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Design, implementation and feasibility of a Serious Game for the assessment of social apathy in patients with mild neurocognitive disorders

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ABSTRACT

Due to the risen average lifespan, we are witnessing a dramatic increase of the incidence of age-related disorders such as dementia. Dementia is a general term describing conditions characterized by impairments in memory, language, problem-solving and other abilities that are severe enough to interfere with daily life. Dementia can result from different causes, the most common being Alzheimer's disease (AD), and it is often preceded by a pre-dementia stage, known as Mild Cognitive Impairment (MCI). MCI is characterized by a cognitive decline greater than expected for an individual's age, which however does not interfere notably with activities of daily living [1, 38].

Depression, anxiety, and apathy are commonly observed neuropsychiatric features in MCI, which have been linked to cognitive and functional decline in daily activities, as well as disease progression [10].

The detection of cognitive impairment at the MCI stage is clinically useful and allows for better communication between doctors, patients, and caregivers as it often acts as a starting point for a care and treatment plan. It has been shown that non-pharmacological interventions at this stage can stabilize or even improve patients' cognitive functioning [2].

Although the importance of an early diagnosis is known, neurocognitive disorders at the early staged still remains underdiagnosed with more than half of cases being undiagnosed. Older adults recognize the importance of having their cognition checked but even in high income countries such as the United States, only a small percentage of older adults receive regular cognitive assessments [3].

The poor detection of neurodegenerative deficits in the early stages is mainly due to the costs it entails and to the fact that general practitioners, who are often the first point of contact between older adults and healthcare services, often fail to diagnose neurodegenerative disorders at the early stage and provide appropriate follow-up and referrals. To improve MCI diagnosis, a slew of research have been initiated in recent years, the most innovative of which focuses on the use of Serious Games and virtual environments to assess cognitive functioning and diagnose cognitive decline. Serious games are videogames with a purpose other than amusement, and their use as diagnostic tools has been proven. [2].

The aim of this thesis project was to design and develop a Serious Game that will have as its ultimate goal the diagnosis of MCI through the detection of one of its most common neuropsychiatric symptoms: the apathy. In this study we focused on investigating the presence in particular of the social component of apathy. The second aim was to obtain feedback from the patients regarding the thoughts on the Serious Game application in order to understand the feasibility and acceptance of this tool. The outcome of this evaluation is intended to ultimately contribute to the improvement of existing protocols for diagnosing neurodegenerative disorders at an early stage.

To evaluate the feasibility of the game developed, 10 patients with mild neurocognitive disorders were recruited between patients coming to the Nice Research Memory Center for a regular medical consultation or a classical neuropsychological assessment and they were asked to test the game. The inclusion period lasted two weeks and involved 10 subjects (2 M; 8 F; mean age: 74,6 years; SD: 5,379; age range= 64-83). All subjects underwent a standard assessment including the Mini-Mental State Examination (MMSE) as well as the diagnostic criteria for apathy and the apathy motivation index (AMI) with a neuropsychologist and a psychiatrist. The neuropsychiatric evaluation revealed that of the total 10 patients, one was apathetic. At the end of each experimental condition, participants were

administered self-report questionnaires concerning the evaluation of their experience. Specifically, participants were presented with 10 points scales and asked to report their level of satisfaction, interest, discomfort, anxiety, motivation, fatigue, difficulty. They were also asked how much they liked some features of the game as the graphic interface, the characters and the content of the stories.

The results are quite encouraging: the patients responded positively to the game, giving high scores to categories like interest, contentment, and motivation while giving low values to those concerning anxiety, discomfort and fatigue. Another significant finding that bodes well for future improvements is that the only apathetic patient who participated in the study received the lowest score of all 10 individuals examined, based on an examination of the values of the scores scored by the patients in the game. Because we are still in the early stages of the study and only 10 subjects have been tested, this result is insufficient to speak about the Serious Game's diagnostic utility. However, it is still a promising result that suggests that this specific application could be useful as a support tool in the complex MCI diagnosis process in the future.

1 INTRODUCTION

Due to the risen average lifespan, we are witnessing a dramatic increase of the incidence of age-related disorders such as dementia: a general term describing conditions characterized by impairments in memory, language, problem-solving and other abilities that are severe enough to interfere with daily life. Dementia can result from different causes, the most common being Alzheimer's disease (AD), and it is often preceded by a pre-dementia stage, known as Mild Cognitive Impairment (MCI), characterized by a cognitive decline greater than expected for an individual's age, which however does not interfere notably with activities of daily living [1, 38].

Dementia has been classified as a global public health priority and its impact in individuals, families, and societies has been enormous. Despite a marked reduction in the prevalence of dementia, mainly in high-income countries, the number of people with dementia is set to triple by 2050 [2].

These data stimulate the scientific community to explore solutions to reduce the negative effects of this disease on patients, their relatives and society. An important starting point for managing this problem could be to have mass screening for dementia diagnosed in the early stages of the disease. In fact, diseases such as Alzheimer degenerate over the years, and if you manage to catch them at the beginning, before there are symptoms that reduce autonomy, prevention strategies are soon to be implemented.

The detection of cognitive impairment at its earliest stages is crucial as it allows for management of reversible causes and better disease management if the cause of impairment is a neurodegenerative disease. Furthermore, it allows for care planning and lifestyle changes that can enhance the quality of life of the patient and their family. Mild cognitive impairment (MCI) represents a diagnostic entity that is often a precursor of dementia. MCI patients exhibit cognitive deficits as measured by neuropsychological tests in comparison to age and education matched cognitively healthy older adults. At the same time, they retain their ability to perform instrumental abilities of daily living and remain high-functioning and able to live autonomously. The detection of cognitive impairment at the MCI stage is clinically useful and allows for better communication between doctors, patients, and caregivers as it often acts as a starting point for a care and treatment plan. It has been shown that non-pharmacological interventions at this stage can stabilize or even improve patients' cognitive functioning [2].

Although the importance of an early diagnosis is known, neurocognitive disorders at the early staged still remains underdiagnosed with more than half of cases being undiagnosed. Older adults recognize the importance of having their cognition checked but even in high income countries such as the United States, only a small percentage of older adults receive regular cognitive assessments [3].

There is no consensus concerning the effectiveness of population-wide screening for cognitive disorders especially when considering the high costs associated with such endeavors [2].

It is in this context that the Serious Games find their place. These are games that do not have entertainment as their main purpose, but are designed for educational and diagnostic purposes, as well as for training and cognitive stimulation (in the latter two cases we speak in particular of exergame). Serious Games are generally educational tools in which the serious and playful components are ideally balanced but lately they are making space in the field of medical diagnostics to evaluate mental performance and detect cognitive decline. They allow for an ecologically sound assessment

and can be configured to detect subtle changes in various aspects of user performance, including space navigation that often declines with the onset of preclinical Alzheimer's disease. The use of serious games as a screening tool can lead us to a new paradigm of cognitive assessment in which screening is de-medicalized, linked to a pleasant activity and self-administered by the elderly themselves in their preferred context [2].

The aim of my thesis is to design and develop a Serious Game meant to support the complex process of diagnosing apathy, a neuropsychiatric symptom that can appear very early in the progression of neurocognitive disorder. My serious game will be designed to evaluate the presence of social apathy in patients with neurocognitive disorders in the early stages. In fact, apathy is one of the most common behavioral and psychological symptoms in people with Alzheimer's disease and Huntington's disease, and is prevalent in other neurodegenerative conditions, such as Parkinson's disease and vascular dementia. It is also found among substantial proportions of individuals following stroke and traumatic brain injury, and psychiatric conditions such as major depressive disorder and schizophrenia. The presence of apathy significantly affects the patient's quality of life, and in neurodegenerative disorders is associated with a faster cognitive and functional decline, representing a risk factor for the conversion from Mild Cognitive Impairment to Alzheimer's disease. For all these reasons, identifying apathy early in disease progression is considered a clinical and research priority [13].

The second aim of the study is to understand if patients and therapists will accept this type of diagnostic tool. In particular, if it will be possible to integrate it into traditional diagnostic protocols to help doctors make early diagnosis. This pilot study will provide the knowledge needed to understand if the chosen method is the right technology and, if not, how to change it.

2 BACKGROUND

2.1 DEMENTIA

Dementia is a general term describing conditions characterized by impairments in memory, language, problem-solving and other abilities that are severe enough to interfere with daily life. Dementia can result from different causes, the most common being Alzheimer's disease (AD), and it is often preceded by a pre-dementia stage, known as Mild Cognitive Impairment (MCI), characterized by a cognitive decline greater than expected for an individual's age, which however does not interfere notably with activities of daily living. Dementia and MCI are characterized by the presence of cognitive symptoms, such as impaired memory, attention, orientation and executive functions, which are often associated with behavioral and psychological symptoms, one of the most common being apathy, a disorder of motivation [1, 38].

In people affected by dementia, you can also observe damage to brain cells. The brain has many distinct regions, each of which is responsible for different functions (for example, memory, judgment and movement). When cells in a specific region are damaged, that region cannot carry out its functions normally. This damage interferes with the ability of brain cells to communicate with each other. When brain cells cannot communicate normally, thinking, behavior and feelings can be affected [38].

Dementia is a term that describes a variety of symptoms affecting a person's cognitive functioning, including their ability to think, remember, and reason; it tends to get worse over time.

There are many different types of dementia; the most common is Alzheimer's disease: a progressive neurologic disorder that causes the brain to shrink (atrophy) and brain cells to die. Other types include:

- Lewy body dementia: type of progressive dementia that leads to a decline in thinking, reasoning and independent function because of abnormal microscopic deposits that damage brain cells over time.

- Frontotemporal dementia: it refers to a group of disorders caused by progressive nerve cell loss in the brain's frontal lobes (the areas behind your forehead) or its temporal lobes (the regions behind your ears).

- Vascular dementia: cognitive deficit caused by an impaired blood circulation in the brain, which deprives some areas of the organ of blood causing the progressive and irreversible death of brain cells.

- Mixed dementia: a combination of types.

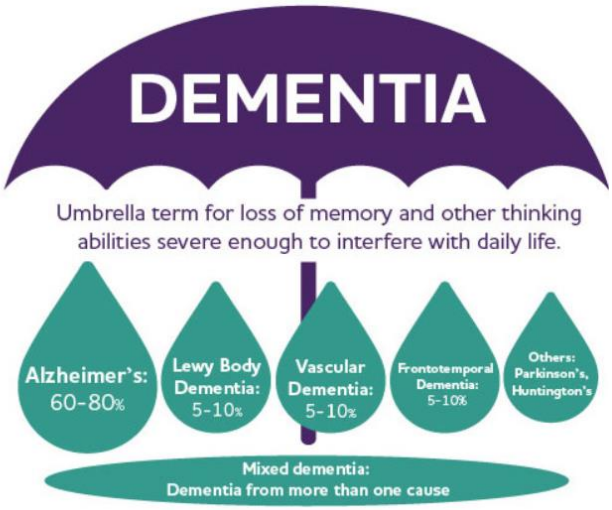


Figure 1: Representative image of the different types of dementia and their occurrence rates [38]

2.1.1 Early signs of dementia

There are 10 typical early signs of dementia. For a person to receive a diagnosis, they would usually experience two or more of these symptoms, and the symptoms would be severe enough to interfere with their daily life [7].

These early signs are:

1. Memory loss:

Memory loss is a common symptom of dementia. A person with dementia may find it difficult to recall information they have recently learned, such as dates or events, or new information. They may find they rely on friends and family or other memory aids for keeping track of things. Most people occasionally forget things more frequently as they age. They usually can recall them later if their memory loss is age-related and not due to dementia.

2. Difficulty planning or solving problems:

A person with dementia may find it difficult to follow a plan, such as a recipe when cooking, or directions when driving. Problem-solving may also get more challenging, such as when adding up numbers to paying bills.

3. Difficulty doing familiar tasks:

A person with dementia may find it difficult to complete tasks they regularly do, such as changing settings on a television, operating a computer, making a cup of tea, or getting to a familiar location. This difficulty with familiar tasks could happen at home or work.

4. Being confused about time or place:

Dementia can make it hard to judge the passing of time. People may also forget where they are at any time. They may find it hard to understand events in the future or the past and may struggle with dates.

5. Challenges understanding visual information:

Visual information can be challenging for a person with dementia. It can be hard for them to read, to judge distances, or work out the differences between colors. Someone who usually drives or cycles may start to find these activities challenging.

6. Problems speaking or writing:

A person with dementia may find it hard to engage in conversations. They may forget what they are saying or what somebody else has said. It can be difficult to enter a conversation. People may also find their spelling, punctuation, and grammar get worse. Some people's handwriting becomes more difficult to read.

7. Misplacing things:

A person with dementia may not be able to remember where they leave everyday objects, such as a remote control, important documents, cash, or their keys. Misplacing possessions can be frustrating and may mean they accuse other people of stealing.

8. Poor judgment or decision-making:

It can be hard for someone with dementia to understand what is fair and reasonable. This may mean they pay too much for things or become easily sure about buying things they do not doneed. Some people with dementia also pay less attention to keeping themselves clean and presentable.

9. Social apathy:

A person with dementia may become uninterested in socializing with other people, whether in their home life or at work. They may become withdrawn and not talk to others, or not pay attention when others are speaking to them. They may stop doing hobbies or sports that involve other people.

10. Changes in personality or mood:

A person with dementia may experience mood swings or personality changes. For example, they may become irritable, depressed, fearful, or anxious. They may also become more disinhibited or act inappropriately.

2.1.2 Epidemiology and social impact of dementia

Dementia has been characterized as a global public health priority and its impact in individuals, families, and societies has been enormous. Neurocognitive disorders, particularly major

neurocognitive disorders (dementias), have tremendous consequences for individuals, their families, the healthcare system, and the economy. In the United States, Alzheimer's disease (AD) is a leading cause of death, hospital admissions, skilled nursing facility admissions, and home health care. The costs of health services and the informal costs of unpaid caregiving for individuals with dementia are high and growing. Family caregivers also experience increased emotional stress, depression, and health problems. In absolute numbers, 35.6 million people worldwide were estimated to be living with dementia in 2010, a number expected to reach 115.4 million people by 2050 [4].

Prevalence of dementia increases exponentially with increasing age and doubles every five years of age after age 65. In higher income countries, prevalence is 5–10% in those aged 65+ years, usually greater among women than among men, in large part because women live longer than men. Within the US, higher prevalence has been reported in African American and Latino/Hispanic populations than in White non-Hispanic populations. Global systematic reviews and meta-analyses suggest that prevalence of dementia is lower in sub-Saharan Africa and higher in Latin America than in the rest of the world [4].

These data make us understand how important it is to find a solution to ensure that this disease affects the relatives of the people affected, society and the patient himself as little as possible. An important starting point for managing this problem could be to have mass screening for dementia diagnosed in the early stages of the disease.

The detection of cognitive impairment at its earliest stages is crucial as it allows for management of reversible causes and better disease management if the cause of impairment is a neurodegenerative disease. Furthermore, it allows for care planning and lifestyle changes that can enhance the quality of life of the patient and their family.

2.1.3 Mild Cognitive Impairment (MCI) and Subjective Cognitive Decline (SCD)

Mild cognitive impairment (MCI) represents a diagnostic entity that is often a precursor of dementia. MCI patients exhibit cognitive deficits as measured by neuropsychological tests in comparison to age and education matched cognitively healthy older adults. At the same time, they retain their ability to perform instrumental abilities of daily living and remain high-functioning and able to live autonomously. The detection of cognitive impairment at the MCI stage is clinically useful and allows for better communication between doctors, patients, and caregivers as it often acts as a starting point for a care and treatment plan. It has been shown that non-pharmacological interventions at this stage can stabilize or even improve patients' cognitive functioning [2].

At the same time, people who present to memory clinics for cognitive testing often have subjective cognitive complaints. The term "subjective cognitive decline" (SCD) has been proposed to describe this stage where the person may be experiencing subjective cognitive decline which is not reflected in objective testing. Older adults with SCD are at risk of progressing to MCI and dementia and they display a higher prevalence of positive biomarkers for amyloidosis and neurodegeneration compared to older adults without SCD. The definition of objective impairment is based on the deviation of a person's performance from the norm of age and education-matched controls in standardized neuropsychological testing. Thus, it is possible that a person's cognitive functioning has declined but decline is subtle enough so that the person still scores within the normal range in neuropsychological testing. Therefore, older adults with SCD may score in the normal range; however, they may score lower than healthy older adults without SCD and therefore their difference in performance with MCI

patients can be smaller than the difference in performance between MCI patients and healthy older adults without SCD. It is imperative to understand if instruments designed to detect MCI among healthy older adults can still detect that condition in older adults who present with SCD as they represent the majority of people who visit memory clinics.

2.2 DIAGNOSIS

Although the importance of an early diagnosis is known, neurocognitive disorders still remain underdiagnosed when at the early staged with more than half of cases being undiagnosed. Older adults recognize the importance of having their cognition checked but even in high income countries such as the United States, only a small percentage of older adults receive regular cognitive assessments [3]. There is in fact no consensus concerning the effectiveness of population-wide screening for cognitive disorders particularly when considering the high costs associated with such endeavors [2]. Dementia evaluation in primary care took between 2 weeks and 2 months before reaching diagnosis. The average cost for all patients evaluated at the primary care level was 477 €, whereas evaluations done on a specialist level reached a cost of 1115 €. Thus, the costs per true diagnosed case consist of the cost for all dementia investigations divided by the number of finalized diagnoses [5]. Adding to the problem of the economic impact on the health system is that general practitioners, who are often the first point of contact between older adults and healthcare services, often fail to diagnose dementia and provide appropriate follow-up and referrals. Lack of knowledge about dementia services, limited consultation time, uncertainty about the procedure of diagnosis and disclosure, as well as pessimistic attitudes toward aging and cognition are some of the causes of dementia under detection in general practices [2].

In clinical practice, the diagnostic process in dementia often consists of two levels, an initial investigation at the Primary Healthcare Centre (PHC) and, if necessary, additional diagnostic procedures at a specialist clinic (e.g., in geriatrics, psychiatry, neurology, internal medicine etc.). The contents of the investigations at these two levels vary depending on local diagnostic traditions and resources. In general, the PHC level includes medical history, sometimes with a structured caregiver interview and a thorough physical examination. General cognitive tests (e.g., Mini Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), clock test) and brain imaging, usually computer tomography (CT) of the brain, are also part of the diagnostic procedure at the PHC level. At the specialist level, additional brain imaging methods such as magnetic resonance imaging (MRI), positron-emission tomography (PET), SPECT/rCBF, and EEG may be used, together with more extensive neuropsychological tests, and analysis of the cerebrospinal fluid (CSF) biomarkers. Even at this stage the clinical assessment plays a central role in the establishment of the diagnosis [5].

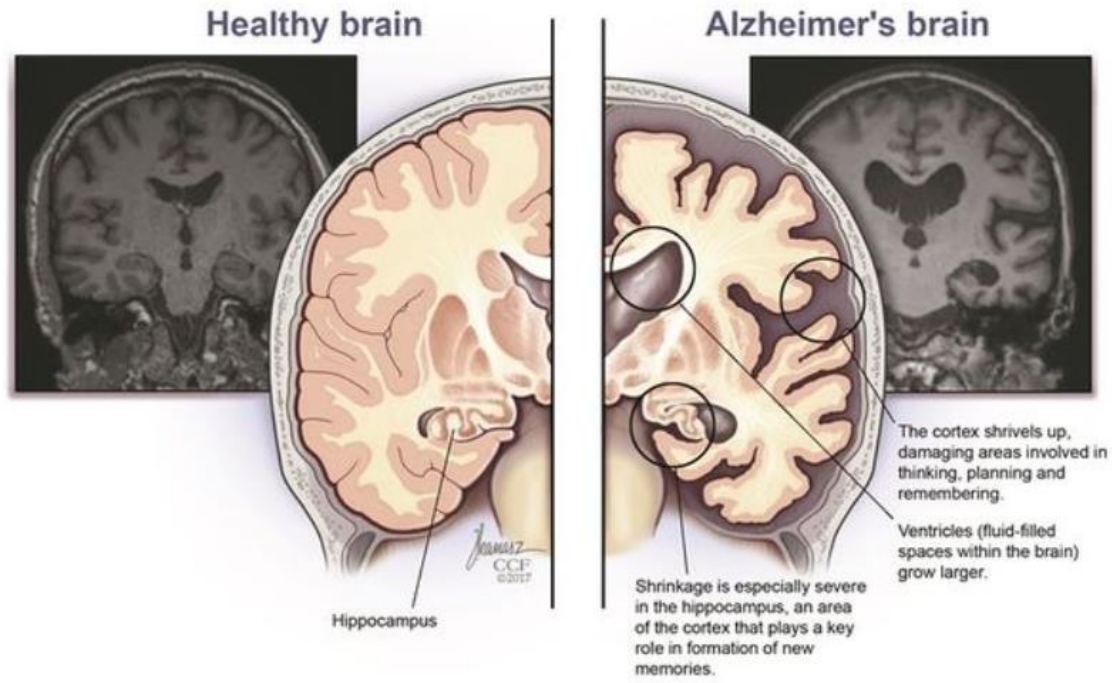


Figure 2: Alzheimer's Disease Brain Comparison. MRI scans (gray) and illustrations (color) show the differences between a brain affected by Alzheimer's disease and a normal brain.

2.2.1 General cognitive test

The cognitive tests most used for the initial assessment are the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA). These two neuropsychological tests are both made up of a series of questions, which refer to different cognitive areas. The score achieved by the patients gives us indications on their cognitive status.

2.2.1.1 Mini-Mental State Examination (MMSE)

The Mini-Mental State Examination, or MMSE, is a neuropsychological test for the evaluation of intellectual efficiency disorders and the presence of cognitive impairment. The MMSE is often used as a screening tool in the investigation of subjects with dementia, and with neuropsychological syndromes of a different nature. The test consists of thirty items (questions), which refer to seven different cognitive areas:

- orientation over time
- orientation in space
- recording of words
- attention and calculation
- re-enactment
- language

- constructive apraxia

The MMSE, is convenient, but not sensitive, as it is influenced by age, socio-economic status and level of education. It assesses primarily language and memory skills and has been found to be insensitive to detecting mild cognitive impairment. Riedel in a large study of 873 Parkinson disease patients found the MMSE had a sensitivity of only 50% [6].

This has a strong "ceiling effect": most cognitively normal and non-cognitively normal subjects get the highest score. Even people with an initial cognitive impairment, but with high schooling can obtain a score equal to 29 and 30, not showing any deterioration on this test.

Importantly, the MMSE is not used on its own to diagnose dementia. A score below 24 is considered indicative of dementia, but it is not enough alone to say that someone who scored 23 or less has dementia. A neurologist would factor that in with other analyses, like the results of brain scans, a neurological exam, an evaluation of medical history, and possibly genetic testing. In other words, no one should take a low score on the MMSE as proof that they have dementia. Instead, consider it a warning sign that means further testing is necessary [34].

Studies have shown that the MMSE is better at ruling out dementia than telling someone whether they have it. Very rarely (about three percent of the time) will the MMSE tell someone who does not have dementia that they do have the disease (this is called a false positive). It is more common for someone who does have dementia to achieve a score that would indicate they do not have the disease. This happens more than 20 percent of the time because people who are highly educated or only in the early stages of the disease can still score above 24 (indicating normal thinking ability) even if Alzheimer's is present in the brain. Again, the MMSE should not be used alone as a tool for diagnosing dementia.

The Mini-Mental State Exam is best administered by a neurologist, or other healthcare professional, in a doctor's office-like environment. However, it is possible to found an online version of the MMSE / Folstein Test that is relatively simple, only takes about 15 minutes to complete and can be administered by a friend or family member without special training. If someone want to take or give the test, there are some basic guidelines to follow:

Step 1 – Download and print the MMSE. There are multiple versions online, and they all ask roughly the same questions.

Step 2 – Seat the person being tested, in a quiet and well-lit room. Ask for attention. Do not set a timer.

Step 3 – Give the person a pencil or pen and a piece of paper. The MMSE is mostly filled out by the administrator, who asks questions and records answers that are either correct or not. There are, however, a few questions that will require writing and drawing. These include "Write a sentence," scored based on whether the sentence is coherent and contains a subject and verb, and "Draw intersecting shapes," where you show them a picture of two pentagons intersecting and ask the person to recreate the image.

Step 4 – Give the person as much time as needed. The MMSE generally takes about 10 minutes to complete, but there is no time limit. Do not rush in any way. In fact, the administrator should be as positive and encouraging as possible.

Step 5 – Review the results. The test is graded as you go, and administrators should be able to tell clearly whether a question was answered correctly or not. It will probably be relatively simple to calculate a score but, again, the MMSE is meant to be administered and scored by a professional.

Step 6 – If more than a few questions were answered incorrectly, you will want to take the finished test to a primary care doctor, who will go over it and decide whether a referral to an expert like a neurologist is appropriate.

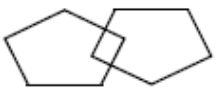
After following the steps just mentioned, you will need to consult a doctor.

Table 1: Example version of an MMSE test (Folstein MF, Folstein SE, McHugh PR: "Mini-mental state: A practical method for grading the cognitive state of patients for the clinician." J Psychiatr Res 1975;12:189-198).

Mini-Mental State Examination (MMSE)

Patient's Name: _____ Date: _____

Instructions: Score one point for each correct response within each question or activity.

Maximum Score	Patient's Score	Questions
5		"What is the year? Season? Date? Day? Month?"
5		"Where are we now? State? County? Town/city? Hospital? Floor?"
3		The examiner names three unrelated objects clearly and slowly, then the instructor asks the patient to name all three of them. The patient's response is used for scoring. The examiner repeats them until patient learns all of them, if possible.
5		"I would like you to count backward from 100 by sevens." (93, 86, 79, 72, 65, ...) Alternative: "Spell WORLD backwards." (D-L-R-O-W)
3		"Earlier I told you the names of three things. Can you tell me what those were?"
2		Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them.
1		"Repeat the phrase: 'No ifs, ands, or buts.'"
3		"Take the paper in your right hand, fold it in half, and put it on the floor." (The examiner gives the patient a piece of blank paper.)
1		"Please read this and do what it says." (Written instruction is "Close your eyes.")
1		"Make up and write a sentence about anything." (This sentence must contain a noun and a verb.)
1		"Please copy this picture." (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.) 
30		TOTAL

Scoring the MMSE

To calculate the test taker's score, it is simply a matter of counting the correct answers. The sum of the correct answers equals the test taker's score. There are 30 questions and therefore the highest possible score is 30. MMSE scores in relation to the severity of dementia is shown in the table below.

Table 2: Instruction of how to interpretate the MMSE (Folstein MF, Folstein SE, McHugh PR: "Mini-mental state: A practical method for grading the cognitive state of patients for the clinician." J Psychiatr Res 1975; 12:189-198).

Interpretation of the MMSE:

Method	Score	Interpretation
Single Cutoff	<24	Abnormal
Range	<21	Increased odds of dementia
	>25	Decreased odds of dementia
Education	21	Abnormal for 8th grade education
	<23	Abnormal for high school education
	<24	Abnormal for college education
Severity	24-30	No cognitive impairment
	18-23	Mild cognitive impairment
	0-17	Severe cognitive impairment

Interpretation of MMSE Scores:

Score	Degree of Impairment	Formal Psychometric Assessment	Day-to-Day Functioning
25-30	Questionably significant	If clinical signs of cognitive impairment are present, formal assessment of cognition may be valuable.	May have clinically significant but mild deficits. Likely to affect only most demanding activities of daily living.
20-25	Mild	Formal assessment may be helpful to better determine pattern and extent of deficits.	Significant effect. May require some supervision, support and assistance.
10-20	Moderate	Formal assessment may be helpful if there are specific clinical indications.	Clear impairment. May require 24-hour supervision.
0-10	Severe	Patient not likely to be testable.	Marked impairment. Likely to require 24-hour supervision and assistance with ADL.

Pros and Cons of the MMSE

Pros: – Useful in multiple ways. The MMSE can be used to screen for suspected dementia, so someone who suspects they're developing the disease might take it; it estimates the stage and severity of dementia for someone who has the disease; and it can show changes over time if taken every year or so. – Easy to administer. No special equipment or training is necessary. – Short and simple. The test only takes about 10 minutes to complete.

Cons: – Less reliability. An educated person with dementia, for instance, might be able to score above 24. – Not sensitive to Mild Cognitive Impairment. MMSE does not do a good job detecting Mild Cognitive Impairment or early dementia. Someone in the beginning stages, in other words, can still

achieve a high score. – Requires a certain level of education. Someone with a sub-eighth-grade level of education should not take the MMSE, because low educational experience can lead to a misdiagnosis.

2.2.1.2 Montreal Cognitive Assessment (MoCA)

The Montreal Cognitive Assessment (MoCA) has been developed as a brief cognitive screening tool to detect mild-moderate cognitive impairment. It has been found to have high sensitivity and specificity for the detection of mild cognitive impairment [15]. A score of less than 25 was found to be the optimal cut-off point for a diagnosis for mild cognitive impairment.

The MoCA test is a one-page 30-point test administered in approximately 10 minutes. The test and administration instructions are available for clinicians online. The test is available in 46 languages and dialects [39].

The MoCA assesses several cognitive domains:

- The short-term memory recall task (5 points) involves two learning trials of five nouns and delayed recall after approximately five minutes.
- Visuospatial abilities are assessed using a clock-drawing task (3 points) and a three-dimensional cube copy (1 point).

Figure 3: In this clock drawing task, the subject is asked to draw a clock with the hours and showing the time 2:30. Successive results show a deterioration of pattern processing ability in a subject as they progress from mild cognitive impairment (MCI)

- Multiple aspects of executive functions are assessed using an alternation task adapted from the trail-making B task (1 point), a phonemic fluency task (1 point), and a two-item verbal abstraction task (2 points).

- Attention, concentration, and working memory are evaluated using a sustained attention task (target detection using tapping; 1 point), a serial subtraction task (3 points), and digits forward and backward (1 point each).
- Language is assessed using a three-item confrontation naming task with low-familiarity animals (lion, camel, rhinoceros; 3 points), repetition of two syntactically complex sentences (2 points), and the aforementioned fluency task.
- Abstract reasoning is assessed using a describe the similarity task with 2 points being available.
- Finally, orientation to time and place is evaluated by asking the subject for the date and the city in which the test is occurring (6 points).

Because MoCA is English specific, linguistic and cultural translations are made to adapt the test in other countries [40]. Multiple cultural and linguistic variables may affect the norms of the MoCA across different countries and languages. Several cut-off scores have been suggested across different languages to compensate for education level of the population, and several modifications were also necessary to accommodate certain linguistic and cultural differences across different languages/countries. However, not all versions have been validated. [15]

2.2.2 Alternatives to neuropsychological tests

Neuropsychological testing is the gold-standard for assessing dementia and cognitive impairment, but it is time-consuming and requires highly trained assessors: it is for this reason that in the last period research has been pushing towards increasingly automated and self-administered diagnostic solutions.

A promising approach in this direction is to use serious games to diagnose. There are some studies that demonstrate its diagnostic precision in comparison to MoCA and MMSE. In a recent study, Stelios Zygouris et al. evaluated the diagnostic accuracy of a game developed by them, compared with the MoCA and the MMSE. The three instruments assessed in this study displayed significantly different performances in differentiating between healthy older adults with Subjective Cognitive Decline (SCD) and MCI patients. The Game displayed a good correct classification rate (CCR), while the MoCA displayed an average CCR and the MMSE displayed a poor CCR. This particular game appears to be a robust tool for detecting MCI in a population of older adults with SCD [2].

2.3 APATHY

Apathy is a lack of feeling, emotion, interest, or concern about something. It is a state of indifference, or the suppression of emotions such as concern, excitement, motivation, or passion. An apathetic individual has an absence of interest in or concern about emotional, social, spiritual, philosophical, virtual, or physical life and the world. The apathetic may lack a sense of purpose, worth, or meaning in their life. They may also exhibit insensibility or sluggishness. In positive psychology, apathy is described as a result of the individuals' feeling they do not possess the level of skill required to confront a challenge (i.e., "flow"). It may also be a result of perceiving no challenge at all (e.g., the challenge is irrelevant to them, or conversely, they have learned helplessness). Apathy is something that all people

face in some capacity and is a natural response to disappointment, dejection, and stress. As a response, apathy is a way to forget about these negative feelings. This type of common apathy is usually felt only in the short term, but sometimes it becomes a long-term or even lifelong state, often leading to deeper social and psychological issues. Apathy should be distinguished from reduced affect display, which refers to reduced emotional expression but not necessarily reduced emotion.

Pathological apathy, characterized by extreme forms of apathy, is now known to occur in many different brain disorders [8], including neurodegenerative conditions often associated with dementia such as Alzheimer's disease [9, 32], and psychiatric disorders such as schizophrenia. Although many patients with pathological apathy also suffer from depression, several studies have shown that the two syndromes are dissociable: apathy can occur independently of depression and vice versa [9].

Theoretical accounts have proposed that apathy is a multidimensional construct which covers motivation within dissociable domains: cognitive, emotional/affective and behavioural. Self-report and clinician administered measures have now been developed to characterize apathy in clinical samples based on this multidimensional construct (Lille Apathy Rating Scale [36], Dimensional Apathy Scale [37]). However, currently there are no validated assessments of apathy in healthy people. As a result, the mechanisms underlying variability in apathy are still poorly understood. It is also unknown whether different domains of apathy can be identified in healthy people, and whether they might be dissociable across individuals [35].

2.3.1 Apathy in neurodegenerative disorders

Apathy is a pervasive neuropsychiatric symptom of most neurocognitive, neurodegenerative, and psychiatric disorders. It represents the most common behavioral and psychological symptom in people with Alzheimer’s disease and Huntington’s disease, and is prevalent in other neurodegenerative conditions, such as Parkinson’s disease and vascular dementia. It is also found among substantial proportions of individuals following stroke and traumatic brain injury, and psychiatric conditions such as major depressive disorder [6] and schizophrenia. The presence of apathy significantly affects the patient’s quality of life, and in neurodegenerative disorders is associated with a faster cognitive and functional decline, representing a risk factor for the conversion from Mild Cognitive Impairment to Alzheimer’s disease. For all these reasons, identifying apathy early in disease progression is considered a clinical and research priority [13].

Depending upon how it has been measured, apathy affects 19–88% percent of individuals with Alzheimer's disease (mean prevalence of 49% across different studies) [9]. It is a neuropsychiatric symptom associated with functional impairment. Brain imaging studies have demonstrated changes in the anterior cingulate cortex, orbitofrontal cortex, dorsolateral prefrontal cortex and ventral striatum in Alzheimer's patients with apathy. Cholinesterase inhibitors, used as the first line of treatment for the cognitive symptoms associated with dementia, have also shown some modest benefit for behavior disturbances such as apathy.[11]

2.3.2 Measurement of Apathy

Several different questionnaires and clinical interview instruments have been used to measure pathological apathy or, more recently, apathy in healthy people [10, 28].

- Apathy Evaluation Scale

Developed by Robert Marin in 1991, the Apathy Evaluation Scale (AES) was the first method developed to measure apathy in clinical populations. Centered around evaluation, this scale can either be self-informed or other-informed. The three versions of the test include self, an informant such as a family member, and clinician. This scale is based around questionnaires that ask about topics including interest, motivation, socialization, and how the individual spends their time. The individual or the informant answers on a scale of "not at all", "slightly", "somewhat" or "a lot". Each item on the evaluation is created with positive or negative syntax and deals with cognition, behavior, and emotion. Each item is then scored and, based on the score, the individual's level of apathy can be evaluated.

- Apathy Motivation Index

The Apathy Motivation Index (AMI) was developed to measure different dimensions of apathy in healthy people. Factor analysis identified three distinct axes of apathy: behavioral, social and emotional. The AMI has since been used to examine apathy in patients with Parkinson's disease who, overall, showed evidence of behavioral and social apathy, but not emotional apathy.

- Dimensional Apathy Scale

The Dimensional Apathy Scale (DAS) is a multidimensional apathy instrument for measuring subtypes of apathy in different clinical populations and healthy adults. It was developed using factor analysis, quantifying Executive apathy (lack of motivation for planning, organizing and attention), Emotional apathy (emotional indifference, neutrality, flatness or blunting) and Initiation apathy (lack of motivation for self-generation of thought/action). There is a self-rated version of the DAS and an informant/carer-rated version of the DAS. Also a clinical brief DAS has been developed. It has been validated for use in motor neuron disease, dementia and Parkinson's disease, showing to differentiate profiles of apathy subtypes between these conditions.

2.3.3 Apathy Motivation Index

The AMI is a reliable measure of individual differences in apathy and might provide a useful means of probing different mechanisms underlying sub-clinical lack of motivation in otherwise healthy individuals. Moreover, associations between apathy and comorbid states may be reflective of problems in different emotional, social and behavioural domains and the AMI is able to assess the presence of different subtypes of apathy trough different questions [35].

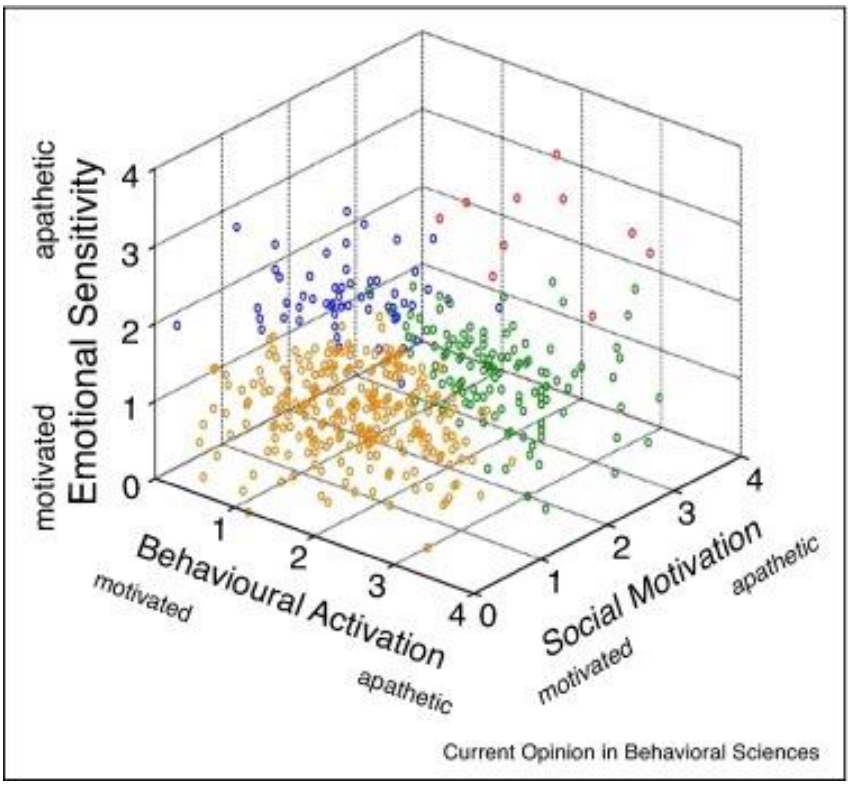


Figure 4: Example of distribution of multidimensional scores on the Apathy Motivation Index collected during a study carried out by Nobis and Husain. 3D scatterplot of each healthy volunteer's mean rating on the multidimensional Apathy Motivation Index (AMI). Scores range from 0 to 4, with a higher mean score indicating greater apathy, for each of the three subscales: Behavioural Activation, Social Motivation and Emotional Sensitivity. Four subtypes of apathy-motivation along the scales were labelled motivated (orange), behaviourally/socially apathetic (green), emotionally apathetic (blue), and generally apathetic (red) [9].

In figure T1 is the apathy motivation index consisting of instructions provided to the patient, questionnaire and scoring instruction. I make a particular focus only on this questionnaire because that is what was used in this study.

Figure T1: Apathy Motivation Index (AMI 1.0 version): instructions, test and scoring instructions.

Below are a number of statements. Each statement asks you to think about your life over the last 2 weeks.

For each statement, select how appropriately it describes your life right now. Select "Completely true" if the statement describes you perfectly, "Completely untrue" if the statement does not describe you at all over the last 2 weeks, and use the answers in between accordingly.

		Completely UNTRUE	Mostly untrue	Neither true nor untrue	Quite true	Completely TRUE
1	I feel sad or upset when I hear bad news.	☐	☐	☐	☐	☐
2	I start conversations with random people.	☐	☐	☐	☐	☐
3	I enjoy doing things with people I have just met.	☐	☐	☐	☐	☐
4	I suggest activities for me and my friends to do.	☐	☐	☐	☐	☐
5	I make decisions firmly and without hesitation.	☐	☐	☐	☐	☐
6	After making a decision, I will wonder if I have made the wrong choice.	☐	☐	☐	☐	☐
7	Based on the last two weeks, I would say I care deeply about how my loved ones think of me.	☐	☐	☐	☐	☐
8	I go out with friends on a weekly basis.	☐	☐	☐	☐	☐
9	When I decide to do something, I am able to make an effort easily.	☐	☐	☐	☐	☐
10	I don't like to laze around.	☐	☐	☐	☐	☐
11	I get things done when they need to be done, without requiring reminders from others.	☐	☐	☐	☐	☐
12	When I decide to do something, I am motivated to see it through to the end.	☐	☐	☐	☐	☐
13	I feel awful if I say something insensitive.	☐	☐	☐	☐	☐
14	I start conversations without being prompted.	☐	☐	☐	☐	☐

15	When I have something I need to do, I do it straightaway so it is out of the way.	☐	☐	☐	☐	☐
16	I feel bad when I hear an acquaintance has an accident or illness.	☐	☐	☐	☐	☐
17	I enjoy choosing what to do from a range of activities.	☐	☐	☐	☐	☐
18	If I realise I have been unpleasant to someone, I will feel terribly guilty afterwards.	☐	☐	☐	☐	☐

Scoring Instructions

Each item is negatively scored i.e. you will need to REVERSE ALL ITEMS:
Completely TRUE = 0
Quite true = 1
Neither true nor untrue = 2
Mostly untrue = 3
Completely UNTRUE = 4

Three domains of apathy-motivation are assessed with the mean score, which ranges from 0-4 (with 0 being motivated and 4 being apathetic).

(1) Behavioural: Q5, 9, 10, 11, 12, 15
(2) Social: Q2, 3, 4, 8, 14, 17
(3) Emotional: Q1, 6, 7, 13, 16, 18

2.3.4 Diagnostic criteria for apathy

Three dimensions of apathy were identified, including deficits in goal-directed behavior, goal-directed cognitive activity, and emotions. In 2008, a task force was set up during the European Psychiatric Association congress to develop diagnostic criteria for apathy. Based on these diagnostic criteria, a patient is classified as apathetic when he/she meets four criteria (A-D). Criterion A specifies the presence of a loss of (or diminished) motivation in comparison to the person's previous level of functioning, which is not consistent with his age or culture. These changes in motivation may be reported by the patient himself or by the observations of others. Criterion B stipulates the presence of symptoms in at least two of three domains (behavior, cognition, and emotion) for a period of at least four weeks and present most of the time. These symptoms can be detected either in self-initiated or environment-stimulated activities. Criterion C specifies that the symptoms (A - B) must cause clinically significant impairment in personal, social, occupational domains, or other important areas of functioning. Finally, Criterion D specifies that the symptoms (A - B) should not exclusively explained or due to physical or motor disabilities, to diminished level of consciousness or to the direct physiological effects of a substance.

In the last decade, there have been considerable advances in the domain of apathy in brain disorders, including the apathy biological and neural based. First, the definition of apathy as a disorder of

'motivation' (Criterion A) has been extensively criticized, as 'motivation' is a psychological interpretation of behavioral internal states, which may be difficult to measure objectively. At the same time, the construct of goal directed behavior/activity - construed as a set of related processes by which an internal state is translated, through observable action, into the attainment of a goal - is increasingly used in the domain of neuroscience, and it has been proposed to be a useful to operationalize apathy, particularly in clinical contexts. Second, the different apathy domains (criterion B) have been object of discussion, and most particularly: a) the distinction between the 'behavior' and 'cognition' domains and its relevance in clinical practice; b) the importance of adding the 'social interaction' as a domain of apathy; c) the importance of considering alternative proposals on apathy subtypes based on the underlying disrupted mechanisms (for instance, the 'emotional–affective', 'cognitive' and 'auto-activation' apathy subtypes. Third, finer assessment tools for apathy have been developed, based on classical instruments (e.g., interviews and self-reports) but also on new Information and Communication Technologies (ICTs).

Given all these advances, a group of experts in the domain of apathy in brain disorders (leaded by PR and KL) decided to revise the diagnostic criteria for apathy proposed in 2008. The main objectives were: a) to revise the definition of apathy (criterion A); b) to update the list of apathy dimensions (criterion B); c) to operationalize the diagnostic criteria using examples of clinical situations and areas of possible impairment (criterion B); and d) to suggest appropriate and updated apathy assessment tools [12].

The new proposed diagnostic criteria for apathy, to be employed both in the clinical and the research domain, are reported in Table 3.

Table 3: Apathy diagnostic criteria 2018 [13]

CRITERION A: A quantitative reduction of goal-directed activity either in behavioral, cognitive, emotional or social dimensions in comparison to the patient's previous level of functioning in these areas. These changes may be reported by the patient himself/herself or by observation of others.

CRITERION B: The presence of at least 2 of the 3 following dimensions for a period of at least four weeks and present most of the time

B1. BEHAVIOUR & COGNITION

Loss of, or diminished, goal-directed behaviour or cognitive activity as evidenced by at least one of the following:

General level of activity: the patient has a reduced level of activity either at home or work, makes less effort to initiate or accomplish tasks spontaneously, or needs to be prompted to perform them.

Persistence of activity: He/she is less persistent in maintaining an activity or conversation, finding solutions to problems or thinking of alternative ways to accomplish them if they become difficult.

Making choices: He/she has less interest or takes longer to make choices when different alternatives exist (e.g., selecting TV programs, preparing meals, choosing from a menu, etc.)

Interest in external issue: He/she has less interest in or reacts less to news, either good or bad, or has less interest in doing new things

Personal wellbeing: He/she is less interested in his/her own health and wellbeing or personal image (general appearance, grooming, clothes, etc.).

B2. EMOTION

Loss of, or diminished, emotion as evidenced by at least one of the following:

Spontaneous emotions: the patient shows less spontaneous (self-generated) emotions regarding their own affairs, or appears less interested in events that should matter to him/her or to people that he/she knows well.

Emotional reactions to environment: He/she expresses less emotional reaction in response to positive or negative events in his/her environment that affect him/her or people he/she knows well (e.g., when things go well or bad, responding to jokes, or events on a TV program or a movie, or when disturbed or prompted to do things he/she would prefer not to do).

Impact on others: He/she is less concerned about the impact of his/her actions or feelings on the people around him/her.

Empathy: He/she shows less empathy to the emotions or feelings of others (e.g., becoming happy or sad when someone is happy or sad, or being moved when others need help).

Verbal or physical expressions: He/she shows less verbal or physical reactions that reveal his/her emotional states.

B3. SOCIAL INTERACTION Loss of, or diminished engagement in social interaction as evidenced by at least one of the following:

Spontaneous social initiative: the patient takes less initiative in spontaneously proposing social or leisure activities to family or others.

Environmentally stimulated social interaction: He/she participates less, or is less comfortable or more indifferent to social or leisure activities suggested by people around him/her.

Relationship with family members: He/she shows less interest in family members (e.g., to know what is happening to them, to meet them or make arrangements to contact them).

Verbal interaction: He/she is less likely to initiate a conversation, or he/she withdraws soon from it

Homebound: He /She prefer to stays at home more frequently or longer than usual and shows less interest in getting out to meet people.

CRITERION C These symptoms (A - B) cause clinically significant impairment in personal, social, occupational, or other important areas of functioning.

CRITERION D The symptoms (A - B) are not exclusively explained or due to physical disabilities (e.g. blindness and loss of hearing), to motor disabilities, to a diminished level of consciousness, to the direct physiological effects of a substance (e.g. drug of abuse, medication), or to major changes in the patient's environment.

2.3.5 Diagnosis of apathy through alternative modalities

Speaking of the diagnosis of apathy, I find it interesting to mention a couple of studies that have attempted to evaluate the presence of apathy with innovative methods compared to previous paradigms.

The first one was conducted by Valerie Bonelle et al. [25]. They designed two paradigms to assess individual differences in physical effort production and effort-based decision making and their relation to apathy in healthy people. In the first study, apathy scores were correlated with the degree to which stake (reward on offer) and difficulty level impacts on physical effort production. Individuals with relatively high apathy traits showed an increased modulation of effort while more motivated individuals generally exerted greater force across different levels of stake. To clarify the underlying mechanisms for this behavior, they designed a second task that allows independent titration of stake and effort levels for which subjects are willing to engage in an effortful response to obtain a reward. The results suggest that apathy traits in the normal population are related to the way reward subjectively affects the estimation of effort costs, and more particularly manifest as decreased willingness to exert effort when rewards are small, or below threshold.

The second study that I think is appropriate to mention was conducted by Patricia L. Lockwood et al. and focuses on prosocial apathy. Prosocial acts are those that are costly to us but benefit from them others and are a central component of human coexistence. While the financial and moral costs of prosocial behaviors they are well understood, everyday prosocial acts are typically not come to such costs. Instead, they require effort. In this study, using computational modeling of an effort-based activity, the authors show that people are prosocially apathetic. They are less available choose to take highly challenging actions for the benefit of others than those who benefit from it. Furthermore, even when choosing to take challenging prosocial actions, people exhibit superficiality, exerting less force in actions who benefit others over those who benefit themselves. These the results were replicated and were present if the other person was anonymous or not, and when the choices were made to earn rewards or avoid losses. Importantly, the less prosocial motivated people had higher subclinical levels of psychopathy and social apathy. So even if sometimes people do "Helping", they are less willing to benefit others and sometimes they are "Superficially prosocial", which can characterize every day prosociality and its interruption in social unrest.

We therefore have that studying the processes by which individuals decide to attribute physical effort to obtain rewards and assess the willingness to perform prosocial acts could be particularly relevant for identifying traits of apathy.

2.4 SERIOUS GAME

Serious games are games that have another purpose besides entertainment. The power of serious games is that they are entertaining, engaging and immersive. Serious games combine learning strategies, knowledge and structures, and game elements to teach specific skills, knowledge and attitudes. They are designed to solve problems in several areas and involve challenges and rewards, using the entertainment and engagement components provided when the user is playing games.

Serious games are used in a lot of different areas since they can be applied to a broad range of problems and challenges. A few areas where we see serious games more than in other areas are:

- Education: Games are used to teach specific subjects through gamified exercises and simulations. This way, students can learn math or learn a new language for example. This is one of the most well-known applications of serious games, also known as educational games.

- Healthcare: Games are also used in rehabilitation by translating exercises to actions in the game. Another use in healthcare is to train medical procedures in a simulated environment.

- Sustainability projects: make people engaged for sustainability project or change their behaviour.

- Training and consultancy: More and more consultancy agencies use serious games to explain and train teamwork and social and logistic dynamics within businesses.

These are just a few areas where serious games are used. Additionally, they are also used in the military for training purpose, in marketing to acquire and retain customers, by governments to create social awareness and for several research purposes [19].

2.4.1 Serious Game in Healthcare area

Healthcare is one of the main issues that affects people the most in every stage of life (from infancy to old age). Many researches [30,31] have shown the need of highly trained and educated health care professionals to avoid medical errors, and the use of serious games in health can provide an additional mean to increase interest in training, education and evaluation of their performance [29].

Repetitive tasks are needed in many cases to treat patients, but patient boredom has a negative impact on the patient's willingness to continue the treatment. The use of tailored games to replace these tasks therefore has good results. Additionally, since the recent explosion of videogames, which now are used in two thirds of households by people of all ages, patients can feel more at ease and enjoy their treatment performing an activity they like. Since 2002 many serious games in the field of e-health have been developed, dealing with a wide variety of aspects of surgeon training, radiology operation, Cardiopulmonary Resuscitation (CPR) and patient care, among others. Games aimed at patients have also been developed [29].

Below we outline the advantages of using Serious Games in the health sector:

- Achieve behavioral change: Serious games are capable of making a change in the behavior of the target audience. Take for example, patients who deal with chronic pain on a daily basis. By playing games, patients learn skills to deal with their pain. In addition, the game is also fun to play.

- Reduce workload: Patients are able to independently do exercises using serious games. When patients are done playing, the data is visible to the practitioner and stored in a protected database. This allows the practitioner to remotely monitor the progress per patient.

- Inexpensive technology: Serious games are cheaper technology than for example, an expensive simulator. An often-used digital technology in serious games is VR (virtual reality). With VR, a

specific step of a medical treatment can become more effective by immersing patients into that experience. This leads to better outcomes for the patient.

- Scientifically validated: During the development of serious games are involved researchers and scientific experts to test if the game really works. This is done in collaboration with domain experts and by collecting and analyzing performance results.

In the particular case of neurocognitive disorders and dementia, the Serious Games are mostly used in two ways: to do cognitive stimulation or to assess the patient's cognitive status and therefore support the diagnosis process [19].

2.4.1.1 Serious Game for Cognitive stimulation

Cognitive stimulation is a component of "active aging", a term was adopted by the World Health Organization (WHO) to promote a better quality of life and improved autonomy and independence of older people. There is evidence that regular engagement in physical and cognitive activity with moderate intensity can delay functional decline and the onset of chronic disorders in older subjects. This not only stimulates neuronal plasticity but also makes use of the "cognitive reserve" as additional brain regions are recruited during the task to compensate the reduced functional capacity. Optimizing cognitive function is an important objective since cognitive decline is associated with adverse outcomes in mental and physical health as well as in longevity. Cognitive stimulation and monitoring of cognitive performance can be implemented with Serious Games. In this case they are generally designed to simulate practical situations of everyday life. The increase utilization of Serious Games in immersive environments and the adoption of non-conventional devices has strengthened the relation with Digital Games. The possibility of generating virtual scenarios can increase motivation of users during the learning process. Previous research demonstrated that Digital Games are beneficial to old age users specifically in visual perception [22], spatial orientation, reaction time, eye-hand coordination and quality of life. Green & Bavalier [22] suggested that these benefits are related to increased dopamine levels in the brain, which decline with age, elicited by Digital Games and that have an important role in cognitive performance following the training session.

Serious Games share some characteristics with other methods of cognitive stimulation, as defined by Franco-Martín e Orihuela-Villameriel [21]. Thus, these games involve a task which is continuous, systematic, stimulating and providing reinforcement, avoiding the routine and repetition. The task can also stimulate specific cognitive domains, especially attention-concentration, facilitating the stimulation of other domains. In addition, Serious Games fulfil the criteria proposed by Thompson e Foth [23] for cognitive stimulation in older persons: easy accessibility, not too expensive and user-friendly. [20]

2.4.1.2 Serious Game for assessment

Generally serious games are training tools in which the serious and playful aspects are ideally balanced but lately they are making space in the field of medical diagnostics to evaluate mental performance

and detect cognitive decline. They allow for an ecologically valid assessment and can be configured to detect subtle changes in various aspects of user performance, including space navigation that often declines with the onset of preclinical Alzheimer's disease. The use of serious games as a screening tool can lead us to a new paradigm of cognitive assessment in which screening is de-medicalized, linked to a pleasant activity and self-administered by the elderly themselves in their preferred context. In fact, studies have been performed to analyze the longitudinal performance in a self-administered serious game that the elderly used at home, for a period of time, to detect MCI and have given very promising results [2].

For all these reasons, in addition to those mentioned in 2.4.1, Serious Games can be considered valid tools for the diagnosis of dementia. In fact, as mentioned in paragraph 2.2.1, the diagnosis of dementia requires a lot of time, a highly qualified technician and a significant economic effort on the part of the health system; all these problems could be solved using Serious Game.

Their validity in the field of medical diagnostics has been ascertained as an ecological and efficient tool for detecting the presence of neurodegenerative diseases.

In general, it is essential to use screening tools that can provide an early diagnosis. Currently, these tools include traditional paper-pencil tasks, which try to evaluate the main cognitive functions that are compromised by the disease, through specific questions aimed at the patient. However, these tests have several limitations: they have a low specificity and sensitivity, especially in the early stages of the disease, and their scores are influenced by multiple factors, such as visual and auditory disturbances, patient education and psychological factors. For this reason, in the last few years researchers have been trying to develop further tools for the evaluation of cognitive functions that overcome these limits and are therefore able to actually measure what they are supposed to measure. This can be achieved by evaluating the symptoms, the impairments, the typical difficulties of the early stages of diseases through VR environments. Virtual Reality has several advantages with respect to traditional paper-pencil tests: ecological validity, i.e., similarity between the assessment environment and the real world; immediate performance feedback; personalization of the environment and task, thus producing engagement in participants [18].

In literature we find numerous studies that try to use virtual reality and in particular serious games to make diagnoses. An example is offered by the Zygouris et al. study [2] which evaluated the performance of a serious game in comparison with that of standard cognitive tests in being able to discriminate MCI from SCD. The results of this study demonstrated that the serious game is much more accurate than pen and paper tests in identifying dementia in primordial diseases. In fact, the Game displayed a correct classification rate (CCR) of 81.91% when differentiating between MCI patients and older adults with SMC, while the MoCA displayed of CCR of 72.04% and the MMSE displayed a CCR of 64.89%. Even the problem of the ceiling effect that occurs with the MMSE, with this particular serious game did not arise.

2.4.1.3 Serious Game and apathy

Our theory of diagnosing apathy through the use of Serious Game is supported by numerous studies that have found the acceptability of these tools by apathetic patients. There are numerous Serious Games tested for evaluating or training patients with MCI or Alzheimer's who have among the patients

who tested the game also a percentage of apathetic patients and it was evaluated that this type of patients accepts the serious game approach [12, 33].

SGs play a fundamental role in the treatment of apathy because, for this particular condition, non-pharmacological methods are preferable [33] and it has been seen that SGs can be considered a good treatment that does not use drugs.

Serious games can also be used to help diagnose apathy: in fact, in addition to the questionnaires, discussed in chapters 2.3.3 and 2.3.4, there is in the existing literature other alternative methods for diagnosing apathy trough a SG [26].

In literature we found a study with the aim to propose a new type of assessment using new technologies designed to assess loss of interest by a more implicit and indirect method [26]. The Interest Game is a form of interactive self-report, where categories of interests are presented in order to quantify them and identify the activities that constitute them. Two indices can be extracted, the number of categories and the number of activities selected. They compared the scores between three groups: Apathetic (A) and Non-Apathetic (NA) subjects (according to the Apathy Diagnostic Criteria) and controls with no objective cognitive impairment. Results showed that subjects from the A group had significantly less interests (both categories and images selected) than the Na group. As expected, the control group selected a higher number of categories than the other groups. The diagnosis (minor or major neurocognitive disorder) and level of education had also a significant effect on the number of categories selected. Furthermore, subjects with major neurocognitive disorder (NCD) had significantly less interests than minor NCD group. The number of categories measure was more sensitive than the number of images selected.

It is possible to draw the conclusion that Serious Game could be a promising tool to quantify and identify subject interests and differentiate between apathetic and non-apathetic subjects.

3 MATERIALS AND METHODOLOGY

In this chapter, I will consider materials and methods used during the design and development of the Serious Game. All the decisions taken during the design phase of the project involved an interdisciplinary research team included engineers from INRIA (Sophia Antipolis, Valbonne) and University of Genoa and clinicians from the Research Memory Center (Institute Claude Pompidou, Nice).

3.1 MATERIALS

For the development of the game, I used Unity and Visual studio, where I wrote some scripts in C # language. An additional tool I used was Fungus: important support to the Unity platform for those who want to develop storytelling games.

3.1.1 The development environment: Unity and Visual Studio

Unity is a game development engine that allows to create video games and export them for multiple platforms, desktop (Mac, Windows and Linux), Web, and for different marketplaces and devices (Windows Store, Windows Phone, iOS, Android, Blackberry, Wii U, PlayStation and XBOX). Unity provides a visual development environment that allows us to work on our games, and the logic can be written in C #, JavaScript and/or Boo. In other words, it is a complete set of tools for creating video games and other interactive projects, simplifying the development process and making it faster.

In Unity we define “Game Objects” the objects that will be part of the game. You can manage all the properties of these objects in a simple way thanks to a few clicks and settings on the panels. The behaviors that each object must have such as reactions to some events, interface management for example, are instead described through code. To put it in "Unity" terminology, it is the so-called Scripts that allow us to define Behavior.

Just double-click on a script to launch the script editor. By default, Unity foresees the modification of the code through MonoDevelop. However, I preferred to change the development environment with the more powerful Visual Studio 2019.

3.1.2 Fungus

Fungus is a free, open-source tool for creating interactive storytelling games in Unity. Fungus provides an intuitive, fast workflow for visual scripting and interactive storytelling. Fungus is being used to create Visual Novels, Point and Click Adventure Games, Children Stories, Hidden Object Games, eLearning apps and also some frankly weird stuff which defies classification.

3.1.3 Tablet Android

The tablet we decided to use was Galaxy Tab 3, model number SM-T820, running under Android 9 (fig 5).

The Samsung Galaxy Tab 3 is a mid-range tablet with the Android operating system. The display of this device is 8 inches in TFT technology. Its resolution is 800 x 1280 pixels and this brings its pixel density to 189 ppi. The camera, located on the back, has a resolution of 5 megapixels. Also on the back, there is a single flash and this camera can record video at 1280 x 720 pixels. On the front we have a second 1.3-megapixel camera. It is a single SIM device with fairly simple connectivity. We have HSUPA network connectivity, and Wi-Fi b / g / n. The processor of this device is a dual Exynos 4212 which works at the frequency of 1.5 GHz and has a Mali 400MP graphics processor. We then have 1.5 GB of RAM and 16 GB of memory, expandable via a microSD. The non-removable battery of this device is 4450 mAh.

Figure 5: Samsung Galaxy Tab 3

3.2 METHODOLOGY

3.2.1 Game design and application

Starting from the Diagnostic Criteria for Apathy (social apathy dimension, *Table 1 B3*), some psychologists of the Research Memory Centre have designed a series of social situations in which to virtually place the patient to assess his degree of social apathy. In particular these situations were design to identify loss of, or diminished engagement in social interaction as evidenced by at least one of the parameters identified in Table 1: spontaneous social initiative, environmentally stimulated social interaction, relationship with family members, verbal interaction, homebound.

The game therefore consists in virtually immersing the patient in a series of social situations and giving him the opportunity to decide whether to interact with other people and how much.

In order to define the specifics of the game, a series of meetings were held between engineers and clinicians in order to find the best solution to make the game as understandable as possible by patients.

In the end we decided that I would develop the game with the following characteristics:

- Application designed in 2D for a tablet

The final application was developed with Unity, using Visual Studio as an editor for implementing the necessary scripts. The choice of 2D rather than 3D was made because elderly patients not used to use technology could not tolerate 3D vision or viewers.

- Initial interface

When starting the game, you are asked in sequence to enter the patient code, the language in which to play, to choose an avatar and to give him a name. Finally, the game instructions are shown on the screen.

- Game interface

Here we have those three different game situations are proposed for the patient to choose from.

- Menu interface

The menu interface appears every time the patient has to choose if and how to interact with the people around him.

- Point counter

The point counter serves to provide data on the degree of apathy based on the choices the patient makes. It is not visible to the user.

- Stopwatch

The stopwatch serves to quantify reaction times. It is not visible to the user.

- Saving system

System for saving on the tablet a file called "codepatient.txt" containing all the choices made by the patient with the relative scores and times. “Codepatient” is the code entered by the clinician at the beginning of the game that uniquely identifies the patient.

- Final interface

The final interface appears only after playing in all three situations and give the possibility to print the results or leave the game. There is no button to quit the game before having done all three situations.

Everything that interfaces with the user is designed to be as simple as possible, since the game is designed for users not used to using technology. The characters and environments are very basic because, if they were too "beautiful" they would have distracted the attention of the patient from the task to be performed. The writings of the dialogues, the narrative parts and the menus have been designed to be as large as possible, compatibly with the space available and even the selection buttons in the menus have been designed to be large but well-spaced, to avoid tapping by mistake the wrong button.

3.2.2 Technical notes

The unity project has been divided in 9 scenes: 4 for the female avatar, 4 for the male avatar and a start scene used for both sexes (fig 6). This section describes the start scene and the 4 scenes for the male avatar. The 4 scenes for the female avatar are not described due to their resemblance to the male counterpart.

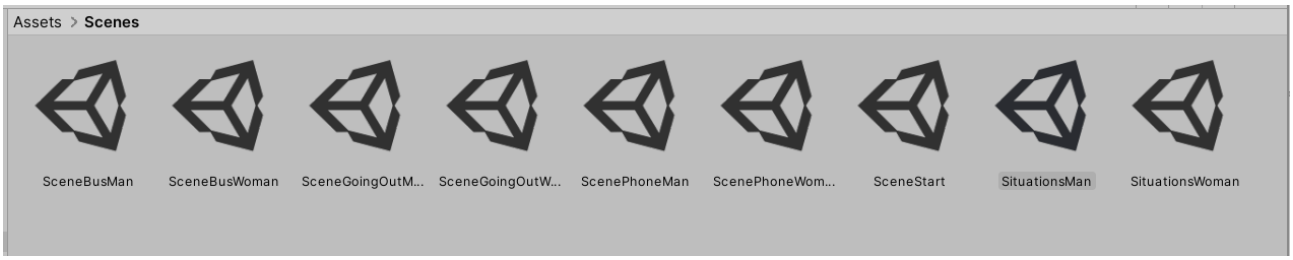


Figure 6: Unity's scenes designed in the Serious Game

- Start scene: here, the operator is required to insert a code for the patient, to set the language between English, French and Italian, to choose an avatar and to give him a name.

- A scene in which is possible to choose the order of appearance of the three game situations. A menu with the three possibilities is presented at the beginning of the trial and every time a game scene is completed. The menu does not show up at the end of the third game scenario. The patient now has to decide if to see her score or to quit the application. There are two scenes for choosing the situation because, although apparently the same, they refer to different game scenes for different avatars.

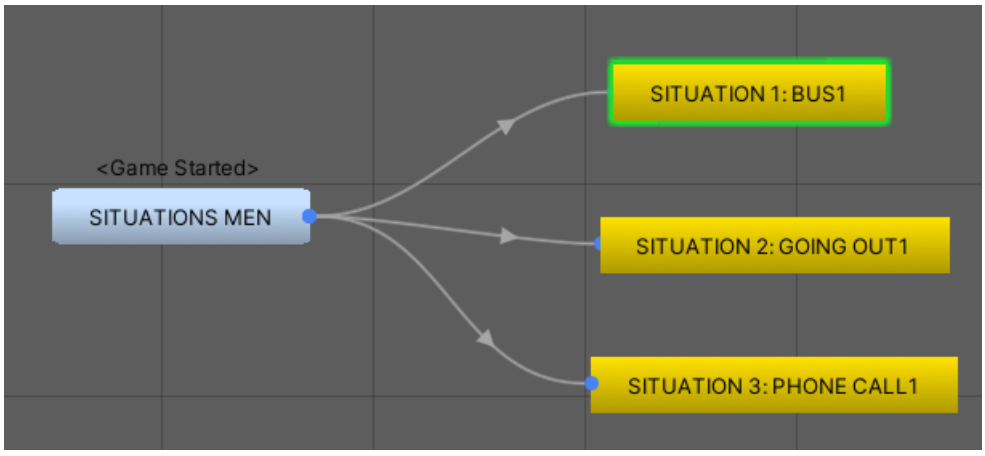


Figure 7: Flowchart of the scene of choice of the situation

- 3 game scenes: each of these scenes is called using the menu described before depending on the choice of the patient.

The use of Fungus was fundamental for the development of each scene. Using this tool, I created a flowchart for each scene which allowed me to create a logical and organized path of what should have happened in the game.

In the flowchart blocks it is possible to define a series of instructions: these may already exist in Fungus or you can create them as a script to be attached to a game object of the scene. I used some of the Fungus methods and some methods I have created by myself.

In each of the flowchart blocks it is possible to define an "Execute on event" thanks to which it is possible to choose the trigger event that activates the instructions of that block. Below is the flow chart of the start scene.

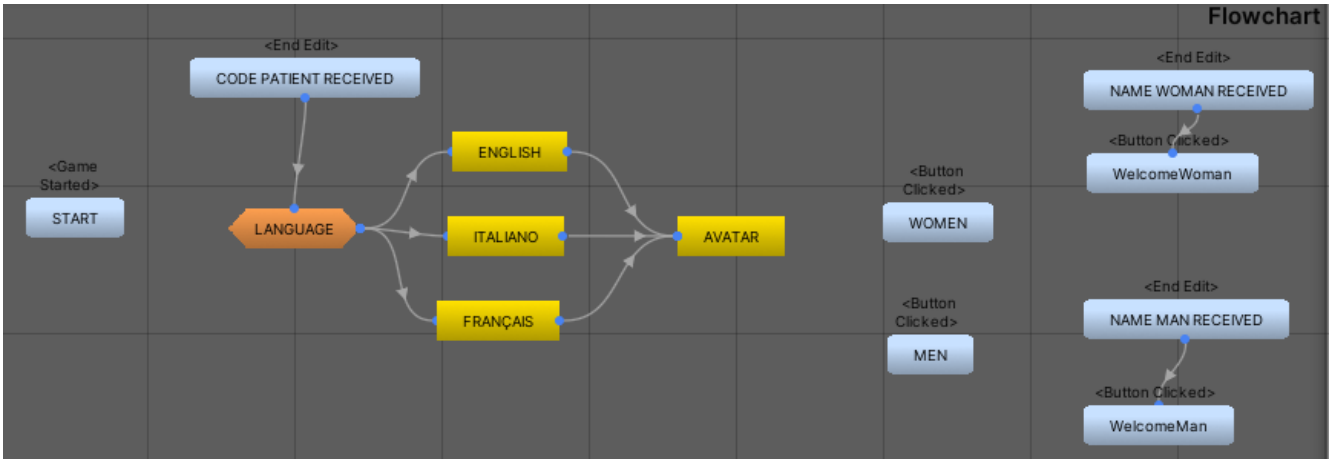


Figure 8: Flowchart showing different kind of block

In the Figure 8 we can see some different kind of blocks I used:

- Game started type block: this is the block called START from which the instructions will start where the scene is launched.
- End edit type block: in this flowchart there are three blocks defined by this type: code patient received, name woman received and name man received (fig 9). The end edit block is triggered by the "ok" button pressed by the clinician or by the patient after they have inserted the requested information.

Figure 9: In these two figures we can see the interface that appears when you are asked to enter the code of the patient and the name of the avatar and the two ok buttons that act as a trigger signal for the start of the respective end edit block

- Button clicked type block: There are two blocks defined by this block type and they are called WOMAN and MAN. This kind of block is triggered by the choice of the avatar (female or male one).

The blocks that do not have a Execute on event, start when they are called by other blocks.

Each scene includes several views that are changed by Fungus commands following the story (fig 10).

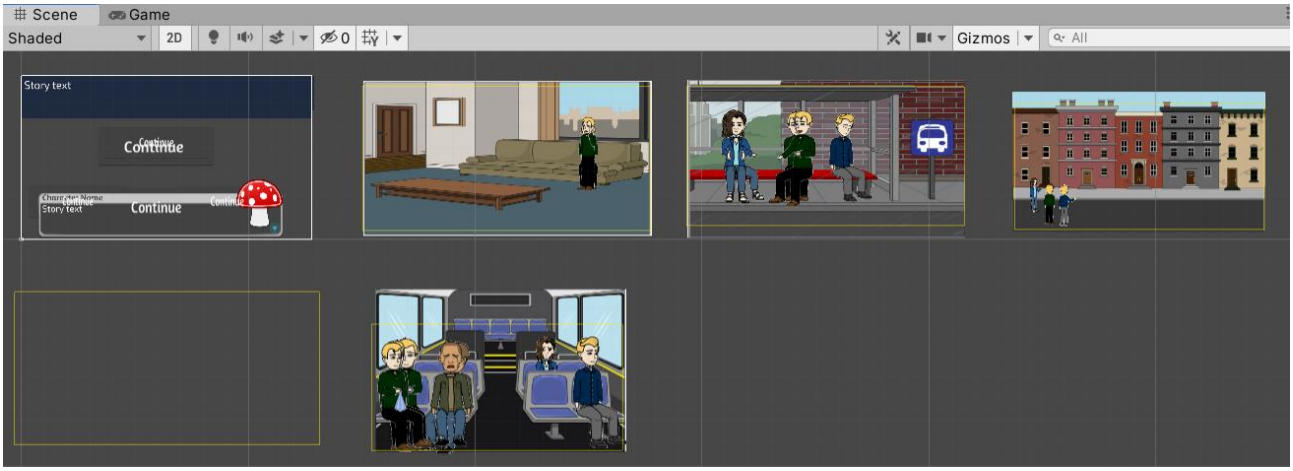


Figure 10: Example of a game scene with different views.

Inside each view we can notice different sprites for each avatar (Fig 11). Sprites are 2d images which represents scene objects. These are shown and hidden using specific commands in order to create the movement illusion.

Figure 11: Example of a scene with different sprites for the same character. We can notice that the principal character (the one in the middle) is represented in 2 different positions: this is because if he will talk with the girl next to him, the app will hide the avatar in the front

All the sprites I used are downloaded from storyboardthat.com and when it was necessary, they have been cropped using an application called GIMP.

As already mentioned, Fungus allows us to take advantage of a series of predefined commands to create a story in the game and set the dialogues between the characters but, having everything predefined, it is not possible to adapt it to all needs. However, it gives the possibility to call methods that can be written and customized by the Unity user in C # language (Fig 12). These methods to be called by fungus must be contained in scripts attached to game object present in the scene in question.

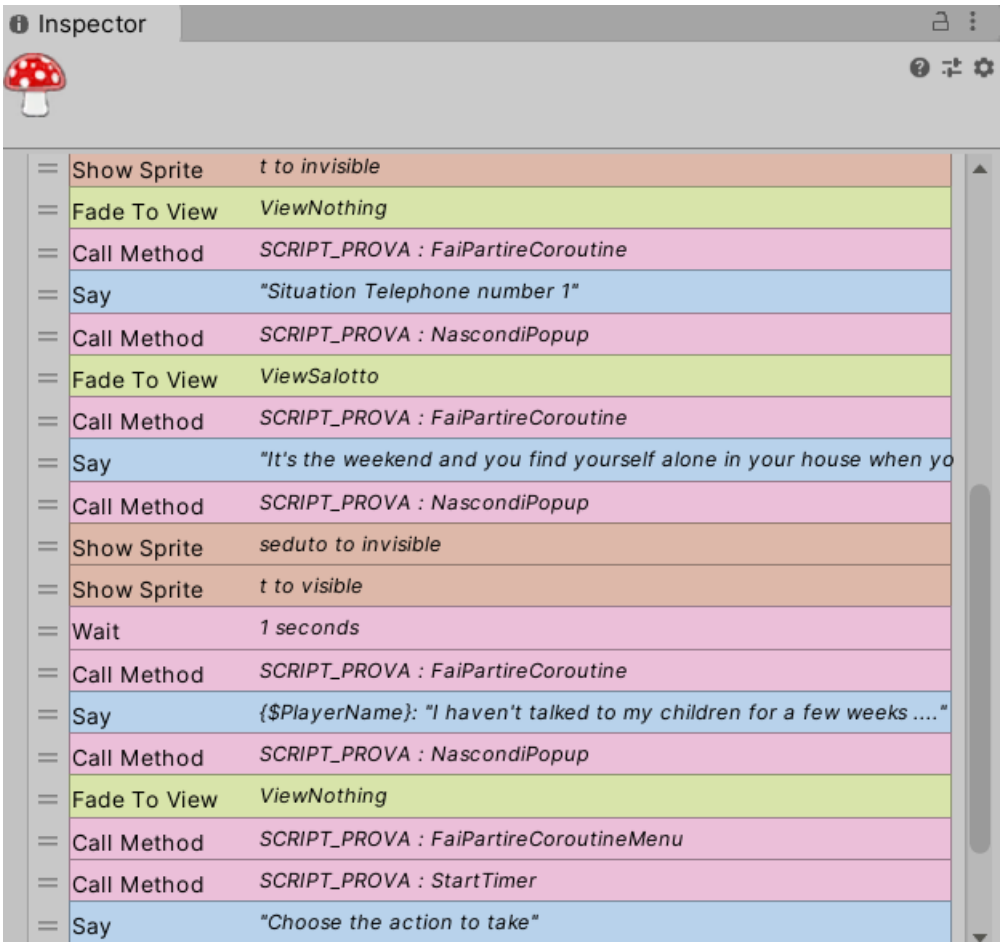


Figure 12: List of commands called from Fungus.

In the Figure 12 it is possible to see a list of different commands. Between Fungus predefined commands we can see “show sprite” which show the sprite we select in the scene, “fade to view” command which change the game view, “say” command which is used to create dialogues and the narrative part of the scene. The wait command delays the start of the following command of a chosen amount of time. I modified these predefined commands in order to personalized the application as it was required. For example, as it is possible to see in the pictures below, I changed the “say” command to set different dialogue scenes to improve the patient comprehension of the game.

Figure 13: Example of a narrative part of the story.

Figure 14: Example of a dialogue part of the story.

In the Figures 13 and 14, you can notice the difference between the narrative part and the dialogue part of the say command. The tag called {$PlayerName} is replaced by the name chosen by the patient or by the name of the character they are interacting with. Also, a small picture of the avatar who is talking is presented with the dialogue to improve the comprehension.

In the Figure 12, it is also possible to see some of the methods I written. They are attached to the SCRIPT_PROVA game object. In this case, these are methods designed to let a popup appear to remember the patient what she has to do to move forward in the game when a certain amount of time is gone without a move by the patient herself. Another method is called to bring the timer to zero if the patient does something before the end of the time set.

3.2.3 Procedure

The game was structured as follows:

3.2.3.1 Initial interface:

- The first screen that appears when starting the game asks you to enter an identification code for the patient. This code is entered by the clinician and is used to give a name to the excel sheet

containing the points scored by the patient in question during the game session. The game is programmed to export a different file for each player.

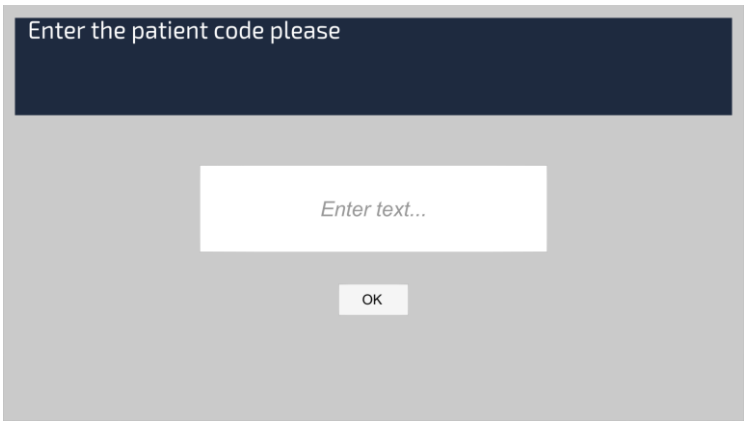


Figure 15: Interface that appears when you are asked to enter the code of the patient.

- After entering the code, the tablet is given to the patient, who is asked to choose the language. The settable languages are English, French and Italian (Figure 16).

Figure 16: Language selection screen.

- At this point, it is required to choose an avatar you want to play with. In this first version I have inserted two avatars: a man and a woman (Figure 17).

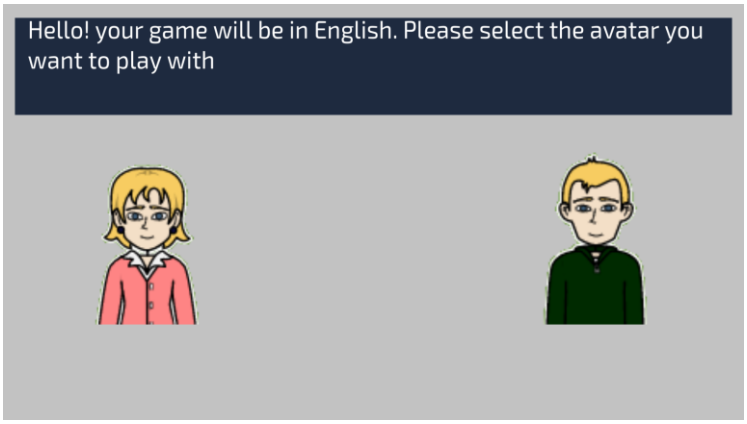


Figure 17: Avatar selection screen.

- You are prompted to give a name to the avatar choose (Figure 18).

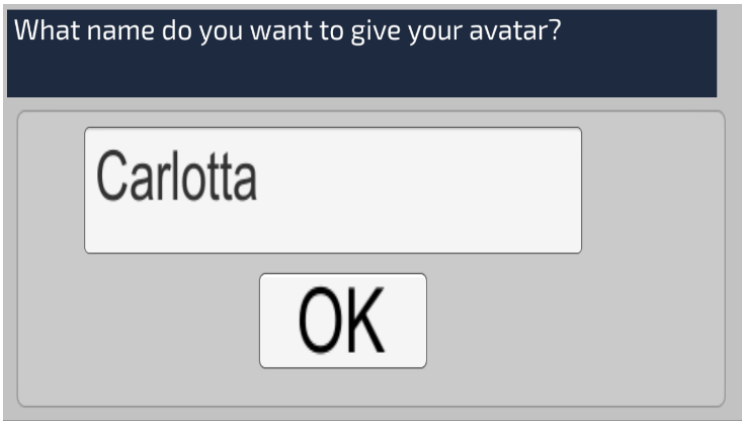


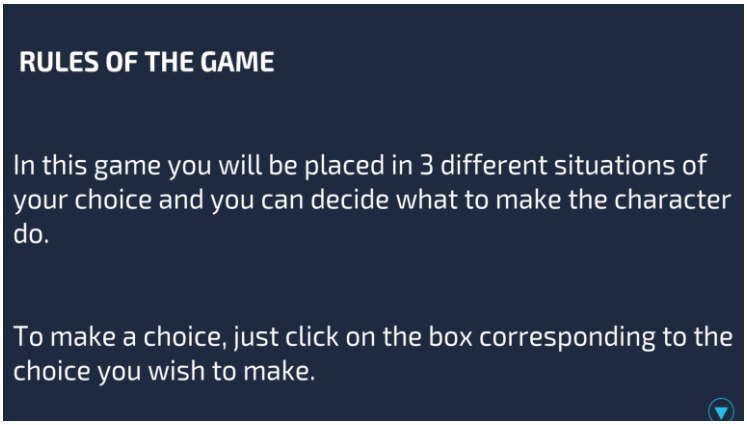
Figure 18: Name selection screen.

- The game is designed to store the name in a variable called PlayerName and bring it back when needed (Figure 19, 20).

Figure 19: Example of the use of the variable PlayerName: give a personalized welcome to the player.

Figure 20: Example of the use of the variable PlayerName: improve understanding in dialogue. It is placed in the window, along with the chosen dialogue avatar when your character is speaking.

- Finally, before immersing the patient in the game, two screens with instructions appear (Figure 21)



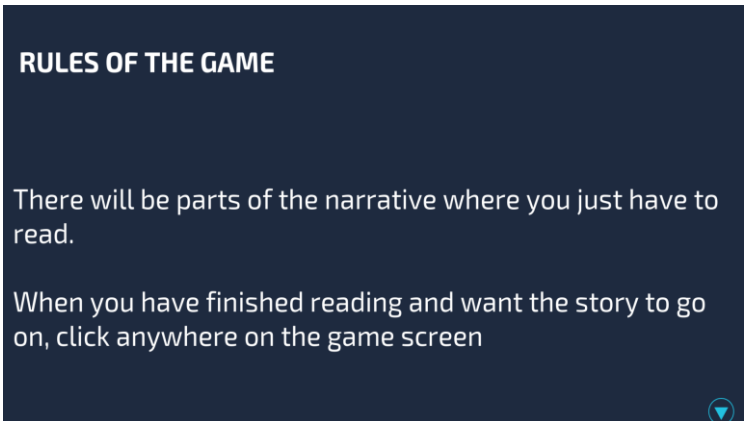


Figure 21: Screens illustrating the rules of the game.

- If during the game the patient forgets the rules and therefore does not click on the screen to continue the story or does not select an alternative from the menu, he will be shown a popup that will remind him what to do.

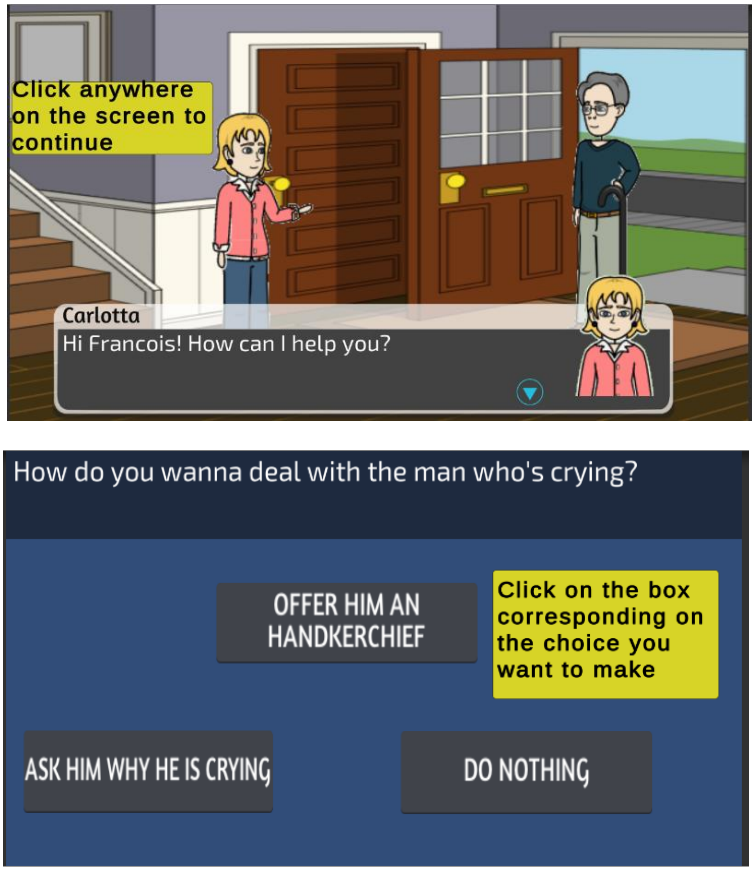


Figure 22: Popup examples

3.2.3.2 Choice of game situation

In this phase the patient is asked to choose in which situation he prefers to play, among the three alternatives that are proposed to him. To complete the game, he will eventually have to play all three situations, but he has the opportunity to choose the order.

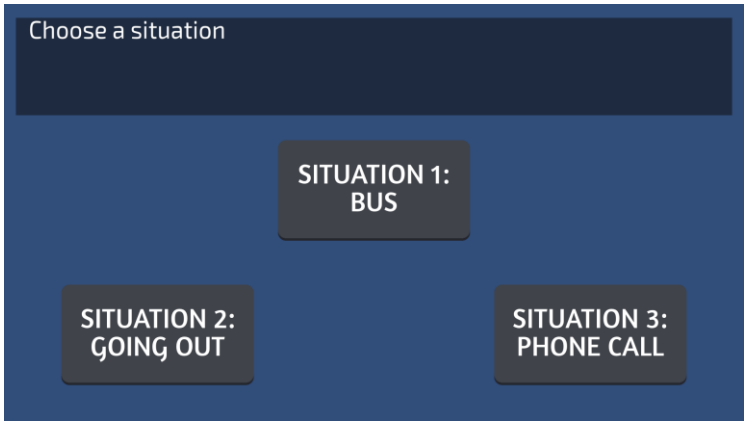


Figure 23: Game situation selection screen

3.2.3.3 SITUATION 1: BUS

This situation can be said to be divided into 3 sub-scenes:

- Sub-scene 1

At the start of this sub-scene the character is at his house when it occurs to him that he has forgotten his doctor's appointment, so he decides to run to the bus stop. Once there (Fig 24), it starts to rain and he is placed in front of the first choice: he can interact or not with a girl who is also at the bus stop (Fig 25).

Figure 24

Depending on whether and how he decides to interact, he will accumulate 0, 1 or 2 points.

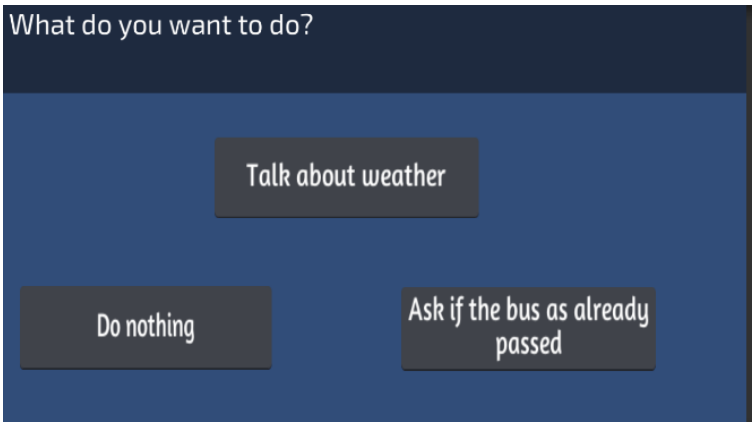


Figure 25: Menu interface Situation bus Sub-scene 1

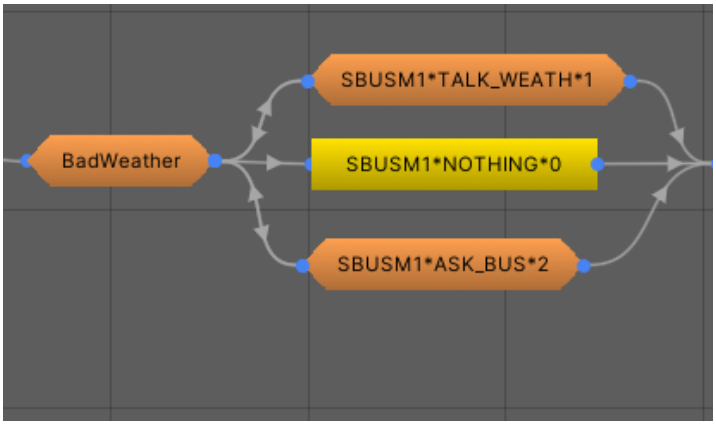


Figure 26: Flowchart menu Situation bus, sub-scene 1

In the flowchart showed in the Figure 26, we observe that the arrows that connect the block called BadWeather with the blocks called SBUSM1 * TALK_WEATH * 1 AND SBUSM1 * ASK_BUS * 2 are bidirectional. This means that, if the patient chooses to interact in a certain way (e.g., talking about bad weather) then, after having interacted according to the choice made, he will be brought back to the menu and can choose whether to interact again (to ask if the bus has passed) or you can decide to end the interaction there by clicking on the DO NOTHING block.
The maximum score the patient can score in this sub-scene is 3.

- **Sub-scene 2**

In this second sub-scene, the patient is presented with another chance of interaction, this time stimulated by the environment (see criteria B3 in table 1). In particular, a girl asks him if he wants to sit down.

Figure 27

Based on his/hers answer (affirmative or negative) he/she may receive more or less points (1 or 0).

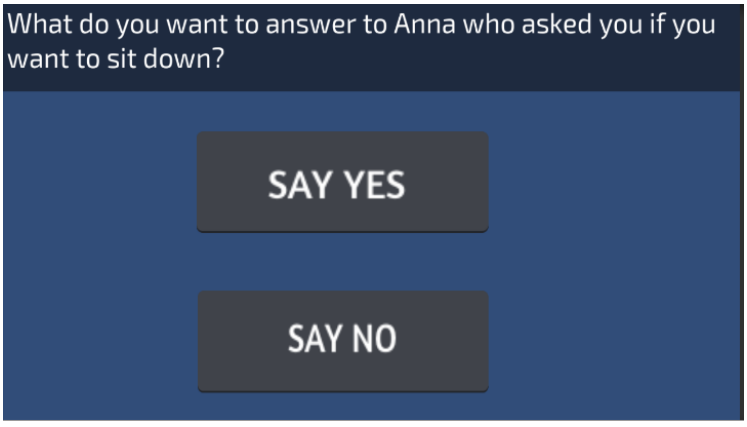


Figure 28: Menu interface Situation bus, sub-scene 2

If the patient answers yes, he/she will be presented with another chance to earn points by talking to the girl next to him. If, on the other hand, he/she hadn't sat down, the story will go directly to the third and final sub-scene.

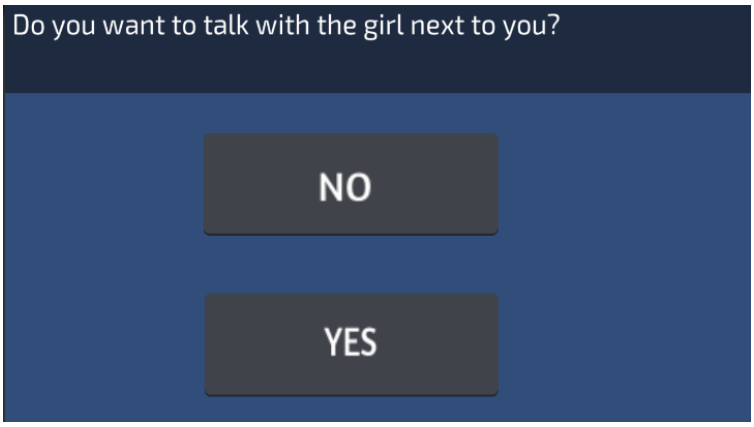


Figure 29: Second menu interface Situation bus, sub-scene 1

Answering yes to the question in the image above would earn the patient 2 points, answering no would give him 0 points.
The maximum score the patient can score in this sub-scene is 3.

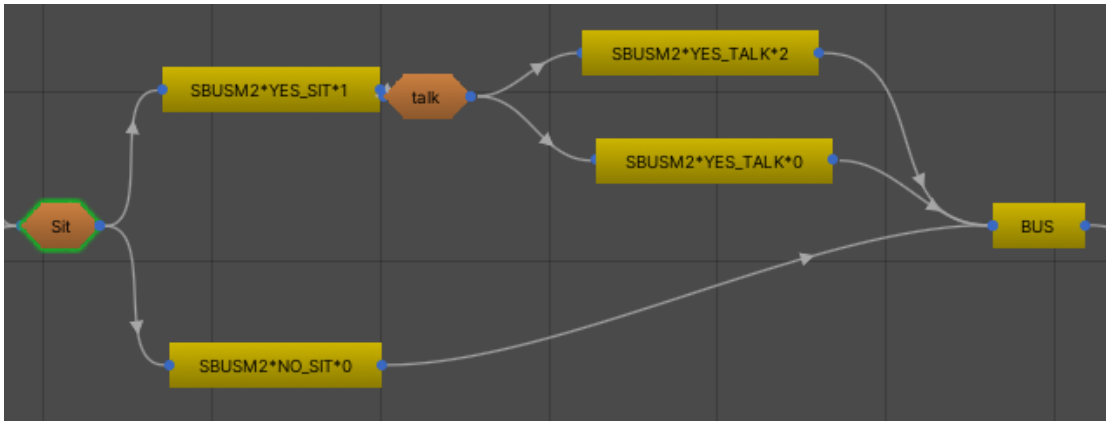


Figure 30: Flowchart Situation bus, sub-scene 2

- **Sub-scene 3**

In this third sub-scene what happens is that the bus arrives, the characters get on and the main character sits on the bus next to a crying man.

Figure 31

The patient is therefore confronted with the usual choice: to interact or not? and, if yes, how much?

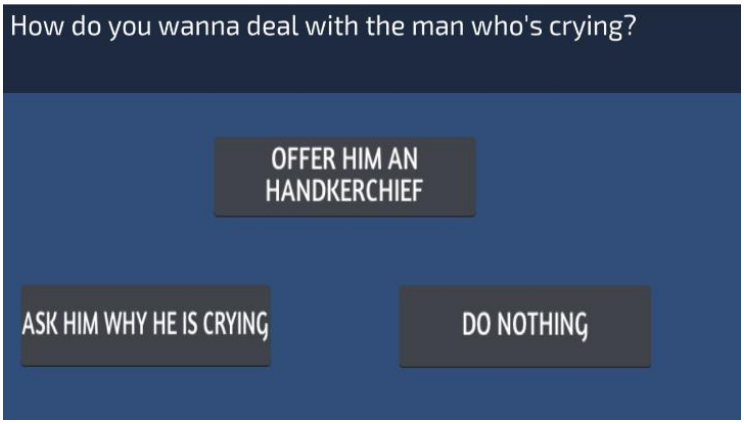


Figure 32: Menu interface Situation bus, sub-scene 3

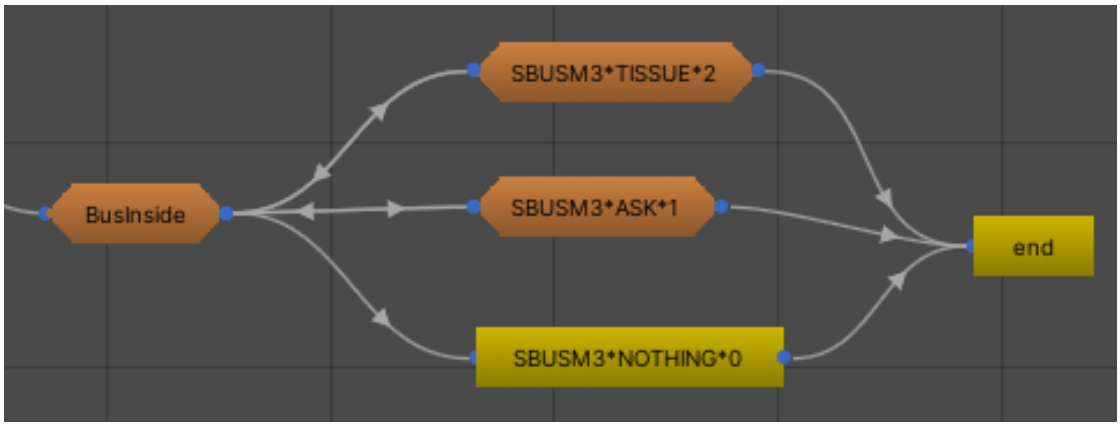


Figure 33: Flowchart Situation bus, sub-scene 3

As for the first sub-scene (Figure 26), in the flowchart in Figure 33, we observe bidirectional arrows. So here too the patient will have the opportunity to interact twice and earn a total of 3 points. In the bus situation the patient can earn a total of 9 points

The Bus situation is meant for testing spontaneous social initiative, environmentally stimulated social interaction, verbal interaction (see Table 3, B3).

3.2.3.4 SITUATION 2: GOING OUT

There are three sub-scenes for this situation as well.

- **Sub-scene 1**

At the beginning of this scene, we see the main character relaxing at home. After a while the doorbell rings and we discover that it was the neighbor who rang. The neighbor asks to be accompanied to the supermarket, because he needs help.

Figure 34

The patient can decide whether to do it or not and why.

Figure 35: Menu interface Situation going out, sub-scene 1

In Figure 36 we have the flowchart for this sub-scene: we immediately notice that there are no bidirectional arrows (like in Figure 26) nor the possibility of further interacting after a first initial interaction (like in Figure 30). The maximum score obtainable is therefore 2 and not 3

Figure 36: Flowchart Situation going out, sub-scene 1

- **Sub-scene 2**

This sub scene begins with the main character sunbathing on the porch of his house. After a while two friends with the dog pass by and offer him to take a walk with them.

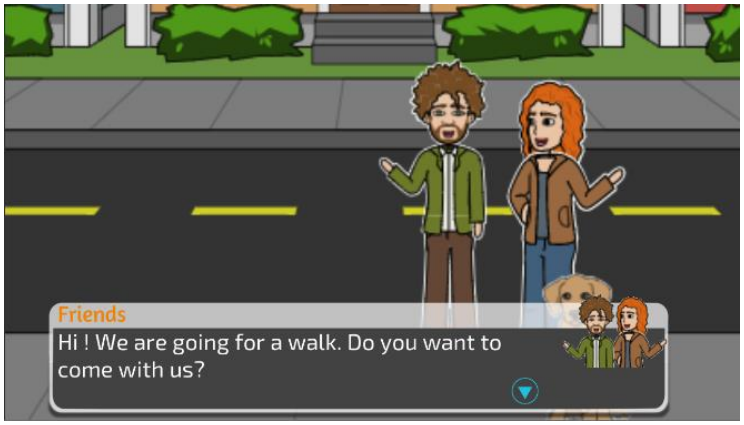


Figure 37

As usual, the patient's response will determine how many points he receives.

Figure 38: Menu interface Situation going out, sub-scene 2

As for the previous substage, the maximum score obtainable will be 2.

Figure 39: Flowchart Situation going out, sub-scene 2

- **Sub-scene 3**

In this third sub-scene we see the patient sitting in the living room and his cell phone is resting on the table. after a while a message arrives on the mobile phone which the patient reads. it is from a friend of his who invites him to go to the mountains.

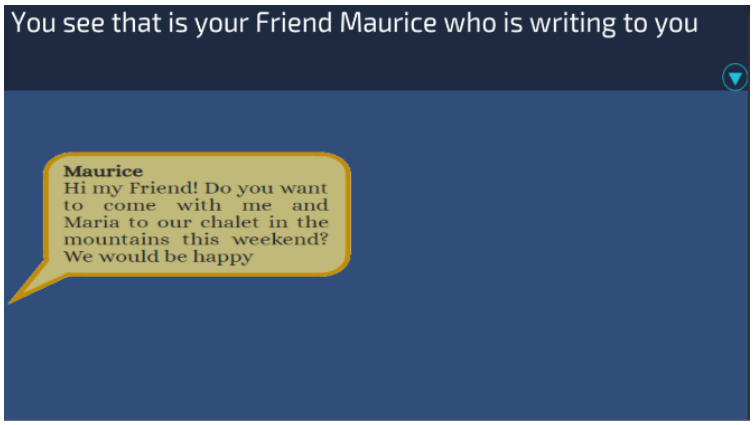


Figure 40

As usual, the patient's response will determine how many points he receives.

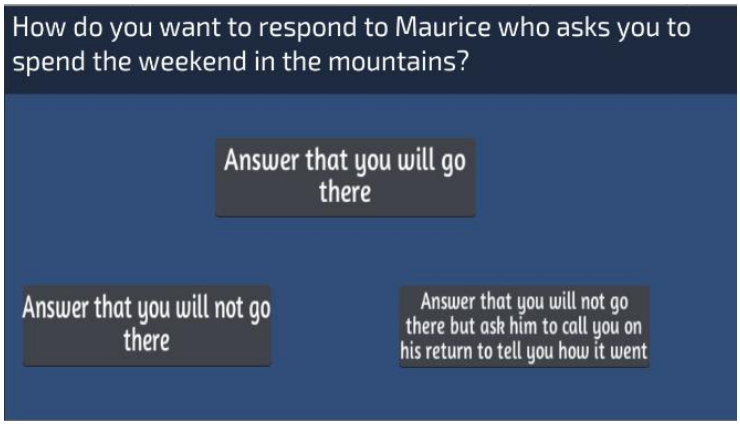


Figure 41: Menu interface Situation going out, sub-scene 3

As for the previous 2 substages, the maximum score obtainable will be 2.

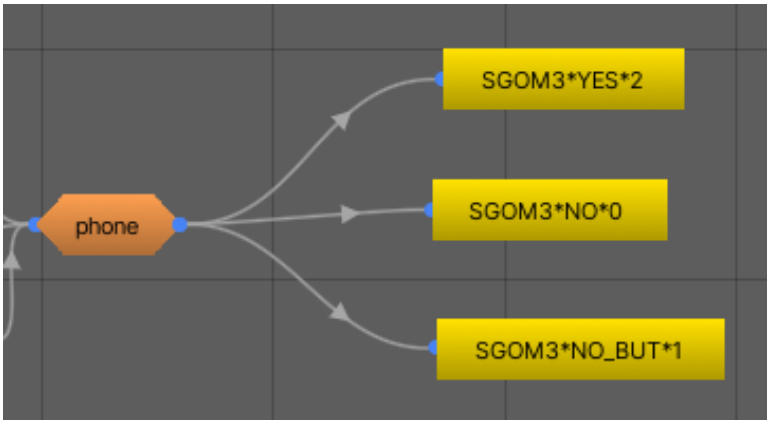


Figure 42: Flowchart Situation going out, sub-scene 3

The Going Out situation is meant for testing Homebound, environmentally stimulated social interaction and spontaneous social initiative (see Table 3, B3).

3.2.3.5 SITUATION 3: PHONE CALL

- **Sub-scene 1**

This scene starts with the chosen avatar sitting in the living room of his house and starting to think about his children that he hasn't heard from very long.

Figure 43

Through a menu, they are therefore offered ways to interact or not by telephone with them.

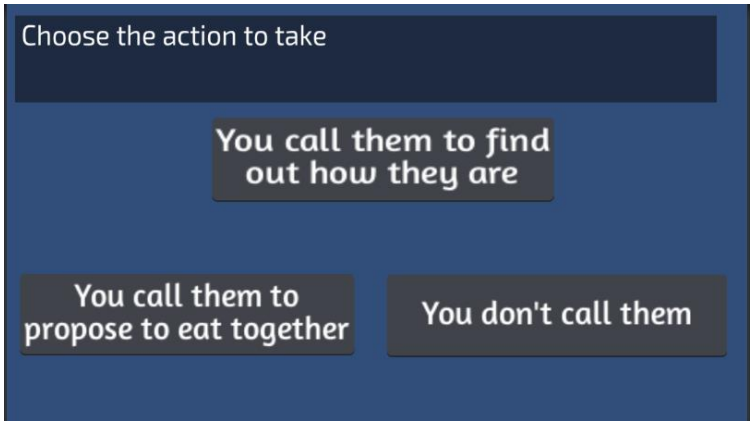


Figure 44: Menu interface Situation phone call, sub-scene 1

Depending on whether and how much he decides to interact with his children, he may receive 0, 1 or 2 points.

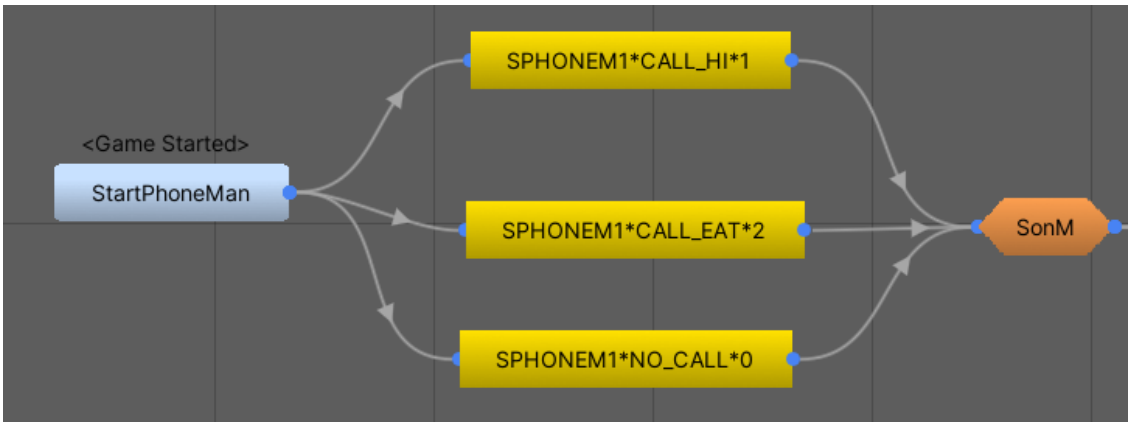


Figure 45: Flowchart Situation phone call, sub-scene 1

We note from the flowchart the absence of the possibility of reaching 3 points.

- **Sub-scene 2**

In the second sub-scene, the patient is presented with a different opportunity to interact by telephone with his children: he receives a call from his son.

Figure 46

What he can do is decide how much to interact with him by answering the phone and, depending on his decision, he will earn 0, 1 or 2 points.

Figure 47: Menu interface Situation phone call, sub-scene 2

As we can see from the flowchart below, even here there is no chance to earn 3 points.

Figure 48: Flowchart Situation phone call, sub-scene 2

- **Sub-scene 3**

In this last sub-scene, it happens that during a phone call, our character is given bad news regarding his brother.

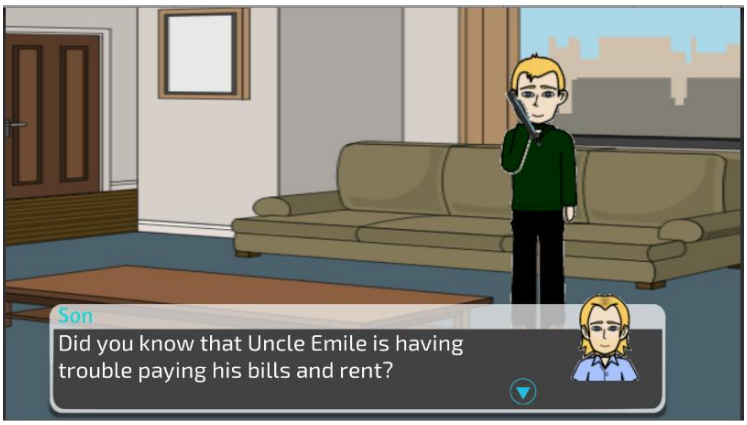


Figure 49

His reaction and planning on how to help / not help his brother will earn him 0, 1 or 2 points.

Figure 50: Menu interface Situation phone call, sub-scene 3

We notice the impossibility of earning 3 points also in this last subscene.

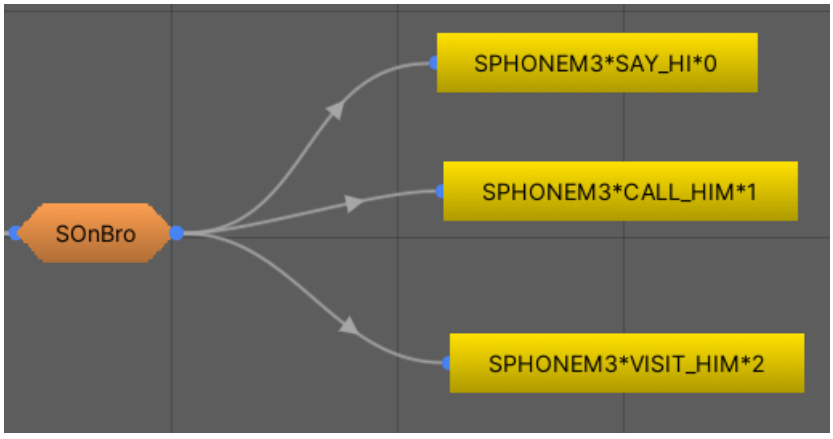


Figure 51: Flowchart Situation phone call, sub-scene 2

The Phone situation is meant to test spontaneous social initiative, environmentally stimulated social interaction, verbal interaction, homebound (see Table 3, B3).

3.2.3.6 Comparison of game situations

As we could see from the detailed description of the three scenes, the bus scene is structured differently than the other two. In the latter, for each sub-scene there is only one opportunity to score more or less points while in the bus scene the opportunity to accumulate more points is presented again if an initial interaction is recorded. The opportunity to interact more after a first interaction is provided to the patient by returning him to the previous menu (see Fig 31, 32, 33) or by providing him with a different opportunity for interaction (see Fig 27, 28, 29, 30). This was an experiment done to make an initial evaluation of different possible approaches.

We note that the three situations are meant to test all subdomains of social apathy: Spontaneous social initiative, environmentally stimulated social interaction, relationship with family members, verbal interaction, homebound (see Table 3, B3).

4 EXPERIMENTS

4.1 POPULATION AND STUDY PROCEDURE

This study was performed as part of the Interreg Alcotra CLIP E-Santé project, European cross-border cooperation program between France and Italy. In particular, the University of Genoa, INRIA (Sophia Antipolis, France) and the Research Memory Centre, located at the Claude Pompidou Institute of Nice, were involved in this particular project. The protocol in which the patients who tested the game were included is called "Tapiscine" and is a clinical protocol for patients with MCI and cognitive complaints.

Patients coming to the Nice Research Memory Center for a regular medical consultation or a classical neuropsychological assessment, if eligible, were invited to take part in the study. The inclusion period lasted two weeks and involved 10 subjects (2 M; 8 F; mean age: 74,6 years; SD: 5,379; age range= 64-83).

All subjects underwent a standard assessment including the Mini-Mental State Examination (MMSE) as well as the diagnostic criteria for apathy and the apathy motivation index (AMI) with a neuropsychologist and a psychiatrist. The neuropsychiatric evaluation revealed that 7 patients had MCI and 3 had SCD. Of the total 10 patients, one was apathetic. This subject tested positive for all the diagnostic criteria of apathy while in the AMI he made a score that would not seem to suggest that he is apathetic. Despite this, the diagnosis made by the neuropsychiatrists for this subject is of apathy and the AMI score is justified by the fact that in the questionnaire patients are asked to rethink the last 2 weeks and this can create confusion and get the results wrong in people with memory deficit.

The Game was then performed in a quiet experimental room with the supervision of a psychologist and mine and the score and time data have been saved in excel sheets (one per patient).

At the end of each experimental condition, participants were administered self-report questionnaires concerning the evaluation of their experience. Specifically, participants were presented with 10 points scales and asked to report their level of satisfaction, interest, discomfort, anxiety, feeling of security and fatigue by checking one of the points ranging from ‘not at all’ to ‘extremely’.

Table 4: Characteristics and group comparisons for apathetic and non-apathetic participants.

	Apathetic (N=1)	Non apathetic (N=9)
Female, n(%)	1	7
Age (years), mean ± SD	74	74,6±5,7
Level of education, n (%)		
Primary education	0	0
Secondary education (first cycle)	0	4
Secondary education (second cycle)	1	1
Higher education	0	4
MMSE, mean ± SD	22	26,5±2,6
Presence of Diagnostic Criteria for Apathy, n (%)	1	0
Apathy Motivation Index, mean ± SD	0,94	0,88±0,18

Table 5: General value of AMI and all the three sub-domains for all the patients

	AMI	Behavioural	Social	Emotional
Patient 1	0,78	1,17	0,83	0,33
Patient 2	1,17	0,67	0,83	2,00
Patient 3	0,78	0,83	0,83	0,67
Patient 4	1,06	0,33	1,67	1,17
Patient 5	0,67	0,33	0,83	0,83
Patient 6	1,06	0,83	1,33	1,00
Patient 7	0,83	0,67	1,00	0,83
Patient 8	0,94	0,67	0,83	1,33
Patient 9	0,89	0,83	1,00	0,83
Patient 10	0,67	1,00	0,33	0,67

4.2 ACQUIRED DATA AND DATA ANALYSIS

At the end of each experimental condition, data indicative of the patient's performance could be saved on the tablet. In particular, these data are:

- Choices made with relative scores indicative of the patient's level of social apathy
- Time taken by the patient to make a choice each time a menu is presented to him

The scores scored by each patient in each scene were placed in a bar graph, normalizing the maximum value to 1 to make the scores of the different scenes comparable to each other. In fact, we had that in scene 1 the maximum score was 9, while in the other 2 the maximum score was 6.

After that, I created another bar graph with the total scores consisting of the normalized values of the scores in the 3 scenes. The normalized maximum is therefore 3, even if we remember that the real maximum for the total score is 21.

A particular focus was made on the scores of the only apathetic patient which were compared with the average scores and were clearly inferior. For this comparison too I used a bar chart.

The data concerning the time taken by the patients to make a choice were then not used in the analysis because they are results not relevant.

After having play the game, participants were administered self-report questionnaires concerning the evaluation of their experience. Specifically, participants were presented with 10 points scales and asked to report their level of:

- Satisfaction
- Interest
- Discomfort
- Anxiety
- Motivation
- Feeling of fatigue
- Difficulty

They were also asked how much he liked the following features of the game:

- The graphic interface
- The characters
- The content of the stories

The last question was instead aimed at understanding how much the patient had identified with the character of the game, so the last parameter we checked was the identification.

In the figure 52 we have an example of the 10-points scale presented to the patients to evaluate their level of interest. They were asked to checking one of the points ranging from ‘not at all’ to ‘extremely’.

Figure 52:

Interest

Can you indicate your interest in this task that you have just completed?

Not at all of interest | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Very great interest

In the complete questionnaire we find 11 of these scales to evaluate the 11 parameters we have just talked about. The original questionnaire was in French because the participants were all French nationals

For the analysis of the data concerning the questionnaire, I graphed the average scores given to each parameter, the scores of the apathetic patient for each parameter and the score in comparison between the answer given from the apathetic patient and the average scores of the others 9 patients.

Finally, I thought it was interesting to evaluate if there was a correlation between the patient's AMI (the general and the social dimension) and the various scores in the game. The correlation function returns the correlation coefficient of two ranges of values (the AMIs and the scores).

The correlation function used is:

$$Correl(X,Y) = \frac{\sum(x-\bar{x})(y-\bar{y})}{\sqrt{\sum(x-\bar{x})^2 \sum(y-\bar{y})^2}}$$

Figure F1: Correlation formula

Where $\bar{x}$ and $\bar{y}$ are the AVERAGE (matrix1) and AVERAGE (matrix2) values of the sample mean. Matrix1 is the matric containing the AMI's values, matrix 2 is the matrix containing the score's values. The value of the correlation coefficient is between -1 and 1. If it is closer to 1 there is a positive correlation, if it is closer to -1 there is a negative correlation. What I hope to find with this evaluation is a negative correlation that associates the increase in the AMI with a decrease in the scores.

5 RESULTS

In this chapter I will graphically analyze the results obtained by the patients in the various game sessions, the answers given to the acceptability questionnaire and I will compare the results obtained by the patient with diagnosed apathy (Patient 8) with the results obtained by the other patients. Finally, I will evaluate the presence of a possible correlation between the AMI of the patients and the scores obtained in the game.

5.1 ANALYSIS OF THE SCORES EARNED IN THE GAME AND OF THE RESULTS OF THE GENERAL ACCEPTABILITY QUESTIONNAIRE

In figures 53, 54 and 55 we can find graphed the results obtained by each patient in each scene. These graphs were obtained by normalizing the maximum score value to one so as to make the scores in the individual scenes summable and graphable. In fact, in figure 56 we have a graph representing the total score obtained by each patient as the sum of the three contributions. The total maximum is therefore normalized to the value of 3.

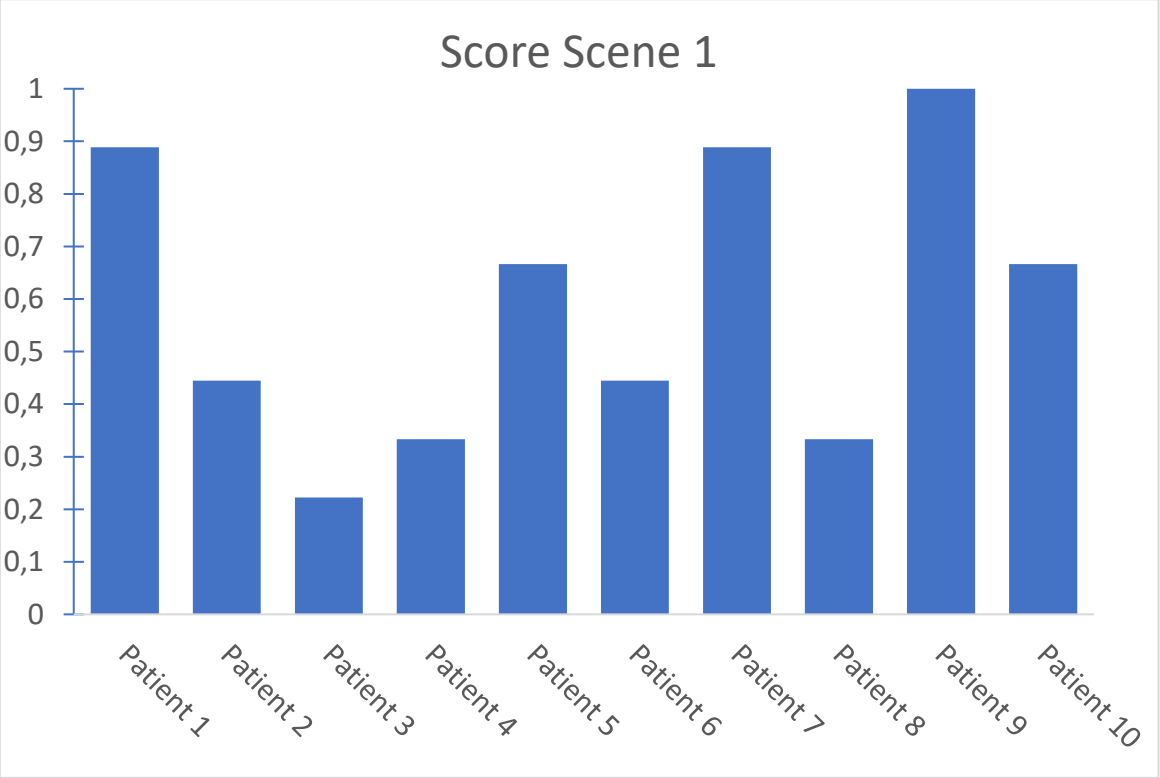


Figure 53: Bar graph representing the scores totaled in scene 1 by each patient. As already mentioned, the maximum score that can be scored in this first scene would be 9, but the results are normalized to 1 to make them comparable with those of the other two situations.

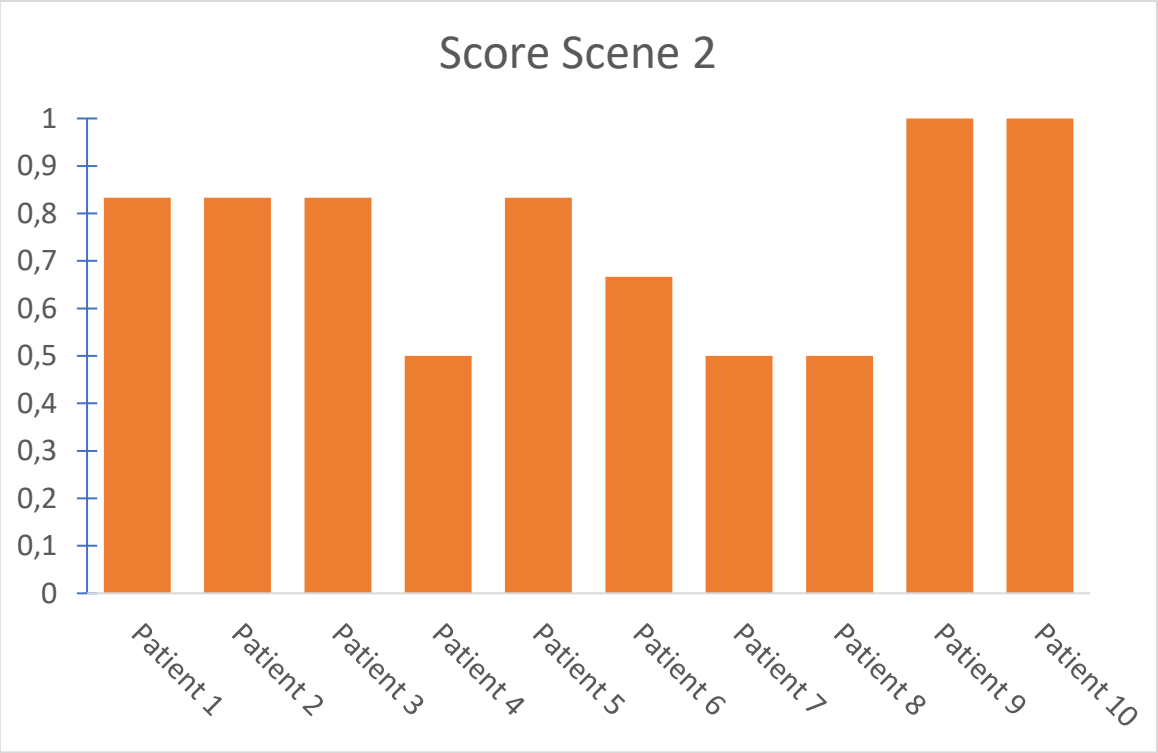


Figure 54: Bar graph representing the scores totaled in scene 2 by each patient. As already mentioned, the maximum score that can be scored in this first scene would be 6, but the results are normalized to 1 to make them comparable with those of the other two situations.

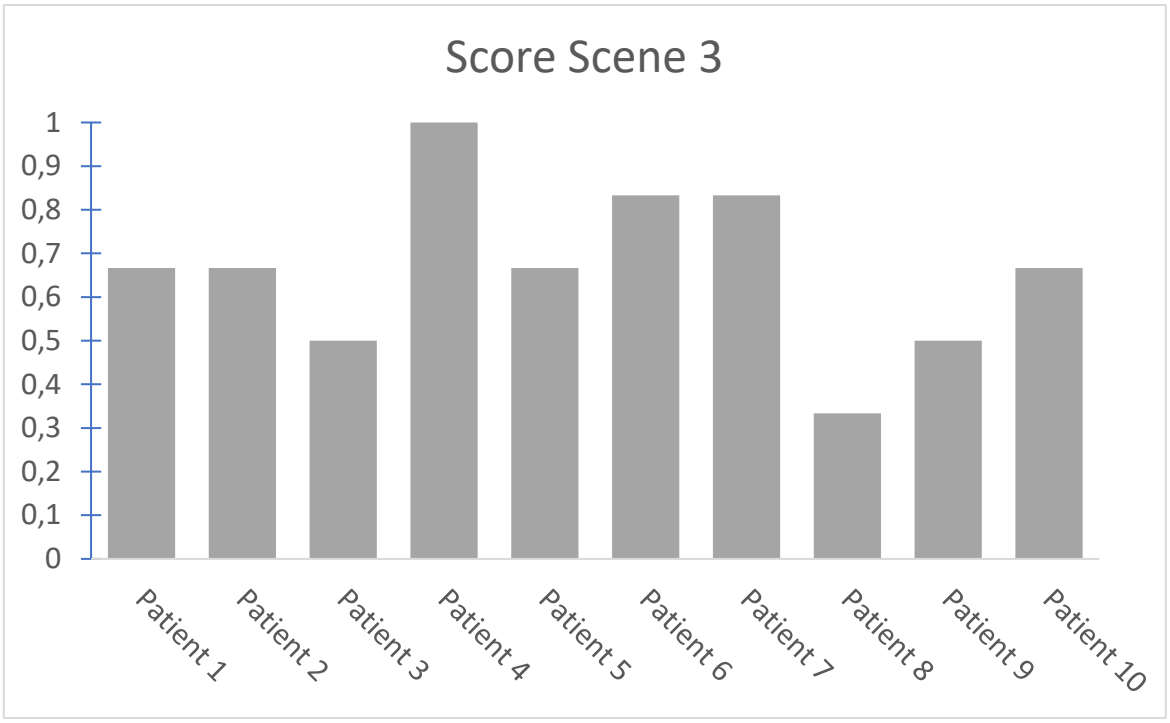


Figure 55: Bar graph representing the scores totaled in scene 3 by each patient. As already mentioned, the maximum score that can be scored in this first scene would be 6, but the results are normalized to 1 to make them comparable with those of the other two situations.

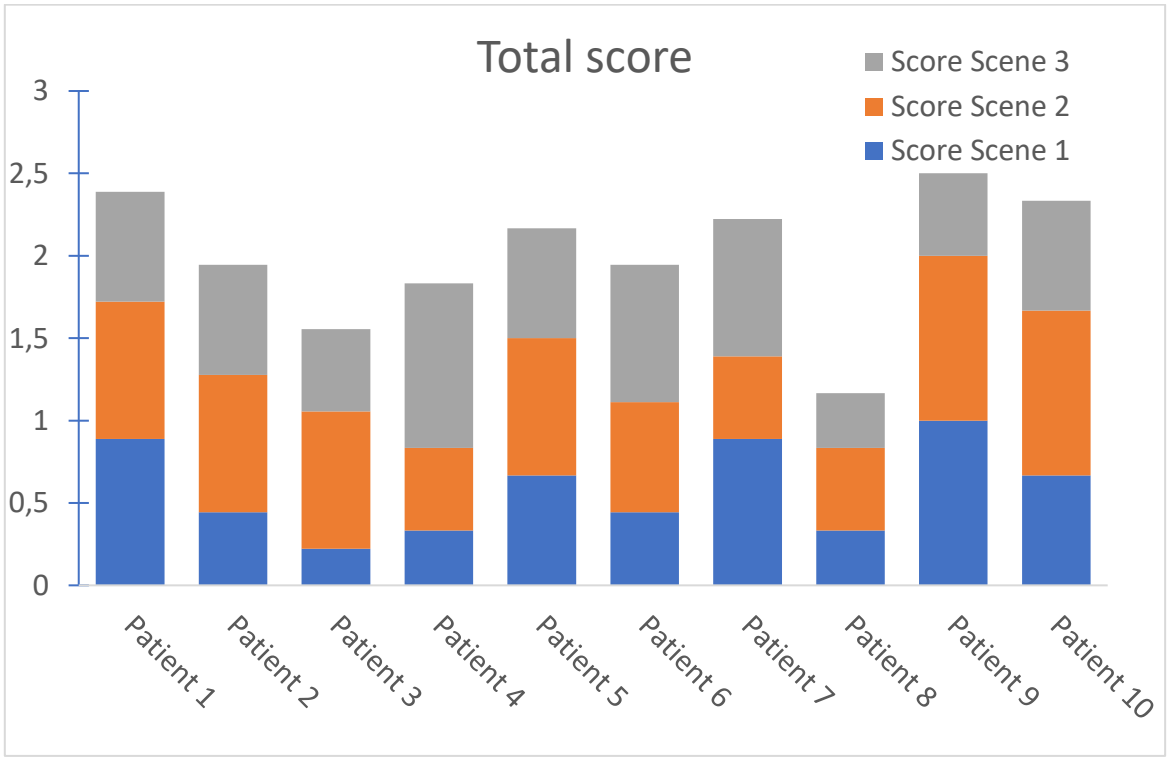


Figure 56: Bar graph representing the total scores totaled in the game by each patient. Each of the three contributions to the total score is represented in a different color

I've listed the score values for each patient in each game condition, as well as the total scores, in table 6. In red we find highlighted all the scores below the average for the first three columns, while in the last column we find highlighted only the lowest score, which is of patient number 8. Patient 8 is the only patient identified with apathy among the patients studied, and though this study is still in its early stages and we can't yet speculate on the game's diagnostic validity, this finding is quite encouraging for future advances.

Table 6: Scores earned by each patient in the different situations, as well as a cumulative score. In the first three columns, below-average scores are marked in red, while the lowest score of all is marked in red in the total score box.

	Score Scene 1	Score Scene 2	Score Scene 3	Total Score
Patient 1	0,89	0,83	0,67	2,39
Patient 2	0,44	0,83	0,67	1,94
Patient 3	0,22	0,83	0,50	1,56
Patient 4	0,33	0,50	1,00	1,83
Patient 5	0,67	0,83	0,67	2,17
Patient 6	0,44	0,67	0,83	1,94
Patient 7	0,89	0,50	0,83	2,22
Patient 8	0,33	0,50	0,33	1,17
Patient 9	1,00	1,00	0,50	2,50
Patient 10	0,67	1,00	0,67	2,33

The averages and standard deviations of the ratings received in each individual scenario, as well as the total, were thereafter the focus of my attention. I chose to conduct this investigation to discover if there was a scene that the patients preferred more or less, and so got more or less points in.

The results suggest that the patients scored the lowest on average in the first scene, that of the bus, 16 percent lower than in scene 2. The second game circumstance was the going out scene, and this is where we got the highest average score. The third situation, on the other hand, was the phone call situation, and an average score was recorded that was in the middle of the other two.

Table 7: Table representing the score's mean and standard deviations of the scores. The cell colored in red represents the lowest average value, the one in green the highest

	SCORE'S MEANS AND STANDARD DEVIATIONS			
	Scene 1	Scene 2	Scene 3	Total Score
Mean	0,59	0,75	0,67	2,01
Standard Deviation	0,27	0,19	0,18	0,41

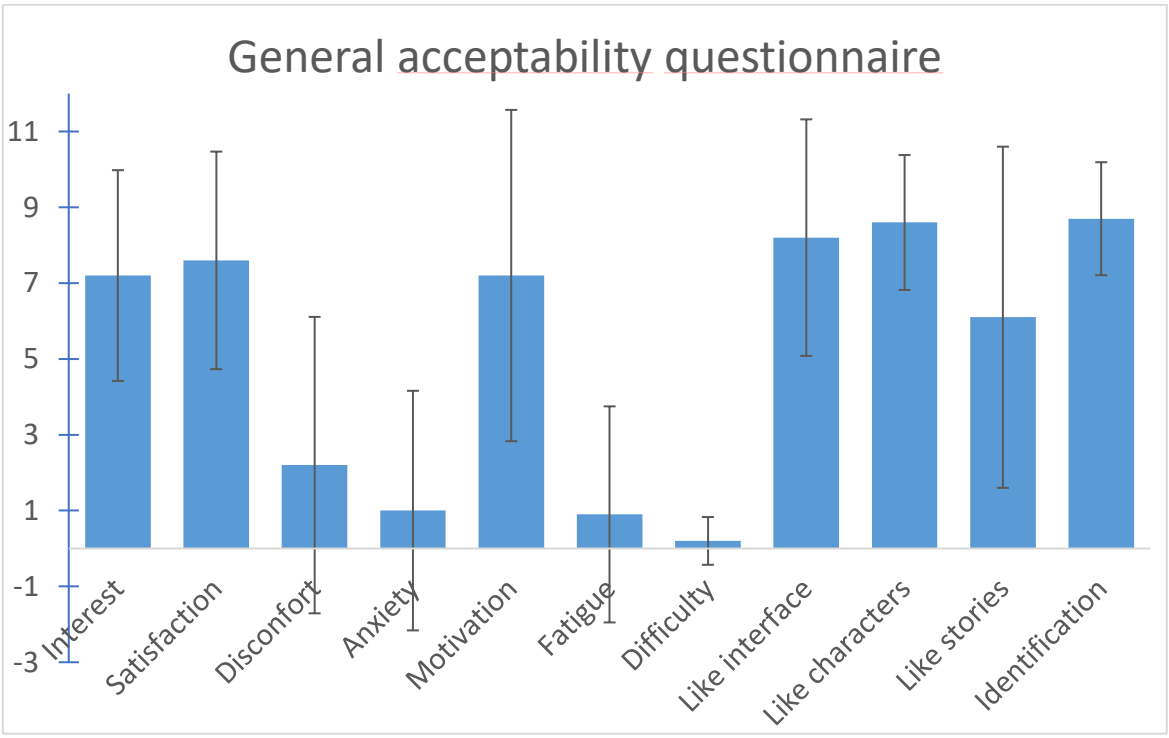


Figure 57: Bar graph representing the mean scores given by patients as answers to the questions of the acceptability questionnaire and their respective standard deviations.

Looking at figure 57, we can deduce that the game was more than accepted by the patients. In fact, we have high levels of interest, satisfaction and motivation and the level of discomfort, anxiety, fatigue and difficulty are very low. As an added bonus to this, we note that the game not only satisfied patients by not causing them any discomfort, but also enjoyed as a game itself. We have in fact that the scores given by patients when asked if they liked the stories, the interface and the characters, turned out to be high scores. The last element of the graph is identification: having reached a high score in this parameter is of fundamental importance because to diagnose apathy it is necessary for the patient to identify with the avatar and make the choices that he himself would make in situations of daily life.

5.2 COMPARISON BETWEEN THE APATHETIC PATIENT AND THE OTHERS

In this sub-chapter I evaluated, using graphs and tables, the differences between the scores scored by the apathetic patient and those scored by the others both in the game and in the questionnaire.

The results shown in figure 58 and table 8 are really interesting as they show that the apathetic patient (Patient 8) scored below average in all 3 game situations, as we hoped it would happen.

In particular, from the numerical data shown in table 8, we note that the apathetic patient scored below the average of 29% for the first game situation, 28% for the second and 37% for the third. The total score of the apathetic patient was therefore lower than the average of the scores of the non-apathetic patients by 31%.

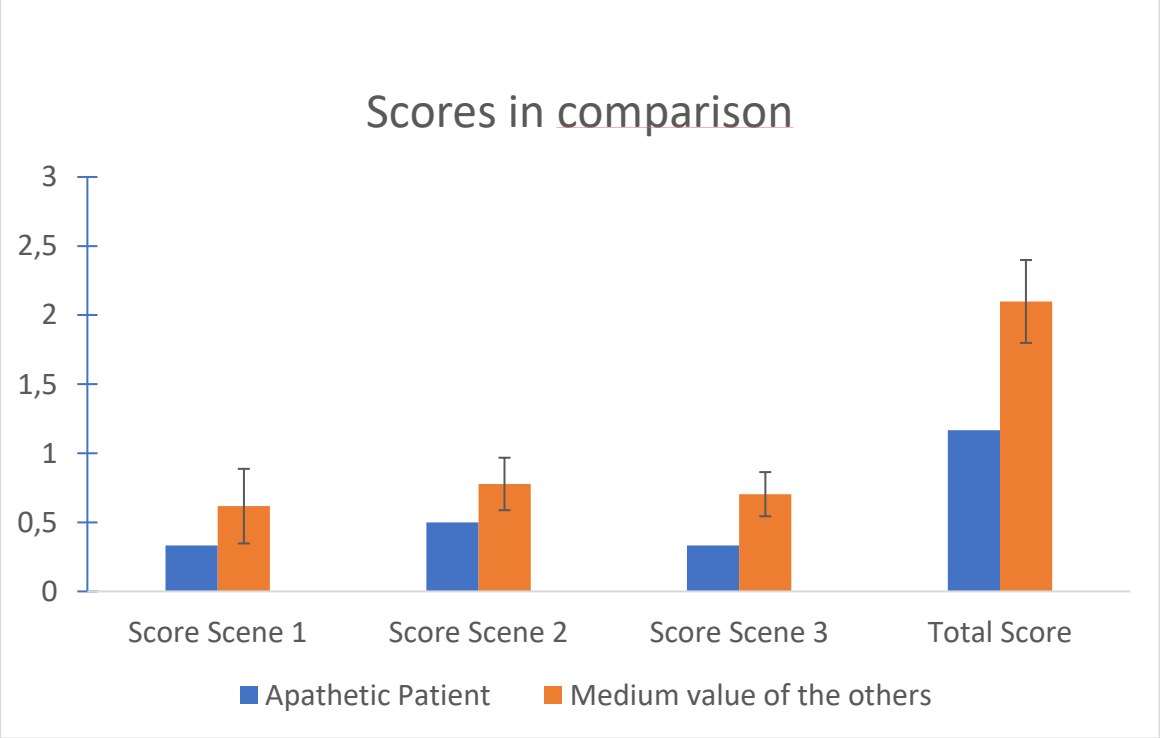


Figure 58: Bar graph comparing the scores earned by the apathetic patient and the mean scores of the other patients and their respective standard deviations.

Table 8: Table comparing the scores earned by the apathetic patient and the mean scores of the other patients, their respective standard deviations and the differences between the scored earned by the apathetic patient and the scores earned by the others.

	Apathetic Patient	Medium value of the others	Standard Deviation for medium values	Difference between scores
Score Scene 1	0,33	0,62	0,27	0,28 (28%)
Score Scene 2	0,50	0,78	0,19	0,28 (28%)
Score Scene 3	0,33	0,70	0,16	0,37 (37%)
Total Score	1,17	2,10	0,30	0,93 (31%)

In figure 59 we find a graph that compares the 11 parameters evaluated in the general acceptability questionnaire. This comparison is made between the values assigned to each parameter by the apathetic patient and the average of the values assigned by the others. Here too we have that the results seem to be encouraging as the apathetic patient assigned excellent values as regards the parameters of acceptability of the game and gave values equal to 0 to the levels of anxiety, fatigue, difficulty and discomfort.

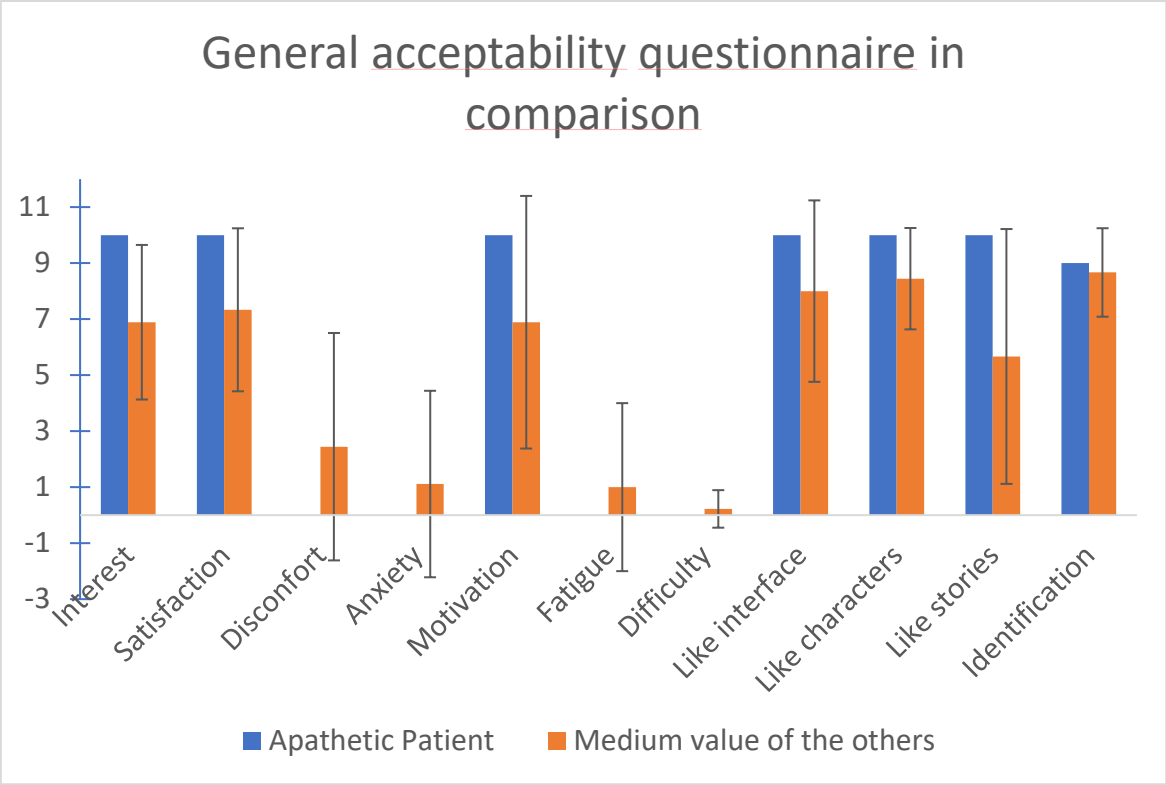


Figure 59: Bar graph comparing the scores of the apathetic patient and the mean scores given by the other patients as answers to the questions of the acceptability questionnaire and their respective standard deviations.

5.3 CORRELATIONS BETWEEN AMI (GLOBAL AND SOCIAL DIMENSION) AND SCORES EARNED IN THE GAME

Finally, in table 9 I have reported the correlation values between the patients' AMIs and the scores scored in the various game situations and the total score. I also found it interesting to investigate the correlations also using the AMI calculated for the evaluation of social apathy, since the ultimate goal of the game is to detect the presence of this type of apathy. For the calculation of the correlation the formula in figure F1 was used.

The results found by the correlation are quite interesting as most of the calculated correlations are negative (red cells), and this is what was hoped because as the AMI value increases the patient is more apathetic and therefore should score lower points in the game. The correlation values calculated for scene 3 are an exception as these gave results greater than zero. The explanation that we can think of giving to this result is that it is the result of the fact that this scene confused the patients: from a qualitative analysis based on the observation of the patients while they were playing the game, we deduced that this was the game situation in which they found it harder to identify with the fact that he simulated phone calls.

Table 9: Correlations Table. In red we can see the negative values.

CORRELATIONS	
AMI - Total Score	-0,37
AMI Social Dimension- Total Score	-0,19
AMI - Score Scene 1	-0,39
AMI Social Dimension - Score Scene 1	-0,24
AMI - Score Scene 2	-0,41
AMI Social Dimension - Score Scene 2	-0,60
AMI-Score Scene 3	0,25
AMI Social Dimension - Score Scene 3	0,59

After making the correlation table, I decided to plot the correlation values between the AMI Social Dimension and the Score in Scene 2 with the respective trend line (Figure 60). I have plotted this particular correlation as an example because it is the one that gave the best value and gives a good idea of the result you want to achieve with this game.

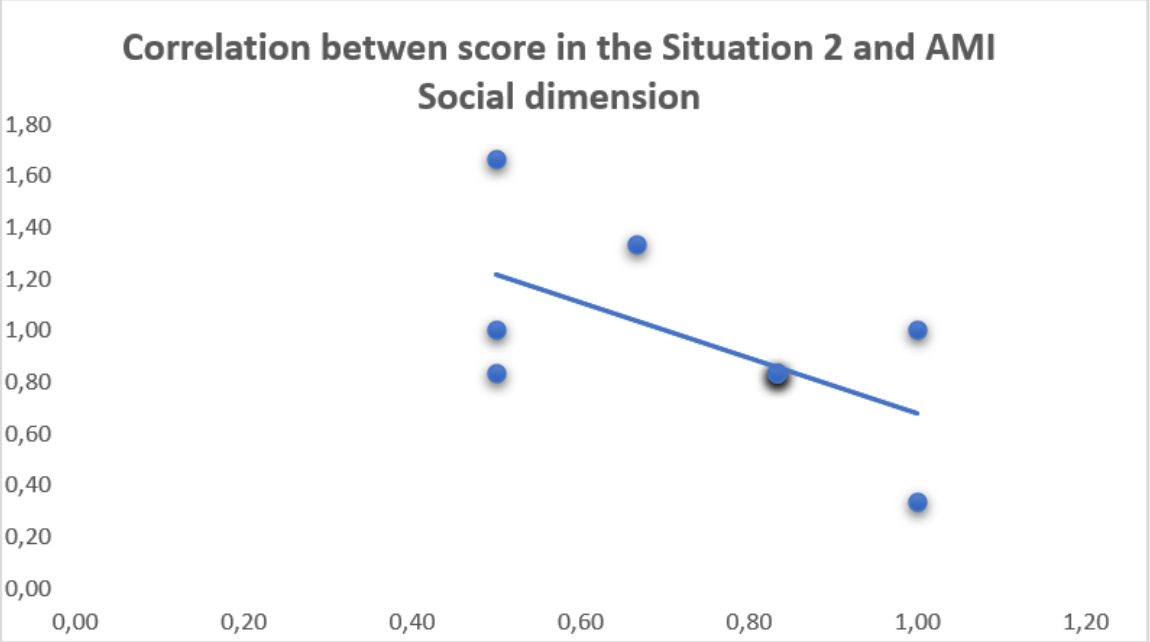


Figure 60: Chart representing an example correlation. The straight line represents the trend line.

6 DISCUSSION

The results of the game's tests in terms of the study of its acceptability by target patients are more than satisfactory: the game was in fact well received by all patients. We reached this conclusion both through a qualitative analysis given by the observation of the subjects while they played the game and through a quantitative analysis of the answers given to the acceptability questionnaire (see Fig 57).

From the qualitative analysis done simply by observing the patients play it was found that the idea of developing the game in this way was a good one. In fact, by offering the game on a tablet, and in 2D we have managed to minimize the inconvenience that technology can cause to unaccustomed people. In fact, the interface turned out to be intuitive for all patients and in all aspects and the only thing patients had trouble understanding for themselves was how to enter the name. In fact, as we can see from figure 18, when the patient is asked to enter the name that he wants to give to his avatar, he is not given instructions on how to do it. Under the box in which the question about the name is asked there is another box in charge of entering the name itself and under it there is an ok button. Any person accustomed to using technology in the slightest would have clicked on the box for entering the name, the keyboard would appear and enter the name and then press the ok key. Unfortunately, people of a certain age do not understand these mechanisms and therefore when this interface was presented to them, they remained perplexed. The solution to improve understanding in this phase could be to provide the patient with more detailed instructions on how to enter the name or to insert a keypad with letters directly into the interface without having to click on the box to make the tablet keyboard appear or again, if this last solution were to involve too much loss of space on the screen, one could think of limiting the patient's choice to a series of proposed names.

A second result obtained without looking for it was that the game, at this first stage, would already seem to have some diagnostic utility. It was in fact observed that the apathetic patient scored the lowest score of all the other patients (see Tab 6) and that it would seem that there is a correlation between the AMIs and the scores earned in the game (see Fig 60).

Obviously talking about scientific validation of the game as a diagnostic tool is risky and makes no sense in this first phase of the study as we only had 10 patients and the goal of this first step was only to design the game and test its acceptability by patients. However, the results in terms of score in the game bode well for its future developments: starting from the data we stored, it makes sense to think that the Serious Game developed as part of my thesis project will actually fit into the context of Serious Games designed to diagnose apathy in order to improve MCI diagnostic protocols.

As for the correlation values between AMI and score, I think it is appropriate to make a couple of hypotheses on the reasons why the correlations with the scores of the third scene are not as we could have hoped.

The first justification I give to these correlation data for game situation 3 is that, although patients were given the possibility to choose the order in which to deal with the different game situations, 6 out of ten patients chose situation 3 for last and this led them to face the last game when they were already mentally fatigued and maybe they paid less attention to the dialogue and answered the questions without thinking much. The choice made by 60% of patients to face situation 3 last may be because the choices were numbered and, although patients were told they could choose the order they preferred, they probably preferred to follow the numerical order as they knew they would eventually have to play all of them three situations and therefore one order was worth the other.

The second justification for the bad correlation data for Situation 3 I think is that this was a situation where family members were referred to as siblings or sons and some of the patients had no sons or siblings or if they had them maybe they lived elsewhere and therefore could not relate to the situation of game. For example, when the possibility of inviting the sons to dinner appeared in the choice menu, there were those who did not do it and then commented that their children live outside the city and that therefore they would not have been able to come to dinner.

For the two problems just mentioned, I have proposed solutions that will probably be taken into consideration for future development of the game. As for the problem of mental fatigue of patients who tend to get distracted in the last scene, one could think of not letting them choose the order in which to play in the three different situations but presenting them directly to them in random order so that the hypothesized factor of mental fatigue has an equal impact on all scenes. Secondly, we could consider letting the patients play the game only rather than having them do other tests on the same day: in this way the results would be more reliable because the patient would not be tired from the tests done previously and would concentrate as much as possible on the game. If these two solutions should not be enough, we could also think of reducing the complexity and length of the game but I think this is a solution that should not be followed because, as we can see from the acceptability questionnaire, the game is already considered very easy by patients and lasts an average of 10 minutes so the patient with an early stage of dementia (MCI or SCD) should be perfectly capable of carrying it out.

As for the second problem mentioned, the situation is a bit more complex. The point is to make people of a generation not used to using technology understand the concept of avatar. When I talk about the "concept of avatar" I mean that those who play must understand that they must act as they would if they were in that same situation, but they must imagine that they are a person with friends, children, brothers and that they have the possibility to see them for example for dinner. The patients in question failed to arrive at this kind of mental abstraction in this first version of the game and this was noted by the comments they made while playing and also by the correlation value between AMI and scores in situation 3, where an attempt was made to introduce family members.

The solutions that I have thought of proposing are two:

1) To make Serious Game as personalized as possible based on the patient's family situation.

2) To introduce a short initial video in which you try to explain to the patient how to act.

Solution 1 could be a good solution, but it would waste a lot of time and resources, in addition to the fact that it could also harm the privacy of the subject. In fact, all patients should first be subjected to a questionnaire asking them for specific information about family members and the relationship they have with them, and then they should move on to developing personalized games. One could think of submitting the same game to groups of patients based on any similarities between their families but in any case, the work to be done would be greater than that which is done by designing a single game.

Solution 2 would solve the problem of wasted resources and time as it would provide a standard game for all patients. What would change would simply be that instead of immersing the patient directly in the game there would be a video that would start after the patient chose the avatar and gave it a name. The video should be explanatory of the situation in which the player must relate. For this game there should be a narrative part that tells the patient something like "Imagine you are a 70-year-old man / woman living alone in the same city where his brothers and sons live with whom he has good relationships" and at the same time the same avatars should appear that will then represent the family

members in the game as well as the avatar of the character himself. It would also be appropriate to introduce some small animations e.g., the avatar of the son who greets and says "Hi, I'm your son Marc".

To evaluate the diagnostic usefulness of the game, it would be appropriate to modify it based on the observations made and retest it. In particular, it would be useful to understand which of the three situations has the best diagnostic utility to evaluate whether to remodel the other situations based on the best one. From the table 8 it would seem that the best situation for our purpose is the third one which offers a 37% difference between the scores scored by the apathetic patient compared to the 28% given by the other 2 scenes but considering the correlation value between score in situation 3 and AMI (see Table 9), you should first make the changes we just talked about to the game and then re-evaluate whether this type of game situation is actually the best at diagnosing social apathy or not.

To make a further comparison between the 3 situations, we could say that situation 1 is the one in which all patients scored on average fewer points (see Tab 7). This could be because, as discussed in the paragraph 3.2.3.3, in the first game situation if a choice is made that is not very sociable, then a second opportunity to earn points is not presented within the same sub-stage (see Fig 26, 30, 33). In any case, if we focus on the differences in points scored by the apathetic patient and by the non-apathetic patients, situation 1 would seem to have the same diagnostic reliability as 2 (see Tab 8). In this analysis I avoid making the comparison with the scores in situation 3 in which, although it would seem that apathetic from non-apathetic patients differ better, it would be better to make changes before carrying out further evaluations.

7 CONCLUSIONS AND FURTHER DEVELOPMENT

The objectives of this thesis were two: the first one was to develop a diagnostic test designed to support the diagnosis process of neurodegenerative disorders at the first stage following the Serious Game approach and the second one was to test its feasibility. Both objectives were successfully achieved: The Serious Game was designed and developed as an Android application, designed to be used on tablets and was subsequently tested by 10 patients suffering from early-stage neurocognitive disorders who positively assessed its feasibility.

For the development of the game, it was used the graphics engine Unity in association with the integrated development environment Visual Studio, in which you can program in C # language. The game specifications have been defined in agreement with therapists at the Nice Research Memory Center and the final application has been designed to be as simple and basic as possible to address the needs of older persons who are unfamiliar with technology. The game developed is designed to detect the presence of social apathy in the subject who plays it. This particular focus on apathy was made as it represents one of the main symptoms of Mild Cognitive Impairment as well as a serious risk factor for progression from mild cognitive disorders to Alzheimer.

In order to test the acceptability of the game by the target subjects, we enrolled 10 Patients with mild neurocognitive disorders that were coming to the Nice Research Memory Center for a regular medical consultation or a classical neuropsychological assessment and asked them if they wanted to participate in the study. The inclusion period lasted two weeks and all subjects underwent a standard assessment including the Mini-Mental State Examination (MMSE) as well as the diagnostic criteria for apathy and the apathy motivation index (AMI) with a neuropsychologist and a psychiatrist. The neuropsychiatric evaluation revealed that of the total 10 patients, one was apathetic.

At the end of each experimental condition, participants were administered self-report questionnaires concerning the evaluation of their experience. Specifically, participants were presented with 10 points scales and asked to report their level of satisfaction, interest, discomfort, anxiety, motivation, fatigue, difficulty. They were also asked how much they liked some features of the game as the graphic interface, the characters and the content of the stories.

The results are quite encouraging: the patients responded positively to the game, giving high scores to categories like interest, contentment, and motivation while giving low values to those concerning anxiety, discomfort and fatigue.

Another significant finding is that the only apathetic patient who participated in the study received the lowest score of all 10 individuals examined, based on an examination of the values of the scores scored by the patients in the game. This result is insufficient to comment about the diagnostic value of this Serious Game because we are still in the early phases of the study and just 10 subjects have been evaluated. However, this is an encouraging outcome, indicating that this application may be beneficial as a support aid in the complex MCI diagnosis process in the future.

Based on the results we have reached, we can say this study backs up a theory that has already been backed by prior researches [2, 18]: that Serious Games can be a useful tool to use for making diagnoses of MCI as they are well accepted even by elderly patients and with neurocognitive disorders.

Considering that the Serious Game in question has been fully accepted by patients and clinicians, it is reasonable to think that in the future it will be included in diagnostic protocols. It is also hoped that

this type of diagnostic tool will be administered to the patient in the future on his device and in his home: this step forward would allow for a first mass screening in subjects at risk of dementia to quickly identify who needs further assessments by specialists.

The future developments of the game in question and of the Serious Game to make a diagnosis in general will probably go hand in hand with the generational change of the people who will need it: at present the main problem in administering this type of technology to elderly patients consists in the fact that they do not have the right mindset to fully understand it and when you go to develop a technology designed for this audience you must impose design constraints by considering the technological limitations that this generation faces.

When generations more and more accustomed to using technologies will come to need to control their cognition, it will be gradually easier to propose technologies with a higher degree of immersion and there will also be less and less need to administer them in a hospital environment with the supervision of a clinician. One could think of the future as a time when if a person's relatives or friends start to suspect that he has cognitive problems, they can simply download an app and have him do a first screening. Obviously, the opinion of specialists will always be essential to make a complete diagnosis, but the possibility of carrying out part of the tests at home and at practically no cost could offer considerable advantages.

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