Technische Universität München

Fakultät für Informatik

etsinf

FINAL PROJECT

ORDERING PET SCANS: CRITERION AND VISUALIZATION

DEGREE: Computer Engineering

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I declare that I have published this thesis independently and only the sources and methods used are specified.

29. March 2012 _____

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Abstract

Neurodegenerative diseases describe a set of diseases caused by abnormalities while certain proteins are processed. These proteins accumulate in the nerve tissue and produce clinical manifestations. The main manifestation is Dementia. The most common type of dementia is Alzheimer's disease, which affects 50-80% of the population [1]. Currently, this type of dementia is considered incurable and irreversible. For this reason, it is important to know all the information about this disease, so the more information we have, the better solution we can find and maybe with the passage of the time this disease can be curable and reversible.

The technique PET can detect this type of diseases during the patient's life. Furthermore, by means of this technique it has been observed that these diseases have several kinds of patterns according to the brain metabolism degradation. Normally, when a brain is affected by this kind of disease, the brain metabolism degradation begins in a specific area of the brain, but as the disease progresses this area can get bigger or affect other areas of the brain.

The goal of this thesis is to analyze a set of PET scans from several people who have some kind of neurodegenerative disease, such as, Mild Cognitive Impairment (MCI) and Alzheimer's Disease (AD). This analysis will allow us to obtain an order among the PET scans according to the affected areas in the brain, and will show the brain metabolism degradation in the development of Alzheimer's disease. This order will be represented by an acyclic directed graph (ADG) that it will be visualized in an application. This application will get the set of PET scans and it will obtain the corresponding graph which will show the order of PET scans. Furthermore, in each node we will display complementary information about each PET scan.

This application, it will not be used only by computer experts but also by unskilled users, in future studies about neurodegenerative diseases, in particular, about Alzheimer's disease.

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Chapter 1

Introduction

The neurodegenerative diseases constitute a set of diseases which manifest an inadequate process of certain proteins that appears in each cellular circuit.

Using the technique PET it has been observed that this type of diseases have different kinds of patterns according to the brain metabolism degradation. In a brain affected by this kind of diseases it has been analyzed that the metabolism degradation begins at a specific region of the brain. As far as the disease progresses this region of the brain can get bigger or affect other regions in the brain.

To analyze how the metabolism develops in a brain affected by this kind of diseases it is an important task and at the same time difficult. However, it can provide a lot of information about these diseases. The more information it knows about diseases evolution the better, so with all this, its early detection can be achieved. Moreover, it will avoid its progress and all this will help that these can be curable and reversible someday. Nowadays, some of them are still incurable and irreversible.

The main goal of this thesis is to create an ordering on PET scans to decide for two scans, whether the brain metabolism degradation of one PET scan, is a progression of the other. This ordering will be then applied to arrange a set of PET scans which have Mild Cognitive Impairment (MCI) and Alzheimer's Disease (AD). This order will show how the brain metabolism degradation progresses for this kind of diseases. As a last step, to visualize this ordering an application will be implemented. This application will show the ordering of a given set of PET scans in a directed acyclic graph (DAG). Furthermore, it will also visualize additional information in each node of the graph about each PET scan.

The application will have a friendly interface which allows people perform studies about neurodegenerative diseases; in particular, studies which are focused in analyze how the brain metabolism degradation progresses by some specific disease. Moreover, its design will offer facility to computers experts and even unskilled users will be able to use it.

Once the study that is going to be performed in this project has been introduced, we will detail the parts which make up this work: Chapter 2 will define the neurodegenerative diseases and will explain the dementia with detail. Chapter 3 will introduce information about PET technique which was used to obtain the analyzed images. Chapter 4 will deal with the typical psychological tests performed in this kind of studies. Chapter 5 will describe the set of images which we will use to make our study. All the process followed to obtain the ordering of PET scans and how this order has been visualized are shown and detailed in Chapter 6. The

performed experiments and the results to evaluate the corresponding graph are presented in Chapter 7. And finally, in Chapter 8 the conclusions about all the research done will be written.

Chapter 2

Neurodegenerative Diseases

Bioinformatics is a research area which applies the information technology to the science of life. This thesis, as a project of Bioinformatics and Medical image, will perform a study about dementia progress from medical images which have Mild Cognitive Impairment (MCI) and Alzheimer's Disease (AD) by using computationally powerful techniques.

To better understand these terms and obtain the necessary knowledge to perform this study, this chapter will provide a short description about neurodegenerative diseases and, with more detail, about dementia. It will explain causes and symptoms of dementia. Moreover, a classification about types of dementia will be also described. In this point, AD and MCI will be more detailed because these are the two types of diseases which will be analyzed in this project.

2.1 Definition

Neurodegenerative diseases are a set of diseases that are caused by an inadequate protein processing in cells. These proteins accumulate in the nerve tissue inside and outside of neurons causing the bad functioning of neurons and their posterior death because they lose their connections with other neurons [2].

These kinds of diseases are chronic and they steadily progress. These diseases are characterized by being a selective and symmetric loss of neurons in the sensory motor and cognitive systems. Although dementia is the main symptom of these diseases, it must not confuse with the normal ageing process because in the normal ageing process the loss of neurons is lower.

Although not all neurodegenerative diseases cause dementia, this is considered the most common manifestation of this type of diseases.

2.2 Dementia

Dementia is not a specific disease but a descriptive term about collection of symptoms which produce a progressive loss of cognitive functions due to brain damage and disorders [3]. These symptoms can coexist with disorders of emotional control, social conduct and motivation.

Dementia usually affects the parts of the brain which control memory, language, reasoning and orientation (Figure 1).

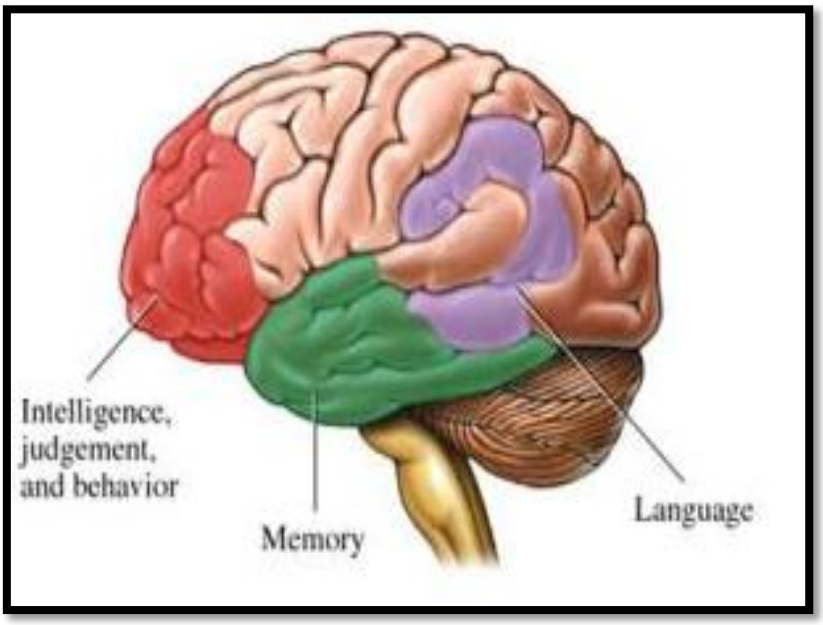


Figure 1: The parts of the brain which are affected by dementia.

2.2.1 Cause

Some demographic factors, such as, age, sex, genetic predisposition, previous cerebral traumatisms, and the education level can increase the risk of dementia development. Nevertheless, the main causes of dementia are usually a set of neurodegenerative diseases; the clearest example is Alzheimer's disease (AD) [4].

These diseases are classified in degenerative and vascular diseases according to the effect in the impairment of cognitive process [5]. If the impairment is irreversible in the cognitive process, then dementia is caused by a degenerative disease. Although the clearest example is AD, there are others diseases which can also cause dementia, such as, Parkinson's disease, Huntington's chorea and frontotemporal dementia or Pick's disease [3].

On the other hand, if the impairment is caused by small strokes then dementia has a vascular cause. Though the brain damages are generally considered irreversible, patients could receive some medical treatment to avoid future strokes. As the mild cognitive impairment is a transitory state, its posterior evolution will determine if it is considered as a cause of dementia or not.

2.2.2 Symptoms

The dementia supposes the irreversible loss of intellectual capacities which include: memory, ability to express and communicate adequately, ability to organize daily life and to have normal life with autonomy. For this reason, in this point we will see how the progress of dementia affects these capacities.

The first capacity affected by dementia is memory. So, the first symptom is the forgetfulness.

As stated before in point 2.2.1, the mild cognitive deterioration is a transitional state between the normal ageing and the development of dementia [6]. Although it does not always progress into a dementia state, in the case of doing so, its first symptoms will be minor problems with the thinking and memory capacities, but which do not interfere in the everyday life, and people suffering them are completely conscious of the forgetfulness they suffer [6].

In the early stages of dementia the symptoms begin to be visible. Patients ask the same question frequently, have personality and mood changes, misplace items and have some difficulty to find the name of familiar objects.

In the intermediate stages of dementia, the symptoms are more distinguished and interfere in their care. Among these symptoms, we emphasize the following: patients need help to dress, to bath, they have difficulty to do basic tasks, such as, cooking, reading and writing, and they forget events in their life or details about recent events. In this stage, people can also have hallucinations and depressions.

In the severe stages of dementia, patients depend absolutely from third people to do the most basic tasks of everyday life. They do not usually know who they are and sometimes they cannot even recognize their familiar members.

Although there are a lot of symptoms which can be observed, in this point we have summarized them just showing the most typical symptoms in the development of dementia.

2.2.3 Classification

The dementia disorders can be classified on several ways. These classification schemes attempt to group disorders according to whether, they are progressive or not, or depending on the affected areas of the brain.

The most frequently used classification is the following [3]:

- The cortical dementia: is the dementia in which the brain damage mainly affects the cerebral cortex or exterior layer. This kind of dementia causes problems in memory, language, thinking and social conduct.

- The subcortical dementia: is the dementia which affects the parts of the brain which are under the cortex. This type of dementia causes memory problems, a part from changes in emotions and movement.

- The progressive dementia: this type of dementia makes worse over time and interferes in many cognitive functions.

- The primary dementia: this dementia is not a result of another disease; for example, Alzheimer's disease.

- The secondary dementia: this dementia occurs as a result of physical disease or lesion, such as, vascular dementia.

Some types of dementia can fit into more of one classification. This is the case of Alzheimer's disease, which is treated as primary, cortical and progressive dementia [3].

Then we see the MCI and AD more detailed, as well as, a short description about some of neurodegenerative diseases which also can cause dementia.

MILD COGNITIVE IMPAIRMENT

The Mild Cognitive Impairment (MCI) is a concept which describes a transitional state between the normal ageing and the development of dementia [6]. This term delimits a group of people who have a higher risk to develop dementia than that observed in the general population.

The first symptom of MCI is forgetfulness, but the patients are conscious of this oblivion, and therefore, their everyday life is not affected.

In the next figure, we can appreciate the brain metabolism degradation in the progress of dementia. So, on the left of figure 2, the PET scan shows normal levels of glucose metabolism, indicated in yellow and red. As we can observe in the others PET scans, the levels of glucose metabolism in the brain are decreases in patients with MCI (the PET scan in the middle of figure 2) and with AD (the PET scan on the right of figure 2).

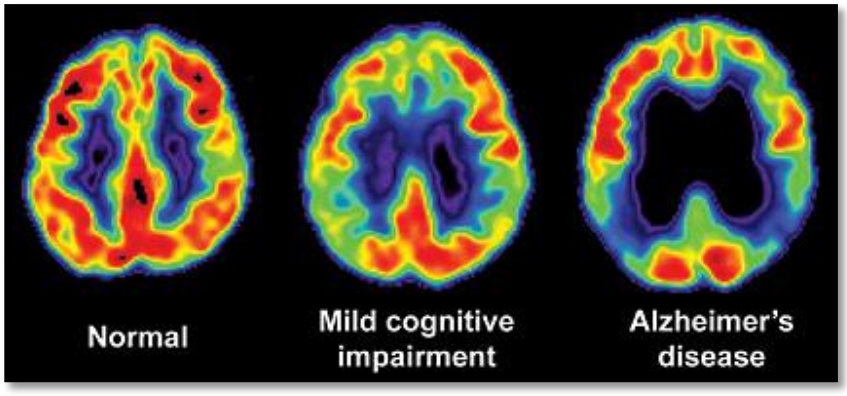


Figure 2: Comparing of levels of glucose metabolism with a Normal patient's brain (left), a Mild cognitive impairment patient's brain (middle) and Alzheimer's disease patient's brain (right).

We have to take into account that the MCI is not a previous stage of AD or others diseases which can cause dementia. This is a transitional stage which can develop some kind of disease, which at the same time can cause dementia, or balance itself and it does not manifest any posterior disease. Therefore, the MCI is only a stage which can increase the risk to suffer some type of dementia in people who suffer it, but its suffering does not implicate the development of dementia.

For this reason, we want to show in the next table a classification of several kinds of MCI, as well as, their associated alterations and possible associated disorders in the case the MCI evolves.

Typology MCI	Cognitive disorders	Related disorders
MCI amnesic	▪ mild memory alteration	▪ Alzheimer disease
MCI diffuse	▪ slight impairment of different cognitive domains	▪ Alzheimer disease ▪ Vascular dementia ▪ normal aging
MCI Focal non-amnestic	▪ Slight alteration of cognitive function different from memory	▪ Frontotemporal dementia ▪ Lewy body dementia ▪ Vascular dementia ▪ Primary progressive aphasia ▪ Parkinson disease ▪ Alzheimer disease

Table 1: Types of Mild cognitive impairment (MCI).

ALZHEIMER DISEASE

Alzheimer's disease (AD) is the most common cause of dementia in elderly people. One out of every ten people older than 65 and, almost half of people over 85, suffer from Alzheimer's disease. In most people the symptoms of this disease turn up soon after 60 ages old and its average expectancy is 10 years [3] but this can change because this depends on the severity of the disease when the diagnostic is done. Currently for this disease there is not any curative treatment.

Alzheimer's disease is a progressive, degenerative and irreversible disease which affects the brain cells and produces memory loss and other intellectual impediments. So, Alzheimer's disease can be defined as a situation which produces a functional inability in the social and working context, sometimes even affecting familiar.

This disease slowly attacks nerve cells in all parts of the brain, but especially in the hippocampus and the amygdala (at the bottom-left of figure 3), which are important parts of the limbic system that coordinate memory storage and recall, and the cerebral cortex (at the top-right of figure 3), the seat of higher-level thinking, memory and language [7].

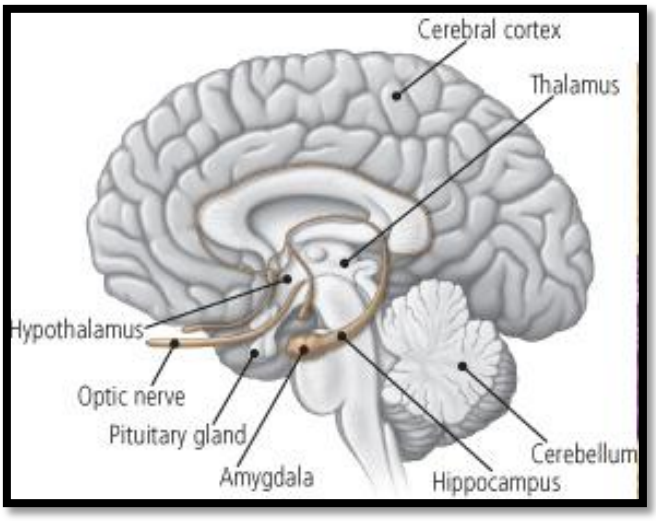


Figure 3: The parts of the brain which are affected in the development of Alzheimer's disease.

Even though, the alteration of the memory is the main feature to diagnose this disease, also the disease can affect other areas, such as, language, decision-making ability, judgment, attention, personality and other areas from mental function.

Alzheimer's disease is characterized by two abnormalities in the brain: the amyloid plaques and the neurofibrillary tangles. The amyloid plaques are agglomerations formed by beta amyloid protein, pieces of degenerated neurons and other cells. These plaques are located between of nerve cells. The neurofibrillary tangles are knots of twisted filaments which are inside the neurons. These tangles are almost entirely composed of a protein which is called tau [3].

In healthy neurons, the tau protein helps the microtubules functioning (on the left of figure 4). These microtubules form the cell's structure and distribute substances across the nerve cell. However, in Alzheimer's disease the tau protein is changed. This is twisted to form pairs of helical filaments which are grouped to form tangles. When this happens, the microtubules cannot function adequately and they disintegrate (on the right of figure 4). This failure in the transport system of the neuron can make difficult the communication between neurons and their posterior death [3].

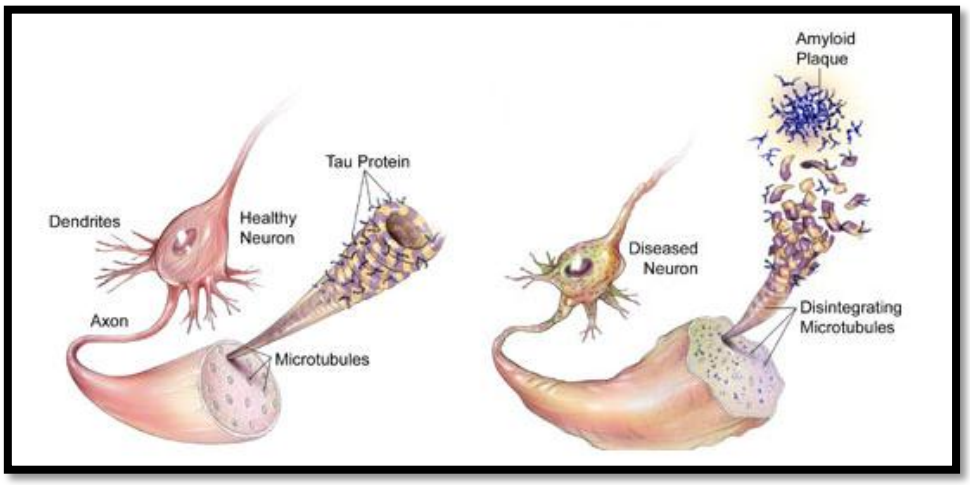


Figure 4: Comparing of normal neuron (left) and disease neuron (right).

In the development of Alzheimer's disease we can observe several stages which are characterized by a continuous and progressive deterioration of the brain (on the right part of figure 5).

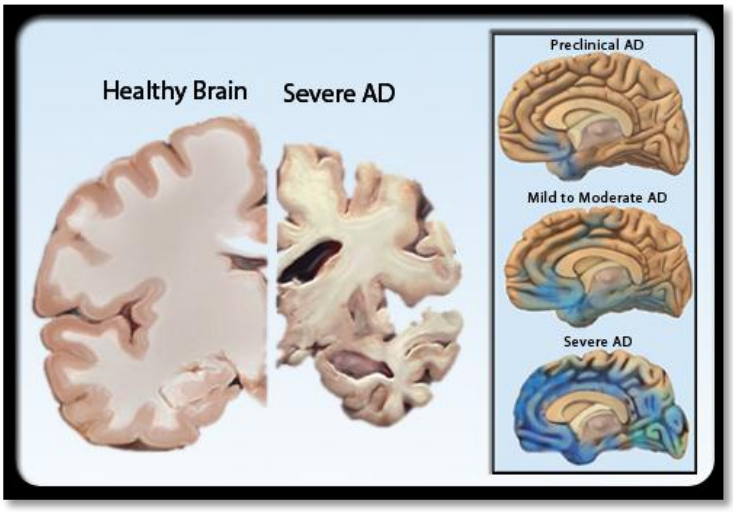


Figure 5: Comparing of Normal patient's brain and Alzheimer's patient's brain (left) and the parts of the brain which are affected in the development of Alzheimer's disease (right).

These stages are the following:

1. **Early stage or Phase 1 (at the top-right of figure 5)**

   This first stage is characterized by some loss of memory which can be mild enough but which can interfere in the daily life of the person with the

passing of time. Regarding behavior, patients have humor changes and even angers. In this stage, they do shorter sentences, mix ideas and have problems to find words but they still reason adequately.

2. **Intermediate stage or Phase 2 (at the center-right of figure 5)**

   In this stage the situation worsens. The recent memory decreases and the changes in behavior are more pronounced. Patients are more dependent than in the previous stage, they need help for self-care. The language is also affected and they begin to lose balance and have spontaneous downfalls.

3. **Advanced stage or Phase 3 (at the bottom-right of figure 5)**

   In the last stage, patients depend absolutely on third people. They need help to do the basic tasks, such as, eating, cleaning, moving, and cooking. The recent and remote memory begins to lose. Their behavior is like a little child and they babble. They have difficulty to swallow and do not control their gestures.

As we can see, Alzheimer's disease has a progressive and slow evolution with slight problems in the first stage, having severe brain damages in the last stages.

VASCULAR DEMENTIA

Vascular dementia, after Alzheimer's disease, is the second most common cause of dementia [8]. This is a secondary dementia because this is caused by chronic reduced blood flow to the brain, usually as the result of a stroke or series of strokes.

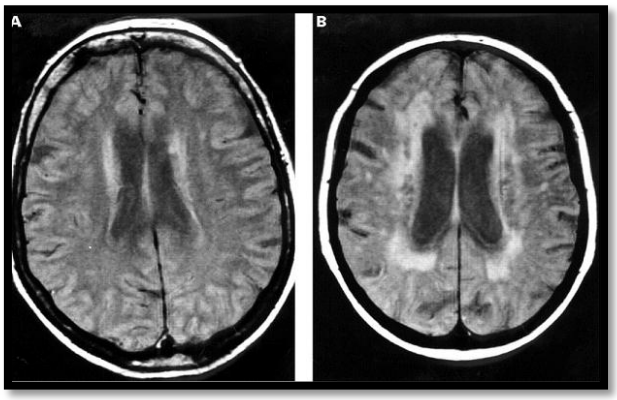


Figure 6: Comparing of Normal patient's brain (left) and Vascular dementia patient's brain (right).

This type of dementia refers to a subtle progressive decline in memory and cognitive functioning. It occurs when the blood supply carrying oxygen and nutrients to the brain is interrupted by a blocked or diseased vascular system (on the right of figure 6). In many cases, the vascular dementia can coexist with Alzheimer's disease.

The incidence to suffer vascular dementia increases in elderly people and it is similar in men and women. Currently, there is not known cure, but the use of practical strategies may help prevent strokes and slow its development [8].

FRONTOTEMPORAL DEMENTIA

The frontotemporal dementia or Pick's disease, describes a set of diseases characterized by a degeneration of nerve cells which are in the frontal and temporal lobes of the brain (Figure 7) [9].

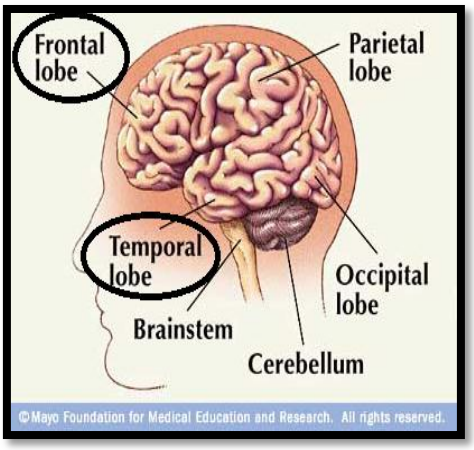


Figure 7: The parts of the brain which are affected by Frontotemporal dementia.

The people which suffer this type of dementia often have problems to maintain normal interactions with other people because this type of dementia affects the frontal and temporal lobes of the brain which control judgment and social behavior.

LEWY BODIES DEMENTIA

This is the second most common type of progressive dementia after Alzheimer's disease [10]. This type of dementia produces the death of cells which are in the cerebral cortex or outer layer, and are also in the black substance, which is located in the medium brain. Many of these nerve cells contain some abnormal structures which are called, Lewy bodies. These structures are abnormal microscopic protein deposits in the brain that disturb the brain's normal functioning causing it to slowly deteriorate. The effects include a degradation of cognitive functioning, similar to Alzheimer's disease, or a degradation of motor control, similar to Parkinson's disease [11].

SUBCORTICAL DEMENTIA

This type of dementia describes a set of dementias which affect the structures below the cortex (Figure 8). Among them we can include degenerative diseases of basal nuclei, such as, Huntington's disease, Parkinson's disease and Wilson disease [12].

Its disorders are characterized by abnormal movements which are often considered as a manifestation of the affection in the basal nuclei (Figure 8). In patients who suffer this type of disease, it is more common to see changes in personality, slowing down of thought processes and some alterations in memory, but language appears largely unaffected [12].

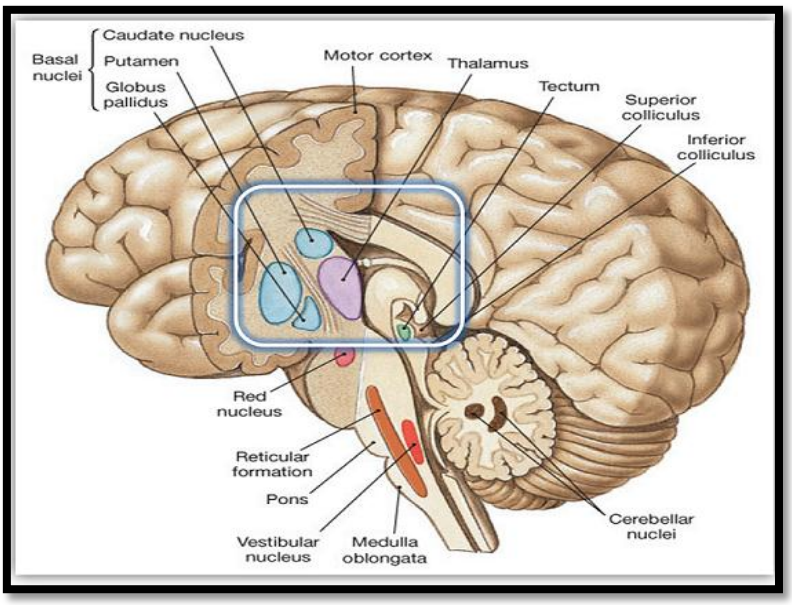


Figure 8: The parts of the brain which are affected by Subcortical dementia.

Chapter 3

Positron Emission Tomography

To achieve the aim of this project, that is to say, to analyze the brain metabolism degradation in the development of Alzheimer's disease, we will have to analyze images which show the brain metabolism. For this reason, in this chapter we will describe the best technique used to obtain this kind of images: The Positron Emission Technique (PET).

So, this chapter is divided in the following way: in the first section, an overview of this technique will be shown; and in the second section, the most common radioisotope and tracers which are used in this technique will be explained.

3.1 Description

Positron Emission Tomography (PET) is an imaging technique of nuclear medicine which provides information about the metabolism and the functioning of various biological systems. This technique is complementary to the morphological techniques (computed tomography (CT) or magnetic resonance (MR)) which offer a closer anatomical and structural detail [13].

Currently, the Positron Emission Tomography (PET) is a very interesting technique in the study of the brain metabolism in various diseases, such as, brain tumors, epilepsy and dementia.

The objective of this technique is to mark a biological molecule (tracer), the behavior of which it wants to follow, with a radioactive atom (radioisotope). This radioisotope is injected into the patient's blood and it goes to areas of the body where the tissue is damaged or is not working adequately. In this way, it is possible to study different biological processes depending on the tracer used [13]. The radiation produced by these radioisotopes will be detected by the system, and after computer analysis, a volume of images formed by voxels can be reconstructed in a 3-dimensional space. This volume of images will show the tracer concentration (metabolism) of the area under study (Figure 9).

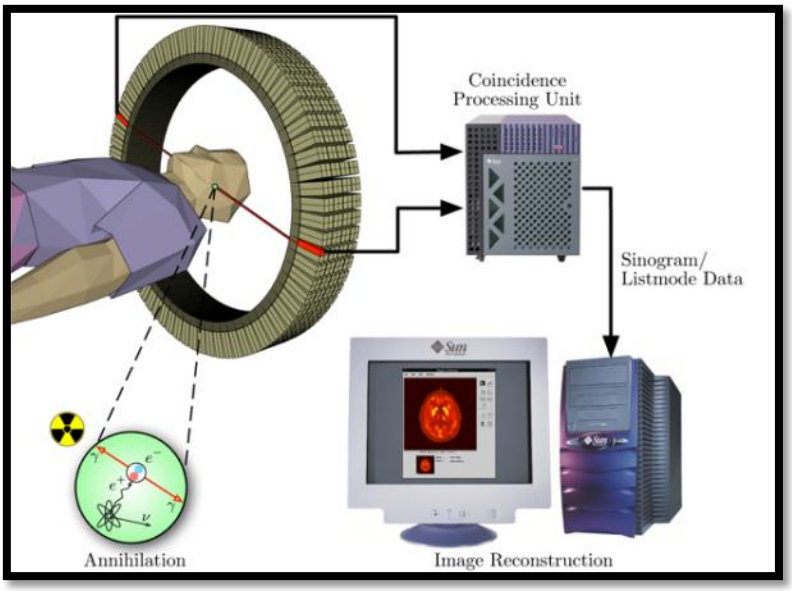


Figure 9: The process of PET scans generation.

The dose of radioisotopes used in these studies is extremely low, but this dose does not cause adverse effects to the patient. However, the cost of these cameras is significantly high. Even so, it is necessary to have a near cyclotron for the synthesis of radioisotopes, which have a short life and which disintegrate rapidly. Therefore, this increases the cost of examinations [13].

3.2 Biomarkers

The PET technique is focused on these two elements: tracer and radioisotope. The tracer or biologic marker is a substance, measure or indicator of a biological state; the radioisotope is an isotope which emits radiation when it is combined with the tracer. This radiation is captured in the PET camera and this will allow us to obtain the corresponding image. Therefore, the tracer allows doctors to study a biological process and the radioisotope joins the tracer to follow its process.

In this way, depending on the used tracer, it is possible to study different biological processes. We can see some examples in table 2:

Radioisotope	+	Tracer	permit	the study of
Oxygen 15		H2O		Cerebral Perfusion or cerebral blood flow.
Carbon 11		Flumazenil		Cerebral Receptors or cerebral tumors

Table 2: The most typical radioisotopes and tracers.

However, the most clinic application of PET technique is the study of metabolism [13]. In this case, the most used radioisotope is the Fluorione-18(F-18) and the tracer is fluoro-desoxy-glucose (FDG), an analogue tracer of glucose (Figure 10).

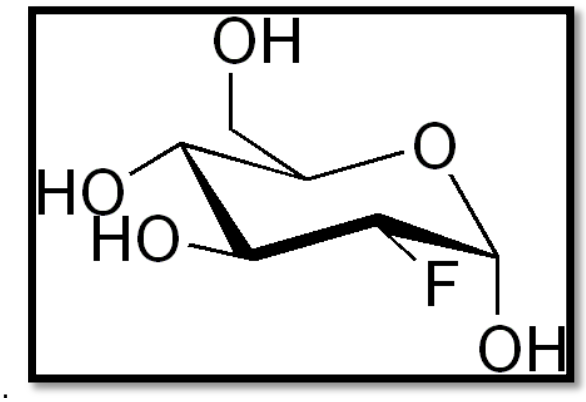


Figure 10: The structure of Fludeoxyglucose.

The FDG is stored into cell, but in contrast to normal glucose, it cannot be used to produce energy, and it is saved into the cell. In this way, the capture of FDG in the cells is proportional to their metabolic level. At the same time the FDG is saved in the cell, the F-18 radioisotope suffers a nuclear disintegration because this radioisotope is unstable. This disintegration provokes the liberation of one positron which is discomposed when this combines with a near electron. This also provokes the emission of 2 photons which travel in opposite sense (Figure 11). The PET camera captures this emission and offers the corresponding image [13].

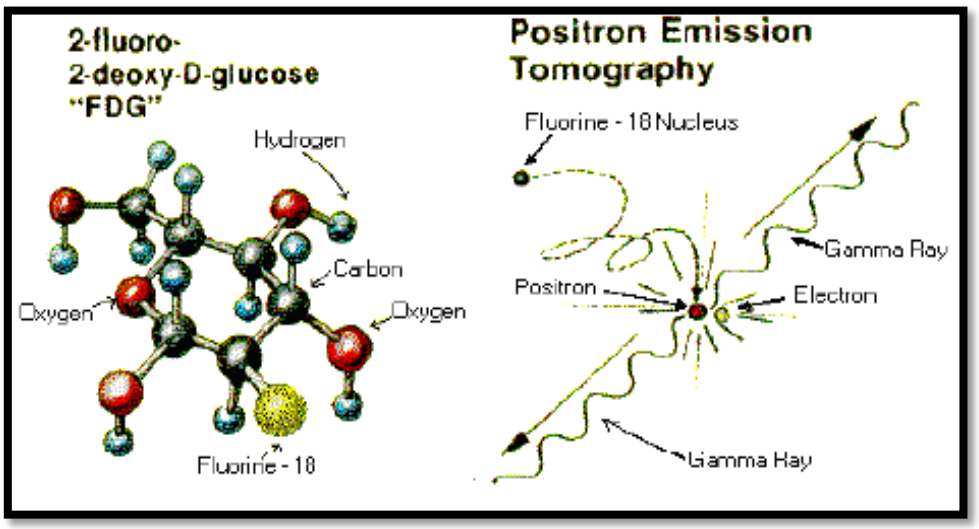


Figure 11: The process of FDG disintegration.

The FDG can be used for the assessment of glucose metabolism in heart and brain, but also, for image tumors in oncology because these types of tissue have a significant higher metabolism (glucose uptake).

So, the main function of PET scans in the diagnosis of Alzheimer's disease is to locate active areas of the brain, and the FDG is used for the assessment of glucose metabolism in the brains of Alzheimer's disease patients.

Chapter 4

Psychological Testing

Most of the symptoms shown by patients with dementia are symptoms of a neuropsychological nature [14]. So, this chapter will show how the neuropsychological evaluation has an important role in the identification of dementia and also in its diagnosis.

This evaluation is composed of a set of methods and techniques which allow doctors define clinically the state of the patient cognitive abilities. Although the psychological tests are considered the best tool to achieve this, this evaluation includes more information than the performance of these tests. For this reason, the application and interpretation of these tests may be performed by a specialized neuropsychologist to achieve certain objectives, such as, early detection, the contribution to the diagnosis, affected cognitive abilities and the severity degree [15].

This is a complex process which main objective is the interpretation of many data and the conclusion of a possible diagnosis. This diagnosis will be then corroborated with the remaining pieces of the evaluation.

In the patients evaluation several tests combinations will be used. These combinations must:

- Be sensitive to different types of cognitive impairment.
- Allow to use them in elderly people.
- Be standardized or have control group scores.
- Have clinic efficiency which has been checked in the classification of several patients with different types of dementia.
- Allow to evaluate more than one cognitive ability.

Then, the characteristics of these tests are explained.

4.1 Initial Evaluation

To start the neuropsychological evaluation it is usually used short tests which are rapidly acquired and which allow the examiner to know the patient cognitive state.

Mini Mental State Examination (MMSE)

This is a short cognitive test which has the greatest validity and international diffusion. This is usually used with other scales, such as, the FAST scale which it will see in table 3. This kind of test is performed in 5 or 10 minutes and it evaluates the orientation, the registration of information, the attention and calculation, memory, language and construction [16].

Its maximum score is 30 and its cut-off point is 26 [16]. A result below of this value suggests a cognitive impairment, but a normal result does not allow doctors to discard some eventual impairment.

Then, an example of some questions which are often done in this type of test are shown:

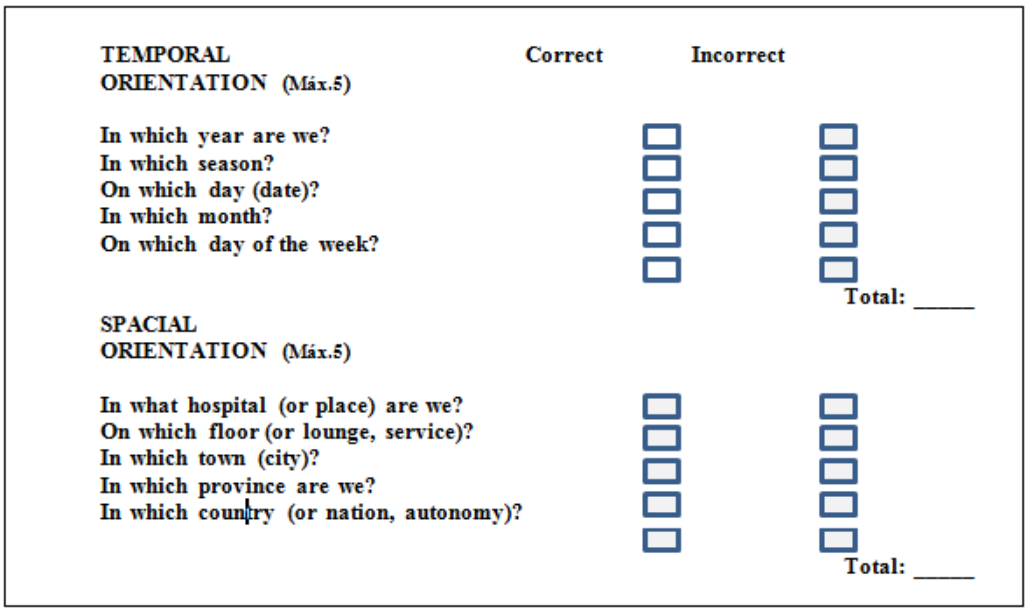


Figure 12: Some questions of MMSE Test.

Though this test is helpful to do an initial examination of cognitive disorders, it must not be used to do a complete neuropsychological examination because it has problems to detect different degrees of severity and it does not evaluate any cognitive abilities.

Clock Drawing Test (CLOCK Test)

This is a screening test to assess the patient cognitive state in the earlier states and for the early diagnosis. In this test the patient have to:

- Draw a clock.
- Draw a sphere,
- Put all hours on the sphere

- Put the hands at 11:10.

In this way, to evaluate the cognitive state of patient, the scoring criterion is the following [17]:

1. Sphere (2 points):

    a. Normal picture (2 points)
    b. Incomplete (1 point)
    c. Completely distorted picture (0 points)

2. Numbers sequence (4 points):

    a. All numbers and correct order (4 points)
    b. Error in 4 or more numbers (3.5 points)
    c. All numbers but bad located (3 points)
    d. Error in the placement of numbers or incorrect alignment (2 points)
    e. Lack or excess of numbers, poor positioning and alignment (1 point)
    f. Low representation of numbers (0 points)

3. Presence and location of the hands (4 points)

    a. Right position and adequate size (4 points)
    b. Right position and equal size (3.5 points)
    c. Errors in the placement and size is not correct (3 points)
    d. Severe distortion in the placement of the hands or not fit in the central area. (2 points)
    e. Error in the placement of the hands they do not join in the central position (1 point)
    f. No hands. (0 points)

In this test, the cut-off point is 6. Therefore, the test is considered positive if the final score is lower than 6, and the test is considered negative if the final score is bigger than 6. The highest scores are used to discard the disease, especially the scores near to 8 and 9 [17].

This test provides useful information about various cognitive areas which are activated when the patient does this short task. These areas are similar to those evaluated in MMSE test, that is to say, language, short-term memory and executive functions. Moreover, the Clock Drawing Test is highly sensitive and specific [17].

The next scales can be also helpful to do an initial evaluation:

- Global Deterioration Scale (GDS)

- Functional Assessment tool for Alzheimer´s Disease (FAST) which we can relate to the MMSE value in the following way:

Scale FAST (state)	MMSE
Normal (1)	29,0 ± 1,7
Ageing (2)	28,2 ± 2,7
Incipient AD (3)	23,8 ± 4,0
Mild AD (4)	20,0 ± 4,8
Moderate AD (5)	14,4 ± 4,8
Moderate – Severe AD (6)	11,1 ± 5,1
Severe AD (7)	0,3 ± 0,8

Table 3: Relations Scale FAST with MMSE Test.

APOE Test

This type of test is frequently used in the initial evaluation. The aim of this test is to identify whether the patients with cognitive disorders have a high genetic risk to develop Alzheimer's disease [18]. The result of this test constitutes one more data about the patient which is registered with all the demographic information of the patient. In order to do this test the only requirement is to do a blood test to the patient and analyze this blood sample by techniques PCR (Polymerase Chain Reaction) [18]. These techniques allow the amplification of the DNA fragment [19], which can be visualized by the specialists in order to analyze the ApoE gene, since this gene is considerate a susceptibility genetic factor to develop Alzheimer's disease.

4.2 Global Evaluation

Alzheimer Disease Assessment Scale (A.D.A.S)

To do global evaluations about dementia, such as, Alzheimer's disease, this is the most used scale. This has an easy and fast administration even in advanced stages of dementia. This scale mainly evaluates language, memory and apraxia. This type of test is performed in 30 or 60 minutes depending on the disease's phase [20].

This scale asses the cognitive state and the behavior of patients who suffer Alzheimer's disease. Its maximum score is 120 points. The highest values correspond to patients who have more impairment [20].

The scale is divided in 11 items which evaluate the cognitive abilities, such as, memory, language, apraxia and orientation; and in 10 items which evaluate the no cognitive abilities, such as, mood and behavior. This evaluation indicates the memory and language items as impairment signs, although apraxia, order

execution and denomination are the most frequently modified. Nevertheless, the orientation item is the one which best shows the disease progress [20].

Consortium to Establish a Registry for Alzheimer's disease (CERAD)

The Consortium to Establish a Registry for Alzheimer's disease (CERAD) was established in 1986 by a grant from the National Institute on Aging (NIA), to standardize procedures for the evaluation and diagnosis of patients with Alzheimer's disease (AD) [21].

CERAD developed the following standardized instruments to assess the various manifestations of Alzheimer's disease:

- Clinical/Neuropsychology
- Neuropathology
- Behavior Rating Scale for Dementia
- Family History Interviews
- Assessment of Service Needs

The above neuropathology criteria are widely used in the US and other countries for the studies of Alzheimer's disease and other dementias of elderly people.

The CERAD Behavior Rating Scale for Dementia (BRSD) is a standardized instrument for rating behavioral abnormalities in demented or cognitively impaired subjects. Descriptive items are scaled according to frequency of psychopathological behavior.

For more information about CERAD, please visit the official CERAD website: http://cerad.mc.duke.edu.

Clinical Dementia Rating Scale (CDR)

This test was developed at Washington University School of Medicine in 1979. Primarily this was developed for diagnosing dementia of the Alzheimer's type, but then this can also be used to evaluate other types of dementia. CDR scores the person's cognitive ability. It is a five-point scale. CDR=0 connotes that people have no cognitive impairment, and the remaining four points are for various stages of dementia [22]:

- CDR = 0: no impairment
- CDR = 0.5: questionable dementia
- CDR = 1: mild dementia
- CDR = 2: moderate dementia
- CDR = 3: severe dementia

The CDR will be tested by an interview with the patients. The CDR score is based on 6 domains: memory, home and hobbies, orientation, judgment, community affairs and personal care. In the following chart the detailed classification rules are shown:

Area	None: 0	Questionable: 0.5	Mild: 1	Moderate: 2	Severe: 3
Memory	No memory loss or slight Inconsistent forgetfulness .	Consistent slight forgetfulness; -partial recollection of events; "benign" forgetfulness	Moderate memory loss: more marked for recent events; defect interferes with everyday activity	severe memory loss, only highly learned material retrained: new material rapidly lost	Severe memory loss only fragments remain.
Orientation	Completely oriented	Fully oriented but with slight difficulty with time relationships	Moderate difficulty with time relationships; oriented for place at examination; may have geographic disorientation elsewhere	Severe difficulty with time relationships; usually disoriented to time, often to place	Oriented to person only
Judgment and Problems resolution	Solves everyday problems and handles business and financial affairs well; judgment good in relation to past performance.	Slight impairment in solving problems, similarities and differences.	Moderate difficulty in handling problems, similarities and differences; social judgment usually maintained.	Severely impaired in handling problems, similarities and differences; social judgment usually impaired.	Unable to make judgments or solve problems
Social life	Independent function as usual in job, shopping, volunteer and social groups	Slight impairment in these activities.	Unable to function independently at these activities though may still be engaged in some; appears normal to casual inspection	No pretenses of independent function home; appears well enough to be taken to functions outside the family home.	Appears too ill to be taken to functions outside the family home

Home and Hobbies	Life at home, hobbies and intellectual interests well maintained	Life at home, hobbies and intellectual interests slightly impaired	Mild but definite impairment of functions at home; more difficult chores, and complicated hobbies and interests abandoned	Only simple chores preserved; very restricted interests, poorly maintained	No significant function in the home
Personal care.	Fully capable of self-care	Fully capable of self-care	Needs prompting	Requires assistance in dressing hygiene and keeping of personal effects	Requires much help with personal care; frequent incontinence

Table 4: The Clinical Dementia Rating scale.

Chapter 5

Image Data

In this chapter, all the necessary information about the PET scans which have been used in this project will be developed. Also, all the steps which have been followed to analyze the PET scans will be explained.

So, this chapter has been organized from the acquisition of the images (PET scans) until its disposition to use them in the creation of the ordering graph.

5.1 Acquisition

Given that, this study is focused on analyzing how the brain metabolism degradation evolves in Alzheimer's disease, it is necessary to use some type of image which allows us to examine the brain metabolism.

Among the medical image techniques that better visualize this type of activity, the functional techniques are highlighted, specifically, the nuclear medicine techniques, that is to say, the PET technique (Positron Emission Tomography) and SPECT technique (Single Photon Emission Computed Tomography). Between them, the PET technique has a greater spatial resolution than SPECT technique. Therefore, the PET technique is the best showing the brain metabolism for different pathologies, such as, dementia. For this reason, we use images which have been obtained by this technique.

So, in order to do this project the images are taken from this website: Alzheimer's disease Neuroimaging Initiative (ADNI; http://adni.loni.ucla.edu/). This is an open-source page which goal is to define the Alzheimer's disease progression. In this site, data from Alzheimer's disease patients, mild cognitive impairment subjects and elderly controls are available to download.

The obtained images are 'co-registered, average' [23] and are classified in three folders: Normal Control (NC), Mild Cognitive Impairment (MCI) and Alzheimer's disease (AD). The NC folder has the PET scans from people who do not have any cognitive disorder, in other words, healthy people. The MCI folder has the PET scans from mild cognitive impairment subjects, and the AD folder has the PET scans from Alzheimer's disease patients.

For the analysis and obtention of the corresponding graph, we use 30 PET images with Normal Control, 52 PET images with Mild Cognitive Impairment and 25 PET images with Alzheimer's disease.

The images with mild cognitive impairment (MCI) and Alzheimer's disease (AD) are put in the same folder which is called "Disease_images"; and the images with normal control (NC), are in another folder, called "Healthy_images".

5.2 Pre-processing

Once we have the PET scans, a preprocessing of these PET scans are performed. This preprocessing is necessary to use and analyze the PET scans in the correct form. So to carry out this preprocessing, the next programs: MATLAB, SPM5 and XMedCon are used.

MATLAB is a numerical computing environment as well as a programming language developed by The MathWorks, Inc [24]. It allows the user to do a lot of things with the data, but in this project, this program is only used to run SPM5.

SPM5 is an update version of SPM (Statistical Parametric Mapping) [25]. SPM is software to construct and evaluate spatially extended statistical processes. SPM is based on MATLAB so it can only run under MATLAB. By using SMP, brain imaging data can be analyzed. For this reason, SPM5 is used to normalize and smooth the PET scans which are used in this project.

The Medical Conversion (MedCon) is an open-source tool which aim is the conversion of medical images. This program is released under the GNU's (L) GLP license, and supports a lot of formats. Its main purpose is image conversion and particularly to reconstruct nuclear medicine images [26]. Even though, this program can be used to do a lot of things, in this project, it is only used to get the images conversion.

Once all the programs used to perform this preprocessing have been mentioned, we show a schematic view about all the steps which are followed to achieve this preprocessing:

1. To normalize each PET scan, we apply:

    a. Spatial normalization by using SPM5 [25]
    b. Smoothing use a kernel size [8 8 8] mm [25]
    c. intensity normalization by 'Grand Mean':

        i. that was done by dividing each voxel's intensity value by (1+1/8)*mu(image), that is:

Voxel (processed) = voxel (original) / ((1+1/8) * mu (image))

        - mu (image) is the mean intensity value of the original image.

        - The reason why (1+1/8) is multiplied because the brain image has certain amount of non-brain voxels that are near 0 (black), thus it is compensated by increasing '1/8' of the mean value.

2. For each normalized PET scans we do:

    a. Conversion to ASCII format

So, the first step of this preprocessing consists of three steps: spatial normalization, smoothing and intensity normalization. These steps are detailed below and are applied to each one of the images which are stored in the folders “Disease_images” and “Healthy_images”.

Firstly, we apply spatial normalization to each image of each folder. This normalization is performed because people have different brains in size and shape. For this reason, the aim of this normalization is to apply a deformation to brain scans to correspond all the brains of the images with the same space or dimension.

Secondly, once we have applied spatial normalization, we apply smoothing. This smoothing is applied to each image of each folder after that images have been spatially normalized. This smoothing is performed because all data acquires certain noise when they are obtained by detection systems, then this noise is reflected in the image. These images can have more or less noise according to the conditions in which images are obtained. For this reason, it is recommendable to apply some smoothing technique to delete or attenuate this noise among images.

Finally, once the previous steps have been applied, the last step is to apply intensity normalization. This normalization is also applied to all images of all folders, after that all images have been spatially normalized and smoothed. This normalization is done because in this type of techniques, the injected dose can be different each time an image of the patient’s brain is obtained. This can lead that not all images have the same intensity in each voxel, and therefore, the goal of this last step is to establish the same intensity in all voxels of all images.

Once all the PET scans have been normalized, the files of PET scans have a new format, and therefore, the next step is to convert these files to another format which will allow us to know the features of the matrices for each PET scan normalized. This conversion is done by using the MedCon program. This program generates the files of PET scans in format ASCII.

In this way, each file contains the matrix of each PET scan where the pixel values are saved. These values represent the brightness of the pixels.

Next, we see the MedCon command which has been used to extract a voxel intensity matrix from the files of PET scans after the normalization [26]:

medcon –c format conversion **–f** folder where the original files are **–o** folder where the convert files have to be saved

As we can observe, the program requires three parameters. In the first parameter, we indicate by –c the format it wants to convert the images; as a second parameter, we indicate by –f the path of folders where the images are and which it wants to convert. In our case, this is the path where the folders “Disease_images” and “Healthy_images” are. Finally, as a third parameter, we indicate by –o the path of folders, where the convert images have to be saved.

Given that, the final files of PET scans have a different format from the original, it is necessary to create new folders to save these new files of PET scans.

So, we create the following folders:

- Disease_imgs_convert
- Healthy_imgs_convert.

These folders store the ASCII files of the PET scans which are in the folders Disease_images and Healthy_images. So, in our case, the third parameter of the MedCon command is the path where the folders “Disease_imgs_convert” and “Healthy_imgs_convert” are.

5.3 Utilization

From the files of PET scans which are contained in the folders: Disease_imgs_convert and Healthy_imgs_convert, we know the features of the matrices that describe the PET scans. Moreover, the values of these matrices represent the pixels values, that is to say, the brain metabolism intensities of the PET scans.

In this way, analyzing the ASCII files of PET scans, it can be observed that each PET scan is composed by 68 slices. These slices make up the PET scan of the whole brain. Furthermore, from each file of PET scan we have extracted that a PET scan has 68*95*79 voxels, and each slice has 95*79 voxels.

In this project, we can work with one slice or with all the slices of the PET scan. So, if we do the analysis of PET scans by using one slice of PET scans, the matrices of PET scans will have 95 rows and 79 columns; otherwise, if we do the analysis of PET scans by using all the slices of the PET scans, then the matrices of PET scans will have 68*95 rows and 79 columns. In short, in this project we will use the values of table 5 according to the study of the PET scans that we want to perform:

MATRIX	ROWS	COLUMNS
One slice of PET scan	95	79
All slices of PET scan	(68*95)	79

Table 5: Features of the matrices associated to the PET scans.

Chapter 6

Ordering and Visualization

This chapter will describe the most important part of this work: the ordering of PET scans and its visualization. That is why it has been divided in three points; in the first one, an overview of the ordering procedure which has been used to get the order of PET scans will be given; in the second point, all this ordering procedure will be detailed; and, in the third point, it will be shown the ordering visualization regarding graph, and also, regarding node.

6.1 Overview of the procedure

The objective of this project is to obtain an ordering among PET scans. This ordering may visualize the brain metabolism degradation in the development of Alzheimer's disease. Therefore, the objective of this project is to obtain an ordering as the one visualized in the following figure:

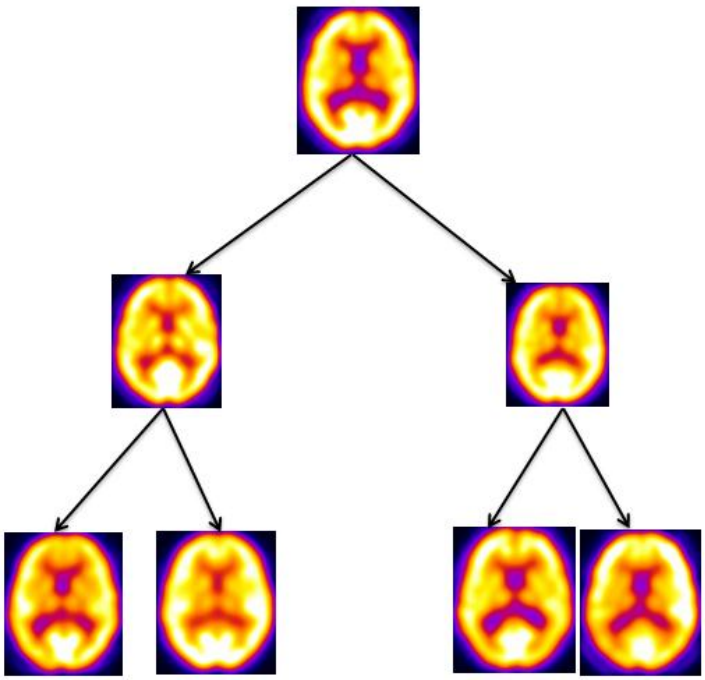


Figure 13: Goal of the ordering

As we can observe in figure 13, the right arc represents the brain metabolism degradation in the development of Alzheimer's disease; and, the left arc of the figure represents the brain metabolism degradation when the mild cognitive impairment appears.

So, to visualize the brain metabolism degradation, the areas of the PET scans that show certain impairment in the brain metabolism, have to be analyzed. To achieve this analysis, the matrices associated to the PET scans have been used.

In this way, to analyze these matrices and to establish the order among PET scans, a procedure is followed. This procedure consists of the following steps:

1) Convert the files of PET scans to ASCII format.

2) Create a healthy control matrix. This matrix will contain the minimum values of the brain metabolism and will serve as a baseline to calculate the disease status of the PET images. The matrix obtained in this step will be the **minimum healthy matrix.**

3) Obtain the matrices that will contain the difference between the matrix calculated in step 2, and the matrices associated to the PET scans. The matrices obtained in this step will be the **difference matrices.**

4) Compare the difference matrices calculated in step 3, using the next variables:

    a. Variable 1: this variable will store the amount of elements of the difference matrix, which will indicate the affected areas of the PET scan. This variable will be called **nvot.**
    b. Variable 2: this variable will store the amount of elements that the difference matrices will have in common. Therefore, this variable will indicate the affected areas which the PET scans will have in common. This variable will be called **nvotaiop.**
    c. Variable 3: this variable will store the percentage of overlap area that the difference matrix will have. Therefore, this variable will indicate the percentage of affected area that the PET scan will have. This variable will be called **content_ratio.**

5) Establish the order among PET scans, using the difference matrices calculated in step 3, and the following parameters:

    a. Parameter 1: this parameter will be used to calculate the variable nvot. This parameter will be called **param_1.**
    b. Parameter 2: this parameter will be used to select the difference matrix with a greater overlap area. This parameter will be called **param_2.**
    c. Parameter 3: this parameter will be used to compare the overlap areas of the difference matrices and establish the order among PET scans. This parameter will be called **param_3.**

So, the procedure that it has been used to obtain the order among PET scans and the visualization of the brain metabolism degradation in the development of Alzheimer's disease has been defined.

In point 6.2, all the calculations performed in each one of the previous steps will be detailed.

6.2 Description procedure

This point describes in more detail the procedure which was explained in the point 6.1. Therefore, the parts that make up this point are: the Input, Processing and Output of the procedure.

To better understand what it will be done in each part everything is shown in the following schematic view:

INPUT

1. Convert the files of PET scans to ASCII format.
2. Variables definition:
    a. nvot
    b. nvotaiop
    c. content_ratio
3. Parameters definition:
    a. param_1
    b. param_2
    c. param_3
4. Connectivity matrix definition.

PROCESSING

1. The obtaining of the **minimum healthy matrix**.
2. The obtaining of the **difference matrices**.
    a. Difference matrices comparison:
        i. Calculate the **variable nvot** for each difference matrix
        ii. Calculate the **variable nvotaiop**
        iii. Calculate the **variable content_ratio** for each difference matrix.
3. The ordering of the PET scans:
        i. Parameters evaluation

OUTPUT

1. The ordering graph.

6.2.1 Input

In this part all the elements which have been used to carry out all the ordering procedure are detailed.

The main component of this procedure is the PET scans that want to be ordered. To analyze these PET scans, it is essential to know the matrices associated to these PET scans. For this reason, the first step was the conversion of the files of the PET scans to ASCII format. This step was explained in chapter 5, and the converted files of PET scans were stored in the following folders:

- **Disease_imgs_convert**
- **Healthy_imgs_convert**

In this way, the files of PET scans in ASCII format have been obtained and the features of the matrices associated to the PET scans are known. The matrices associated to these PET scans have the features shown in the table 5 of chapter 5.

The second step of this procedure is to obtain the matrix that will store the minimum values of the brain metabolism. For this reason, it has to be defined one matrix to save these values. This matrix is called: **minimum_healthy_matrix** and it is an input of this procedure.

The third step of this procedure is to obtain the difference matrices. The values of these difference matrices are stored in files. Given that the PET scans are formed by slices, we can obtain the ordering of PET scans by analyzing one slice or analyzing all the slices of PET scans. Therefore, the calculation of the difference matrices also depends on the type of study that we do. So, these two studies imply the definition of two folders to save the files with the values of the difference matrices according to the study that we do.

Given that in this study it is used the slice 32 of PET scans, because it is the slice which better shows all the areas in the brain. Therefore the difference matrices are stored in the following folders:

- **Difference_imgs_32:** this folder stores the difference matrices when one slice of PET scans is used.

- **Difference_imgs_all:** this folder stores the difference matrices when all the slices of PET scans are analyzed.

Once all the folders have been explained, the variables and parameters which will be used to compare the difference matrices and to get the order among PET scans will be defined. This is, the variables: nvot, nvotaiop, content_ratio; and the parameters: param_1, param_2 and param_3.

Once all the folders have been created, and the variables and parameters which are needed have been defined, it only remains to define the output of all procedure, this is: the ordering graph. This is represented as a connectivity matrix. This connectivity matrix will store all the connections of the ordering graph. This matrix is called graph1 and its size will be defined according to the analysis that will be done. So, analyzing the table 5 of chapter 5, the size of graph1 will be 95

rows and 79 columns, if we analyze one slice of the PET scans; otherwise, the size of graph1 will be 6.528 rows and 79 columns, if we analyze all the slices of the PET scans.

In this way, all the elements that have been needed to perform this procedure have been detailed. So, in point 6.2.2 the processing part is explained.

6.2.2 Processing

In this part all the calculations to get the ordering among PET scans are detailed.

First of all, it is necessary to know which areas of the PET scans are affected by disease, that is to say, which areas of the PET scans have certain impairment in the brain metabolism. For this reason, the first step of this procedure is to relate the healthy and diseased images.

Analyzing the PET scans of healthy people, it can be observed that not all brains will have the same shape and active areas. So, it depends on some factors, such as, the age, education and sex of the person. Therefore, to extract correctly the affected areas of the PET scans of diseased people the whole set of PET scans of healthy people is used.

So, to know which areas of PET scans of diseased people have impairment in the brain metabolism, it should be known which the minimum brain metabolism is observed in the healthy people. For this reason, the first step of this procedure is to calculate a matrix which will contain the minimum values of the brain metabolism in healthy people.

6.2.2.1 The obtaining of the minimum healthy matrix

The size of this matrix also depends on the study which wants to be carried out. So, analyzing the table 5 of chapter 5, the size of this matrix will be 95 rows and 79 columns, if we analyze one slice of the PET scans; otherwise, the size of this matrix will be 6.528 rows and 79 columns, if we analyze all the slices of the PET scans.

Therefore, this matrix is obtained in the following way:

```
For each voxel in healthy image
    If (healthy_image [ ] [ ] < min)
        minimum_healthy_matrix [ ] [ ] = value1;
```

Once the minimum healthy matrix has been calculated, the next step is the calculation of the difference matrices.

6.2.2.2 The obtaining of the difference matrices

These matrices will contain the difference between the minimum healthy matrix and the matrices associated to the PET scans of diseased people. In this way, the affected areas of the PET scans of diseased people will be got. This is the calculation:

```
For each element in minimum healthy matrix
  For each element in disease matrix
    difference_matrix [ ] [ ] = minimum_healthy_matrix [ ] [ ] – disease_matrix [ ] [ ];
```

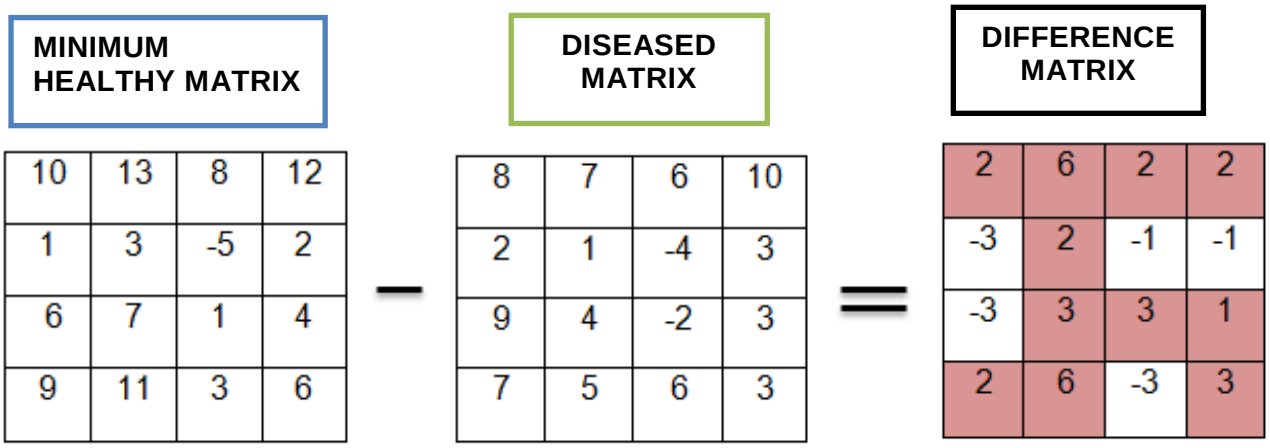
From this calculation, the difference matrices have the values that help to detect which areas of the PET scans of diseased people have certain impairment in the brain metabolism. Therefore to know these areas, the values of these difference matrices are analyzed.

So, the difference matrices have positive and negative values. The positive values determine that the minimum metabolism is higher than the metabolism in the PET scan of the diseased person. In the other case, the negative values determine that the minimum metabolism is lower than the metabolism in the PET scan of the diseased person.

Given that we want to analyze which areas of the PET scans of the diseased people have certain impairment in the brain metabolism, we select the values of the difference matrices which indicate this impairment in the brain metabolism.

So, these values are the positive values of the difference matrices because they represent that the brain metabolism in the PET scans of the diseased people is lower than the minimum brain metabolism which has been observed in the PET scans of the healthy people, and therefore, they represent the areas of the PET scans of diseased people that have some impairment in the brain metabolism.

To better understand this explanation, the following example is introduced:



As it can be observed, the colored values are the positive values. These values indicate that, the values of the minimum healthy matrix are higher than the values of the matrix associated to the PET scan of the diseased person. Given that the values of these matrices are the values of the brain metabolism, it can be confirm that the positive values of the difference matrix indicate that, in the PET scan of the diseased person there is certain impairment in the brain metabolism because this metabolism is lower than the minimum metabolism observed in the PET scans of healthy people.

Once it has been understood the reason by which the positive values have been selected in the difference matrices, the next step is: The comparison of the difference matrices.

6.2.2.3 The Comparison of the difference matrices

In this step, the difference matrices are compared to know how much affected area has each one. This knowledge about the affected areas in the PET scans allows us to obtain the order among PET scans.

So, to compare the difference matrices and to get the order among the PET scans, some calculations using the difference matrices are done. So, in the following points (6.2.2.3.1, 6.2.2.3.2 and 6.2.2.3.3) all these calculations are explained.

6.2.2.3.1 The calculation of the nvot variable.

The first calculation is to calculate the amount of elements of the difference matrices that indicate areas with certain impairment in the brain metabolism of the PET scans of the diseased people. The elements of the difference matrices that indicate this impairment in the brain metabolism, are the positive values (see point 6.2.2.2). Given that the parameter 1 has to select these elements in the difference matrices, this parameter is initialized with the value 0.

As we have seen in the point 6.1, this calculation corresponds with the variable 1 called, nvot. This variable is calculated for all difference matrices in the following way:

```
For each voxel in difference image
    If (difference_matrix [ ] [ ] >= param_1)
            Count ++;
```

6.2.2.3.2 The calculation of the nvotaiop variable.

The second calculation is to calculate the amount of elements that the difference matrices have in common. The values of this variable indicate the affected areas that the PET scans of diseased people have in common.

As it can be seen in the point 6.1, this calculation corresponds with the variable 2 called, nvotaiop. This variable is calculated in the following way:

```
For each voxel in difference_matrix1 and difference_matrix2
    If (difference_matrix1 [  ] [  ] >= param_1 &&
        difference_matrix2 [  ] [  ] >= param_1)
            Count++;
```

6.2.2.3.3 The calculation of the content_ ratio variable

The third calculation is to calculate the percentage of the overlap area that the difference matrices have. These percentages indicate the overlap area that the PET scans of diseased people have.

As it can be seen in the point 6.1, this calculation corresponds with the variable 3 called, content_ratio. This variable is calculated in the following way:

```
content_ratio = (nvotaiop /nvot) * 100;
```

In this way, all the necessary calculations to order the PET scans of the diseased people have been done. Therefore, the next step is the ordering of PET scans.

6.2.2.4 The Ordering of PET scans.

To obtain the ordering among PET scans of the diseased people, the difference matrices are compared by using the values of the content_ratios and the parameters 2 and 3. Then, the parameters evaluation is explained.

6.2.2.4.1 Parameters Evaluation

The first step to get the ordering among PET scans of the diseased people is to calculate the maximum content_ratio of the two difference matrices which are compared. This maximum determines which difference matrix has more overlap area.

When the maximum content_ratio have been calculated, the second step is to evaluate this maximum content_ratio with parameter 2. So, this parameter determine if the PET scan associated to the difference matrix with a maximum content_ratio, should be anterior than the other PET scan associated to the other difference matrix which is compared. However, the position of one PET scan cannot be confirmed until performing the evaluation with parameter 3.

In order to do this comparison, first the difference among the values of content_ratios is performed. This difference indicates if the overlap areas of difference matrices are similar or not.

Once the calculation of the difference among the values of the corresponding content_ratios has been done, the next step is to compare this difference with parameter 3. This parameter determines if this difference is enough high to put the PET scans one before the other, or if this difference is low and the PET scans should be in the same level in the ordering graph.

All the before procedure is done for all difference matrices which have been calculated. Then, all these steps are shown:

```
Max = we calculate the maximum value of the content_ratios;
If (max >= param_2)
    To obtain the difference among the content_ratios;
    If (difference >= param_3)
            The images are progression;
            Grafo1 [ ] [ ] = 1;
    Else
            The images aren't progression;
            Grafo1 [ ] [ ] = 0;
```

In this way, the order among PET scans of the diseased people is got, and the degradation in the brain metabolism in the development of Alzheimer's disease is shown.

EXAMPLE

Finally, an example is developed to better understand all the before comparison and all the ordering procedure. First of all, two difference matrices are defined to do all the calculations. These difference matrices are the following:

Difference_img1

-2	-4	2	1
-1	3	5	-2
-6	9	-7	-10
-13	-20	-10	-9

Difference_img2

-6	-7	4	3
-3	-10	5	-8
-9	12	7	10
-16	-21	-11	2

As a first step, we select the positive values of the difference matrices. To do that, we need to compare all the values of the difference matrices with the parameter 1 which value is 0, and we select all the values over of this parameter. As we can see above, these values are the colored ones.

Once we have selected the positive values, we calculate the variable nvot, that is to say, the amount of positive values that are in each difference matrix. So, for the difference matrix 1 we have nvot1 = 5, and for the difference matrix 2 we have nvot2 = 7.

Now, the next step is to calculate the variable nvotaiop, that is to say, the amount of positive values that are in the same position in both difference matrices. Then, we see how we have to do it:

Difference_img1

-2	-4	2	1
-1	3	5	-2
-6	9	-7	-10
-13	-20	-10	-9

Difference_img2

-6	-7	4	3
-3	-10	5	-8
-9	12	7	10
-16	-21	-11	2

As we can see, the rounded values are in the same position in both matrices, and therefore, the value of the nvotaiop variable is 4 because there are 4 positive values in the same position in both matrices. So, this variable establishes the area that both difference matrices have in common, and therefore, the affected area which the associated PET scans have in common.

When all these values have been calculated, the last step is to calculate the values of the content_ratio variable for each difference matrix. These values are a percentage which describes how much overlap area there is in each difference matrix.

For our difference matrices, we have:

Difference matrix 1 → CR1 = (nvot1 / nvotaiop) * 100 = (4/5) * 100 = 80%

Difference matrix 2 → CR2 = (nvot2 / nvotaiop) * 100 = (4/7) * 100 = 57%

We see all the preceding calculations in table 6:

Image1/Image2	NVOT	NVOTAIOP	Content_ratio
PET1/PET2	5	4	80%
PET2/PET1	7	4	57%

Table 6: Results of the calculations in the example.

As we can see in table 6, PET scan 1 associated to difference matrix 1, has more overlap area than PET scan 2 associated to difference matrix 2. So, that means that, PET scan 1 has a lower affected area than PET scan 2, and therefore, the brain metabolism degradation is more appreciated in PET scan 2. For this reason, we could put PET scan 2 after PET scan 1, but to confirm this order, we have to continue with the procedure. So, the next step is the parameters evaluation.

The first step to do the evaluation of the parameters is to calculate the maximum content_ratio. In this example, observing table 6 we know that the maximum content_ratio is the content_ratio of PET scan 1 associated to difference matrix 1. So, this value is 80%.

The second step in this part of the procedure is to compare this maximum content_ratio with parameter 2. So, if we suppose a value for parameter 2 = 50%, the comparison is true because 80 is bigger than 50. Therefore, we compare the difference among content_ratios with parameter 3 to know the order.

In this way, the last step of this part is to calculate the difference between the values of the content_ratios associated to the difference matrices which we are comparing. So, we make this difference as we can see below:

Difference = max (content_ratio) – content_ratio =

= content_ratio 1 – content_ratio 2 = 80% - 57% = 23%

Finally, we compare this difference with parameter 3. So, if we suppose a value for parameter 3 = 10%, the comparison is also true because 23% is bigger than 10%. Therefore, we can establish the order between the PET scans associated to the difference matrices which we are comparing. Therefore, and as we can observe in this example, PET scan 1 should be anterior to PET scan 2.

So, these are all the steps which have been followed to get the order.

Although in this example the connection between the PET scans is possible, it could appear the case in which the connection would not be possible. Therefore, the connections will depend on the values in the parameters 2 and 3. These parameters are the most important to get a correct order, so, good values will have to be chosen. These values will be discussed in chapter 7, where several orderings will be shown in different examples and which will help to conclude which values are the best for these parameters.

6.2.3 Output

The output of this procedure is the connectivity matrix, graph1. In this graph all the connections among nodes are stored, and therefore, this is the matrix which determines the order among PET scans of the diseased people.

In point 6.3, the visualization of this graph is explained, as well as, the visualization regarding node. In this visualization additional information about PET scans is displayed. This information will be helpful to better understand the connections in the graph.

6.3 Application Description

To visualize the order of PET scans a java application has been implemented using the tool Netbeans: an integrated development environment (IDE) [27]. Nowadays, this is considered the most popular IDEs in the development of Java applications. That is why we have used this tool to implement our application. It is

free to download and easy to install. Furthermore, there are plenty of help documents on the internet, which make its use easier.

This application will show the ordering of PET scans using a directed acyclic graph (DAG) which can move around the screen, as well as, change its size. Furthermore, this application will allow the user to move the nodes and visualize additional information for each node clicking the corresponding node.

The next points (6.3.1 and 6.3.2) show the information which is obtained by using the graph visualization, and complementary information is offered in the node visualization.

6.3.1 Graph Visualization

In this part, the connectivity matrix, graph1, is visualized. This matrix has been obtained using the procedure developed in point 6.1. So, the visualization of this graph allows the user to observe which connections have been established and which nodes have connected them. These connections determine the order of PET scans, as each node represents each analyzed PET scan.

In the graph, the connections depend on the level used to do the study of PET scans. So, if the study is done at slice level, the visualized graph will offer some connections that can change if the study is done at whole brain level.

Therefore, this application may know which level is used in the analysis of PET scans to obtain the order among them. So, the window of figure 14 is offered by this application to indicate the level of the analysis:

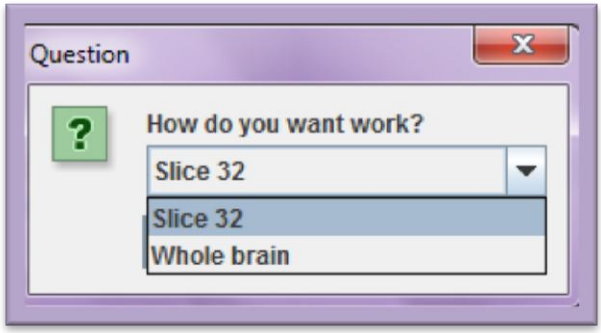


Figure 14: Window application to select the study level.

Once the level of the study has been indicated, the application displays the graph which corresponds to the connectivity matrix, graph1. This matrix stores the connections among PET scans and has been created previously.

Figure 15 shows an example of visualized graph using the slice level:

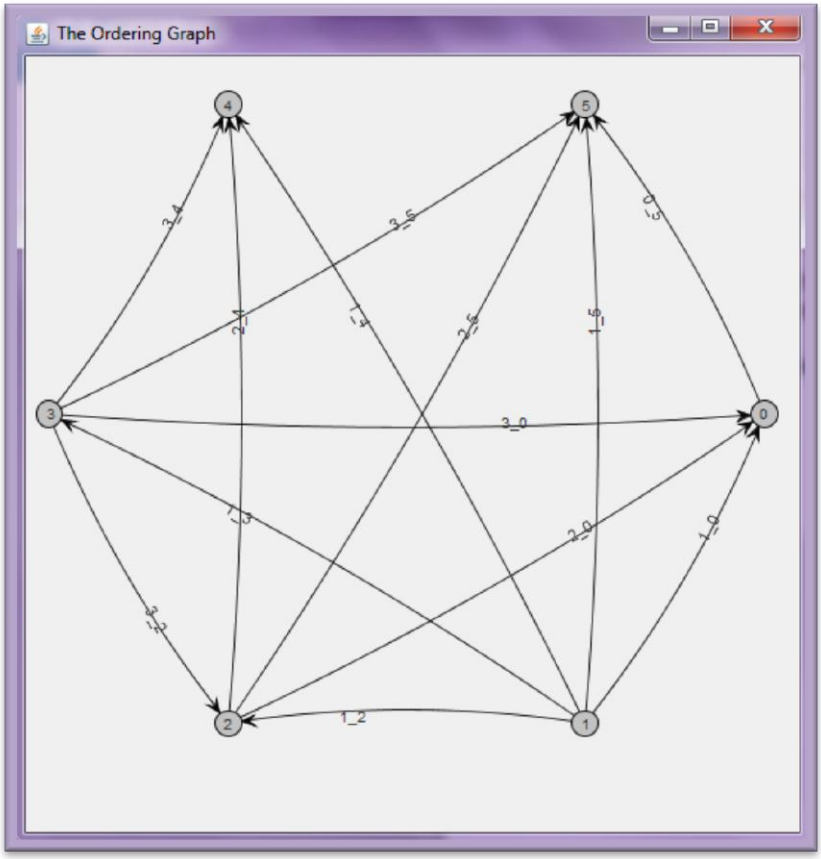


Figure 15: Graph visualization.

As the visualized graph is a directed an acyclic graph, the connections, which are represented by the edges, will only have one direction and do not produce cycles.

As it can be seen in figure 15, the nodes are labeled with the number of PET scan which each node represents; and the edges are labeled with the names of the nodes which each edge connects. This label has in the first position the name of origin node and in the second position the name of the destination node.

The graph visualization allows the user to observe the number of nodes, that is to say, the number of diseased images which are analyzed; as well as, the number of connections which are established among these images.

In this example, the graph of figure 15 has 6 nodes, that is to say, 6 diseased images have been analyzed and 13 connections have been established among them. We can see these connections in table 7:

ORIGIN NODE	NODE/S DESTINATION/S
node_0	node_5
node_1	node_0,node_2, node_3 node_4 and node_5
node_2	node_0, node_5 and node_4
node_3	node_0, node_2, node_4 and node_5
node_4	
node_5	

Table 7: Connections in the graph.

As it can be observed in table 7, we can find nodes without connections, such as, the node_4 and node_5. The reason could be that these nodes correspond with PET scans which have severe brain metabolism degradation, and therefore, the ordering procedure has considered them as leaves in the ordering graph. Otherwise, it could be because the parameters 2 and 3 have high values which can produce that some nodes do not connect with other nodes. For this reason, it is important that the parameters 2 and 3 have appropriate values since, the more approximated these values are the better order of PET scans will be obtained.

So, it is important to know the number of connections in the graph because this will help in the analysis of the values of the parameters 2 and 3. In this way, depending on the values of these parameters, it will have more or less connections in the ordering graph.

Point 6.3.2 shows the node visualization. This visualization offers more information about nodes and help to better understand the connections among them.

6.3.2 Node Visualization

In this point, all the additional information which can be visualized for each node of the ordering graph is explained

The application visualizes this information when the corresponding node is clicked twice. Before that, the application shows the window of figure 16. In this window, the user can select the type of information which he wants to visualize:

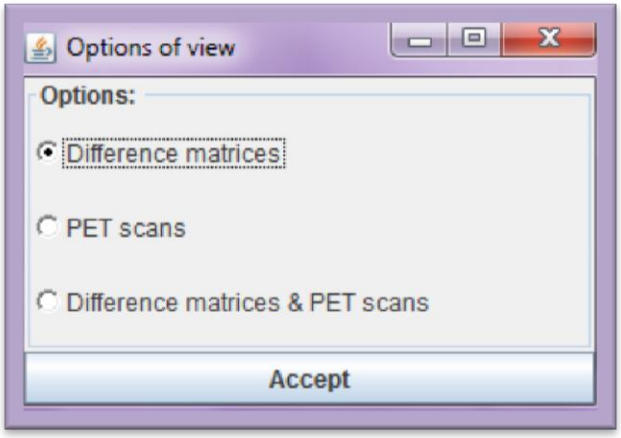


Figure 16: Window application to select the information.

Then, all the information offered by each one of the three previous options is detailed.

Difference matrices

With this option, the application visualizes the Excel file which contains the values of difference matrix corresponding to the PET scan that the selected node represents.

The difference matrices can have positive and negative values. So, the positive values represent the parts of the brain which show certain degradation in the brain metabolism. Given that these parts are the ones which we want to analyze, the tool Microsoft Excel has been used to select them.

The positive values are in a range from 0 to a maximum value so this range is selected in a red color. In addition, a degradation of the red color is shown from the maximum value to the values near 0. In this way, the affected areas of the PET scans corresponding to the difference matrices are selected.

The result of this process can be seen in figure 17:

Figure 17: Difference matrix visualization.

As it can be appreciated in figure 17, this image offers the zones of PET scans which have certain brain metabolism degradation.

The values of difference matrices are the differences between the values of minimum healthy matrix and the values of diseased matrix. So, a high value in the difference matrix means that, the value of the diseased matrix is smaller than the value of the minimum healthy matrix, and therefore, the difference among them is higher. In this way, this high value indicates that in the diseased image the metabolism is lower than the minimum metabolism, and therefore, it is an area with a greater impairment in the brain metabolism. In this case, this area is more affected by illness. For this reason, the areas with high values are colored with an intensive red.

On the other hand, the areas with a less intense red represent a lower impairment in the brain metabolism, and therefore, zones less affected by illness. However, these areas could be zones that the illness is beginning to affect. So, the obtaining of these images for each difference matrix provides a greater knowledge about the areas affected by the illness. In addition, the visualization of these images will help to better understand the position of the PET scans in the ordering graph.

PET scans

With this option, the application visualizes the PET scan corresponding to the clicked node. Moreover, the application allows the user to execute two programs of medical image processing. These programs will offer the user more information about the visualized PET scan, but also, other functionalities that will help to analyze the PET scans.

If this option is selected, the window of figure 18 will be displayed:

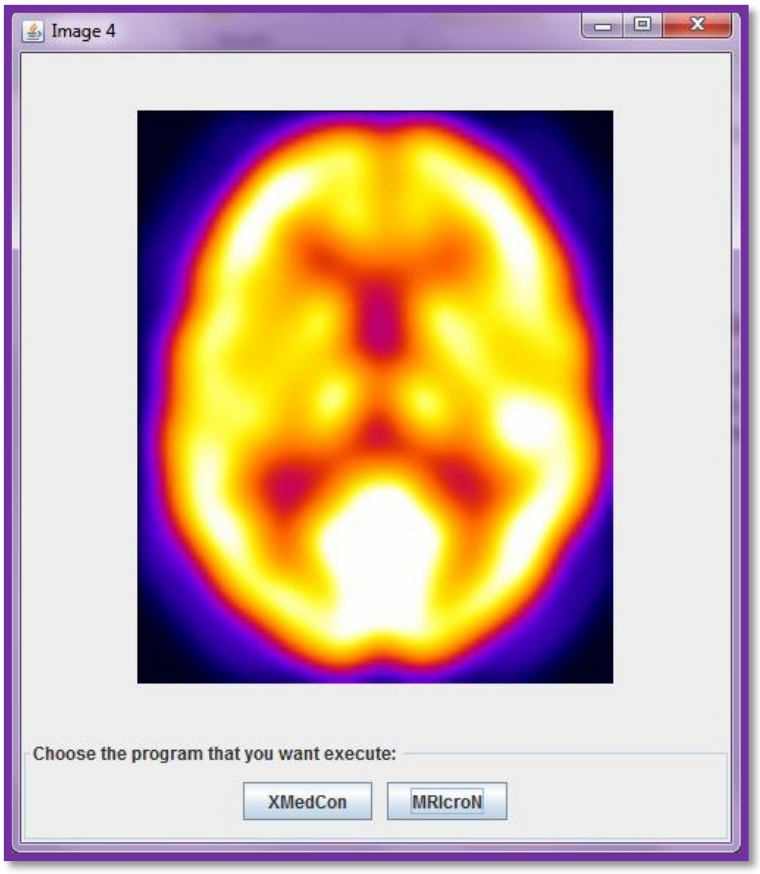


Figure 18: PET scan visualization.

As it can be appreciated in figure 18, the programs XMedCon and MRIcroN can be executed to better analyze the visualized PET scan. So, these programs can be executed using the buttons which are located at the bottom part of the image.

In this way, using the left button the user can run the XMedCon program. This program is usually used to converse medical images, but it also offers a graphical user interface in which all the slices of PET scans can be visualized. So, running this program in the application, the GUI of XMedCon will be displayed:

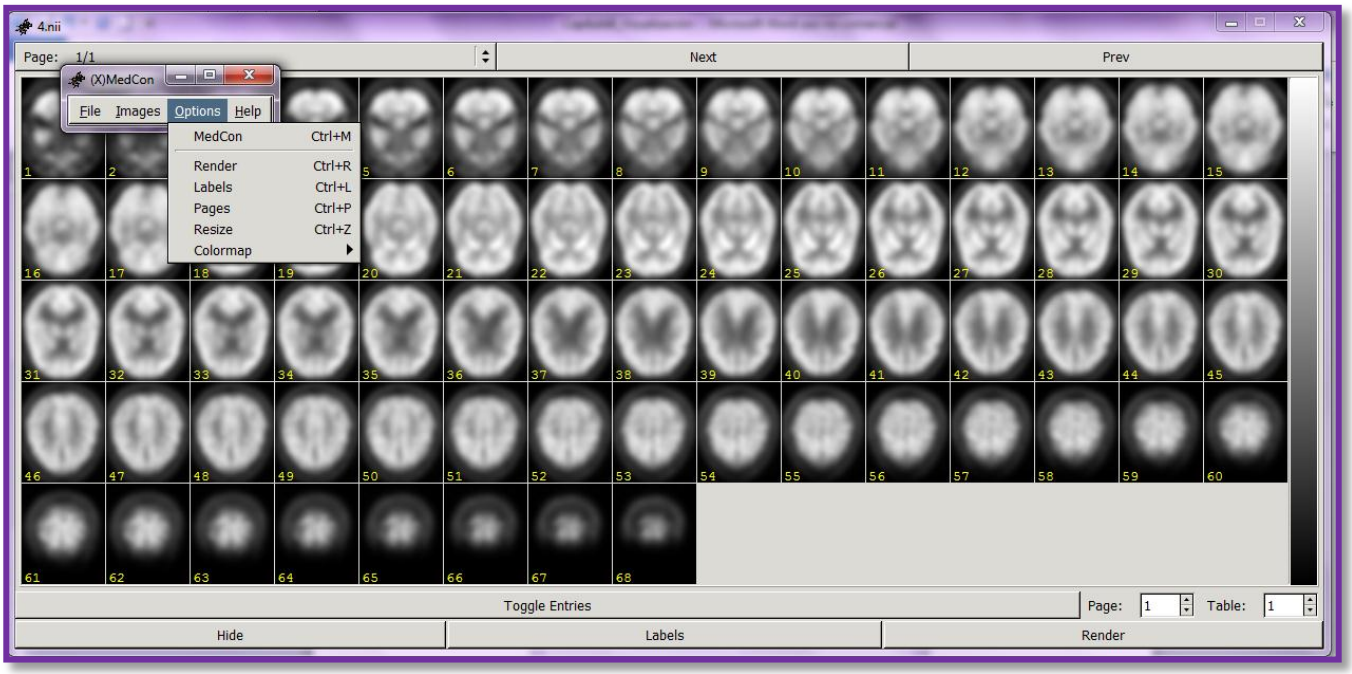


Figure 19: The user interface of XMedCon.

In figure 19, it can be appreciated that this program offers a lot of options to analyze the medical images (at the top-left of figure 19). However, in this project this program has been only used to convert the image and visualize the slices of PET scans. Therefore, this program has been added in the node visualization because, in a future work, all the functionalities of this program could be used to analyze in depth the PET scans.

On the other hand, using the right button the user can run the MRIcroN program. This is another of the most used software in medical image processing. MRIcroN offers a graphical user interface which allows the user to visualize the PET scans in their different views: axial, sagittal and coronal. The GUI of MRIcroN is shown in figure 20:

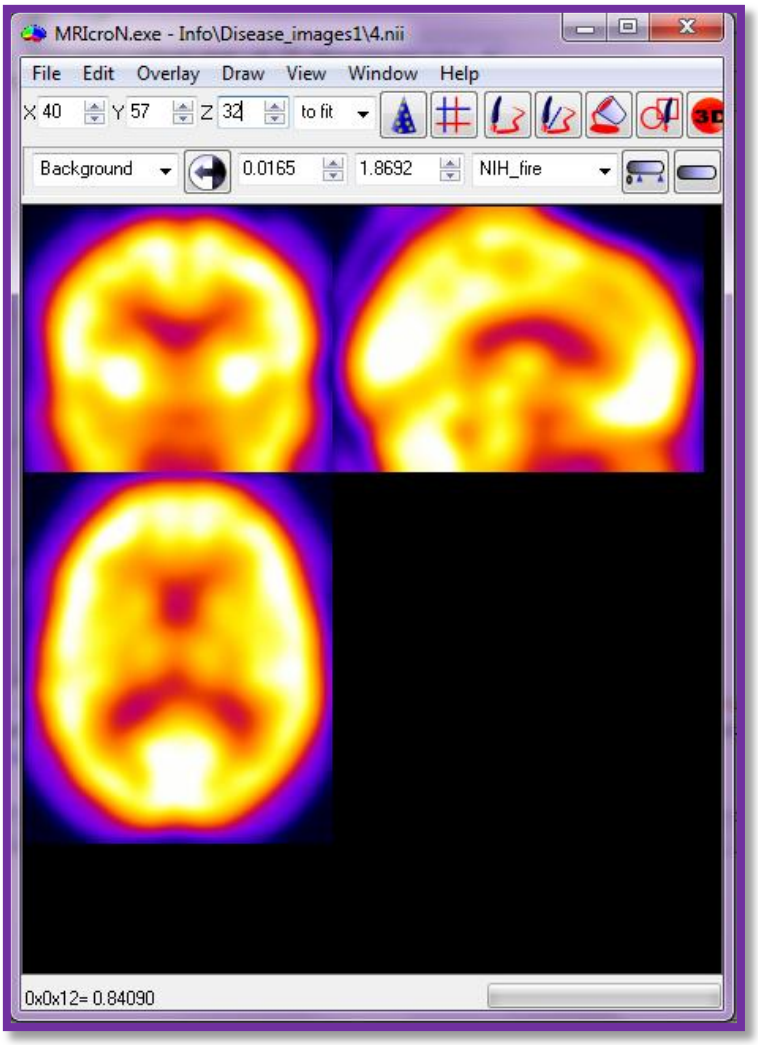


Figure 20: The user interface of MRICroN.

This program is usually used to locate regions of interests (ROIs, e.g. tumors). However, in this project this program has been only used to obtain the axial view of the slice 32 of the PET scans, and to get the PET scans with the colors that can be appreciated above. Nevertheless, this program offers lots of options to analyze the medical images. Therefore, this program has been added in the node visualization, because in a future work all the functionalities of this program could be used to analyze in depth the PET scans or to locate the ROIs of these PET scans.

Difference matrices & PET scans

Finally, with the third option all the information which it has been shown in the previous options can be visualized. In addition, the information about the diagnosis and the psychological tests, which are performed to the patients whose PET scans have been analyzed, are shown. This visualization can be seen in figure 21:

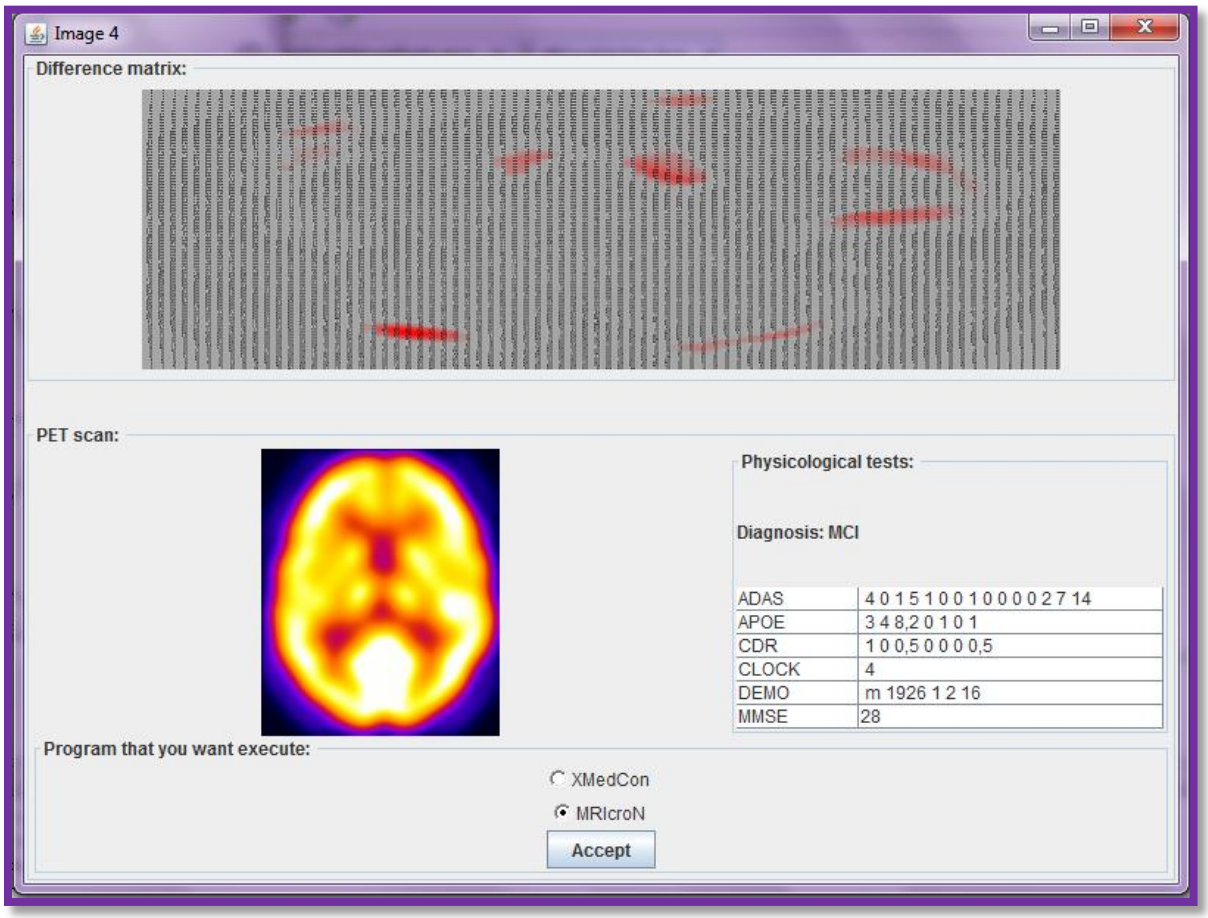


Figure 21: PET scans and difference matrices visualization.

On the right part of figure 21, all the information about the patient diagnosis is displayed, as well as, the results of the psychological tests which are performed to the patients. Furthermore, to know the parameters of each test, this application displays in small informative windows the values of each parameter for each psychological test. These informative windows appear when the name of the psychological test is clicked.

Figure 22 shows the informative windows of each psychological test:

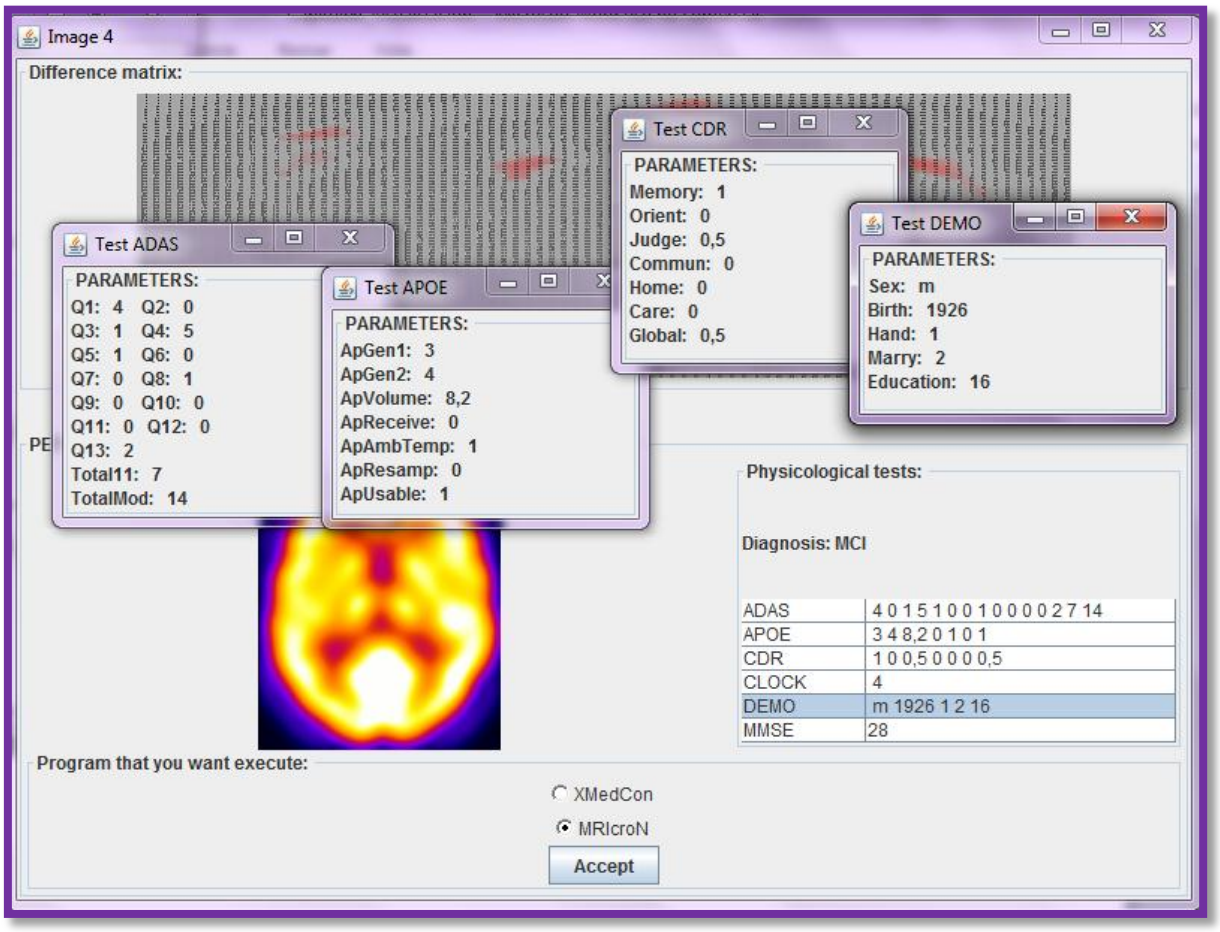


Figure 22: Information about psychological tests visualization.

In this way, all the information shown in this third option is helpful to analyze and evaluate the ordering graph which has been obtained.

Chapter 7

Evaluation

Once the procedure to obtain the order among PET scans has been explained, it can be observed that, the obtained order among PET scans will depend on the values which will be established for the parameters 2 and 3. For this reason, this chapter will analyze which values will be the most appropriate for these parameters.

To perform this analysis, two different approaches have been used. In the first approach, the best values for parameters 2 and 3 will be analyzed to order the PET scans of a particular patient who suffers Alzheimer's disease. In this way, the brain metabolism degradation in Alzheimer`s disease will be particularly visualized. In the second approach, the best values for the parameters 2 and 3 will be analyzed to order a set of PET scans of different patients who have different diagnose (MCI and AD). In this way, the overall brain metabolism degradation in Alzheimer's disease will be visualized. So, in both approaches, the analysis at slice level and at the whole brain level will be done.

All the experiments done in each approach and the measures used to evaluate the orderings will be described in the first section of this chapter. The obtained results and the most appropriate values for the parameters 2 and 3 will be shown and discussed in the second section of this chapter.

7.1 Experiment Settings

Recalling that, the value of parameter 2 for two given PET scans will determine which of them will have more overlap area; and, the value of parameter 3 will determine if the affected areas of two PET scans are similar or not. The object of these experiments will be to obtain the ordering graphs for each pair of values of the parameters 2 and 3, and to evaluate these graphs by using the evaluation measures of each test.

In each test, the ordering graphs will be evaluated by using the range of values from 10% to 90% for parameter 2, and the range of values from 0% to 20% for parameter 3.

7.1.1 Patients History Test

In this test, we evaluate which values for parameters 2 and 3 provide the best PET scans order from a particular patient, and therefore, the best visualization of the deterioration of metabolism in Alzheimer's disease in a particular case.

So, we see in the first section, which PET scans are analyzed, and in the second section, which evaluation measures are used to evaluate the order in this test.

7.1.1.1 Experiments

To achieve this test and its evaluation, we have used three sets of 6 PET scans from three different patients. So, we have applied the ordering procedure for each set of PET scans of each patient by using different values for the parameters 2 and 3. In this way, we have obtained the corresponding ordering graphs.

Given that in this test we have the original graphs of the PET scans by using their dates, we can do the comparison between the obtained graphs and the original graphs. So, by using the measures which we see in point 7.1.1.2, each obtained graph will be assessed in comparison with the original graph. In this way, the pair of values of the parameters 2 and 3, which will provide high scores, will be the most appropriate values for these parameters. Therefore with these values, the best orderings among PET scans of each patient will be obtained.

7.1.1.2 Evaluation measures

The measures that allow us to evaluate the obtained graphs in this test are: F-measure, median and average.

The measure F-measure evaluates the accuracy of the obtained graphs for each pair of values of the parameters 2 and 3. To apply this measure, two calculations have to be done previously:

$$\text{Precision (p)} = \frac{\text{correct\_connections}}{\text{correct\_connections} + \text{correct\_connections\_not\_obtained}}$$

$$\text{Recall (r)} = \frac{\text{correct\_connections}}{\text{correct\_connections} + \text{obtained\_connections\_not\_correct}}$$

The correct_connections are the connections that are in the original graph and also, in the obtained graph; the correct_connections_not_obtained, are the connections that are in the original graph but are not in the obtained graph; and finally, the obtained_connections_not_correct, are the connections that are in the obtained graph but are not in the original graph.

Therefore, the measure F-measure has been calculated in the following way:

$$F = \frac{2 \cdot \text{precision} \cdot \text{recall}}{(\text{precision} + \text{recall})}$$

Figure 23: Calculation of F-measure

In this way, we have obtained the scores of the obtained graphs for each patient, and for each pair of values of the parameters 2 and 3.

Finally, we have calculated the measures average and median. The values of these measures are done in the following way:

Average: this calculation is done by using the next formula:

$$\bar{x} = \frac{1}{n}\sum_{i=1}^{n} a_i = \frac{a_1 + a_2 + \cdots + a_n}{n}$$

Figure 24: Calculation of average

Median: to calculate this value, we have followed these steps:

1. Sort the values.
2. Calculate the median by using the formula: ((n+1)/ 2), n is the number of values.

In this way, we have obtained the values of median and average from the three values of F-measure which have been calculated for each pair of values of the parameters 2 and 3. The values of these measures allow us to know the middle values for each pair of the values of the parameters 2 and 3. Therefore, analyzing the values of median, average and F-measure for each pair of values of the

parameters 2 and 3, we will know which values are the most appropriate for these parameters to obtain a good order among PET scans of the diseased person, and therefore, a particularly good visualization of the brain metabolism degradation in Alzheimer's disease.

7.1.2 Disease degradation Test

In this test, we evaluate which values for parameters 2 and 3 provide the best PET scans order from different patients, and therefore, a best visualization of the deterioration of metabolism in Alzheimer's disease in a general way.

So, we see in the first section, which PET scans are analyzed, and in the second section, which evaluation measures are used to evaluate the PET scans order in this test.

7.1.2.1 Experiments

To achieve this test and its evaluation, we have used a set of 77 PET scans from different patients who have different diagnose (MCI or AD). So, we have applied the ordering procedure to all set of PET scans by using different values for the parameters 2 and 3. In this way, we have obtained the corresponding ordering graphs.

Given that in this test we do not have the history of PET scans for each patient, an original graph cannot be used to evaluate the obtained graphs for each pair of values of the parameters 2 and 3. Therefore in this test, we use some features of PET scans to obtain the scores of the obtained graphs for each pair of values of the parameters 2 and 3. In this way, the pair of values, for these parameters, that will provide high scores, will be the most appropriate values for these parameters, and therefore, we will obtain with them a good order among PET scans of the diseased people, and as a consequence, we will also obtain a good visualization of the overall brain metabolism degradation in Alzheimer's disease.

7.1.2.2 Evaluation measures

Considering that we want to analyze the progress of the brain metabolism degradation in Alzheimer's disease, we have selected as evaluation measures those features of PET scans which can represent this progress.

So, we have used the diagnosis and the value of MMSE test as measures to evaluate the accuracy of the obtained graphs because both features show the state of dementia of the patients, whose PET scans are analyzed. This accuracy will represent the percentage of correct connections in the obtained graphs for each pair of values of the parameters 2 and 3.

Given that the PET scans have the following diagnosis:

- MCI: the patient suffers mild cognitive impairment but he/she does not develop Alzheimer's disease.

- MCI_conv: the patient suffers mild cognitive impairment and he/she can develop Alzheimer's disease.

- AD: the patient suffers Alzheimer's disease

The connections that fulfill the next conditions will be considered as correct in the obtained graphs:

- MCI→MCI
- MCI→MCI_conv
- MCI_conv→MCI_conv
- MCI_conv→AD
- AD→AD

The value of MMSE test can decrease 1 or 2 points and it does not mean there is impairment in the brain metabolism. For this reason, we have introduced three types of tolerances to evaluate the values of MMSE test in the connections of the obtained graphs. These tolerances are the following:

1) MMSE_prev >= MMSE_sig
2) MMSE_prev+1 >= MMSE_sig
3) MMSE_prev+2 >= MMSE_sig

In this way, to analyze if a connection among two PET scans (PET_scan1→PET_scan2) will be correct, we will compare the values of MMSE test for both PET scans. The value of MMSE test for the previous PET scan (PET_scan1) will be the MMSE_prev, and the value of MMSE test for the next PET scan (PET_scan2) will be the MMSE_sig.

So, we evaluate which tolerance provides more correct connections in the obtained graphs for each pair of values of the parameters 2 and 3. To obtain this evaluation, the next values have been selected:

- parameter 2 ϵ [10, 30]
- parameter 3 ϵ [0, 20]

In table 8 we show the results:

P2	P3	SCORE_MMSE1	SCORE_MMSE2	SCORE_MMSE3	SCORE_DIAGNOSE	SCORE_TOTAL	CONNECTIONS
10%	0%	72.32	80.51	87.158	61.84	55.57	1355
10%	5%	74.49	82.64	89.48	62.22	56.96	1141
10%	10%	75.45	83.15	89.53	62.93	57.280	831
10%	20%	79.21	87.528	92.609	65.35	60.739	433
20%	0%	74.48	81.609	88.39	64.94	58.62	870
20%	5%	75.40	82.27	89.13	64.41	58.55	801
20%	10%	75.71	83.096	89.488	64.06	58.238	704
20%	20%	79.21	87.528	92.609	65.35	60.73	433
30%	0%	73.60	82.52	88.475	65.24	58.73	538
30%	5%	74.85	83.62	89.668	64.91	59.259	513
30%	10%	75.10	84.23	90.248	64.73	59.33	482
30%	20%	78.44	87.53	92.72	65.19	60.77	385

Table 8: Scores for the tolerances of MMSE test

As we can analyze in table 8, the third tolerance is the one which obtains the highest scores. For this reason, we have selected tolerance 3 as the best tolerance to obtain good orderings among PET scans.

Therefore, we consider as correct connections in the obtained graphs, the connections that fulfill the condition of diagnosis and the condition of the value of MMSE test using the third tolerance (MMSE_prev+2 >= MMSE_sig). In this way, the final scores will be the percentages of correct connections in each obtained graph for each pair of values of the parameters 2 and 3.

So, analyzing the obtained scores for each pair of values of these parameters, we will know which values will be the most appropriate to obtain a good order among PET scans of the diseased people, and therefore, a good visualization of the overall brain metabolism degradation in Alzheimer's disease.

7.2 Results and Discussion

In this point, we see the scores of the ordering graphs which have been obtained for each pair of values of the parameters 2 and 3, and we discuss which values of these parameters are the most appropriate for each one of the performed tests.

7.2.1 Patients history test

In this type of test, we have evaluated each obtained graph by using the measure F-measure. This measure evaluates the accuracy of the obtained graphs regarding the original graph. Furthermore, for each pair of values of the parameters 2 and 3, the average and median are calculated to obtain the middle scores. In table 9, we show which scores have been obtained:

VALUES PARAMETERS P2 AND P3	SCORE PATIENT 009_S_1030	SCORE PATIENT 007_S_0128	SCORE PATIENT 007_S_0101	AVERAGE	MEDIAN
P2=10% **P3**=0%	0,20	0,38	0,38	0,32	0,38
P2=10% **P3**=5%	0,21	0,35	0,35	0,31	0,35
P2=10% **P3**=10%	0,22	0,37	0,37	0,32	0,37
P2=10% **P3**=20%	0,31	0,15	0,15	0,20	0,15
P2=20% **P3**=0%	0,20	0,38	0,38	0,32	0,38
P2=20% **P3**=5%	0,21	0,35	0,35	0,31	0,35
P2=20% **P3**=10%	0,22	0,37	0,37	0,32	0,37
P2=20% **P3**=20%	0,31	0,15	0,15	0,20	0,15
P2=30% **P3**=0%	0,20	0,38	0,38	0,32	0,38
P2=30% **P3**=5%	0,21	0,35	0,35	0,31	0,35
P2=30% **P3**=10%	0,22	0,37	0,37	0,32	0,37
P2=30% **P3**=20%	0,31	0,15	0,15	0,20	0,15
P2=40% **P3**=0%	0,20	0,38	0,38	0,32	0,38

P2=40%	**P3**=5%	0,21	0,35	0,35	0,31	0,35
P2=40%	**P3**=10%	0,22	0,37	0,37	0,32	0,37
P2=40%	**P3**=20%	0,31	0,15	0,15	0,20	0,15
P2=50%	**P3**=0%	0,20	0,38	0,30	0,29	0,30
P2=50%	**P3**=5%	0,21	0,35	0,25	0,27	0,25
P2=50%	**P3**=10%	0,22	0,37	0,27	0,29	0,26
P2=50%	**P3**=20%	0,31	0,15	0,15	0,20	0,15
P2=55%	**P3**=0%	0,20	0,25	0,25	0,23	0,25
P2=55%	**P3**=5%	0,21	0,29	0,28	0,26	0,29
P2=55%	**P3**=10%	0,22	0,31	0,31	0,28	0,31
P2=55%	**P3**=20%	0,31	0,18	0,18	0,22	0,18
P2=60%	**P3**=0%	0,20	0,15	0,15	0,17	0,15
P2=60%	**P3**=5%	0,21	0,17	0,17	0,18	0,17
P2=60%	**P3**=10%	0,22	0,18	0,18	0,19	0,18
P2=60%	**P3**=20%	0,31	0,20	0,20	0,24	0,20
P2=70%	**P3**=0%	0,20	0,17	0,17	0,18	0,17
P2=70%	**P3**=5%	0,21	0,18	0,18	0,19	0,18
P2=70%	**P3**=10%	0,22	0,20	0,20	0,21	0,20
P2=70%	**P3**=20%	0,31	0,20	0,20	0,24	0,20
P2=75%	**P3**=0%	0,22	0,18	0,18	0,19	0,18
P2=75%	**P3**=5%	0,23	0,20	0,20	0,21	0,20
P2=75%	**P3**=10%	0,25	0,22	0,22	0,23	0,22
P2=75%	**P3**=20%	0,31	0,22	0,22	0,25	0,22
P2=80%	**P3**=0%	0,22	0,22	0,22	0,22	0,22
P2=80%	**P3**=5%	0,23	0,22	0,22	0,22	0,22
P2=80%	**P3**=10%	0,25	0,22	0,22	0,23	0,22
P2=80%	**P3**=20%	0,31	0,22	0,22	0,25	0,22
P2=90%	**P3**=0%	0,25	0,25	0,25	0,25	0,25

Table 9: Scores of the Patients History Test

Analyzing table 9, it can be observed that all the calculated scores are below 1. Therefore, neither pair of values, for the parameters 2 and 3, provides an ordering like the original which has been obtained by using the date of the PET scans. So, we proceed to analyze which pair of values, for the parameters 2 and 3, shows the best orderings among PET scans.

We will begin analyzing the most appropriate values for parameter 2, and then, we will analyze which values will be the most appropriate for parameter 3. In this way, the most appropriate range of values for these parameters will be established. This range will offer the best order among PET scans, and therefore, the best visualization of the brain metabolism degradation in Alzheimer's disease, in a particular case.

As we can see in table 9, the lowest scores, for parameter 2, are in the area of the percentages above 50%, and the highest scores are in the area of the percentages below 50%. Therefore, the percentages below 50% are the most appropriate for parameter 2, because with these values the best results have been obtained. We see these values in table 10:

VALUES PARAMETERS P2 AND P3	SCORE PATIENT 009_S_1030	SCORE PATIENT 007_S_0128	SCORE PATIENT 007_S_0101	AVERAGE	MEDIAN
P2=10% **P3**=0%	0,20	0,38	0,38	0,32	0,38
P2=10% **P3**=5%	0,21	0,35	0,35	0,31	0,35
P2=10% **P3**=10%	0,22	0,37	0,37	0,32	0,37
P2=10% **P3**=20%	0,31	0,15	0,15	0,20	0,15
P2=20% **P3**=0%	0,20	0,38	0,38	0,32	0,38
P2=20% **P3**=5%	0,21	0,35	0,35	0,31	0,35
P2=20% **P3**=10%	0,22	0,37	0,37	0,32	0,37
P2=20% **P3**=20%	0,31	0,15	0,15	0,20	0,15
P2=30% **P3**=0%	0,20	0,38	0,38	0,32	0,38
P2=30% **P3**=5%	0,21	0,35	0,35	0,31	0,35
P2=30% **P3**=10%	0,22	0,37	0,37	0,32	0,37
P2=30% **P3**=20%	0,31	0,15	0,15	0,20	0,15
P2=40% **P3**=0%	0,20	0,38	0,38	0,32	0,38
P2=40% **P3**=5%	0,21	0,35	0,35	0,31	0,35
P2=40% **P3**=10%	0,22	0,37	0,37	0,32	0,37
P2=40% **P3**=20%	0,31	0,15	0,15	0,20	0,15
P2=50% **P3**=0%	0,20	0,38	0,3	0,29	0,30
P2=50% **P3**=5%	0,21	0,35	0,25	0,27	0,25
P2=50% **P3**=10%	0,22	0,37	0,27	0,29	0,26
P2=50% **P3**=20%	0,31	0,15	0,15	0,20	0,15

Table 10: The best scores of the Patients History Test

From table 10, it can be observed that for patient 007_S_0101, the best scores are in the area of percentages below 40% because with a 50% their scores are lower. So, we consider that percentage 50% does not guarantee good orderings for all patients. For this reason, this percentage is not an appropriate value for parameter 2, and this can be discarded.

Recalling the meaning of parameter 2, the percentages 10%, 20% and 30% are not restrictive conditions to evaluate the overlap areas of the PET scans. However, the percentage of 40% is a restrictive condition to evaluate the overlap areas of the PET scans. For this reason, we consider this percentage as the most appropriate for parameter 2 in this type of study. So, the most appropriate value for parameter 2 is showed in table 11:

VALUES PARAMETERS P2 AND P3		SCORE PATIENT 009_S_1030	SCORE PATIENT 007_S_0128	SCORE PATIENT 007_S_0101	AVERAGE	MEDIAN
P2=40%	**P3**=0%	0,20	0,38	0,38	0,32	0,38
P2=40%	**P3**=5%	0,21	0,35	0,35	0,31	0,35
P2=40%	**P3**=10%	0,22	0,37	0,37	0,32	0,37
P2=40%	**P3**=20%	0,31	0,15	0,15	0,20	0,15

Table 11: The most appropriate values for parameter 2 in the Patients History Test.

Once we know the most appropriate value for parameter 2 (table 11), we proceed with the analysis of the values for parameter 3.

The value of parameter 3 determines if the overlap areas of two PET scans are similar or different. So, if the overlap areas are similar the value of parameter 3 will place these PET scans in the same level in the ordering graph. On the other hand, if the overlap areas are different, the value of parameter 3 will place the PET scan with more overlap area before the PET scan with less overlap area, in the ordering graph. In this way, the brain metabolism degradation can be visualized.

Therefore, we see which values for parameter 3 provide the best results according to the value of 40% for parameter 2.

Analyzing table 11, the lowest scores are obtained with the percentage of 20%, and the highest scores with the remaining percentages (0%, 5% and 10%). Therefore, we consider that the percentages below 20% are the most appropriate for the parameter 3 in this approach. We see these values in table 12:

VALUES PARAMETERS P2 AND P3		SCORE PATIENT 009_S_1030	SCORE PATIENT 007_S_0128	SCORE PATIENT 007_S_0101	AVERAGE	MEDIAN
P2=40%	**P3**=0%	0,20	0,38	0,38	0,32	0,38
P2=40%	**P3**=5%	0,21	0,35	0,35	0,31	0,35
P2=40%	**P3**=10%	0,22	0,37	0,37	0,32	0,37

Table 12: The most appropriate values for parameter 2 and parameter 3 in the Patients History Test.

According to the meaning of parameter 3, we consider that the percentage of 0% is not a restrictive percentage to evaluate the difference between the overlap areas of PET scans, although with this percentage the results are better. So, with this percentage the ordering procedure does not take into account if the PET scans have similar overlap areas or not.

However, we consider that the percentage of 10% is more restrictive and the obtained orderings make more sense, although this percentage offers lower scores than the scores with a percentage of 0%. In this way, if the difference among the overlap areas of two PET scans is higher than 10%, this will mean that one of these PET scans provides more information about affected areas, and therefore, this PET scan should be posterior in the ordering graph.

In contrast, if the difference is lower than 10%, this will mean that both PET scans provide the same information about affected areas, and therefore, these PET scans should be in the same level in the ordering graph. In the case that two PET scans have different affected areas, the difference among their overlap areas will be also low, and therefore, these PET scans should be also in the same level in the ordering graph because they will be showing different information about the brain metabolism degradation.

So, with the percentage 10% for parameter 3, the brain metabolism degradation is better visualized.

Given that with the percentage 0% we obtain better results than the percentage 10%, we consider both values as the most appropriate values for parameter 3. Therefore, we conclude showing the most appropriate values for parameters 2 and 3, in table 13:

VALUES PARAMETERS P2 AND P3	SCORE PATIENT 009_S_1030	SCORE PATIENT 007_S_0128	SCORE PATIENT 007_S_0101	AVERAGE	MEDIAN
P2=40% **P3**=0%	0,20	0,38	0,38	0,32	0,38
P2=40% **P3**=10%	0,22	0,37	0,37	0,32	0,37

Table 13: Final values for parameters 2 and 3 in the Patients History Test.

Given that the above values, for the parameters 2 and 3, are the ones which better scores provide, they cannot be considered the best values for these parameters because their scores are not high enough. To better understand if the above values provide good orderings for this approach, we will analyze the obtained graphs by using the values of table 13 for the parameters 2 and 3.

So, we will evaluate the reason why the obtained graphs do not provide the same order as in the original graph. In addition, we will analyze the difference among obtained graphs according to the values of parameter 3 (0% and 10%) for the first patient and we will discuss which value is better. In this way, the ordering graphs of the other patients will be obtained by using the best value for parameter 3.

We begin the study of the obtained graphs with patient 009_S_1030. So, we show the original graph which has been obtained by using the dates of PET scans of this patient, in figure 25:

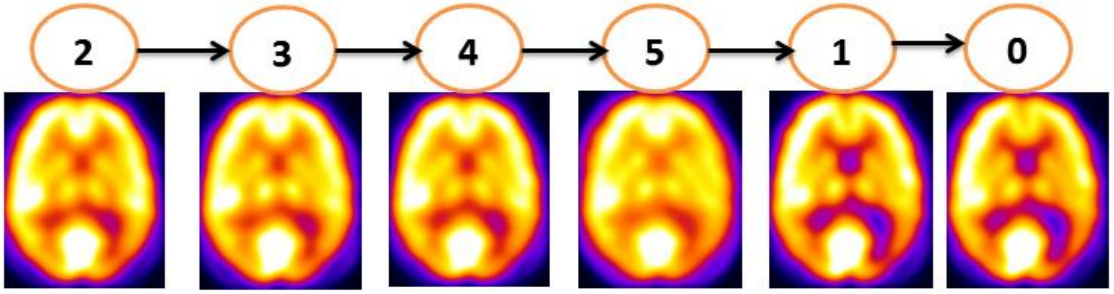


Figure 25: Original Graph of Patient 009_S_1030

As we can observe in figure 25, the structure of the original graph is a straight line because the order among PET scans is obtained according to their date. So, we will also analyze the structures of the obtained graphs, according to the values for parameters 2 and 3 of table 13.

In the first place, we analyze the difference between the obtained graph with the values 40% and 0% for the parameters 2 and 3, and the original graph shown in figure 25. So, we see the obtained graph in figure 26:

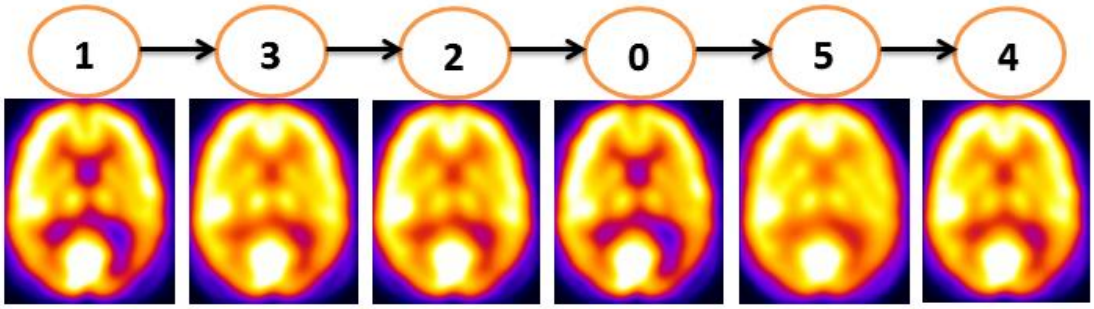


Figure 26: Ordering graph with p2=40% and p3=0%

As we can observe in figure 26, this obtained graph also has the same structure than the original graph (figure 25). However, the connections between the nodes 2 and 3, and the nodes 4 and 5 have opposite direction in relation to the original graph (figure 25). Therefore, we analyze the affected areas of these PET scans to understand why the ordering procedure has performed these connections in the obtained graph of figure 26. To do this, we use the images that show the affected areas of each PET scan. In the figures 27, 28, 29 and 30, we see the corresponding images to the PET scans 2, 3, 4 and 5:

Connection 3→2:

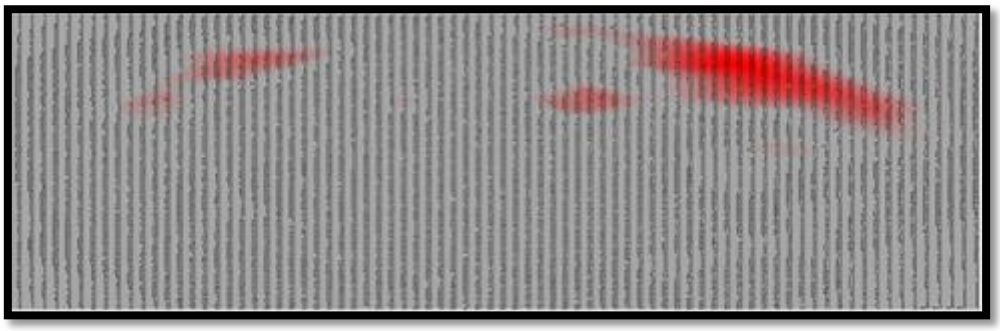


Figure 27: The affected areas of PET scan nº 3 (Patient: 009_S_1030)

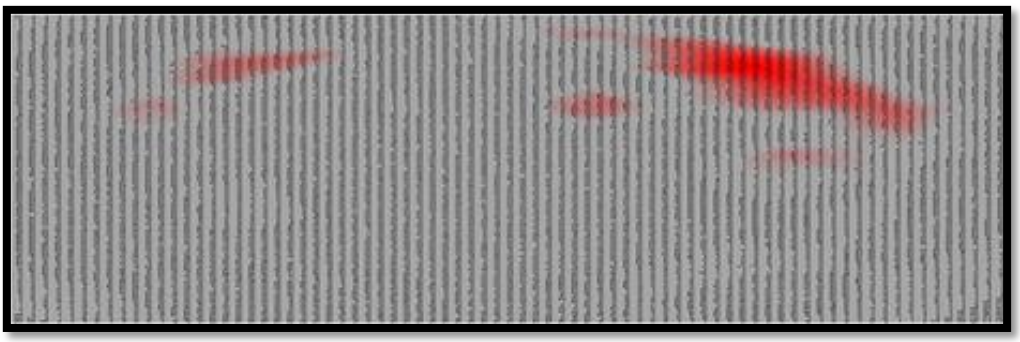


Figure 28: The affected areas of PET scan nº 2 (Patient: 009_S_1030)

As we can observe, in both figures (27 and 28) the affected areas are the same. However, in figure 28, the affected areas are better appreciated and on the right part of the image, there is an affected area which cannot be observed in figure 27. For this reason, the ordering procedure has placed PET scan 2 after PET scan 3. Nevertheless, this connection is right because shows certain degradation in the brain metabolism. This degradation can be observed because PET scan 2 has more affected areas than PET scan 3.

This connection is a clear example to explain why a high value for parameter 3 is better than a low value. In this example, the differences among these PET scans are small and their connection shows a small progression in the brain metabolism degradation. Therefore, with a high value for parameter 3 we will obtain a better order because the ordering procedure will place these PET scans at the same level in the ordering graph. We will see this when the order is done using the value 10% in parameter 3.

Then, we analyze the affected areas of the PET scans 5 and 4 to better understand their connection.

Connection 5→4:

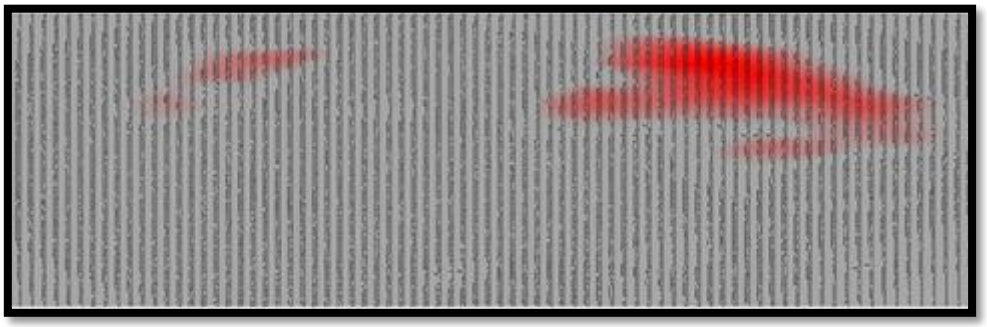


Figure 29: The affected areas of PET scan nº 5 (Patient: 009_S_1030)

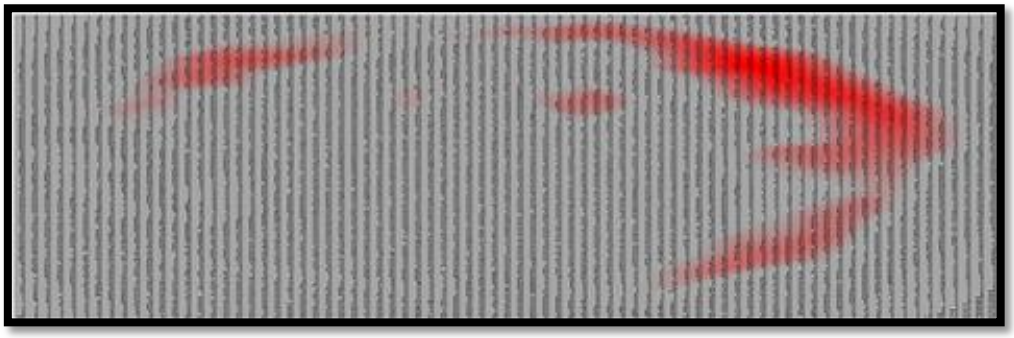


Figure 30: The affected areas of PET scan nº 4 (Patient: 009_S_1030)

Analyzing the figures 29 and 30, we can appreciate that this connection shows a progression in the brain metabolism degradation, since PET scan 4 shows a greater affected area. Nevertheless, PET scan 4 was obtained before that PET scan 5. Analyzing both figures, we observe that at the top of figure 29 the affected area has increased. However, the affected area which appears at the bottom-right of figure 30 cannot be observed in figure 29. This can be because the used dose of the tracer to obtain PET scan 5 was lower than the dose used to obtain PET scan 4. For this reason, the bottom-right affected area of figure 30 has not been detected in PET scan 5. Therefore, the ordering procedure has established PET scan 5 before PET scan 4 because this PET scan shows more affected areas than PET scan 5.

So, once we have analyzed why the ordering procedure has placed the above connections in opposite direction in relation to the original graph (figure 25), we compare the ordering graph of figure 26 with the ordering graph obtained using the percentages 40% and 10% for the parameters 2 and 3, respectively.

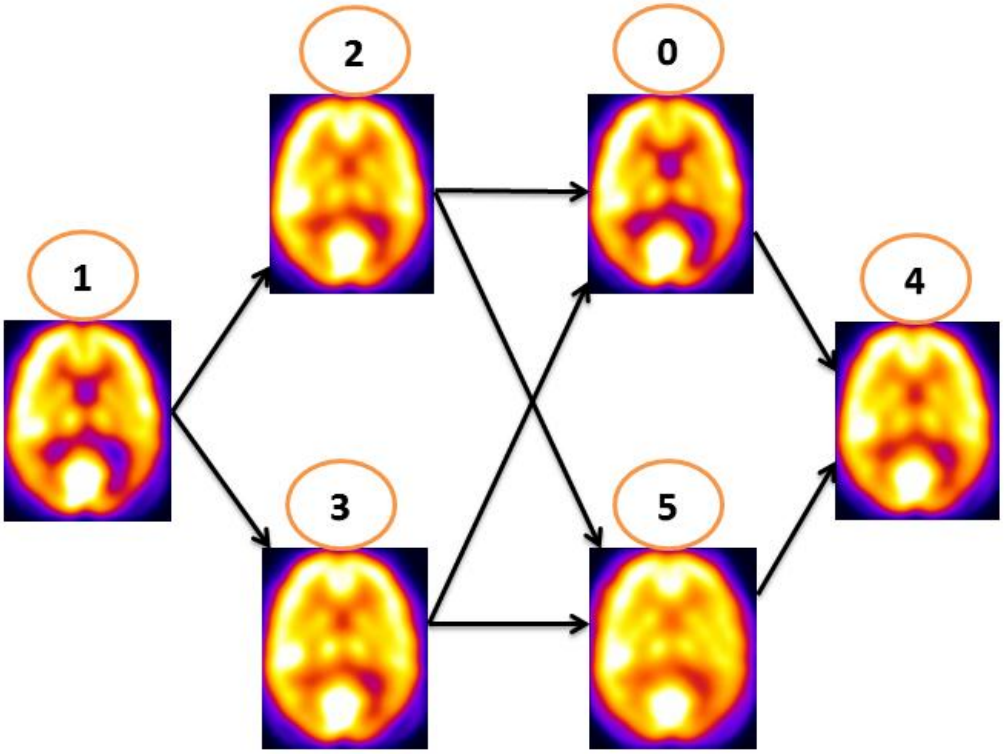


Figure 31: Ordering graph with p2=40% and p3=10% (Patient: 009_S_1030)

Analyzing the figures 31 and 26, we observe that with a percentage of 10% for parameter 3, some PET scans are located at the same level in the graph, (PET scans 2, 3, 0 and 5). Moreover, with this percentage the structure of the graph is not a straight line but a directed graph. So, we will analyze if the obtained graph of figure 31 will make more sense than the ordering graph of figure 26.

As we can observe in figure 31, the PET scans 2, 3, 5, and 0 are at the same level in the graph. For this reason, we will analyze these PET scans to understand why they are at the same level in the graph, and why the PET scans 2 and 3 are in a previous level than the PET scans 0 and 5. Finally, we will analyze why PET scan 1 is the root of the graph, as well as, why PET scan 4 is the last PET scan in the ordering graph of figure 31.

In this way, in the first place we analyze the affected areas of the PET scans 2, 3, 0 and 5 to understand their positions in the graph of figure 31.

So, analyzing the figures 27 and 28, we see that the PET scans 2 and 3, show the affected areas in the same part of the brain. Although, PET scan 2 was obtained before than PET scan 3, their relation shows a poor progression in the brain metabolism degradation. For this reason, the ordering procedure has placed these PET scans at the same level in the ordering graph of figure 31.

On the other hand, analyzing the figures 29 and 32, we see that the PET scans 5 and 0, show the affected areas in the same part of the brain. In addition, their relation also shows a poor progression in the brain metabolism degradation. For this reason, the ordering procedure has also placed these PET scans at the same level in the ordering graph of figure 31.

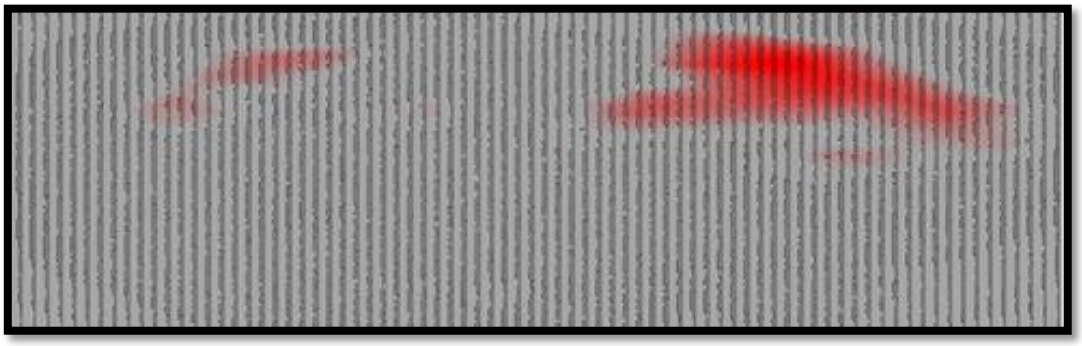


Figure 32: The affected areas of PET scan nº 0 (Patient: 009_S_1030)

So, analyzing the figures 27, 28, 29 and 32, we observe that the PET scans 2, 3, 5 and 0 are at the same level in the ordering graph because they show similar overlap areas, that is to say, similar affected areas in the brain. Furthermore, the PET scans 2 and 3 are in a previous level because they show less information about the brain metabolism degradation than the PET scans 5 and 0. Therefore, the visualization of the brain metabolism degradation makes more sense by using the percentage of 10% than with the percentage of 0% for parameter 3. So, the graph structure of figure 31 is better than the graph structure of figure 26.

Finally, we analyze the affected areas of the PET scans 1 and 4 to understand why PET scan 1 is the root of the graph and why PET scan 4 is the last PET scan in the graph of figure 31. Their affected areas can be observed in the figures 30 and 33:

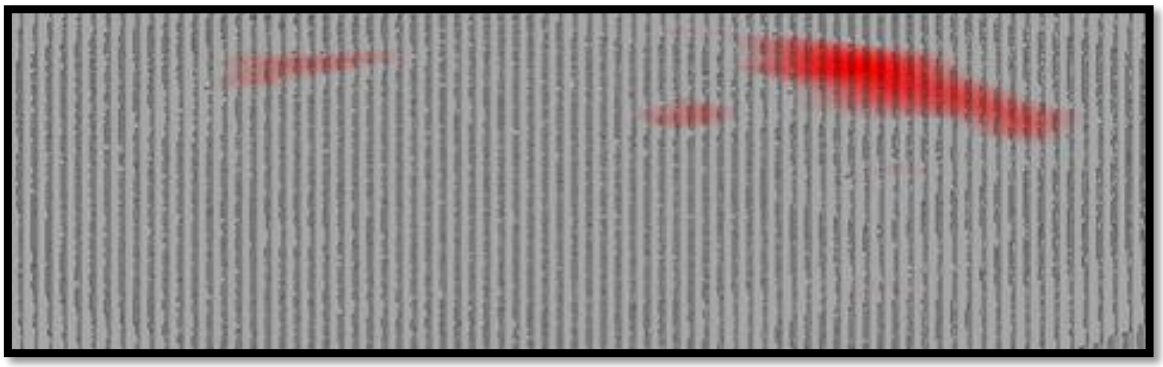


Figure 33: The affected areas of PET scan nº 1 (Patient 009_S_1030)

Analyzing the figures 30 and 33, we observe that PET scan 4 shows more affected areas than the remaining PET scans which have been visualized, previously. Furthermore, this PET scan shows a greater impairment in the brain metabolism in the right part of the image. In relation to PET scan 1, this shows less affected areas than the rest of PET scans. For this reason, and after the procedure compares all the affected areas of all PET scans, the procedure has placed PET scan 1 as a root of the ordering graph and PET scan 4 as a leaf of the ordering graph.

Therefore, we analyze the obtained graphs for the rest of the patients by using the values 40% and 10% for the parameters 2 and 3, respectively.

We continue the analysis of the obtained graphs with patient 007_S_0128. In figure 34, we show the original graph according to the date of the PET scans of this patient:

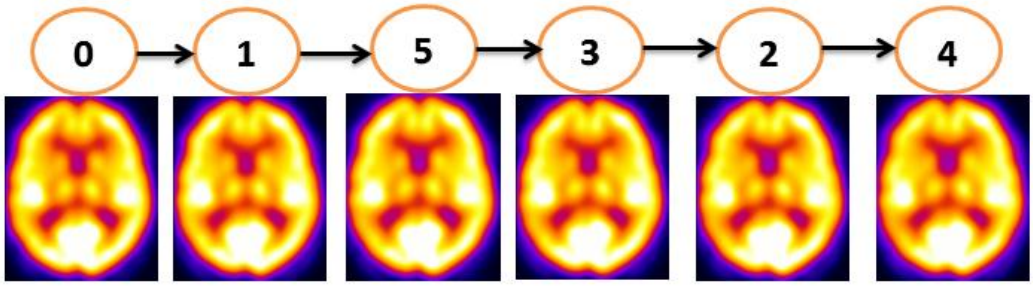


Figure 34: Original Graph of Patient 007_S_0128

As we can observe in figure 34, the PET scans of this patient are very similar, and therefore, this is a hard example to obtain a good order among PET scans. Nevertheless, we analyze which ordering among the PET scans of this patient has been obtained by using the values 40% and 10% for the parameters 2 and 3, respectively. We see this ordering in figure 35:

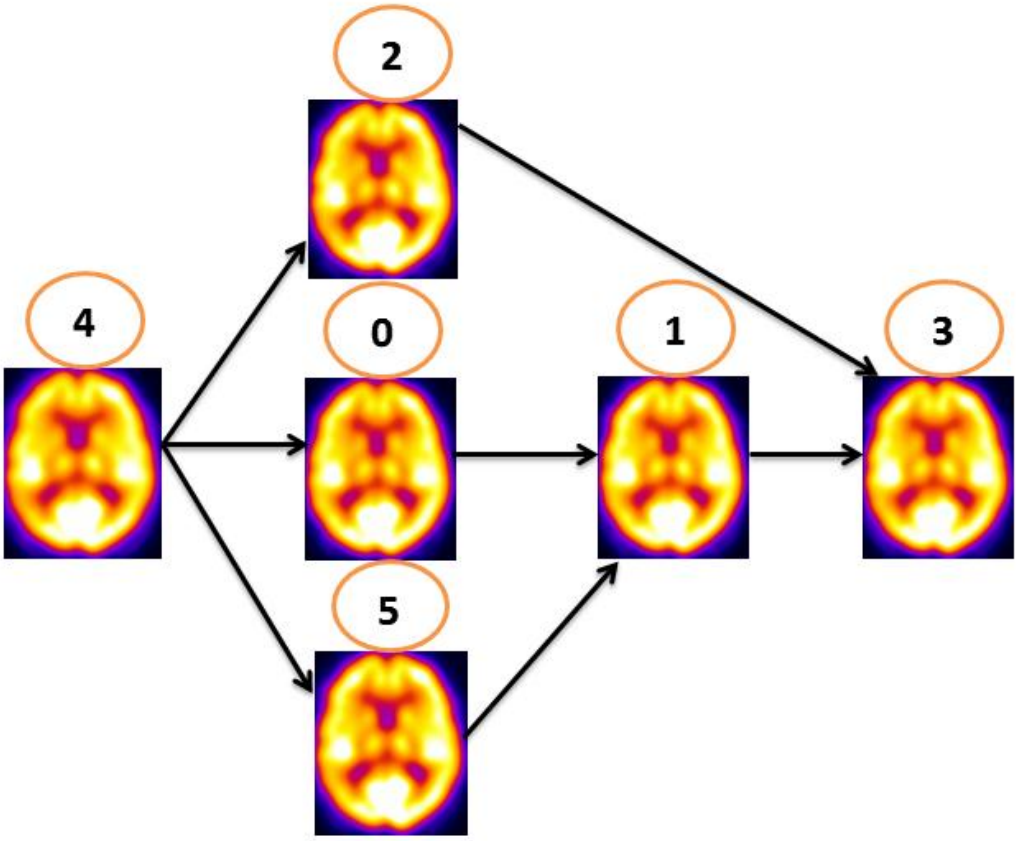


Figure 35: Ordering graph with p2=40% and p3=10% (Patient 007_S_0128)

As we can appreciate in figure 35, the PET scans 2, 0 and 5 are at the same level in the graph. So, we will analyze why the ordering procedure has placed these PET scans in this level. Moreover, we will analyze why the ordering procedure has placed PET scan 5 before PET scan 1, if in the original graph (figure 34) this connection has an opposite direction. Finally, we will analyze why PET scan 4 is the root of the graph and PET scan 3 is the last PET scan in the ordering graph of figure 35.

Then, we study the affected areas of the PET scans 2, 0 and 5 to understand why they are at the same level in the graph of figure 35. For this, we show the images of their affected areas in figures 36, 37 and 38:

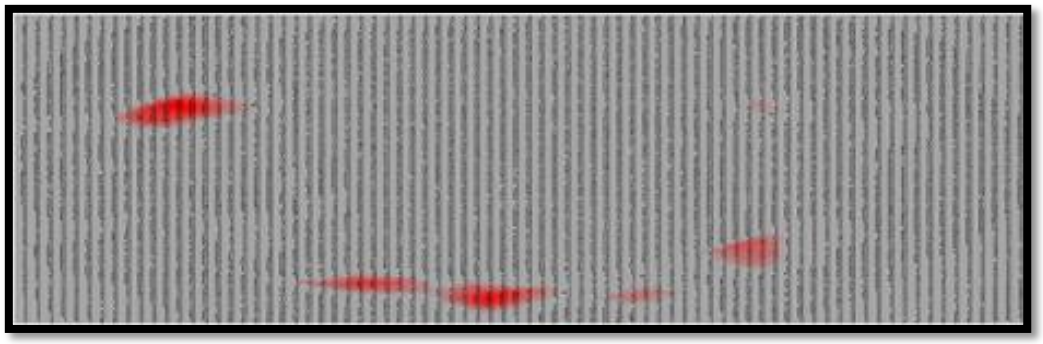


Figure 36: The affected areas of PET scan nº 0 (Patient 007_S_0128)

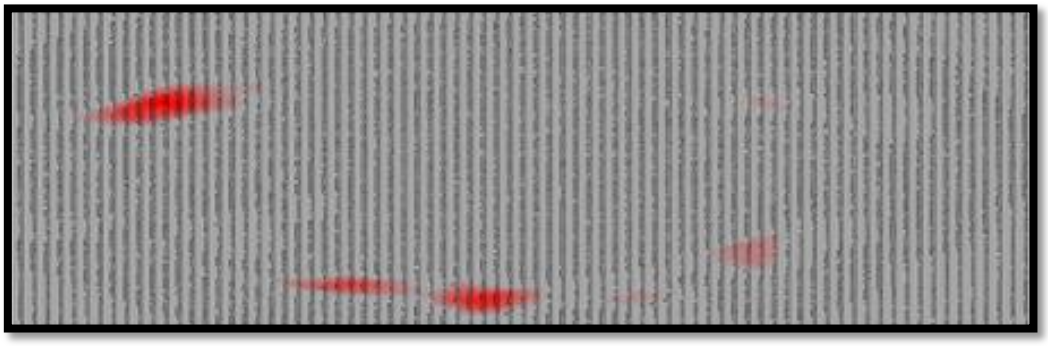


Figure 37: The affected areas of PET scan nº 2 (Patient 007_S_0128)

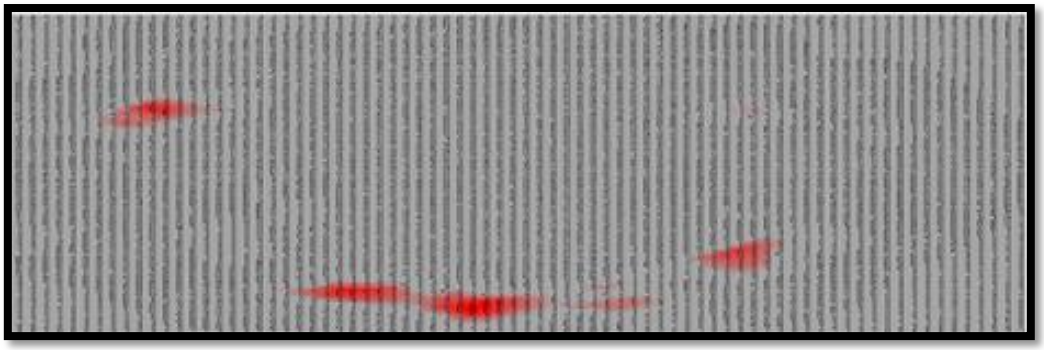


Figure 38: The affected areas of PET scan nº 5 (Patient 007_S_0128)

The three PET scans show the same affected areas at the bottom of the images (36, 37 and 38). Furthermore, the differences among these PET scans are small, and their relation shows a poor evolution in the brain metabolism degradation. Therefore, all these are enough conditions to place these PET scans at the same level in the ordering graph of figure 35.

Then, we study why the ordering procedure has placed PET scan 5 before PET scan 1, since PET scan 1 was obtained before PET scan 5. So, we see which affected areas show each of them in the figures 38 and 39:

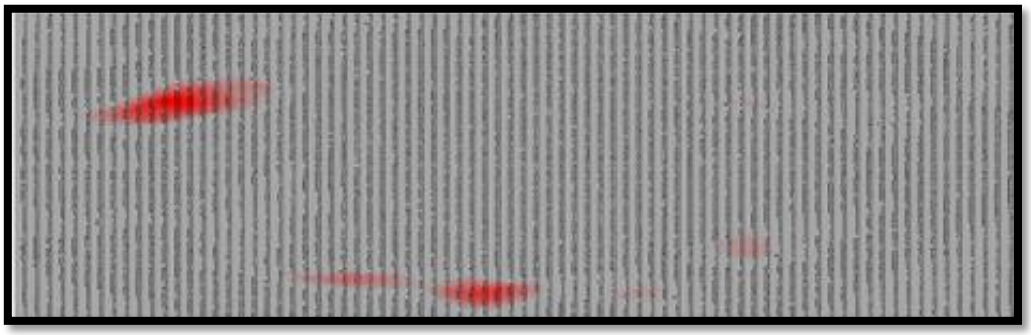


Figure 39: The affected areas of PET scan nº 1 (Patient 007_S_0128)

Analyzing the figures 38 and 39, we observe that figure 38 shows the affected areas at the bottom of the image better than figure 39. This makes sense because PET scan 5 was obtained after PET scan 1, and therefore, the affected areas of figure 38 indicate more impairment in the brain metabolism. However, the area which appears at the top-left of the images is bigger in figure 39 than in figure 38. In this case, we can suppose that the dose of tracer used to obtain PET scan 5 has not been enough to show the whole affected area which is observed in PET scan 1. For this reason, the distinction of these areas has provoked that the ordering procedure considers PET scan 1 before PET scan 5.

Finally, we study the affected areas of the PET scans 4 and 3 to understand why PET scan 4 is the root of the graph and PET 3 is the leaf of the graph. In this way, first we show the images of their affected areas in the figures 40 and 41:

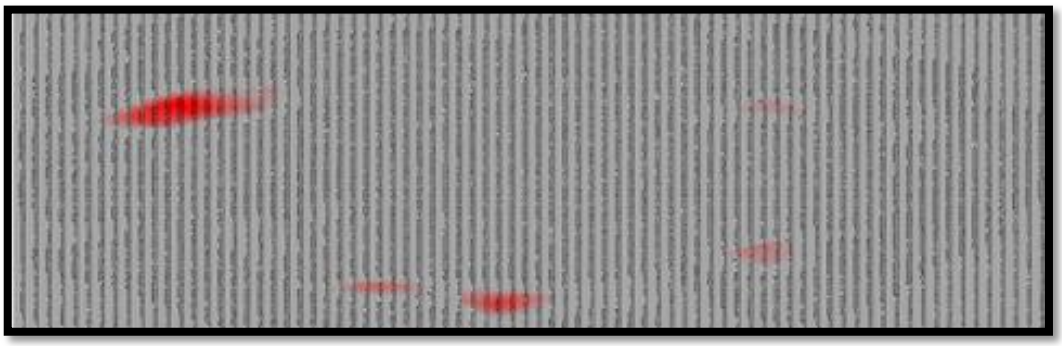


Figure 40: Affected areas of PET scan nº 4 (Patient 007_S_0128)

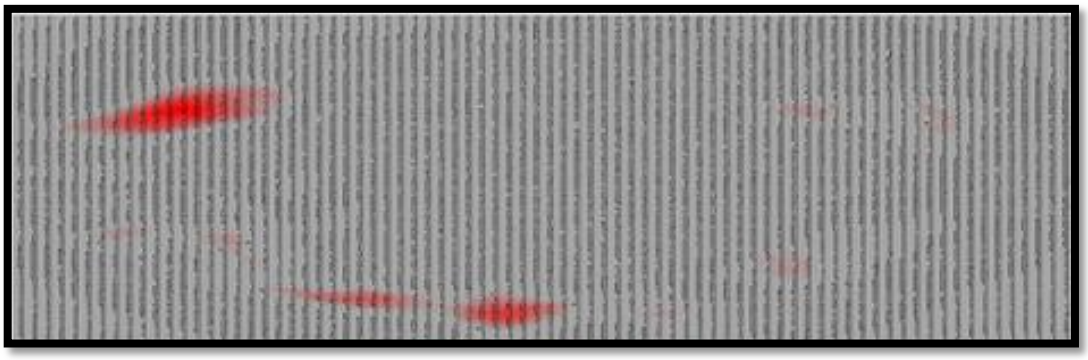


Figure 41: The affected areas of PET scan nº 3 (Patient 007_S_0128)

At the top-left of figure 40, the affected area is visualized with more intensity than in figure 41. However, the affected areas at the bottom of figure 40 are visualized with less intensity than the rest of PET scans. This provokes that PET scan 4 provides less affected areas than the remaining PET scans, and as a consequence this PET scan has been placed as a root of the graph.

In figure 41, the affected areas at the bottom of the images are visualized with less intensity than in figure 40. However, we can observe more affected areas at the top-right than in figure 40. This provokes that PET scan 3 has more affected areas than the remaining PET scans. For this reason, the ordering procedure has placed this PET scan as a leaf of the graph.

Finally, the last patient in the analysis of the obtained graphs is patient 007_S_0101. So, in figure 42, we show the original graph according to the date of the PET scans of this patient.

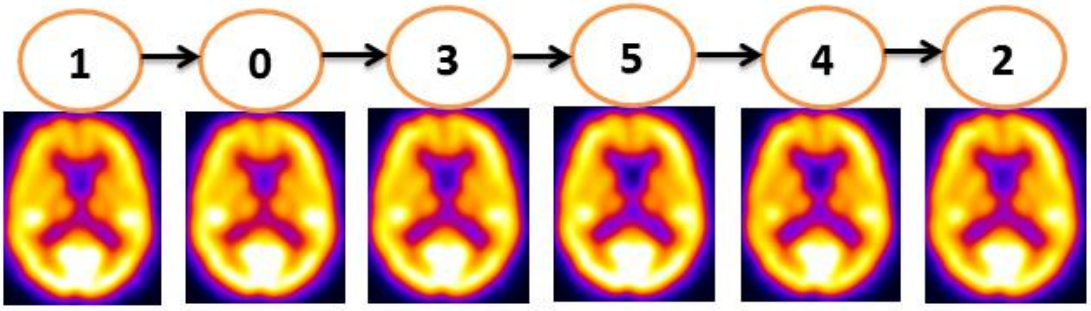


Figure 42: Original graph of patient 007_S_0101

We analyze which ordering among PET scans of this patient has been obtained by using the values 40% and 10% for the parameters 2 and 3, respectively. We see this ordering in figure 43:

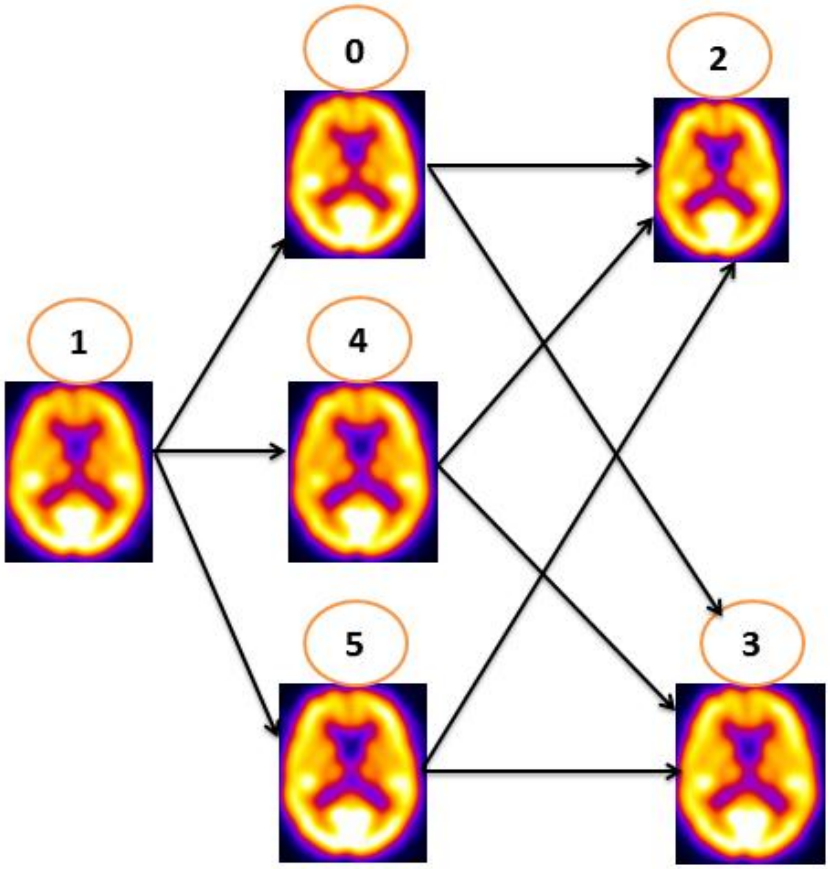


Figure 43: Ordering graph with p2=40% and p3=10% (Patient 007_S_0101)

Comparing the graph of figure 43 with the original graph (figure 42), we observe that the following connections are fulfilled: 1→0, 0→3 and 4→2.

In this way, we will analyze the PET scans 0, 4 and 5 to understand why the ordering procedure has placed these PET scans at the same level in the graph of figure 43. In addition, we will analyze the PET scans 3 and 2 to visualize the brain metabolism degradation that the connections 0→3, 5→2 and 4→3 will offer. Finally, we will analyze PET scan 1 to check its affected areas, since this is the first PET scan of the patient and also, the root of the ordering graph shown in figure 43.

Then, we examine the affected areas of the PET scans 0, 4 and 5 to understand their position in the ordering graph of figure 43. We see their affected areas in the figures 44, 45 and 46:

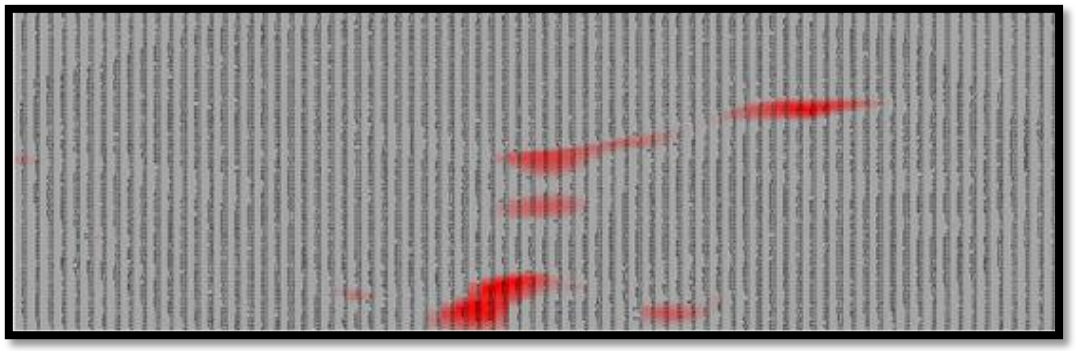


Figure 44: The affected areas of PET scan nº 0 (Patient 007_S_0101)

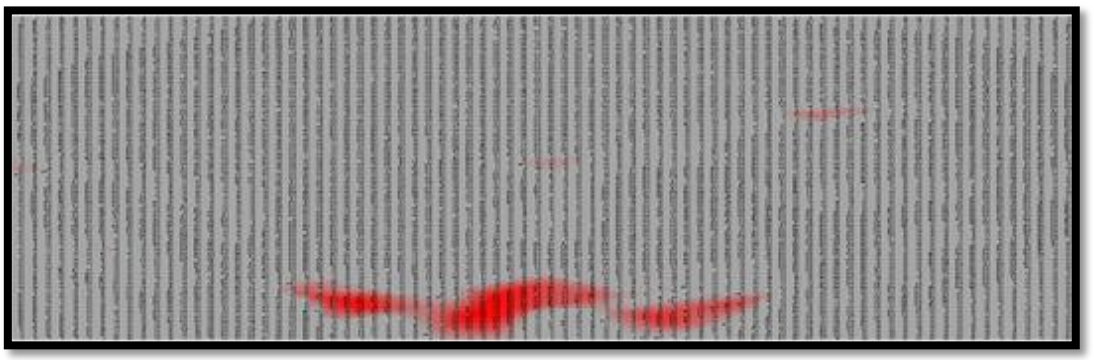


Figure 45: The affected areas of PET scan nº 4 (Patient 007_S_0101)

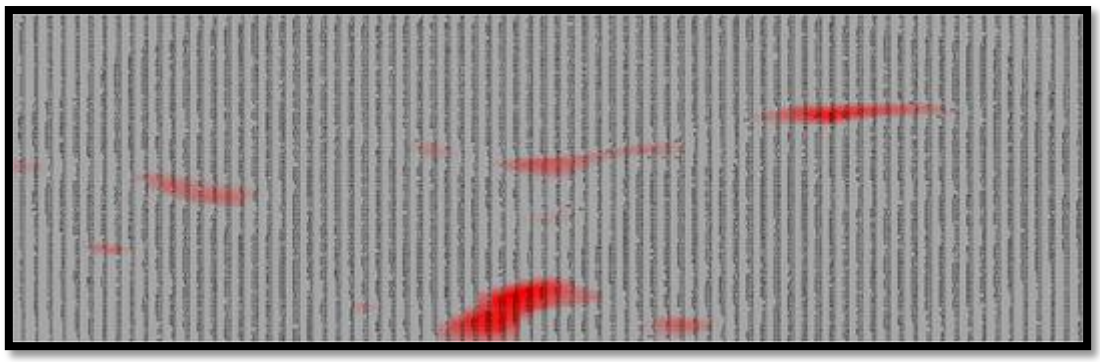


Figure 46: The affected areas of PET scan nº 5 (Patient 007_S_0101)

Analyzing the figures 44, 45 and 46, we observe that the PET scans 0, 4 and 5 show a common affected area at the bottom of these figures, but the progression of the brain metabolism degradation is different in each PET scan. In this way, we cannot establish connections among them because they do not show a relation among brain metabolism degradations. For this reason, the ordering procedure has placed these threes PET scans at the same level in the ordering graph of figure 43.

Then, we see the connections: 0→3, 5→2 and 4→3, to analyze the brain metabolism degradation which is offered for each one of these connections.

The connection between PET scan 0 and PET scan 3 shows the brain metabolism degradation visualized in the figures 44 and 47. So, we analyze these figures to understand why the graph of figure 43 has established this connection.

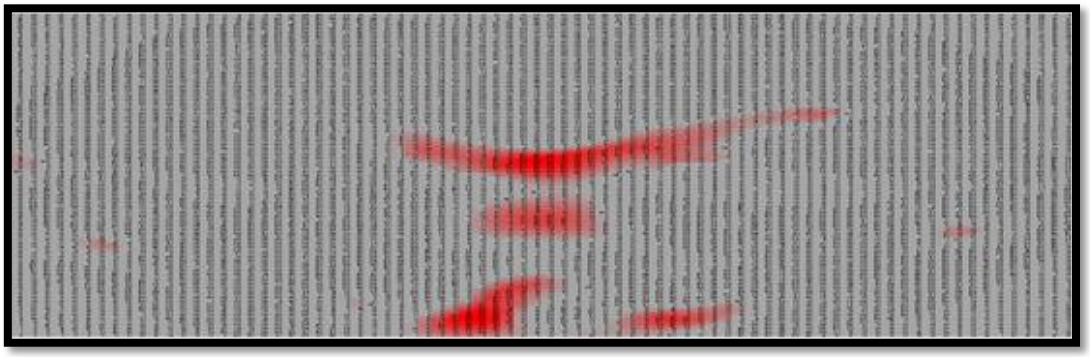


Figure 47: The affected areas of PET scan nº 3 (Patient 007_S_0101)

Analyzing the figures 44 and 47, we observe that the PET scans 0 and 3 show the same affected areas. However, in this connection we can observe a progression in the brain metabolism degradation because in PET scan 3 the affected areas are more increased. Therefore, their connection is correct, and moreover is a real connection because it also appears in the original graph (figure 42). In this way, we can confirm that when the affected areas are well visualized, the ordering procedure establishes real connections among PET scans.

The connection between PET scan 5 and PET scan 2 shows the brain metabolism degradation visualized in the figures 46 and 48. So, we analyze these figures to understand why the graph of figure 43 has established this connection.

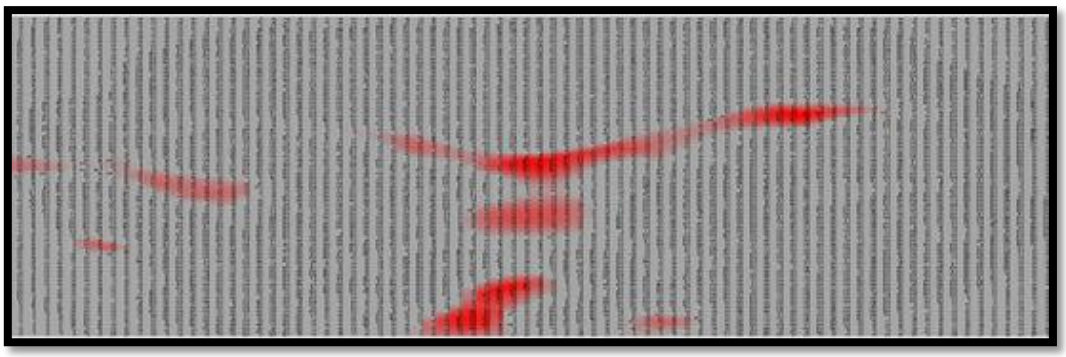


Figure 48: The affected areas of PET scan nº 2 (Patient 007_S_0101)

Analyzing the figures 46 and 48, we observe that the PET scans 5 and 2 also show the same affected areas. Furthermore, they visualize a progression in the brain metabolism degradation because in PET scan 2 the affected areas are more increased. So, these areas show a greater impairment in the brain metabolism. For this reason, the ordering procedure has placed PET scan 2 after PET scan 5. In this case, this connection is also correct and the order of the original graph (figure 42) is also fulfilled.

The connection between the PET scans 4 and 3 does not fulfill the established order in the original graph (figure 42). So, analyzing the figures 45 and 47, we observe that the PET scans 4 and 3 show the brain metabolism degradation in the central zone of the images. In this case, PET scan 4 was obtained after PET scan 3, and therefore, the affected areas at the bottom of the image are more visualized in figure 45 than in figure 47. However, analyzing the figures 45 and 47, we observe that PET scan 3 shows more affected areas than PET scan 4. For this reason, the ordering procedure has placed PET scan 4 before than PET scan 3.

Finally, we analyze the affected areas of PET scan 1. We see its affected areas in figure 49:

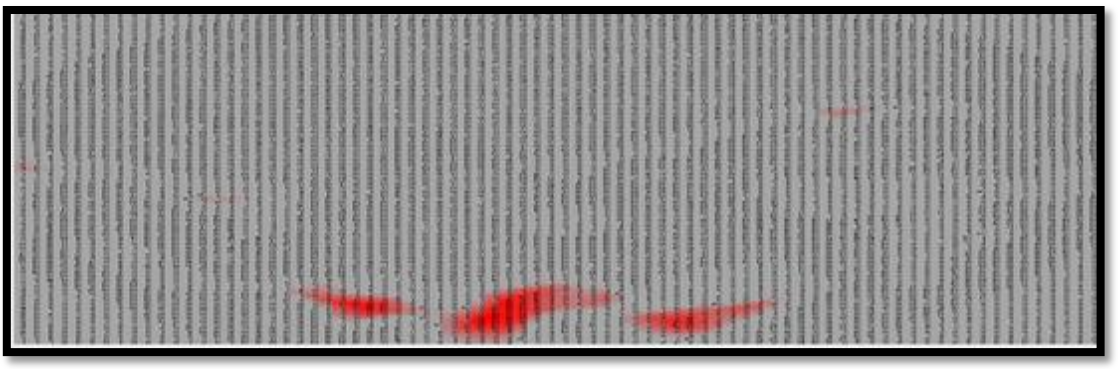


Figure 49: The affected areas of PET scan nº 1 (Patient 007_S_0101)

In figure 48 we observe that PET scan 1 has less affected areas than the rest of PET scans. This makes sense because PET scan 1 is the first PET scan of the patient, and therefore, its position in the graph of figure 43 is correct. Furthermore, this is also a real position according to the date of this PET scan.

Therefore, we can conclude that analyzing the images of affected areas, the ordering graph obtained by the ordering procedure is better understood. Furthermore, with these images we can better understand why the obtained graphs are different in relation to the original graph.

Then, we study which are the most appropriate values for the parameters 2 and 3 when the whole brain is analyzed. In table 14 we see the scores obtained in this study and we will know if the values of these parameters are the same as in table 13, or probably these values change in the analysis of the whole brain:

VALUES PARAMETERS P2 AND P3	SCORE PATIENT 009_S_1030	SCORE PATIENT 007_S_0128	SCORE PATIENT 007_S_0101	AVERAGE	MEDIAN
P2=10% **P3**=0%	0,30	0,20	0,30	0,27	0,30
P2=10% **P3**=5%	0,21	0,20	0,33	0,25	0,21
P2=10% **P3**=10%	0,25	0,24	0,37	0,29	0,25
P2=10% **P3**=20%	0,33	0,36	0,43	0,37	0,36
P2=20% **P3**=0%	0,30	0,20	0,30	0,27	0,30
P2=20% **P3**=5%	0,21	0,20	0,33	0,25	0,21
P2=20% **P3**=10%	0,25	0,24	0,37	0,29	0,25
P2=20% **P3**=20%	0,33	0,36	0,43	0,37	0,36
P2=30% **P3**=0%	0,30	0,20	0,30	0,27	0,30
P2=30% **P3**=5%	0,21	0,20	0,33	0,25	0,21
P2=30% **P3**=10%	0,25	0,24	0,37	0,29	0,25
P2=30% **P3**=20%	0,33	0,36	0,43	0,37	0,36
P2=40% **P3**=0%	0,30	0,20	0,30	0,27	0,30
P2=40% **P3**=5%	0,21	0,20	0,33	0,25	0,21
P2=40% **P3**=10%	0,25	0,24	0,37	0,29	0,25
P2=40% **P3**=20%	0,33	0,36	0,43	0,37	0,36
P2=50% **P3**=0%	0,30	0,20	0,30	0,27	0,3
P2=50% **P3**=5%	0,21	0,20	0,33	0,25	0,21
P2=50% **P3**=10%	0,25	0,24	0,37	0,29	0,25
P2=50% **P3**=20%	0,33	0,36	0,43	0,37	0,36
P2=55% **P3**=0%	0,30	0,20	0,30	0,27	0,3
P2=55% **P3**=5%	0,21	0,20	0,33	0,25	0,21
P2=55% **P3**=10%	0,25	0,24	0,37	0,29	0,25
P2=55% **P3**=20%	0,33	0,36	0,43	0,37	0,36
P2=60% **P3**=0%	0,30	0,20	0,30	0,27	0,30
P2=60% **P3**=5%	0,21	0,20	0,33	0,25	0,21
P2=60% **P3**=10%	0,25	0,24	0,37	0,29	0,25
P2=60% **P3**=20%	0,33	0,36	0,43	0,37	0,36
P2=70% **P3**=0%	0,30	0,20	0,24	0,25	0,24
P2=70% **P3**=5%	0,21	0,20	0,25	0,22	0,21
P2=70% **P3**=10%	0,25	0,24	0,29	0,26	0,25
P2=70% **P3**=20%	0,33	0,36	0,31	0,33	0,33
P2=75% **P3**=0%	0,30	0,20	0,13	0,21	0,20
P2=75% **P3**=5%	0,21	0,20	0,14	0,18	0,20
P2=75% **P3**=10%	0,25	0,24	0,15	0,22	0,24
P2=75% **P3**=20%	0,33	0,36	0,17	0,29	0,33
P2=80% **P3**=0%	0,33	0,11	0,20	0,21	0,20
P2=80% **P3**=5%	0,23	0,11	0,20	0,18	0,20
P2=80% **P3**=10%	0,28	0,13	0,22	0,21	0,22
P2=80% **P3**=20%	0,33	0,20	0,22	0,25	0,22

P2=90% **P3**=0%	0,28	0,16	0	0,15	0,16

Table 14: Scores of the Patients history test analyzing the whole brain.

From table 14, we observe that the lowest scores are in the area of the percentages above 60%. So, with these percentages the best results have not been obtained, and therefore, we can discard them because they are not appropriate for the parameter 2.

Analyzing the area of the percentages below 60% in table 14, we observe that all the scores are the same. That could be because the PET scans could have a lot of overlap area, and these values for parameter 2 are small enough. For this reason, we can consider that the percentages of 55% and 60% are the most restrictive to the condition of parameter 2, and therefore, the most appropriate if we want to obtain good orderings among PET scans by analyzing the whole brain. So, we show in table 15 the most appropriate values for parameter 2:

VALUES PARAMETERS P2 AND P3	SCORE PATIENT 009_S_1030	SCORE PATIENT 007_S_0128	SCORE PATIENT 007_S_0101	AVERAGE	MEDIAN
P2=55% **P3**=0%	0,30	0,20	0,30	0,27	0,30
P2=55% **P3**=5%	0,21	0,20	0,33	0,25	0,21
P2=55% **P3**=10%	0,25	0,24	0,37	0,29	0,25
P2=55% **P3**=20%	0,33	0,36	0,43	0,37	0,36
P2=60% **P3**=0%	0,30	0,20	0,30	0,27	0,3
P2=60% **P3**=5%	0,21	0,20	0,33	0,25	0,21
P2=60% **P3**=10%	0,25	0,24	0,37	0,29	0,25
P2=60% **P3**=20%	0,33	0,36	0,43	0,37	0,36

Table 15: The most appropriate values for parameter 2 in the Patients history test analyzing the whole brain.

Finally, analyzing the scores according to the values of parameter 3 in table 15, we observe that, with the percentages 10% and 20% we have obtained the highest scores. So, with these values the best orderings among PET scans have been obtained.

Therefore, the most appropriate values for the parameters 2 and 3 in the analysis of the whole brain are shown in table 16:

VALUES PARAMETERS P2 AND P3	SCORE PATIENT 009_S_1030	SCORE PATIENT 007_S_0128	SCORE PATIENT 007_S_0101	AVERAGE	MEDIAN
P2=55% **P3**=10%	0,25	0,24	0,37	0,29	0,25
P2=55% **P3**=20%	0,33	0,36	0,43	0,37	0,36
P2=60% **P3**=10%	0,25	0,24	0,37	0,29	0,25
P2=60% **P3**=20%	0,33	0,36	0,43	0,37	0,36

Table 16: The best values for parameter 2 and parameter 3 in the Patients history test analyzing the whole brain.

In this study, we observe that sometimes the dose of tracer used in the obtention of PET scans is not the same and that is why, the affected areas of the PET scans are not shown very well in all the PET scans. For this reason, the orderings among PET scans do not provide the same order than the original ordering according to the date of the PET scans. Nevertheless, analyzing the images of affected areas, the obtained orderings among PET scans are good.

In this way, we can conclude that the orderings among PET scans (figures 31, 35 and 43) are quite good for the most appropriate values of the parameters 2 and 3 when one slice of the PET scans is analyzed. In this way, using these graphs (figures 31, 35 and 43) we can show particularly the brain metabolism degradation in the development of Alzheimer's disease.

On the other hand, the analysis at the whole brain level is more complicated to do because it is a 3-dimensional analysis. For this reason, in this study the analysis using one slice of the PET scans has been done in more detail.

7.2.2 Disease degradation test

In this test, we have analyzed 77 PET scans and we have used the features of these PET scans (diagnose and value of MMSE test), to evaluate the obtained graphs according to the values of the parameters 2 and 3. In this evaluation, we have calculated a percentage of the connections which fulfill the conditions about diagnose and the value of MMSE test. These percentages have been calculated regarding to the total connections which have been established in the graph according to the values for the parameters 2 and 3.

In table 17 the obtained scores are shown:

P2	P3	SCORE_MMSE3	SCORE_DIAGNOSE	TOTAL_SCORE	CONNECTIONS
10%	0%	87.16	61.84	55.57	1355
10%	5%	89.48	62.22	56.96	1141
10%	10%	89.53	62.93	57.28	831
10%	20%	92.61	65.35	60.74	433
20%	0%	88.39	64.94	58.62	870
20%	5%	89.13	64.41	58.55	801

20%	10%	89.49	64.06	58.24	704
20%	20%	92.61	65.35	60.73	433
30%	0%	88.48	65.24	58.73	538
30%	5%	89.67	64.91	59.26	513
30%	10%	90.25	64.73	59.33	482
30%	20%	92.72	65.19	60.77	385
40%	0%	88.59	67.42	60.91	307
40%	5%	89.03	66.77	60.79	301
40%	10%	90.34	67.24	61.72	290
40%	20%	90.80	67.43	61.68	261
50%	0%	91.11	71.11	65.00	180
50%	5%	91.01	70.78	64.60	178
50%	10%	91.47	70.45	64.77	176
50%	20%	92.53	70.68	65.51	174
55%	0%	89.21	71.94	64.03	139
55%	5%	89.13	71.74	63.77	138
55%	10%	89.70	71.32	63.97	136
55%	20%	90.37	71.11	64.44	135
60%	0%	92.08	68.32	63.36	101
60%	5%	92.00	68.00	63.00	100
60%	10%	92.00	68.00	63.00	100
60%	20%	92.00	68.00	63.00	100
70%	0%	93.10	72.41	67.24	58
70%	5%	93.10	72.41	67.24	58
70%	10%	93.10	72.41	67.24	58
70%	20%	93.10	72.41	67.24	58
75%	0%	95.55	71.11	66.66	45
75%	5%	95.55	71.11	66.66	45
75%	10%	95.55	71.11	66.66	45
75%	20%	95.55	71.11	66.66	45
80%	0%	96.66	73.33	70.0	30
80%	5%	96.66	73.33	70.0	30
80%	10%	96.66	73.33	70.0	30
80%	20%	96.66	73.33	70.0	30
90%	0%	100.0	80.95	80.95	21

Table 17: Scores of the Disease degradation test

To better understand table 17 we detail the meaning of each column:

- **"score_mmse3":** this column contains the percentage of connections which fulfill the condition of the value of MMSE test;

- **“score_diagnose”:** this column contains the percentage of connections which fulfill the diagnosis condition;

- **“total_score”:** this column contains the percentage of connections that fulfill the MMSE test condition and the diagnosis condition;

- **“connections”:** this column contains the total connections which have been established in the graph for each pair of values of the parameters 2 and 3.

Once the columns of table 17 have been described, we proceed to the analysis of the most appropriate values for the parameters 2 and 3. We will begin analyzing the most appropriate values for parameter 2, and then, we will analyze which values will be the most appropriate for parameter 3. In this way, the most appropriate range of values for these parameters will be established. This range will offer the best order among PET scans, and therefore, the best visualization of the overall brain metabolism degradation in Alzheimer’s disease.

Analyzing table 17, we observe that in the column **“total_score”** the highest values are in the area of percentages above 55%. However, in this area the number of total connections is enough small, and as a consequence, the number of correct connections is lower than the total of PET scans which have been analyzed. Therefore, the area of percentages above 55% does not offer appropriate values for parameter 2. Table 18 shows the best values for parameter 2:

P2	P3	SCORE_MMSE3	SCORE_DIAGNOSE	SCORE_TOTAL	CONNECTIONS
10%	0%	87.158	61.84	55.57	1355
10%	5%	89.48	62.22	56.96	1141
10%	10%	89.53	62.93	57.280	831
10%	20%	92.609	65.35	60.739	433
20%	0%	88.39	64.94	58.62	870
20%	5%	89.13	64.41	58.55	801
20%	10%	89.488	64.06	58.238	704
20%	20%	92.609	65.35	60.73	433
30%	0%	88.475	65.24	58.73	538
30%	5%	89.668	64.91	59.259	513
30%	10%	90.248	64.73	59.33	482
30%	20%	92.72	65.19	60.77	385
40%	0%	88.59	67.42	60.91	307
40%	5%	89.03	66.77	60.79	301
40%	10%	90.34	67.24	61.72	290
40%	20%	90.80	67.43	61.68	261
50%	0%	91.11	71.11	65.0	180
50%	5%	91.011	70.78	64.60	178
50%	10%	91.47	70.45	64.77	176

50%	20%	92.528	70.68	65.51	174
55%	0%	89.208	71.94	64.028	139
55%	5%	89.13	71.739	63.768	138
55%	10%	89.70	71.32	63.97	136
55%	20%	90.37	71.11	64.444	135

Table 18: The best values for parameter 2 in the Disease degradation test

Analyzing table 18, we observe that with the percentages 50% and 55% we have obtained the highest scores. However, analyzing the number of total connections and evaluating the percentages of correct connections, we obtain less correct connections in relation to the total connections. In this case, some PET scans cannot be connected. Therefore, the percentages 50% and 55% are not appropriate for parameter 2 so we can discard them.

In this way, the most appropriate values for parameter 2 are in the area of percentages below 40%. We can see these values in table 19:

P2	P3	SCORE_MMSE3	SCORE_DIAGNOSE	SCORE_TOTAL	CONNECTIONS
10%	0%	87.158	61.84	55.57	1355
10%	5%	89.48	62.22	56.96	1141
10%	10%	89.53	62.93	57.280	831
10%	20%	92.609	65.35	60.739	433
20%	0%	88.39	64.94	58.62	870
20%	5%	89.13	64.41	58.55	801
20%	10%	89.488	64.06	58.238	704
20%	20%	92.609	65.35	60.73	433
30%	0%	88.475	65.24	58.73	538
30%	5%	89.668	64.91	59.259	513
30%	10%	90.248	64.73	59.33	482
30%	20%	92.72	65.19	60.77	385
40%	0%	88.59	67.42	60.91	307
40%	5%	89.03	66.77	60.79	301
40%	10%	90.34	67.24	61.72	290
40%	20%	90.80	67.43	61.68	261

Table 19: The most appropriate values for parameter 2 in the Disease degradation Test

From table 19 we evaluate which values for parameter 3 offer the best results.

The value of parameter 3 determines if the overlap areas of two PET scans are similar or different. So, if the overlap areas are similar the value of parameter 3 will place these PET scans in the same level in the ordering graph. On the other hand, if the overlap areas are different, the value of parameter 3 will place the PET scan

with more overlap area before the PET scan with less overlap area, in the ordering graph. In this way, the brain metabolism degradation can be visualized.

Analyzing table 19, we observe that the highest scores are in the percentages 10% and 20%. However, analyzing the total connections, the percentages 0% and 5% offer more correct connections. Nevertheless, the percentages 10% and 20% are more restrictive than the percentages 0% and 5%. Therefore, with the percentages 10% and 20% the PET scans with similar affected areas are located at the same level in the order. In this way, the obtained ordering graphs will be better.

So, we show in table 20 the most appropriate values for the parameters 2 and 3:

P2	P3	SCORE_MMSE3	SCORE_DIAGNOSE	SCORE_TOTAL	CONNECTIONS
10%	10%	89.53	62.93	57.280	831
10%	20%	92.609	65.35	60.739	433
20%	10%	89.488	64.06	58.238	704
20%	20%	92.609	65.35	60.73	433
30%	10%	90.248	64.73	59.33	482
30%	20%	92.72	65.19	60.77	385
40%	10%	90.34	67.24	61.72	290
40%	20%	90.80	67.43	61.68	261

Table 20: The most appropriate values for parameter 2 and parameter 3 in the Disease degradation Test

Given that there are a lot of connections among all 77 PET scans, it is difficult to show an ordering graph with all 77 PET scans. Therefore, we show an ordering among PET scans taking a set of them.

In figure 50, we show the ordering among PET scans which has been obtained by using the values 40% and 20% for the parameters 2 and 3.

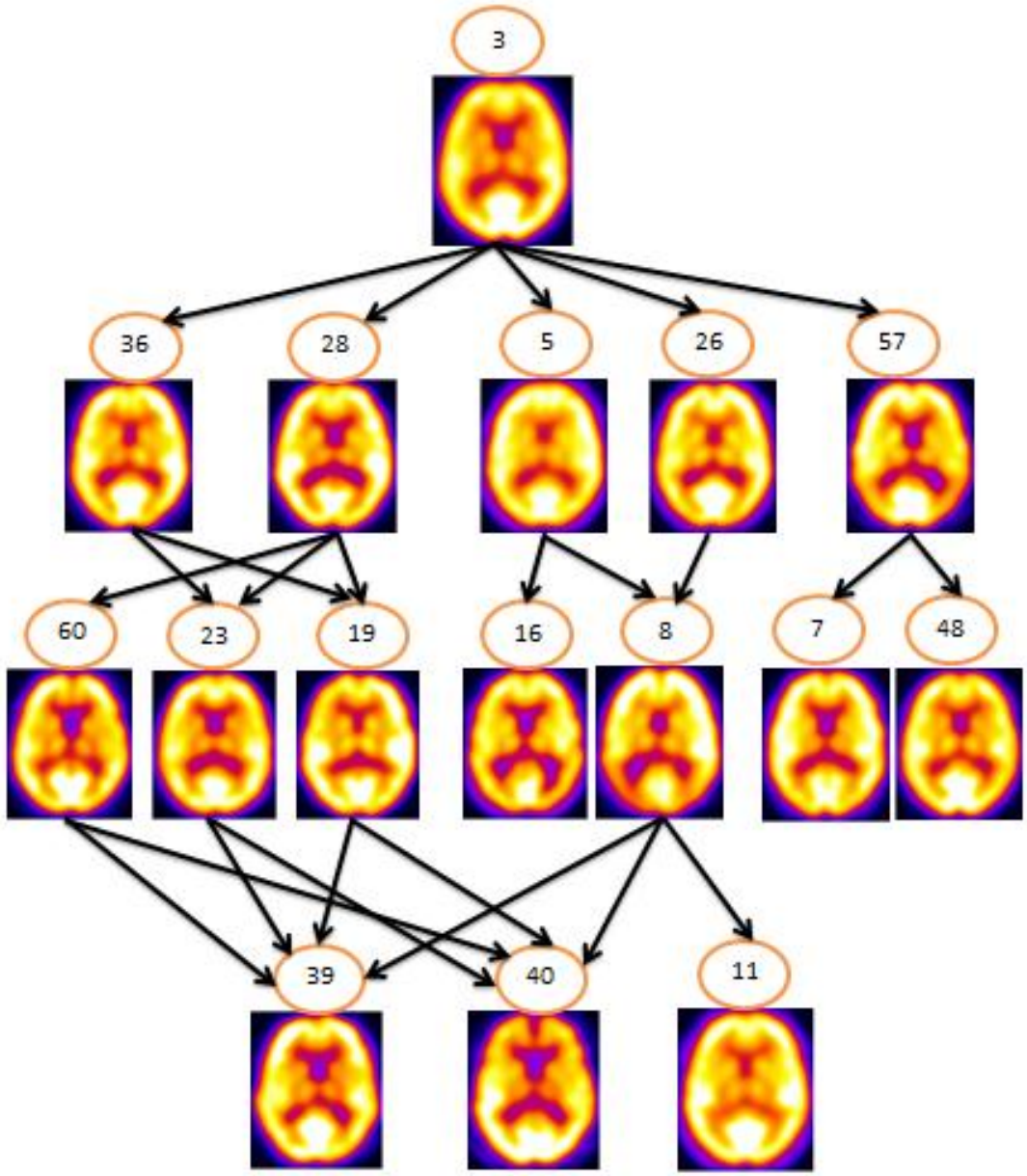


Figure 50: An example of ordering graph for the Disease degradation test.

In this approach, the ordering among PET scans of figure 50 cannot be compared with an original graph of the PET scans because we do not have the history about the date of PET scans. So, we can only analyze the number of correct connections in the obtained graph to evaluate its accuracy.

As we can observe in table 20 the obtained graphs provide more correct connections when the condition of MMSE value is analyzed, than when the condition of diagnosis is evaluated. For this reason, when both conditions are evaluated the correct connections are lower. So, we can conclude that in the ordering among PET scans, there are more connections which fulfill the condition of MMSE value than connections which fulfill the condition of diagnosis.

The condition of diagnosis can be less fulfilled because some of the PET scans with serious diagnosis has been obtained after than other PET scans with less serious diagnosis, and therefore, the dose used in the obtention of the PET scans with serious diagnosis is lower than the dose used in the obtention of the PET scans with less serious diagnosis. That is why, the affected areas of the PET scan with serious diagnosis can be less appreciated than the affected areas of the other PET scans with less serious diagnosis, and therefore, when the ordering procedure analyses the overlap areas in two PET scans it locates the PET scan with more overlap area before than the other PET scan with less overlap area.

On the other hand, the condition of the value of MMSE test can be more fulfilled because the value obtained by the patient in this test depends on some factors, such as, age, sex, education level. Therefore, in the graph we can find some PET scans with the same diagnosis and different values in MMSE test.

This can be checked, analyzing some connections of the graph of figure 50. So, we analyze the next connections:

The connection between PET scan 3 and PET scan 57 fulfills the condition of diagnosis and the condition of the value of MMSE test. In figures 51 and 52, the affected areas of these PET scans are shown:

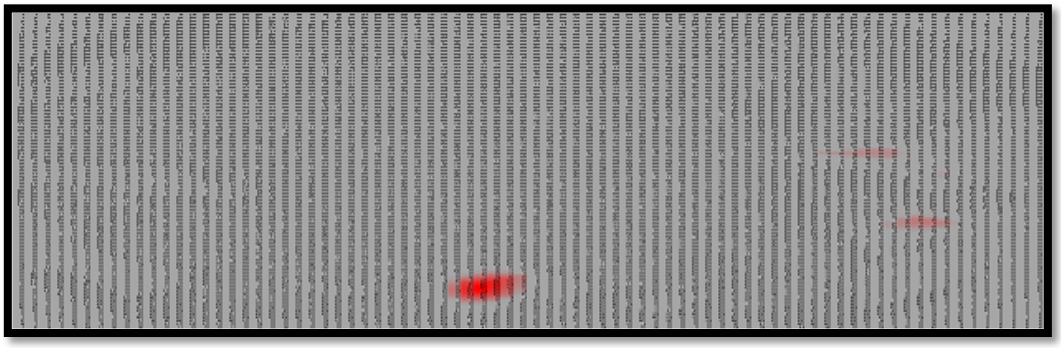


Figure 51: The affected areas of PET scan nº 3 (Graph figure 50)

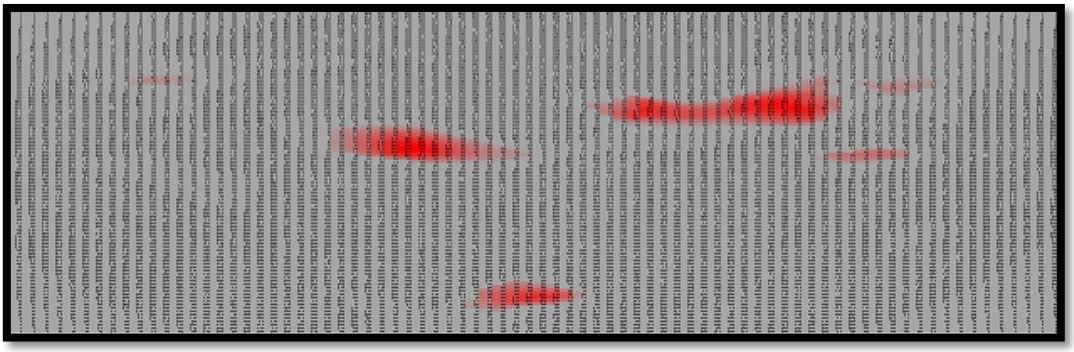


Figure 52: The affected areas of PET scan nº 57 (Graph figure 50)

PET scan 3 has MCI_conv diagnosis and value 30 in MMSE test and PET scan 57 has AD diagnosis and value 20 in MMSE test. So, the condition of diagnosis is fulfilled because PET scan 2 has a MCI_conv diagnosis which should be anterior to AD diagnosis. On the other hand, the condition of the MMSE test is also fulfilled because the MMSE values of both PET scans fulfill the third tolerance of MMSE test:

MMSE_prev +2 → the MMSE value of PET scan 3 +2 = 30+2=32

MMSE_sig → MMSE value of PET scan 57 = 20

3) MMSE_prev+2 >= MMSE_sig → 32 >= 20

For this reason, figure 52 shows more affected areas than figure 51. Furthermore, analyzing both figures, we observe that this connection shows the progress of the brain metabolism degradation in the middle of the brain.

The connection between PET scan 3 and PET scan 36 does not fulfill the condition of the diagnosis but their values of MMSE test are decreased. In figures 51 and 53, the affected areas of these PET scans are shown. So, we analyze their affected areas, and then, we evaluate why PET scan 3 is before PET scan 36.

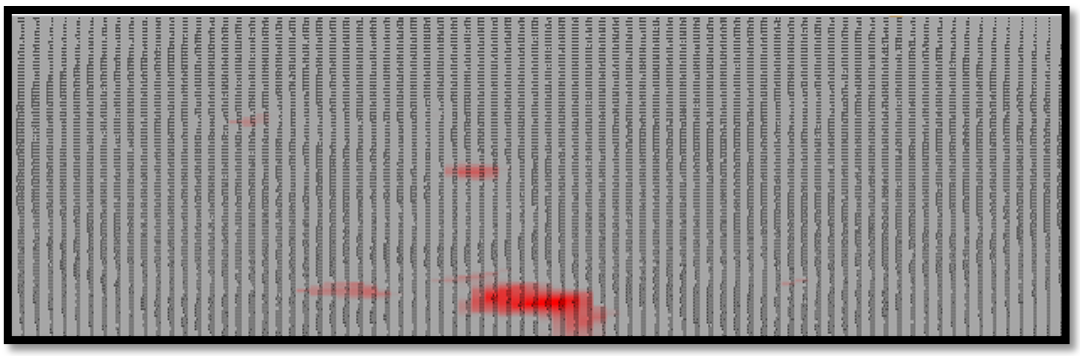


Figure 53: The affected areas of PET scan nº 36 (Graph figure 50)

Figure 53 represents PET scan 36 which has MCI diagnosis and value 28 in MMSE test. In this connection, the condition of diagnosis does not fulfill because PET scan 3 has MCI_conv diagnosis which should be posterior to MCI diagnosis of PET scan 36. On the other hand, in this connection the condition of MMSE test is fulfilled because the MMSE values of both PET scans fulfill the third tolerance of MMSE test:

MMSE_prev +2 → the MMSE value of PET scan 3 +2 = 30+2=32

MMSE_sig → MMSE value of PET scan 36 = 28

3) MMSE_prev+2 >= MMSE_sig → 32 >= 28

So, the reason of this connection could be that the dose used in the obtention of both PET scans is different. As we can observe, the affected areas in figure 53 are more visible than in figure 51. However, in figure 51 some affected area appears on the left part of the figure. So, we can conclude that the dose used in the obtention of PET scan 3 was lower than the dose used in PET scan 36. For this reason the affected areas in figure 53 are more visible than in figure 51, and therefore, the procedure has placed PET scan 3 before PET scan 36.

Finally, we see a connection that fulfills the condition of the diagnosis but it does not fulfill the condition of the value of MMSE test. This is the connection between PET scan 57 and PET scan 7. In figures 52 and 54, the affected areas of these PET scans are shown. So, we analyze their affected areas, and then, we evaluate why PET scan 57 is before PET scan 7.

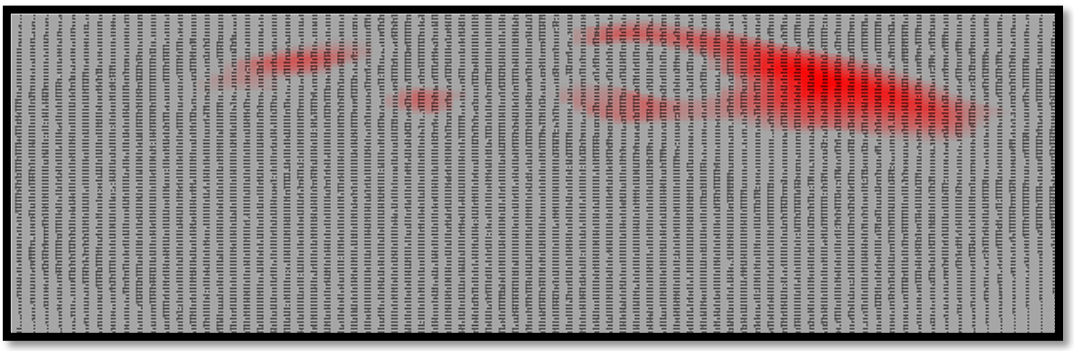


Figure 54: The affected areas of PET scan nº 7 (Graph figure 50)

Figure 54 represents PET scan 7 which has AD diagnosis and value 26 in MMSE test. In this connection the condition of diagnosis is fulfilled because both PET scans have AD diagnosis. On the other hand, in this connection the condition of the value of MMSE test does not fulfill because MMSE value of PET scan 57 is 20 and MMSE value of PET scan 7 is 26, and therefore, they do not fulfill the third tolerance of MMSE test:

MMSE_prev +2 → the MMSE value of PET scan 57 +2 = 20+2=22

MMSE_sig → MMSE value of PET scan 7 = 26

3) MMSE_prev+2 >= MMSE_sig → 22 >= 26 ✗

However, analyzing the figures 52 and 54 we can observe that at the top of figure 54 the affected area has been increased; otherwise, figure 52 shows other affected areas that cannot be appreciated in figure 54. The reason could be that the dose used in the obtention of these PET scans is different. Nevertheless, the connection is correct because PET scan 7 has more degradation in the brain metabolism than PET scan 57. Therefore, the condition of the value of MMSE test does not fulfill because the patient of PET scan 7 could have a higher education level than the patient of PET scan 57. So, both patients have developed Alzheimer's disease but one of them has obtained the best value in MMSE test.

Therefore analyzing these connections, we can observe that in this study, the doses used in the obtention of PET scans are also a problem to order the PET scans in a right way. However, we can conclude that the orderings among PET scans are quite good for the most appropriate values of the parameters 2 and 3 when one slice of the PET scans is analyzed. In this way, the overall brain metabolism degradation in the development of Alzheimer's disease can be shown.

Then, we study which are the most appropriate values for the parameters 2 and 3 when the whole brain is analyzed. In table 21 we see the scores obtained in this study and we will know if the values of these parameters are the same as in table 20, or probably these values change in the analysis of the whole brain:

P2	P3	SCORE_MMSE3	SCORE_DIAGNOSE	SCORE_TOTAL	CONNECTIONS
10%	0%	87.29	63.57	57.69	1598
10%	5%	89.35	63.09	57.68	1203
10%	10%	91.95	62.42	58.77	684
10%	20%	93.61	65.42	62.23	188
20%	0%	86.14	66.14	59.37	635
20%	5%	88.73	66.19	60.73	568
20%	10%	91.08	64.80	61.28	483
20%	20%	93.61	65.42	62.23	188
30%	0%	86.25	69.16	61.66	240
30%	5%	88.10	69.16	62.99	227
30%	10%	89.42	67.78	62.98	208
30%	20%	93.66	69.01	64.78	142
40%	0%	92.31	71.79	66.60	78
40%	5%	92.10	71.05	65.79	76
40%	10%	93.05	69.44	65.27	72
40%	20%	98.27	67.24	65.52	58
50%	0%	83.33	70.83	54.16	24
50%	5%	83.33	70.83	54.16	24
50%	10%	86.95	69.56	56.52	23
50%	20%	94.73	63.15	57.89	19
55%	0%	80.00	73.30	53.30	15
55%	5%	80.00	73.30	53.30	15
55%	10%	80.00	73.30	53.30	15
55%	20%	91.66	66.60	58.30	12
60%	0%	100.00	60.00	60.00	5
60%	5%	100.00	60.00	60.00	5
60%	10%	100.00	60.00	60.00	5
60%	20%	100.00	50.00	50.00	4
70%	0%	100.00	100.00	100.00	1
70%	5%	100.00	100.00	100.00	1

70%	10%	100.00	100.00	100.00	1
70%	20%	100.00	100.00	100.00	1

Table 21: Scores of the Disease degradation test analyzing the whole brain.

Analyzing table 21, we observe that the highest scores are in the area of percentages above 30%. However, in this area the obtained graphs have few connections. Therefore, in these graphs we could find nodes which are not connected. For this reason, we can discard these values for parameter 2 because they do not offer good orderings among PET scans.

So, the most appropriate values for parameter 2 in the analysis of the whole brain are shown in table 22:

P2	P3	SCORE_MMSE3	SCORE_DIAGNOSE	SCORE_TOTAL	CONNECTIONS
10%	0%	87.29	63.57	57.69	1598
10%	5%	89.35	63.092	57.68	1203
10%	10%	91.95	62.42	58.77	684
10%	20%	93.61	65.42	62.23	188
20%	0%	86.14	66.14	59.37	635
20%	5%	88.73	66.19	60.73	568
20%	10%	91.097	64.80	61.28	483
20%	20%	93.61	65.42	62.23	188
30%	0%	86.25	69.16	61.66	240
30%	5%	88.10	69.16	62.99	227
30%	10%	89.42	67.78	62.98	208
30%	20%	93.66	69.01	64.78	142

Table 22: The most appropriate values for parameter 2 in the Disease degradation test analyzing the whole brain.

Then, we proceed with the analysis of the values for parameter 3.

Analyzing table 22, we observe that the highest values are in the percentages 10% and 20%. Nevertheless, the total connections with these percentages are lower than with the percentages 0% and 5%. Given that the percentages 10% and 20% are more restrictive than 0% and 5%, the obtained orderings are better and make more sense. Therefore, we show in table 23 the most appropriate values for the parameters 2 and 3:

P2	P3	SCORE_MMSE3	SCORE_DIAGNOSE	SCORE_TOTAL	CONNECTIONS
10%	10%	91.95	62.42	58.77	684
10%	20%	93.61	65.42	62.23	188
20%	10%	91.097	64.80	61.28	483
20%	20%	93.61	65.42	62.23	188
30%	10%	89.42	67.78	62.98	208
30%	20%	93.66	69.01	64.78	142

Table 23: The most appropriate values for the parameters 2 and 3 in the Disease degradation test analyzing the whole brain.

In this study, the analysis at the whole brain level is also more complicated to do because it is a 3-dimensional analysis. For this reason, in this study only the analysis by using one slice of the PET scans has been done in more detail.

Chapter 8

Conclusions

In the realization of this work, we have implemented an application that allows us to visualize an ordering among the PET scans of patients who suffer Alzheimer's disease. In this way, we have observed how the brain metabolism degradation is in the development of Alzheimer's disease.

To obtain the order among PET scans and visualize the brain metabolism degradation, we have used an ordering procedure. This procedure is based on the analysis of the PET scans areas which have some impairment in the brain metabolism. So, once we have obtained the order, we have evaluated the accuracy of this order using the psychological tests which are performed to the patients before or after to obtain the PET scan.

Although, the used procedure offers a good ordering among PET scans, this ordering could be improved using, in addition, the results of psychological test in the order analysis.

So, with the analysis done in this work and the obtained results, we get more information about the development of Alzheimer's disease. However, the improvement of this work, could offer a greater accuracy in the information about the development of Alzheimer's disease. So, we propose this improvement as a future work, since, this could help in the early diagnosis of the Alzheimer's disease.

Even though this study can help in the early diagnosis of the disease, more studies should be carried about Alzheimer's disease, to achieve a common goal that is making this disease curable and reversible.

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