A Tool to Aid in the Neuropsychological Diagnosis of Alzheimer's Disease

Ana Karoline Araújo de Castro, Plácido Rogério Pinheiro, and Mirian Calíope Dantas Pinheiro
Graduate Program in Applied Computer Sciences, University of Fortaleza, Fortaleza, Ceará, Brazil

Abstract - A hybrid model, combining influence diagrams and a multicriteria method, is presented in order to assist with the decision making about which questions would be more attractive to the definition of the diagnosis of Alzheimer's disease, considering the stages of CDR (Clinical Dementia Rating). Due to the increase in life expectancy there is higher incidence of dementias. Alzheimer’s disease is the most common dementia, accounting for 50% of the cases. Because of this and due to limitations in treatment at late stages of the disease early diagnosis is fundamental because it improves quality of life for patients and their families. The modeling and evaluation processes were carried out through a battery of standardized assessments for the evaluation of cases with Alzheimer’s disease developed by Consortium to Establish a Registry for Alzheimer’s disease (CERAD).

Keywords: Alzheimer’s disease, Diagnosis, Multicriteria Method, Bayesian Network, Influence Diagram

1 Introduction

With the advance of sciences applied to the health area in the last few years, there has been a considerable increase in the life expectancy of the population. Such fact can be stated based on demographic studies in developed and developing countries, which have showed a progressive and significant increase in the elderly population in the last years [1]. Along with this fact, a major increase in the number of health problems among the elderly can be noticed. These problems, besides being long-duration problems, require skilled personnel, a multidisciplinary team, equipment and additional high-cost tests.

The Alzheimer’s disease is the most frequent cause of dementia and is responsible (alone or in association with other diseases) for 50% of the cases in western countries [1][2][3].

The main focus of this work is to develop a hybrid model, combining influence diagrams and multicriteria methods, for aiding on the establishment of which questions are the most attractive, considering the stages of CDR (Clinical Dementia Rating), in decision making of the diagnosis of Alzheimer’s disease. The information needed to do this was based on the data collected from a battery of tests.

It is known that multicriteria methodologies help to generate knowledge about the decision context, thus, increasing the confidence of those who make decisions on the results. This way, the judgment matrixes are constructed to obtain cardinal value scales which are implemented through the MACBETH Multicriteria Methodology. The influence diagram is implemented using the GeNie tool.

It was never thought of applying multicriteria methods in the health area, especially with the aim of assisting in the diagnosis of the Alzheimer’s disease. The first model developed [4] was validated using small study cases presented on other papers [7]. Then, a model [6] [7] validated with a Brazilian battery [8], which was based on study cases of University of São Paulo, was presented.

The model was extended later [10] and was validated by the data provided on the battery of CERAD [2]. This last model was based on three previous papers developed [10] [11].

Nowadays, there are also other works that apply multicriteria in the health area [12] [13] [14] [15] [16].

The battery of tests used in this work is from the Consortium to Establish a Registry for Alzheimer’s disease (CERAD). It was necessary to construct value scales originating from semantic judgments of value with the aim of defining a ranking representing the classification of the questions impact considering to the stages of the CDR.

Therefore, the paper is structured as follows: Section 2 gives a brief view of how the diagnosis of the Alzheimer’s disease is performed; Section 3 gives an overview of the CERAD (its history, proposals, and structure), which provided the battery of tests being used in this paper; Section 4 presents a step-by-step of the model structuring; and, finally, conclusions and futures works are shown in Section 5.

2 Diagnosis of the Alzheimer’s Disease

The diagnosis of the Alzheimer’s disease can be established based on several steps [3] [18]. This way, with the decline of the normal functioning over the nervous and other bodily systems, and with the natural behavioral and personality changes, the identification of what constitutes abnormal impairment becomes a hard task.
This study aims to help deciding which the best manner to reach a diagnosis is. To do this, we sought to choose the most important questions to the diagnosis of the Alzheimer’s disease, using a battery of tests from CERAD. This battery was chosen because it encompasses all the steps of the diagnosis and it has been used all over the world.

Therefore, the questions selected through this decision making process will be applied preferentially, because, in accordance to the decision maker, these questions play a main role in the diagnosis.

3 CERAD - An Overview

The original mandate of the CERAD in 1986 was to develop a battery of standardized assessments for the evaluation of cases with Alzheimer’s disease who were enrolled in NIA-sponsored Alzheimer’s Disease Centers (ADCs) or in other dementia research programs. Despite the growing interest in clinical investigations of this illness at that time, uniform guidelines were lacking as to diagnostic criteria, testing procedures, and staging of severity.

CERAD developed the following standardized instruments to assess the various manifestations of Alzheimer’s disease [2]: Clinical Neuropsychology[20], Neuropathology, Behavior Rating Scale for Dementia, Family History Interviews and Assessment of Service Needs.

4 Construction of the Model

4.1 Definition of Problem

In the present study, we sought to validate the model considering the identification of issues that have greater impact on each stage of the Clinical Dementia Rating (CDR). The diagnosis of the Alzheimer’s disease will be held by the combination of the neuropsychological tests battery of CERAD based on the functional scale CDR [5].

We selected six of the eight tests of the neuropsychological battery of CERAD for the application of the decision support model that will assess which issues (among all the issues that are implemented in selected tests) have the greatest attractiveness on each stage of CDR, for the definition of the diagnosis of the Alzheimer’s disease. The tests selected are: Verbal Fluency (J1), Boston Naming Test (J2), Word List Memory (J4), Constructional Praxis (J5), Word List Recall (J6) and Word List Recognition (J7) [20].

The CDR was chosen to be a tool that allows the classification of the prevalence of the various degrees of dementia based on six cognitive-behavioral categories: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care [5].

Furthermore, the CDR identifies the questionable cases, or those that are not classified as normal subjects. These cases may correspond to the so-called cognitive decline associated with aging, to the mild cognitive impairment, or to other epidemiological studies that are part of the group that has a higher rate of conversion to dementia.

Despite being represented only five stages of dementia on the CDR: none, questionable, mild, moderate and severe; the CERAD implemented a change in the scale including two stages: profound and terminal. For the application of the model, it will be taken into account the scale of the CDR modified by CERAD [17].

Next, the application of the decision model will be presented to solve the problem of choosing the questions that are considered to be the most attractive in the definition of the neuropsychological diagnosis of the Alzheimer’s disease.

4.2 Phase 1: Structuring – Identification and Organization of the Evaluation Elements

4.2.1 Step 1: Identify the decision makers

The individuals classified as cases in the database of CERAD were defined as the decision makers (actors) involved in the process of building the model to the definition of the issues of greatest impact in the neuropsychological diagnosis of AD. This decision was taken considering that the degree of dementia was defined based on the values (responses) obtained on the patients tests.

Analyzing the data pertaining to the cases through the database of CERAD was found a negligible quantity of actors to evaluate the attractiveness of the model in multicriteria. The degrees of dementia: none, profound and terminal, are the answers 0, 1 and 2 respectively, i.e. between the cases that have been assessed with dementia-type: none, profound and terminal, only 0, 1 and 2 people respectively, answered each of the issues of the CERAD battery. Therefore, these degrees of dementia have not been evaluated on the model.

4.2.2 Step 2: Identify the alternatives and the criteria relevant to the decision issue: Definition of the hierarchical structure of the problem

This step involves the identification of the variables of interest and the determination of the interrelationship between them. The variables can be classified as: objectives, decision problem, actions, criteria, restrictions and factors, as shown in Table 1.

The end result of this step is the definition of the problem’s hierarchical structure by creating a graphic model represented by a Directed Acyclic Graph (DAG), as shown in Fig. 1.

It was identified 23 nodes of probability, including one decision node and seven utility nodes [28].
Once the network structure is defined, it is necessary to calculate the probabilities in the form of Conditional Probability Table (CTP) for each chance node of the network, based on the data obtained from the database of the CERAD.

Table 1. Classification of the variables of the decision problem

<table>
<thead>
<tr>
<th>Problem: Definition of the issues of greatest impact on each stage of the CDR in the neuropsychological diagnosis of the Alzheimer's disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objectives</strong></td>
</tr>
<tr>
<td><strong>The set of the possible actions</strong></td>
</tr>
<tr>
<td><strong>Criteria</strong></td>
</tr>
<tr>
<td><strong>Restrictions (properties of criteria that are specified as desirable)</strong></td>
</tr>
<tr>
<td>- CDR_QUESTIONABLE &gt; 0 and CDR_QUESTIONABLE ≤ 0.5;</td>
</tr>
<tr>
<td>- CDR_MILD &gt; 0.5 and CDR_MILD ≤ 1;</td>
</tr>
<tr>
<td>- CDR_MODERATE &gt; 1 and CDR_MODERATE ≤ 2;</td>
</tr>
<tr>
<td>- CDR_SEVERE &gt; 2 and CDR_SEVERE ≤ 3</td>
</tr>
</tbody>
</table>

Fig. 1. Hierarchical structure of the decision problem to stage the CDR questionable

For the definition of the most attractive issues, it is necessary to examine the level of impact (or attraction) of the actors’ responses in each of the stages of the CDR. This initial assessment is important because one can discover, based on the responses of a particular actor on the database of the CERAD, which is his/her stage of CDR.

The attractiveness of the responses is measured by means of judgments matrixes of value and the scales of global value for each question can be obtained. Table 2 shows the values of each level of impact for all Fundamental Point of Views (FPV) in relation to FV15.

With this result, it is possible to apply the model in order to define the attractiveness of the issues involved in the neuropsychological battery of CERAD for each stage of the CDR.
4.2.3  **Step 3: Definition of descriptors**

The construction of descriptors should be made for each fundamental point of view of the problem. Thus, for this problem, two sets of descriptors have been identified considering the three phases: (i) description of each descriptor for each of the fundamental points of view (FPVs), (ii) obtainment of the impacts levels according to each key point of view, and (iii) analysis of the impacts according to each fundamental point of view.

The number of states of each FPV will always be equivalent. It was defined 16 descriptors for each FPV.

The states of FPVs are not equivalent; therefore, they cannot be the representation of more than one state at a single level of impact. Table 3 shows the descriptors for the FPV1. The levels of impact of each descriptor were ordered based on each issue that was relevant for the definition of each stage of the CDR, as regards the issue that has the greatest influence in defining the diagnosis of AD. This relevance was defined based on the sum of the results obtained in the judgment matrixes of decision in the application of the model on the answers of the questions.

4.2.4  **Step 4: Perform the analysis of impacts**

This step is related to the definition of the impact assessment according to each FPV. We defined the upper and lower values of each impact and the relevant aspects of the distribution of impacts in each of them. For all FPVs of this model, the scoring was attributed to the degree of dementia in accordance with each stage of the CDR which is being evaluated.

Table 4 presents the descriptors and their lower and higher values to be considered for obtaining the basis of value for each FPV.

<table>
<thead>
<tr>
<th>Alternatives</th>
<th>FPV1 – Questionable</th>
<th>FPV2 – Mild</th>
<th>FPV3 – Moderate</th>
<th>FPV4 – Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>FV15_99</td>
<td>0.50</td>
<td>1.00</td>
<td>2.00</td>
<td>3.00</td>
</tr>
<tr>
<td>FV15_0</td>
<td>0.46</td>
<td>0.96</td>
<td>1.92</td>
<td>2.92</td>
</tr>
<tr>
<td>FV15_1</td>
<td>0.42</td>
<td>0.92</td>
<td>1.84</td>
<td>2.84</td>
</tr>
<tr>
<td>FV15_2</td>
<td>0.38</td>
<td>0.88</td>
<td>1.75</td>
<td>2.75</td>
</tr>
<tr>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>FV15_9</td>
<td>0.08</td>
<td>0.59</td>
<td>1.18</td>
<td>2.17</td>
</tr>
<tr>
<td>FV15_10</td>
<td>0.04</td>
<td>0.55</td>
<td>1.09</td>
<td>2.09</td>
</tr>
<tr>
<td>FV15_11</td>
<td>0.00</td>
<td>0.51</td>
<td>1.01</td>
<td>2.01</td>
</tr>
</tbody>
</table>

Table 2. Values of each level of impact for each FPV in relation to FV15

<table>
<thead>
<tr>
<th>NI</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>N16</td>
<td>FV15: I want you to tell me all the animals you can think (from 0-15 seconds)</td>
</tr>
<tr>
<td>N15</td>
<td>MP2: Repeat a list of ten words - attempt 2</td>
</tr>
<tr>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>N02</td>
<td>EP: Recall a list of ten words</td>
</tr>
<tr>
<td>N01</td>
<td>PC1: Draw circle</td>
</tr>
</tbody>
</table>

Table 3. Classification of variables in the decision problem
4.3 Phase 2: Evaluation – Construction of a Quantitative Model of Values

4.3.1 Step 5: Definition of a function of value for each alternative

This function was obtained by the division of the sum of the results obtained through the judgment matrixes in relation to the responses to a question, by the sum of the results obtained through the judgment matrixes in relation to the issue or set of issues that are part of a subtest of the neuropsychological battery of CERAD, considering a determined stage of the CDR.

\[
\phi(\beta) = \frac{1}{\sum_{i=1}^{n} \beta_i}
\]

where: \( a \in A \) (represents all the alternatives - issues), i.e. \( A = \{a_i, a_{i-1}, ..., a_1\} \); \( b \in B \) (represents the subtest), i.e. \( B = \{b_j, b_{j-1}, ..., b_n\} \).

4.4 Phase 4: Evaluation – Evaluation of the alternatives

4.4.1 Step 6: Construction of the judgment matrixes

In this step, the following steps were performed: (i) the construction of the judgments matrixes based on the differences of attractiveness for each pair of alternatives; and (ii) the obtainment of the cardinal value scales for each fundamental point of view defined.

For the issues evaluation, all the FPVs were worked through a descriptor with 16 reference levels, and a lower limit (which was generated from the lower value, the sum obtained regarding the outcome of the evaluation of the issues), an upper limit (which was generated from the higher value, the sum obtained regarding the outcome of the evaluation of the issues) and 14 intermediate levels of reference. Fig. 2 shows a matrix of assessment of value and scale of cardinal value obtained with the methodology for the FPV1 MACBETH - CDR: Questionable [22].

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Table 4. Summary table of descriptors and impacts according to each FPV

<table>
<thead>
<tr>
<th>FPV</th>
<th>Descriptor</th>
<th>Upper Level</th>
<th>Lower Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPV1 – CDR: Questionable</td>
<td>Answers a question from the battery of neuropsychological of CERAD</td>
<td>0.51</td>
<td>1</td>
</tr>
<tr>
<td>FPV2 – CDR: Mild</td>
<td>Answers a question from the battery of neuropsychological of CERAD</td>
<td>1.01</td>
<td>2</td>
</tr>
<tr>
<td>FPV3 – CDR: Moderate</td>
<td>Answers a question from the battery of neuropsychological of CERAD</td>
<td>2.01</td>
<td>3</td>
</tr>
</tbody>
</table>

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Fig. 2. Matrix of judgment of value and scale for the FPV1 - CDR: Questionable
Following the procedure for construction of judgments matrices of value and obtain the scales of global value for each of the FPV.

The result of the judgment matrixes shows that the stage of the CDR was questionable that most benefited from the implementation of the model. CDR: questionable obtained the highest value in relation to other criteria, and through the accumulated weights for each option, with the CDR: questionable accumulating 50% of the total weight of the criteria.

This result is very positive, because one of the major goals of medicine in the search for a diagnosis, especially that of Alzheimer's disease, is get it in earlier stages of the disease.

5 Conclusion

There is a major importance nowadays on identifying the cases in which the risks of developing the Alzheimer’s disease are higher. As factors that contribute to this fact, we can say that currently there are few alternative therapies to the pathology treatment, and that the effectiveness of treatments is greater when the early diagnosis is possible [17].

Besides, according to studies conducted by the Alzheimer’s Association [23], the Alzheimer’s disease treatments have significant resulting costs, and it is known that it is one of the costliest diseases, second only to cancer and cardiovascular diseases.

The diagnosis of Alzheimer’s disease can be established based on several steps. The first step is to verify if the patient has any kind of dementia, and then the patient is assessed in order to discover if s/he has the Alzheimer’s disease.

The results of this study were obtained by the model developed through the application of methodologies such as Influence Diagrams and Multiple Criteria Decision Aid. These results reaffirm the importance of the tool to support the physicians’ decision on giving the diagnosis of the Alzheimer's disease and the like, considering that it enables the accurate and the differential diagnosis.

This way, a cost optimization and a reduction of the time a patient would spent without treatment (which could happen because s/he was not early diagnosed) can be provided, delaying the loss of cognitive and psychomotor abilities caused either by the disease, or other dementias.

The methodologies applied have been crucial to the analysis of the most attractive questions to the definition of the diagnosis of the Alzheimer's disease. The methodological design of the model mapped the possibilities regarding the performance results for the decision.

The model presented, which applies structured assumptions in decision-making problems, provided important impacts for the research and it was supported by the chain of neuropsychological responses to identify the diagnostic criteria.

The structure of the model applies the influence diagram, which enabled the triangulation of data for areas of cognition and functionality or praxis, based on the CERAD neuropsychological battery.

This data interface makes room for perspectives for modeling on many different areas of knowledge, whether in health, computer science, education, or others.

Therefore, the application of the influence diagrams in academic models through scientific research, aiming the costs optimization, is extremely appropriate, opening up possibilities for future studies.

6 Future Works

As a proposal for improvement and extension of the work, we intend to extend the model, considering the process of recommendation, so that a further analysis of the results of the model is included, such as the analysis of sensitivity and robustness.

We also intend to implement a new analysis of the model through the inclusion of values in the utility node of the influence diagram. This way, it will be possible to make inferences on the network aiming the definition of the diagnosis by the application of only the most attractive questions.

Then, an application of the model on the complete neuropsychological battery of tests of CERAD is aimed. Or even the inclusion of the forms: Mini-Mental State Examination (Mini-Mental State Examination) and Recall of Praxis (Praxis Evocation); on the set of evaluated forms.

7 Acknowledgements

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8 References


