (normal about 27) is also bad then *CDRSUM* is also above 2.25 which means the questionable impairment [6]. In Eq. 2, *TRAILB* is between normal and too long, *FCORR* (speech fluency) is good (above 15), *REYRECALL* is below normal values then *CDRSUM* is below 2.25 which suggests questionable cognitive impairment. We have used 324 general rules (Mixed Rules) from GroupM1 to predict *CDRSUM* of the normal patients (GroupN, n = 21), and we found that three patients might have a potential impairment:

$$(Pat = 164087)\&(LOGMEM\,1A = \text{“}(-Inf, 15.5)''))\&(LOGMEM\,2A = \text{“}(-Inf, 16.5)''\text{)}\& \\ (TRAILA = \text{“}(35.5, Inf)''\text{)}\&(TRAILB = \text{“}(74.5, 153.0)''\text{)}\&(FCORR = \text{“}(-Inf, 16.5)''\text{)}\& \\ (REYRECAL = \text{“}(15.75, 25.25)''\text{)}\&(PAIRD2 = \text{“}(-Inf, 6.5)''\text{)}\&(age = \text{“}(-Inf, 76.5)''\text{)}\ \& \\ (APOE = 1) => (CDRSUM = \text{“}(2.25, Inf)''\text{)} \quad (3)$$

$$(Pat = 401297)\&(LOGMEM\,1A = \text{“}(-Inf, 15.5)''))\&(LOGMEM\,2A = \text{“}(-Inf, 16.5)''\text{)}\& \\ (TRAILA = \text{“}(-Inf, 23.5)''\text{)}\&(TRAILB = \text{“}(-Inf, 74.5)''\text{)}\&(FCORR = \text{“}(-Inf, 16.5)''\text{)}\& \\ (REYRECAL = \text{“}(-Inf, 15.75)''\text{)}\&(PAIRD2 = \text{“}(6.5, Inf)''\text{)}\&(age = \text{“}(-Inf, 76.5)''\text{)}\ \& \\ (APOE = 1) => (CDRSUM = \text{“}(2.25, Inf)''\text{)} \quad (4)$$

$$(Pat = 808698)\&(LOGMEM\,1A = \text{“}(15.5, 20.5)''))\&(LOGMEM\,2A = \text{“}(16.5, Inf)''\text{)}\& \\ (TRAILA = \text{“}(-Inf, 23.5)''\text{)}\&(TRAILB = \text{“}(-Inf, 74.5)''\text{)}\&(FCORR = \text{“}(-Inf, 16.5)''\text{)}\& \\ (REYRECAL = \text{“}(15.75, 25.25)''\text{)}\&(PAIRD2 = \text{“}(6.5, Inf)''\text{)}\&(age = \text{“}(-Inf, 76.5)''\text{)}\ \& \\ (APOE = 1) => (CDRSUM = \text{“}(0.75,\ 2.25)''\text{)} \quad (5)$$

The first patient *(Pat = 164087)* Eq. 3 has affected logical memories: immediate and delayed, executive functions (*Trial A&B*), are in the border of the normal range, *FCORR*

below 15 is bad, low values of *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 (*Trial A&B*), and bad *FCORR* and *REYRECALL* and in addition bad APOE genotype that determines *CDRSUM* above 2.25. The third patient is *(Pat = 808698)* (Eq. 5) 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]).

In this study, at first, we reduced the number of attributes from 14 to the following **five**: *APOE, FCORR, DSST, and TRAILB,* which are a mixture of the execution function (*TRAILB*) and short memory (*DSST*), with the language fluency (*FCORR*) with the decision attribute was *CDRSUM*. These condition attributes are significant as the early predictors of AD.

The *APOE* genotype, individuals who are *ApoE4* is an important genetic factor that influences the probability of AD. One of the early predictors of AD is poor language performance, quantified by the *FCORR* test. Another one is related to the *DSST* test. The third indicator is related to slow processing speed (*TRAILB* test). We put all data in the decision table (as described in the Methods section). With RSES help, after discretization, we found with a 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:

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

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

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

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

A significant attribute is the genetic *APOE* genotype, and in these approximate rules, the lack of *ApoE4* carriers (*APOE = 0*) is related to health (very low *CDRSUM*). Another attribute, the *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 *Trail B* is slower than in normal subjects, with *APOE = 1* influencing *CDRSUM*. In Eq. 9 execution (*TrailB*) is very slow and, *APOE = 1* with language fluency problems (low value of *FCORR below 15*) are the main factors that such patients have indications of mild dementia (*CDRSUM* is larger than 4.25).

By applying all 82 rules to the healthy patients (GroupN, n = 21) with clinically confirmed *CDRSUM = 0,* we found one patient with *CDRSUM* significantly larger than 0 in the following classification:

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

The Eq. 10 indicates based on 4 condition attributes, as a low *DSST*, bad *FCORR* (below 15), and above normal *TRAILB* that patient *164087* might have *CDRSUM* = *“(2.25,3.25)”* that suggests very mild dementia [6].

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

We have obtained 104 rules from GroupM1 patients and applied them to GroupN (n = 21) normal subjects, and got the following classifications (two examples):

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

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

It is interesting that for *Pat = 164087* more condition attributes are in Eq. 12 in comparison to Eq. 10 gives 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. Both subjects have below the min. norm *FCORR* results (below 15), in the low range *REYRECAL* (27 norm), and especially the low scores of *DSST* (Eqs. 11, 12).

3.3 Granular Computing for Reference of GroupM2 Patients

Figure 2 presents a large variability of CDRSUM in GroupM2.

In this part, we have reduced the number of attributes from 14 to the following, same as above, **five** condition attributes: *APOE, DSST, FCORR, TRAILB,* and 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 examples of the 2 (Eqs. 13, 14) rules are shown below:

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

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

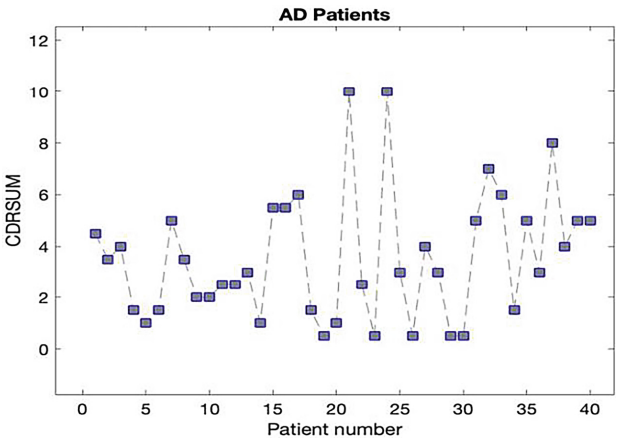


Fig. 2. Shows the values of *CDRSUM* obtained by clinicians for all AD patients used in this study (GroupM2).

What is unusual is that there is 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 GroupM1 to predict the *CDRSUM* of GroupN.By using these rules for normal patients, we got the $CDRSUM > 0$. 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:

$$(Pat = 164087)\&(APOE = 1))\&\big(DSST = \text{“}(45.0, 56.0)''\big)\&\big(FCORR = \text{“}(-Inf, 15.5)''\big)$$
$$\&\,(TRAILB = \text{“}(-Inf, 128.5)'' => (CDRSUM = \text{“}(3.25,\ Inf)'') \tag{15}$$

$$(Pat = 242874)\&(APOE = 1))\&\big(DSST = \text{“}(45.0, 56.0)''\big)\&\big(FCORR = \text{“}(-Inf, 15.5)''\big)$$
$$\&\,(TRAILB = \text{“}(-Inf, 128.5)'' => (CDRSUM = \text{“}(3.25,\ Inf)'') \tag{16}$$

In the two above equations (Eqs. 15, 16), speech fluency (*FCORR*) is affected. The executive function *TRAILB* is below 128.5s, but this classification is rather crude. It does not give us the lower value (from other equations (e.g., Eq. 11). We know that $Pat = 164087$ is above 72s which is a good value, but almost one minute more is not a very good result). In two last Eqs. 15 and 16 *DSST* is relatively 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 GroupM2 subjects, and as an example, we present below one rule with only 3 attributes:

$$\big(LOGMEM\,1A = \text{“}(13.5, 15.5)''\big)\&\big(FCORR = \text{“}(-Inf, 12.5)''\big)$$
$$=> \big(CDRSUM = \text{“}(4.5, 6.5)''[2]\big)\,2 \tag{17}$$

Interpretation: Eq. 17, if Logical Memory Immediate (LOGMEM1A) is in the low range between 13.5 and 15.1 and the Verbal Fluency (*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 two cases in our 40 AD patients.

$$(Pat = 164087)\&\big(LOGMEM\,1A = \text{“}(13.5, 15.5)''\big)\&\big(DSST = \text{“}(39.5, Inf)''\big)$$
$$\&\big(FCOR = \text{“}(-Inf,\ 12.5)''\big)\&\big(BOSTON\ = \text{“}(24.5, Inf)''\big)\&(APOE = 1)$$
$$=> \big(CDRSUM\ = \text{“}(4.5,\ 6.5)''\big) \tag{18}$$

$$(Pat = 164087)\&\big(TRAILA = \text{“}(-Inf, 73.5)''\big)\&\big(TRAILB = \text{“}(52.5, Inf)''\big))$$
$$\&\big(FCOR = \text{“}(-Inf,\ 17.0)''\big)\&(PAIRED1 = \text{“}(14.5, Inf)''\big)\&(PAIRED2 = \text{“}(-Inf, 5.5)''))$$
$$\&\big(BOSTON = \text{“}(-Inf,\ 27.5)''\big)\&\big(CVLT = \text{“}(33.5, Inf)''\big)\&\ (APOE = 1)$$
$$=> \big(CDRSUM\ = \text{“}(5.75, 6.5)''\big) \tag{19}$$

One subject, *Pat = 164087* (Eq. 18), had *CDRSUM* between 4.5 and 6, which means that they might have mild dementia [6]. The patient has a low logical short memory score and bad language fluency (*FCOR*). 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. 19 confirms our previous results and adds execution function *TRAILB* and bad *PAIRED2* delayed memory. It gives a narrower *CDRSUM* range between 5.75 and 6.5 related to mild dementia [6].

3.4 Granular Computing Limited to Memory and Cognitive Functions Reference of GroupM2 Patients

The last, most important part concentrates on cognitive, and memory-related tests limited to *REYRECAL, LOGMEM2, PAIRED2, DSST, CVLT, BOSTON, APOE,* and the decision attribute *CDRSUM.*

This part should show which patients have serious memory and cognitive problems which means amnestic MCI that leads to dementia.

$$(Pat = 579794)\&(REYRECAL = \text{“}(13.5, Inf)'')\&(PAIRED2 = \text{“}(5.5, Inf)'')$$
$$\&\big(DSST = \text{“}(40.5,\ Inf)''\big)\ \&\big(CVLT\ =\ \text{“}(33.5, 53.5)''\big)\&(APOE = 0)$$
$$=> \big(CDRSUM\ = \text{“}(1.75, 2.75)''\big) \tag{20}$$

$$(Pat = 373705)\&(REYRECAL = \text{“}(13.5, Inf)'')\&(PAIRED2 = \text{“}(5.5, Inf)'')$$
$$\&\big(DSST = \text{“}(40.5,\ Inf)''\big)\ \&\big(CVLT\ =\ \text{“}(-Inf, 53.5)''\big)\&(APOE = 0)$$
$$=> \big(CDRSUM\ = \text{“}(1.75, 2.75)''\big) \tag{21}$$

$$(Pat = 164087)\&(PAIRED2 = \text{“}(-Inf, 5.5)'')\&\big(LOGMEM\,2A = \text{“}(5.5, Inf)''\big)$$
$$\&(BOSTON\ =\ \text{“}(25.5, Inf)''))\&\big(LOGMEM\,1A = \text{“}(14, Inf)''\big))$$
$$\&(CVLT = (\text{“}(53.5, Inf)''))\&(APOE = 1) => \big(CDRSUM\ = \text{“}(3.75, Inf)''\big) \tag{22}$$

$$(Pat = 558865)\&(REYRECAL = \text{“}(13.5, 26))\&(PAIRED2 = \text{“}(-Inf, 6.5)'')$$

$$\&\big(DSST = \text{“}(Inf,\ 40.5)''\big)\&\big(LOGMEM\,2A = \text{“}(12.5, Inf)''\big)$$
$$\&(BOSTON = \text{“}(-Inf, 27.5)''\&(CVLT = \text{“}(33.5,\ Inf)''\&(APOE = 1)$$
$$=> \big(CDRSUM = \text{“}(4.25, Inf)''\big) \tag{23}$$

Patients described by Eqs. 20, and 21 have low results (below 53) of *CVLT* (Verbal Learning Test), the main cognitive problem. In well-studied *Pat = 164087* Eq. 22 (see also above Eqs. 18, 19), the problem is delayed paired memory *(PAIRD2)* therefore *CDRSUM* does not show so high values as above (Eqs. 18, 19). That means that this patient's problems are not mainly related to memory and cognitive issues, even if previous scores show mild dementia (see above).

Our concerns are on *Pat = 558865* (Eq. 23) with several problems: low *PAIRD2* results (paired delayed memory), bad digital symbol substitution results *DSST* (see Fig. 3b), and bad *BOSTON* naming test results, which means that the patient does not remember the names of everyday objects showed on pictures.

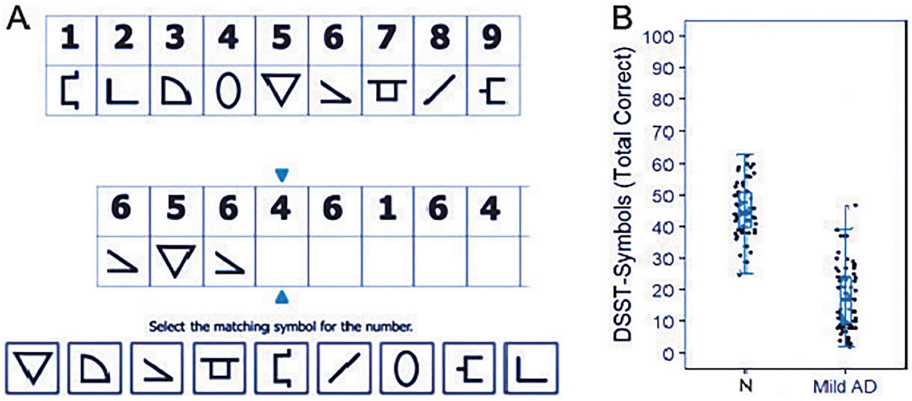


Fig. 3. (A) Computer-based Digital Symbol Substitution Test. The top two rows show Arabic numbers and abstract symbols as pairs. The middle row shows the patient's progression. The bottom row shows the symbol matching the number. (B) The plot of the correct results for normal (N) and mild AD subjects. Plots are based on [14].

Even if the patient's results are in the very mild dementia range, the main problems of this patient are related to bad memory that gives a risk of amnestic MCI leading to dementia. Indeed, the new test results 2023 demonstrated that this patient *(558865)* evaluated as normal in 2020, was classified as MCI by a neurologist in 2023 **giving the clinical meaning and application to our tests.**

4 Discussion

Alzheimer's disease (AD) has a prodromal phase that can last up to 20–30 years, during which brain changes occur before the onset of the first symptoms [3]. This phase before symptoms onset is a change for slowing down neurodegenerative processes. Therefore,

the clinical pipelining of the project is to find the early pre-AD phase of the disease. When the first symptoms are clinically confirmed, there is no cure. Normally, patients do not notice the extensive neurodegeneration during this period due to brain plasticity and adaptation processes. To address this challenge, we proposed novel AI-related tools to increase the precision, sensitivity, and accuracy in monitoring ongoing neurodegeneration. Our AI tools are based on complex object recognition by the visual system [12].

Our visual world is dominated by noise and complexity. In the higher brain areas, we memorized many different objects. When we see an image of a new object in unknown conditions like position, illumination, or environment, our brains compare its features with known, saved patterns. In this comparison, or 'tunning', the main role is played by the back projecting pathway that can influence the properties of different sensors (neurons) to fit a particular part of the observed object [12]. If the difference between possible patterns and actual saved patterns is negligible then the object is recognized (in the rough set theory approach, we say that if the difference between upper and lower approximation sets is insignificant then the classification is exact) [12].

Therefore, as saved models (objects) we use the cognitive features of the more advanced AD patients as models. We are using a granular computing approach to put together important elementary features (granules) related to different symptoms of AD patients. Our save models are expressed as granular rules. We analyzed data from the BIOCARD study and compared different sets of attributes (granules) to find possible patterns in normal subjects (n = 21) that might have similarities to granules observed in Alzheimer's patients. We used all available, in the BIOCARD project, Alzheimer's patients (n = 40), and part of their MCI patients (n = 70), and verified their normal, healthy patients (n = 20) as the reference groups. We looked for different granules in all reference groups as GroupM1 and in only the Alzheimer's group (n = 40) - GroupM2. In this study, by changing the number of attributes we got different rules. An important part of our method is to clarify the neurological meaning of obtained rules. Our research involved similar estimations to those performed on Parkinson's disease patients [15].

We divided our subjects into two groups: GroupM1 included normal subjects, MCI, and AD patients, and we used this group to generate a large set of rules that represented different stages of the disease from normal to dementia. Different algorithms and granularities can yield different classifications, but our rules belong to the upper approximation set and are not certain. Therefore, we aimed to find classifications that gave similar results with different sets of rules. GroupM1 provided us with subtle rules that identified the beginning of possible symptoms. Additionally, we classified our subjects using 5 or 7 attributes in addition to our previous 14-attribute classifications [5]. These new granules supported our previous classifications, providing further evidence for our findings. We used an advanced version of GroupM2 to develop rules for patients with AD, which resulted in higher CRDSUM values, allowing us to classify subjects with mild dementia. By using only 5 attributes, we established five new rules that were easier to understand and confirmed our previous classifications. We also tested classifications using 15 attributes, which provided better precision in identifying patients with mild dementia. However, since our rules were derived from a single population and applied to different subjects, we cannot be certain of their accuracy. Therefore, our next step is

to validate our findings using clinical confirmation. This is the first study to estimate a complex pattern of individual patient symptoms, and we hope our research will lead to a better understanding and treatment of AD. The most important part of our study concerns the pattern difference in disease development between amnestic and non-amnestic subjects. As we have earlier demonstrated, applying our rules to normal subjects resulted from hypotheses that some patients qualified by doctors as normal might have already begun the neurodegenerative brain changes. However, such changes very difficult to differentiate the age-related changes. If they are not directly related to significant changes in MTL (medial temporal lobe), subjects might live independently till the end of their lives. Therefore, our recent approach concentrates specifically on memory and cognitive tests. As we have demonstrated on several normal subjects by using well-established tests [1, 2], qualifying somebody with mild dementia, might less affect the patient than with very mild dementia, but with main changes in memory and cognition (compare Eqs. 18, 19, 22 with 23). Our results suggest that we need more specific early tests (like [17–21]) that will show us how to sense and eventually influence a particular pathway of neurodegeneration in our brains. It is also important to study subtle changes in daily functioning to predict conversion from normal to MCI [22], and to find if this conversion is to amnestic or non-amnestic MCI [23, 24]. There are also other factors playing a role in such conversions, like vascular problems [24], and conversion from questionable dementia [25]. In the literature review of 15450 results, authors selected 42 studies using longitudinal studies and machine learning to predict amnestic and no amnestic MCI [26].

Based on the recent reviews from [22–26], the conversion to amnestic or non-amnestic MCI is one of the major issues in Alzheimer's disease prevention and treatment. The above papers use large databases, different algorithms in multimodal studies, and ML methods but do not obtain clear conclusions. In contrast, our findings exemplified only one of 21 normal subjects, with our universal rules (see above). Because our approach is mainly based on cognitive attributes, it can be computerized and used online for a large population of normal, older subjects. As there are different country-related cultures, our study might find country-dependent rules that may play preventive roles in falling into dementia. However, [27] focuses on early AD's automatic diagnosis based on artificial NN, and deep learning, see commentary in [16].

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