



Desenvolvimento de uma aplicação para diagnóstico, monitorização e reabilitação de doenças neurodegenerativas

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**DEVELOPMENT OF AN
APPLICATION FOR DIAGNOSIS,
MONITORING AND
REHABILITATION OF
NEURODEGENERATIVE DISEASES**

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Thesis/Dissertation course of the program Master's degree in Biomedical
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*"A journey will have pain and failure.
It is not only the steps forward that we must accept.
It is the stumbles. The trials. The knowledge that we will fail.
But if we stop, if we accept the person we are when we fall, the journey ends."
Oathbringer, by Brandon Sanderson*

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Abstract

The progress of healthcare over the last years led to an aging of the world population, increasing the prevalence of age-related diseases in the society, mainly neurodegenerative diseases. These pathologies currently affect more than 30 million people worldwide, and there is currently no cure for them. The high costs experienced by patients and their families are largely due to the individual monitoring performed by technicians. New technologies are providing alternatives for monitoring, diagnosis and rehabilitation of individuals with these diseases. This project includes the development of a web application which allows patients with neurodegenerative diseases to be monitored with less invasion and costs, enabling greater adherence. The application follows several examples from the literature for the construction of games, includes diagnostic assessments used in the medical field and promotes its use through gamification techniques. The construction of the web server used the Python language and the Flask framework because of the availability of useful modules, large supporting community and scalability. The software was specially designed for people with Parkinson's disease, featuring a simple navigation between menus and an easy-to-use interface. The web application was named "Mentalist". The development of the application was followed by professional neurologists and the results obtained were guided by clinicians' practice. According to these experts, the developed functionalities cover the most important aspects of diagnosis, monitoring and rehabilitation, making it a tool of high importance and applicability in daily clinical practice.

Keywords: Neurodegenerative Diseases, Monitoring, Diagnostic, Rehabilitation, Games, Gamification, Web App, Python, Flask.

Resumo

A melhoria das condições de vida e dos cuidados de saúde nos últimos anos tem originado um envelhecimento da população mundial, aumentando a prevalência de doenças relacionadas com a idade. Neste grupo de doenças destacam-se as doenças neurodegenerativas, que afetam mais de 30 milhões de pessoas e não têm, atualmente, cura. Os elevados custos experienciados pelos pacientes e pelas suas famílias devem-se, em grande parte, ao acompanhamento individual realizado por técnicos. Novas tecnologias têm possibilitado alternativas para o acompanhamento, diagnóstico e reabilitação de indivíduos com estas doenças. Este projeto inclui o desenvolvimento de uma aplicação web que permite a monitorização de pacientes com menos invasão e custos, proporcionando uma maior adesão. A aplicação segue exemplos da literatura para a construção dos jogos, inclui questionários de diagnóstico utilizados no ramo médico e promove a sua utilização através de técnicas de gamificação. Foi utilizada a linguagem Python e o framework Flask para a construção do servidor devido à existência de módulos úteis, grande comunidade de desenvolvedores e escalabilidade. O software foi desenvolvido especialmente para pacientes com a doença de Parkinson, apresentando uma navegação simples entre menus e uma interface fácil de usar. A aplicação web foi denominada "Mentalist". O desenvolvimento da aplicação foi seguido por neurologistas profissionais e os resultados obtidos foram guiados pela experiência dos clínicos. De acordo com estes especialistas, as funcionalidades desenvolvidas contemplam os principais aspetos relativos ao diagnóstico, monitorização e reabilitação, tornando-a num instrumento de grande importância e aplicabilidade na prática clínica diária.

Palavras-Chave: Doenças Neurodegenerativas, Monitorização, Diagnóstico, Reabilitação, Jogos, Gamificação, Aplicação Web, Python, Flask.

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Glossary

Disability-Adjusted Life Years

number of years lost due to ill-health, disability or early death.

incidence

new cases of a disease in a given period of time in a defined population, providing a risk for developing the disease.

prevalence

existing cases of a disease in a population at a given time.

List of Acronyms

10MWT	10 Meter Walk Test
ACE-R	Addenbrooke's Cognitive Evaluation
AD	Alzheimer's Disease
ALS	Amyotrophic Lateral Sclerosis
BADLS	Bristol Instrumental Activities of Daily Living
CDT	Clock Drawing Test
CSS	Cascading Style Sheet
DALYs	Disability-Adjusted Life Years
EU	European Union
FDA	U.S. Food and Drug Administration
FTLD	Frontotemporal Dementia
FTT	Finger-Tapping Test
HD	Huntington's Disease
HTML	Hypertext Markup Language
HTTP	Hypertext Transfer Protocol
LIADL	Lawton Instrumental Activities of Daily Living
MCI	Mild Cognitive Impairment
MMSE	Mini-Mental State Examination
MOCA	Montreal Cognitive Assessment
PD	Parkinson's Disease
PWAs	Progressive Web Apps
SCWT	Stroop Color and Word Test

SG Serious Games

UML Unified Modeling Language

UPDRS Unified Parkinson’s Disease Rating Scale

Chapter 1

Introduction

1 Introduction

The following thesis was developed for the Master's degree in Biomedical Engineering of Instituto Superior de Engenharia do Porto, during the academic year of 2021/2022, under the supervision of Engineer Luís Coelho.

The improved healthcare and living conditions around the world are contributing to an increase in the average life expectancy of the world's population. This has led to an increase in the prevalence of age-related diseases in society, especially neurodegenerative diseases [1]. Neurological diseases, which are mainly composed by neurodegenerative diseases, have become a leading cause of disability in the world, reaching 11.6% of the Disability-Adjusted Life Years (DALYs) and 16.5% of all deaths, ranking second only behind cardiovascular diseases [2].

Neurodegenerative diseases affect over 30 million people worldwide [3]. As there is currently no treatment, these pathologies have devastating consequences for patients and their families, with almost 7 million people dying from it every year [3, 4].

Neurodegenerative diseases are a group of pathologies that cause the deterioration and death of neurons in the brain, which can lead to a variety of symptoms. These symptoms depend on the region of the brain that is being affected and may include memory loss, decreased cognitive ability, and abnormal movements [5, 6, 7].

The literature states that the monitoring and training of individuals with neurodegenerative diseases can improve or, at least, stabilize, the cognitive and motor functions [8]. However, traditional approaches are expensive and inconvenient for patients and their families, which originates a reduction in adherence [9]. As a result, multiple digital approaches, which are more cost-effective and practical, are becoming increasingly relevant for rehabilitation [10].

These new types of approaches aim to decrease the costs on rehabilitation and follow-up, increase the number of available data for physicians, and increase patient motivation and adherence to treatment by using approaches that are more intuitive, accessible and interesting from the patient's point of view.

The digital smartphone stores are currently flooded with a variety of games, tests and tasks that claim to improve cognition domains, such as memory or processing speed, however, most of them are not supported by any scientific studies

or designed for the specific needs of these patients [9, 11, 12]. On the other hand, applications developed specifically for these target groups seem to not have a lot of traction and market share.

Considering the problem at hand, there is evidence that there is room for new solutions that take advantage of the constant development of technology to facilitate the access to new types of healthcare, reduce expenses for rehabilitation, and make two-way communication between doctors and patients easier and simpler.

The suggested solution is a web-based application that includes brain stimulation and enhance cognitive ability through games, common assessments used by doctors that can be filled online and the possibility to report their symptoms and medication times. Healthcare professional can then monitor the patient's evolution according to a set of parameters obtained from those interactions, study the effects of the medication on the patients' symptoms and adjust the medication accordingly.

The application is expected to include games, assessments and surveys used regularly by doctors in face-to-face diagnosis, information regarding the most common diseases and the presentation of the results for analysis by the responsible health professionals.

With the final goal of creating a suitable application, the objectives of this dissertation and their goals are listed below:

- Review the literature on neurodegenerative diseases, with focus on finding how digital technologies can help to tackle the related challenges;
- List and understand disease symptoms and assessment methods, with the aim of designing digital games that can support or extend current clinical practice;
- Investigate and describe the problems faced by medical staff, patients and caregivers, in the global context of neurodegenerative diseases;
- State-of-art review regarding current games and applications for neurodegenerative diseases, how they are implemented and their functionalities, including the different types of games, interfaces and parameters that are integrated;
- Develop a suitable application for patients with neurodegenerative diseases;
- Test the application with real users, namely patients with neurodegenerative diseases;
- Obtain the opinion of health professionals on the developed application.

This dissertation is divided into five chapters: Introduction, Literature Review, Methodology, Results and Conclusion. Chapter 1 comprises the identification of the problem at hand, the proposed solution to mitigate this problem and the objectives of the study. Chapter 2 presents an introduction to neurodegenerative diseases, with a deeper approach into Alzheimer's disease and Parkinson's diseases, followed by a review on digital technologies related with neurodegenerative diseases. Chapter 3 describes the system architecture, the requirements and the technologies used. The results are featured in Chapter 4, which also includes a discussion about them. Finally, Chapter 5 contains the conclusions drawn from the development of this study, presented along with future work to be developed on this subject.

Chapter 2

Literature Review

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2 Literature Review

This chapter provides an overview on neurodegenerative diseases, with emphasis on Alzheimer's disease and Parkinson's disease, followed by a state-of-the-art of digital technologies related with these diseases. The review on Alzheimer's Disease (AD) and Parkinson's Disease (PD) includes their prevalence, biological origin, diagnosis, treatments and symptoms. The review on the current digital market for applications that focus on these diseases considers the common assessments, parameters that are obtained, user interfaces and user experience approaches, the effects of gamification and examples of games. The aim of this chapter is to compile information that ensures that the application will be developed in the most appropriate way, that is, by creating a suitable design for the patients and maximizing their user experience, while ensuring that the data can be properly analysed by healthcare professionals.

2.1 Neurodegenerative diseases

Neurodegenerative diseases are a class of neurological disorders that occur with damage and death of specific nerve cells, causing several disabilities [6, 13], such as impairments in memory, cognition, emotions, movement, speech and breath [1, 13]. There are currently more than 30 million people affected by this group of diseases in the world [3].

The location where nerve cells die in the nervous system defines the disease and the corresponding symptoms, being the most prevalent AD, PD, Huntington's Disease (HD), Amyotrophic Lateral Sclerosis (ALS), Frontotemporal Dementia (FTLD) and Spinocerebellar Ataxia [1], with death of neurons in hippocampus, midbrain, frontal and temporal lobes of cerebral cortex, basal ganglia, cerebellum and motor neurons, respectively [14].

This group of diseases is an important source of morbidity and premature mortality in the world [2]. The prevalence and incidence of neurodegenerative diseases increases with age, thus is expected that the number of cases keeps rising in the future as the life spans of almost every country continues to increase [13, 15], mainly due to better healthcare [1].

A small fraction of neurodegenerative diseases are caused by mutation of disease-related genes, such as the HD, but most of them are sporadic, where

environmental factor and aging play a predominant role [5], like AD, PD and ALS.

Even though that the symptoms of these diseases are heterogeneous, as well as their underlying physiology, there are overlapping characteristics between them, such as the progressive accumulation of misfolded proteins and the ageing as a risk factor [16].

The fight against the neurodegenerative diseases is conducted in several ways, such as studying the changes that these diseases cause in the brain, finding the factors responsible for their development, discover means to prevent or slow its development and relieve the patient's condition [17].

As more individuals live to older ages, putting them at higher risk for this type of disorders, the economic burden of providing nursing home and medical care to ill people, along with the difficult life of those who suffer, their families and their caregivers, constitutes a problem with increasing magnitude [18].

Neurodegenerative diseases are problematic for several reasons, such as their cause being mostly unknown, not having a cure yet, only being confirmed after death, being tardily identified and being costly, due to the need for caregivers and medication to relieve the symptoms [6].

Although a large number of neurodegenerative diseases can be defined, only those with the highest prevalence and that have become a major social concern are presented below with more detail.

2.1.1 Alzheimer's Disease

Alzheimer's Disease, named after the German psychiatric Alois Alzheimer [19] that first describe it in 1906 [20], is the most common neurodegenerative disease and also represents the most frequent cause of dementia, accounting for around 70% of all cases [15, 21, 22].

According to guidelines set in 1984, AD was diagnosed to individuals that had symptoms such as extensive problems with learning, thinking or memory. However, under the guidelines established in 2011, individuals can receive a diagnosis of AD if they have the characteristic brain changes of this disease, even if they don't show any symptoms, which may occur only several years later [20].

The main clinical manifestation of AD is dementia, which is an accelerated loss of cognitive function beyond what is normal due to aging, but other symptoms are alterations in mood, personality and behaviour, memory loss, disorientation, aphasia, language difficulties [6, 15] and, ultimately, motor difficulties, delusions and hallucinations [6, 23]. As the disease progresses, the individuals lose the ability to perform most daily tasks, such as bathing, cooking, managing finances or drive a car. The symptoms change over time and reflect the progressive damage to the neurons in different parts of the brain [20].

A healthy adult brain has about 100 billion neurons, each of them with long, branching extensions, leading to around 100 trillion synapses, which allow to transfer data through the brain, creating the basis for memory, thoughts, sensations, emotions, movements and skills [20]. The damage and death of neurons with AD occurs mainly in the hippocampus and frontal cerebral cortex [14, 15], resulting from the accumulation of a protein fragment beta-amyloid, called beta-amyloid plaques or senile plaques, outside of neurons, and the accumulation of an abnormal form of the protein tau, called neurofibrillary tangles, inside neurons [6, 19, 20]. It is believed that beta-amyloid plaques result in cell death by damaging the axons and interfering with neuron-to-neuron communication at synapses and that neurofibrillary tangles block the transportation of nutrients and other essential molecules into the neurons, as well as disintegrate the cell's cytoskeletal microtubules [19, 20]. Both structures are dispersed in the brain of a Alzheimer's patient, mainly in the affected zones, and they are shown in Figure 2.1.

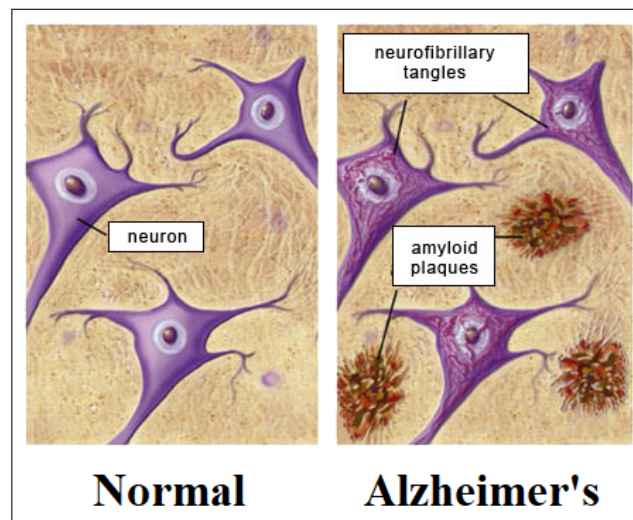


Figure 2.1: Beta-amyloid plaques and neurofibrillary tangles in Alzheimer's patient neurons.

In a macro analysis of the human brain in people with Alzheimer's, it is visible

that occurs a massive loss of neurons, resulting in a shrinkage of the cerebral cortex and the hippocampus, as show in Figure 2.2.

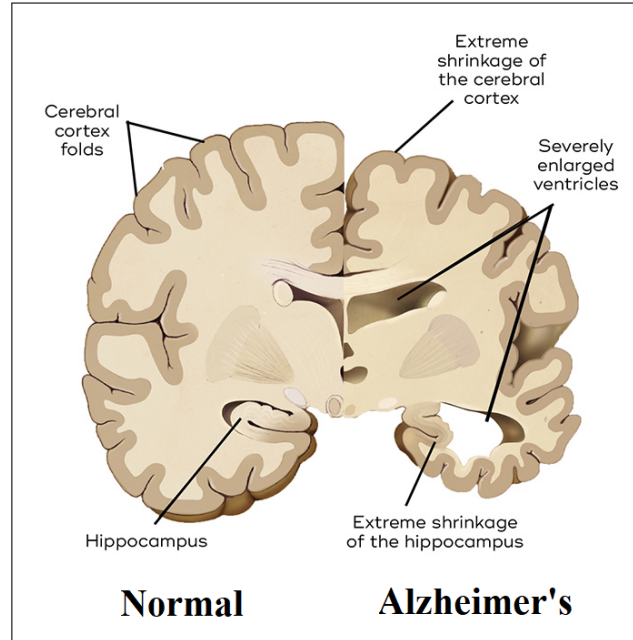


Figure 2.2: Differences between a normal person's brain and the brain of an Alzheimer's patient.

With respect to the diagnostic of this disease, AD may often co-exist with dementia or other cognitive impairment causes, being the most frequently vascular dementia due to small or large strokes [6], which complicates the diagnosis by physicians. The diagnosis of AD is usually a long process and can only be confirmed after death with autopsy [6], as there is no single test for Alzheimer's, but rather a set of approaches and tools that help specialists make a diagnosis, such as:

- Medical history of the individual and family, including the history in psychiatry and changes in cognition and behaviour;
- Family testimonies regarding changes in thinking skills and behaviour;
- Cognitive tests and physical and neurological examinations;
- Blood tests and brain imaging to rule out other potential causes for the symptoms;
- Presence of AD biomarkers assessed through MRI or PET images [6], such as detection of high levels of beta-amyloid [20].

Regarding the cognitive assessments, the Mini-Mental State Examination (MMSE) is one of the most frequently advised assessment tools for dementia, being

subdivided in five categories: Orientation, Registration, Attention & Calculation, Recall and Language [11]. This test has a sensitivity of 0.85 and a specificity of 0.90 [11], which is not enough to detect small changes in patients, therefore other scales have been developed, such as the Addenbrooke's Cognitive Evaluation (ACE-R), composed by 23 questions of five domains: Attention & Concentration, Memory, Fluencies, Language and Visual and Spatial abilities. The ACE-R has a sensitivity of 0.94 and a specificity of 0.89 [11]. There are other tests, with different purposes, such as the Montreal Cognitive Assessment (MOCA), the Disability Assessment for Dementia (DAD), the Bristol Activities of Daily Living Scale (BADLS) or the Instrumental Activities of Daily Living (IADL), that include distinct categories of assessment, each one with a total score and a minimal threshold that indicates the presence or absence of disease.

Studies point to more than 50 million people suffering from this disease currently, expecting this number to reach 150 million by 2050 [19, 22]. Despite being able to occur in younger people, which represents between 4 and 5% of AD cases, it is primarily a disease of the elderly [21]. It usually begins after the age of 65, affecting up to 10% of all people older than this age [21], reaching up to 17% in people between 75 and 84 years and 32% among people over 85 [17]. Early-onset AD corresponds to those where this disease comes before the age of 65 [21], which is extremely rare, except in cases of familiar AD, which represents 5 to 10% of total cases [15]. Most cases of AD present the usual amnesic form, whereas up to 15% of cases are considered atypical, presenting early impairments in vision and motor skills [21]. Regarding gender, AD is more prevalent in women than in men [21].

As Alzheimer's is the most frequent cause of dementia, the statistics of this symptom will be presented, since it can be objectively diagnosed, unlike Alzheimer's. Considering the population older than 30 living in Portugal, there were 193.516 people living with dementia in 2018, which accounted for 1.88% of the total population. As the population in Portugal is expected to decrease until 2050 and the overall number of people with dementia is expected to increase, the percentage of population with this impairment, in Portugal, is expected to more than double by 2050, increasing from 1.88% to 3.82%. The most affected age groups are people older than 70, accounting for around 91% of total cases in Portugal, in 2018, and expecting to be greater than 95.6% by 2050, as the population gets older [24]. The difference in the prevalence of Alzheimer's between genders is noticeable, as women comprise around 69% of the total cases [24].

Regarding the European Union (EU), the prevalence of AD in Portugal ranks fourth (1.88%), only behind Italy (2.12%), Greece (1.99%) and Germany (1.91%),

which can be explained by the fact that Portugal's population is amongst the oldest. Additionally, the average prevalence in EU is 1.73%, which is 0.15% less than Portugal's. Similarly, estimations for 2025 expect Portugal's prevalence to increase up to 2.29%, as the EU average is expected to reach 2.00% [24].

Experts believe that Alzheimer's is the result of multiple factors [20], the biggest being ageing, family history of Alzheimer's and carrying the APO-E-e4 gene [20]. Other risk factors include cardiovascular diseases, head traumas, smoking, dietary antioxidants and fats, alcohol, exposure to solvents and pesticides and electromagnetic fields [15].

The APO-E gene encodes a protein that is highly expressed in the liver, brain astrocytes and some microglia. The APO-E4 isoform, which is a risk for AD, is mostly found in women. APO-E plays an important role in the Beta-Amyloid protein deposition, originating beta-amyloid plaques, which is a marker for AD [19].

Available treatments usually offer, at most, a temporary slowing of the symptomatic deterioration. Drug discovery for AD is very challenging [22] and there are only six drugs approved by the U.S. Food and Drug Administration (FDA) for the treatment of AD. These drugs reduce the symptoms by increasing the amount of neurotransmitters in the brain and the results might differ from one person to another. Many factors contribute to the difficulty in developing new drugs to treat AD, such as inability of animal models to recreate Alzheimer's, the slow pace of clinical recruitment and the long time to observe if the treatment affects the disease progression [20]. Apart from drugs, studies found that physical exercise and cognitive stimulation are beneficial to people with Alzheimer's [20].

The total lifetime cost for someone with dementia is estimated at more than 373 thousand dollars, considering the buying power of the dollar in 2020. This costs mainly include the expenses with caregivers and medication [20]. Annually, the global costs with AD are estimated to be over 1 trillion dollars, affecting the economy, the individuals and their families [19].

2.1.2 Parkinson's Disease

Parkinson's Disease was firstly described by James Parkinson, in his 1817 publication [25], and it is mainly characterized by an impairment in motor skills [14]. It is currently the second most common neurodegenerative disease [14, 15] and its prevalence has been increasing faster than the others [26]. Parkinson's Disease is also the most common type of parkinsonism, which refers to the group of diseases

with Parkinson-like motor problems, such as rigidity, slowness and tremors [26]. As the rest of the neurodegenerative diseases, it typically occurs at older ages, with a median age of onset being 60 and its prevalence has been increasing with the ageing of the world population [21].

Parkinson's disease is characterized by the loss of neurons that produce dopamine in the *substantia nigra pars compacta*, located in the midbrain [14, 25]. The damage and death of neurons in this area is believed to be due to the accumulation of proteins, mainly alpha-synuclein and ubiquitin, but might also occur with others [6, 15]. Other factors that are involved in PD are the deficiency in removing the protein aggregates, altered dopamine metabolism, impaired mitochondrial function, oxidative stress, inflammation, necrosis and accelerated apoptosis [15]. Dopamine is important to the human body as it transmits electrical signals from the brain to the muscles, controlling human movement. The damage of dopamine-producing cells and the reduction of dopamine originates impairments in muscle control, either affecting harder tasks, such as walking, or easier ones, such as swallowing [27].

The most predominant symptoms of PD are motor impairments, including bradykinesia, which is the slow down of movements, resting tremors, muscle rigidity, postural problems and difficulties in speaking or swallowing. Other impairments comprise sleep and mood disorders, tiny handwriting, vision problems, dysautonomia, anosmia, depression and pain [6, 21, 26]. As the disease progresses, different impairments in muscle movements can be seen in patients [6, 15]. Parkinson's symptoms vary with age, which helps to classify this disease.

One way to categorize Parkinson's Disease is to divide it into 3 classes, according to the patient's motor and non-motor symptoms:

- Mild motor predominant - Occurs at a younger age, includes mild motor and non-motor symptoms, has slow progression and good response to medication;
- Intermediate - Occurs at an intermediate age and is characterized by intermediate symptomatology, with moderate or good response to medication;
- Diffuse malignant - Several motor symptoms, accompanied by rapid eye movement, sleep disorders, mild cognitive impairment, worse response to medication and rapid progression [26].

Categorized in this way, the Mild Motor Predominant class is the most common, with 49 to 53% of the cases, followed by the intermediate with 35 to 39% and the least common is the diffuse malignant, with 9 to 16% of Parkinson's cases [26].

Another approach to subdivide this disease is by taking into account the predominant type of symptoms, considering between the tremors and the postural instability and gait problems. In this perspective, we can find the following classes:

- Tremor-predominant - Presented at an earlier age, with slower progression and great response to dopamine replacement;
- Postural Instability and Gait Difficulties (PIGD) - Faster cognitive decline, higher incidence of dementia and worse response to medication [21].

The tremor-predominant phenotype relates to the mild motor predominant class and the postural instability and gait difficulties phenotype is closer to the diffuse malignant, as the younger individuals usually present more symptoms related with tremors.

The diagnostic of PD is based on the clinical symptoms, such as bradykinesia, resting tremor, rigidity and postural instability, on medical history and on physical examination, such as reflexes, sensitivity and agility [21, 27]. Currently, physicians use different subjective analysis for PD, like the Unified Parkinson's Disease Rating Scale (UPDRS), to quantify the severity of the neural disease in the patient, according to motor and non-motor impairments visually measured by the expert [28]. Brain imaging and laboratory tests help physicians to exclude other conditions, such as Alzheimer's, vascular diseases or tumors [21]. To check if the diagnosis is correct, physicians perform the L-Dopa test, that consists in providing a replacement to dopamine, such as levodopa, and check if the symptoms improve, which is a sign of Parkinson's. Studies are currently trying to predict and detect the disease before the symptoms appear, using blood or imaging-based biomarkers [1]. Brain scans show a reduction in serotonin as Parkinson's disease progresses, as shown in Figure 2.3, and are being studied to detect and monitor this disease.

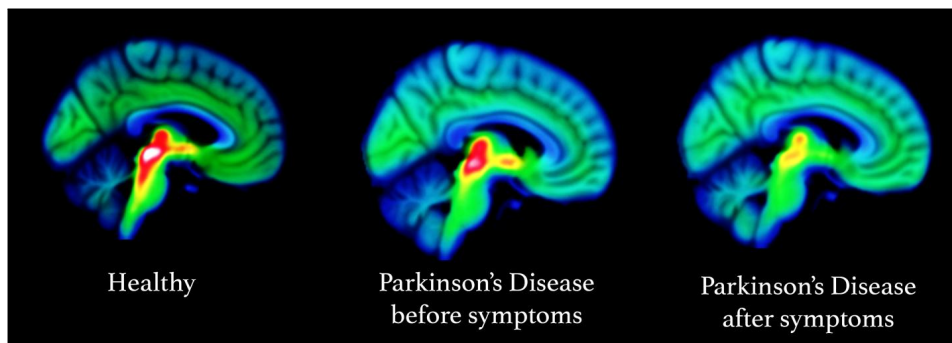


Figure 2.3: Reduction in serotonin as Parkinson's disease progresses.

Parkinson's disease doesn't currently have a cure and treatments focus on relieving symptoms, using medication, physical therapy and deep brain stimulation [6]. The pharmacologic therapies that target the motor impairments caused by Parkinson's enhance dopamine signaling, either by direct replacement, by a dopamine receptor agonist or by dopamine metabolism reduction [21]. As the disease progresses, the symptoms get worse and the medication becomes less effective, therefore doctors have to keep adjusting the type and dose of medication [27]. As Parkinson's patients start moving their bodies less, their muscles become weaker, so daily physical exercises can help to improve movement and coordination [27]. If these options do not help to alleviate the symptoms, deep brain stimulation is recommended, which consists of constantly sending electrical signals through the brain using implanted electrodes [27].

Most cases from Parkinson's are sporadic, however, genetic and environmental contributions are known [21, 26]. Patients with PD are twice more likely to have a first degree relative with this disease, when compared with normal people [21]. The functional consequences of the mutations in the genes is not completely understood [15]. Apart from ageing, the most consistent epidemiologic evidence has been an inverse relation between cigarette smoking and PD, as smokers having approximately half the prevalence as never smokers [15].

Studies from 2017 have estimated that 8.52 million individuals were suffering from Parkinson's in the world, with an annual incidence of 1.02 million and approximately 340 thousand people dying every year [22]. Parkinson's disease has approximately 0.3% prevalence in general population, 1% in people older than 60, 2% in people aged more than 65 and 3% in people with 80 or older [15, 21]. Its annual incidence rate is between 8 and 18 individuals in 100 thousand [21], which is one-tenth of Alzheimer's [20]. Epidemiological surveys have indicated an higher prevalence and incidence in men, being around 1.5 times higher, and a greater age of onset in women, being 53.4 years versus 51.3 for men [21]. Women are also reported to suffer from milder symptoms, higher rate of tremors and slower progression of the motor impairments [21]. Surveys, medical records and death certificates have demonstrated that the prevalence of PD has been increasing worldwide in the recent years [22], being expected to increase dramatically in the next years, doubling in the next two decades [25], and it is expected to reach 12 million Parkinson's cases by 2050 [22]. This increasing prevalence is mainly attributed to the aging populations and greater life expectancy, but also from improved methods used to detect and diagnose PD, to the greater awareness of the disease and to the increased environmental exposures [26]. A postmortem analysis found that people typically live between 6.9 and 14.3 years after the diagnosis of the disease [26].

The costs of living with Parkinson's disease are ranged between 7000€ and 17000€ per year, which is an amount most families can't afford [29]. As this diseases become more prevalent in the society, its social and economical burden has been escalating. For this reason, there is a need for more effective treatments, cures or ways to prevent and detect this disease earlier.

2.1.3 Common assessments

Most neurodegenerative diseases have their own assessments to detect the disease and its condition, with segments that focus in several important areas that are targeted in this diseases, such as memory, cognition or motor skills. However, many assessments are designed to evaluate functions, like the cognitive deficit of the patient. These group of assessments can be generalized to the general population in order to assess the desired capabilities.

There are plenty of subjective and objective analysis used by physicians, depending on the patient's age, cognitive status, neurodegenerative disease or domain under study.

Regarding the evaluation of patients through questionnaires, the most frequent are the Mini-Mental State Examination (MMSE), the Addenbrooke's Cognitive Evaluation (ACE-R), the Montreal Cognitive Assessment (MOCA), the Lawton Instrumental Activities of Daily Living (LIADL) and the UPDRS. These assessment are composed by questions that must be answered by the patient, by the physician analysing the patient or by both.

The MMSE is the most used test to detect dementia, with a sensitivity of 0.85 and a specificity of 0.90 [11]. This test is popular because it's simple, short, has high accuracy and specificity and assesses a large number of cognitive functions [30]. On the other hand, its intellectual property issues is a financial barrier for doctors, it has a limited testing of visuospatial capability and the results are influenced by subject's language ability [30].

The ACE-R is an alternative to MMSE, with an increased sensitivity and specificity. This test is easy to administer and tests visuospatial capability [30]. As it was developed based on MMSE, also has issues related with intellectual property [30].

Unlike the previous ones, the MOCA is freely available. It has a high sensitivity (0.98), but a lower specificity than the others (0.52) [31]. It is short, focus on many cognition areas and tests the visuospatial capability. Sensory impairments affect the patient's score and the failure rates of the questions vary [30].

The LIADL is different, as it evaluates the patients ability to perform daily tasks, such as laundry, cooking or shopping [32]. There are other similar assessments with some adjustments, such as the Bristol Instrumental Activities of Daily Living (BADLS), developed specifically to be used in people with dementia [33].

Regarding Parkinson's, the standard assessment used by physicians for its detection is the UPDRS. The UPDRS is composed of several sections, some of which are answered by the patient and others by the physician, by analyzing the subject or contacting family members. Variations include different parts, but the main ones focus on behaviour and humor, daily life activities, motor functions examined by the doctor and motor complications in the days before the assessment [34].

Apart from the previous question/answer assessments, there are tests that include different approaches to interact with the patient.

In the Clock Drawing Test (CDT), the physician asks the patient to draw an analog clock with a certain time, usually 11:10. There are different scoring systems, but usually points are awarded for drawing the different elements of the clock, such as the shape, numbers or hands. This assessment is simple, easy to understand, assesses visuospatial reasoning and takes a short time to administer. However, the scoring is inconsistent and depends on the doctor analysis, does not test language and correlates with education level [30].

The kinematics of the drawing are effective at indicating physiological parameters, such as the amplitude of tremors, bradykinesia or dyskinesia [35]. Spiral drawing is a skilled and complex coordinated motor activity, making it suitable for the assessment of motor functions [36]. Patients are asked to draw a spiral on paper, which is then analysed by experts, who are able to detect early signs of PD [35]. The accuracy of the spiral drawing correlates with the motor functions ability, which is affected by bradykinesia or rigidity, common symptoms of Parkinson's [35].

The 10 Meter Walk Test (10MWT) has been widely used for locomotion analysis, with patients trying to walk in a straight line for 10 meters. Different

variations use different walking lengths, such as 4 or 14 meters. Studies can obtain different set of parameters from the walking analysis, including the walking speed, stride length and step rate. The assessment is useful for PD, as one of the main symptoms is deficits in motor functions, which affect the patient's gait [37].

The Stroop Color and Word Test (SCWT) is a test used to assess the ability to inhibit cognitive interference when processing a specific stimulus. A list of color names is printed in a different color and shown to the patients, and it is expected from them to say the color of the ink instead of reading the word. What happens is that patients have to perform a less automated task (say the color), instead of performing the automated task (read the word). The difficulty that occurs in these cases is called the Stroop effect [38]. The SCWT has been shown to correlate with PD [29].

Finally, the Finger-Tapping Test (FTT), which is the most practiced task to evaluate muscle control and motor ability of the upper extremities, and has been used for over a century in patients with AD, PD and other neurological diseases [39]. Mainly using their index fingers, one hand at a time, patients are asked to tap as quickly as possible during a 10 second interval [40]. The original procedure requires 5 consecutive trials with all 5 fingers for each hand [40], but variations have been developed. Several devices have been used to record the number of taps, such as mechanical counters, electronic switches and computer keyboards [39].

Many studies have been criticizing the traditional neuropsychological assessments due to several of their characteristics, mainly the unsuitability for repeated use, the time demand, practice effects, the limited sensitivity for subtle cognitive changes and lack of validity since many times there is no correlation between the tests and daily activities performed by the patient [41].

2.1.4 Cognitive enhance

With aging and as neurodegenerative diseases worsen, both cognitive and motor functions decline, especially in Parkinson's disease patients, who suffer severely from the presence of tremors.

An extensive body of research has stated the effects of cognitive stimulation on learning and neuroplasticity [42], as effortful mental activity produces and strengthens synaptic connections and stimulates the neurogenesis process [43]. Cognitive training is effective at improving the cognitive performance of older adults, both in specific domains and globally [9, 11]. Not only that, but studies also

refer the occurrence of transfer effects, meaning that improvements not only occur in skills that are trained, but also in others that are not stimulated. Thus, the stimulation on the cognitive domain is a great approach to improve both intellectual and motor functions [8, 44]. [44] related that the performance gains on people with Mild Cognitive Impairment (MCI) remained stable for 6 months after training, without any boosters.

With this in mind, reports have studied the usage of neuropsychological software and video games to improve cognitive abilities [9]. Evidences have shown that games are an effective mean to enhance reaction time, processing speed, working memory, executive function, visual spatial ability and attention [9]. Not only video games hold the promise to improve cognition, but traditional leisure activities, such as Bingo, Dominoes [45], chess [43], card games [46], reading or dancing [43] follow the same premise.

Regarding PD, Alisson Lima suggests that the practice of gaming, independently of wins or losses, favorably modifies the dopaminergic circuitry, which is one of the main domains affected by the disease, improving executive function and motor skills [45].

Manuel Lillo-Crespo and his colleagues studied the influence of these approaches in delaying the appearance of cognitive impairments, namely dementia, and concluded that patients involved in at least 10 mind exercises were able to delay AD by nearly 1.5 years [43]. According to Jean Dartigues et al. on his study about board games, the risk of developing dementia between players and non-players was 3% versus 6% in a 3 year follow-up, 16% versus 27% after 10 years and 47% versus 58% in a 20 year period [47].

2.2 Technologies for neurodegenerative diseases

The current technologies for prevention, monitoring and rehabilitation of neurodegenerative diseases, with special focus on Alzheimer's disease and Parkinson's disease, will now be presented.

Multiples reports in the literature suggest that the cognitive and motor functions of patients with neurodegenerative diseases can be improved or, at least, stabilized, with monitoring and training by certified professionals [8]. The best results came from patients that combine cognitive and physical treatments, improving the

patients cognitive and motor skills [8, 11].

The traditional approaches are delivered in individual or group format by a trained instructor and can differ on the type of training, frequency and strategies [9]. Each training involves the identification of a convenient meeting place, coordinating schedules and travel time, which makes face-to-face training programs expensive [9].

The considerable costs of these techniques, which are not generally feasible for ordinary families, as well as the inconvenience of travelling to the training site, are factors that lead to a decrease in training frequency and a reduction in adherence [4]. Adding the fact that this group of diseases has been increasing its prevalence and incidence in the last years and it's not expected to stop, and the fact that the diagnosis, treatment and management of these diseases is a complex process that requires a continuous, intensive and prolonged rehabilitation [48, 49], a burden affecting the global economy is increasing and does not seem to slow down.

With this in mind, the development of digital technologies has provided an until now unavailable opportunity to make healthcare access easier and cheaper.

2.2.1 Digital technologies

The use of information and communication technologies in healthcare in the context of neurodegenerative diseases includes smartphone applications, sensors at home and wearables, which are minimally invasive, can measure a great set of parameters without patients notice and cause little or no extra costs to use them [10]. The use of these devices at home has significant advantages, such as greater cost-effectiveness, easier and more convenient access regardless of location, less patient discomfort and greater personalization in training [9, 50].

As said before, the evolution of technology in recent years provides many tools that weren't available for monitoring and rehabilitation of patients in the past. The usage of digital technologies is addressed by hundreds of millions of people around the world to make their lives easier, in multiple domains, from government to healthcare [48]. In fact, a variety of apps have already been developed and applied with success for self-management by patients with other diseases, such as hypertension, diabetes or other chronic diseases [51].

Considering practicability, video-games and apps in general are developed for a large number of devices, such as smartphones, tablets, computers, consoles or

smart TVs, and interfaces, namely touchscreen, virtual reality, augmented reality or handheld devices, which makes them universally available and a powerful tool for medical interactions [42].

Not only that, but the fact that people are used to and comfortable with this type of technology supports the idea of using non-invasive equipment, with the main goal of monitor and recover patient conditions without them notice, unlike traditional equipment that is expensive, uncomfortable and invasive [48]. In addition to all these advantages about using digital-based approaches, the effects seen in patients with these interventions are similar to traditional training techniques, which justifies the development of digital-based interventions in the future [9].

Contrary to common belief, a considerable proportion of regular digital gamers, between 20% and 29%, are older than 50 years [44]. In fact, they are also the fastest growing segment of internet users, as the percentage of adults that use the internet increased exponentially from 2000 until 2010, namely adults aged between 50 and 64 increased from 50% to 78% and adults older than 65 went from 15% to 42% [9]. Also, latest technologies have a huge presence of elder people, for example Virtual Reality games, in which people older than 60 account for 43% of total users in America [4].

With the increase in the ownership of digital gadgets and in the internet prevalence across older age groups, developers and healthcare professionals can take full advantage of the situation and enhance the lives of patients with neurodegenerative diseases, improving monitoring, assessment or rehabilitation [9].

As previously describe, although they have distinct clinical manifestations, the neurodegenerative diseases share some symptoms, most notably cognitive impairment, which includes loss of problem-solving ability and memory. Previous studies have stated that digital activities should be developed in particular for degenerative diseases and that otherwise, patients might have difficulties with skills that are beyond their capabilities [7, 46]. Due to their condition, patients may not be able to complete multi-step cognitive tasks, remember facts and information or understand rules in the game [46]. In this sense, certain conditions must be fulfilled in developing content for this group of people, such as create simple activities and adjustable difficulty [46].

The chinese report from [51], studying the acceptability of smartphone applications for patients with Parkinson's aging more than 65, concluded that

around 67% of participants owned smartphones or had access to them and that 50% browsed in internet, of which 20% used the computer to do it and 80% used smartphones [51]. All answers from PD patients stated that they received information about diseases from doctors in clinics, but only 15% from smartphones and 7% from other media [51]. More than half of the surveyed patients claimed that they would only use the apps if they were provided for free, could be used to remind the user to take medication, respected the users' privacy and reduced the economic and psychological burden [51]. Apart from that, it was deducted from the answers that younger patients with higher levels of education were more likely to appreciate the opportunities of smart devices.

With such positive feedback from the target audience, further development is expected to be made in this area, making technology available and adapted for everyone. The usage of digital technologies to monitor neurodegenerative diseases can be implemented in multiple paths, such as cognitive games to enhance mental function, exergames to include physical exercise in patients routine, notifications to increase the adherence of medication or contact with health professionals [48].

2.2.2 Digital assessments

Approaches to detecting and monitoring diseases are constantly evolving. For the diseases under study, the current focus has been on using technology that performs an objective assessment, with the usage of machine learning algorithms or artificial intelligence. These algorithms can be fed either by data obtained from the common assessments displayed in the Subsection 2.1.3, such as the spiral drawing, or by newly discovered techniques.

The digitization of the spiral drawing is the most frequent approach found in literature that uses a common procedure and implements it with new technologies, with the aim of analysing the data and process the answer in an objective way. In 2017, [35] proposed a methodology to detect different stages of PD, based on the speed and pen-pressure of sketching a spiral with guidance from dots on the paper, obtaining the data from live recording and analysis. The classification of the subjects using the combination of both features achieved an accuracy of 68.2%. More frequently are found methodologies where subjects have to draw the spirals on tablets or smartphones, such as the work developed by [52], with the goal of assessing essential tremor and Parkinson's disease. Different data was obtained from the spirals, and the best results occurred with the relation between the visual rating scale and the logarithm of the mean ratio between the distance and the angle of every single point that belongs to the spiral. [36] and [53] followed similar

approaches but with other features. [36] calculated 16 parameters, such as the drawing time, number of strokes, stroke speed or stroke acceleration. [53] obtained the normal velocity, entropy, overall time duration, among others. The study from [53] obtained better results when compared to [36]. Data from spiral draws are great features to monitor neurodegenerative patients and a similar approach should be implemented in the app.

Diogo Braga et al [54] proposed a methodology to detect early signs of Parkinson through speech, as voice is affected by the deterioration of motor functions. The method used recordings of the sustained vowels "a" and "o", extracting important features of speech, namely the jitter, shimmer, HNR and pitch, however the study relies mainly in jitter and shimmer, which are the popular features used for the study of phonation biokinetics. Jitter is defined as the variation of the fundamental frequency from cycle to cycle, while shimmer relates to the amplitude variation of the wave in successive cycles [55]. The highest score was obtained with the Random Forest algorithm, with an accuracy of 99.4% [54]. Jitter and shimmer are important voice parameters that can characterise the health of patients, so they are expected to be included for monitoring in the application.

Table 2.1 provides an overview on the different assessments used for detection of neurodegenerative diseases, how they are used and what is being measured. The marked cells in the table are procedures that were incorporated in the application for the monitoring of the patients.

Table 2.1: Diagnostic assessments overview.

Name	Content
LIADL *	Assess daily activities.
UPDRS *	Assess Parkinson's disease.
CDT *	User is asked to draw a clock with a certain time to assess cognitive function.
Spiral drawing *	User is asked to draw a spiral for the assessment of motor functions.
10MWT	Obtain different set of parameters from the walking analysis, useful for assessing PD.
SCWT	Assess the ability to inhibit cognitive interference when processing a specific stimulus, which is correlated with PD.

FTT *	Most practiced task to evaluate muscle control and motor ability of the upper extremities, used for patients with AD, PD and other neurological diseases.
Voice *	Voice parameters (Jitter and Shimmer) were able to characterise the health of patients with high accuracy.

* Similar implementation on the application.

2.2.3 Gamification

As specified previously, traditional therapy is expensive and consists of exercises that are repeated, tiring and boring [4]. The term gamification is used to refer to the usage of gaming techniques in non-gaming areas, in order to increase users' engagement and participation [4].

It is seen that in neurodegenerative diseases, patients don't follow crucial parts of rehabilitation, such as taking medication and practice physical exercise [4], and usually adherence declines with time. Gamification is being used successfully for the rehabilitation of patients suffering from ND disorders, either by active video games, exergames or virtual reality games, in order to assist healthcare clinicians and boost patient motivation [4].

In recent years, games have been used for intentions other than personal or collective entertainment [56]. These games are called Serious Games (SG) and are used for serious purposes, such as education, training, health, communication, marketing or politics, among others [42, 44], with both enjoyable and recreational aspects [42]. This approach uses different kinds of interactions to deliver knowledge, messages, skills or information to the player [57]. SG include a variety of genres, from computer and smartphone-based games to outdoor games [44].

Some examples of SG include military games, commonly dedicated to tactical and strategic training for the army, educational games, used in a school context, advergames, whose main objective is to share a commercial message, newsgames, based on current events or journalist issues, and health games, dedicated to the health sector, with the aim of improving players' cognitive and physical abilities, as well as share valuable information about their diseases [44].

SG application in the rehabilitation of neurodegenerative diseases provides patients with literacy about the disease they are facing, enhances their engagement and produces a proper feedback [4].

Video games increase compliance with the therapy because they are fun and exciting, unlike traditional assessments, as well as provide difficulty adjustments to avoid practice effects [41]. Apart from that, it is a low-barrier and cheap opportunity for patients to improve and delay the onset of impairments [58], keep closer contact with health staff and stay informed.

All this characteristics make Serious Games a great approach for keeping neurodegenerative diseases patients with high motivation and attention to the challenges, which leads to greater engagement and adherence to the rehabilitation programs [11, 42], increasing the chances of a healthy recover.

A correct approach to this games must follow a design that takes in account the needs and capabilities of the patients, offers challenging, rewarding, motivating, and engaging experiences, and provide them the possibility to share the points, ranking or achievements with other players, family or friends [49].

2.2.4 Games

Games in general should follow a set of practices to enhance user experience. The usage of general games for people with neurodegenerative diseases is not appropriate for 2 main reasons: the unsuitability of this games for the patients, due to requirements of high processing speed, movements and difficult tasks [42]; the lack of information on the relationship between scores and cognitive assessment [11].

The current digital market, mainly regarding smartphones, is flooded with commercial brain games that claim to increase cognitive functions, such as memory, attention or creativity, but most of them aren't specifically designed for patients with cognitive deficits, backed by any scientific study or lack the information about the relation between the scores obtained in these games and the cognitive abilities of the patients [9, 11, 12]. Some of the key characteristics to make suitable games are the balance between the activity difficulty and personal skills, the presentation of clear game objectives, a clear and immediate feedback and a rewarding activity [59]. Ultimately, design for games and applications for people with impairments should be provided or reviewed by health professionals, in order to assure maximum suitability.

Authors from [11] developed 7 smartphone games to assess the cognitive function of elderly people with and without cognitive impairment. The names, domains and objective of the games are presented in Table 2.2 and images of these games are presented in Figure 2.4.

Name	Domain	Objective
Square Numbers	Arithmetic	Combine 2 or more blocks in order to achieve the target number at the top.
Memory Sweep	Working Memory	Memorize the highlighted tiles to choose them later.
Word Pair	Language	Pair words according to a specific rule, such as "similar" or "opposite".
Bubble Bots	Language	Create the maximum number of words of at least 3 letters given 6 letters.
Must Sort	Attention	Sorting the items correctly by tapping on the correct side of the screen.
Unique	Attention	Find the odd element and tap it.
Rush Back	Working Memory	Memorize the card and tell if matches the card showed before.

Table 2.2: The names, domains and objectives of the games developed by [11].

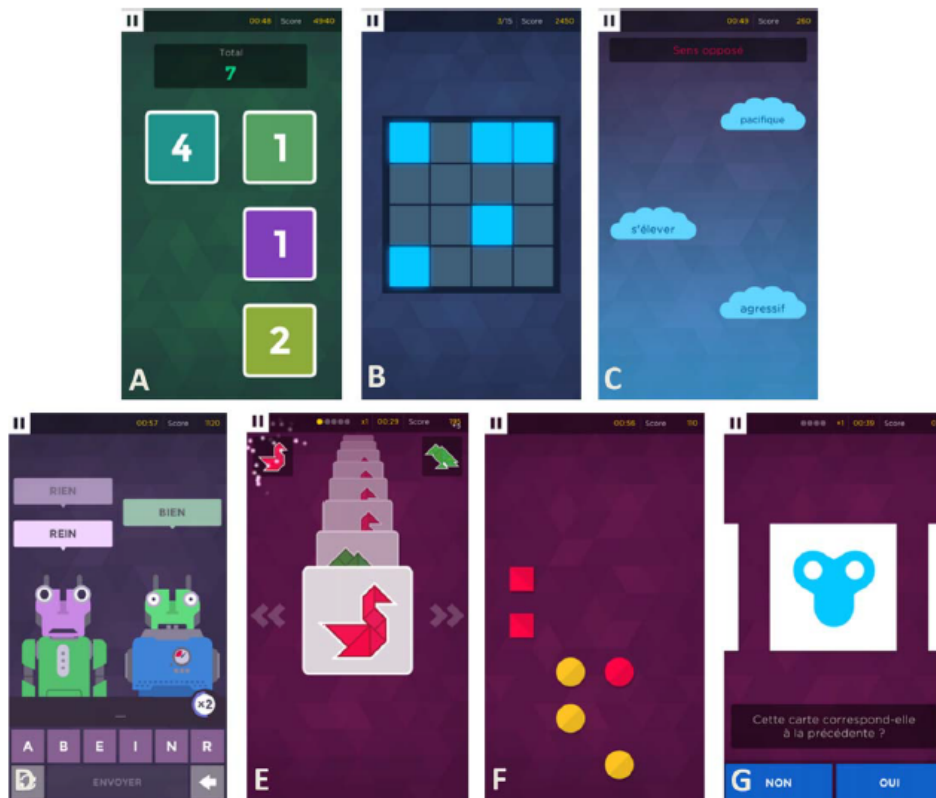


Figure 2.4: Games developed by [11]. A) Square Numbers, B) Memory Sweep, C) Word Pair, D) Bubble Bots, E) Must Sort, F) Unique, G) Rush Back.

[42] developed a digital training approach for Parkinson's disease. The game was called Rhythm Workers, was playable on smartphones and tablets and its main goal was to construct buildings whose aesthetic quality was dependent on the player's rhythmic performance in a finger tapping task. The patients had to tap their finger on the screen according to a variety of beats, and the quality of the tapping performance, that is, the accuracy and variability of the taps with the beat, determined the performance in the game. Figure 2.5 demonstrates an example of Rhythm Workers.

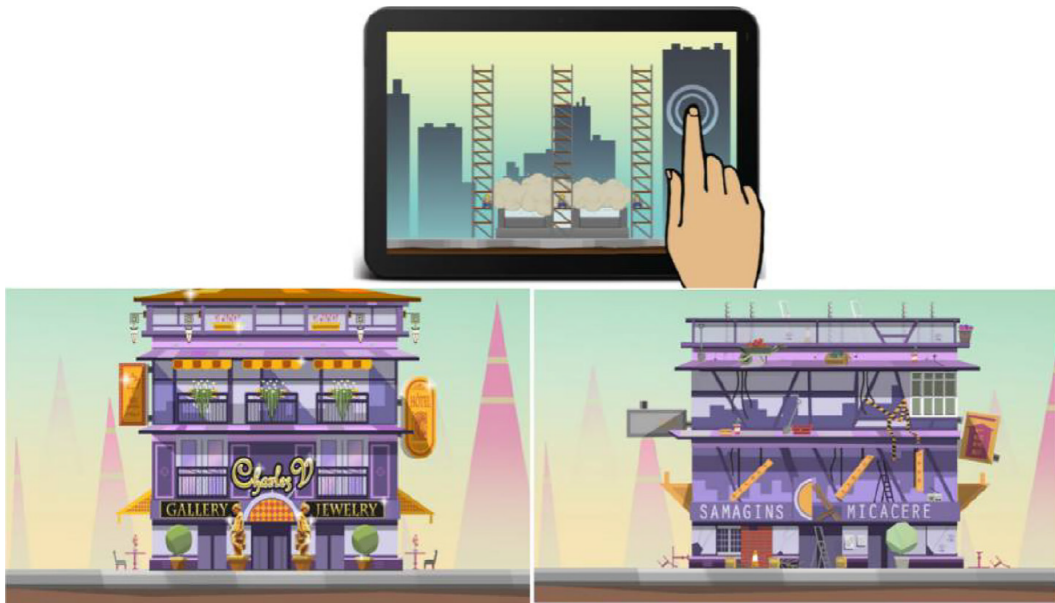


Figure 2.5: Rhythm Workers. On the bottom left, a building corresponding to good performance and, on the bottom right, a building corresponding to bad performance.

The study in [60] used the freely available Gallery Game, deployed in the Mezurio smartphone app platform, too assess long-term memory in adults at risk of AD. This game was divided in 3 phases. An image was presented to the participant and he had to classify it as previously seen or new image, being this phase called Recognition phase, Subfigure 2.6 b. In case of a new image, it would redirect to the Learning phase, where an object image was shown to the user, with an arrow pointing left, up or right, such as Subfigure 2.6 a. The user was required to swipe in the arrow direction, in order to learn the association between the image and the direction. On the other hand, if the image was already known for the patient, he entered the Recall phase, Subfigure 2.6 c, where he had to specify the swipe direction learnt in the Learning phase.

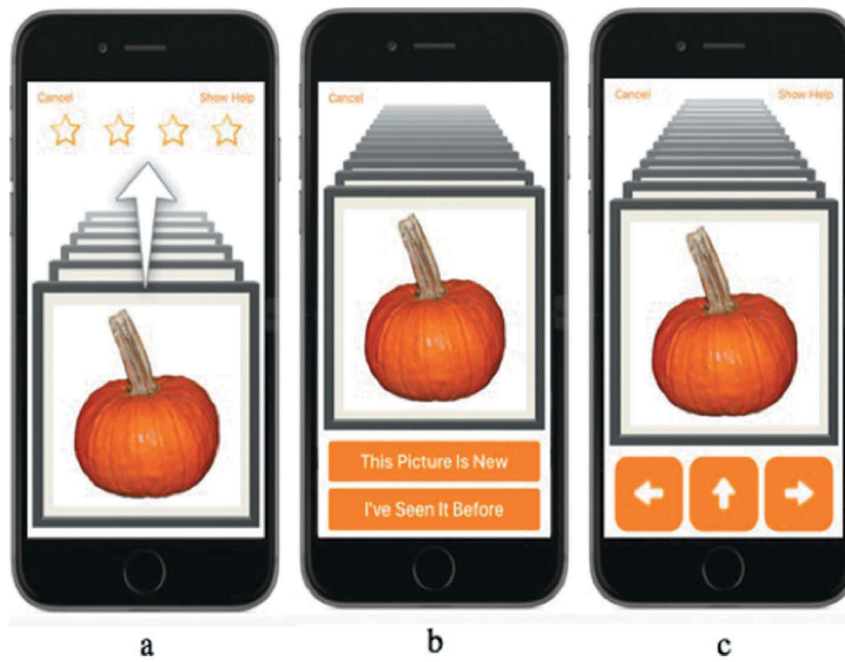


Figure 2.6: Gallery Game. Each image represents a different stage.
a) Learning, b) Recognition, c) Recall.

[48] proposed a iOS mobile application that used the smartphone's sensors to obtain objective measures from Alzheimer's patients symptoms. This app includes 3 assessments which try to measure patient's symptoms in an objective way. The first test is called Manual Dexterity - Subfigure 2.7a, in which the patient is asked to press two buttons alternately for 20 seconds using different fingers from the same hand. The parameters registered in this test include the buttons' coordinates, number of presses in each button and the starting timestamp. The Walking test was designed to evaluate the patient's gait, as he was asked to walk in a straight line for a specific time, namely 20 seconds, as showed in Subfigure 2.7b. Finally, the Memory test, which tries to objectively assess the user's memory, Subfigure 2.7c, in which participants had to memorize a sequence of buttons which they had to press later in the same order, with the sequence getting harder after each successful try.



Figure 2.7: iOS app to assess Alzheimer's symptoms.

[41] suggested a maze-like game to assess cognitive and motor functions. The evaluated game was a Numberlink puzzle game, a popular genre of games available for free in smartphone apps marketplaces. To resolve the puzzle, the user must connect all pairs of dots with non-intersecting lines and all empty cells must be part of a path. As other puzzle games, difficulty can be adapted with a greater number of pairs and empty cells, such as it shows in Figure 2.8. The goal of this study was to evaluate the possibility of using maze-like games to assess changes in psychomotor, visuoconstructional and executive functions with aging and neurodegenerative diseases.

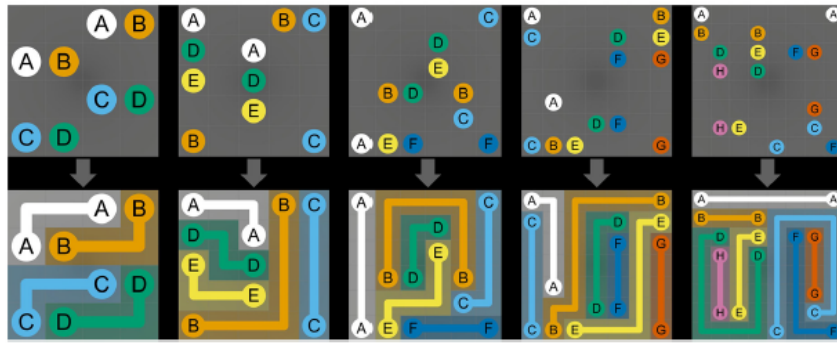


Figure 2.8: Numberlink puzzles. Variations with increased difficulty.

[61] studied the usability and playability of a collection of games called Panoramix, developed to detect cognitive impairment in senior adults using serious games. Panoramix was composed by 7 games, each one to evaluate different cognitive areas: Episodix to assess episodic memory, Attentix for attention, Executix for executive functions, Workix for working memory, Semantix for semantic memory, Procedurix for prospective memory and Gnosix for gnosia. The games were developed in the Unity software and were run in a tablet. Figure 2.9 shows some of these games.

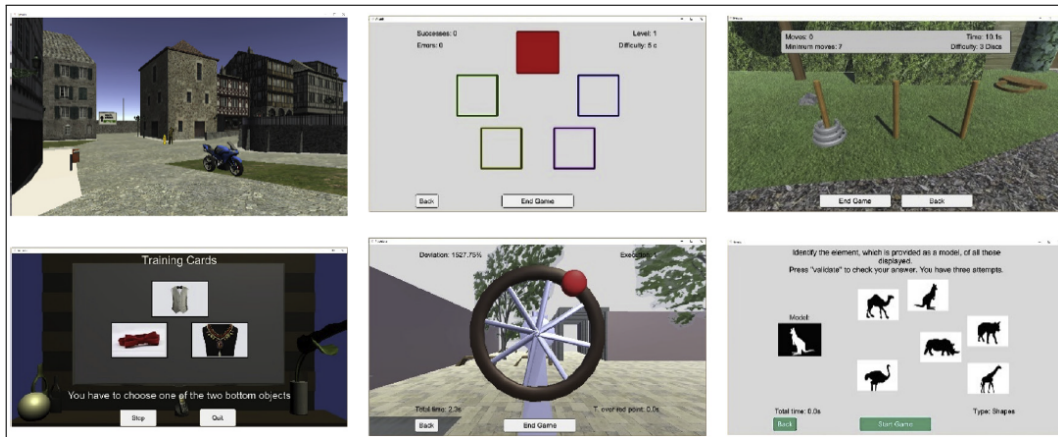


Figure 2.9: Panoramix games. Top left: Episodix, Top center: Attentix, Top right: Executix, Bottom left: Semantix, Bottom center: Procedurix, Bottom right: Gnosix.

[62] used a serious game based on a cooking task to assess MCI and AD, while stimulating executive functions. It was called "Kitchen and cooking" and could be installed on a tablet, making it flexible to be employed at home or in nursing homes. Participants were able to choose from four different cooking scenarios, and had to choose the ingredients, plan the tasks and perform specific gestures to accomplish the tasks, with the goals of object recognition and attention, executive

function and praxis abilities. The game tracked the time spent and the number of errors in each activity.

With some premises matching the two previous studies, [63] created an open world game where users could navigate and perform virtual daily tasks, namely a shopping, cooking and table preparation task, in order to assess visuospatial orientation, spatial memory, prospective memory, episodic memory, executive functions and attention. The game was running in a touchscreen computer, with patients using the touchscreen for the shopping, cooking and table preparation tasks and a joystick for navigation. The measured parameters included the times of completion for each task and how correct each task was performed. The Figure 2.10 has screenshots from the different activities available in this game.

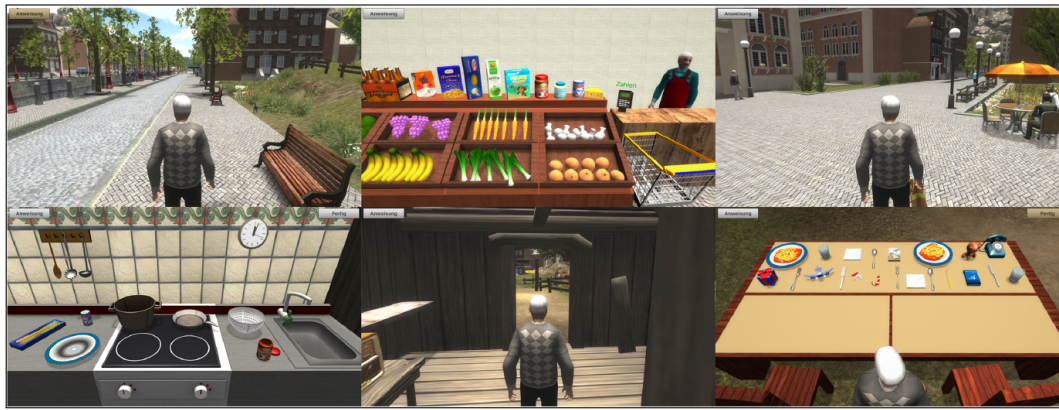


Figure 2.10: Activities presented in [63] Serious Game. Top left: Navigation task "Go to the shop", Top center: Shopping task, Top right: Navigation task "Go back home", Bottom left: Cooking task, Bottom center: Navigation task "Go to the garden", Bottom right: Table preparation task.

The usage of different devices and interfaces, other than smartphones and tablets, which might not be so easily accessible, such as motion detector hardware or joysticks, is also frequently found in the literature.

[64] used a robotic manipulandum to control an object hitting game, in order to assess cognitive and motor skills in PD patients. The tasks allowed to test visual discrimination, rapid motor decisions and precise arm movements, providing the hand's kinematics and cognitive performance parameters simultaneously.

Motion games are a genre of SG used the assessment of neurodegenerative diseases, because it offers a natural interface for the player and also stimulates physical and mental abilities simultaneously. These motion games require specific

movement sensors, such as the Microsoft Kinect, the Leap Motion Controller [57] or the Playstation EyeToy [65].

[66] developed a game called WuppDi!, that included 5 motion games. This game didn't required additional hardware, only a computer with a webcam. Games were developed using the Microsoft XNA Game Studio, making them playable in any computer running Windows. This study was innovative at the time because it didn't require the specific movement sensors defined before. The skills evaluated by these games were rhythmic skills, memory, coordination and hand movements. Figure 2.11 has screenshots of these games.



Figure 2.11: Games developed by [66]. Top left: Game menu, Top right: Cinderella, Center left: Ali-Baba, Center right: Town Musicians, Bottom left: Frog Prince, Bottom right: Star Money.

[57] used the Leap Motion Controller in order to detect hand and finger movements in 3D. The authors created three game prototypes, named Pinchicken, Finger-Hero and Grabduzeedo, presented in Figure 2.12. The focus of the games was to involve hand movements, coordination between hands and finger activation in order to evaluate PD.

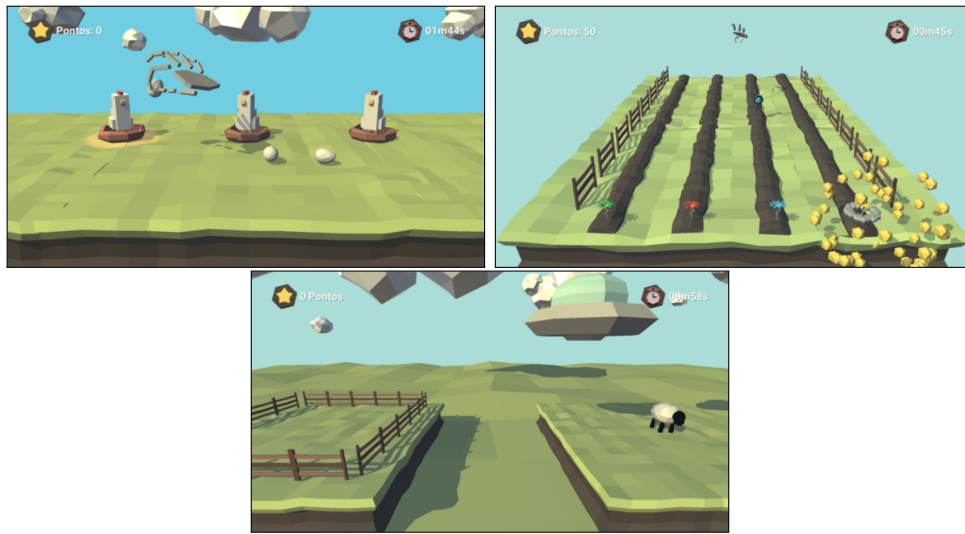


Figure 2.12: Games developed in [57] study. Pinchicken on the top left, Finger-Hero in the top right and Grabduzeedo on the bottom.

The Leap Motion Controller was also used in [65] as the interface for their Motion Games, with the goal of assessing the functionality of the upper limbs in PD patients. Six games were created for this study: Piano Game, Reach Game, Sequence Game, Grab Game, Pinch Game and Flip Game. These games stimulated various domains but, in general, the goal was to perform and measure arm, hand and finger movements, as well as stimulate their relationship with the brain. The six developed games are showed in Figure 2.13.

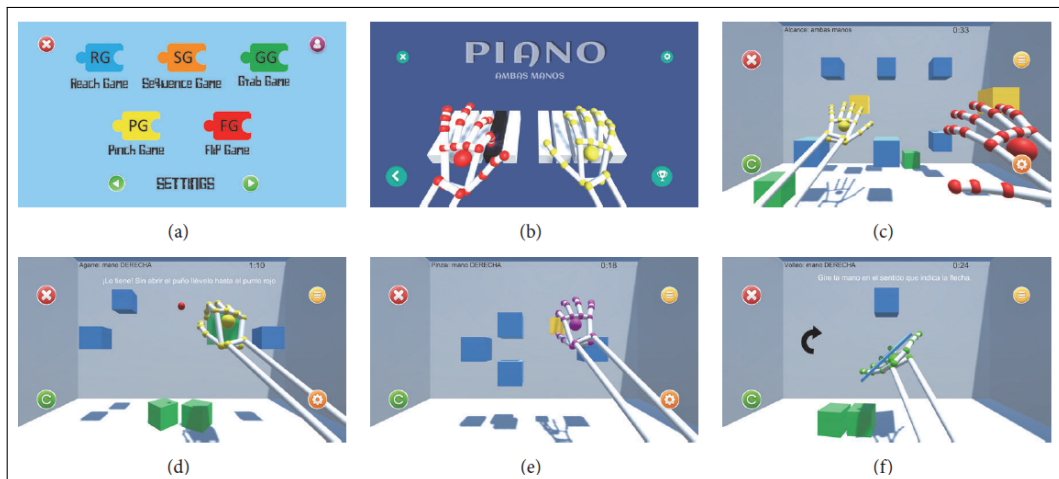


Figure 2.13: The six games developed for [65] study. a) Game menu, b) Piano Game, c) Reach Game, d) Grab Game, e) Pinch Game, f) Flip Game.

The systematic review on computerized cognitive training for older adults from [9] included several approaches used for cognitive development. This study included

off the shelf games, such as Pac-Man, Donkey Kong or Tetris, and applications designed specifically for this task, such as CogniFit, Posit Science InSight and Memory Trainer. CogniFit comprises neuropsychological evaluation tests and cognitive stimulation programs designed exactly for measuring and training of cognitive skills. Posit Science InSight is a subscription service that offers clinically proven exercises for the brain. Einstein Memory Trainer is a app available for Android and iOS that follows the gamification rules in order to increase patient adherence and stimulate cognition through a great variety of games. We can see examples of the referred apps in Figure 2.14.



Figure 2.14: Examples of applications with cognitive tests.

Common measures including in these games are the reaction time, which is the time needed to process and respond to a stimulus, processing speed, the ability to quickly process information, memory, meaning the ability to retain, store and recall information, executive function, which includes a broad spectrum of abilities, such as planning and abstract thinking, and attention, mainly selective attention, which is the process by which an individual focus on specific auditory or visual stimuli [9].

Table 2.3 provides an overview of the smartphone and tablet games, the parameters that are measured and the results obtained, with the marked rows referring to processes incorporated in the developed application.

Table 2.3: Smartphone games overview.

Authors	Results
Bruno [11]	Seven games to assess cognition in elderly, focusing on arithmetic, memory, language and attention, found to have statistically highly significant differences. The parameters were the scores obtained in the games.
Celia [42]	Rhythm game for people with dementia was successful in improving patient rhythm. The assessment considered the correlation between patients touches and the music beats.
Claire [60]	Found little association between Gallery Game outcomes and established in-clinic memory assessments.
* Miguel [48]	It was seen a decrease in the score of patients with PD when compared to the control group. Parameters include the number of taps in the screen, the balance and memory.
Tobias [41]	The Numberlink puzzle game suggests that puzzles might provide data as digital biomarkers, to assess body functions. Parameters include reaction and solving time, number of tries, draws and memory.
Sonia [61]	Health professionals confirm the usability and playability of Panoramix in senior adults. Parameters are the number of tries, time spent and number of errors.
Valeria [62]	The cooking game tracked the time spent and the number of errors in each activity. AD patients took significantly longer to complete the scenarios than patients with MCI.
Vanessa [63]	Performance comparison between healthy patients and Alzheimer's patients indicate a significant difference in terms of percentage of achievement and in terms of time they needed to achieve the several tasks. Parameters for this study are the times for completing the task and the percentage of task completion.

Following next page

Continuation of the Table 2.3

Authors	Results
* Alexandra [9]	Parameters from off the shelf games and specifically design applications are reaction time, processing speed, memory, executive function and attention. Most studies mentioned found that not only do video games improve specific cognitive domains for older adults, evidence suggests they can affect global cognitive functioning as well.
* Similar implementation on the application.	

The development of the application is in accordance with the literature review presented above, making it suitable for patients with neurodegenerative diseases and the health professionals responsible for the analysis of their evolution. Some ideas were obtained from this review, while others were proposed by physicians assisting in the development of this application.

Chapter 3

Application Development

Contents

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3 Application Development

The project followed common software development practices. As the project evolved, its original objective changed as a result of regular discussions and requests from health experts who were following the project, originating constant modifications in the requirements. The purpose of this follow-up with health professionals was to design the application according to their needs and to include features that would be helpful in their daily tasks.

3.1 Specifications

The initial concept behind this project was the use of video games to monitor patients with neurodegenerative diseases. These games would be able to measure important parameters related to their symptoms, such as memory, executive function, or tremors. The cooperation with Parkinson's disease specialists shifted the focus of this investigation to this pathology, as well as provided new functionalities that the physicians would like to see implemented. Moreover, the development of the introduction concerning neurodegenerative diseases, as well as the state-of-art on applications targeting this subject, allowed for an improvement in the original requirements. For this reason, while the introduction provides an analysis on neurodegenerative diseases as a whole, Alzheimer's disease and Parkinson's disease, the built application targets Parkinson's patients and includes information and diagnostics related to Parkinson's.

The requirements that led to the final version of the application are summarized in the following tables. Some of these requirements were not completed as they are not as important in the current stage of this proof of concept. The Table 3.1 and 3.2 present the functional requirements and the non-functional requirements, respectively. Functional requirements are requirements that demand the functionalities that the system should offer to the user, while non-functional requirements are usually related with quality constraints or personal desires.

Table 3.1: Functional requirements.

ID	Description	Priority
FR01	Users create their account by specifying the username, email and password.	High

Following next page

Continuation of the Table 3.1

ID	Description	Priority
FR02	Users login to their account by entering the email-password combination.	High
FR03	Users login to their account by entering the username-password combination.	High
FR04	Users logout from their accounts.	High
FR05*	Users change their passwords.	Medium
FR06*	Users recover their passwords.	Medium
FR07*	Users change their username.	Low
FR08	Users play games to measure symptoms.	Medium
FR09	Users get a random game to play.	Medium
FR10	Users choose the game to play.	Medium
FR11	Users see their high scores for each game.	Low
FR12	The app includes at least 5 games, in order to avoid learning bias and making it less boring.	Medium
FR13	A game for assessing executive function is included.	Medium
FR14	A game for assessing memory is included.	Medium
FR15	A game for assessing tremors is included.	Medium
FR16	Users leave the game if they don't want to play it.	Low
FR17	Users fill common assessments used by doctors to diagnose diseases.	High
FR18	Users specify how are their symptoms throughout the day.	High
FR19	Users specify their medication intake times.	High
FR20	Information for Parkinson's disease is available in the app.	Low
FR21	Users earn achievements by performing tasks.	Medium
FR22	Users check their locked and unlocked achievements.	Medium
FR23	Users install the web app.	High

Following next page

Continuation of the Table 3.1

ID	Description	Priority
FR24*	An admin creates a doctor account.	High
FR25*	Doctors login into their account.	High
FR26*	Doctors logout from their account.	High
FR27*	Doctors change their passwords.	Medium
FR28*	Doctors recover their passwords.	Medium
FR29*	Doctors change their username.	Low
FR30**	Doctors check the progress of the patient's game results by day.	High
FR31**	Doctors check the variation of the patient's symptoms.	High
FR32**	Doctors relate the variation in symptoms with medication times.	High
FR33**	Doctors choose the time period for analysis of the symptoms.	Medium
FR34**	Doctors see the patient's answer to the assessments.	Low
FR35**	Doctors see the patient's score to the assessments.	Medium
FR36	Text fields show errors after wrong parameter input.	Medium
FR37	Malicious code is checked in text fields input.	High
FR38	Passwords are saved in the database using encryption.	High

* Functional requirements that were not implemented.

** Functional requirements that were implemented but are in the user app.

Table 3.2: Non-functional requirements.

ID	Description	Priority
NFR01	Navigation between pages is fast.	High
NFR02	Pages are responsive (adaptable to any screen size).	High
NFR03	Menu navigation is easy.	High

Following next page

Continuation of the Table 3.2

ID	Description	Priority
NFR04	Application works for every operating system.	Low
NFR05	The application is developed for the browser.	Medium
NFR06	The web server is developed using Python and the Flask framework.	Low
NFR07	A SQL Database is used.	Low
NFR08	The system ensures the confidentiality, integrity and availability of the data stored in the database.	Medium
NFR09	The system prevents the injection of code in input fields.	High
NFR10	The application is suitable for people with neurodegenerative diseases.	Medium

3.2 System architecture

The architecture of a system is a formal description and representation that defines the structure of the software, how it's organized, the relationships between its components and the interaction with other systems, with the objective of declaring the goals of the project and the design and development of the new system.

The architecture of the proposed system will be presented using Unified Modeling Language (UML) diagrams, with information regarding the functionalities of the application, the principles used for the design and the components that integrate the software.

The Data Model Diagram, displayed in Figure 3.1, illustrates the different entities that are incorporated in the system, their properties and the database relations between them.

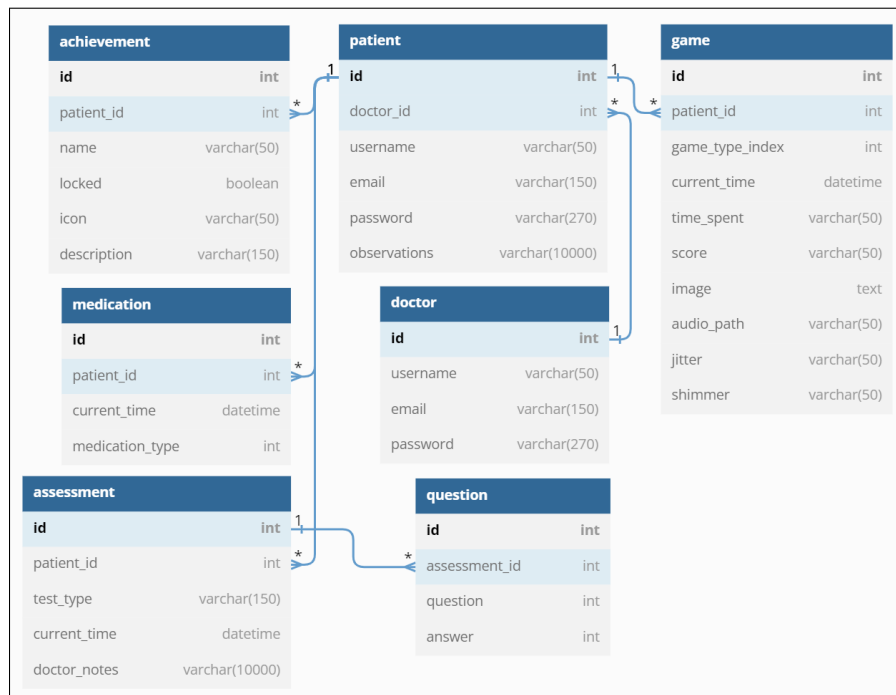


Figure 3.1: Data Model Diagram.

As it is visible, the database is composed of seven tables. The *patient* table contains all the users' information, namely their username, email, password, doctor notes and the responsible doctor ID. This table is the centre of the whole system, used for authentication and for association with all other user information. The table *doctor* is not currently in use, since all the functionalities were developed for the patients' app. The *game* table includes the parameters extracted from the games played by the user, the time of completion, the time spent in the game and the corresponding user ID for identification. Each *achievement* instance has the following properties: the name of the achievement, who it is assigned to, whether it is locked or unlocked, the matching icon, and a brief description. The *medication* table records the patient's ID, the medication schedule, and the type of drug. The *assessment* table and the *question* table are deeply interconnected. The patient's ID, the assessment type, the completion time, and the doctor's notes are the properties stored in the *assessment* table. Each *assessment* table entry is linked to various elements of the *question* table, which stores the assessment ID, the location of the question within the assessment, and the user's response to the question, implying that each assessment is made up of several questions.

Figure 3.2, referred to as the Use Case Diagram, shows the main functionalities that arise from the requirements and that are expected to be implemented in the web app, from both the perspectives of the patients and the doctors.

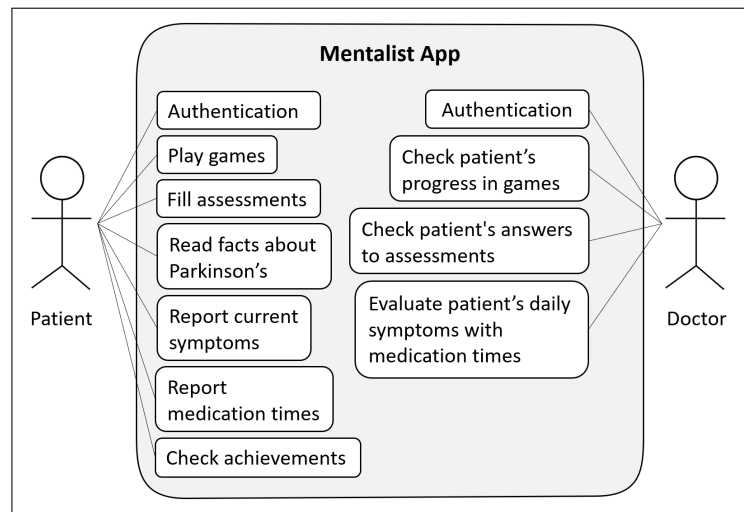


Figure 3.2: Use cases diagram.

As seen in Figure 3.2, patients must be capable of authenticating, which includes registration, login and logout, playing games, completing assessments, reading information about Parkinson's Disease, reporting current symptoms, reporting medication times, and checking their achievements. Physicians should be able to authenticate, monitor the patients' progress in games, assess their responses to assessments, and evaluate the relationship between their symptoms and medication times.

The interactions between the different application components, since the user accesses the browser, until the page is displayed, are shown in Figure 3.3. As can be seen, the chain begins with the user accessing the application's URL in the browser, which triggers a Hypertext Transfer Protocol (HTTP) GET request from the server. The server recognizes and analyses the request. The server can access the database to retrieve useful data if necessary. The server then prepares the HTTP response, including the necessary headers and files, such as the Hypertext Markup Language (HTML), Cascading Style Sheet (CSS) and JavaScript files.

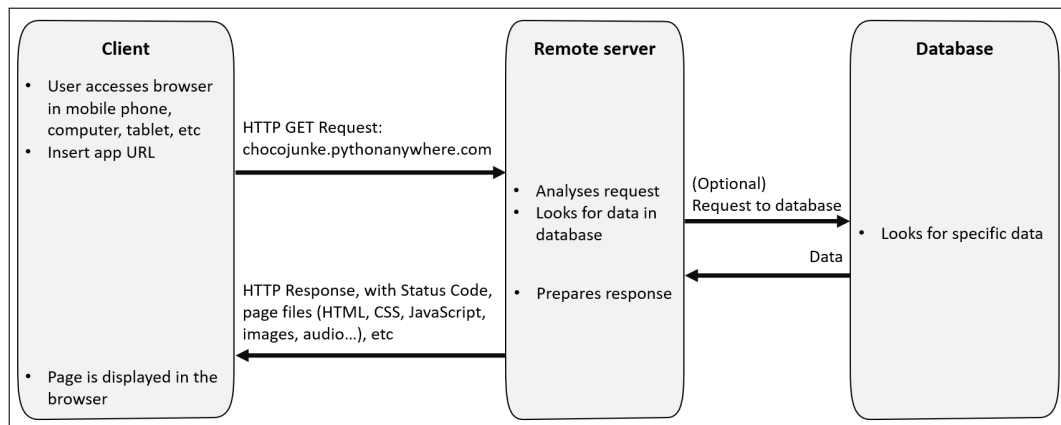


Figure 3.3: Interaction between different components in the system.

The Activity Diagram illustrates how the user interacts with the application, namely how to access the menus and perform the functions defined in the Use Case Diagram. This chart can be used by developers to work on the navigation between menus, their relationships, and the data exchanges that occur. Figure 3.4 shows an Activity Diagram constructed in UML notation that covers every potential navigation that occurs in the system, that is, how the user can perform all of its features.

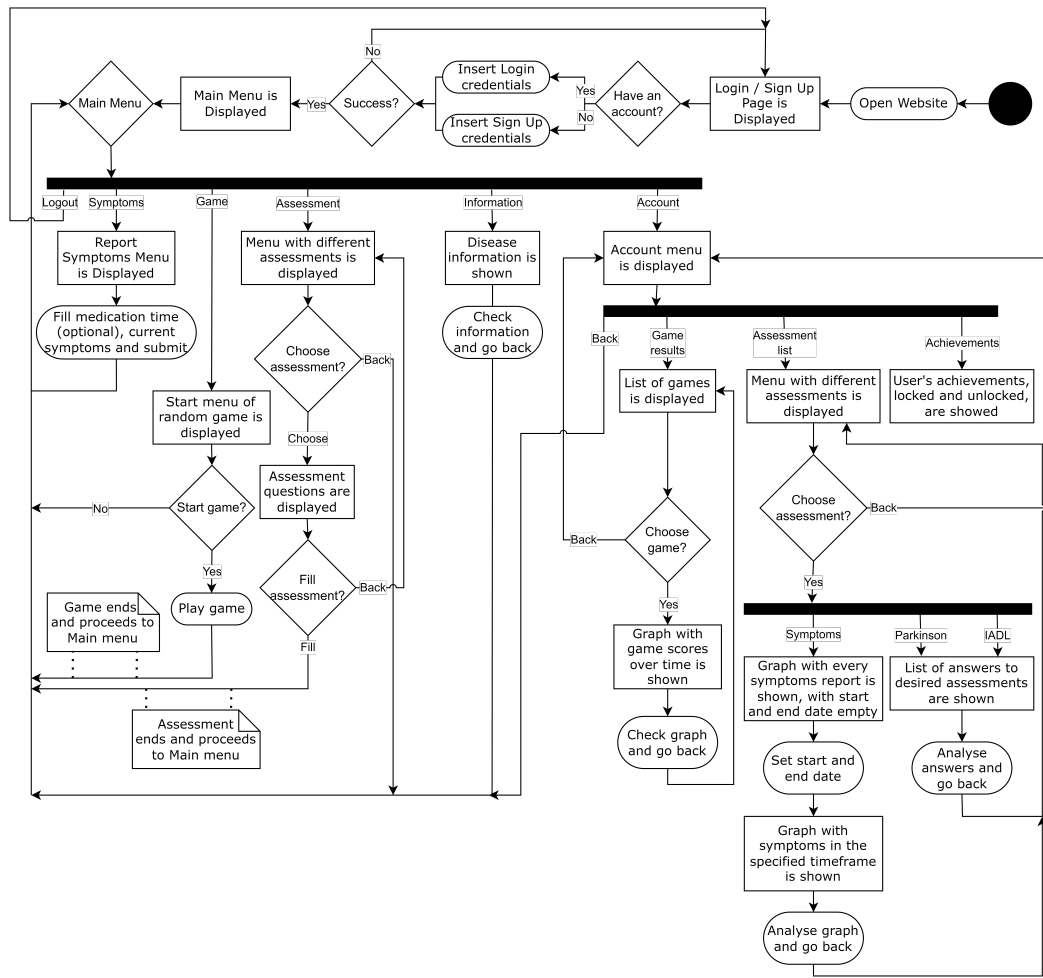


Figure 3.4: How to navigate in the application.

As specified in Section 3.1, the conversation with health professionals changed the focus of this investigation and provided new requirements for the application. One of the Parkinson's disease specialists expressed their interest in having an application whose purpose would be to allow doctors to fill the Part III of the UPDRS, in order to facilitate their work. After completing the assessment, the date and time of the diagnosis should be displayed, as well as the final result and the partial score of each of the answers. This would allow doctors to carry out a recurrent assessment in a more simple, automated, and environment-friendly way. The proposed application is an addition to the previously described program, which is the main focus of this thesis. For this reason, the secondary application does not have a requirements table or an architecture design like the main application, and only considers the concerns of the doctor, who described it as an application to fill their most frequent assessment. This would make the calculation of the points and the diagnosis easier for the professionals.

3.3 Tools

Web applications are gaining more and more popularity and becoming the main way to access personal and professional data, mainly thanks to the wide availability of fast Internet and mobile connectivity, enabling users to access their data and applications from anywhere, on any device [67]. Progressive Web Apps (PWAs) are a new technology inspired by native and web apps, combining attributes from both methodologies.

The main advantages of PWAs are:

- its reliability and speed, independently from the network speed;
- installable, which can be added to the user's home screen, making it accessible without the need of a browser tab;
- responsible, scalable and accessible from any platform and browser, such as smartphones, computers or tablets;
- fresh, being constantly updated without the need to distribute and install new software on millions of devices after each release [68].

Websites require three different languages in order to present their content in an appropriate and attractive way, which are HTML, CSS and JavaScript [69]. HTML is the official hypertext standard since the beginning of the web, with the aim of describing the structure and the components of the web page [70]. The goal of CSS is to improve the page appearance, allowing the developers to change the position, color, size and many other attributes from the components. Finally, JavaScript allows programmers to create pages with dynamic content, control multimedia and images, fetch information and much more. These languages, which are considered the backbone of web development, were included in the pages contained in the app, in order to provide users with appealing, functional and suitable pages.

A pre-built template for the login and signup pages served as the foundation for the design and development of the rest of the interface. The development followed several guidelines to offer a great user experience, particularly for patients with neurodegenerative disorders who may suffer higher difficulties utilizing applications. In order to minimize visualization issues, these principles call for a straightforward user interface with few components, large buttons and letters that are simple to understand and use, and a good contrast between the primary and secondary colors, blue and white, respectively.

To display these pages to the end user, a web server must be available to receive a request, find and fetch the desired data, and send the completed web page to the user. Different programming languages can be used to develop web servers. Python is often used for its ease of use and readability, while JavaScript is popular for its interactive nature and ease of use in creating AJAX-based web applications. Java is a more traditional choice for server-side programming, and is often used for its reliability and performance. Most programming languages come with frameworks that make development easier. Frameworks can automate common tasks, such as defining and handling dependencies. For the development of this application, it was chosen the Flask framework from the Python environment. Flask is a free and popular Python framework suitable for this project because it is fast, can scale up to complex applications and has an easy learning curve. Other important Python modules used in this project are flask_login, flask_sqlalchemy, PIL, parselmouth, werkzeug, os and datetime. The reasons for using these modules are shown in Table 3.3.

Name	Usage
Flask	Render pages, deal with requests and sessions, create server instance and send files.
os	Saving image and audio files.
datetime	Date and time manipulation.
re	Use of regular expressions (Username, email and password).
werkzeug	Secure filenames and password encryption.
PIL	Image processing (Calculating drawing accuracy).
parselmouth	Audio processing (Calculating voice parameters).
flask_login	User authentication: login, registration and logout.
flask_sqlalchemy	Support for SQL database management.

Table 3.3: Main Python modules used in the app.

Git is a version control program that enables online hosting of repositories, peer collaboration, and tracking of file changes. Git was utilized in this project for two reasons: keeping track of the software changes made over time and having a secure repository saved in the cloud to prevent losing all the work.

The developed application was hosted for free on the website `https:`

`//www.pythonanywhere.com`, which the creators describe as a "easy-to-use web-based Python development environment that can be accessed from any device with a browser."

3.4 Testing

Quality assurance is the process of checking the quality of a product or service before it is released to the public and consists of two phases: the verification process ensures that the software is developed in the right way, and will be discussed in Section 4.3; the validation process ensures that it meets the specific needs of the customer.

The validation planned for this application requires a testing in the field and will follow the next topics.

Testing group

Since Parkinson's patients are the target group for this application, they would have to be the ones to test and see if it meets their needs, with regards to their intellectual and motor skills. The health professionals responsible for their monitoring would use the application to check the patient evolution through their scores, assessments and symptoms report.

It would be interesting to gather as many perspectives on the application as possible, and it is planned to be tested with at least 10 patients over the course of a week to get a feasible feedback, as well as the opinion of the doctors on the results.

Surveys

The surveys were created for the two groups of users: the doctors and the Parkinson's patients. Both surveys have questions regarding personal data and the opinion on the software.

Regarding personal data, people answering the survey must indicate their date of birth, gender and, in the case of patients, when Parkinson's disease was detected.

Regarding their perception of the app, physicians express their opinion on the usability of the application considering the patients' limitations, its advantages, the importance of the app and suggestions for new functionalities. Patients are asked

on how easy it is to navigate in the app, whether they enjoy using it, if they can reach every menu, the difficulty to understand the games, whether they can play by themselves, and whether they can insert their symptoms and medication intake times.

The surveys were developed using Google Forms and are available for physicians and patients.

Chapter 4

Results and Discussion

Contents

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4 Results and Discussion

The architecture design, specifications and descriptions presented in the previous chapter led to the development of two web apps, one of which had the requirements implemented and respected the UML charts. On the other hand, the application regarding UPDRS diagnosis was developed taking into account only the description of the health professional who supported in the design of the main application.

4.1 Main App

The main application, named "Mentalist", will have its functionalities and menus presented, including smartphone screenshots demonstrating how the software is delivered.

Sign-up Page

The Figure 4.1a displays the sign-up screen, where users are able to create their accounts. In order to do it, they must enter their credentials, namely username, email address and password. The application follows several rules for the acceptance of each of these fields. The username must be unique, have a minimum of 4 and a maximum of 50 characters, not start by a number, only contain alphanumeric characters and the symbols "." and "_" and not contain spaces. The current email validation only requires the "@" symbol and the email to be unique, since it's not used for any other function other than logging in. The password must be at least 8 characters long and contain a variety of characters, including capital and small letters, numbers, and symbols. If the user does not follow some of the guidelines, an error message will be shown in their next attempt, with the proper error. For example, in Subfigure 4.1b, the user inserted an username that was already in use. Users are able to access the login page by clicking on the button saying "INICIAR SESSÃO", highlighted in Subfigure 4.1c.

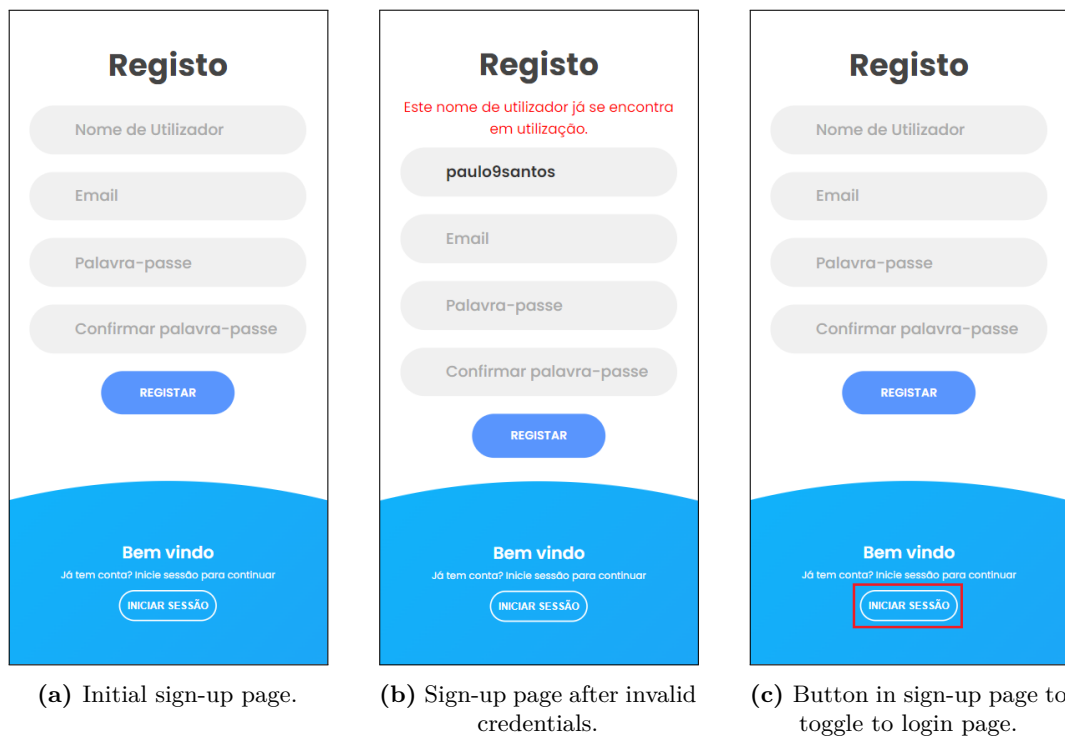


Figure 4.1: Sign-up Page.

Login Page

To log in, users can enter their email address and password or their username and password in the text fields displayed in Subfigure 4.2a. If the user fails to input a proper combination, an error indicating that the credentials are invalid is displayed, as illustrated in Figure 4.2b. The application toggles back to the sign-up page by clicking in the button with the text "REGISTO", highlighted in Subfigure 4.2c.

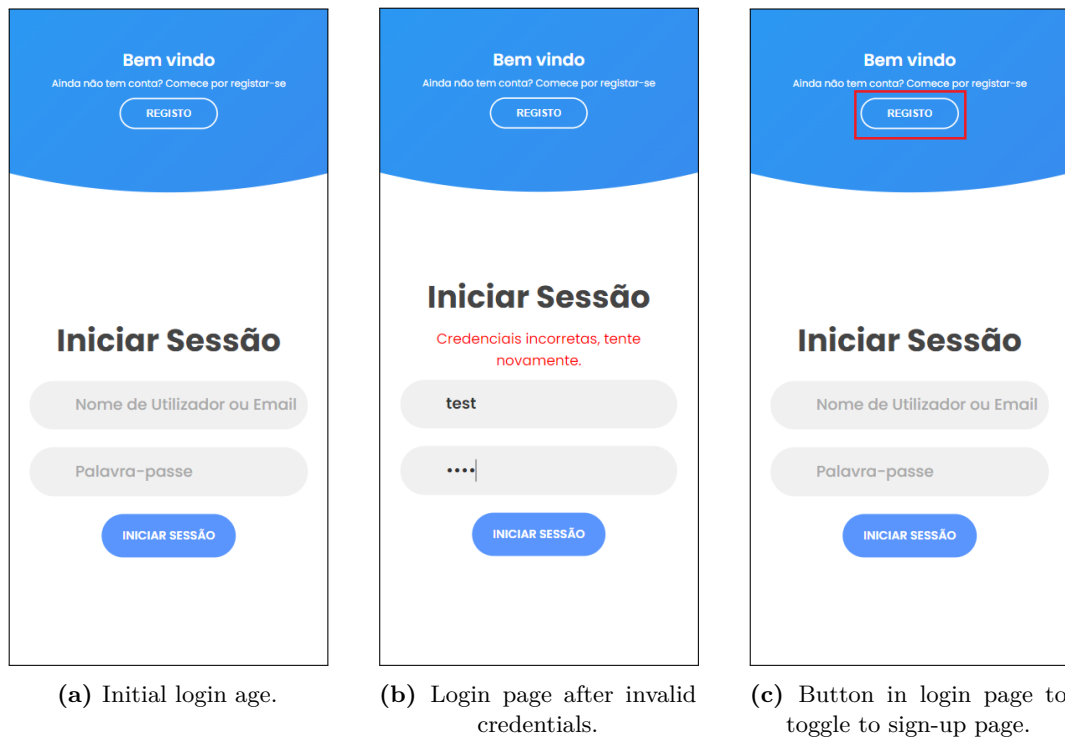


Figure 4.2: Login Page.

Main Menu

After a successful login or registration, user are redirected to the main menu of the application, Figure 4.3, being presented with a variety of options. Related with the previous menu, users can logout by clicking in the last button of the main menu, with the text "TERMINAR SESSÃO", returning to the authentication page.

The remaining buttons on the screen allow to access different menus. The first button opens the page to report the symptoms and medication times, the "JOGAR" button redirects to the games menu, the "QUESTIONÁRIO" button leads to the assessments menu, the "INFORMAÇÕES" button opens the information page and the "CONTA" button opens the account options menu.

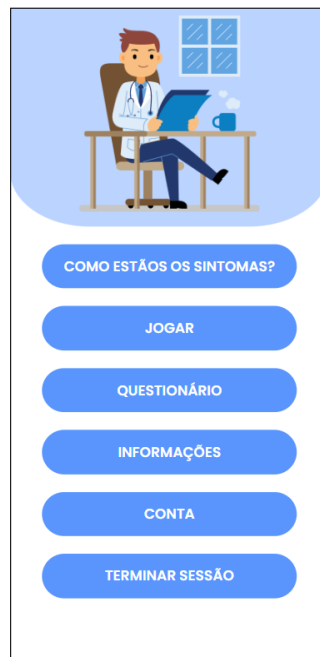


Figure 4.3: Main menu.

Symptoms and Medication Reporting Page

As specified, the button "COMO ESTÃO OS SEUS SINTOMAS?", highlighted in Subfigure 4.4a, opens the page responsible for collecting the user current symptoms and store the medication intake times, displayed in Subfigure 4.4b. The button was added to the main page to make it as accessible as possible, as this feature should be used frequently during the day. An example of the page filled in with the time of medication and current symptoms is displayed in Subfigure 4.4c.

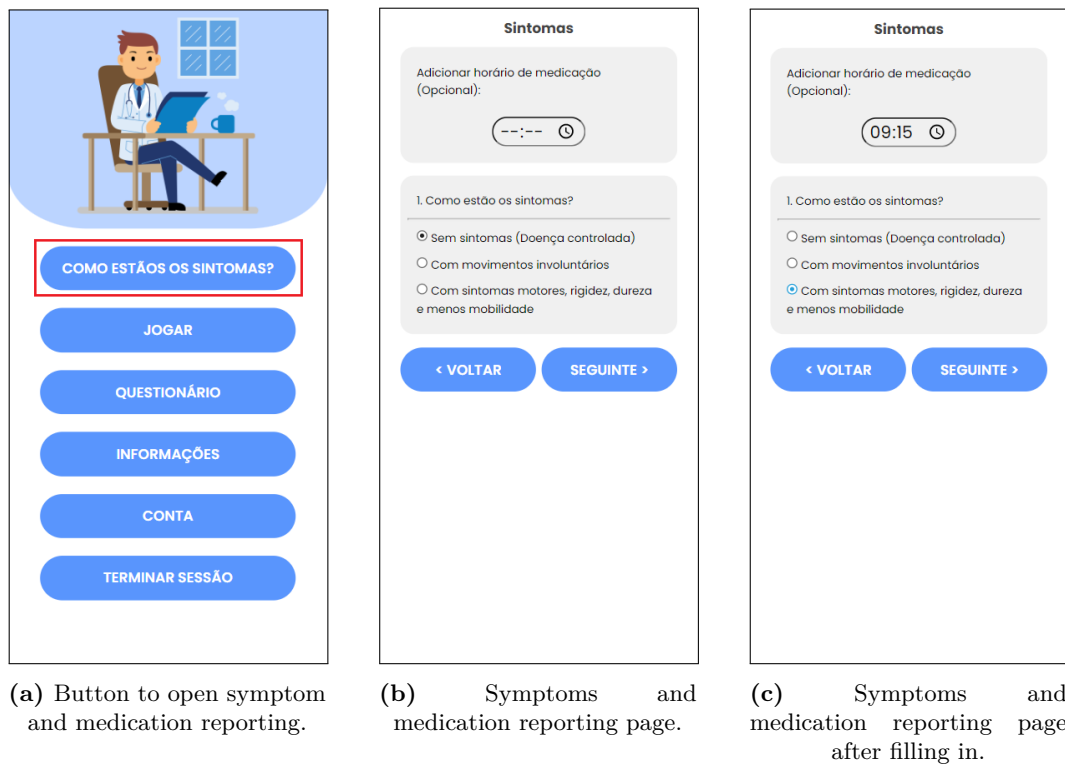


Figure 4.4: Symptoms and medication report.

Games Submenu

The second button in the main menu page, "JOGAR", highlighted in Subfigure 4.5a, leads to the games submenu, Subfigure 4.5b, where the user can choose the game they want to play. The first button, "ALEATÓRIO", selects a game at random, while the others redirect to the desired game. The randomness of the game selection takes into account the device type, so that the balance game is not chosen for devices without the necessary sensors. In order, the buttons open the following games: reaction, tapping, memory, draw, balance and speech, which will be further explained in more detail. It is good to know that the medication input field is optional and can empty for submission.

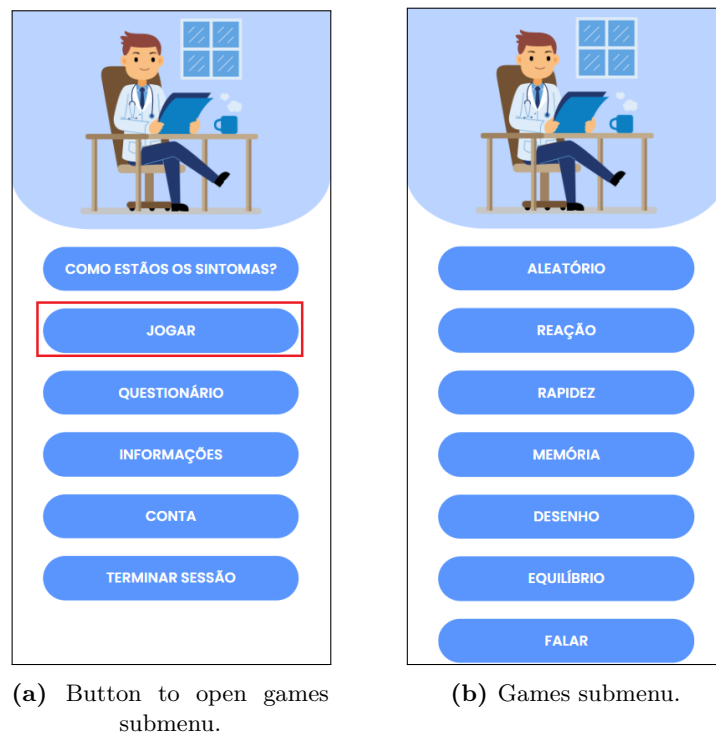


Figure 4.5: Open and check games submenu.

Games Page

The games play an important role in the application, retrieving parameters that can help characterize different symptoms of patients. The data obtained from each game session includes how long it took to complete the game and how well the player performed.

The games in the app share a common pattern. The user is first presented with an introduction page that displays information about the game, namely its name, Subfigure 4.6a, and how to play, Subfigure 4.6b. They can then choose to return to the previous menu or start the game with the buttons highlighted in Subfigure 4.6d. If the user has already played this game before, their current record is displayed under the game information, similar to Subfigure 4.6c, otherwise it does not show anything.

Apart from the page elements described before, the loading page shown in Subfigure 4.6e is displayed after the game ends. The page is used as a loading screen during the save of the game score in the database, and then redirects to the main menu of the application.

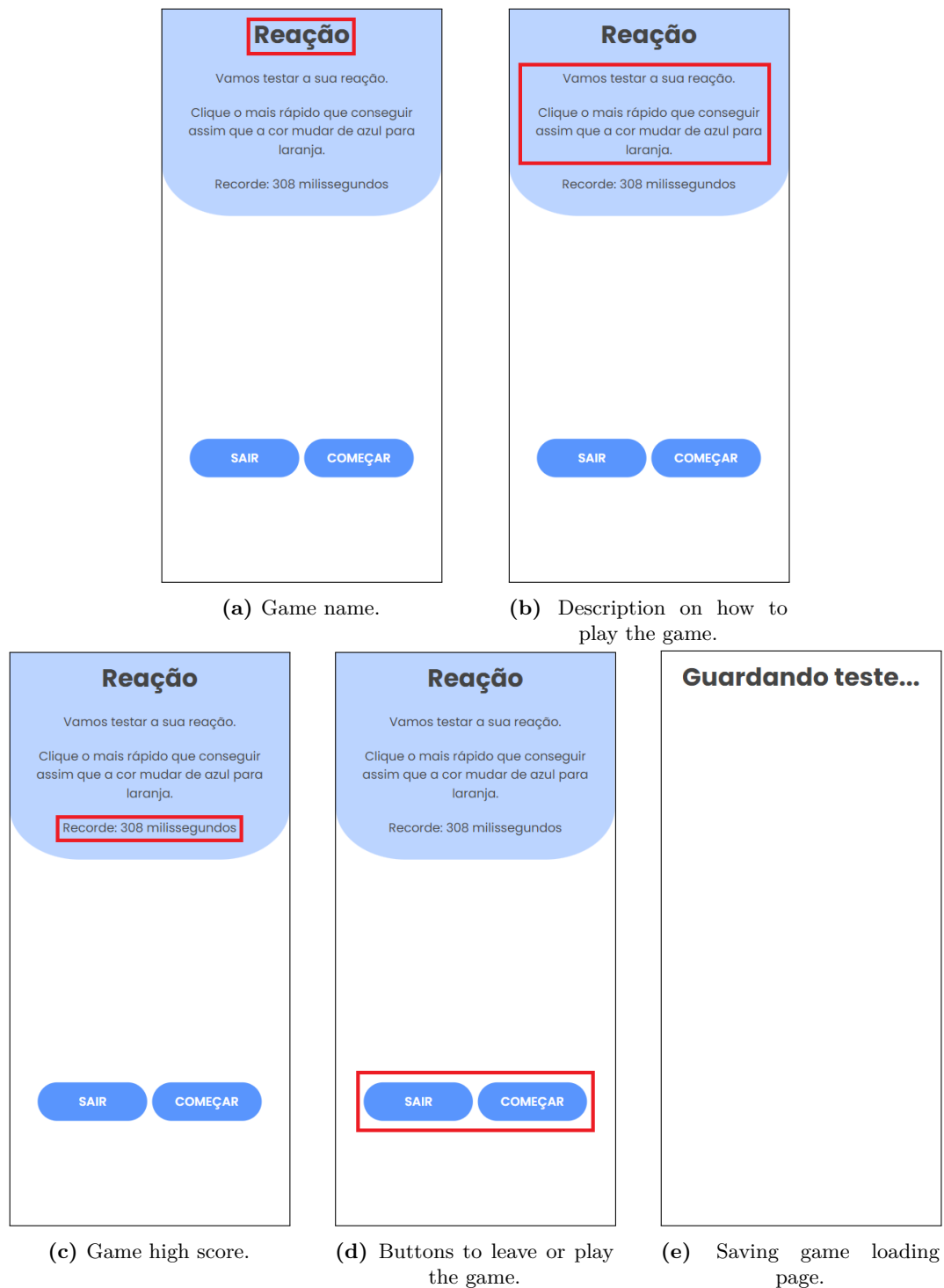


Figure 4.6: Common elements from the games pages.

Reaction Game

The first game developed has the objective of measuring the user's reaction time, a parameter that can be related to the processing speed and executive function. With the deterioration of the brain in neurodegenerative diseases, the reduction of neurons originates a slow down on brain availability, leading to a worse reaction time. Thus, would be expected to see an increase in the result of this game as the diseases progress. When playing, user is faced with a colored square which, after a random amount of time, changes its color. The user must touch as quick as possible after the color change in order to record the least amount of time. The information in Subfigure 4.7a explains how the reaction game is played, Subfigure 4.7b shows the reaction game in the beginning and Subfigure 4.7c shows the moment where the user must react.

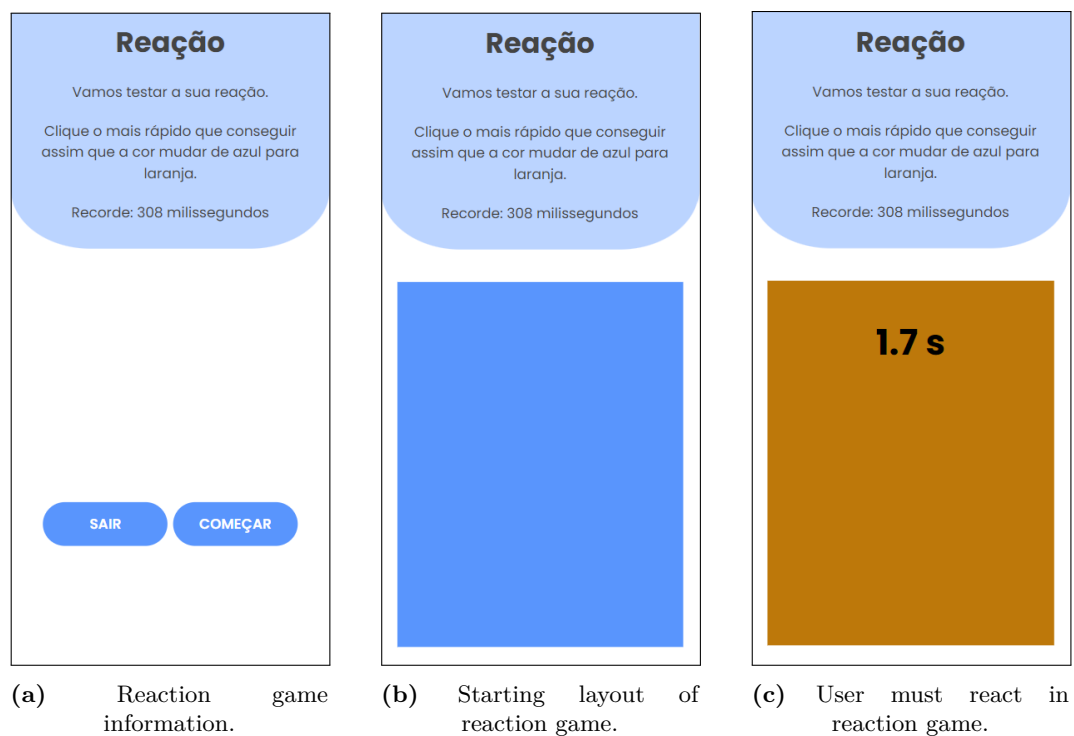


Figure 4.7: Game 1 - Reaction game.

Tapping Game

The tapping game follows the premises of the FTT assessment, described in Subsection 2.1.3. This diagnostic used by doctors allows to detect impairments in the motor function by analysing the user tapping ability. It is expected that the deterioration of the user ability in this game correlates with the deterioration in motor functions that patients suffer as the disease worsens. This game layout

is similar to the Reaction Game, however, when the color changes, user have to tap on the screen as many times as possible during the following 10 seconds. The number of taps is then recorded in the database, and is expected that this score decreases with time as patients age and the diseases get worse. The Subfigure 4.8a displays the Tapping Game information, Subfigure 4.8b shows the game layout and Subfigure 4.8c shows the time frame where the user taps as much as possible.

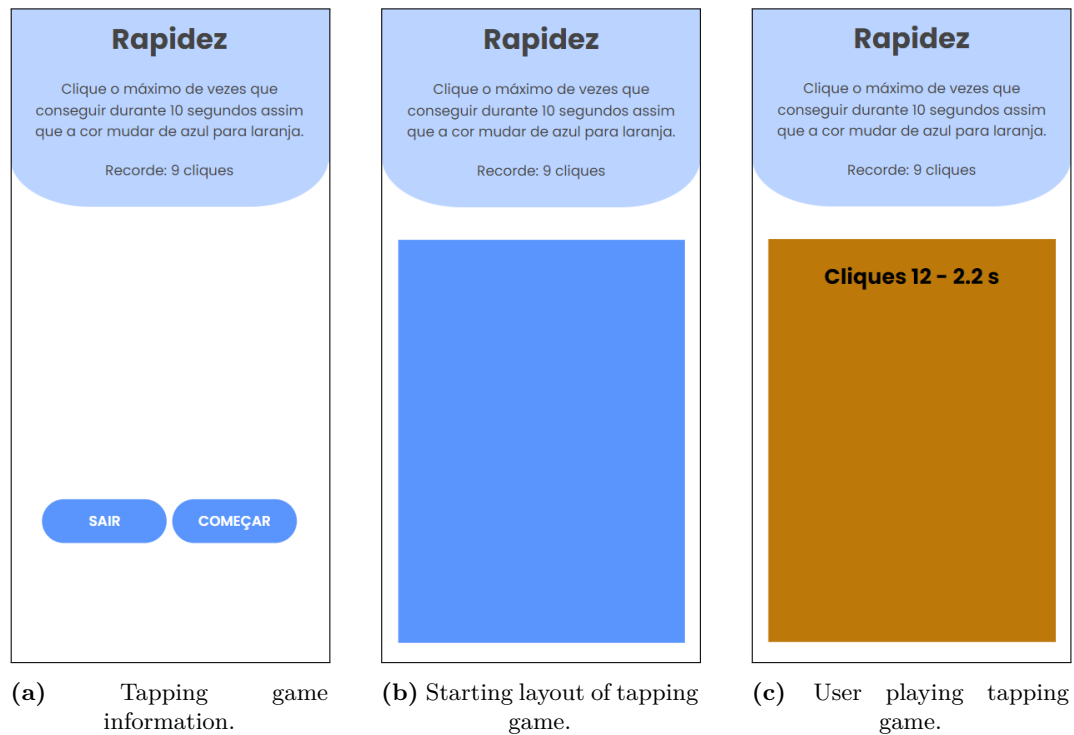


Figure 4.8: Game 2 - Tapping game.

Memory Game

The memory game has the goal of measuring a common symptom of neurodegenerative diseases, but not as relevant for Parkinson's. Following the initial premises of this investigation, where the application would be suitable for the general neurodegenerative diseases, the game was created focusing on the Alzheimer's disease main symptom, the deterioration of the patients' memory. The game is the traditional memory game, where the user has to find the pairs of cards. The game starts with 16 cards faced down, each with a letter, as displayed in Subfigure 4.9b. By flipping two cards at a time, the user needs to discover which cards have the same letter. Every time the user makes a guess, the number of tries increases, with the final value being stored in the database. The game finishes when all the cards are faced up, which means that the user found every pair of cards. The Subfigure 4.9a displays the introduction page and the Subfigure 4.9c shows the

user playing the game after discovering 3 pairs.

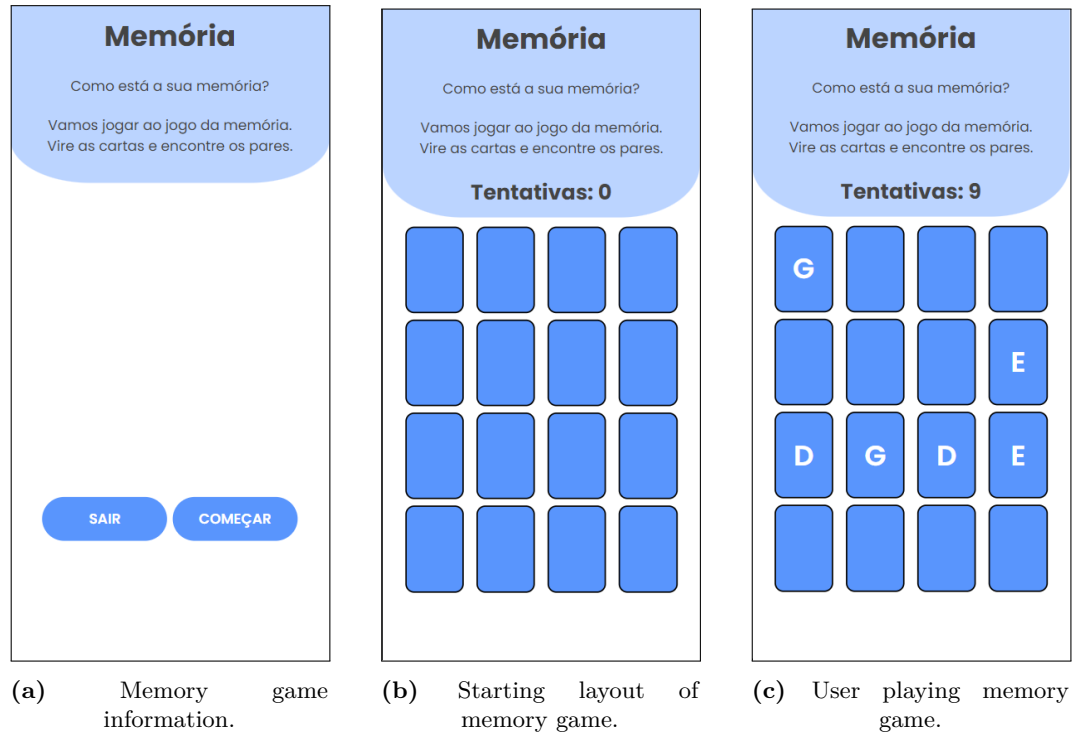


Figure 4.9: Game 3 - Memory game.

Drawing Game

As specified in Subsection 2.1.3, the kinematics of the drawing are effective at indicating physiological parameters, such as the amplitude of tremors, the main symptom of Parkinson's. The drawing game was included to see the evolution of the patients tremors with aging, since the drawing accuracy can be correlated with the disease current state. The drawing game includes 3 different alternatives.

The spiral draw is frequently used by physicians because it is a complex coordinated motor activity, which allows experts to predict and monitor the evolution of Parkinson's. The user is asked to draw the spiral over the reference image that is displayed as a dashed line under the drawing area. The score of the game corresponds to the accuracy between the reference image and the user's draw. The drawing game regarding the spiral is shown in Figure 4.10, where Figure 4.10b shows the reference image and Figure 4.10c shows the patient drawing.

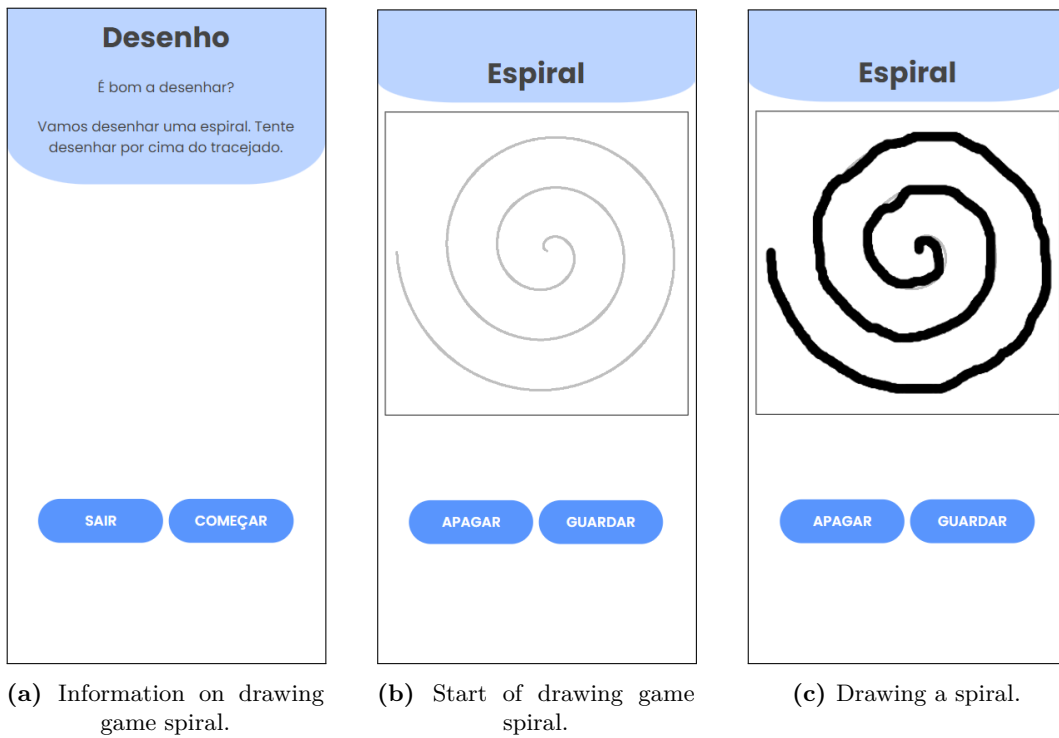


Figure 4.10: Game 4 - Draw game of type spiral.

Studies related with the spiral drawing also found correlation between wave drawing and Parkinson's Disease detection, such as the case in [71]. The drawing of the wave was implemented similarly to the spiral drawing, only differing in the reference image. The score of this game is also obtained with the calculation of the accuracy between the reference image and the drawing. The reference image for this game and an example of the draw are displayed in Subfigure 4.11b and 4.11c, respectively.

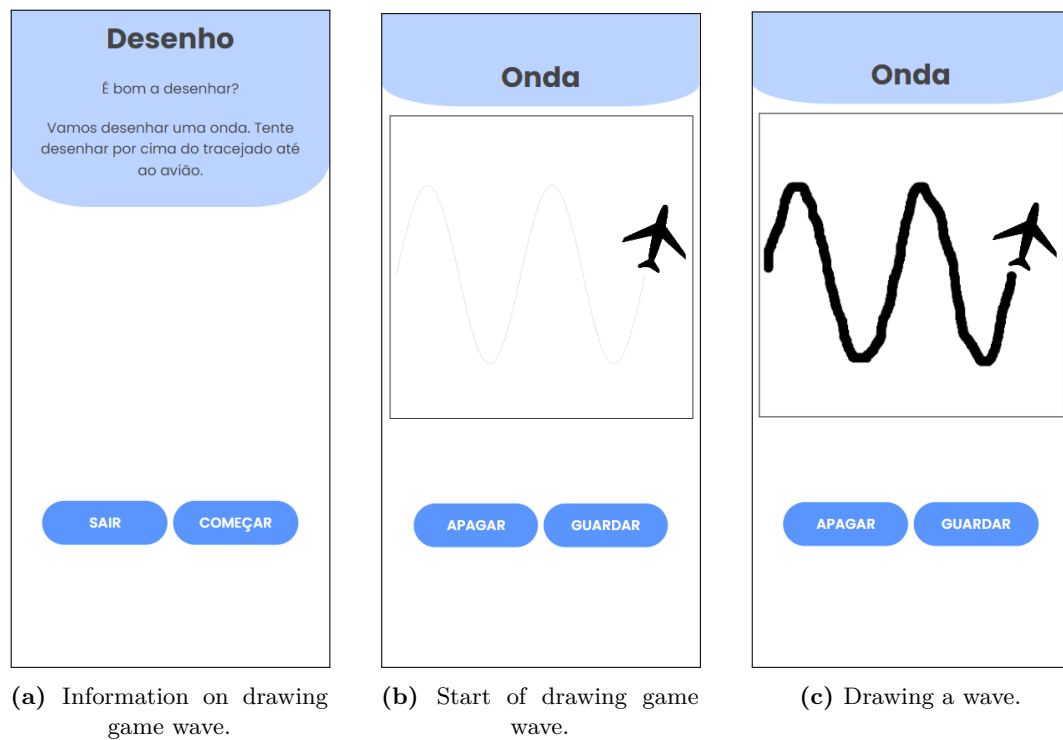


Figure 4.11: Game 4 - Draw game of type wave.

The drawing game also included the CDT, which was described in Subsection 2.1.3. It was not possible to implement an algorithm to score the draw based on the various elements, so the score is only based on the user's ability to know where to draw the clock hands at the desired time. For future works, integrating a machine learning algorithm that can accurately score based on the different elements drew would be interesting. The clock draw game information, including the desired time, is displayed in Subfigure 4.12a, the reference image in Subfigure 4.12b and a draw example in Subfigure 4.12c.

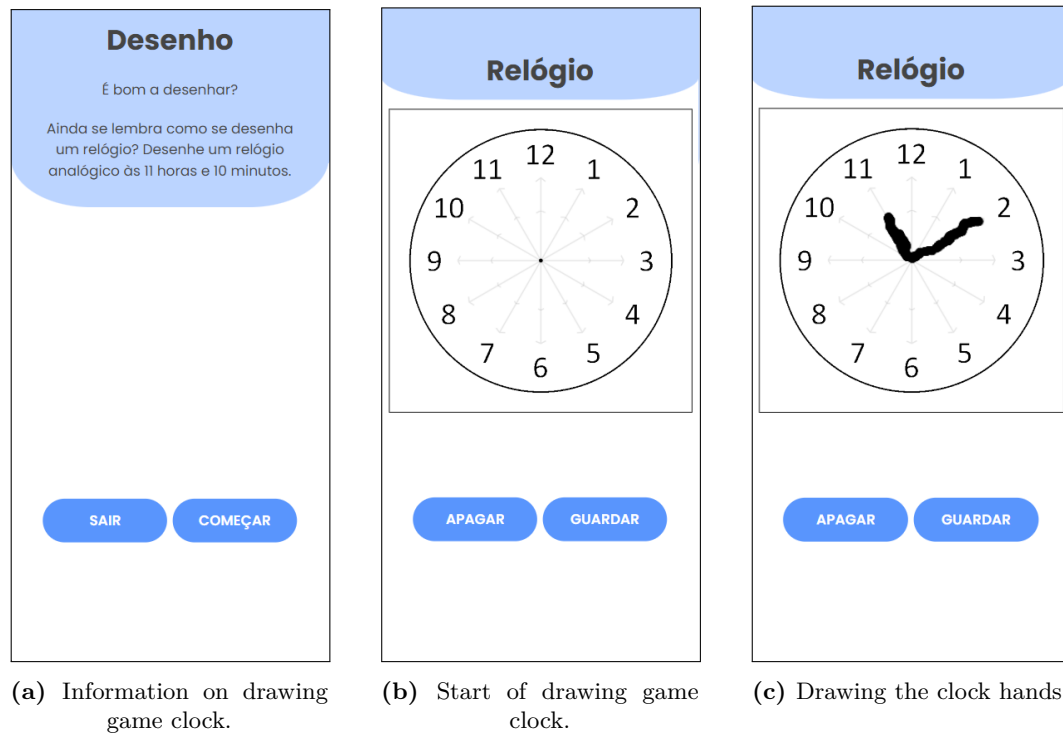


Figure 4.12: Game 4 - Draw game of type clock.

Balance Game

The balance game was designed to measure patients' tremors more objectively than the drawing game. The user is asked to keep the device as still as possible while playing the game to receive the highest score. Any rotation or translation of the device will subtract from the initial total points. This game is only available for mobile devices due to the lack of accelerometers and gyroscopes on computers, therefore the application will be redirected to the games submenu if this condition is not met, with the message displayed in Subfigure 4.13c to notify the user about the issue. This game will use the sensors to detect these information about the device, and if the user does not accept this permission, the application is redirected to the main menu. The Subfigure 4.13a shows the balance game introduction and the Subfigure 4.13b shows how the game is being played.

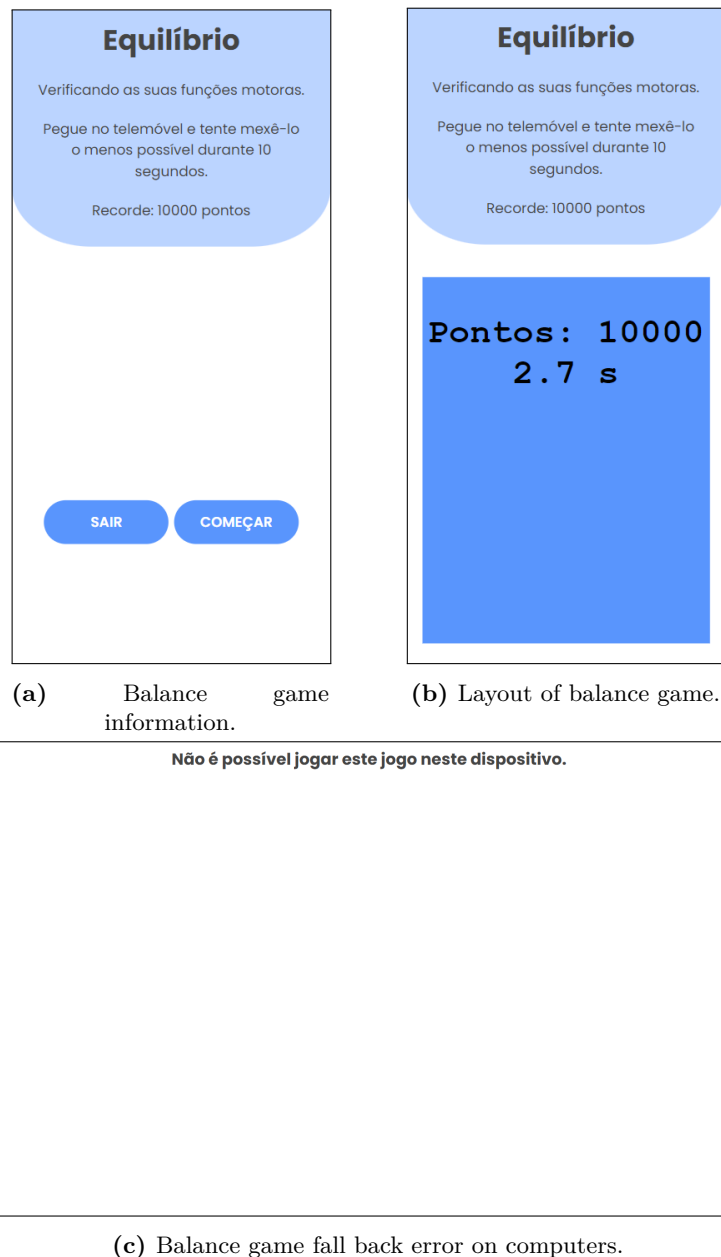


Figure 4.13: Game 5 - Balance game.

Speech Game

The speech game was developed based on the research findings by Diogo et al [54], which demonstrates that voice parameters can accurately identify people who have Parkinson's disease. Following the procedure in that article, which used the Praat application for speech analysis, the application uses the *parselmouth* Python module to act as interface between Python and the Praat code, allowing for the calculation of the voice parameters Jitter and Shimmer. The user is asked to say the vowel "A" during 5 seconds. Similar to the balance game, the speech game

requires a permission to use the microphone and, if the user does not accept it, the application is redirected to the main menu. The speech game does not have a score itself, but saves the voice parameters in the database. The Subfigure 4.14a shows the game introduction, the Subfigure 4.14b displays the button for recording and the Subfigure 4.14c occurs during the voice recording.

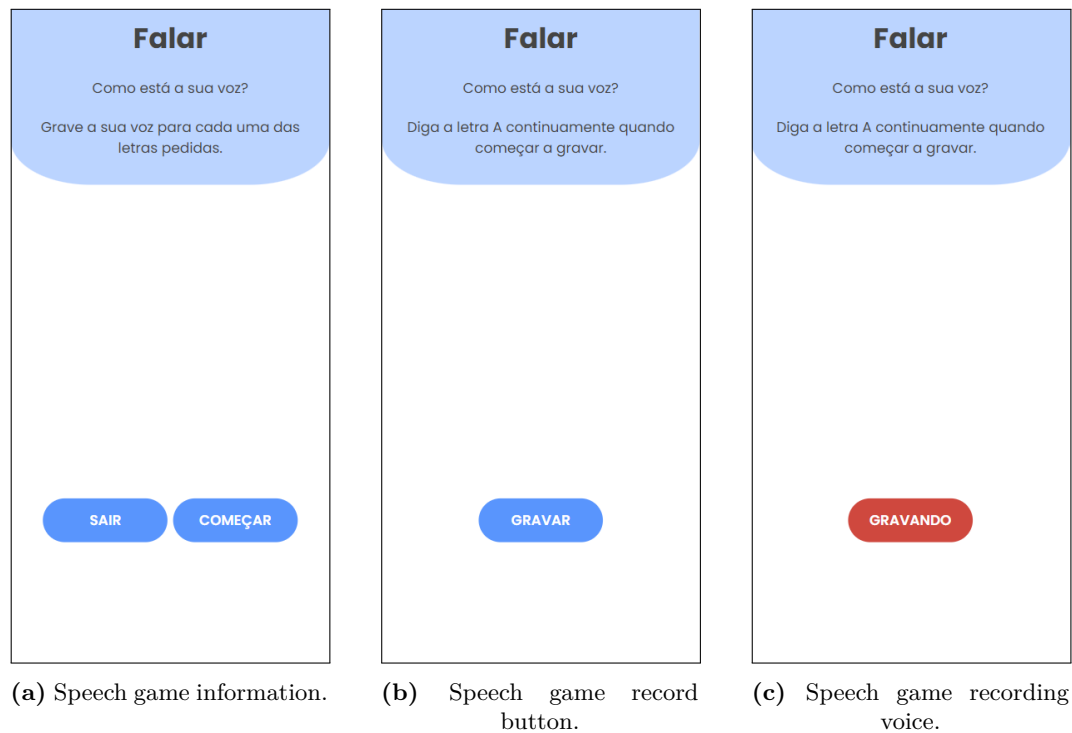


Figure 4.14: Game 6 - Speech game.

Assessments Submenu

The third button in the main menu, Subfigure 4.15a, leads to the assessments submenu, Subfigure 4.15b. This submenu displays common assessments available in the app. Currently the application includes two assessments, the part I of UPDRS and the BADLS. It is up to the users to decide whether or not they want to complete these assessments, but it is interesting from a medical point to have them saved, in order to be accessed whenever necessary. New useful assessments could be added to the application according to the health professionals needs.

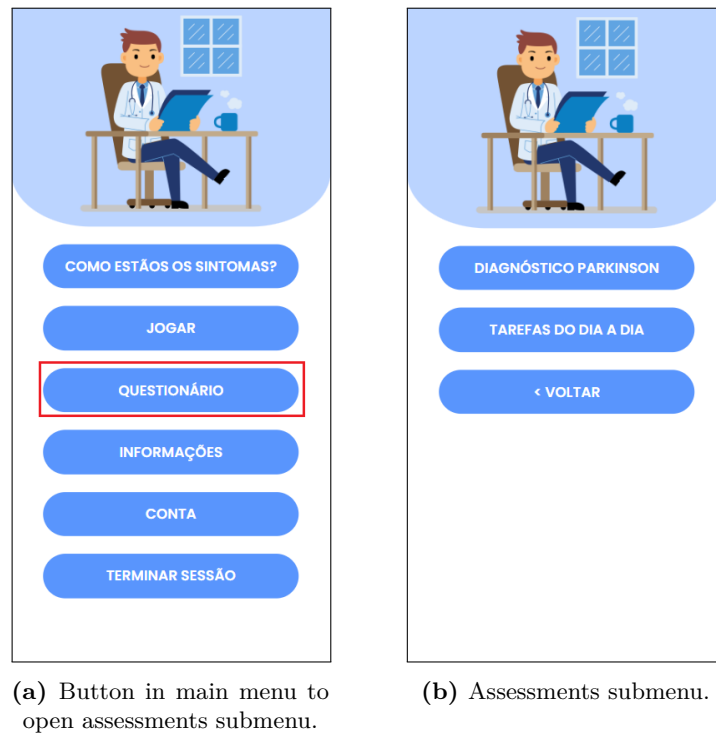


Figure 4.15: Assessments submenu.

Assessment

The assessment's questions are presented in a sequential order. To answer the questions, users can choose from a range of possible alternatives. In the first question, the user has the option to move on to the next question or return to the previous menu, as shown in Figure 4.16a. On the other hand, the last question allows to go back to the previous question or to submit the answer to the database, Subfigure 4.16b. All other questions provide a way to navigate between the questions, either backwards or forwards.

Diagnóstico Parkinson

1. Durante a última semana, você teve algum problema para adormecer à noite ou em permanecer dormindo durante a noite? Considere o quanto descansado se sentiu ao acordar de manhã.

☒ Sem problemas.

☐ Os problemas do sono existem, mas habitualmente não impedem que tenha uma noite de sono completa.

☐ Os problemas do sono causam habitualmente alguma dificuldade em ter uma noite de sono completa.

☐ Os problemas do sono causam muitas dificuldades em ter uma noite de sono completa, mas habitualmente ainda durmo mais de metade da noite.

☐ Habitualmente não consigo dormir durante a maior parte da noite.

[< VOLTAR](#) [SEGUINTE >](#)

Diagnóstico Parkinson

7. Durante a última semana, sentiu-se habitualmente fatigado? Esta sensação não é por estar com sono ou triste.

☒ Sem fadiga.

☐ Sinto fadiga. No entanto, não me causa dificuldade em fazer coisas ou em estar com pessoas.

☐ A fadiga causa-me alguma dificuldade em fazer coisas ou em estar com pessoas.

☐ A fadiga causa-me muita dificuldade em fazer coisas ou em estar com pessoas. No entanto, não me impede de fazer nada.

☐ A fadiga impede-me de fazer coisas ou de estar com pessoas.

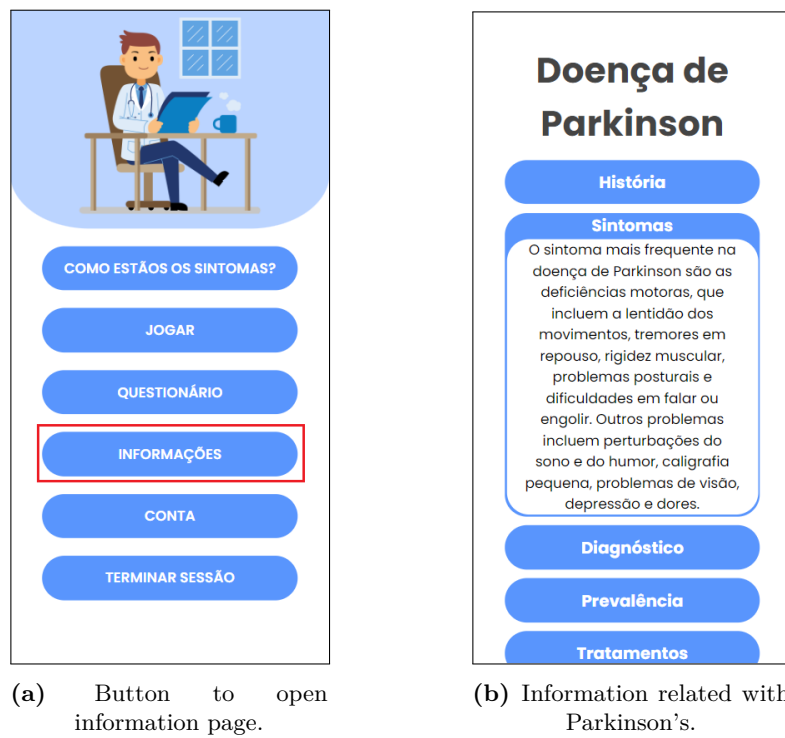
[< ANTERIOR](#) [SUBMITER](#)

(a) First question of an assessment. (b) Last question of an assessment.

Figure 4.16: Example of an assessment.

Information

One of the main features of SG is the delivery of information to users, regarding the subject of the respective app. The button highlighted in Subfigure 4.17a opens the information page displayed in Subfigure 4.17b. The application only contains information about Parkinson's disease, but it can be used to provide information about other neurodegenerative diseases if the target group is changed. The information page includes several boxes associated with each topic that can be expanded to show the information or collapsed to hide the information and shorten the space.



(a) Button to open information page.

(b) Information related with Parkinson's.

Figure 4.17: Information displayed in the app.

Account Submenu

The "CONTA" button in the main menu, Subfigure 4.18a, redirects to the account options, Subfigure 4.18b. The account submenu is the entry point to access general data of the account, namely the game scores, the completed assessments and the achievements.

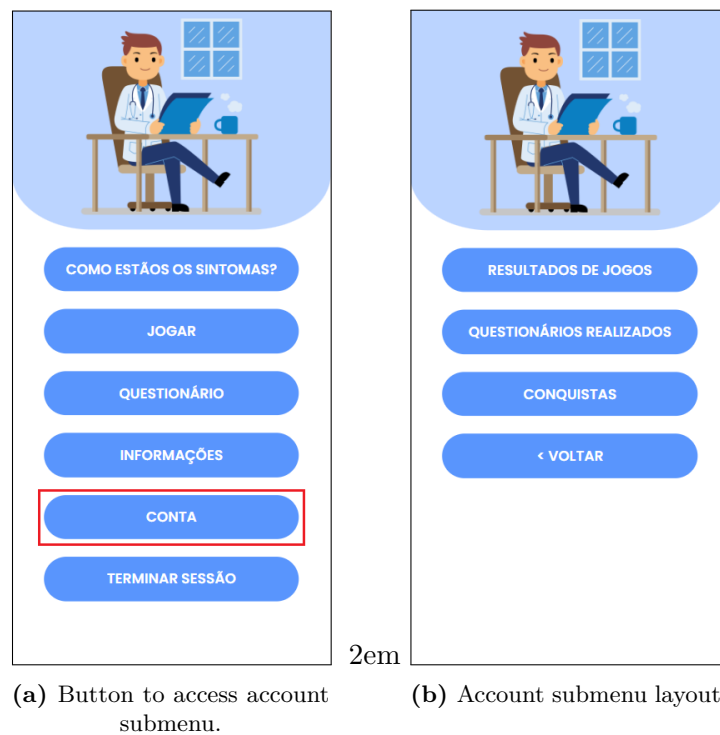


Figure 4.18: Account submenu.

Game Results Submenu

The game results submenu, which is accessible via the account submenu and the button highlighted in Subfigure 4.19a, contains the different games available in the app - Subfigure 4.19b, where each option will open the corresponding game score evolution.

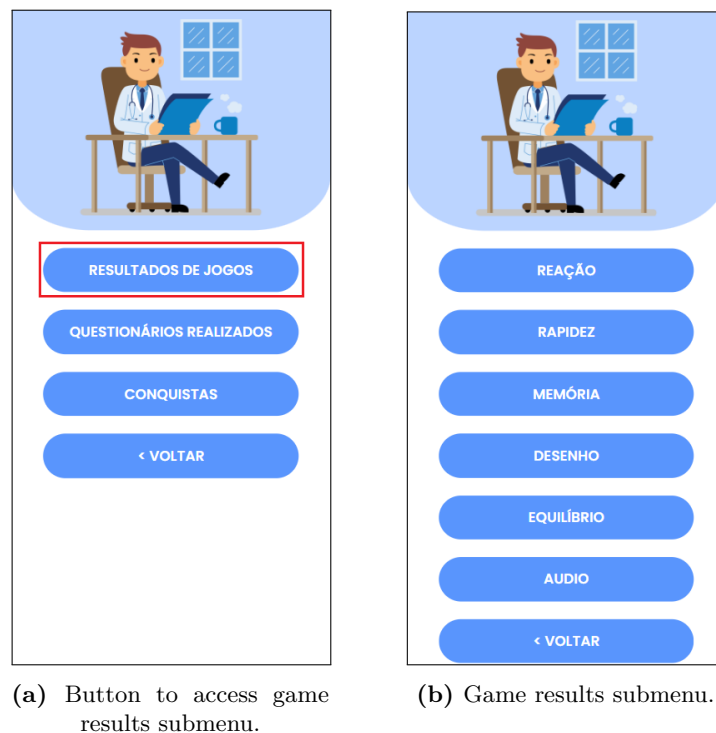
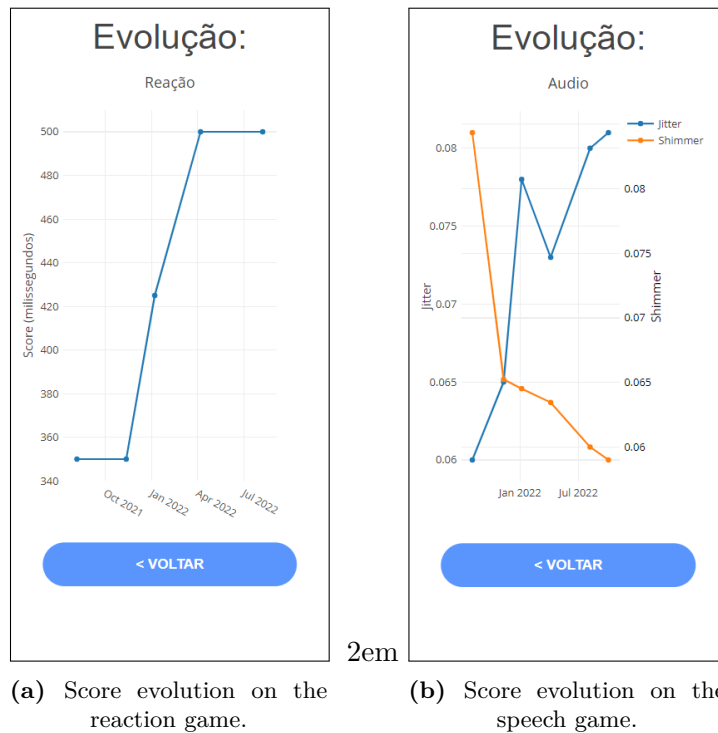


Figure 4.19: Account submenu.

Game Results

The display of the game scores in the form of a graph, according to the moment in which they took place, facilitates the analysis of the evolution of the patients' symptoms, and therefore a better evaluation of the progress of the disease. This feature was developed for physicians, but is included in the patient's app to simplify the development of this proof-of-concept, as an app for physicians has not yet been developed.

The different games measure different parameters which result in different graphs, such as the graph for the reaction game in Subfigure 4.20a and the graph for the speech game in Subfigure 4.20b. Future versions of this application could include the ability to choose the time period of analysis, as well as plot the medication times with the scores to understand the medication's influence on the symptoms.



(a) Score evolution on the reaction game.

(b) Score evolution on the speech game.

Figure 4.20: Game's score evolution.

Assessments' answers submenu

This menu provides a list of assessments that the user can choose to see the answers, including the symptoms and medication reporting. The app's current options are shown in Subfigure 4.21b.

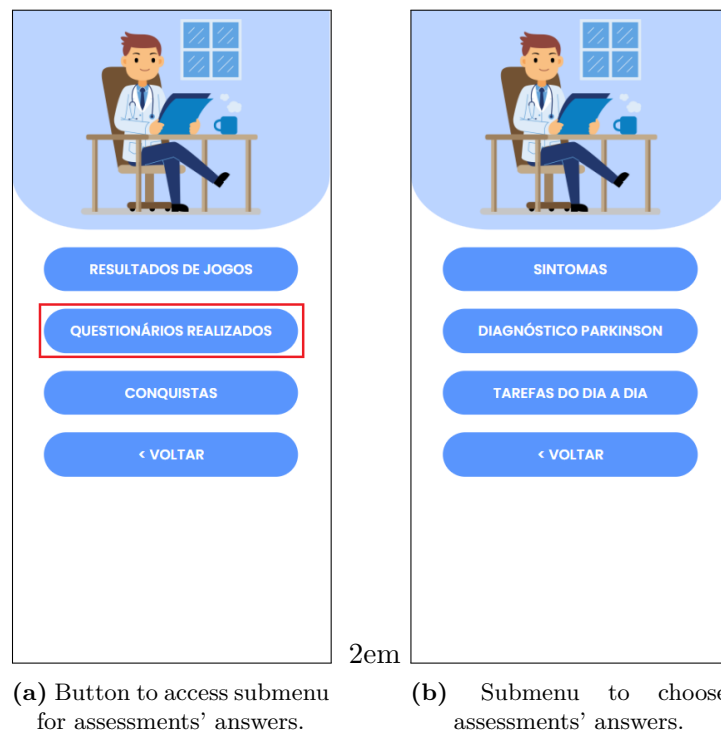


Figure 4.21: Choose assessments' answers submenu.

Symptoms journal

As explained before, the follow up of symptoms during the day was a feature requested by doctors, with the goal of tracking how active are the patients' symptoms during the day and let health professionals correlate it with the medication intake times, allowing for adjustments in the medication. The initial page displayed is similar to Subfigure 4.22b, as it considers the current day, but after the physician specify the day of evaluation, the graph is built and displayed as in the Subfigure 4.22c.

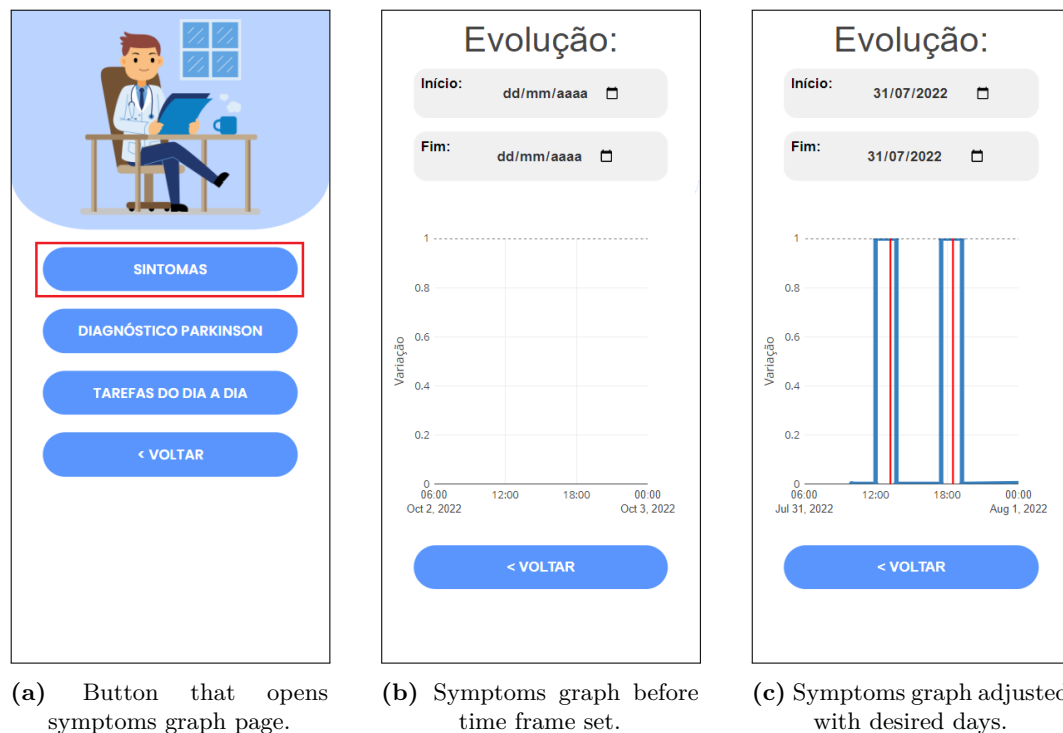


Figure 4.22: Graph with symptoms and medication reporting.

Assessments' answers

The answers to commonly used medical assessments are useful for doctors to have at their disposal, regardless of how often they change. These assessments can also help to diagnose diseases in healthy people and monitor the evolution of patients. The Subfigure 4.23b illustrates an example of the answers to the UPDRS assessment.

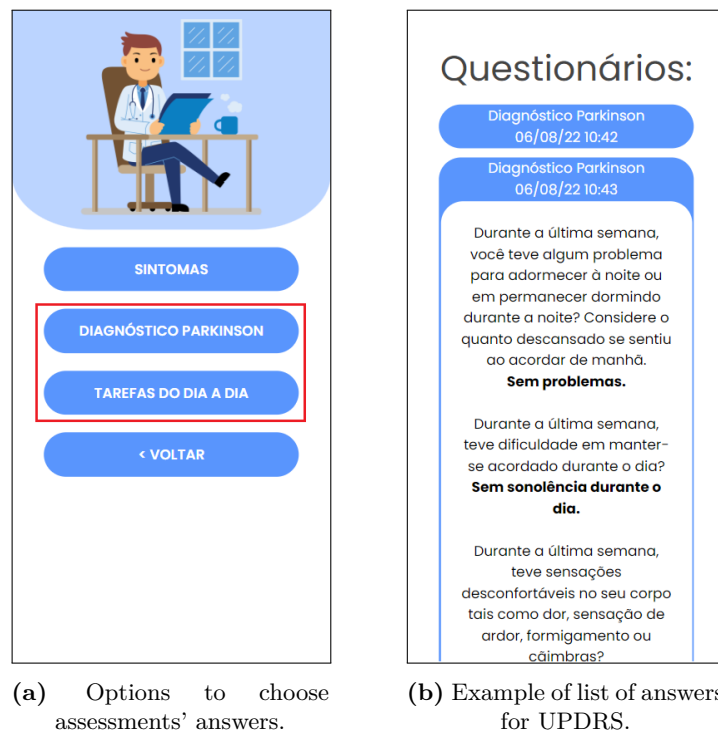


Figure 4.23: Assessments' answers list.

Achievements

The gamification techniques described in Subsection 2.2.3 were incorporated in the app to increase the patient adherence to the application, by including achievements that the user unlocks by completing tasks. The achievements and how they are unlocked are described in Table 4.1 and the badges are presented in the Subfigure 4.24b.

Name	Objective
Player	Play at least one game.
Reaction	Play at least once the reaction game.
Speed	Play at least once the tapping game.
Memory	Play at least once the memory game.
Draw	Play at least once the draw game.
Balance	Play at least once the balance game.
Speech	Do at least once the speech test.
Master	Play all games at least once.
Assessment	Do at least one assessment.
Symptoms	Indicate at least once how you feel about your symptoms.
UPDRS	Perform at least once the UPDRS assessment.
Tasks	Perform at least once the daily activities assessment.

Table 4.1: List of achievements available in the app and how to unlock it.

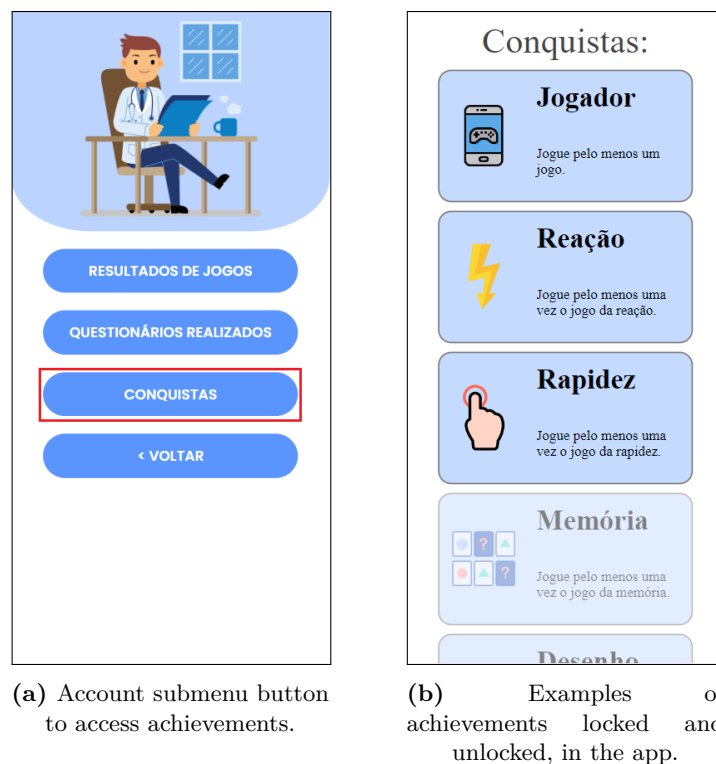


Figure 4.24: Achievements in the application.

Server Endpoints

To understand how the application works, mainly related with the navigation and its functionalities, the list of endpoints from the server are represented on Table 4.2, with information regarding the endpoint, the domain on which is inserted, the HTTP method and the function for which it is used. Apart from the */login* and */signup*, all other access points require the user to be logged in, otherwise they are redirected to the login page.

Table 4.2: Server endpoints.

Domain	Endpoint	Method	Function
Authentication	/login	GET	Render login page.
		POST	Triggers a new login.
	/logout	POST	User logout.
	/update	POST	Triggers new credentials update.
	/signup	GET	Render sign-up page.
		POST	Triggers a new registration.
Menu	/	GET	Render the main menu page.
	/account_options	GET	Render the account options page.
Games	/game	POST	Adds new game entry to database.
	/game/<int:index>	GET	Calculate the high score and render the corresponding game.
	/evolution/<int:index>	GET	Render graph for game <i>index</i> with scores over time.
	/choose_game_evolution	GET	Render page to choose the game to check graph.
	/games_data/<int:index>	GET	Return user data for a specific game (game records, type and units).
Assessments	/choose_assessment	GET	Render page for choosing assessment.
	/assessment	GET	Render assessment.
		POST	Add assessment and answers to database.

Following next page

Continuation of the Table 4.2

Domain	Endpoint	Method	Function
Assessments	/choose__assessment__list	GET	Render page to choose list of assessments to show.
	/choose__assessment/<int:index>	GET	If <i>index</i> corresponds to symptoms' assessment, render its graph, otherwise render list of assessments from the specific <i>index</i> .
	/assessments	GET	Render page with all completed assessments by the user.
	/assessments__data	GET	Returns data with list of completed assessments.
Information	/info	GET	Render information about Parkinson's.
	/info_choose	GET	Render page to select the disease to obtain information.
Achievements	/achievements	GET	Render page with user's list of achievements.
Files	/<path:path>	GET	Return files for PWAs (manifest, icons and JavaScript).

4.2 UPDRS App

For the Parkinson's assessment app, the constraints to its development were just two: use the questions in Part III of UPDRS and show the total score and answers after filling the assessment.

With this in mind, the application was also developed using the same set of tools and hosted online. The results are shown in Figure 4.25, with a question example in Subfigure 4.25a and the result from the assessment in Subfigure 4.25b, where we can see the final result, each of the answers and their scores, and the current date and time.

Digital UPDRS - PARTE 3

3.10. Marcha.

☒ [0] - Sem problemas. Normal.

☐ [1] - Marcha independente com mínima alteração. Discreto.

☐ [2] - Marcha independente mas com alteração substancial. Ligeiro.

☐ [3] - Precisa de um auxílio de marcha (bengala, muleta, andador) para andar em segurança, mas não de outra pessoa. Moderado.

☐ [4] - Incapaz de caminhar ou consegue apenas com ajuda de outra pessoa. Grave.

< ANTERIOR
SEGUINTE >

Digital UPDRS - PARTE 3

RECOMEÇAR

10/09/2022, 08:38:28
Total: 3

Fala.
Perda de modulação, dicção ou volume, mas todas as palavras são facilmente compreensíveis. Discreto. [1]

Expressão Facial.
Além da diminuição da frequência do piscar de olhos, presença de fâcies inexpressiva na parte inferior da face, particularmente nos movimentos da boca, tal como menos sorriso espontâneo, mas sem afastamento dos lábios. Ligeiro. [2]

Rigidez.
Sem rigidez. Normal. [0]

Bater dos dedos na mão (Pinça).
Sem problemas. Normal. [0]

(a) UPDRS Question example.
(b) UPDRS assessment result.

Figure 4.25: UPDRS Part III application.

The pages of this application use the same layout as the assessments in the main application. Each question in the game has the ability to move backward or forward, except the first and the last, which will restart the game and end the assessment, respectively.

4.3 Discussion

From the 38 functional requirements defined in Table 3.1, 29 of them were achieved, which corresponds to approximately 76%. Regarding non-functional requirements, all of them have been implemented.

In terms of security issues, both requirements have been met, which are the usage of password encryption and the handling of injected code in text fields, making the app secure and reliable.

Considering the authentication domain, the requirements with higher importance, namely the login, the registration and the logout of the patients, were achieved. On the other hand, the authentication referring to the health professionals was not implemented since all the desired functionalities were included in the patients' application, thus facilitating the development process of this proof

of concept.

The requirements related with games were all completed. In the app, users are able to play a random game or choose a game, seeing their high scores when available⁸. The app features 6 games to avoid learning bias, each of the games measuring different parameters that evaluate symptoms.

The application includes common assessments used by professionals, namely a part of the UPDRS and BADLS, which can be recorded in the database to access when needed.

The functionalities required by the doctors that followed the app development were also achieved. Patients are able to report their current symptoms and their medication intake times. The doctors are then able to see a chart that correlates the symptoms with the medication over a time frame that they can define. This feature helps physicians to adapt the medication intake to the patients needs.

The information and achievements, features related with Serious Games and Gamification, respectively, were also important topics taken into consideration and included in the application.

Finally, the development of an application specially designed for individuals with neurodegenerative diseases was a topic always considered. Therefore, non-functional requirements were given a special consideration, mainly regarding the front end. For this, the CSS was extremely useful in order to adapt the page appearance to these individuals. Due to their limited capabilities, the following design rules were considered during the application development:

- Suggestion after wrong input in text fields;
- Memorising the name or email in login;
- Fast navigation between menus and quick response to actions, limited by the use of a free server, in order to avoid user boredom;
- Intuitive navigation between menus, in order for users to know where each functionality is available;
- Pages responsive to any screen size, regardless of their shape or appearance. This was obtained using relative sizes, margins, fonts, spacing and other CSS properties, as well as defining media queries;

- Browser-based application that can be accessed on any device with internet access, independent of the operating system used. This characteristic makes the application available on smartphones, tablets, smart TVs, computers, among others devices;
- Same template used across the application, regarding titles, buttons and images implemented;
- Use of high contrast colors, namely blue and white. The color blue is seen as refreshing, friendly, and inviting by psychologists;
- A simple interface, with few elements, makes the application easier to use when patients do not have the help of doctors or caregivers.
- The games are simple, with only one action at a time;
- The text is simple, well-written and informative;
- Use of large buttons and fonts, appropriate for the target group.

When questioned about these properties, the doctors stated that the application was well adapted to Parkinson's patients.

Testing

The testing of the application in the field, with Parkinson's patients and their doctors, was not carried out as proposed due to the necessary paperwork, which would take too long to obtain, and the copyright issues related with the version of the UPDRS used, which would make it impossible to release the application without the consent of the Movement Disorder Society. Facing this issue, the final version of the application was presented to doctors who analysed it and provided feedback on the usability for their daily tasks and the functionalities that were included.

A general neurologist found the application useful, stating that its most interesting part was the ability for patients to record their symptoms through the day, making the common process of these patients easier, accessible, and digital. He also stated that he would use the app in his day to day life, mainly because of this functionality.

Confirming what was presented earlier, he stated that Parkinson's medication varies a lot between patients and, therefore, has to be personalised for each individual. Thus, he declared that it would be advantageous to use this

functionality for a few days, to adjust and check the effects of the medication on the patients.

This Doctor also suggested that seeing the scores of the games correlated with the medication times, similar to what is displayed with the symptoms, would be a good feature to have and investigate the relation between the medication intakes and the scores.

This physician also expressed interest in having the completed assessments available and stored in the application for easy access when needed.

The Doctor offered to test this application in the field for a few days and discuss the results.

Dr. Luísa Sousa, the expert on Parkinson's disease who assisted in the development of the application, provided a detailed opinion which is available on Annex A.

In short, states that the application has the potential to be useful for doctors that monitor Parkinson's patients, allowing the Doctor to have a more reliable notion on how the symptoms change through the day with the effects from medication.

Additionally, refers that the possibility of cognitive training through gamification at home would be useful for other neurodegenerative diseases that suffer from mild cognitive deficits.

Chapter 5

Conclusion

Contents

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5 Conclusion

5.1 Achieved goals

As proposed, the investigation includes an extensive review on neurodegenerative diseases, with focus on Alzheimer's and Parkinson's, the two with higher prevalence. The literature review also included a state-of-art on common assessments used by doctors for neurodegenerative diseases, new technologies in the health sector and games developed in investigations related with these diseases.

With the information gathered in the Literature Review, the functional app obtained was suitable for patients with Parkinson's, where users can report their symptoms and medication, play games, complete assessments, obtain information about the disease and check their achievements.

The application that was developed is hosted online, making it accessible to anyone with internet access, regardless of the device, since it was developed for the browser and is responsive to any screen resolution.

The app was designed with the target audience in mind, the Parkinson's disease patients, so that includes features that make it easy to use, such as being responsive to any device, using a high-contrast colors, having a simple interface with few elements and an easy navigation between the menus.

The testing of the application was not possible because of the lack of time and necessary paperwork, but the gathering of physicians' opinions was possible and included and in Section 4.3. One of the most highlighted aspects of the application was the ability to monitor patients whose medication is still under the supervision of a healthcare professional and being adjusted according to their symptoms.

5.2 Limitations

The functionalities designed for doctors, such as presenting the patients' scores over time, checking the symptoms and medication report and consulting the completed assessments, should have been included as part of their own application. These features are currently inserted in the patients' app and, in order for the doctors to analyze them, the patients must log in to their account and present the

results within it, which is not ideal and was only designed like this for research purposes.

Other less important authentication features, such as password recovery, password change, or username change, were not implemented due to time constraints and a less priority given to them. These features do not affect much the usability of the application.

5.3 Future work

The features that were not implemented should be included in the application to make it more appealing for release, avoiding the frustration of users when they forget their password or want to change their username.

The software designed only for the doctors would ease their work and separate the two types of users. For this, some of the functionalities displayed in the current application would be transferred to the new one, designed for doctors.

The testing of the application in the field is important to understand if the application is appreciated by the users and if some value can be retrieved from the interaction between the patients and the physicians using the app. The testing described in this thesis, with the filling of the surveys already created, would provide useful information on this topic.

A machine learning algorithm could be implemented to interact with the application in several functions, such as evaluating the patients drawing or diagnose diseases based on the answers to the assessments. Investigations on this issues already exist, so an API coming from these projects would be enough to include these features. These functionalities would ease the health professionals' job and only recommend the monitoring of certain patients when the right conditions were met.

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Appendix A

Doctor's opinion

Exmos. Senhores,

Colaborei com o aluno Paulo Santos durante este ano enquanto desenvolveu uma aplicação para apoio na consulta e de suporte no dia a dia de doentes com doenças neurodegenerativas. Ao longo das nossas interações, o Paulo demonstrou elevado interesse e conhecimento sobre tema e sobre os recursos semelhantes disponíveis no mercado; uma excelente capacidade de trabalho, com flexibilidade para adaptar a aplicação às sugestões que foram dadas e às particularidades do trabalho clínico com estes doentes. Foi particularmente notável a rapidez com que conseguiu modificar a app face às minhas sugestões. Demonstrou também boas capacidades de comunicação e de profissionalismo nas nossas reuniões.

No global, a aplicação desenvolvida tem potencial para ser muito útil na consulta de pessoas com doença de Parkinson e para permitir ao médico ter uma noção mais real de como se modificam os sintomas da doença ao longo do dia. A app permite também o treino cognitivo feito pelos doentes em casa, útil para outras doenças degenerativas em que exista declínio cognitivo ligeiro.

Santa Maria da Feira, 4 de outubro de 2022,



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