AI Classifications Applied to Neuropsychological Trials in Normal Individuals that Predict Progression to Cognitive Decline

Andrzej W. Przybyszewski[1,2(✉)] and the BIOCARD Study Team*

[1] Polish-Japanese Academy of Information Technology, 02-008 Warsaw, Poland
przy@pjwstk.edu.pl
[2] Department Neurology, University of Massachusetts Medical School, Worcester, MA 01655, USA
Andrzej.Przybyszewski@umassmed.edu

Abstract. The processes of neurodegeneration related to Alzheimer's disease (AD) begin several decades before the first symptoms. We have used granular computing rules (rough set theory) to classify cognitive data from BIOCARD study that have been started over 20 years ago with 354 normal subjects. Patients were evaluated every year by team of neuropsychologists and neurologists and classified as normal, with MCI (mild cognitive impairments), or with dementia. As the decision attribute we have used CDRSUM (Clinical Dementia Rating Sum of Boxes) as more quantitative measure than above classification. Based on 150 stable subjects with different stages of AD we have found rules (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 other 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: Granular computing · Rough set · Rules · Cognition

1 Introduction

As our population is aging, it causes that the prevalence of AD related dementia is fast increasing [1]. About 5.7 million Americans have actually AD, and the prevalence worldwide is estimated to be as high as 24 million. By 2050, AD number could potentially rise to 14 million in the US [1], and dementia (60–70% AD) to 139 millions worldwide (World Health Organization, 2021). Because AD biomarkers were identified in recent years, AD related changes might be found in the preclinical AD phase that opens possibilities of the new preventive methods developments.

Cognitive changes are dominant symptoms in the Alzheimer's disease (AD). In the most cases of AD neurodegeneration starts from the hippocampus and frontal cortex, and it related to memory and orientation problems. With the disease progression, other

D. Groen et al. (Eds.): ICCS 2022, LNCS 13352, pp. 150–156, 2022.
https://doi.org/10.1007/978-3-031-08757-8_14

brain regions become also affected. There is no cure for AD, as during the diagnosis of the first clinical symptoms many parts of the brain are already dead.

As each patient has dissimilar neurodegeneration developments, their compensation (brain plasticity) and in the consequence symptoms might be various; finding partial optimal treatment is an art for an experienced neurologist.

The neurodegeneration developments that start several decades before first symptoms, and they were registered as changes in the Cerebral Spinal Fluid (CSF) t-tau. Whereas the cognitive tests had changepoints in about a decade before symptoms onset [2, 3]. As cognitive changes can be easy and in the noninvasive way measured online, in this project, we have predicted disease onset with sets of psychophysical attributes found as the most meaningful in patients from the BIOCARD study publications [4, 5]. In addition, we have combined them with results of the apolipoprotein E ApoE genotype [4]. Albert et al. [5] have 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: CSF β-amyloid and p-tau, MRI hippocampal and entorhinal cortex volumes, cognitive tests scores, and APOE genotype. However, their predictions were for the whole populations and with many different parameters [5], and ours are for each individual subject based on APOE genotype and only cognitive attributes.

This study is the continuation of the rough set theory application to follow predominantly the cognitive changes in the neurodegenerative diseases (ND) such as Parkinson's [6] and now in Alzheimer's diseases.

2 Methods

We have analyzed cognitive and APOE data of 150 subjects consist of: 40 normal subjects, 70 MCI (Mild Cognitive Impairment), and 40 subjects with dementias (AD). These data were basis of our general basic model (G Model) connecting cognitive attributes with different disease stages related to CDRSUM (Clinical Dementia Rating Sum of Boxes). We have also used 40 AD subjects from this group as another model for advanced patients - AD Model. We have tested using above two Models, on 21 of classified by clinicians as normal subjects (N Group), with the purpose to estimate their stages (CDRSUM) on similarities to our models.

In all subjects with recorded their age, had the following neuropsychological tests performed every year: Logical Memory Immediate (LOGMEM1A), Logical Memory Delayed (LOGMEM2A), Trail Making, Part A (TrailA - connecting time in sec of random placed numbers), Trail Making Part B (TrailB - connecting time in sec of random placed numbers and letters), Digit Symbol Substitution Test (DSST), Verbal Fluency Letter F (FCORR), Rey Figure Recall (REYRECAL), Paired Associate Immediate (PAIRED1), Paired Associate Delayed (PAIRED2), Boston Naming Test (BOSTON), and CVLT (California Verbal Learning Test). In addition, we have subjects' age (years), APOE genotype; individuals who are *ApoE-4* carriers vs. non-carriers (digitized as 1 vs. 0), and CDRSUM (sum of boxes) as precise and quantitative general index of the Clinical Dementia Rating [7]. There are the following CDRSUM values related to different stages of normal, pre-, and clinical confirmed AD patients: for prodromal patients are: (0.0) – normal; (0.5–4.0) – questionable cognitive impairment; (0.5–2.5) – questionable impairment; (3.0–4.0) – very mild dementia; (4.5–9.0) – mild dementia [7].

*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).

2.1 Rough Set Theory

Our data mining analysis follows rough set theory (RST) discovered by Prof. Zdzislaw Pawlak [8], whose solutions of the vague concept of boundaries were approximated by sharp sets of the upper and lower approximations [8]. It was demonstrated previously that RST gave the best results in the PD symptoms classifications in comparison to other methodologies [9]. Details of RST were described in the previous ICCS conference [10]. We have used Rough Set Exploration System RSES 2.2 as a toolset for analyzing data with rough set methods [11].

3 Results

3.1 Statistics

We have performed statistical analysis for all 15 attributes, and we found that 7 attributes had stat. sig. difference of means: FCORR, REYRECAL, PAIRED1, PAIRED2, BOSTON, CVLT, CDRSUM. It was found for different groups of subjects: normal (N), mixture of normal MCI, and AD (G Model), and AD (AD Model).

3.2 Rules from General Model (G Model)

We have placed G Model data in the following information table (Table 1):

Table 1. Part of the decision table for Model1 subjects

P#	age	Lgm1A	Lgm2A	TrailA	TrailB	DSST	Fcorr	Reyrcl	APOE	…	CDRSUM
67643	74	9	8	40	208	35	14	18	1	…	0.5
70407	88	8	5	66	150	21	21	10	0	…	4.5
102541	71	15	25	25	202	52	17	23.5	0	…	1
119156	92	7	34	34	386	40	20	10.5	0	…	3.5
139134	81	6	51	51	60	49	13	6	1	…	2.5
142376	76	18	54	54	50	19	14	12	0	…	0

The complete Table 1 has 150 rows, and 15 columns, there are shown the following condition attributes: P# - number given to each patients, age –age of subject, Lgm1A -Logical Memory Immediate, Lgm2A - Logical Memory Delayed, TrailA -Trail Making Part A, TrailB -Trail Making Part B, DSST - Digit Symbol Substitution Test, Fcorr -Verbal Fluency Letter F, TrailA and TrailB are growing from N to AD, DSST is decreasing from N to AD in a similar way as Fcorr (FCORR). Reyrcl - Rey Figure Recall, APOE

- *ApoE* genotype, … CDRSUM -sum of boxes- index of the Clinical Dementia Rating. We have used RSES 2.2 for G Model group discretization with the global cuts (RSES 2.2) [13]. There were the following 3 ranges of the decision attribute CDRSUM: "(-Inf, 0.75)", "(0.75, 1.25)", "(1.25, Inf)". We had obtained 2581 rules using the exhaustive algorithm for G Model subjects. There are two rules below:

(FCORR="(-Inf,10.5)")&(REYRECAL="(-Inf,15.75)")&(APOE=1) => (CDRSUM = "(1.25,Inf)"[7]) 7 (1)

(LOGMEM1A="(16.0,20.5)")&(BOSTON="(-Inf,26.5)")&(age="(73.5,86.5)") =>(CDRSUM="(0.75,1.25)"[5]) 5 (2)

We read above equations (Eq. 1) as following: it fulfils 7 cases that if FCORR is below 10.5 and REYRECAL is below 15.75 and APOE is 1 then CDRSUM is above 1.25 that means questionable impairment. Equation 2 is for CDRSUM between 0.77 and 1.25 and is based on not very good Boston naming (BOSTON) results.

By rules obtained from the G Model we have predicted the CDRSUM of each subject the N Group. There were 21 normal (with CDRSUM = 0) subjects.

Table 2. Confusion matrix for CDRSUM of N Group by rules obtained from G Model by local cuts [11].

Predicted				
Actual	"(-Inf, 0.75)	"(1.25, Inf)"	"(0.75, 1.25)"	ACC
"(-Inf, 0.75)"	17.0	2.0	2.0	0.81
"(1.25, Inf)"	0.0	0.0	0.0	0.0
"(0.75, 1.25)"	0.0	0.0	0.0	0.0
TPR	1.0	0.0	0.0	

TPR: True positive rates for decision classes; ACC: Accuracy for decision classes: the global coverage was 1.0 and the global accuracy was 0.81, the coverage for decision classes was 1.0, 0.0, 0.0.

We were interested in those normal subjects who had predicted values of the CDRSUM > 0. It Table 2 states that 17 are normal, there were two subjects with predicted values of CDRSUM = (0.75, 1.25), and two others with CDRSUM > 1.25. All four might have cognitive impairments.

In Table 3 we have also used RSES 2.2 for G Model group discretization by the *global cuts* [11]. There were the following 3 ranges of the decision attribute CDRSUM: "(-Inf, 0.75)", "(0.75, 2.25)", "(2.25, Inf)". We have obtained 324 rules with the genetic algorithm for G Model subjects.

Table 3. Confusion matrix for CDRSUM of N Group by rules obtained from G Model by the *global cuts* [11]. Predicted.

Actual	"(-Inf, 0.75)"	"(2.25, Inf)"	"(0.75, 2.25)"	ACC
"(-Inf, 0.75)"	15.0	2.0	4.0	0.71
"(2.25, Inf)"	0.0	0.0	0.0	0.0
"(0.75, 2.25)"	0.0	0.0	0.0	0.0
TPR	1.0	0.0	0.0	

TPR: True positive rates for decision classes; ACC: Accuracy for decision classes: the global coverage was 1.0 and the global accuracy was 0.714, the coverage for decision classes was 1.0, 0.0, 0.0.

We were interested in those normal subjects who had predicted values of the CDRSUM > 0. From Table 3 there were four subjects with CDRSUM = (0.75, 2.25) that with values between (0.5–2.5) might have a questionable impairment [9], and two subjects with CDRSUM = (2.25, Inf)): *401297* and *164087* that means that they might have a very mild dementia or mild dementia [7] as below in Eqs. 3 and 4.

(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)"

(3)

The first patient *(Pat = 401297)* as states in Eq. 3 has the low *FCORR* (below 16.5) and *REYRECAL* (below 15.75) values, as well as bad APOE genotype that mainly caused his CDRSUM above 2.25. That might suggest very mild dementia.

By using rules from the AD Model group, we have also found that *(Pat = 164087)* has even larger CDRSUM that is related to the execution function timing (long *TrailB*), and the low *FCORR* and *PAIRD2* values (Eq. 4).

(Pat=164087)&(LOGMEM1A="(14.5,15.5)")&LOGMEM2A="(7.0,Inf)")&(TrailB "(74.5,153.0)")&(FCOR="(-Inf,12.5)")&(REYRECAL="(-Inf,21.5)")&(PAIRD2= "(-Inf,6.5)")&((BOSTON="(25.5,Inf)=>(CDRSUM="("(4.5,7.0)"

(4)

As CDRSUM of *(Pat = 164087)* was predicted above as to be higher than 4.5 it means that this patient's cognitive results suggested that he might have mild dementia.

4 Discussion

Alzheimer's disease has long prodromal phase, with neurodegeneration beginning decades before symptoms onset (first clinical manifestation). This creates a challenge to the development of therapeutics since it is much more difficult to reverse the disease process and recover normal neuronal function without the ability to detect changes earlier.

Brain plasticity may partially explain why individuals can have no or minimal symptoms despite several decades of extensive neurodegeneration. During this long period, individual compensatory processes may develop differently between subjects. In this study, we aim to detect the beginning of compensatory changes reflective of underlying neurodegeneration in those developing dementia. We have developed novel tool to more easily and accuracy monitor ongoing progression by looking into patterns of cognitive attributes' values and comparing them with our Models (general and AD).

We have applied rough set theory and its rules as the granular computing to estimate a possible disease progression in normal subjects from the BIOCARD study. We used the intelligent granular computing with the rough set rules to investigates tests results set as granules for individual patients. To estimate their properties, we need to have a Model that has the meaning and tells us what the importance of the pattern (granule) is. In fact, our granules are complex (c-granules) as they are changing their properties with time of the neurodegeneration development till become like granules of the patients with dementia or PD [12]. In this work, we have limited our test to the static granules (in one time moment) and we have tried to estimate what is the meaning of a particular, individual granule. We have used two models: G Model (general model) have granules related to normal subjects, MCI and AD patients. On its basis we have obtained a large set of rules that have represented subjects' different stages of the disease from the 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 and estimated what 'normal' means. Also, rules can be created with different granularity and algorithms that might give different classifications.

Therefore, we were looking for classifications that are universal e.g., they give similar results with different sets of rules. G Model has given us rules that are subtle and determine the beginning of possible symptoms. In the next step, we have used a model based on the more advanced patients in the progression of the disease– AD Model that gave rules based on AD patients. We got higher values of the CRDSUM that gave us only classifications of the possibly subjects with the mild dementia. Looking into different rules, some of them is easy to interpret, but other patients' granules look relatively normal. As our rules are applied to different subjects there are not certain, and we have confirmed our classifications by using different set of rules with different granularity and algorithms that may give different consistent or inconsistent classifications. Therefore, they are only indications for the clinician to test certain patients more carefully as they might already have some unnoticed dementia related symptoms.

5 Conclusions

Our main assumption was to have a universal *dementia related Model* that represents expertise of the clinical doctors: neurologists and neuropsychologists. We have used the supervised learning to get granules that connect patterns of 13 cognitive tests with the clinical symptoms measured as the CDRSUM (quantitative measure related to different dementia stages [7]). In our population there are 42 patients with dementia (two of them did not have cognitive tests), therefore, in our Model we have used 40 AD, 40 normal subjects, and we found 70 MCI that have consistent symptom.

We have concentrated on the predictions of the conversion from normal to prodromal AD of the individual subjects in contrast to the population of patients as in many of the studies e.g., [2–5]. We have applied rules form our Model to the cognitive test results of each patient with the purpose to find similarities indicating dementia. We have obtained some consistent results, but the core of our model (AD patients) is relatively small (40 patients) that does not give power (number of rules) to cover many individual cases, and therefore gives us, in part inconsistent classifications. However, classifying individual subjects for the prodromal stage of AD seems encouraging.

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